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MINIREVIEWS

COVID-19 in liver transplant patients: Impact and considerations

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Abstract

The coronavirus disease 2019 pandemic has significantly impacted liver transplantation worldwide, leading to major effects on the transplant process, including the pretransplant, perioperative, and post-transplant periods. It is believed that patients with chronic liver disease, especially those with cirrhosis, have a higher risk of complications from coronavirus disease 2019 infection compared to the general population. However, evaluation of coronavirus disease 2019 effects on liver transplant patients has not uniformly demonstrated worse outcomes. Nonetheless, the pandemic created significant challenges and restrictions on transplant policies and organ allocation.

Key Words: COVID-19; Liver transplantation; Immunosuppression; Living donor; Mortality

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Core Tip: The coronavirus disease 2019 pandemic exerted significant challenges to the liver transplant structure worldwide, initially resulting in a decline in liver transplants but soon after rebounded. A better understanding of this infection together with robust guidance by the international transplant societies helped offset this decline. A multitude of considerations should be exercised throughout the liver transplant process to maintain acceptable safety and outcomes.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic was declared an emergency by the World Health Organization in March 2020[1]. Since then it has had major impacts on many aspects of healthcare, including liver transplant in the United States. It greatly affected the pretransplant, perioperative, and post-transplant periods of liver transplantation.

It is widely accepted that patients with chronic liver disease, specifically those with cirrhosis, have a higher rate of hospitalization, length of hospital stay, morbidity, and mortality from COVID-19 infection compared to the general population[2]. In a large meta-analysis that included 40 studies primarily from the United States and China with more than 900000 participants, COVID-19 patients with chronic liver disease had higher odds of developing a severe infection [pooled odds ratio (OR) = 2.44; 95% confidence interval (CI): 1.89-3.16] and mortality (pooled OR = 2.35; 95%CI: 1.85-3.00) when compared to COVID-19 patients without chronic liver disease[3].

In contrast, literature evaluating COVID-19 effects on liver transplant recipients did not consistently demonstrate worse outcomes[4,5]. A systematic review of 1522 liver transplantation recipients who were infected with COVID-19 did not find a difference in cumulative incidence in mortality compared to patients who were not liver transplantation recipients. Additionally, the review did not find a difference in mortality between non-liver transplantation recipients *vs* liver transplantation recipients in patients who received a liver transplantation within 1 year *vs* 1-year post-transplant[4]. Still, the COVID-19 pandemic added significant challenges and restrictions to transplant policies and organ allocation. The healthcare structure was overwhelmed by critically ill patients with COVID-19 resulting in diversion of medical resources away from liver transplantation[6]. Furthermore, early concerns of patients contracting severe COVID-19 infection in light of immunosuppression discouraged their use. These uncertainties culminated in initial hardships in the overall management of patients with chronic liver disease thereby negatively affecting liver transplantation.

To revive the liver transplant process and provide organs for those in dire need, significant changes in liver transplant practice have been implemented per major transplant societies' recommendations[7]. After an initial drop in the number of liver transplants performed in the United States in early 2020, a quick recovery in the latter half of 2020 and early 2021 followed[8]. This was likely due to better understanding of COVID-19, improved adherence to infection prevention recommendations, and replenished healthcare resources. Later, COVID-19 vaccination emerged as an efficient and cost-effective preventive strategy for patients with chronic liver disease, further helping to offset COVID-19-related shortcomings[9].

This comprehensive review discussed the major aspects and effects of the pandemic on the liver transplant process as a whole.

COVID-19 INFECTION IN PATIENTS WITH CIRRHOSIS

Pathogenesis

The liver is prone to direct COVID-19 infection because of expressed angiotensin-converting enzyme 2 receptor in the hepatobiliary epithelial cells. Although not fully understood, it is hypothesized that binding of the virus spike protein to angiotensin-converting enzyme 2 receptors allows viral entry and subsequent host cellular damage[10]. Indirect hepatotoxicity may occur due to hemodynamic instability, drug-induced liver damage, COVID-19-induced immune dysfunction, coagulopathy, and intestinal dysbiosis[11]. Moreover, since the angiotensin-converting enzyme 2 receptors are also expressed on cholangiocytes, some suggest that COVID-19 infection may worsen cholestasis in patients with primary biliary cholangitis and primary sclerosing cholangitis[12].

Clinical presentation

Similar to patients without underlying liver disease, patients with cirrhosis typically develop mildly elevated aminotransferase levels (< 5 times the upper limit of normal); nevertheless, severe acute hepatitis and even acute liver failure have also been reported[13]. Commonly, a pattern of aspartate transaminase greater than alanine transaminase is associated with disease severity[14]. Likewise, a low albumin level is linked to worse COVID-19 disease severity. It is unknown if this is just a marker of disease severity or merely a risk factor for severe disease.

In patients with cirrhosis, COVID-19 infection may result in hepatic decompensation, similar to other infections. In a retrospective, multicenter study from 13 Asian countries, 29% of COVID-19 patients with chronic liver disease presented with hepatic decompensation[15].

Histopathological findings

Liver biopsy in patients with COVID-19-induced liver injury is nonspecific. Histopathological changes include microvesicular steatosis, portal and lobular activity, and zone 3 focal necrosis[16,17]. In an autopsy-based series that included 48 cases, liver histologic findings included variable degrees of parenchymal lymphocytic infiltration in almost all patients and hepatic vascular alterations in some cases[18]. In our opinion, performing a liver biopsy does not add diagnostic benefit unless an alternative diagnosis is considered.

Clinical outcomes

A significant body of research suggests increased mortality in COVID-19 patients with chronic liver disease. According to a multicenter, observational study from the United States, the presence of cirrhosis in those with COVID-19 infection was associated with higher mortality when compared to those without cirrhosis (relative risk: 4.6, 95%CI: 2.6-8.3)[19]. In a database study of COVID-19 patients with chronic liver disease, after adjusting for relevant confounders, the presence of cirrhosis was associated with higher 30-d mortality compared to those without cirrhosis (8.9% *vs* 1.7%; 95%CI: 2.91-3.77)[20]. A subsequent cohort study found that COVID-19-related mortality increased with cirrhosis progression; patients with Child-Pugh class B or C cirrhosis were found to have increased mortality (OR = 4.90, 95%CI: 1.16-20.61 and OR = 28.07, 95%CI: 4.42-178.46, respectively). Mortality was mostly attributed to pulmonary complications (79%), whereas liver-related mortality was seen in 12% of patients[21].

A rare but important long-term sequela of severe COVID-19 is cholangiopathy, at times resulting in progressive biliary destruction and liver failure requiring liver transplantation[22]. In a retrospective study by Faruqui *et al*[22] on patients hospitalized for severe COVID-19, 12 patients ultimately developed some degree of cholangiopathy defined by evidence of cholestasis (alkaline phosphatase ≥ 3 upper limit of normal) or radiologic biliary abnormalities. The majority were male (92%) with a mean time of cholangiopathy diagnosis of 118 d from COVID-19. One patient underwent liver transplantation.

Management

COVID-19 management in patients with cirrhosis follows the same supportive routine measures for the general population, including the use of COVID-specific drug therapy. Deranged liver biochemistries are not an absolute contraindication to using therapy such as remdesivir. Remdesivir use alone can cause a further elevation in liver enzymes (up to 10 times the baseline)[23]. However, its use is discouraged if the alanine transaminase level is ≥ 5 upper limit of normal[24]. Although Paxlovid (combination nirmatrelvir and ritonavir) trials did not show any concerns about its use in cirrhotic patients, it is extensively metabolized by liver cytochrome P450 enzymes. Thus, this drug harbors the risk of accumulation and toxicity in patients with decompensated cirrhosis. We think this medication should be used judicially and in collaboration with infectious disease specialists.

The use of COVID-19 monoclonal antibodies is encouraged early in the infection course in cirrhosis. This is particularly important because cirrhotic patients tend to mount suboptimal humoral responses to COVID-19 vaccination and likely infection as well. Other immunomodulatory COVID-19 therapies include JAK inhibitors (baricitinib) and IL-6 receptor antagonists (tocilizumab)[25]. We learned from baricitinib use in rheumatological disorders that it may cause liver biochemistry abnormalities, and caution and regular monitoring should be exercised[26]. Additionally, the risk of hepatitis B virus reactivation has been documented with both baricitinib and tocilizumab; therefore, obtaining hepatitis B serology before treatment initiation is warranted to assess the need for prophylactic nucleoside analogue therapy[27].

Prevention

Adherence to general preventive measures to avoid COVID-19 in patients with cirrhosis is paramount. These include social distancing, hand hygiene, proper use of personal protective equipment, and telemedicine clinic visits[28]. It is strongly recommended for patients with cirrhosis to receive the COVID-19 vaccine[9]. In a prospective, multicenter study aimed at comparing the humoral response to the COVID-19 vaccine between patients with chronic liver disease (437 individuals) and healthy controls (144 individuals), chronic liver disease was associated with lower rates of post-vaccination COVID-19 antibody positivity (77% *vs* 90%, $P = 0.008$). The rate of antibody positivity was similar among patients with chronic liver disease regardless of cirrhosis presence or even decompensation ($P = 0.894$)[9]. These findings suggest additional doses of COVID-19 vaccine might be warranted in this high-risk patient population to achieve adequate immunity[29]. In a propensity score-matched cohort study of United States veterans with cirrhosis, receiving only one dose of the COVID-19 vaccine (either Pfizer BNT162b2 mRNA or a Moderna mRNA-1273) resulted in a 64.8% reduction in COVID-19 infection and 100% prevention of hospitalization or mortality due to COVID-19 infection after 28 d[30].

PRETRANSPLANT IMPACT AND CONSIDERATIONS

Effect on liver transplant volume

The United States performs the most liver transplants worldwide per year. The second-leading country in the number of liver transplants performed is China, followed closely by Brazil[31]. Currently, over 9000 liver transplants are performed every year in the United States. For the past 9 years, the number of annual liver transplants has increased steadily, setting annual records[32]. Despite the challenges of the COVID-19 pandemic, the year 2020 was no different, as we witnessed an increase of 10.1% in deceased donor liver transplantation. The major impact the pandemic had was on living donor liver transplants, which suffered a significant decline of 22% between February and April 2020. The liver transplants performed in the United States between 2018-2021 is depicted in Figure 1[33].

During the height of the pandemic, non-urgent liver transplantation was deferred to conserve hospital resources. Since the Centers for Medicare and Medicaid services have classified organ transplantation as a tier 3b activity, liver transplant centers were urged to continue the process similar to before the pandemic[34]. However, patients had to wait longer to receive a liver transplant during the pandemic, especially for living donor liver transplants. There is data suggesting that patients who were wait-listed for other solid organ transplantation, such as kidney transplant patients, had worse outcomes with a higher risk of hospitalization and death compared to patients who got the transplant sooner[35]. Data on liver transplant patients is lacking in this regard. The COVID-19 effects on liver transplant-listed patients are highlighted in a special online report by the United Network for Organ Sharing[36] (Figure 2).

On the other hand, the recent changes in the organ allocation system helped offset some of the COVID-19 challenges. As a replacement for geographic areas, nautical miles are now utilized. Priority for receiving organs is triaged by medical urgency within a concentric circle radius of 150, 250, and then 500 nautical miles. While this new policy is imperfect as it better serves well-occupied areas in the center of the United States when compared to other coastal areas, it indeed improved access to solid organs across the country[37].

COVID-19-positive liver transplant donors and candidates

The American Society of Transplantation guidelines and Organ Procurement and Transplantation Network formulated guidelines on using COVID-19-positive donors. The consensus early in the pandemic was to avoid liver transplants in active donor-positive situations due to the risk of developing acute respiratory distress syndrome or COVID-19-related thrombosis. However, given the high prevalence of the virus in the community, some transplant centers started transplanting patients with donor positivity in emergent situations.

In one Italian study, 17 liver transplant patients were studied for more than 1 year from their transplant with a COVID-19-positive donation. One patient tested positive 21 d after transplantation. However, no patients experienced severe complications from COVID-19[38]. Of note, post-transplant immunosuppression was not adjusted, and there was no use of anti-COVID-19 therapy after the transplant. It is important to mention that this study was limited by the small sample size but provided hope for patients receiving a liver transplant from COVID-19-positive donors.

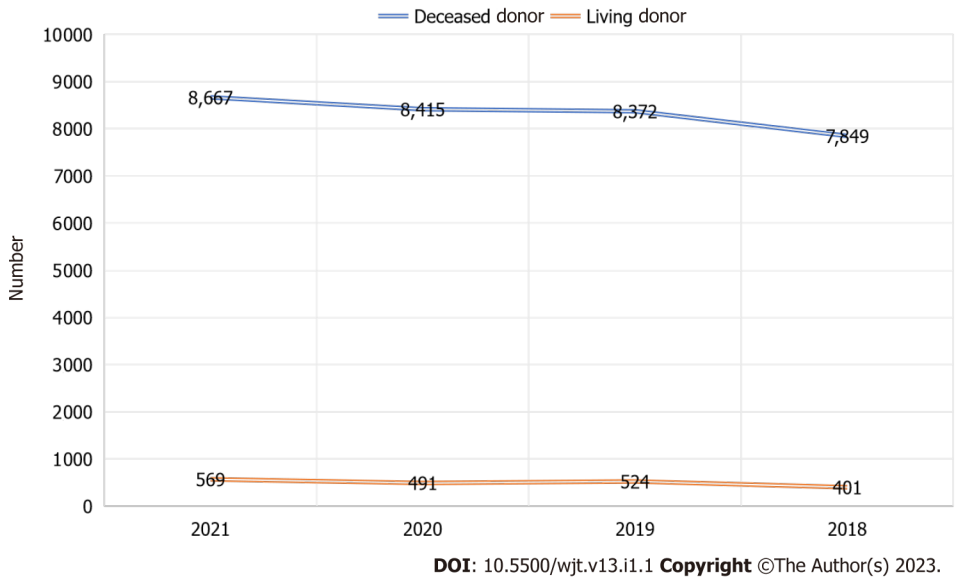
Concern regarding the blood-borne transmission of COVID-19 during liver transplantation discouraged living donor liver transplants during the initial period of the pandemic. However, studies showed that, unlike lung transplant recipients, the risk of transmitting donor-derived COVID-19 infection was not likely in liver transplant patients[39]. Blood-borne transmission does not pose much risk as the degree of COVID-19 viremia is low[40].

Current literature also suggests a higher risk of contracting COVID-19 infection among healthcare providers compared to the general population[41]. Organ donation from a COVID-19-positive patient also has the risk of exposing all transplant team health professionals who typically work closely with other high-risk cirrhotic patients. On the occasion of transmitted COVID-19 infection to medical staff, self-isolation will exert further strain on healthcare staffing and resources. It is therefore imperative to assess the risks and benefits of using organs from a potential COVID-19-infected donor.

Liver transplant centers across the nation have developed their protocols and policies to manage listed patients having COVID-19 infection[42]. This is to ensure maximum benefits for their patients and to cause no harm. In our center, for example, listed patients who are infected with COVID-19 are temporarily inactivated until they are symptom-free and 3 wk have elapsed since their diagnosis. Moreover, we often perform a contrast-enhanced computed tomography of the chest and pulmonary function tests if the patient had respiratory symptoms prior to reactivation. On the contrary, if the patient did not develop any respiratory symptoms, they are reactivated without any further testing.

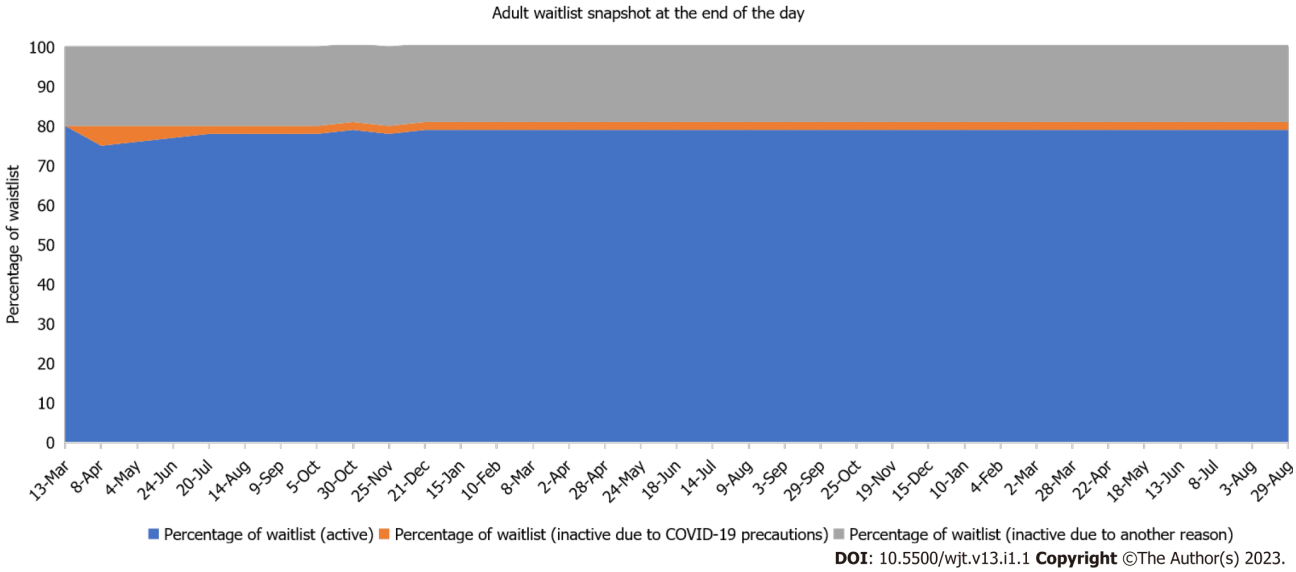
Ethical considerations

Fair allocation of liver grafts, possibly the scarcest organ of all, remains an ethical question in those with active COVID-19 infection[43]. The main principle of allocation is to achieve the greatest good for both the patient and the community. While benefiting those needing livers is likely to result in improved survival and health of patients and grafts, real risks of increased mortality or significant surgical



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Figure 1 The Organ Procurement and Transplantation Network report of liver transplants by donor type between 2018-2021.



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Figure 2 United Network for Organ Sharing special report of adult liver transplant waitlist showing coronavirus disease 2019 effects between March 2020 to August 2022. COVID-19: Coronavirus disease 2019.

complications exists in those with active COVID-19 infection. Considering the uncertainty regarding outcomes of liver transplant in candidates with active COVID-19 infection, these vital organs are better redirected to more suitable candidates with a higher chance of benefit pending infection resolution[44].

Additionally, it is important to note that exposure of health care providers to infected transplant patients continues to significantly burden hospital structures throughout the country. The ethical principles of justice and utility should dictate the just allocation of organs to those who would get the greatest benefit[45].

POST-TRANSPLANT IMPACT CONSIDERATIONS

Risk in liver transplant recipients

The post-transplant risk of COVID-19 is the risk of acquiring severe infection as a solid organ recipient on chronic immunosuppression with an inherent risk of prolonged viral shedding. The Spanish Society of Liver Transplantation found that liver transplant recipients may have double the risk of acquiring COVID-19 within an epidemic scenario (standardized incidence ratio: 191.2; 95%CI: 190.3-192.2) as

compared to an age and sex-matched cohort[46]. A 2022 prospective double-center study from southern Italy followed 30 liver transplant recipients who were infected with COVID-19 and found that liver transplant recipients were more often symptomatic but did not have an increased risk for hospitalization or mortality[47].

Clinical presentation and outcomes

The clinical presentation reported in observational studies included fever (61.4%), cough (58.6%), and dyspnea (36.2%)[48]. Webb *et al*[49] reported that gastrointestinal symptoms were common (27.9%). Interestingly, the liver transplant recipients had more gastrointestinal symptoms compared to the control group (30% *vs* 12%, $P < 0.0001$), whereas no significant difference was observed in respiratory symptoms. The same study compared outcomes of COVID-19 infection between those who underwent liver transplant (124 patients) and matched cohorts (474 patients). No difference in hospitalization (82% *vs* 76%, $P = 0.106$) or need for intensive care unit (31% *vs* 30%, $P = 0.837$) were observed. Overall, 28 (19%) patients in the liver transplant cohort died compared to 167 (27%) patients in the matched cohort ($P = 0.046$).

In a meta-analysis and systematic review by Kulkarni *et al*[4], which included 18 studies with a total of 1522 COVID-19-infected liver transplant recipients, there was no difference in mortality between liver transplant and non-liver transplant COVID-19 patients up to 1 year post-transplant. Approximately 23% of liver transplant patients had severe COVID-19 infection. Regarding immunosuppression, 71% and 49% of patients were on tacrolimus and mycophenolate mofetil, respectively. More than half of these patients required some adjustment of their immunosuppression medication. This analysis suggested that COVID-19-infected liver transplant recipients are not at an increased risk of poor outcomes.

Management

The severity of COVID-19 infection often dictates the management of immunosuppressive agents. For example, those with a mild disease not requiring oxygen therapy may be managed as an outpatient without adjustment in their immunosuppressive agents. In contrast, liver recipient patients with moderate-to-severe COVID-19 infection are often managed in the hospital. Guidance for managing these patients stems largely from expert opinions. It is generally advised to lower the cumulative degree of immunosuppression, particularly mycophenolate. While steroid dose generally requires no modification during an active infection, calcineurin inhibitor drug monitoring is recommended to avoid acute kidney injury.

Other agents used in treating COVID-19 infection include oral antivirals such as molnupiravir and Paxlovid. The former is likely safe and effective in liver transplant recipient patients and considered a drug of choice by many hepatologists[50]. Paxlovid strongly interacts with calcineurin and mammalian target of rapamycin inhibitors. Therefore, concomitant use is prohibited[51]. In a single-center, retrospective study that included liver and kidney transplant recipients, COVID-19 monoclonal antibody treatment (casirivimab-imdevimab or bamlanivimab) reduced hospitalization from 32% to 15% ($P = 0.045$) with no mortality (13% *vs* 0%, $P = 0.04$)[52].

The Food and Drug Administration issued an Emergency Use Authorization in January of 2022 for Evusheld (tixagevimab and cilgavimab), a long-acting monoclonal antibody for pre-exposure prophylaxis of COVID-19, in patients with moderate-to-severe immune suppression including those who received a solid organ transplant[53]. This is an appealing preventive option for high-risk liver transplant recipients.

It is important to note that the quality of the literature presented in this review was affected by the evolving understanding of the COVID-19 virus and the ensuing rapid changes in liver society guidelines in response. Moreover, most of the discussed studies were limited by small sample size and retrospective, single center designs affecting the generalizability of their outcomes. In addition, the changes in liver allocation policies that occurred midway through the pandemic may have confounded the overall number of liver transplants performed in the United States.

CONCLUSION

While COVID-19 infection appears to be poorly tolerated in patients with chronic liver disease, liver transplant recipients, despite immunosuppression, have a similar rate of complications and mortality when compared to the general population. It is imperative to recognize important drug-drug interactions in liver transplant patients, notably Paxlovid interaction with calcineurin inhibitors to avoid drug toxicity. We also advocate for wider utilization of monoclonal antibody pre-exposure prophylaxis of COVID-19 infection in liver transplant patients.

FOOTNOTES

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META-ANALYSIS

Outcomes of total pancreatectomy with islet autotransplantation: A systematic review and meta-analysis

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Abstract

BACKGROUND

Despite the increased use of total pancreatectomy with islet autotransplantation (TPIAT), systematic evidence of its outcomes remains limited.

AIM

To evaluate the outcomes of TPIAT.

METHODS

We searched PubMed, EMBASE, and Cochrane databases from inception through March 2019 for studies on TPIAT outcomes. Data were extracted and analyzed using comprehensive meta-analysis software. The random-effects model was used for all variables. Heterogeneity was assessed using the I^2 measure and Cochrane Q-statistic. Publication bias was assessed using Egger's test.

RESULTS

Twenty-one studies published between 1980 and 2017 examining 1011 patients

were included. Eighteen studies were of adults, while three studied pediatric populations. Narcotic independence was achieved in 53.5% [95% Confidence Interval (CI): 45-62, $P < 0.05$, $I^2 = 81\%$] of adults compared to 51.9% (95%CI: 17-85, $P < 0.05$, $I^2 = 84\%$) of children. Insulin-independence post-procedure was achieved in 31.8% (95%CI: 26-38, $P < 0.05$, $I^2 = 64\%$) of adults with considerable heterogeneity compared to 47.7% (95%CI: 20-77, $P < 0.05$, $I^2 = 82\%$) in children. Glycated hemoglobin (HbA_{1C}) 12 mo post-surgery was reported in four studies with a pooled value of 6.76% ($P = 0.27$). Neither stratification by age of the studied population nor meta-regression analysis considering both the study publication date and the islet-cell-equivalent/kg weight explained the marked heterogeneity between studies.

CONCLUSION

These results indicate acceptable success for TPIAT. Future studies should evaluate the discussed measures before and after surgery for comparison.

Key Words: Islet autotransplantation; Pancreatectomy; Pancreatitis; Narcotics

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Core Tip: Surgical intervention is required for the management of debilitating and refractory abdominal pain in chronic pancreatitis (CP) patients failing medical therapy. Since first introduced in 1978, total pancreatectomy with islet autotransplantation (TPIAT) has shown promising results in CP patients, but the literature remains limited. This systematic review and meta-analysis found that TPIAT provided acceptable levels of pain relief and insulin independence.

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INTRODUCTION

Chronic pancreatitis (CP) is characterized by progressive inflammation of the pancreas with eventual fibrosis, ductal alteration, and permanent structural damage. CP has a reported mortality of nearly 50% within the first 20-25 years of diagnosis[1,2]. It significantly impairs the quality of life (QoL) of the affected patients, often requiring frequent Emergency Department (ED) visits and hospitalizations due to pain, infections, malnutrition, and recurrent acute on chronic pancreatitis[3]. The clinical manifestations include varying degrees of abdominal pain, malabsorption from exocrine insufficiency, and the development of diabetes mellitus (DM). Although the compromised exocrine function and DM can be treated with oral pancreatic enzyme supplementation and insulin, the hallmark symptom of CP is pain, which often is intractable and debilitating[4].

The commonly used first-line therapies for CP primarily focus on mitigating the unrelenting and recurring abdominal pain. These include dietary modifications with a low-fat diet, pancreatic enzyme supplementation, strict smoking cessation, and alcohol abstinence[5]. Despite these initial measures, many patients often end up requiring frequent escalating doses of narcotics with consequent opioid dependence[6]. Patients who require chronic opioids are often candidates for invasive procedures in an attempt to eliminate or modify the underlying source of pain[7]. Frequently, endoscopic treatments such as sphincterotomy and/or stent placement are employed to treat fibrotic strictures of the pancreatic duct or stone extraction if present[8,9]. When the usual medical and endoscopic therapies fail to address the severe pain and subsequent life disruption, surgical treatments, including functional operative diversion (*i.e.*, pancreatojejunostomy) or operative gland extirpation (*i.e.*, pancreatectomy), are advocated depending on the pancreatic ductal and parenchymal anatomy.

A recent randomized control trial (RCT) demonstrated that surgical approaches are more effective at eliminating pain and have more extended durability, thus reducing the need for repeated interventions when compared to endoscopic therapies. The creation of a longitudinal pancreatojejunostomy in functional diversion alleviates some of the exocrine insufficiency in CP; however, the retained native gland often leads to the recurrence of chronic pain and subsequent treatment failure. This pitfall also applies to the other types of partial pancreatectomies, such as the isolated resection of the pancreatic head (with or without duodenal preservation) or resection of the body/tail of the pancreas.

Total pancreatectomy (TP), which involves the excision of the entire gland, is often successful in eradicating the underlying cause of pain in CP. TP has historically been avoided due to the heightened risk of exocrine dysfunction and the difficulty in managing the brittle endocrine dysfunction associated with this procedure[10]. Subsequently, TP with islet autotransplantation (TPIAT) was introduced for the management of CP[11]. This procedure involves complete resection of the pancreas with trans portal islet cell transplantation (IAT)[12]. This comprehensive procedure has been postulated to eliminate the visceral source of pain along with a reduced risk of post-surgical DM. The use of concomitant IAT has been demonstrated to reduce or eliminate the need for exogenous insulin administration after a TP in many modern studies[13-16]. TPIAT has been reported to be more cost-effective than the medical management of CP in a recent single-center cost analysis. While it was initially recommended for adult patients with long-standing pancreatitis, TPIAT is now also being utilized in pediatric patients with CP and even in adults with intractable acute recurrent pancreatitis[17,18]. Although the open approach remains the standard, this surgical procedure has evolved over time, with some centers offering minimally invasive laparoscopic operative options.

Despite the emerging popularity of TPIAT for CP, the available data on the appropriate indications, procedural technique, and short and long-term outcomes-such as narcotic dependence and development of DM-is variable. Thus, we conducted a systematic review and meta-analysis of the available clinical trials to determine the overall outcomes of CP patients treated with TPIAT.

MATERIALS AND METHODS

Search strategy and selection criteria

We performed a comprehensive literature search in PubMed, EMBASE, and Cochrane databases from inception through March 2019, to identify all studies that evaluated post-procedural insulin or narcotic independence rates after TPIAT. We used the following keywords in different combinations for our search: Pancreatectomy, pancreatic resection, islet, autotransplantation, chronic, pancreatitis, insulin independence, narcotic independence, pain, outcome, and diabetes. The search was limited to human studies with no restrictions placed on region, publication type, or language. References of all included studies were manually searched for additional eligible papers.

Data extraction and quality assessment

Two authors independently performed the literature review (SB and BE). The data from the included studies were entered into a standardized table for analysis. To be included, studies were required to meet the following criteria: (1) Implemented a well-defined RCT, case-control, cohort, or case-series design; and (2) either presented an odds ratio (OR) for our main outcomes with a 95% confidence interval (CI) or presented the data sufficient to calculate the OR with a 95%CI. Studies were excluded if they provided insufficient information to calculate the OR for narcotic independence, insulin-independence, or HbA_{1C} levels 12 mo post-surgery. Studies were excluded if they were letters to editors, case reports, or review articles.

The quality of included studies was assessed independently by two of the authors (ZI and BE) using the Newcastle-Ottawa scale for cohort studies (Table 1) and the Murad tool for case series (Table 2), respectively[19,20]. Case series were considered of good methodological quality if they reported adequately on the domains of selection, exposure, outcome, and follow-up. Two authors (ZI and BE) addressed the discrepancies by joint evaluation of the original article.

Statistical analysis

Statistical analysis was performed using the Comprehensive Meta-Analysis (CMA), Version 3 software (BioStat, Inc., Englewood, NJ, United States). Effect estimates from the individual studies were extracted and combined using the random-effect, generic inverse variance method of DerSimonian and Laird[21]. A random effect model was used as a high probability of between-study variance was suspected due to variation in the study population and methodology. A pooled OR was calculated. A Cochran's *Q*-test and an I^2 statistic were used to evaluate heterogeneity and quantify variation across the selected studies [22]. A funnel plot was then created to evaluate for publication and other reporting biases and then the plot was examined visually for asymmetry. Then, an Egger test for the asymmetry of a funnel plot was conducted. All authors had access to the study data and reviewed and approved the final manuscript.

RESULTS

Search results

Our initial comprehensive search yielded 280 citations. All citations underwent a title and abstract review, with the majority being excluded as duplicates, letters to editors, case reports, review articles, or unrelated to the study subject. Of our initial yield, 33 citations underwent a full-length article review. Of

Table 1 Risk of Bias assessment for cohort studies using the Newcastle Ottawa Scale

Ref.	Publish year	Study design	Q1[1]	Q2[2]	Q3[3]	Q4[4]	Q5[5]	Q6[6]	Q7[7]	Q8[8]	Total
Adult cohorts											
Argo *et al*[39]	2008	Cohort, R	*		*	*		*	*	*	******(6)
Najarian *et al*[30]	1980	Cohort, R	*	*	*	*			*	*	******(6)
White *et al*[31]	2001	Cohort, P	*	*	*	*	*	*	*	*	********(8)
Mokadem *et al*[32]	2016	Cohort, R	*	*	*	*		*	*		******(6)
Garcae *et al*[24]	2013	Cohort, P	*	*	*	*		*	*	*	*******(7)
Gruessner *et al*[33]	2014	Cohort, P	*		*	*		*	*	*	******(6)
Wilson *et al*[15]	2014	Cohort, R	*		*	*		*	*	*	******(6)
Sutherland *et al*[16]	2012	Cohort, R	*		*	*		*	*	*	******(6)
Colling *et al*[35]	2017	Cohort, R	*	*	*	*	**	*	*	*	*********(9)
Ahmad *et al*[29]	2005	Cohort, R	*		*	*		*	*	*	******(6)
Solomina *et al*[25]	2017	Cohort, R	*		*	*		*	*	*	******(6)
Wang *et al*[36]	2013	Cohort, R	*		*	*		*	*	*	*******(7)
Bellin *et al*[18]	2016	Cohort, P	*		*	*		*	*	*	******(6)
Rabkin *et al*[37]	1999	Cohort, R	*		*	*		*	*	*	******(6)
Valente *et al*[41]	1985	Cohort, R	*		*	*		*	*	*	******(6)
Wahoff *et al*[50]	1995	Cohort, R	*		*	*		*	*	*	******(6)
Garcea *et al*[51]	2009	Cohort, P	*	*	*	*		*	*	*	*******(7)
Pediatric cohorts											
Sutton *et al*[44]	2010	Cohort, R	*		*	*		*	*	*	******(6)
Chinnakotla *et al*[17]	2014	Cohort, R	*		*	*		*	*	*	******(6)
Bellin *et al*[18]	2016	Cohort, R	*	*	*	*		*	*	*	*******(7)
Bellin *et al*[52]	2010	Cohort, R	*		*	*		*	*		*****(5)

[1]Representativeness of the exposed cohort.
[2]Selection of the non-exposed cohort.
[3]Ascertainment of exposure.
[4]Demonstration that outcome of interest was not present at the beginning of the study.
[5]Cohort comparability based on design.
[6]Assessment of outcome.
[7]Was follow-up long enough for outcomes to occur.
[8]Follow-up adequacy in terms of completeness.
R: Retrospective; P: Prospective; Q: Question.

these, 12 were excluded as review articles or did not provide sufficient information to calculate post-procedural insulin or narcotic independence rates in the studied populations. A flow diagram illustrates the selection process, in Figure 1. Consequently, a total of 21 studies met our inclusion criteria and were included in the meta-analysis. Published between 1980 and 2017, these papers included 1011 patients. Eighteen papers reviewed adult populations, while three studied pediatric populations (SM2). The baseline characteristics of the included studies and involved cohorts are summarized in Tables 3 and 4.

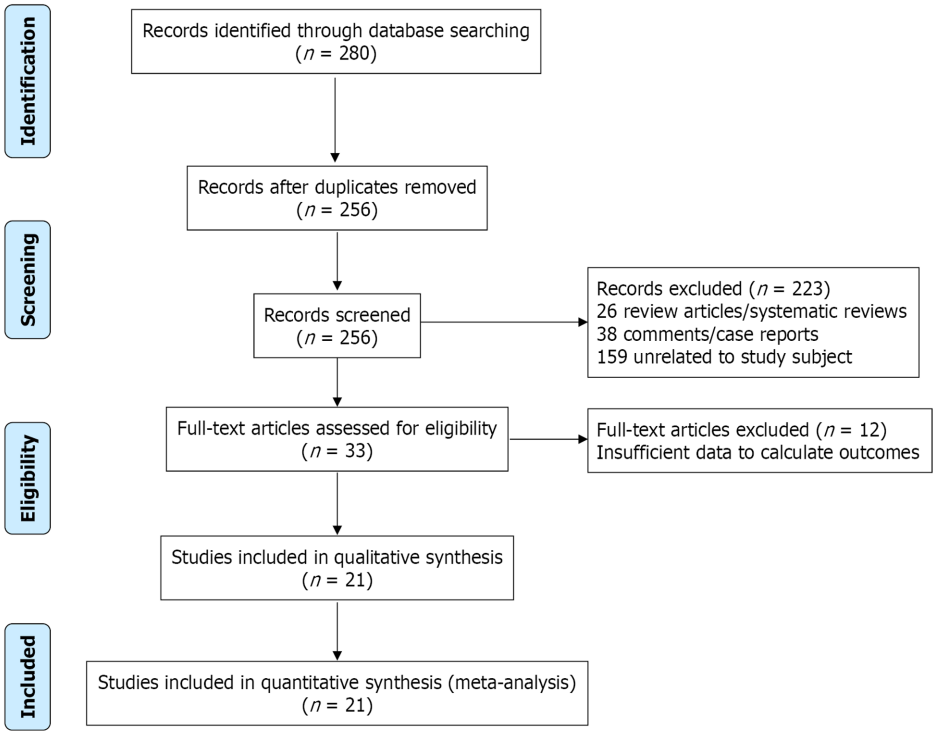
Post-procedural insulin and narcotic independence rates

Twenty-one studies examining 1011 patients were included in this study. Insulin-independence post-procedure was achieved in 31.8% (95%CI: 26-38, $P < 0.05$, $I^2 = 64\%$) of adults compared to 47.7% (95%CI: 20-77, $P < 0.05$, $I^2 = 82\%$) of children, Figure 2. Narcotic independence was achieved in 53.5% (95%CI: 45-62, $P < 0.05$, $I^2 = 81\%$) of adults compared to 51.9% (95%CI: 17-85, $P < 0.05$, $I^2 = 84\%$) of children (Figure 3). Glycated hemoglobin (HbA_{1C}) 12 mo post-surgery was reported in four studies evaluating adult populations with a pooled value of 6.76% ($P = 0.27$) (Figure 4).

Table 2 Methodological quality of case series using the Murad tool

Ref.	Year	Design	Q1[1]	Q2[2]	Q3[3]	Q4[4]	Q5[5]	Q6[6]	Q7[7]	Q8[8]	Overall quality
Fan *et al*[34]	2017	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good
Toledo-Pereyra *et al*[40]	1983	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good
Rossi *et al*[38]	1986	Case series	Y	Y	Y	N	NA	NA	Y	Y	Good

[1]Does the patient(s) represent the whole experience of the investigator?
[2]Was the exposure (diagnosis) adequately ascertained?
[3]Was the outcome adequately ascertained?
[4]Were other alternative causes that may explain the observation ruled out?
[5]Was there a challenge/re-challenge phenomenon?
[6]Was there a dose-response effect?
[7]Was follow-up long enough for outcomes to occur?
[8]Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners maker inferences related to their own practice?
Q: question, Y: Yes, N: No, NA: Not available.



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Figure 1 Flow diagram illustrating the selection process.

Evaluation for publication bias

Funnel plots were generated to evaluate post-procedural insulin and narcotic independence. The plots are symmetric and do not suggest the presence of publication bias. Egger's regression asymmetry testing was also done to demonstrate no evidence of publication bias ($P > 0.05$).

Sensitivity analysis

Neither stratification by age of the studied population nor meta-regression analysis considering both the study publication date and the islet-cell-equivalent/kg weight were able to explain the marked heterogeneity between studies.

Table 3 Data summary of the included studies

Ref.	Study design	Data collected	Year published	Participants enrolled, *n*	Patients underwent TPIAT, *n*	Age, mean (SD)/range, yr	Female sex, *n* (%)
Adults							
Argo *et al*[39]	Retrospective cohort	2005-2007	2008	26	26	43.8 (2.1)	12 (46)
Najarian *et al*[30]	Retrospective cohort	1977-1980	1980	18	10	24-57	4 (40)
White *et al*[31]	Prospective cohort study	1994-1999	2001	37	24	44 (NA)	14 (58)
Mokadem *et al*[32]	Retrospective cohort	1998-2008	2016	70	57	39.9 (14)	32 (56)
Garcae *et al*[24]	Prospective cohort study	1990-2012	2013	97	60	43 (NA) 21-65	Unknown
Gruessner *et al*[33]	Prospective cohort study	2009-2013	2014	61	61	42.2 (1.6)	39 (64)
Fan *et al*[34]	Case series	2013-2015	2017	32	20	39 (13) 21-58	12 (60)
Wilson *et al*[15]	Retrospective cohort	2000-2013	2014	166	166	37.3 (1.1) 14-62	75 (67)
Sutherland *et al*[16]	Retrospective cohort	1977-2011	2012	409	409[1]	35.3 (0.7) 5-69	301 (74)
Colling *et al*[35]	Retrospective cohort	2002- 2014	2017	59	59	Unknown	30 (51)
Toledo-Pereyra *et al*[40]	Case series	1979-1981	1983	6	6	35.5 (6.0) 28-41	1 (17)
Ahmad *et al*[29]	Retrospective cohort	2000-2004	2005	45	45	39 (NA) 16-62	30 (67)
Solomina *et al*[25]	Retrospective cohort	unknown	2017	20	20	41 (NA) 15-60	13 (65)
Wang *et al*[36]	Retrospective cohort	2009-2011	2013	76	76	42.1 (11.4)	Unknown
Bellin *et al*[18]	Retrospective cohort	2007-2013	2016	49	49	32.8 (7.8)	42 (86)
Rabkin *et al*[37]	Retrospective cohort	1994-1997	1999	5	5	42 (NA)	4 (80)
Valente *et al*[41]	Retrospective cohort	unknown	1985	25	22	Unknown	Unknown
Rossi *et al*[38]	Case series	1981-1985	1986	10	10	34 (NA) 23-65	6 (60)
Wahoff *et al*[50]	Retrospective cohort	1977-1995	1995	48	48	35 (NA) 12-60	36 (75)
Garcea *et al*[51]	Prospective cohort study	1996-2006	2009	85	50	43 (NA) 21-65	26 (52)
Pediatrics							
Sutton *et al*[44]	Retrospective cohort	2000-2009	2010	188	118	31.4 (NA) 15-59	8 (50)
Chinnakotla *et al*[17]	Retrospective cohort	1989-2012	2014	75	75	13.8 (0.4)	42 (56)
Bellin *et al*[18]	Retrospective cohort	2000-2014	2016	17	17	6.8 (NA)	9 (53)
Bellin *et al*[52]	Retrospective cohort	1989-2006	2010	18	18	12.8 (4.08) 5.8-18.9	10 (55.6)

[1]Includes 53 children.

NA: Not available.

DISCUSSION

When persistent abdominal pain in patients with CP becomes debilitating and the best medical management cannot stop the intractable pain, surgical intervention is indicated. Since first described by Sutherland *et al*[23] in 1978, TPIAT has shown promising results for patients with CP. Sutherland *et al* [23] hypothesized that by combining TP with IAT, TPIAT removes the primary pain source while maintaining endocrine function. TPIAT preserves insulin-secreting capacity and avoids post-surgical DM through the conservation of beta cell mass and C-peptide positivity[23]. In the years following the first-performed TPIATs, the procedure is being increasingly used for patients with CP and intractable pain[24]. QoL metrics show TPIAT as equal or superior to traditional TPs[24-27]. Morbidity and mortality metrics also support TPIAT as a safe and feasible procedure[28]. However, over this same time, minimal systematic evidence has been collected on metabolic function and pain control following TPIAT. In this paper, we present the most current meta-analysis to date and a systemic review of literature on insulin and narcotic independence after TPIAT.

Our study examined 1011 patients across 21 studies and found that 31.8% of adults were insulin independent after TPIAT[15,16,18,24,25,29-41]. Additionally, many patients who were not insulin-independent following TPIAT required only minimal amounts of exogenous insulin to achieve blood sugar control. HbA_{1c} is 6.76% 12 mo post-surgery in four studies of 240 adult patients[15,18,34,37]. In total, these studies describe populations that vary by age, sex, and disease etiology. Data were collected on patients from two countries and nearly four decades to present the largest known meta-analysis to date on this topic.

Our analysis also reviewed insulin and narcotic independence after TPIAT in pediatric patients. The first TPIAT performed on a pediatric patient occurred in 1996[42]. Since, several authors have reviewed QoL, morbidity, and mortality metrics in this particular patient population. We identified studies that have reviewed insulin dependence after TPIAT in pediatric populations, totaling 181 patients[16,17,43, 44]. Our research found 47.7% of children were insulin-independent post-TPIAT.

The majority of TPIATs were performed on patients with idiopathic CP (49.10%). Other common etiologies were genetically linked pancreatitis (21.10%), pancreatic divisum (11.60%), alcohol-induced CP (11.00%), and biliary tract disease (6.90%). Six percent of patients were insulin-dependent before TPIAT. Among pediatric patients, the majority of TPIATs were performed on patients with genetically linked CP (74.40%). Twenty-four percent of pediatric patients had idiopathic CP, and one pediatric patient had pancreatic divisum (0.44%).

Insulin independence and insulin requirements after TPIAT generally appear to correlate with higher islet yield, defined as the number of islet equivalents (IEs) transplanted per kilogram (kg) of recipient body weight[16,35,36,42,45,46]. However, overall TPIAT outcomes are likely multifactorial[31]. Several studies, including White *et al*[31], suggest additional factors may influence whether a patient achieves insulin independence after TPIAT: Prior pancreatic operations; poor islet yield due to pathogenic severity, calcification, and/or fibrosis; pathologic damage preventing islet purification of pancreatic tissue; toxic damage from reagents with high levels of endotoxins used in islet purification; the intraportal site being a suboptimal place for islet transplantation as it does not regulate insulin or glucose secretion; and chronic rejection of islet allotransplants[31,35].

Wang *et al*[36] showed that prior surgery is strongly correlated with pancreatic fibrosis and islet yield. Fewer islets are obtained from more fibrotic pancreases, because of both the disease process itself and increased difficulty in islet processing for transplant[36]. Prior history of pancreatic surgery may be used to predict postoperative islet function and determine the optimal timing for TPIAT surgery[36]. Sutton *et al*[44] make a similar observation regarding TPIAT in pediatric patients with genetically linked CP. Sixty-three percent of patients in Sutton *et al*[44] have the CFTR mutation. The authors advocate against trial resections or decompression surgeries before TP, as this treatment often compromises future endocrine function by limiting islet yield. None of the patients who had undergone previous pancreatic operations were insulin independent after TPIAT, and patients with previous pancreatic operations had approximately half the islet yield compared to patients without previous surgery.

The probability of TPIAT success is predicted by the morphologic features of the pancreas[42]. With plain films, ultrasonography, computed tomography (CT), or Endoscopic retrograde cholangiopancreatography (ERCP), Wahoff *et al*[42] suggest that the pre-operative prediction of the severity of the fibrosis helps estimate the number of islets available for autotransplantation. The severity of pain is notably an unreliable predictor of pancreas morphology and islets available for transplantation[42]. ERCP with transduodenal biopsy allows for assessing pancreas morphology directly and is likely the most useful means of evaluating islets pre-operatively[42].

Multiple papers suggest that women have better C-peptide positivity and glycemic control postoperatively because they often receive more IEs/kg. Univariate analyses by Ahmad *et al*[29] demonstrate that female gender, lower body weight, lower mean insulin requirements for the first 24 h postoperatively, and lower mean insulin requirements at the time of discharge are also associated with insulin

Table 4 Data summary of the included studies (continued)

Ref.	Pre-operative diabetes, *n* (%)	Alcohol induced pancreatitis, *n* (%)	Biliary tract disease, *n* (%)	Idiopathic pancreatitis, *n* (%)	Genetic mutation, *n* (%)	Pancreatic divism, *n* (%)	Autoimmune pancreatitis, *n* (%)	Post-operative narcotic independence, *n* (%)	Post-operative insulin independence, *n* (%)	Mean percent glycosylated hga1c, %, (SD), range
Adults										
Argo *et al*[39]	Unknown	9 (35)	1 (4)	8 (31)	0	6 (23)	0	3 (60)	0 (0)	
Najarian *et al*[30]	0 (0)	6 (60)	1 (10)	3 (30)	1 (10)[1]	0 (0)	0 (0)	7 (78)	4 (40) at range 1-38 mo	
White *et al*[31]	0 (0)	8 (18)	2 (5)	13 (30)[2]	0 (0)	1 (2)	0 (0)	16 (77)	8 (33) transient/3 (13) at writing	
Mokadem *et al*[32]	0 (0)	4 (7)	2 (4)	19 (63)	0 (0)	5 (17)	0 (0)	9 (16)	4 (15)	
Garcae *et al*[24]	Unknown	19 (32)	5 (8)	31 (52)	0 (0)	0 (0)	0 (0)	27 (45)	11 (19)	
Gruessner *et al*[33]	Unknown	7 (11)	0 (0)	45 (73)	10 (16)	0 (0)	0 (0)	43 (71)	12 (19) at range 1-24 mo	
Fan *et al*[34]	Unknown	2 (10)	0 (0)	6 (30)	9 (45)	3 (15)	0 (0)	12 (60) at 6 mo	5 (25) at 12.5 mo	7.4 (0.5)
Wilson *et al*[15]	14 (13)	3 (3)	0 (0)	84 (75)	15 (13)	10 (9)	0 (0)	91 (55) at 1 yr /121 (73) at 5 yr	62 (38) at 1 yr/45 (27) at 5 yr	6.9 (0.3) 5.85-8.3
Sutherland *et al*[16]	32 (8)	27 (7)	36 (9)	169 (41)	58 (14)	71 (17)	0 (0)	241 (59) at 2 yr[3]	123 (30) at 3 yr[4]	
Colling *et al*[35]	3 (5)	0 (0)	2 (3)	6 (10)	49 (83)	4 (7)	0 (0)	35 (66) at 1 yr	19 (32) at 1 yr	
Toledo-Pereyra *et al*[40]	0 (0)	3 (50)	0 (0)	3 (50)	0 (0)	0 (0)	0 (0)		2 (50) at 20 and 25 mo	
Ahmad *et al*[29]	1 (2)	2 (4)	0 (0)	39 (87)	1 (2)	8 (18)	0 (0)	23 (72) at 5 mo	18 (40) at mean 18 mo	
Solomina *et al*[25]	Unknown	0 (0)	0 (0)	3 (15)	13 (65)	3 (15)	1 (5)	18 (87) at 1 yr	8 (53) at 1 yr	
Wang *et al*[36]	11 (14)	Unknown	Unknown	Unknown	Unknown	Unknown	0 (0)	NA	31 (41) at 6 mo	
Bellin *et al*[18]	2 (4)	0 (0)	13 (27)	18 (37)	4 (8)	11 (22)	0 (0)	22 (46) at 1 yr	21 (45) at 1 yr	6.0 (0.9) at 1 yr
Rabkin *et al*[37]	0 (0)	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	3 (60)	4 (80)	3 (60) at median 23 mo	6.43 (1.50) 5.1-8.0
Valente *et al*[41]	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	14 (64) at mean 5 yr	

Rossi *et al*[38]	Unknown	2 (20)	0 (0)	8 (80)	0 (0)	1 (10)	0 (0)	9 (90)	7 (70) at 2 yr	
Wahoff *et al* [50]	2 (4)	9 (19)	8 (16)	27 (56)	0 (0)	2 (4)	0 (0)	31 (81)	13 (34)	
Garcea *et al*[51]	0 (0)	18 (36)	5 (10)	24 (48)	0 (0)	0 (0)	0 (0)	30 (59.8) at 1 yr		
Pediatrics										
Sutton *et al*[44]	0 (0)	0 (0)	0 (0)	0 (0)	16 (100)	0 (0)	0 (0)	10 (63) at mean 22 mo	4 (25) at mean 22 mo	
Chinnakotla *et al*[17]	Unknown	0 (0)	0 (0)	21 (28)	41 (55)	0 (0)	0 (0)	13(17)	31 (41)	
Bellin *et al*[18]	0 (0)	0 (0)	0 (0)	2 (12)	14 (82)	1 (6)	0 (0)	17 (100)	14 (82)	
Bellin *et al*[52]	0 (0)	0(0)	1 (6)	7 (39)	7 (39)	3 (17)	0 (0)	11 (61) at median 2.5 (0.2-17.1)	11 (61) at 1 year or longer	6.40 (2.34) 5.0-12.5 at 4.5 (5.2); n = 8

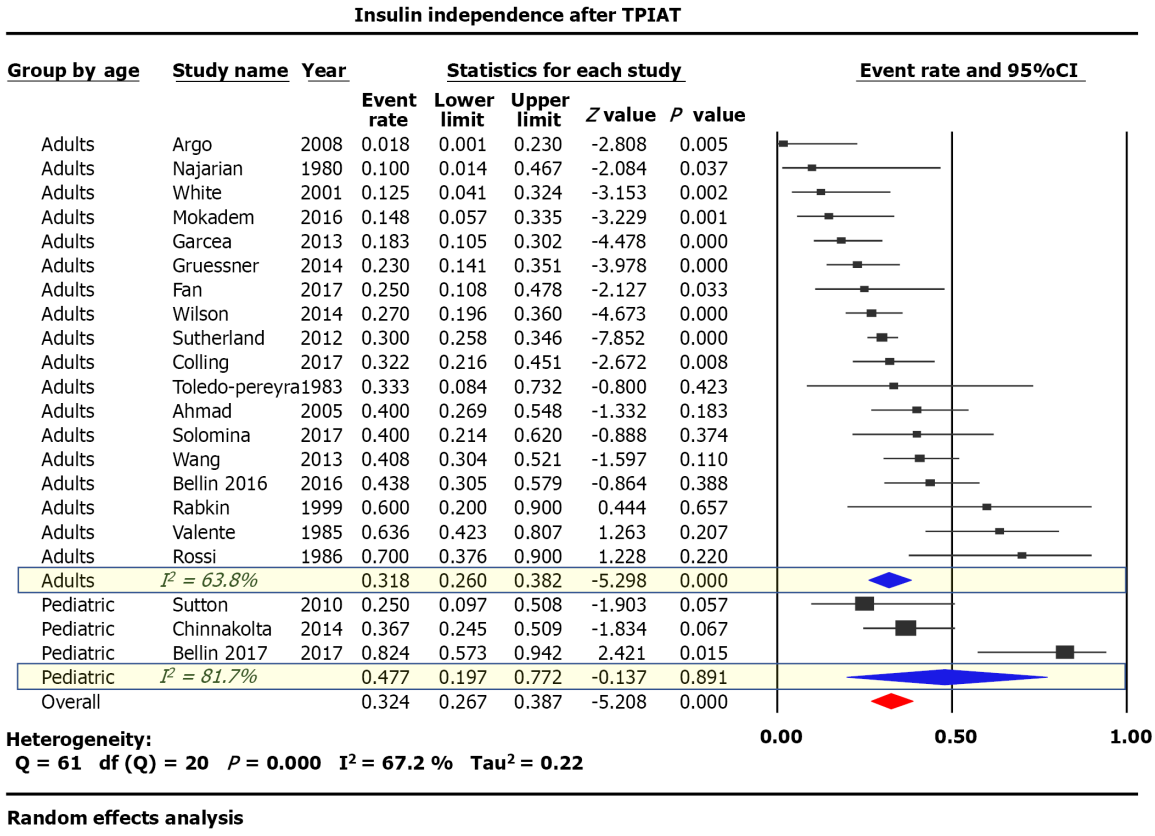
[1]Unconfirmed.
[2]Two identified as idiopathic/trauma.
[3]61% in pediatric patients.
[4]25% in adults, 55% in pediatric patients.
RC: Retrospective cohort; PCS: Prospective control study; CS: Case series; TPIAT: Total pancreatectomy with islet autotransplantation; NA: Not available.

independence. Seventeen of 18 insulin-free patients were female in Ahmad *et al*[29]. Multiple logistic regressions including gender, body mass index (BMI), and IEs/kg found gender to be an important independent variable. In their series, men were heavier than women on average by 10 kg, and they explained these findings as the result of weight differences among the sexes, saying patients with increased BMI are less likely to benefit from TPIAT and ought to be counseled on losing weight before surgery as their likelihood of glycemic control afterward is associated with their BMI[29].

Insulin independence and insulin requirements after TPIAT appear to correlate with higher islet yield in pediatric patients as well[17,44]. Multivariate analysis by Chinnakotla *et al*[17], demonstrated male gender, lower body surface area, and higher total IEs/kg were associated with insulin independence after TPIAT in pediatric populations. Total IEs greater than 2500 IE/kg was the most strongly associated with insulin independence.

In addition to gender, BMI, and previous pancreatic operations, the amount of time between CP diagnosis and TPIAT procedure has been demonstrated to have a direct impact on islet yield[33]. Gruessner *et al*[33] discovered that outcomes improved when patients were referred at earlier disease stages, before surgical procedures, and after inadequate endoscopies. Gruessner *et al*[33] was the first paper to document fully robotically assisted TPIAT. They found that approximately 80% of their patients had undergone previous surgical procedures and that 91% had abnormal results on preoperative continuous glucose monitoring tests[33].

The auto-transplanted islet function appears to be durable[15,47]. Wilson *et al*[15] conducted one of the largest series reviewing long-term outcomes after TPIAT. The study found that insulin independence rates decline over time but that most patients maintain stable glycemic control past 13



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Figure 2 Summary of event rates assessing insulin independence after total pancreatectomy with islet autotransplantation.

years post-operation and have minimal long-term complications associated with DM. Wilson *et al*[15] hypothesize that the toxic environment created by the liver is what ultimately contributes to declines in islet function over time.

While preservation of beta cell function is an important consideration, the success of TPIAT is ultimately determined by its ability to relieve pain and restore QoL in patients with CP[16]. Constant pain is the strongest predictor of poor QoL in patients with CP[48]. Relieving pain and reducing narcotic use is the primary objective of TPIAT[49]. In our meta-analysis, narcotic independence was achieved in 53.5% of adults post-TPIAT and 51.9% of children post-TPIAT[15-17,25,29,30,32-35,37,39,43,44,50-52].

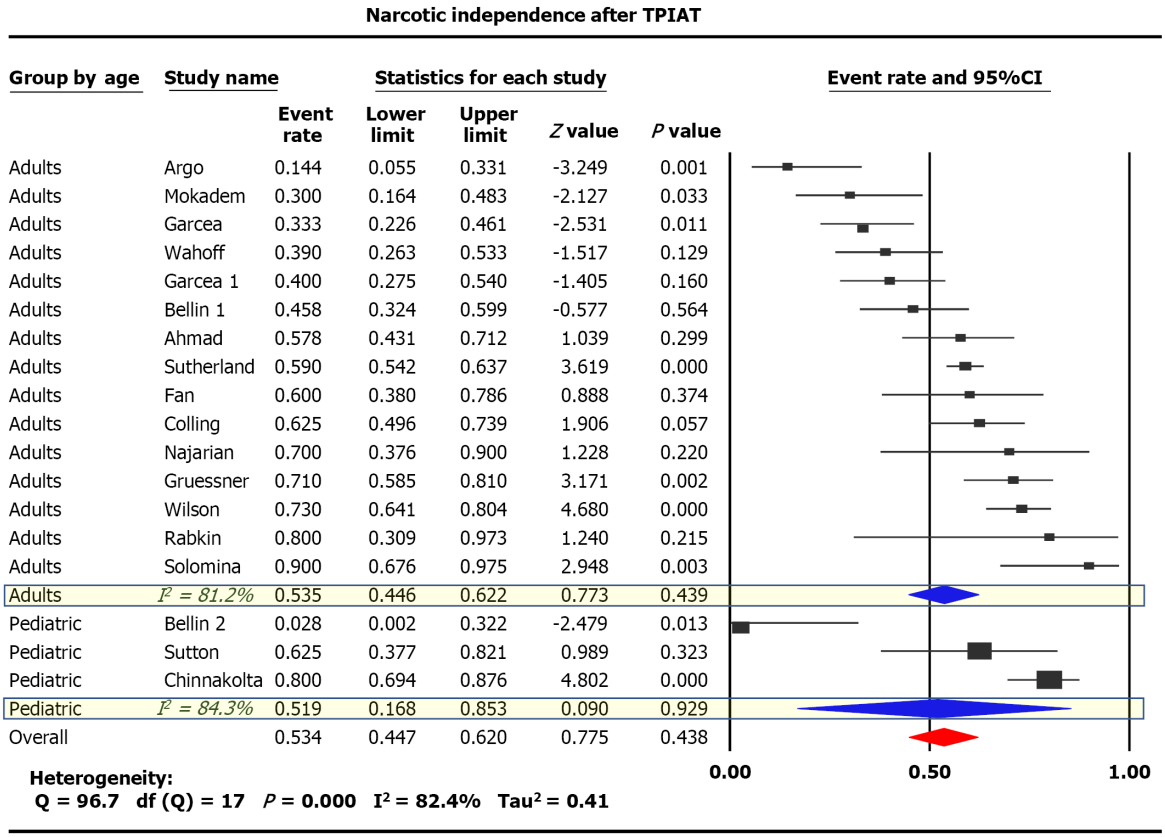
Some authors suggest that CP patients often have multiple comorbidities that cause pain after TP[53]. Patients with these additional comorbidities often require opioid analgesia beyond patients undergoing TP without comorbidities[53]. Additionally, long-term use of opioids can lead to dependence and addiction, causing long-term analgesic requirements[33,53].

Surgical intervention earlier in the course of the disease is associated with improved pain control and less narcotic use[26,54,55]. Interestingly, Bellin *et al*[18] demonstrated that TPIAT benefits even those without evident CP by improving QoL and reducing narcotic use. Patients with recurrent acute pancreatitis and limited surgical treatment options after medical and endoscopic therapy failed to remit their pain had outcomes similar to those patients with CP[18].

Several studies, including Colling *et al*[35], demonstrated that TPIAT can be an effective and safe treatment option for patients with cystic fibrosis (CF) and debilitating CP. Of note, these patients are likely at increased risk for pulmonary and luminal GI tract complications. Colling *et al*[35] had a cohort of 20 patients with CF and 19 CFTR carriers with TPIAT outcomes similar to other patient populations. Sutton *et al*[44] also demonstrated TPIAT was a successful treatment option in patients with genetically linked pancreatitis, finding narcotic independence rates of 63% and drastic decreases in narcotic requirements.

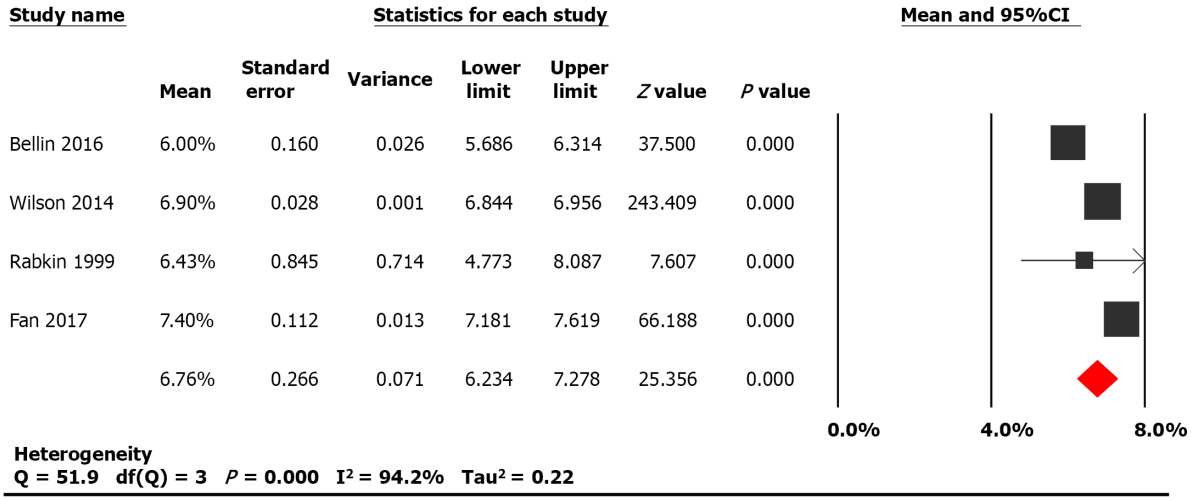
Fan *et al*[34] demonstrated that laparoscopic TPIAT (L-TPIAT) can be beneficial to CP patients as it reduced total operative and islet isolation time, shortened length of stay, and minimized the surgical pain spike compared to open and robot-assisted TPIATs. Fan *et al*[34] suggest reducing these metrics by performing L-TPIATs allows for opioid independence to be achieved more quickly. To Fan *et al*[34]'s point, Wilson *et al*[15] argue that minimizing warm ischemia time to the islets is one of the most important considerations during the operation.

While our meta-analysis spanned 37 years, data on TPIAT outcomes remains sparse. Various researchers have used a variety of evaluative tools to evaluate pain after TPIAT, including visual analog



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Figure 3 Summary of event rates assessing narcotic independence after total pancreatectomy with islet autotransplantation.



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Figure 4 Pooled HgA_{1c} means after total pancreatectomy with islet autotransplantation.

pain scores and inference scores. Treatment centers have followed patients for various lengths of time post-operatively, tracking their insulin independence at a variety of different post-operative times. Our meta-analysis draws on a large cohort of patients with CP undergoing TPIAT. The current study incorporates multiple treatment centers in two countries and a diversity of disease etiology, duration, and severity. We chose to evaluate the most objective data regarding post-operative pain and endocrine function: insulin and narcotic independence. As such, our meta-analysis uses the strengths of the available literature to maximize the reliability of our results.

CONCLUSION

TPIAT produces acceptable levels of pain relief in patients with CP. Over half of patients were narcotic-independent post-operatively. Regaining endocrine function after TPIAT appears to be multifactorial as a majority of patients continue to remain insulin-dependent following surgery, albeit there is a substantial improvement in glycemic control as reflected by lower HBA1C levels in the postoperative period. Future studies should evaluate the discussed measures before and after surgery for comparison. Clear definitions of patient populations, surgical procedures as well as post-surgical care are needed to limit heterogeneity in outcomes. Long-term prospective studies will be needed to further examine the longevity of insulin and opioid independence.

ARTICLE HIGHLIGHTS

Research background

Debilitating abdominal pain and diabetes mellitus are hallmark clinical manifestations of chronic pancreatitis (CP). Current management strategies revolve around pain mitigation and treatment of endocrine failure. One available treatment option is total pancreatectomy with islet cell auto transplantation (TP-IAT). Although several studies have suggested a promising role of TP-IAT in CP patients; minimal systematic evidence has been collected on the effect of this procedure on endocrine failure and pain relief in patients with CP.

Research motivation

Emerging data from multiple studies highlight that TP-IAT results in considerable pain relief and insulin independence; however, systemic evidence from high-quality studies is limited.

Research objectives

We performed a systemic review and meta-analysis to evaluate clinical outcomes such as pain control and glucose intolerance following TP-IAT.

Research methods

A comprehensive literature search spanning Pubmed, EMBASE, and Cochrane databases was performed from inception to March 2019. Studies conducted on outcomes of TP-IAT in patients with CP were identified. Comprehensive meta-analysis software was used to extract and analyze data. The random-effects model was used for all variables. Heterogeneity was assessed using the I^2 measure and Cochrane Q-statistic. Publication bias was assessed using Egger's test.

Research results

Our meta-analysis evaluated a total of 1100 patients across 21 studies. We found that TI-IAT results in narcotic independence in over 50% of adult and pediatric patients with CP. IAT results in meaningful islet cell function with insulin independence noted in almost one-third of adults and nearly half of pediatric patients following surgery.

Research conclusions

TP-IAT results in acceptable narcotic independence and preservation of beta cell function.

Research perspectives

Long-term prospective studies with clear definitions of patient populations, surgical procedures, and post-surgical care are needed to definitively evaluate insulin and narcotic independence before and after surgery.

FOOTNOTES

Author contributions: Khazaaleh S and Babar S contributed to study design, data interpretation, manuscript writing, and administrative support; Alomari M contributed to literature review and data collection; Imam Z and Chadalavada AJ contributed to data assembly, and data analysis including statistical analysis and creating tables and graphs; Kurdi BE contributed to supervisory role, data interpretation and primary investigator; all authors contributed to the paper writing, and manuscript revision and approved the submitted version of this manuscript.

Conflict-of-interest statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The Transplant Team of the University of Thessaloniki, Greece.

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EDITORIAL

Translational research and innovation in modern transplant practice: Paradigms from Greece and around the world

Georgios Tsoulfas, Ioannis Boletis, Vassilios Papalois

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Abstract

The continuous clinical and technological advances, together with the social, health and economic challenges that the global population faces, have created an environment where the evolution of the field of transplantation is essentially necessary. The goal of this special issue is to provide a picture of the current status of transplantation in Greece as well as in many other countries in Europe and around the world. Authors from Greece and several other countries provide us with valuable insight into their respective areas of transplant expertise, with a main focus on the field of translational research and innovation. The papers that are part of this Special Issue "Translational Research and Innovation and the current status of Transplantation in Greece" have presented innovative and meaningful approaches in modern transplant research and practice. They provide us with a clear overview of the current landscape in transplantation, including liver transplantation in the context of a major pandemic, the evolution of living donor kidney transplantation or the evolution of the effect of hepatitis C virus infection in transplantation, while at the same time explore more recent challenges, such as the issue of frailty in the transplant candidate and the changes brought by newer treatments, such as immunotherapy, in transplant oncology. Additionally, they offer us a glimpse of the effect that technological innovations, such as virtual reality, can have on transplantation, both in terms of clinical and educational aspects. Just as critical is the fact that this Special Issue emphasizes the multidisciplinary, collaborative efforts currently taking place that link transplant research and innovation with other cutting-edge disciplines such as bioengineering, advanced information technology and artificial intelligence. In this Special Issue, in addition to the clinical and research evolution of the field of

transplantation, we are witnessing the importance of interdisciplinary collaboration in medicine.

Key Words: Translational research; Non-alcoholic fatty liver disease; Immunotherapy; Pandemic; Liver transplantation; Bioengineering; Artificial intelligence; Immunosuppression; Transplant oncology; Living donor kidney transplantation

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Core Tip: The goal of this special issue is to provide a picture of the current status of transplantation in Greece as well as in many other countries in Europe and around the world. The issue will focus on presenting innovative and meaningful approaches in modern transplant research and practice as well as to emphasize the multidisciplinary, collaborative efforts currently taking place that link transplant research and innovation with other cutting-edge disciplines such as bioengineering, advanced information technology and artificial intelligence.

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INTRODUCTION

Transplantation represents to all of us the "Field of Dreams". The reason is that this multidisciplinary vocation of modern medical practice combines the opportunity to significantly improve and, in most cases, save human lives, with adrenaline-filled surgical procedures, together with a constant need for innovation and improvement in a variety of areas including nephrology, hepatology, endocrinology, immunology, pharmacology, anesthesia, radiology and surgery. Most importantly, it is an area where most of the biggest questions have yet to be answered, such as those of achieving tolerance and avoiding immunosuppression. All of the above, make the field of transplantation an actively evolving science on many different levels, where every step forward counts, since human lives are at stake.

The goal of this special issue is to provide a picture of the current status of transplantation in Greece as well as in many other countries in Europe and around the world. The issue will focus on presenting innovative and meaningful approaches in modern transplant research and practice as well as to emphasize the multidisciplinary, collaborative efforts currently taking place that link transplant research and innovation with other cutting-edge disciplines such as bioengineering, advanced information technology and artificial intelligence. Furthermore, we wish to demonstrate that a negative national and international financial climate and the massive effect of the coronavirus disease 2019 pandemic, do not stop the advancement of the field of transplantation and, on certain occasions, they can be the drive for it.

The authors participating in this special issue provide us with a clear overview of the current landscape in transplantation, including liver transplantation in the context of a major pandemic, the evolution of living donor kidney transplantation or the evolution of the effect of hepatitis C virus infection in transplantation, while at the same time explore more recent challenges, such as the issue of frailty in the transplant candidate and the changes brought by newer treatments, such as immunotherapy, in transplant oncology[1]. Additionally, they offer us a glimpse of the effect that technological innovations, such as virtual reality, can have on transplantation, both in terms of clinical and educational aspects.

Most importantly, the papers in this special issue stress the need for interdisciplinary and international collaboration in the field of transplantation and the fact that it remains our "Field of Dreams". Yesterday's dream is today's aspirational research and tomorrow's established practice.

CONCLUSION

The papers in this Special Issue[2-12] are evidence that global economic and health challenges cannot and should not stop the ongoing evolution of a scientific field as active and as necessary as transplantation.

FOOTNOTES

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OPINION REVIEW

Changing landscape in living kidney donation in Greece

Nikolaos Karydis, Ioannis Maroulis

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Abstract

Patients with end-stage renal disease in Greece are facing long waiting times to receive a kidney transplant from a deceased donor. Living kidney donation offers a valuable alternative that provides optimal outcomes and significantly expands the donor pool but still remains relatively underutilised. Developments around the world in the field of kidney transplantation mandate a change in current practice to include additional options for living donation through paired exchange, antibody-incompatible transplantation and other strategies, following careful consideration of the cultural and ethical factors involved in these complex clinical decisions. An increase in living donation rates may be achieved in several ways, including targeted campaigning to overcome potential barriers. Educating clinicians on transplantation will prove as equally important as informing patients and prospective donors but requires training and resources. Adoption of established practices and implementation of new strategies must be tailored to the needs of the Greek donor and recipient population. Local beliefs about donation, perception of associated risk and other social characteristics must be considered in the design of future strategies. Facilitating living donation in a safe environment with appropriate donor and recipient education will form the solid foundation of a new era of kidney transplantation in Greece.

Key Words: Living kidney donation; Paired exchange; Incompatible transplantation; Unrelated donors; Greece

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Core Tip: Living kidney donation is the driving force behind every successful kidney transplant programme worldwide. In Greece, in particular, it accounts for nearly half of performed transplants annually. Its role is of paramount importance since deceased donor kidney transplant waiting times are currently unacceptably long. Paired exchange and other options will form the basis to expand the donor pool and facilitate future developments in the field.

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INTRODUCTION

Living kidney donation remains the optimal source of kidney transplants worldwide, despite advances in deceased donor organ utilisation and preservation. Living donor kidneys offer excellent long-term outcomes in terms of patient and graft survival[1,2]. Apart from this, living donation has gradually served as the basis for expansion and development of novel patient pathways in kidney transplantation. Antibody-incompatible transplant programmes have been largely successful, enabling discontinuation of dialysis and prolongation of survival in highly sensitised recipients[3,4]. Kidney exchange programmes have been met with great enthusiasm among physicians, surgeons, transplant coordinators and patients alike, dramatically reducing the need for more immunologically complex treatments[5]. Other areas of recent developments include the cross-linking between deceased donor and living donor pathways, providing new insights in the utilisation and optimal matching of available organs to the most suitable recipients[6].

National living donor programmes share many common features but also differ in many ways, even among countries with obvious geographical and cultural similarities. The plausible explanation lies in the complexities of healthcare systems to identify and utilise the maximum number of potential donors, both deceased and living. Furthermore, disparities in training and education may inevitably magnify the differences in donation and transplant rates. Greece is currently entering a new era in kidney transplantation, in particular living donor transplantation, with major new developments that could substantially increase the transplant rates.

LIVING DONATION IS THE DRIVING FORCE IN KIDNEY TRANSPLANTATION

Although donation and transplant rates are low in Greece at approximately five deceased donors per million population[7], the actual living donor kidney transplant rate, ranging between 38%-50% of all transplants the last 5 years, is easily comparable to countries with well-established deceased donor and living donor programmes[8]. This simple observation justifies the argument that an appropriate expansion of the living donor pool could, at least to some extent, "generate" many more high-quality kidney grafts. Additionally, it provides important clues regarding the intention of the Greek population to donate organs albeit usually within the limits of close or extended family.

Deceased donor kidney transplantation currently suffers from unacceptably long waiting times due to multifactorial long-standing issues that effectively limit the number of brain-dead donors who proceed to donation. The obvious advantage of living donation over deceased kidney donation is the relative independence from complicated donor pathways, lack of suitable infrastructure, staffing issues, limitations of laboratory workflows and cultural trends towards donation in general. The latter has been studied in a relatively small sample of an urban population but has provided very useful insight into the attitudes towards organ donation in Greece[9]. Although the vast majority (90.0%-98.0%) of participants demonstrated a high level of understanding around brain death, organ donation and transplantation, only 3.8% were formally registered with the national organ donor register. Half of the participants would be willing to donate the organs of a relative, however more than half would feel guilty doing so. Another emerging concern in this survey was the fear about the process of organ removal, which probably reflects a lack of trust in the processes and regulatory framework related to organ donation in general. Interestingly, religious beliefs did not emerge as significant potential obstacles to donation, and willingness to donate was actually higher among Greek Orthodox participants (63.7%) than the study sample average (48.3%).

Other significant advantages of living over deceased donation include shorter workup times for living donor pairs, presumably due to the willingness of donors and recipients alike to proceed with a transplant, improved immunological matching between family members, ability to proceed with incompatible transplants and finally the relative ease to manage logistical issues, from access to the

operating theatre to specialist perioperative and postoperative care. Deceased donation rates are expected to grow over the next few years in Greece, owing to changes in legislation and the investment of financial and staffing resources to national and local transplant coordination. Until then, living kidney donors will likely drive the country into the new era of transplantation by offering invaluable organs to their respective recipients and by acting as ambassadors of donation and transplantation in the general population. The latter may be more impactful on the public's attitude towards issues surrounding transplantation in general but also requires a coordinated approach led by donors and clinicians in equal parts. The United Network for Organ Sharing has developed a volunteer programme with the primary goal of raising awareness and educating prospective donors through real-life experiences of other donors[10]. Becoming an ambassador of living donation involves an initial orientation and education phase, after which living donors share their personal experience through local events, the United Network for Organ Sharing website and social media. Similar programmes are being developed around the world by national transplant organisations, such as the United Kingdom's National Health Service Blood and Transplant, and are expected to improve communication between transplant professionals and the public.

Highlighting the successes of living donation as well as the safety of modern techniques[11], *i.e.*, minimally invasive donor nephrectomy, quick recovery time, reduced postoperative pain, short length of hospital stay, minimal postoperative complications and excellent long-term outcomes in terms of general health and donor survival, is central to any communication relating to transplantation to strengthen the public's trust. Transparency and publication of interval donation and transplant-related statistics on a scheduled basis in an easily accessible public domain will eliminate suspicion and fear around unacceptable practices that have been reported elsewhere in the world from time to time.

OPTIONS FOR LIVING KIDNEY DONATION IN GREECE

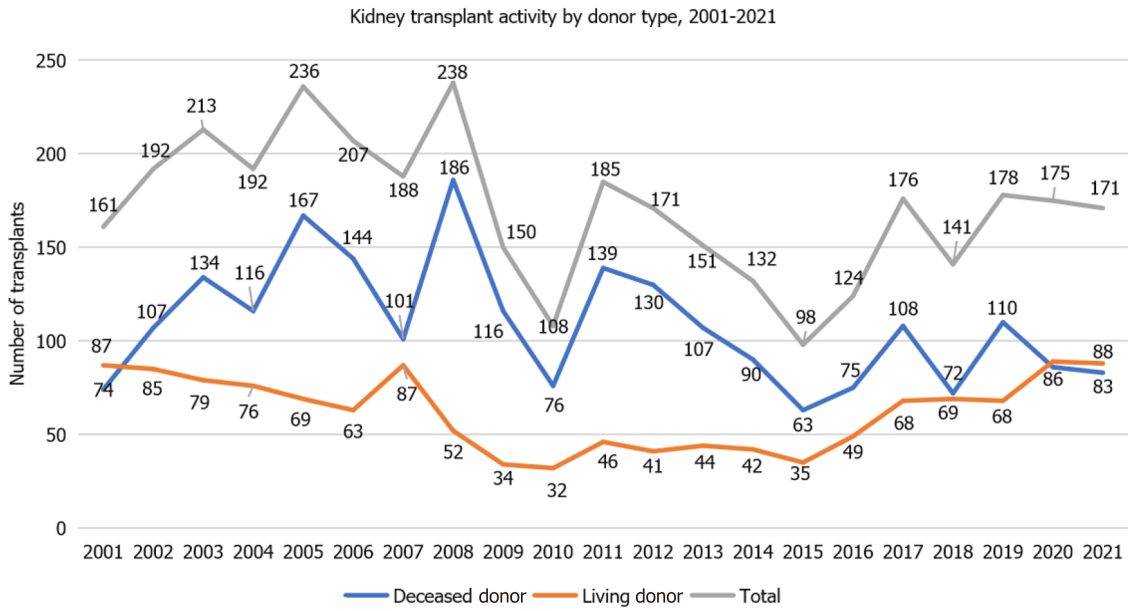
In the recent past, the norm in living kidney donation would be a donor who would come forward and donate to a specified, compatible recipient, usually a member of their close or extended family. Although life-changing behaviours as simple as the above literally transformed modern transplantation and taught clinicians many valuable lessons around modern immunology, we have since made huge progress in terms of living donor organ utilisation. A realistic approach to kidney transplantation dictates that every living donor should be encouraged and facilitated to donate within a safe and coercion-free environment after a fully informed consent process.

The boundaries of living donation have been pushed significantly to make every living donor kidney count for patients in need of an organ, either directly or indirectly[12]. In this context, every suitable living donor should proceed either with a direct or indirect transplant to their intended recipient, which has allowed the development of complex paired exchange networks, mostly but not exclusively geographically confined within their countries. In some instances, these complex networks "interact" with deceased donor pathways to create novel opportunities for highly sensitised or difficult-to-transplant patients who would otherwise not have any chance to receive a kidney transplant. The notion of a "donor-recipient" pair is becoming less clear in this reality, and programmes around the world are being challenged to keep up with developments.

The landscape of living kidney donation has significantly changed in Greece over the last few years, though there is still a long way to cover in certain areas. However, most efforts have concentrated on encouraging living donation, thus the conditions to allow living kidney transplantation to flourish are already in place. Official data from the National Transplant Organisation indicate a rising number of living donor kidney transplants (Figure 1), despite adverse circumstances such as the coronavirus disease 2019 pandemic.

A direct living donor transplant is in many ways the "gold" standard of care. It allows for an immunologically straightforward kidney transplant, in the context of blood group (ABO) and human leukocyte antigen (HLA) compatibility between donor and recipient. Until recently, such transplants were only allowed within extended families, excluding several other types of living donors. The last decade has seen significant legislative changes that have permitted directed donation from unrelated donors, following a formal approval process, which has also been further simplified in the last few years. We consider this change a fundamentally positive step into the new era of transplantation, although official data on its practical applicability so far are lacking. To our knowledge, unrelated undirected, *i.e.*, altruistic, kidney donation, has not yet taken place in Greece due to legislative restrictions. From a practical perspective, the extent to which such donation would make an actual difference in transplant rates is probably very limited, based on cultural perceptions. Indeed, a quite thorough study on the patterns of blood donation in Greece revealed that the concept of "need" is a stronger motivator than the sense of altruistic "offer" for blood donors[13].

The emergence of unrelated donors has inevitably introduced new challenges for the transplant community. Quite a few donors will have an incompatible blood group with the recipient and/or a positive immunological crossmatch. There is sufficient evidence and experience worldwide to suggest that ABO-incompatible kidney transplants have comparable graft and patient outcomes and should be



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Figure 1 Annual deceased and living donor kidney transplant activity in Greece, 2001-2021.

routinely considered as a valid option in suitable pairs[14]. Blood group-incompatible kidney transplants are performed in only one of the transplant units in Greece, although we believe that recipients with relatively low anti-A or anti-B titres could be managed successfully in smaller centres as well. Anecdotal evidence suggests that such donors may have been discouraged from donation due to lack of expertise or suitable infrastructure, and alternative donors may have been sought instead. However, the availability of multiple living donor options is realistically a luxury for the majority of patients, partly due to widely prevalent cultural views that limit living donation from certain age groups. The bottom line is that occasionally living donors may exist but are not able to proceed.

The issue of antibody-incompatible kidney transplantation has a few possible solutions, all of which are available in Greece, albeit still underdeveloped to a variable extent. These solutions include paired exchange or kidney sharing schemes (programmes of kidney exchange between incompatible donor-recipient pairs) and have transformed living donor kidney transplantation over the last two decades[15, 16]. Despite several points of criticism and concerns from both patients and clinicians, the huge success of these programmes has established their role in daily practice. Even well-established and active antibody-incompatible programmes have now shrunk to serve only a small number of patients that cannot be transplanted through paired exchange. In the United Kingdom, for example, the combined number of ABO- and HLA-incompatible kidney transplants has declined gradually from 171 in 2012 to 25 in 2021, as shown graphically in the most recent annual activity report[17].

Engagement from all participating units in a country is obviously of paramount importance to allow the creation of a candidate pool large enough to facilitate ABO and HLA matching. Long chains of such pairs are possible, although logistical issues should be considered to minimise ischaemia times and optimise outcomes. The combination of kidney exchange with altruistic donation has enabled kidney transplantation for highly sensitised or difficult-to-match patients at the end of commonly long chains. In-centre kidney exchange has taken place in Greece in the recent past, however this is potentially more complicated from a logistical perspective, *e.g.*, access to operating theatres, where nephrectomies and transplants all take place on the same day. Between-centres kidney exchange poses its own challenges, but certainly still remains an underutilised option. With appropriate communication and standardisation of donor and recipient procedures, as well as HLA typing and matching, transplant units in Greece could easily transition into a new era of collaboration.

Building a large enough pool possibly requires a radically new approach to living donation altogether. Donors that may have previously been discouraged or misinformed should be given a second chance to consider donation and participate in paired exchange. Our experience shows that donors and recipients are open to the idea of paired exchange and are willing to consider all possibilities in order to avoid long waiting times on the deceased donor waiting list.

Incompatible donors are legally allowed to donate to the deceased donor waiting list, in exchange for their recipient to be prioritised on the waiting list to receive the first available deceased donor kidney. Although there are reasonable concerns around matching the quality of a living donor kidney to a kidney from a deceased donor, in terms of age, medical background, cause of death and terminal kidney function, it remains a valid option for some recipients, compared to a long average waiting time of 8

years. Recipients that fall into this prioritisation list are also allowed to turn down an offer that does not "match" their living donor. Although this is a relatively new option, it is becoming increasingly popular among incompatible pairs, and 17 pairs have been successfully transplanted so far through this scheme.

Antibody-incompatible transplantation remains a popular option, particularly for ABO-incompatible pairs. The literature clearly supports ABO-i kidney transplantation over remaining on haemodialysis [18], thus we believe every transplant unit in Greece could develop an ABO-i programme to enable transplantation for the relatively small number of patients that will proceed with this form of transplant, at least until a robust national paired exchange programme becomes established. Clearly, some centres will accumulate greater expertise in this field, but smaller units could enable transplants with lower anti-A or anti-B titres at the early stages of their development[19]. HLA-incompatible transplantation, although proven superior to haemodialysis[4], remains a challenging procedure with significant risks for the recipients. Early antibody-mediated rejection possibly contributes to inferior graft survival up to 5 years post-transplant[20]. Enhanced immunosuppression may lead to serious bacterial and viral complications that may threaten both graft and patient survival[14]. Indeed, a recent meta-analysis showed increased mortality risk in ABO-i recipients up to 8 years post-transplant[20]. At the same time, the actual number of potential ABO-incompatible transplants in Greece may not adequately justify the risks at this point in time.

FUTURE PROSPECTS

Transplant units need to adapt and invest in the novel options that are now available to our recipients, particularly under the burden of very long waiting times on the deceased donor list. Direct or "indirect" living kidney donation is key to the existence and development of all the above options. Clearly, the kind intentions of every living donor should be honoured in the best possible way after detailed discussion with both the donor and the recipient[21]. The mental and psychological process involved in every aspect of living donation deserves dedication in time and resources to ensure donors will not be discouraged by logistical complexities or delays. Training and education of all staff involved is of utmost importance to provide a seamless and positive experience to donors, who will become advocates of living donation in the community. Emphasizing the safety and quick recovery after living donation with minimally invasive techniques as well as the excellent long-term health outcomes for donors compared to the age-matched general population are also essential to reassure the public and promote living donation[22].

Introducing new concepts around living kidney donation in Greece should also start early to allow for adequate public discussion and engagement. Donation from offspring to parent rarely takes place in Greece. Although any adult individual may be considered for donation by law, there is reluctance even among transplant clinicians to consider young donors. Donation at an early age is a well-established and accepted practice in other countries, with excellent psychological and medical outcomes for both donors and recipients. In 2021 in the United Kingdom, 20% of all living donors were aged 18-34[17]. During the same period, only one donor (1%) was younger than 30 years in Greece. The age distribution of living donors over the last few years is depicted in Table 1, where it becomes evident that most donors are middle-aged or older. Clearly, widening the age criteria for donation in transplant units with appropriate consenting of younger donors will enable more transplants in the future.

Transplant candidates are often reluctant to approach and recruit living donors. Separating the advocate from the patient has proved to be an effective strategy but needs appropriate training[23]. The introduction of programmes aiming to facilitate identification of potential donors and elicit their interest to proceed with donation should form a part of a national strategy. Examples of successful implementation include the Live Donor Champion Program at Johns Hopkins[24], the University of Pittsburgh Medical Center Living Donor Champion Program[25] and more recently the Kidney Coach Program at Mount Sinai Hospital[26]. These programmes have achieved a substantial increase in donor inquiries and a modest increase in donor evaluations and number of living donor transplants.

Donating indirectly to someone *via* a waiting list "voucher" is an emerging concept worldwide that still remains to be validated but certainly shows the direction of modern transplantation and proves the concept that every living donor deserves to be "utilised" in the best possible way. This approach usually applies to donors that would probably be too old to donate when their recipient would actually need a kidney transplant, *e.g.*, a grandfather donating to their grandchild *via* the general waiting list. Simply put, transplant vouchers provide a means to overcome chronological incompatibility between donation and transplantation. The donor donates in the deceased donor list and the prospective recipient receives a "voucher" or a "priority ticket" that can be redeemed for a future transplant that will probably take place years later[27].

Reducing financial barriers for living donation and accounting for potential income losses remains a matter of debate for many years across the globe. Despite concerns around commercialisation of donation, a rational approach to protect and support prospective donors in their decision was proposed a few years ago by the American Society of Transplantation's Live Donor Community of Practice after careful and systematic exploration of factors such as employment, insurance and medical cost of

Table 1 Age distribution of living donors in Greece, 2016-2021, *n* (%)

Age group	Number of living donors by year					
	2016	2017	2018	2019	2020	2021
20-30	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
31-40	2 (4)	4 (6)	5 (7)	2 (3)	1 (1)	8 (9)
41-50	9 (18)	9 (13)	16 (23)	19 (28)	19 (21)	12 (13)
51-60	14 (29)	24 (35)	16 (23)	22 (32)	34 (38)	34 (37)
61-70	19 (39)	22 (32)	27 (40)	20 (3)	23 (26)	24 (27)
71-90	5 (10)	9 (14)	5 (7)	5 (7)	12 (14)	12 (13)
Total	49 (100)	68 (100)	69 (100)	68 (100)	89 (100)	91 (100)

donation. It became clear that the creation of a standardised financial toolkit for donors, adapted to each country's requirements and limitations is a perfectly actionable way to encourage living donation and remove any sense of insecurity in the process before and after donation[28].

Lastly, but equally important, we believe that further research is needed to understand living donation trends and perceptions in the public. These may vary significantly between different parts of the world. Therefore, extrapolation of conclusions from previous work elsewhere should be done with caution. Focus groups with patients and donors at a local level will shed light on various cultural barriers that could be potentially resolved with appropriate targeted campaigns. Additionally, transplant clinicians will have a unique opportunity to understand what matters most for living donors and how to better support them through the journey of donation[29,30].

CONCLUSION

Living donor kidney transplantation is undergoing a phase of transformation in Greece. New legislation and crucial changes in transplant policies pave the way for expansion of the donor pool, especially through living donation. The role of transplant professionals in this process of change and adaptation is to lead the developments in a safe and productive way for the benefit of patients. We have a duty to campaign for all the above and extend this knowledge to all parts involved in transplantation, from central organisation to local patient groups. Through living donation we have a unique opportunity to make progress and catch up with the growing need for more transplants in Greece by creating a positive environment in the community around transplantation in general. Every prospective living donor deserves to receive education, delivered responsibly, and high-quality care in every step of the way to donation, knowing that their generous offer will be fully appreciated. Clinicians on the other hand need to continue to explore ways that will encourage living donors to come forward. Identifying potential barriers to donation is the first important step into the future.

FOOTNOTES

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MINIREVIEWS

Exploring the use of virtual reality in surgical education

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Abstract

Virtual reality (VR) technologies have rapidly developed in the past few years. The most common application of the technology, apart from gaming, is for educational purposes. In the field of healthcare, VR technologies have been applied in several areas. Among them is surgical education. With the use of VR, surgical pathways along with the training of surgical skills can be explored safely, in a cost-effective manner. The aim of this mini-review was to explore the use of VR in surgical education and in the 3D reconstruction of internal organs and viable surgical pathways. Finally, based on the outcomes of the included studies, an ecosystem for the implementation of surgical training was proposed.

Key Words: Surgical education; Virtual reality; Abdominal surgery; Simulation

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Core Tip: This mini-review aims to explore the use of virtual reality in surgical education and in the 3D reconstruction of internal organs and viable surgical pathways. For this purpose, a non-systematic literature review was conducted and three highly influential scientific papers were selected and discussed. The main topics addressed are the use of technologies in surgical education, the methodologies for the implementation of the training systems, the evaluation approaches and the strengths and limitations of the studies. Finally, the review concluded with a comparative synthesis of the main findings and a discussion on the proposal of a system for implementing these findings on surgical education in the field of organ transplantation.

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INTRODUCTION

During the past few years, the use of virtual reality (VR) has increased rapidly in a number of sectors, like education[1,2] transportation[3,4] and healthcare[5]. In the case of education, the main advantage of using VR, is the immersion it provides, by using personalized experiences, promoting engagement, and providing hints that it may enhance learning[6], through the motivation aligned with the active participation of students.

As the immersion of the system increases, the effectiveness of the training module increases [7,8]. Additionally, the level of immersion of VR has been found to be proportional to the number of modalities involved[9].

VR has also found numerous applications in medical education[10-12]. More specifically, in the case of surgical education, the use of VR has been favored, due to many reasons, such as lack of mentors, reduction in training hours and various issues concerning operative procedures[13]. In order to exploit all these advantages, many solutions have been implemented, like the da Vinci Skills Simulator[14] and the LAP Mentor VR laparoscopic surgical simulator[15].

The aim of the present mini-review was to explore the use of VR simulators either alone or in combination with head-mounted displays (HMDs) in surgical education and in the construction of 3D models of internal organs[16]. For this purpose, three highly influential scientific papers were selected and discussed. The main topics addressed were the use of technologies in surgical education, the methodologies for the implementation of the training systems, the evaluation approaches and the strengths and limitations of the studies. Finally, the review concluded with a comparative synthesis of the main findings and a discussion on the proposal of a system for implementing these findings on surgical education in the field of organ transplantation.

METHODOLOGY

In April 2022, we performed a non-systematic literature search on the Google Scholar database using the terms “Virtual Reality”, “surgical education”, “surgery”, “medical education” to identify peer-reviewed articles, written in the English language, published after 2016, that seemingly explored the area of interest. The selected articles adhered to the following inclusion criteria: (1) Implement training in surgical skills with the use of VR technology; (2) Perform skill or full procedure training in abdominal surgeries; and (3) Include participants who were either surgical trainees or experienced surgeons.

All the information of interest was extracted from the selected articles. The information was used for the authors to identify main opportunities and limitations in the use of VR systems in surgical education and finally propose an infrastructure for extended reality (XR) technologies in order to implement a surgical training ecosystem.

TECHNOLOGIES

The devices used for promoting surgical education with the use of VR are mostly expensive[17,18] simulators (LapSim and Lap Mentor), often combined with some additional HMDs[18,19], like HTC Vive 360 or Google VR, to create an immersive and engaging user experience. Most simulation technologies include special controllers (some with haptic feedback) that accurately simulate the use of surgical instruments[17]. The LapSim emulator includes Simball 4D Joystick hardware and the Lap

Mentor includes a syringe allowing realistic fluid delivery and BAL performance, while a wide variety of bronchoscopy instruments, such as biopsy forceps, cytology brush, suction and more can also be simulated. Both simulators offer a high-resolution display of the virtual environment (VE). The combination of VR HMDs and the VR simulators promotes immersiveness and enhances the interaction between the participants and the VE (Table 1).

While the aforementioned devices offer a unique interactive experience, their cost can be extremely high. During the past years, there has been a rapid shift in the exploration of low-cost devices, offering the possibility of a larger market to the creators of any application. Such devices are the Oculus Rift, Meta Quest, HTC Vive, Pico[18,19]. The cost of these devices does not exceed $500, making surgical training more accessible to any hospital setting and open to more participants. Sampogna *et al*[19] used the Oculus Rift device combined with the Leap Motion sensor. The Oculus Rift requires a wired computer connection as well as the installation of the Oculus software on the computer and then through screencast displays the 3D VE on the glasses of the Rift device. The device includes two controllers, but in this study, they used the Leap Motion in order to keep the participants' hands free. Leap Motion is a motion sensor that recognizes users' actions and translates them into commands on a VR device or computer.

IMPLEMENTATION METHODS

When implementing surgical training in VR, the simulation can include either some basic tasks that are performed during specific surgeries[17,18], or full surgical procedures[17]. Simulators that specialize in specific surgeries, like the LAP simulator, have already integrated most of the corresponding tasks and require no further configurations in order to be ready for use. Huber *et al*[18] combined such a VR laparoscopic simulator with a 360° video depicting an operating room, thus creating a highly immersive scenario, and offering, for the first time, a structured surrounding environment for the simulation to be accumulated in.

All the images and 3D models contained in the aforementioned simulators, are based on magnetic resonance imaging (MRI) and recordings of *in vivo* procedures. In order to create realistic 3D models of internal organs, a collection of computed tomography scans and MRIs are required. Sampogna *et al*[19] described in detail the procedure of recreating 3D reconstructions based on medical imaging.

EVALUATION AND OUTCOME MEASURES

When implementing an evaluation of the efficacy of new training methodologies, usually the learning impact of the new method needs to be compared to traditional methods. In the selected studies there was heterogeneity in the outcome measures, which did not follow a common evaluation protocol (Table 2).

There are some common measurements between the study of Beyer-Berjot *et al*[17] and Huber *et al*[18] such as the completion time of each task and the number of errors, but other than that, the focus of the evaluation was shifted in opposite directions.

The outcome measures used in the study of Beyer-Berjot *et al*[17] were: (1) Time taken to complete the task; (2) Time spent *per* hand; (3) Accuracy of the surgical procedure; (4) Depth of incisions; (5) Number of errors; (6) Number of ripped and burned vessels; and (7) Overall score of the LapSim system based on the calculation of all the components. Questionnaires were also administered, evaluating the degree of interaction, concentration and realism.

In the study of Huber *et al*[18], different outcome measures were considered, focusing on the degree of interaction of clipping and grasping, 2-handed maneuvers (time, number of movements, and path length) in 4 tasks, medial dissection, lateral dissection, anastomosis and full large single copy. The fidelity and content validity were measured on a Likert scale.

Sampogna *et al*[19] developed questionnaires to measure simplicity, precision and fidelity, guidance, satisfaction, 3D reconstruction quality, VR immersiveness.

CRITICAL REVISIT

As mentioned before, the main advantage of using VR in surgical education is the immersiveness the technology provides. This advantage was exploited in full when VR was implemented with the use of HMD, as described by Huber *et al*[18], Sampogna *et al*[19]. Furthermore, Huber *et al*[18] introduced noise cancelling headphones for increasing immersion. Haptic feedback is a modality often used in VR environments in order to engage the sense of touch. Beyer-Berjot *et al*[17] used a simulator that integrated with haptic feedback.

Table 1 Comparison of technologies

	Beyer-Berjot *et al*[17], 2016–Lap Mentor VR	Huber *et al*[18], 2017-LapSim	Sampogna *et al*[19], 2017-Oculus Rift and Leap motion
Technology used for training	Virtual reality		
Equipment used for training	Custom hardware and software-Lap Mentor VR	Custom hardware and software-LapSim	Windows 10-Oculus Quest Rift S
Additional technology used for training	Haptic		
Additional equipment used for training	Lap Mentor realistic tactile surgical tools	LapSim realistic tactile surgical tools	Oculus gestures + Leap Motion
Operating system	Lap Mentor software	LapSim software	Windows 10

VR: Virtual reality.

Table 2 Beyer-Berjot *et al*[17], 2016 and Huber *et al*[18], 2017 outcome measures

Beyer-Berjot *et al*[17], 2016–Lap Mentor VR		Huber *et al*[18], 2017-LapSim	
Tasks	**Outcome measures**	**Tasks**	**Outcome measures**
Initial assessment	Time (s)	Peg transfer	Time (s)
Clipping and grasping	No. of movements	Fine dissection	Left time (s)
2-Handed maneuvers	Path length (cm)	Cholecystectomy	Right time (s)
Full laparoscopic sigmoid colectomy			Time (z-score)
Median dissection			Left path length (m)
Lateral dissection			Left angular path (degree)
Anastomosis			Left grasps (*n*)
Full LSC			Right path length (m)
			Right angular path (degree)
			Right grasps (*n*)
			Economics (z-score)
			Maximum drops (*n*)
			Errors (z-score)
			Total (z-score)

VR: Virtual reality; LSC: Large single copy.

The enrolment of participants of different gaming and surgical skills can prove beneficial when evaluating a VR surgical education application. Huber *et al*[18] used participants of 3 different laparoscopic experience levels, while about half of them had never played video games or had any exposure to VR. Beyer-Berjot *et al*[17] implemented a similar design for the selection of the participants, but additionally they recruited a small number of video game players. The fact that the participants of these two studies had varying gaming skills, can offer a more subjective view on the usability and acceptability of the system, while the different surgical levels can assess the effectiveness of the system in terms of education.

LIMITATIONS

Despite the great advantages of using VR technology in surgical education, there are also a couple of limitations that need to be considered. The use of VR simulators implemented without the use of HMDs, as described by Beyer-Berjot *et al*[17], did not exploit the full potential of the technology, lacking in immersion and users' engagement. Furthermore, the limited number of participants when performing a

feasibility study along with the non-comparison of a new teaching method versus the traditional one[17-19] can lead to barriers in evaluating the impact on learning and skill development. Also, limitations of the use of VR may appear in older adults due to lack of acquittance with the technology. Finally, as Sampogna *et al*[19] pointed out, if the first operators have rich experience on the skills the new systems aspire to train, the effect of the developed applications on speeding-up the learning curve cannot be evaluated properly. The aforementioned limitations should be considered in terms of the publishing date and in the context of the technological advances of the time. Since then, VR technology has made major progress and the scope of its capabilities has improved vastly.

COMPARATIVE SYNTHESIS

Among the selected studies, two used high-end VR simulation equipment and performed their study with precision sensors[17,18]. In the two studies, during each simulated task, a variety of data were collected, and they were displayed after the completion of the simulation. Some of them were time-on-task, and number of errors as well as some other indicators were designed during the implementation of the systems. The main difference between the simulators used the surgical task they focus on. LipSim can perform fine dissection, peg transfer, and cholecystectomy while LapMentor offers the option of training in sigmoid colectomy. In the study of Sampogna *et al*[19], MRIs were collected from different patients and then reconstruction of the internal organs was performed. The 3D models were imported in the Unity3D environment, and an application was created for Oculus Rift.

In all selected studies, the participants were either surgeons or surgical residents. Beyer-Berjot *et al*[17] and Huber *et al*[18] divided their participants into experimental groups based on the number of operations they had carried out in their careers and on their expertise, while Sampogna *et al*[19] did not categorize their participants. In all three studies, before the beginning of the studies, participants had the opportunity to perform some warm-up tasks in order to get acquainted with the VR technology. The main aim of this exercise was to minimize the errors caused due to difficulties in operating the simulators and the HDMs.

FUTURE STEPS

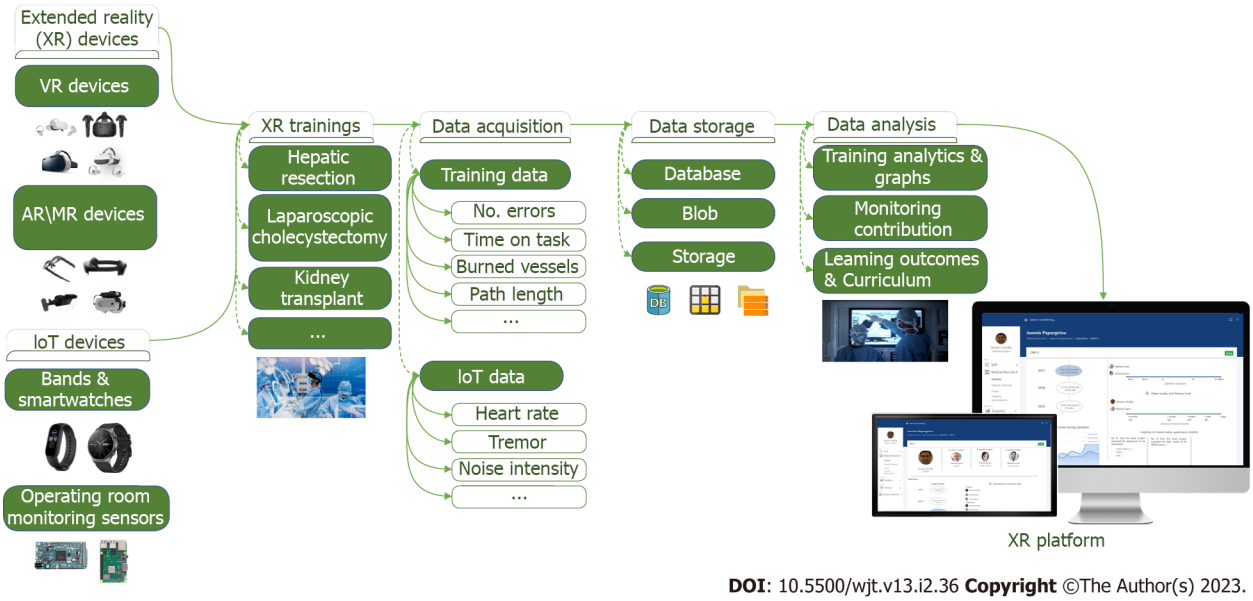
In the past few years, expensive devices and applications have been used in the field of surgical education and surgical procedure, which imposes significant limitations to their extensive use. So, it is important to explore the use of less expensive XR technologies (augmented reality, VR, mixed reality). It is also important to explore the difficulties in co-surgery and in team surgery, due to cooperation problems that may arise. There is also a lack of intra-operative applications that focus on surgeon interactions. In addition, although some studies have been conducted on VR applications in the field of transplantation in general, there is a lack of studies on abdominal transplantations. Also, it will be useful to explore XR not only in surgical training but also during the surgical procedure.

Based on the findings of the comparative synthesis of the already existing approaches, we proposed a roadmap and its application could foster the training of surgeries (Figure 1). A 5-layered system could be constructed according to the following paradigm.

The first layer includes low-cost devices XR. More specifically, future studies should investigate VR devices such as Meta Quest 2, Pico and AR devices such as NReal Light, Toshiba DynaEdge, which cost no more than $500 each and are affordable for not only surgeons but also mass purchases by hospitals and universities. Also, within the same layer we propose the inclusion of IoT devices such as bands and smartwatches as well as Arduino and Raspberry devices that allow sensorial, real-world, big data acquisition, like speech and motion capture analysis. The second layer focuses on co-designing and co-creating virtual and augmented surgeons' training, based on participatory activities that will take place among healthcare and technology-oriented professionals[20]. In the third layer, a big data acquisition system is designed during the training activities. Data are gathered from heterogeneous sources such as training metrics, biomarkers, and sensory recordings[21] that could help assess the quality of the surgical procedure. In the fourth layer, biosensors are programmed to collect periodic data from the surgeons, which are uploaded on a cloud-based infrastructure where they are stored in a suitable database for analysis. Additional factors could be studied, such as the noise in the virtual surgery as well as the fatigue of the surgeon during the sessions. The analysis of these data is likely to create new approaches to deal with medical errors in operating rooms. In the fifth layer a platform is constructed that graphically presents the training analytics and the course of the surgeries for each surgeon.

CONCLUSION

VR technologies are becoming more accessible and are a potential cognitive enhancer in the field of



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Figure 1 Extended reality proposed ecosystem[21-27]. XR: Extended reality; VR: Virtual reality; AR: Augmented reality; MR: Mixed reality.

surgical education. The findings of this mini-review offer insight into the devices and systems used to train surgeons, as well as to low-cost devices that are rapidly being developed to offer a solution in surgical training. Interestingly, we found a lack of VR training in the field of organ transplantation. In order to tackle this, an ecosystem for promoting learning through XR systems is proposed to be implemented for use in training for transplantation. In order to assess the proposed architecture, a feasibility study along with a cost-effectiveness analysis should be performed. The implementation and evaluation of the system falls outside the scope of this mini-review. Nevertheless, it could prove to be a valuable tool in the field of surgical and more specifically transplantation training, especially if evaluated against a transplantation simulator.

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FOOTNOTES

Author contributions: Ntakakis G search the database; Ntakakis G and Plomariti C check the articles against the inclusion criteria; Ntakakis G, Plomariti C, Frantzidis C, and Antoniou PE wrote the manuscript; All authors have read and approved the final version to be submitted.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Analysis of the effects of donor and recipient hepatitis C infection on kidney transplant outcomes in the United States

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Abstract

BACKGROUND

As Hepatitis C virus infection (HCV+) rates in kidney donors and transplant recipients rise, direct-acting antivirals (DAA) may affect outcomes.

AIM

To analyze the effects of HCV+ in donors, recipients, or both, on deceased-donor (DD) kidney transplantation (KT) outcomes, and the impact of DAAs on those effects.

METHODS

The Organ Procurement and Transplantation Network data of adult first solitary DD-KT recipients 1994-2019 were allocated into four groups by donor and recipient HCV+ status. We performed patient survival (PS) and death-censored graft survival (DCGS) pairwise comparisons after propensity score matching to

assess the effects of HCV+ in donors and/or recipients, stratifying our study by DAA era to evaluate potential effect modification.

RESULTS

Pre-DAA, for HCV+ recipients, receiving an HCV+ kidney was associated with 1.28-fold higher mortality (HR $_{1.15}$1.28$_{1.42}$) and 1.22-fold higher death-censored graft failure (HR $_{1.08}$1.22$_{1.39}$) compared to receiving an HCV- kidney and the absolute risk difference was 3.3% (95%CI: 1.8%-4.7%) for PS and 3.1% (95%CI: 1.2%-5%) for DCGS at 3 years. The HCV dual-infection (donor plus recipient) group had worse PS (0.56-fold) and DCGS (0.71-fold) than the dual-uninfected. Donor HCV+ derived worse post-transplant outcomes than recipient HCV+ (PS 0.36-fold, DCGS 0.34-fold). In the DAA era, the risk associated with HCV+ in donors and/or recipients was no longer statistically significant, except for impaired PS in the dual-infected *vs* dual-uninfected (0.43-fold).

CONCLUSION

Prior to DAA introduction, donor HCV+ negatively influenced kidney transplant outcomes in all recipients, while recipient infection only relatively impaired outcomes for uninfected donors. These adverse effects disappeared with the introduction of DAA.

Key Words: Hepatitis C virus; Kidney transplantation; Direct-acting antiviral therapy; Propensity score matching

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Core Tip: In this paper, using data from across 25 years, we demonstrate that the adverse effects of hepatitis C infection in donors and/or recipients on kidney transplant outcomes have disappeared since the introduction of direct-acting antiviral agents.

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INTRODUCTION

By improving patients' quality of life and survival, kidney transplantation (KT) is the optimal treatment for advanced kidney disease, even for Hepatitis C virus infected (HCV+) dialysis patients[1,2]. HCV+ donor kidneys could alleviate transplant organ shortages[3], and most kidney waitlist patients favor accepting an HCV+ kidney over waiting longer for an uninfected (HCV-) kidney[4]. Nonetheless, likely driven by concerns over HCV transmission and transplant outcomes, HCV+ kidneys have traditionally been discarded rather than transplanted into HCV- recipients[5].

Since December 2013, direct-acting antivirals (DAA), including NS3/4A inhibitors (boceprevir, telaprevir, simeprevir, asunaprevir, grazoprevir and paritaprevir), NS5A inhibitors (ombitasvir, ledipasvir, daclatasvir, elbasvir and velpatasvir), NS5B inhibitors (sofosbuvir and dasabuvir)[6], have revolutionized HCV treatment by consistently achieving 95% or better sustained virologic responses[7]. Before the introduction of DAAs, a combination of interferon and ribavirin were the standard scheme for HCV treatment[8]. Concurrently, United States donors who died as a result of drug overdose, many of whom were HCV+, increased from 66 to 1263 between 2000 and 2016. Notably, these donors were young: median age of 31 years[3]. HCV+ kidneys' superior quality, the increased prevalence of HCV+ in donors and recipients, and DAA treatments, have contributed to soaring numbers of HCV+ donor and/or recipient transplants. In the DAA era, because of the promise of HCV treatment, waitlisted transplant candidates were 2.2 times more likely willing to accept an HCV+ kidney and HCV+ recipients were 1.95 times more likely to receive an HCV+ kidney when compared to the pre-DAA era[5].

Despite HCV antiviral advancements, the Organ Procurement and Transplantation Network (OPTN) deceased donor (DD) kidneys allocation algorithm uses the Kidney Donor Risk Index (KDRI), for which donor HCV+ status has the largest coefficient amongst dichotomous factors in the calculation[9]. This outdated system overestimates HCV+ kidneys' risk in the DAA era, depriving candidates of high-quality HCV+ kidneys if they, or their accepting center, decline kidney offers based on KDRI thresholds, thus contributing to HCV+ kidneys' high discard rate.

We sought to understand the effect of HCV+ in donors and recipients on DD-KT outcomes and discern whether those effects differed among various HCV+ donor and recipient combinations. We hypothesized that donor HCV status could modify HCV effect in recipients, recipient HCV status could modify HCV effect in donors, and those modifications would change favorably following DAA availability. We used national registry data with propensity score matching (PSM) to systematically characterize the effect of HCV+ on KT outcomes both prior to and following the introduction of DAAs.

MATERIALS AND METHODS

Data sources

We used the OPTN Analysis and Research file released in June 2019 based on data collected through March 2019. The content in this paper is the responsibility of the authors alone and does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the United States Government.

Study population

We identified all adult (age ≥ 18) first-time solitary KT recipients from ABO-compatible DD between January 1994 and March 2019 in the United States Patients with missing or uncertain HCV-antibody status in the donor or recipient were excluded. Patients were allocated into four groups according to HCV+ in the donor (D+) or recipient (R+): D-R-, D+R-, D-R+, and D+R+.

Outcome and exposure classification

The study outcomes were patient survival (PS) and death-censored graft survival (DCGS) following KT. DCGS was defined as time to re-transplantation or dialysis reinstatement, whichever came first. Recipient HCV status is reported but not necessarily confirmed or assessed at transplant. HCV+ status was defined as HCV Ab+ or HCV nucleic acid test (NAT) positive, while HCV- was defined as HCV Ab- without HCV NAT+.

PSM

We performed pairwise PS and DCGS comparisons after PSM to assess the effect of donor and recipient HCV+ status on outcomes. Briefly, transplantation of HCV (+) or (-) donors into HCV (-) recipients was used to assess the effect of HCV+ in naïve recipients, as compared to D+R+ *vs* D-R+ combinations to assess the effect of HCV donor status in HCV infected recipients. D+R- *vs* D-R- patients addressed HCV donor infection effect in uninfected recipients, while D+R+ *vs* D-R+ patients addressed the effect in HCV+ recipients. Similarly, D+R+ *vs* D+R- pairings were compared for the effect of recipient HCV+ on HCV+ donor kidneys' outcomes, and D-R+ *vs* D-R- pairings were compared for the effect in HCV- donor kidneys. Finally, D+R+ *vs* D-R- pairings addressed the effect of HCV+ in both donors and recipients on outcomes, and D+R- *vs* D-R+ pairings addressed whether HCV+ in donors or recipients alone was more detrimental.

Subject pairs were matched by the probability of positive HCV exposure based on a multivariable logistic regression model with 40 potential predictors from the donor, recipient, and transplant procedure. Supplementary Table 1 shows model variables and missingness. Variables were chosen based on The Scientific Registry of Transplant Recipients risk adjustment models[10]. We used complete-case analysis for categorical variables missing fewer than 1% of values and included a missing indicator in the initial step for those missing more than 1%. For continuous variables, the missing values were imputed with the median, and a missing indicator was also included for those missing percentage > 1% (Supplementary Table 1). The potential outliers of continuous variables were winsorized at 1 and 99 percentiles. By focusing on HCV exposure effect in a sample of subjects that resembles the exposed subjects, we estimated the average treatment effect in the treated. We used the nearest neighbor matching with 1:1 ratio, without replacement, and with a caliper of width equal to 0.2 of the standard deviation (SD) of the logit of the propensity score. We performed balance diagnosis comparing matched groups' characteristics. An SD greater than 0.1 was considered an imbalance sign, and the propensity score prediction model was refitted ensuring matched groups' balance (Supplementary Table 1). We further stratified our study by DAA era (before or after December 2013) to evaluate potential effect modification.

Statistical analysis

Survival rates were presented in Kaplan-Meier curves and analyzed by log-rank tests. Time to outcome was defined as the interval from date-of-transplant to date-of-outcome (death or graft failure) and censored for loss to follow-up or end of study period. Absolute and relative risk differences in mortality and death-censored graft failure (DCGF) were estimated using Austin's methods[11]. All analyses were performed using RStudio software, version 1.1.456 (R. RStudio, Inc., Boston, MA). A *P*-value of less than 0.05 identified statistical significance, and all confidence intervals used a 95% threshold.

RESULTS

Changing characteristics of KT relative to HCV in donors and recipients

We identified 166,160 D-R-, 6,251 D-R+, 3,854 D+R+, and 1,672 D+R- pairings during the study (Figure 1). D+R+ transplants increased at a similar rate to D-R- transplants in the pre-DAA era, while D+R- and D-R+ transplants remained stable for two decades. However, HCV+ kidney utilization surged in the DAA era, initially with the traditional operating paradigm (D+ to R+), which peaked in 2016 and soon shifted to more robust HCV+ kidneys utilization (D+ to R-) (Figure 2).

Tables 1-3 and Supplementary Table 2 and 3 detail all cohorts' donor, recipient, and transplant characteristics. The D+R- donors pre-DAA were predominantly male, white or African American, with low body mass index, who succumbed to head trauma, with relatively low serum creatinine, and low rates of donation after circulatory death (DCD), diabetes, and hypertension (Supplementary Table 2A). In contrast, D+R- recipients tended to be older (57 [IQR, 47, 65]) and had less dialysis time. Thirty-seven percent of D+R- and 38% of D+R+ were shared nationally, and D+R- had the longest cold ischemia time (CIT) at 20 h [IQR, 16.0, 26.0]. D+R- and D+R+ cohorts had higher HLA mismatch than D-R- and D-R+. However, the incidence of delayed graft function (DGF) in D+R- was 25.3%, lower than in the D-R+ or D+R+ cohorts and similar to the D-R- cohort (Supplementary Table 2C).

In the DAA era, HCV+ donors were younger than HCV- donors, with lower rates of diabetes and hypertension. D+R- donors were predominantly white (85.2%) and died primarily of anoxic brain injury (72%) (Supplementary Table 3A). D+R- recipients tended to be white (45.7%), highly educated (30.6% with post high school degree), and less likely to have hypertension as the etiology of renal failure (Supplementary Table 3B). Similar to the pre-DAA transplants, D+R- transplants had the lowest rate of DGF (20.5%) despite the longest CIT (18.4[IQR, 13.1, 23.8]) (Supplementary Table 3C).

The association between donor HCV+ and transplant outcome in the Pre-DAA era

Prior to the DAA era, D-R- patients had the best crude PS and DCGS, while D+R- patients had the worst crude PS and DCGS (Figure 3A and B). The crude 3-year PS was 89.6%, 73.1%, 86.7% and 84.8% for D-R-, D+R-, D-R+ and D+R+, respectively. The crude 3-year DCGS was 88.8%, 80.1%, 84.2% and 82% for D-R-, D+R-, D-R+ and D+R+, respectively (Table 4).

After matching, 1272 pairs of HCV+ and 528 pairs of HCV- recipients were generated. Among the HCV+ recipients, receiving an HCV+ DD kidney was associated with 1.28-fold higher mortality (HR $_{1.15}$1.28$_{1.42}$) and 1.22-fold higher DCGF (HR $_{1.08}$1.22$_{1.39}$) compared to receiving an HCV- kidney over the observed period (Figure 4A). The absolute risk difference (aRD) was 3.3% (95%CI: 1.8%, 4.7%) for PS and 3.1% (95%CI: 1.2%, 5%) for DCGS at 3 years (Table 4).

Among HCV- recipients, receiving an HCV+ kidney was associated with 1.55-fold higher mortality (HR $_{1.33}$1.55$_{1.80}$) and 1.64-fold higher DCGF (HR $_{1.33}$1.64$_{2.02}$) compared to an HCV- kidney (Figure 4A). The aRD was 8% (95%CI: 5.2%, 10.9%) for PS and 7.4% (95%CI: 4.3%, 10.5%) for DCGS at 3 years (Table 4).

The association between donor HCV+ and transplant outcome in the DAA era

In the DAA era, comparable crude PS and DCGS were observed among all four cohorts (Figure 3C and D). The crude 3-year PS were 91%, 86.1%, 88.1% and 89.8% for D-R-, D+R-, D-R+ and D+R+, respectively. The crude 3-year DCGS were 92.5%, 92.6%, 92.4% and 94.2% for D-R-, D+R-, D-R+ and D+R+, respectively (Table 4). After matching, there were 290 pairs of HCV+ and 791 pairs of HCV- recipients. In contrast with pre-DAA era risks, the risks for PS and DCGS associated with receiving an HCV+ kidney in either HCV+ or HCV- recipients were not statistically significantly different in the DAA era (Figure 4B).

The association between recipient HCV+ and transplant outcome

Pre-DAA, HCV+ in recipients of HCV- donor kidneys corelated with significant declines in both crude PS and DCGS. However, HCV+ in recipients of HCV+ donors demonstrated a relative protective effect on mortality by 22% (D+R- *vs* D+R+, adjusted $P < 0.001$ for log-Rank test, HR$_{0.69}$0.78$_{0.87}$), despite the DCGS remaining comparable between two groups (D+R- *vs* D+R+, adjusted $P = 0.988$ for log-Rank test) (Figure 3A and B).

After matching, we generated 461 pairs of HCV+ and 4646 pairs of HCV- DD. HCV+ in recipients of HCV- donor kidneys was associated with 1.25-fold higher mortality (HR $_{1.18}$1.25$_{1.33}$) and 1.31-fold higher DCGF (HR $_{1.22}$1.31$_{1.41}$). The aRD between D-R- and D-R+ was 2.6% (95%CI: 1.9%, 3.2%) for PS and 3.5% (95%CI: 2.6%, 4.4%) for DCGS at 3 years (Table 4). In contrast, HCV+ and HCV- recipients of HCV+ donors demonstrated comparable outcomes (HR $_{0.86}$1$_{1.18}$ for mortality, $_{0.87}$1.01$_{1.31}$ for DCGS) (Figure 4A).

In the DAA era, we generated 508 pairs of HCV+ and 1440 pairs of HCV- recipients after matching. The risk associated with recipient's HCV+ when receiving either HCV+ or HCV- kidneys was not statistically significantly different in PS or DCGS (Figure 4B).

The association between donor plus recipient HCV+ and post-transplant outcome

Pre-DAA, HCV+ in the donor and recipient significantly impaired both PS and DCGS (D-R- *vs* D+R+, adjusted $P < 0.001$ for log-Rank test) (Figure 3A and B). There were 2150 pairs of D-R- and D+R+

Table 1 Characteristics of donors in the pre-direct-acting antivirals era and the post-direct-acting antivirals era

Characteristics		D-R-	D-R+	D+R-	D+R+	*P* value
n	Pre	116108	4646	550	2455	
	Post	46099	1443	1082	1303	
Age (median [IQR])	Pre	40.0 [23.0, 51.0]	40.0 [24.0, 51.0]	41.0 [34.0, 46.0]	42.0 [33.0, 49.0]	< 0.001
	Post	40.0 [27.0, 52.0]	42.0 [29.0, 52.0]	35.0 [29.0, 44.0]	32.0 [26.0, 39.0]	< 0.001
Gender = M (%)	Pre	69042 (59.5)	2762 (59.4)	380 (69.1)	1574 (64.1)	< 0.001
	Post	28136 (61.0)	853 (59.1)	617 (57.0)	818 (62.8)	0.012
BMI (median [IQR])	Pre	25.6 [22.4, 29.7]	25.6 [22.3, 29.4]	24.8 [22.1, 28.0]	25.1 [22.3, 28.6]	< 0.001
	Post	27.1 [23.4, 31.9]	27.5 [23.7, 32.2]	26.3 [23.3, 30.5]	25.6 [22.8, 29.4]	< 0.001
Race (%)						
White	Pre	83490 (71.9)	3209 (69.1)	409 (74.4)	1824 (74.3)	< 0.001
African American		14085 (12.1)	698 (15.0)	91 (16.5)	341 (13.9)	
Hispanic		14482 (12.5)	574 (12.4)	45 (8.2)	260 (10.6)	
Other		4051 (3.5)	165 (3.6)	5 (0.9)	30 (1.2)	
White	Post	31238 (67.8)	929 (64.4)	922 (85.2)	1103 (84.7)	< 0.001
African American		6325 (13.7)	273 (18.9)	44 (4.1)	58 (4.5)	
Hispanic		6421 (13.9)	187 (13.0)	94 (8.7)	116 (8.9)	
Other		2115 (4.6)	54 (3.7)	22 (2.0)	26 (2.0)	
Cause of death (%)						
Anoxia	Pre	19852 (17.1)	750 (16.1)	67 (12.2)	470 (19.1)	< 0.001
Cerebrovascular/stroke		44318 (38.2)	1800 (38.7)	196 (35.6)	985 (40.1)	
Head trauma		48450 (41.7)	1926 (41.5)	281 (51.1)	960 (39.1)	
Other		3488 (3.0)	170 (3.7)	6 (1.1)	40 (1.6)	
Anoxia	Post	18056 (39.2)	574 (39.8)	779 (72.0)	882 (67.7)	< 0.001
Cerebrovascular/stroke		12337 (26.8)	397 (27.5)	109 (10.1)	127 (9.7)	
Head trauma		14151 (30.7)	430 (29.8)	176 (16.3)	272 (20.9)	
Other		1555 (3.4)	42 (2.9)	18 (1.7)	22 (1.7)	
DCD = yes (%)	Pre	10101 (8.7)	368 (7.9)	11 (2.0)	105 (4.3)	< 0.001
	Post	10519 (22.8)	329 (22.8)	151 (14.0)	128 (9.8)	< 0.001
SCR (median [IQR])	Pre	1.0 [0.7, 1.3]	1.0 [0.7, 1.3]	0.9 [0.7, 1.2]	0.9 [0.7, 1.1]	< 0.001
	Post	0.9 [0.7, 1.4]	1.0 [0.7, 1.4]	0.9 [0.7, 1.3]	0.9 [0.7, 1.1]	< 0.001
History of diabetes = yes (%)	Pre	6712 (5.8)	254 (5.5)	14 (2.5)	95 (3.9)	< 0.001
	Post	3616 (7.8)	123 (8.5)	41 (3.8)	30 (2.3)	< 0.001
History of hypertension = yes (%)	Pre	28967 (24.9)	1137 (24.5)	114 (20.7)	576 (23.5)	0.038
	Post	13638 (29.6)	453 (31.4)	226 (20.9)	173 (13.3)	< 0.001
Smoking history = no (%)	Pre	78484 (67.6)	3039 (65.4)	234 (42.5)	1068 (43.5)	< 0.001
	Post	36564 (79.3)	1154 (80.0)	723 (66.8)	953 (73.1)	< 0.001

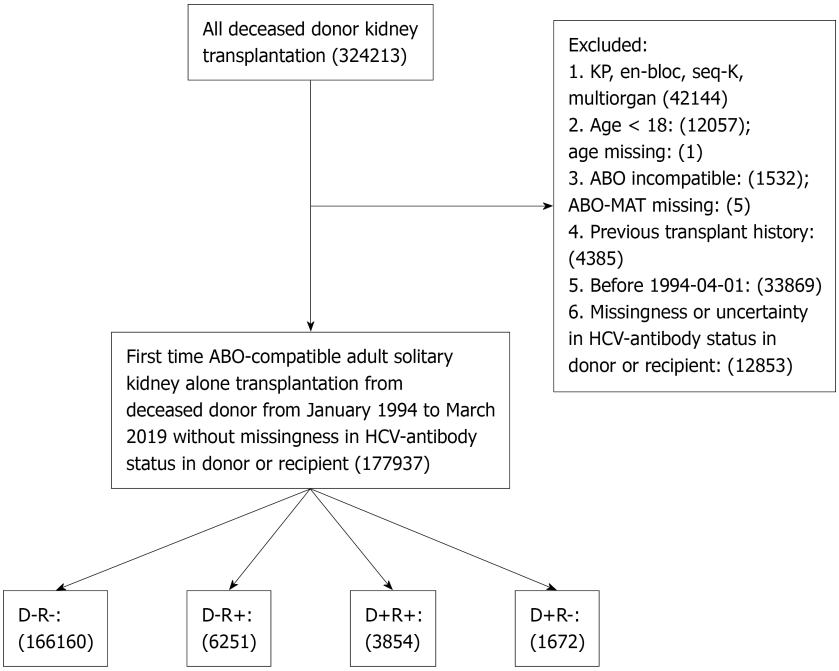
D(-/+) R(-/+), hepatitis C virus (-) or (+) donors into hepatitis C virus (-) or (+) recipients. BMI: Body mass index; DCD: Donation after circulatory death; IQR: Interquartile range; M: male; Pre: Pre-direct-acting antivirals era; Post: Post-direct-acting antivirals era; SCR: Serum creatinine.

transplants after matching. HCV+ in donor and recipient was associated with 1.56-fold higher mortality (HR $_{1.43}1.56_{1.7}$) and 1.71-fold higher DCGF (HR $_{1.54}1.71_{1.9}$) compared to the D-R- transplants. The aRD between D-R- and D+R+ were 5.3% (95%CI: 4.3%, 6.4%) for PS and 7.1% (95%CI: 5.7%, 8.5%) for DCGS

Table 2 Characteristics of recipients in the pre-direct-acting antivirals era and the post-direct-acting antivirals era

Characteristics		D-R-	D-R+	D+R-	D+R+	*P* value
n	Pre	116108	4646	550	2455	
	Post	46099	1443	1082	1303	
Age (median [IQR])	Pre	53.0 [42.0, 61.0]	51.0 [44.0, 58.0]	57.0 [47.0, 65.0]	53.0 [47.0, 59.0]	< 0.001
	Post	55.0 [44.0, 64.0]	59.0 [52.0, 64.0]	60.0 [52.0, 67.0]	60.0 [55.5, 65.0]	< 0.001
Gender = M (%)	Pre	69448 (59.8)	3251 (70.0)	406 (73.8)	1995 (81.3)	< 0.001
	Post	27135 (58.9)	994 (68.9)	739 (68.3)	1017 (78.1)	< 0.001
BMI (median [IQR])	Pre	26.8 [23.6, 30.9]	26.1 [23.0, 29.9]	26.5 [23.6, 29.4]	26.4 [23.3, 29.8]	< 0.001
	Post	28.6 [24.9, 32.8]	27.8 [24.4, 31.6]	29.1 [25.7, 33.3]	27.8 [24.5, 31.5]	< 0.001
Race (%)						
White	Pre	56376 (48.6)	1383 (29.8)	211 (38.4)	404 (16.5)	< 0.001
African American		34683 (29.9)	2447 (52.7)	290 (52.7)	1789 (72.9)	
Hispanic		15940 (13.7)	517 (11.1)	27 (4.9)	201 (8.2)	
Other		9109 (7.8)	299 (6.4)	22 (4.0)	61 (2.5)	
White	Post	16501 (35.8)	334 (23.1)	494 (45.7)	267 (20.5)	< 0.001
African American		15762 (34.2)	784 (54.3)	392 (36.2)	855 (65.6)	
Hispanic		9079 (19.7)	226 (15.7)	117 (10.8)	137 (10.5)	
Other		4757 (10.3)	99 (6.9)	79 (7.3)	44 (3.4)	
Insurance = nonprivate (%)	Pre	83051 (71.5)	3733 (80.3)	418 (76.0)	1831 (74.6)	< 0.001
	Post	37085 (80.4)	1265 (87.7)	831 (76.8)	993 (76.2)	< 0.001
Education level (%)						
High school	Pre	44906 (38.7)	1923 (41.4)	222 (40.4)	1195 (48.7)	< 0.001
Technical		22531 (19.4)	931 (20.0)	86 (15.6)	450 (18.3)	
Post high school degree		18972 (16.3)	494 (10.6)	59 (10.7)	254 (10.3)	
High school	Post	19085 (41.4)	741 (51.4)	403 (37.2)	680 (52.2)	< 0.001
Technical		11577 (25.1)	369 (25.6)	280 (25.9)	318 (24.4)	
Post high school degree		10687 (23.2)	230 (15.9)	331 (30.6)	214 (16.4)	
ESRD (%)						
Diabetes	Pre	32208 (27.7)	1193 (25.7)	178 (32.4)	783 (31.9)	< 0.001
Hypertension		30368 (26.2)	1745 (37.6)	221 (40.2)	1108 (45.1)	
Other		53532 (46.1)	1708 (36.8)	151 (27.5)	564 (23.0)	
Diabetes	Post	14439 (31.3)	477 (33.1)	438 (40.5)	601 (46.1)	< 0.001
Hypertension		12513 (27.1)	543 (37.6)	270 (25.0)	444 (34.1)	
Other		19147 (41.5)	423 (29.3)	374 (34.6)	258 (19.8)	
Dialysis time, day, (median [IQR])	Pre	1143 [708, 1691]	1344 [889, 2164]	976 [580, 1388]	1118 [603, 1596]	< 0.001
	Post	1661 [1043, 2373]	1999 [1364, 2988]	1257 [637, 1674]	1065 [593, 1661]	< 0.001
CPRA (median [IQR])	Pre	0.0 [0.0, 2.0]	0.0 [0.0, 2.0]	0.0 [0.0, 0.0]	0.0 [0.0, 0.0]	< 0.001
CPRA (mean [SD])	Post	19.3 (32.8)	20.5 (33.5)	9.4 (21.9)	9.3 (21.3)	< 0.001
PVD = yes (%)	Pre	5374 (4.6)	210 (4.5)	26 (4.7)	111 (4.5)	< 0.001
	Post	4590 (10.0)	186 (12.9)	118 (10.9)	148 (11.4)	0.001
Diabetes = yes (%)	Pre	38827 (33.4)	1491 (32.1)	225 (40.9)	1014 (41.3)	< 0.001
	Post	17213 (37.3)	583 (40.4)	521 (48.2)	714 (54.8)	< 0.001

D(-/+) R(-/+), hepatitis C virus (-) or (+) donors into hepatitis C virus (-) or (+) recipients. BMI: Body mass index; ESRD: End stage renal disease; IQR: Interquartile range; M: Male; Pre: Pre-direct-acting antivirals era; Post: Post-direct-acting antivirals era; CPRA: Calculated panel reaction antibody; PVD: Peripheral vascular disease.



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Figure 1 Flowchart of study cohorts identification. We identified all adult (age ≥ 18) first-time solitary kidney transplantation recipients from an ABO-compatible deceased donor between January 1994 and March 2019 in the United States Patients with missing or uncertain hepatitis C virus (HCV)-antibody status in the donor or recipient were excluded. Patients were allocated into four groups according to HCV infection in the donor (D+) or recipient (R+): D-R-, D+R-, D-R+, and D+R+. KP: Kidney-pancreas; HCV: Hepatitis C virus; ABO-MAT: ABO-blood type match.

at 3 years (Figure 4A, Table 4).

In the DAA era, 803 pairs of D-R- and D+R+ transplants were generated after matching. HCV+ in donor and recipient marginally significantly increased the mortality (P = 0.049 for log-rank test). The cox proportional hazard model showed a mortality increase by 1.43-fold (HR $_{1.0}$1.43$_{2.04}$) as compared to the D-R- transplants, with an aRD of 3.3% (95%CI: 0, 6.7%) at 3 years. The 3-year PS were 91.8% and 88.4% for D-R- and D+R+ recipients, respectively. HCV+ in donor and recipient did not statistically significantly affect DCGS (Figure 4B, Table 4).

The association between donor or recipient HCV+ and post-transplant outcome

In the pre-DAA era, HCV+ in the donor had more impact on patient survival than did infection in the recipient (D+R- *vs* D-R+, adjusted P < 0.001 for log-Rank test, HR$_{1.49}$1.69$_{1.83}$) (Figure 3A and B). After matching, there were 444 pairs of D+R- and D-R+ transplants. Donor HCV+ was associated with 1.36-fold higher mortality (HR $_{1.16}$1.36$_{1.61}$) and 1.34-fold higher DCGF (HR $_{1.08}$1.34$_{1.67}$) than recipient HCV+. The aRD between D+R- and D-R+ were 5.4% (95%CI: 2.6%, 8.6%) for PS and 4.8% (95%CI: 1.4%, 8.2%) for DCGS at 3 years (Figure 4A, Table 4).

In the DAA era, 253 pairs of D-R+ and D+R- transplants were identified after matching, with both PS (HR$_{0.52}$1.28$_{2.87}$) and DCGS (HR$_{0.58}$1.73$_{4.91}$) in the matched cohorts being comparable (Figure 4B, Table 4).

DISCUSSION

In our national study of 177937 DD KT across 25 years, we found a marked increase in HCV+ kidney utilization after DAA availability, initially with KTs of HCV+ kidneys to HCV+ recipients in 2014, followed by a dramatic shift towards transplants into HCV- recipients. This shift in 2016 likely reflects knowledge around the safety of HCV transplants with concurrent use of DAA. Pre-DAA D+R- recipients, despite generally being older, with less dialysis time and higher malignancy prevalence, received younger donors' kidneys. Interestingly, in the DAA era, recipients' education level was highest in the D+R- cohort, suggesting superior health literacy potentially facilitating informed consent and

Table 3 Characteristics of transplantation in the pre-direct-acting antivirals era and the post-direct-acting antivirals era

Characteristics		D-R-	D-R+	D+R-	D+R+	*P* value
n	Pre	116108	4646	550	2455	
	Post	46099	1443	1082	1303	
TX year (median [IQR])	Pre	2005 [2000, 2010]	2004 [1999, 2009]	2001 [1997, 2007]	2006 [2001, 2010]	< 0.001
	Post	2016 [2015, 2018]	2016 [2015, 2018]	2018 [2017, 2018]	2016 [2015, 2017]	< 0.001
Region (%)						
1	Pre	4694 (4.0)	167 (3.6)	11 (2.0)	74 (3.0)	< 0.001
2		14123 (12.2)	661 (14.2)	112 (20.4)	823 (33.5)	
3		17507 (15.1)	704 (15.2)	64 (11.6)	235 (9.6)	
4		10816 (9.3)	414 (8.9)	29 (5.3)	136 (5.5)	
5		17680 (15.2)	655 (14.1)	63 (11.5)	260 (10.6)	
6		4356 (3.8)	156 (3.4)	6 (1.1)	7 (0.3)	
7		9360 (8.1)	403 (8.7)	54 (9.8)	137 (5.6)	
8		7738 (6.7)	252 (5.4)	23 (4.2)	55 (2.2)	
9		7150 (6.2)	355 (7.6)	29 (5.3)	222 (9.0)	
10		10186 (8.8)	457 (9.8)	104 (18.9)	192 (7.8)	
11		12498 (10.8)	422 (9.1)	55 (10.0)	314 (12.8)	
1	Post	1601 (3.5)	62 (4.3)	35 (3.2)	65 (5.0)	< 0.001
2		5404 (11.7)	182 (12.6)	151 (14.0)	349 (26.8)	
3		6590 (14.3)	221 (15.3)	181 (16.7)	150 (11.5)	
4		4526 (9.8)	173 (12.0)	45 (4.2)	67 (5.1)	
5		8107 (17.6)	238 (16.5)	101 (9.3)	144 (11.1)	
6		1911 (4.1)	55 (3.8)	13 (1.2)	6 (0.5)	
7		3192 (6.9)	110 (7.6)	37 (3.4)	45 (3.5)	
8		3130 (6.8)	86 (6.0)	5 (0.5)	44 (3.4)	
9		3057 (6.6)	85 (5.9)	125 (11.6)	174 (13.4)	
10		3507 (7.6)	79 (5.5)	195 (18.0)	84 (6.4)	
11		5074 (11.0)	152 (10.5)	194 (17.9)	175 (13.4)	
Shared (%)						
Local	Pre	85197 (73.4)	3464 (74.6)	223 (40.5)	931 (37.9)	< 0.001
Regional		9559 (8.2)	377 (8.1)	124 (22.5)	591 (24.1)	
National		21352 (18.4)	805 (17.3)	203 (36.9)	933 (38.0)	
Local	Post	35095 (76.1)	1115 (77.3)	337 (31.1)	379 (29.1)	< 0.001
Regional		5349 (11.6)	157 (10.9)	345 (31.9)	348 (26.7)	
National		5655 (12.3)	171 (11.9)	400 (37.0)	576 (44.2)	
CIT (median [IQR])	Pre	18.0 [13.0, 23.1]	18.0 [13.0, 23.5]	20.0 [16.0, 26.0]	19.0 [15.0, 25.0]	< 0.001
	Post	16.7 [11.4, 22.6]	16.5 [11.0, 22.0]	18.4 [13.1, 23.8]	18.0 [12.3, 23.5]	< 0.001
HLA mismatch = 4-6 (%)	Pre	76253 (65.7)	3238 (69.7)	452 (82.2)	2151 (87.6)	< 0.001
	Post	35126 (76.2)	1170 (81.1)	894 (82.6)	1154 (88.6)	< 0.001
DGF = yes (%)	Pre	28919 (24.9)	1440 (31.0)	139 (25.3)	756 (30.8)	< 0.001
	Post	13468 (29.2)	496 (34.4)	222 (20.5)	284 (21.8)	< 0.001

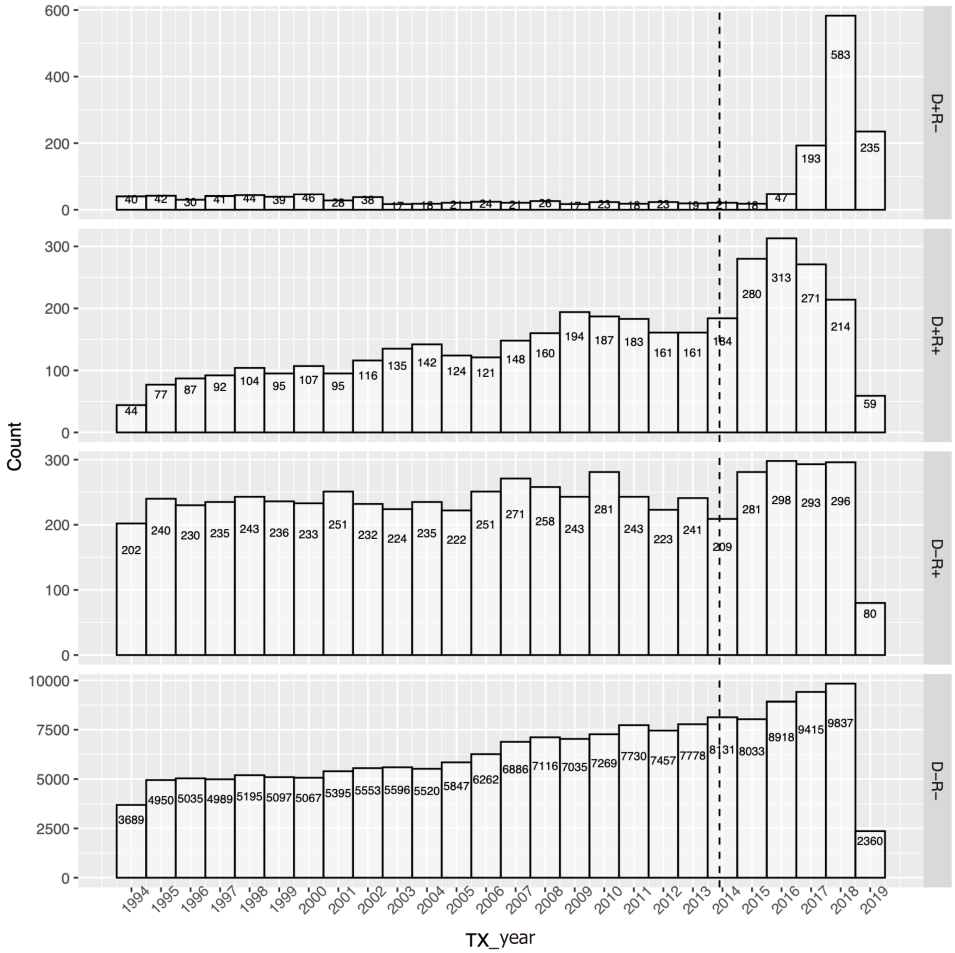
D(-/+) R(-/+), hepatitis C virus (-) or (+) donors into hepatitis C virus (-) or (+) recipients. CIT: Cold ischemia time; DGF: Delayed graft function; HLA: Human leukocyte antigen; IQR: Interquartile range; Pre: Pre-direct-acting antivirals era; Post: Post-direct-acting antivirals era; TX: Transplantation.

Table 4 Patient survival and death-censored graft survival at 3 years in the pre-direct-acting antivirals era and the post-direct-acting antivirals era

Cohorts in comparison (%)			D-R+	D+R+	D-R-	D+R-	Absolute risk difference
Crude	Patient survival	Pre	86.7 (85.8, 87.7)	84.8 (83.4, 86.3)	89.6 (89.5, 89.8)	73.1 (69.4, 76.9)	-
		Post	88.1 (85.7, 90.5)	89.8 (87.7, 92)	91 (90.6, 91.3)	86.1 (77.6, 95.6)	-
	Death-censored graft survival	Pre	84.2 (83.1, 85.3)	82 (80.4, 83.6)	88.8 (88.6, 89)	80.1 (76.6, 83.7)	-
		Post	92.4 (90.6, 94.2)	94.2 (92.5, 96)	92.5 (92.2, 92.8)	92.6 (87.3, 98.3)	-
D+ *vs* D- in R+	Patient survival	Pre	86.3 (84.4, 88.2)	84.8 (82.8, 86.8)	-	-	3.3 (1.8, 4.7)
		Post	90.2 (85.5, 95)	88.7 (84, 93.7)	-	-	2.7 (-2.9, 8.1)
	Death-censored graft survival	Pre	83.6 (81.5, 85.8)	81.6 (79.4, 83.9)	-	-	3.1 (1.2, 5)
		Post	90.1 (85.5, 94.9)	92 (87.9, 96.3)	-	-	0.4 (-5, 6.1)
D+ *vs* D- in R-	Patient survival	Pre	-	-	85.3 (82.3, 88.4)	73.5 (69.8, 77.4)	8 (5.2, 10.9)
		Post	-	-	89.1 (83.6, 94.9)	88.6 (81.6, 96.2)	-0.3 (-5.9, 6.1)
	Death-censored graft survival	Pre	-	-	86.9 (83.9, 89.9)	80.4 (76.8, 84.1)	7.4 (4.3, 10.5)
		Post	-	-	92.2 (87.8, 96.8)	93.8 (88.5, 99.4)	-2.3 (-7.4, 2.1)
R+ *vs* R- in D+	Patient survival	Pre	-	80.9 (77.3, 84.6)	-	76.7 (72.8, 80.7)	0.1 (-2.9, 3.1)
		Post	-	88.4 (84.3, 92.8)	-	85.1 (75.4, 96)	1.1 (-6.1, 7)
	Death-censored graft survival	Pre	-	79.4 (75.5, 83.5)	-	80.6 (76.9, 84.6)	1.2 (-2.5, 4.9)
		Post	-	93 (89.6, 96.5)	-	92.3 (86.2, 98.8)	0.7 (-5, 5.4)
R+ *vs* R- in D-	Patient survival	Pre	86.7 (85.8, 87.7)	-	88.7 (87.8, 89.6)	-	2.6 (1.9, 3.2)
		Post	88.1 (85.7, 90.5)	-	89.5 (87.3, 91.8)	-	-0.5 (-3.3, 2.2)
	Death-censored graft survival	Pre	84.2 (83.1, 85.3)	-	86.5 (85.5, 87.5)	-	3.5 (2.6, 4.4)
		Post	92.4 (90.6, 94.2)	-	92.1 (90.2, 94.1)	-	-0.2 (-2.4, 2)
D+R+ *vs* D-R-	Patient survival	Pre	-	85 (83.4, 86.5)	89 (87.7, 90.4)	-	5.3 (4.3, 6.4)
		Post	-	88.4 (85.5, 91.4)	91.8 (89.2, 94.4)	-	3.3 (0, 6.7)
	Death-censored graft survival	Pre	-	82.7 (81, 84.4)	87.8 (86.4, 89.2)	-	7.1 (5.7, 8.5)
		Post	-	93.3 (90.9, 95.8)	93.3 (90.9, 95.8)	-	1.7 (-1.4, 4.5)
D+R- *vs* D-R+	Patient survival	Pre	85.4 (82.1, 88.8)	-	-	75.6 (71.6, 79.7)	5.4 (2.6, 8.6)
		Post	88.7 (81.8, 96.3)	-	-	91.5 (85, 98.6)	3.2 (-5.9, 11.6)
	Death-censored graft survival	Pre	84.5 (81.1, 88.1)	-	-	81.1 (77.3, 85.1)	4.8 (1.4, 8.2)
		Post	94.4 (89.3, 99.7)	-	-	93.3 (87.4, 99.5)	2.5 (-3.6, 10)

D(-/+) R(-/+), hepatitis C virus (-) or (+) donors into hepatitis C virus (-) or (+) recipients. Pre: Pre-direct-acting antivirals era; Post: Post-direct-acting antivirals era.

appreciation of DAA effects in decreasing HCV+ kidney risks[12]. DGF was reduced in D+R- transplants, despite the longest CIT and higher HLA mismatch compared with other cohorts in both the pre- and post-DAA eras, which could be the result of lower DCD rates and other unmeasured donor factors. In the pre DAA-era, HCV+ in either the donor or recipient of HCV- kidneys was associated with poorer PS and DCGS, but donor HCV+ status impacted PS and DCGS moreso than did recipient HCV+ status. Additionally, donor plus recipient HCV+ (D+R+ *vs* D-R-) and donor infection in HCV- recipients (D+R- *vs* D-R-) displayed the largest absolute increase in mortality and DCGF. Importantly, the risks on PS and DCGS associated with HCV+ in donors and/or recipients were no longer statistically significant after the widespread adoption of DAA in 2015, except for a marginally significantly impaired PS in



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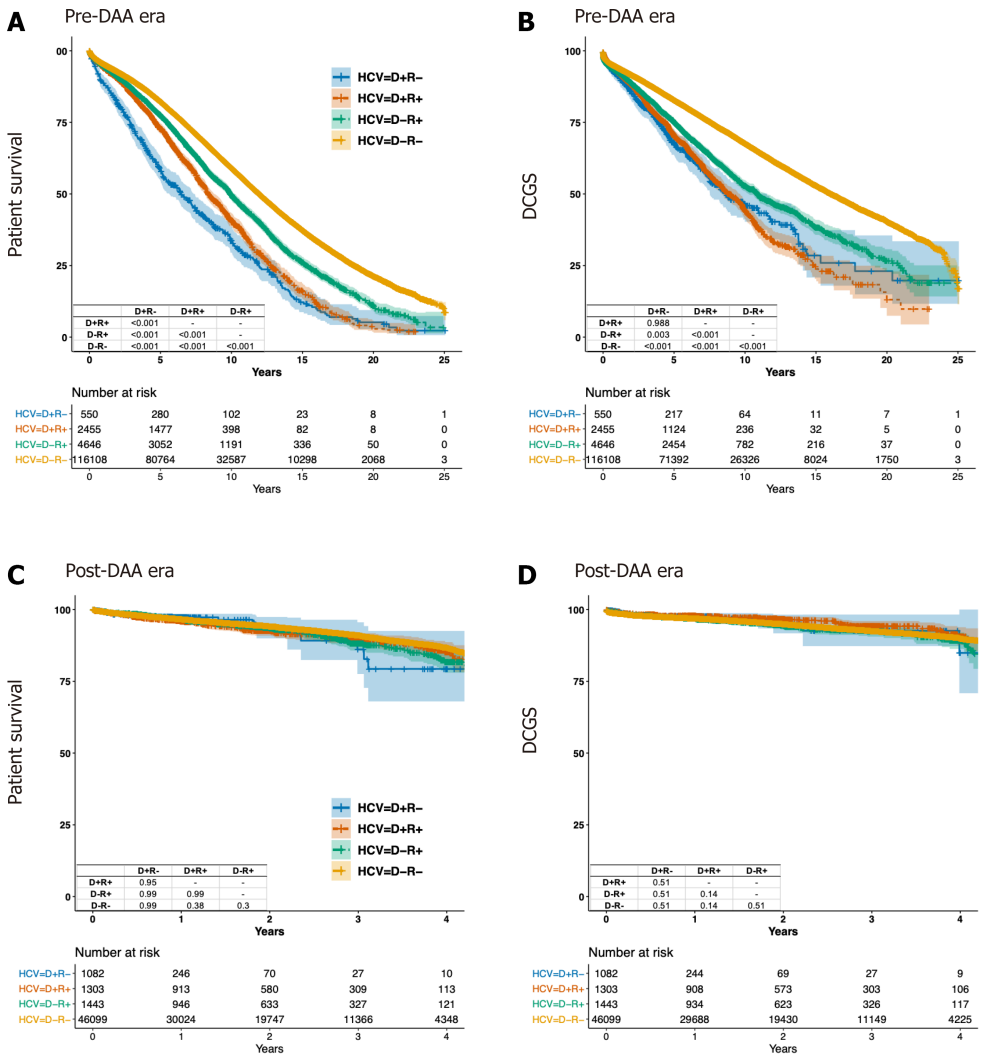
Figure 2 Yearly distribution of the kidney transplantation stratified by hepatitis C virus status in donor and/or recipient. Numbers of kidney transplants performed each year from January 1994 and March 2019 were plotted and stratified into four groups according to hepatitis C virus infection in the donor or recipient: D-R-, D+R-, D-R+, and D+R+.

D+R+ *vs* D-R-, which possessed the largest risk difference in the pre-DAA era.

The presumed risks of viral transmission in HCV+ transplants made these transplants scarce in the pre-DAA era (< 50 annually D+R-)[13-15]. DAAs encouraged broader acceptance of HCV+ candidates and more aggressive utilization of HCV+ kidneys. Two pilot trials in 2017 and 2018 of HCV+ kidney transplants into HCV- recipients found that, despite inevitable HCV transmission, subsequent DAA therapy provided HCV cure in a cost-effective approach that also resulted in well-functioning allografts [16,17]. Similarly, our observational study shows equivalent outcomes between D+R- and D-R- cohorts in the DAA era.

Many studies evaluated the effect of donor HCV+ on KT outcomes prior to the introduction of DAA [13-15], with HCV+ KT improving survival among all patients when compared to staying waitlisted and not receiving a kidney[2]. A single-center analysis summarizing 1990-2007 data compared long-term D+R+ outcomes to D-R+, showing that HCV+ donor status in HCV+ recipients did not significantly influence mortality, graft failure, or liver disease[14]. However, 1995-2008 national registry data showed D+R+ patients had a 2.6-fold higher hazard of joining the liver wait-list ($P < 0.001$). Nonetheless, the absolute risk difference in subsequently listing for liver transplant was < 2% between recipients of HCV+ and HCV- kidneys[15]. A recent study using 2005-2017 data reported that among HCV+ recipients, receiving an HCV+ kidney was associated with 19% higher mortality (aHR, $_{1.07}1.19_{1.32}$), an effect that disappeared in the DAA era[5]. Our study evaluated the HCV effect of donor separately in HCV+ recipients and HCV- recipients and found similar trends of donor HCV associated PS and DCGS impairment in both recipients groups. with both mortality and DCGF absolute risk differences being larger in HCV- than HCV+ recipients (Table 4).

Two meta-analyses have evaluated the effect of recipient HCV+ status on KT outcomes[18,19], finding HCV+ correlated with increased mortality (aHR: $_{1.49}1.85_{2.31}$, $_{1.33}1.69_{1.97}$) and graft failure (aHR: $_{1.46}1.76_{2.11}$, $_{1.22}1.56_{2.00}$). However, neither distinguished donor HCV status. Our study found that the effect of recipients' HCV+ status was dramatically modified by the donor's HCV status—recipient's HCV+ only impaired transplant outcomes when receiving an HCV-, but not HCV+, kidney. This finding parallels

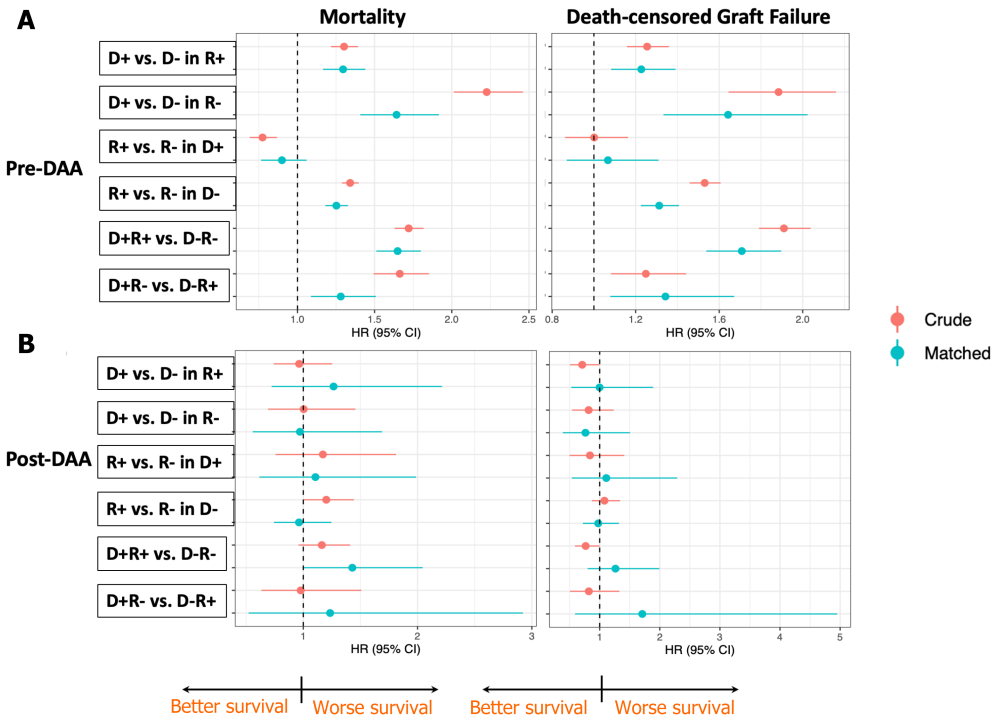


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Figure 3 Crude patient survival and death-censored graft survival among four cohorts in the pre- and post-direct-acting antivirals eras. Survival was presented in Kaplan-Meier curves and analyzed by log-rank tests. Multiple comparison was adjusted by Bonferroni correction. A: Crude patient survival in the pre-direct-acting antivirals (DAA) era; B: Crude death-censored graft survival (DCGS) in the pre-DAA era; C: Crude patient survival in the post-DAA era; D: crude DCGS in the post-DAA era. DAA: Direct-acting antivirals; HCV: Hepatitis C virus; DCGS: Death-censored graft survival.

our previous study analyzing outcomes of transplanting the same donor's pair of kidneys to one HCV+ and to one HCV- recipient[20].

There are several limitations to our study. First, most D+R- patients received transplants in the DAA era with relatively short follow up. Dividing the dataset into pre- and DAA eras resulted in smaller sample sizes. Second, PSM use to eliminate confounders between comparator groups could be biased by unmeasured potential confounders, including HCV genotype, viral load, infection duration and severity, graft rejection, and immunosuppression intensity, none of which is found in the used registry data. Third, we lack viremia data—while most viremic patients are antibody positive, a small portion of antibody positive patients are aviremic. We defined HCV+ by antibody status prior to 2015, and by antibody and NAT results since 2015. Antibody positive aviremic donors or recipients were included as HCV+ in both eras' analyses, and a miniscule fraction of viremic patients who are antibody negative would have been included in the HCV- cohort in the pre-DAA analysis. Including these patients would yield worse outcomes in the uninfected population, underestimating the difference observed between infected and uninfected groups. Fourth, the registry data does not verify DAA treatment. Fifth, we used a pair matching method to estimate the "average treatment effect in the treated." Some exposed subjects were excluded from the matched sample because of no available unexposed subjects within the specified caliper distance of the exposed subjects. There might be potential bias generated when unmatched exposed subjects differ systematically from the matched exposed subjects[21]. Other statistical methods, including full matching or inverse probability weighting, with the aim to include all the samples in both groups in comparison could also result in biased estimation due to increased heterogenicity within each group. Lastly, we used single imputation for variables with missingness over 1 percent. Limited impact was found on the magnitude of the hazard ratio or the significance of the



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Figure 4 Relative risk of mortality and death-censored graft failure in six pair-wised comparison in the pre- and post-direct-acting antivirals eras. Four groups of patients classified by hepatitis C virus infection in the donor or recipient: D-R-, D+R-, D-R+, and D+R+, were compared pair-wisely before and after propensity score matching. Hazard ratio were presented in the forest plot with dot represented the HR and line represented the 95% confidence interval. D+ *vs* D- in R+ represented the relative risk of mortality or death-censored graft failure (DCGF) in D+R+ patients as compared with D-R+ patients. Similar interpretation in the other five pairs of comparison. The dashed line represented HR = 1. Dots located in the right of the dashed line means higher mortality or DCGF (worse survival) compared to the reference group. A: Relative risk in the pre-direct-acting antivirals (DAA) era; B: Relative risk in the post-DAA era. DAA: Direct-acting antivirals.

findings of DCGS and patient survival, with multiple imputation method.

CONCLUSION

In conclusion, although HCV+ in either KT donors or recipients negatively impacted PS and DCGS pre-DAA, neither donor nor recipient HCV+ appears to portend worse outcomes in the DAA era, supporting increased utilization of HCV+ kidneys as the standard of care. Given comparable outcomes across all four patient cohorts in the DAA era, a new allocation algorithm, eliminating HCV+ kidneys' negative influence on the KDRI, is urgently needed to improve utilization and allocation of this under-utilized resource.

ARTICLE HIGHLIGHTS

Research background

While Hepatitis C virus infection (HCV+) kidneys have traditionally been discarded rather than transplanted into HCV- recipients, the introduction of direct-acting antivirals (DAAs) in 2013 revolutionized HCV treatment by consistently achieving sustained virologic responses, opening the door for transplantation of HCV+ organs.

Research motivation

As HCV+ rates in kidney donors and transplant recipients rise, the introduction of DAA may effect transplant outcomes.

Research objectives

To analyze the effects of HCV+ in donors, recipients, or both, on deceased-donor (DD) kidney

transplantation (KT) outcomes, and the impact of DAAs on those effects.

Research methods

The Organ Procurement and Transplantation Network data of adult first solitary DD-KT recipients 1994-2019 were allocated into four groups by donor and recipient HCV+ status. We performed patient survival (PS) and death-censored graft survival (DCGS) pairwise comparisons after propensity score matching to assess the effects of HCV+ in donors and/or recipients, stratifying our study by DAA era to evaluate potential effect modification.

Research results

Pre-DAA, for HCV+ recipients, receiving an HCV+ kidney was associated with 1.28-fold higher mortality (HR $_{1.15}1.28_{1.42}$) and 1.22-fold higher death-censored graft failure (HR $_{1.08}1.22_{1.39}$) compared to receiving an HCV- kidney and the absolute risk difference was 3.3% (95%CI: 1.8%-4.7%) for PS and 3.1% (95%CI: 1.2%-5%) for DCGS at 3 years. The HCV dual-infection (donor plus recipient) group had worse PS (0.56-fold) and DCGS (0.71-fold) than the dual-uninfected. Donor HCV+ derived worse post-transplant outcomes than recipient HCV+ (PS 0.36-fold, DCGS 0.34-fold). In the DAA era, the risk associated with HCV+ in donors and/or recipients was no longer statistically significant, except for impaired PS in the dual-infected *vs* dual-uninfected (0.43-fold).

Research conclusions

Prior to DAA introduction, donor HCV+ negatively influenced kidney transplant outcomes in all recipients, while recipient infection only relatively impaired outcomes for uninfected donors. These adverse effects disappeared with the introduction of DAA.

Research perspectives

Given comparable outcomes across all four patient cohorts in the DAA era, a new allocation algorithm, eliminating HCV+ kidneys' negative influence on the KDRI, is urgently needed to improve utilization and allocation of this under-utilized resource.

FOOTNOTES

Author contributions: Yuan Q and Elias N contributed to study conception and design; Acquisition of data: Elias N contributed to analysis and interpretation of data; Yuan Q, Hong S, Leya G, Roth E, Tsoulfas G, Williams WW and Elias N contributed to analysis and interpretation of data; Yuan Q, Hong S, Leya G, Roth E, Tsoulfas G, Williams WW and Elias N contributed to drafting of manuscript; all authors have read and approve the final manuscript.

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REVIEW

Primary graft dysfunction following lung transplantation: From pathogenesis to future frontiers

Sanjeet Singh Avtaar Singh, Sudeep Das De, Ahmed Al-Adhami, Ramesh Singh, Peter MA Hopkins, Philip Alan Curry

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Abstract

Lung transplantation is the treatment of choice for patients with end-stage lung disease. Currently, just under 5000 lung transplants are performed worldwide annually. However, a major scourge leading to 90-d and 1-year mortality remains primary graft dysfunction. It is a spectrum of lung injury ranging from mild to severe depending on the level of hypoxaemia and lung injury post-transplant. This review aims to provide an in-depth analysis of the epidemiology, patho-physiology, risk factors, outcomes, and future frontiers involved in mitigating primary graft dysfunction. The current diagnostic criteria are examined alongside changes from the previous definition. We also highlight the issues surrounding chronic lung allograft dysfunction and identify the novel therapies available for ex-vivo lung perfusion. Although primary graft dysfunction remains a significant

contributor to 90-d and 1-year mortality, ongoing research and development abreast with current technological advancements have shed some light on the issue in pursuit of future diagnostic and therapeutic tools.

Key Words: Primary graft dysfunction; Lung transplantation; Pathophysiology; Risk factors; Extracorporeal membranous oxygenation

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Core Tip: Primary graft dysfunction is spectrum of lung injury ranging from mild to severe depending on the level of hypoxaemia and lung injury post-transplant. It has significant bearings on short and long term mortality and morbidity with chronic lung allograft dysfunction playing a major part. While the pathophysiology remains uncertain, it is felt to be a result of ischaemic reperfusion injury. The contributive factors, risks and treatment and management options are scrutinized in this manuscript to provide the readers with a clear insight into the enigma that is primary graft dysfunction.

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INTRODUCTION

Lung transplantation remains the only definitive treatment for patients with end-stage lung disease due to obstructive lung disease, fibrotic lung disease, vascular lung disease, and other causes (*e.g.*, infection). In highly selective conditions, it may also be used in pulmonary malignancy[1]. The first successful lung transplant procedure was performed in Toronto, 19 years after the first heart transplantation[2]. In the current era, just under 5000 adult lung transplants are performed annually worldwide[3]. Primary graft dysfunction (PGD) after lung transplantation represents a spectrum of lung injury ranging from mild to severe depending on the level of hypoxaemia and lung injury post-transplant[4]. It is characterised by radiographic findings of non-specific pulmonary infiltrates and hypoxaemia. It represents the leading cause of early mortality post-transplantation and phenotypically resembles acute respiratory distress syndrome (ARDS)[4]. Prior to 2005, there was no unified definition for PGD, making it difficult to ascertain a true incidence. Different terms were also used to define the syndrome, indicative of possible pathogeneses, such as ischaemic-reperfusion lung injury, primary non-function of the lung, early graft dysfunction, reperfusion oedema, re-implantation oedema, primary graft failure, post-transplant acute respiratory distress syndrome, acute lung injury and non-cardiogenic pulmonary oedema[5]. There were also significantly variable rates of associated risk factors and mortality indicating the need for a consensus definition[6-8].

It is a major cause of early morbidity and mortality at 90-d (up to 23%) and 1 year (up to 34%)[9]. Diagnosis initially relied on the degree of hypoxaemia but has since been updated to primarily be reliant on chest radiograph findings and the degree of support required[10].

INTERNATIONAL SOCIETY OF HEART AND LUNG TRANSPLANTATION 2005 AND 2016 STATEMENT

In 2005, the International Society of Heart and Lung Transplantation (ISHLT) published a standardised definition of PGD. In summary, the assessment was performed by evaluating the PaO_2/FiO_2 (P/F) ratio and the presence of bilateral infiltrates on a chest radiograph. These assessments are carried out at 6 h, 24 h, 48 h, and 72 h post-operatively and should be measured on FiO_2 of 1.0 with positive end-expiratory pressure (PEEP) of 5 cmH_2O.

Radiographic findings of PGD are relatively non-specific including perihilar ground glass opacities, reticular interstitial, and parenchymal opacities, alongside perivascular thickening.

In 2016, an updated ISHLT statement specified a 'start' time for the PGD clock beginning after the removal of the PA cross-clamp of the second lung. The commencement of reperfusion is noted to be T0 with assessments performed at T24, T48, and T72 h as per the 2005 edition. However, the absence of pulmonary oedema on radiographic imaging should be classified as grade 0 regardless of the PaO_2/FiO_2 ratio. This is highlighted in Table 1 below.

Table 1 The International Society for Heart and Lung Transplantation primary graft dysfunction definition and severity grading 2005 and 2016

PGD stage	PaO_2/FiO_2 ratio (mmHg)	Chest X-ray findings	2016 update
0	> 300	Normal	Any P/F ratio
1	> 300	Diffuse allograft infiltration/pulmonary oedema	No changes
2	200-300	Diffuse allograft infiltration/pulmonary oedema	No changes
3	< 200	Diffuse allograft infiltration/pulmonary oedema	No changes

PGD: Primary graft dysfunction.

Another pertinent detail is the inclusion of an adjunct for the PaO_2/FiO_2 ratio due to the high incidence of missing data from the lack of partial pressure of arterial oxygen (PaO_2) measurement using oxygen saturations instead (SaO_2/FiO_2), with different cutoffs of 235 and 315[10].

Despite this, the consensus statement remains a work in progress with several areas requiring further evaluation. For instance, subjects on mechanical ventilation with FiO_2 > 50% or requiring inhaled nitric oxide (iNO) beyond T48 are classified as grade 3 PGD alongside patients on mechanical circulatory support. In addition, the definition has not taken into account the debate of single versus double lung transplantation. In an era of increasing austerity in organ allocation, the need to compare outcomes is of utmost importance and has been highlighted. Oto *et al*[11] identified an increased rate of PGD grade 3 in recipients of single lung transplants compared to bilateral transplants although the authors noted several differences such as protective ventilation strategies in the single lung transplant cohort and earlier extubation times which would invariably affect the PaO_2/FiO_2 ratio. Their study shed some light on the applicability of the current definition, especially in the single lung transplant cohort. Other potential mechanisms for the higher incidence of PGD in single lung transplant recipients include the admixture of poorly oxygenated blood associated with shunting in the native lung, higher cardiac output *via* the relatively lower pulmonary vascular resistance of the graft vasculature, and increased relevance of changes in the unilateral transplanted lung. The use of MCS may also be misleading as the role of 'prophylactic' extracorporeal membranous oxygenation (ECMO) institutions in high-risk recipients may lead to an overestimation of the true incidence of PGD, which raises questions regarding an interventional-based severity grade[12].

EPIDEMIOLOGY

Early reports following the 2005 consensus definition indicated an incidence of around 30% early post-transplant and reduced to just under 20% at T72[8]. However, 10%-20% of these patients contract the severe form, PGD grade 3[8,9]. The higher incidence of PGD reported early on is probably due to the clinical and pathological similarities it shares with reversible pulmonary oedema, ARDS, and transfusion-related acute lung injury (TRALI). Analysis of the United Network for Organ Sharing (UNOS)/ISHLT database (1994-2000) noted a significantly higher all-cause mortality in all PGD *vs* non-PGD comparisons at 30 d (42.1% *vs* 6.1%, $P < 0.001$) and 1 year (64.9% *vs* 20.4% $P < 0.001$)[13]. A subsequent study by Diamond *et al* using the 2005 definition highlighted an overall PGD grade 3 rate of 30.8%, reducing to 16.8% after the exclusion of PGD Grade 3 classifications before T48[9]. Christie *et al*[4] noted increasing mortality with each grade of PGD. This ordinal pattern was present at all time points following the transplant (T24, T48, T72). PGD Grade 3 had the highest mortality which was also replicated in an analysis of biomarkers of insult severity. Many studies have used PGD grade 3 as a dichotomous outcome when discriminating between PGD and non-PGD due to the more distinct features *i.e.*, prolonged mechanical circulatory support, mechanical ventilation with FiO_2 > 50%, iNO or iEPO usage, and PaO_2/FiO_2 ratio < 200, leaving little room for ambiguity.

Given the heterogeneity in the locoregional donor, recipient, and procedural characteristics, ascertaining the true epidemiology of the lesser grades of PGD is slightly more challenging and remains variable. Another important consideration for PGD is the link with chronic lung allograft dysfunction (CLAD). Table 2 shows the phenotypes of CLAD.

CLAD

Bronchiolitis Obliterans syndrome was the term initially coined to describe allograft dysfunction occurring after lung transplantation. Ischaemic reperfusion injury plays a major part in the pathophysiology as highlighted in Figure 1. This syndrome has since undergone several revisions and

Table 2 Basic phenotypes of chronic lung allograft dysfunction

Phenotypes	Spirometry changes	CT opacities
CLAD	Persistent ≥ 20% decline in FEV1 (based on 2 FEV1 values ≥3 wk apart) compared to baseline	
BOS	CLAD and obstruction (FEV1/FVC < 0.7)	No
RAS	CLAD and restriction (≥ 10% decline in TLC from baseline)	Yes
Mixed phenotype	CLAD with obstruction and restriction	Yes
Undefined phenotype	CLAD with obstruction and/or restriction	Yes/No

Adapted from the 2019 Consensus Definition. FVC: Forced vital capacity; BOS: Bronchiolitis obliterans syndrome; RAS: Restrictive allograft syndrome; CLAD: Chronic lung allograft dysfunction; CT: Computed tomography.

refinements with the most recent definition using the umbrella term CLAD highlighting a series of phenotypes post transplantation[14].

According to the 2019 consensus statement, CLAD is defined as a substantial and persistent decline [≥ 20% in measured forced expiratory volume in one second (FEV1)] in the baseline. This is broadly classified into obstructive ventilatory pattern, restrictive, or mixed[14].

The tipping point is the drop in FEV1 with/without a change in the forced vital capacity. Secondary causes should be ruled out such as surgical complications, infections, rejection, and mechanical obstructions (effusions, stenosis, tumours, *etc*)[14]. After investigating, managing, and ruling out the secondary causes, there should be at least 3 wk between the first and 2nd FEV1 readings that indicate the reduction (≥ 20%). The staging of CLAD is also shown in Table 3.

Pathophysiology

The exact pathophysiology behind PGD remains unclear but is thought to be a summation of multiple insults that occur during the procurement, storage, and implantation of the lung. Ischaemic-reperfusion injury (IRI) is thought to be a major contributor to the pathophysiology. Native lungs have a dual vascular supply *via* bronchial vessels and pulmonary circulation, alongside available oxygen from alveolar ventilation. The pathogenic mechanism of IRI in the lungs, therefore, differs from other end organs which are often rendered ischaemic on cessation of blood flow[15]. From an anatomical perspective, there is a change in the vasculature of the lungs post-transplantation. In the native lungs, the airways are supplied by a dual circulation derived from the bronchial arteries and the pulmonary artery[16]. The post-transplant lung has the pulmonary artery circulation surgically restored but the bronchial anastomosis and distal airways may be exquisitely susceptible to further ischemia and hypoxic injury due to the loss of these bronchial arteries.

On a molecular level, IRI is driven but the formation of reactive oxygen species (ROS) (Figure 2). Traditionally, the lung is hypothermically stored to reduce the metabolic oxygen demand - hence reducing the rate of biochemical reactions which results in attenuated degradation of cellular components[17]. Adenosine triphosphate (ATP) stores however continuously deplete, which inactivates the ATP-dependent membrane pumps[15]. This causes accumulation of cytosolic calcium alongside activation of inflammatory pathways causing eicosanoid formation and ROS generation - eventually leading to more inflammation and spiraling escalation of inflammation leading to cell death[18]. IRI also induces necroptosis and apoptosis in laboratory-based studies, which also contribute to ROS formulation *via* accumulation of cytosolic calcium leading to further necrosis of pulmonary epithelial cells[19,20].

ROS GENERATION

During aerobic metabolism, ATP is converted to urea and xanthine by xanthine dehydrogenase. Xanthine dehydrogenase either undergoes reversible sulfhydryl oxidation or irreversible proteolytic modification to form xanthine oxidase[21,22]. This irreversible modification occurs in IRI and breaks down hypoxanthine to ROS during rapid reoxygenation. In addition to the pathway illustrated in Figure 2, ROS is also generated by the NADPH (Nicotinamide Adenine Dinucleotide Phosphate) oxidase system. It is present on the membrane surfaces of phagocytic cells, where NADPH is oxidised to $NADP^+$, releasing an electron into the phagocytic vacuole, where oxygen is reduced to superoxide anions in large quantities[21]. It plays a major role in pathogen killing but may also be aggravated inflammatory diseases[21]. The superoxide anion, hydrogen peroxide, and hydroxyl radical form part of the family of ROS, which damage cellular membranes by lipid peroxidation[22] as shown in Figure 3.

Table 3 2019 chronic lung allograft dysfunction staging from the 2019 consensus definition

CLAD stage	Spirometric values
CLAD 0	Current FEV_1 > 80% baseline
CLAD 1	Current FEV_1 > 65%-80% baseline
CLAD 2	Current FEV_1 > 50%-65% baseline
CLAD 3	Current FEV_1> 35%-50% baseline
CLAD 4	Current FEV_1 ≤ 35% baseline

CLAD: Chronic lung allograft dysfunction; FEV_1: Forced expiratory volume in one second.

The inflammatory pathway is activated by ROS generation which causes a release of proinflammatory cytokines by macrophages. Neutrophils and lymphocytes are therefore recruited to the lung and extravasate into tissues due to increased vascular permeability as a sequalae of the acute inflammatory response[23]. The macrophages and recruited neutrophils generate more ROS alongside non-specific lysis proteins like proteolytic enzymes, lysozymes, and lactoferrin which contribute to cell damage[23]. Leukocytes can also mediate IRI through the elaboration of elastases and proteases, production of inflammatory cytokines, and neutrophil aggregation causing plugging of capillaries and no-reflow phenomena with endothelial damage[24].

ENDOTHELIAL DAMAGE

In addition to the activation of inflammatory pathways *via* neutrophil activation, the pulmonary endothelium also contributes to the pathophysiology of PGD. TNF-α and IL-1β are non-specific pro-inflammatory cytokines that promote molecule adhesion to the endothelial surface. Several processes have been implicated in the propagation of this chemotaxis including upregulation of receptors for advanced glycation end products[25], platelet aggregation[26], and increased levels of intercellular adhesion molecule-1 (ICAM-1)[27]. These promote the migration of macrophages and polymorphonuclear cells into the air spaces in the lungs.

During LIRI, the processes above occur resulting in the extravascular displacement of leukocytes through chemotaxis-induced migration. The reperfusion causes cell depolarization which disrupts the homeostatic mechanisms within the endothelium. Pulmonary artery pressure during reperfusion was shown to have a significant effect on the endothelial wall with an increased likelihood of developing Grade 3 PGD in patients with higher PA pressures in a cohort of patients with idiopathic pulmonary fibrosis (38.5 ± 16.3 mmHg *vs* 29.6 ± 11.5 mmHg for patients without PGD [mean difference, 8.9 mmHg (95%CI: 3.6 to 14.2); P = 0.001][28]. Recipient leukocyte depletion attenuated this effect, implicating the circulating host leukocytes in the pathophysiology as demonstrated by Schnickel *et al*[24]. In addition, some studies have identified the role of donor innate lymphoid cell subsets with some protective against PGD and some associated with PGD[29].

Other studies have also shown that increased left-sided cardiac pressures have a detrimental effect and increase the risk of PGD development, further inculpating the role of endothelial integrity in the pathophysiology. Porteous *et al*[30] noted that preoperative diastolic dysfunction measured by echocardiography increased the risk of Grade 3 PGD. These patients had significantly higher mPAP and pulmonary vascular resistance. Li *et al*[31] noted a similar finding using LVEDP and mPCWP as a surrogate for increased left-sided pressures. The Toronto group highlighted a higher incidence of ECLS use post-transplant in patients with preoperative signs of diastolic dysfunction[32].

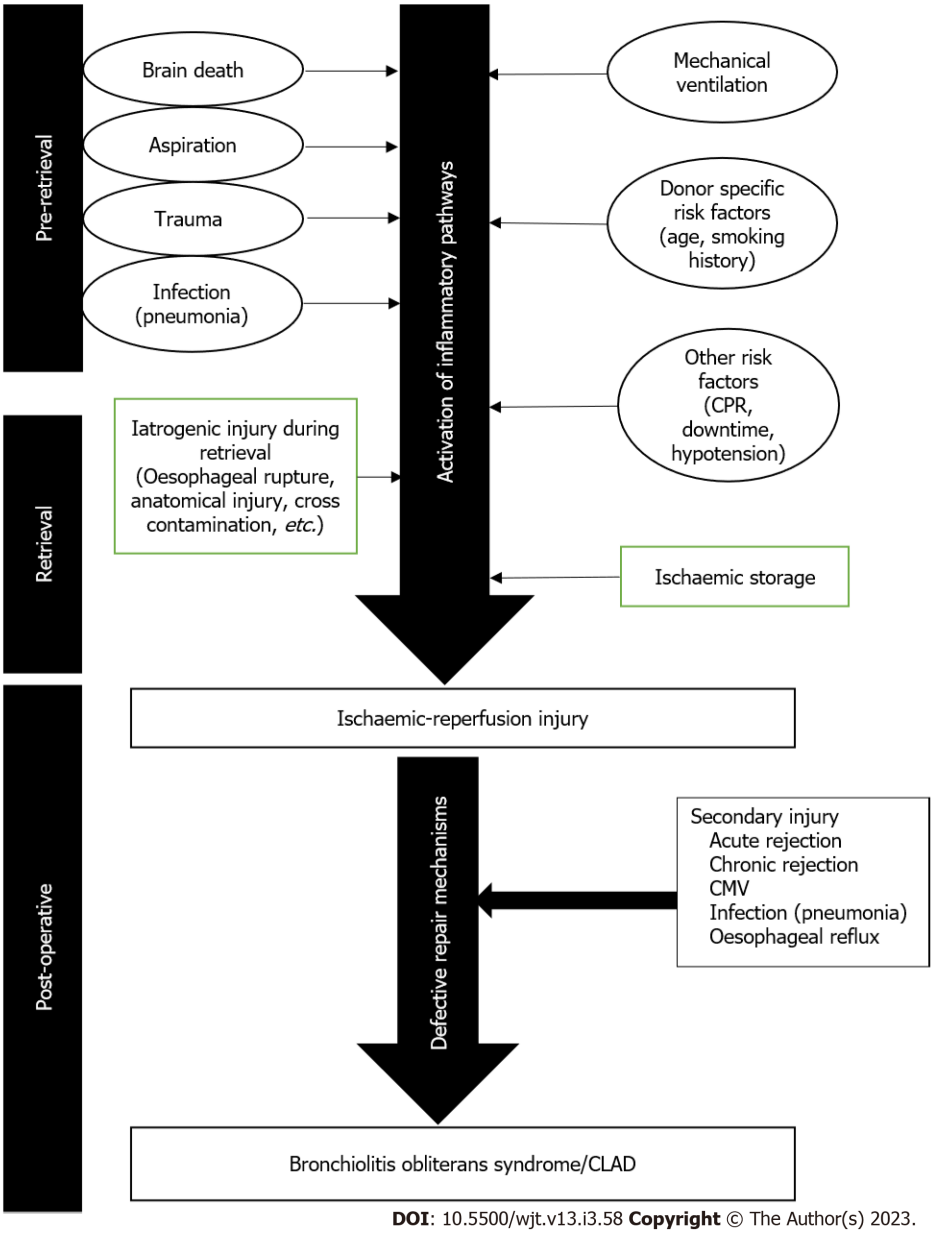
RISK FACTORS

Multiple risk factors have been identified through various studies since the PGD consensus definition. We have identified donor, recipient, and procedural variables as follows.

DONOR-SPECIFIC RISK FACTORS

Donor smoking history

Donor history of cigarette smoking is perhaps the best-reported risk factor of PGD. It has been



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Figure 1 Pathophysiological mechanisms that lead to ischaemic-reperfusion injury and subsequently chronic lung allograft dysfunction.
CLAD: Chronic lung allograft dysfunction.

associated with PGD in multiple studies[8,9,33]. In a large North American multicenter study, a positive donor smoking history was independently associated with PGD[9]. In addition to PGD, the United Kingdom national data revealed inferior post-transplantation survival showed inferior survival by donor history of smoking at 30 and 90 d after transplantation and sustained for up to 3 years post-transplant[34]. In addition, these patients also had a significantly higher perioperative morbidity with longer ICU and in-hospital length of stay[34]. Despite no mention of PGD in the study, one can infer that a high proportion of early morbidity and mortality would be directly related to PGD. The authors however did note that the survival benefit to recipients of smokers' lungs compared to those remaining on the waitlist and waiting for a non-smoking donor[34].

The exact role of smoking in the pathophysiology of PGD remains elusive. Ware *et al* noted that smokers' lungs had a higher incidence of pulmonary edema (408 *vs* 385 g, $P = 0.009$), lower median PaO_2/FiO_2 ratios (214 mmHg *vs* 266 mmHg, $P = 0.02$), higher levels of pro-inflammatory chemokine IL-8 levels, and lower Surfactant Protein D (SP-D) levels but similar rates of alveolar fluid clearance[35]. However, they noted a lower rate of alveolar fluid clearance in heavier smokers (≥ 20 pack-years)[35]. Higher IL-8 levels were also noted by Kuschner *et al*[36] in smokers' lungs *vs* non-smokers' lungs.

Oxidative injury with the generation of ROS may be potentiated by donor exposure to cigarette smoke[37]. Lipid peroxidation is a ROS-mediated chain of reactions that, once initiated, results in an oxidative deterioration of polyunsaturated lipids[38]. Biomarkers of lipid peroxidation such as thiobarbituric acid reacting substances are increased in bronchoalveolar lavage fluid of smokers (both acute

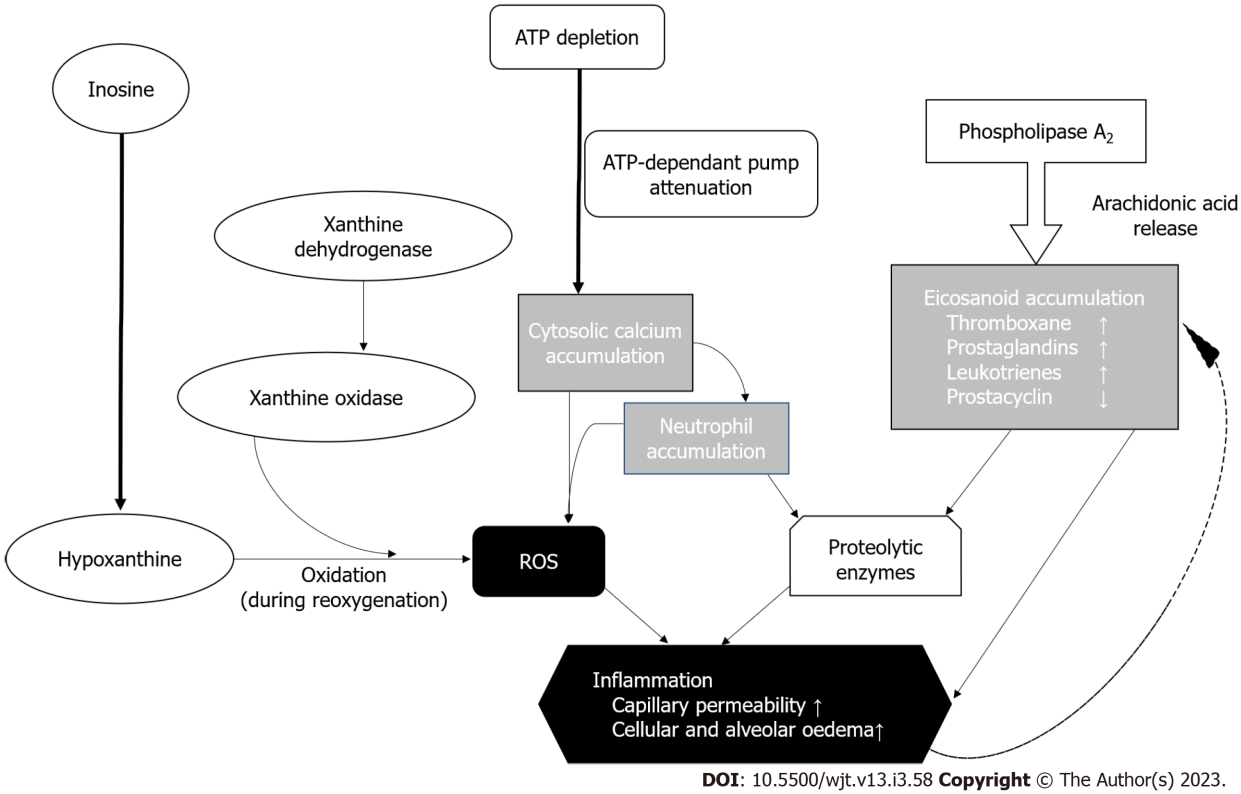


Figure 2 Pathophysiology of lung ischemia-reperfusion injury. ROS: Reactive oxygen species.

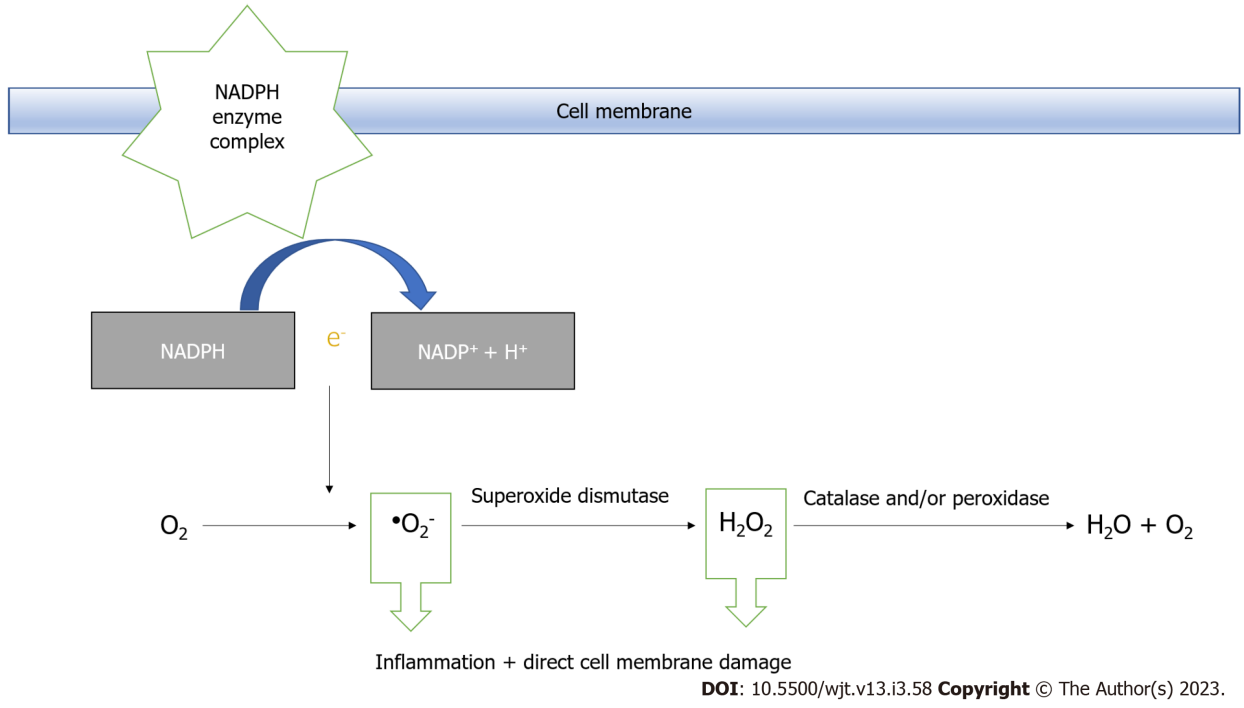


Figure 3 Nicotinamide adenine dinucleotide phosphate oxidase system and the generation of superoxide anion. NADPH: Nicotinamide adenine dinucleotide phosphate.

and chronic) compared to non-smoking controls[39]. It is therefore conceivable that the lungs of smokers are more susceptible to IRI due to the increased accumulation of the byproducts of lipid peroxidation[37].

DONOR ALCOHOL CONSUMPTION

Chronic alcohol consumption has been linked with an increased risk of developing ARDS based on a metanalysis of 17 case-controlled and cohort studies with a total of 177674 patients[40]. Extending this to lungs for transplantation was reproducible in one study which showed 8.7 times greater odds of developing severe PGD following lung transplant compared to recipients whose donors did not consume alcohol after controlling for other variables (P = 0.0190)[41]. However, there was no difference in risk of developing PGD in recipients of donors with moderate alcohol consumption as compared to donors with no alcohol use[41]. The same study also showed worse acute lung injury post-transplant with poorer gas exchange and a trend of poorer survival following transplantation when lungs from heavy alcohol consumers were implanted[41]. Heavy alcohol use in donors was also related to a higher rate of PGD in another retrospective single-center study[42]. Heavy intake of alcohol is also linked with other high-risk behaviors including road traffic accidents, violence[43,44], and self-injuries including suicide attempts[45], thus, at risk of trauma and subsequent brain death, representing a significant proportion of donors. The exact pathophysiology of this is speculative but is probably a combination of poor mucociliary clearance, a degree of epithelial dysfunction, and impaired immune responses in the alveolar spaces which increases the susceptibility to oxidative stressors[41]. There is also evidence that chronic alcohol abuse impairs surfactant production in pneumocytes, impairing the epithelial barrier function[46]. There is also some evidence of glutathione depletion which increases susceptibility to oxidative stressors such as reperfusion injury post-cold ischaemic storage[47]. Animal models have been utilized to demonstrate the effects of modulating ischaemia-reperfusion. In a rat tracheal transplant model, alcohol intake increased inflammatory signaling with transforming growth factor-beta (TGF-β) and interleukin 13 (IL-13), which may induce fibrosis[48].

DONOR AGE

Donor age is a significant risk factor for PGD in other organs such as the heart[49], kidney, liver, and pancreas[50]. Analyzing the American Organ Procurement and Transplantation Network database, Baldwin *et al*[51] noted that there was a higher risk of graft failure at 1 year when using lungs from donors < 18 years old and > 65 years, and echoed by De Perrot[52]. This was not reproduced in other studies by the Pittsburgh group[53] and the Hannover group[54]. The 2016 ISHLT Working Group on Primary Lung Graft Dysfunction Report noted that recent data suggest the age-related risk of PGD is lower than previously believed and restricted to the extremes of ages[8].

PULMONARY EMBOLISM

In the 1990s, 2 case reports were published describing the impact of donor-related pulmonary emboli diagnosed by lung biopsy after transplantation from fat emboli following multiple fractures in a donor for an RTA[55] and cerebral emboli[56] respectively. Oto *et al* showed a significant association between donor pulmonary embolism and PGD in lungs[57]. On multivariate analysis, PGD rates following lung transplantation were 20.6-fold (P = 0.0002) higher with fat emboli and 4.8-fold (P = 0.02) with pulmonary embolism compared with those who received lungs without pulmonary embolism[57]. In a subsequent study by the same authors, emboli were diagnosed using retrograde flushing of the pulmonary arteries at the time of retrieval. They noted that donor death due to trauma with fractures and a smoking history of more than 20 pack-years were significant risk factors for pulmonary embolism [58]. The pathophysiology suggested by the authors is the failure to correct the ventilation-perfusion mismatch by the denervated lung in addition to a localized inflammatory response which may aggravate the IRI. They noted increased interstitial infiltration and opacities on chest radiographs in up to 93% of lungs post-transplantation. However, studies examining donor causes of death have shown no differences between donors with traumatic causes of death *vs* non-traumatic[59].

SIZE MISMATCH

A likely issue that may account for PGD includes lung size mismatch, or specifically undersizing[60]. This is thought to be due to the changes in the pulmonary vasculature and potentially detrimental tidal volumes during mechanical ventilation. The undersized pulmonary vasculature provides increased resistance and thus a higher pulmonary artery pressure at reperfusion which is thought to be a contributing factor. The Lung Transplant Outcome Group noted that donor undersizing (Donor Lung < Recipient Lung) rather than donor sex or race conferred an increased risk as male lungs were generally larger than females[8,60]. A quotient called the predicted donor-recipient total lung capacity ratio (donor pTLC/recipient pTLC) of < 1 was noted as a risk factor for PGD post-bilateral lung trans-

plantation[60]. In addition, a recent study by the Toronto group noted that patients with donor pTLC/recipient pTLC ratio of ≥ 0.8 or < 1.2 for double lung transplantation significantly improved overall survival and CLAD-free survival[61]. This benefit however was not noted in the single lung transplant group.

RECIPIENT SPECIFIC RISK FACTORS

Aetiology of disease

The causative pathology of lung disease has also been implicated as a risk factor for PGD. Diamond *et al*[9] noted that patients with pre-operative sarcoidosis (OR: 2.5; 95%CI: 1.1 to 5.6; $P = 0.03$) or pulmonary arterial hypertension (OR: 3.5; 95%CI: 1.6 to 7.7; $P = 0.002$) were at an increased risk of developing PGD. Pulmonary hypertension is linked to right ventricular dysfunction and the sudden peripheral vascular resistance reduction in the transplanted lungs may result in endothelial shear stressors, further worsening the reperfusion injury. However, similar findings were not noted in patients with cystic fibrosis regardless of pulmonary hypertension based on ISHLT database findings, indicating a disease process rather than the presence of elevated pulmonary pressures may be causative[62]. Fang *et al*[28] noted that secondary pulmonary hypertension in patients with idiopathic pulmonary fibrosis (IPF) was independently associated with PGD development. This could be explained by the progressive nature of the disease and implicate the role of vasoactive mediators (*e.g.*, Endothelin-1, fibroblast growth factor) which have been linked with the pathogenesis of IPF[63]. The restrictive pattern of lung disease may also result in smaller-than-predicted total lung capacity. This causes progressive changes to the chest wall which may result in poorer graft function due to the irreversible mechanics of remodeling within the recipient's chest wall to accommodate the 'shrinking' lung[64,65].

Body mass index

A raised body mass index (BMI) was previously shown to be a risk factor for prolonged ICU length of stay and mortality in lung transplant recipients[66,67]. Diamond *et al*[9] also conducted a large cohort study and showed a direct relationship between a raised BMI and PGD. Specifically, the odds ratio for developing PGD increased to 1.8 for BMI 25-30 and 2.3 for BMI > 30.

This may be directly related to the technical surgical challenges in obese recipients alongside the inflammatory milieu produced during IR. Leptin is a protein encoded by the obese gene located on human chromosome 7[68]. It is classically noted to be a hormone due to its effects in regulating food intake and energy exposure. In addition, it is also a member of the type 1 cytokine family. Other conditions such as type II diabetes are associated with hyperleptinemia and acquired resistance to signaling through the leptin receptors[69]. Serum levels of leptin are directly correlated to BMI and are increased in sepsis and ARDS, suggesting a pathogenic contribution[70]. A study by Jain *et al*[71] showed that lung leptin levels were increased in mice with acute lung injury. The Lung Transplant Outcomes Group then published data on over 500 patients who underwent transplantation for either COPD or ILD indicating a higher risk for PGD in patients with higher plasma leptin levels. In their study, the graphical depiction showed a stark increase in the risk of PGD with an inflection point noted just above 10 ng/mL. The associations between leptin and PGD were stronger when the cardiopulmonary bypass was not used[72]. The role of other modulators such as resistin and adiponectin have been postulated in the past from work done in animal models but have yet to be translated into clinical practice[73].

Previous pleurodesis or pleural diseases

In humans, two pleurae (visceral and parietal) line the thoracic cavity and lungs. The pleurae are serous membranes that fold back onto themselves to form a two-layered membranous structure with a small amount of pleural fluid which plays a role in transmitting movements of the chest wall to the lungs during respiration[74]. Pleural symphysis or pleurodesis is a commonly performed procedure for the treatment of pneumothoraces and effusions. The team at the University of Pittsburgh noted that patients with prior pleurodesis had the highest incidence of severe PGD, alongside other early post-operative complications such as re-exploration for bleeding, phrenic nerve injury, chylothorax, and respiratory complications[75]. Although the post-operative rate of other complications was also increased in patients with prior thoracic surgery, the increased rate of PGD was specific to pleurodesis alone. On multivariate analysis, they noted an increased risk of death post-transplant in patients with prolonged cardiopulmonary bypass (CPB) time, chemical pleurodesis, and high transfusion requirements (> 20 units). The technical challenges intraoperatively due to the multiple adhesions post pleurodesis, combined with heparinization during CPB contribute to the high transfusion requirements, making elucidation of the exact pathophysiological mechanism difficult. The Harefield group noted that recipients with pleural disease defined as pleural thickening, plaque, or fibrosis either confirmed on a computed tomographic scan during assessment for transplantation or detected intraoperatively at the time of the transplantation, had worse 3-mo mortality and a trend toward poorer 30-d mortality despite similar CPB usage, albeit with significantly higher transfusion rates[76].

Extracorporeal life support as a bridge to transplant

The use of extracorporeal life support (ECLS) preoperatively increases the risk of PGD postoperatively [77,78]. While the use of ECMO for treatment for severe PGD is well established, its use preoperatively as a bridging strategy to transplantation has been condemned in the past due to poor outcomes[79]. Analysis of the UNOS database in 2012 identified that only 1.3% of patients transplanted were bridged with ECMO[80]. Unadjusted survival of these patients was significantly worse compared to non-bridged recipients[81]. The increased acuity and deconditioning of these recipients due to the inability to mobilize and multiple pre-transplant interventions potentially creates a hostile environment for the donor graft[82]. It should be noted that the current devices used for ECLS last longer and are less prone to malfunctioning (improved oxygenators and circuits)[83]. Center-specific outcomes also denote improved survival with ECLS pre-transplant in larger, more experienced centers with similar survival outcomes to non-bridged patients reported, supporting its use in the current era[84,85].

PROCEDURAL

ECLS during implantation

Lung transplantation can be performed with or without ECLS. CPB was the traditional method for intraoperative cardiopulmonary support to permit low-pressure reperfusion in cases of severe pulmonary arterial hypertension, failing oxygenation, poor hemodynamic tolerance, or acute bleeding from major vessels[86]. Caveats of the use of CPB include its proinflammatory effects and the associated complications of full systemic heparinization[86]. Other techniques that are now more commonly used to avoid the use of CPB include transplantations with the use of ECMO support or transplantations with single lung ventilation without ECLS[86].

In most institutions worldwide, ECLS is reserved for patients who cannot tolerate single-lung ventilation, complex patients, or those who become haemodynamically unstable during the procedure. ECMO has, by and large, replaced CPB in this setting. CPB has been linked with the activation of cytokines, leukocytes, and the complement cascade alongside a higher transfusion requirement and postoperative coagulopathy probably secondary to the higher levels of anticoagulation required[62,86]. Several reasons have been cited such as the increased blood-activating surfaces present in the CPB tubing, venous reservoir, oxygenator, and cardiotomy compared to ECMO circuits which are closed circuits, without venous reservoirs or additional cardiotomy suction thereby eliminating the air-liquid interface and avoiding blood being washed and returned[87]. Newer ECMO systems have increased biocompatibility by using heparin-coated tubing with polymer-coated centrifugal pumps and oxygenators, permitting prolonged usage pre and post-transplant with limited metabolic derangement [87]. When CPB was used, patients had longer intubation times, higher rates of PGD, and reduced survival[62]. However, it should be noted that the use of CPB is also often linked with adverse donor-recipient characteristics, which may not directly infer causality. A metanalysis comparing the use of ECMO and CPB highlighted that CPB was more likely used in patients with severe pulmonary hypertension, increased risk of intraoperative bleeding, and combined cardiac defects[86].

Moreover, in a recent Austrian study, Hoetzenecker *et al*[88] compared bilateral lung transplantations performed without ECLS with those performed with the routine use of intraoperative ECMO support. The authors favoured central venoarterial ECMO intraoperatively and converted it to peripheral femoral venoarterial cannulation postoperatively if this was deemed necessary. They reported improved 1-, 3-, and 5-year survival compared to non-ECMO patients (91% *vs* 82%, 85% *vs* 76%, and 80% *vs* 74%; log-rank $P = 0.041$) along with a trend towards a reduced incidence of grade 2 and 3 PGD in the intraoperative ECMO group. The authors attribute these findings to the ability to ventilate patients with low tidal volumes and low ventilation pressures (protective ventilation conditions) during the implantation of the second lung, hemodynamic stability even with extensive heart manipulation, and shorter operation times by reducing unnecessary hands-off periods.

Ischaemic time and donation after circulatory death

Ischaemic time has been shown to be a risk factor for PGD in multiple studies for other solid organs[89-91]. The link between ischaemic time and PGD in the lungs, however, is slightly less prominent. Multiple studies have published conflicting findings in this respect[92-95]. One reason for this could be due to the variability in reporting ischaemic times across the different centers[96]. Thabut *et al*[92] noted that prolonged ischaemic time led to increased tissue oedema and poorer 30-d survival. Snell *et al*[97] noted that in their series in the early 90s, ischaemic times exceeding 5 h led to poorer survival ($P = 0.02$, hazard ratio: 3.44, 95%CI: 1.12 to 9.8). Gammie showed no differences in early survival and late (3-year) survival with increased ischaemic time[98]. A recent Swedish study noted that there were early differences in outcomes with increasing ischaemic times alongside increased mortality of up to 24% within 5 years for every 2 h of ischaemic time increment[99].

The lungs also have shown to be less affected by ischaemia compared to the other organs as noted by the good outcomes of lungs procured in donation after circulatory death (DCD)[100]. There is also a probable threshold ischaemic time for the development of ischaemic reperfusion injury which is

dependent on both warm and cold ischaemic times. Conflicting results may therefore be attributed to the variable definitions of ischaemic time which is even more variable in the DCD cohort[101]. Although DCD donors (Maastricht Category III) are not affected by the catecholamine surge and inflammatory milieu after brainstem death, they are exposed to several different ischaemic insults. After the withdrawal of life-sustaining therapy (WLST) during the process of procurement, the donor becomes hypoxemic and hypercarbic. The functional warm ischemia time ensues after WLST when the systolic blood pressure is less than 50 mmHg, with some centers also utilizing the oxygen saturations < 70% as a cut-off. There is then a universal stand-off period of 5 min before organ retrieval commencement[102]. This warm ischemia is associated with intracellular acidosis, activation of the Na^+/H^+ exchanger causing accumulation of intracellular Ca^{2+} worsening IRI. Reducing warm ischemia remains challenging during DCD lung procurement.

A bronchoscopic examination is usually performed and any aspiration is suctioned while the retrieval is happening. As the perfusion fluid is delivered, cyclic ventilation is performed to evenly distribute the preservation fluid followed by inflation to about 50%-75% of the lung capacity and a retrograde flush. Rat model studies have shown that inflation of the lungs with oxygenated air ensures the integrity of pulmonary surfactant alongside improved epithelial fluid transport[103,104]. Healey *et al*[105] recently published a case series of uncontrolled DCD donors and noted no PGD in their cohort, probably signifying a degree of tolerance towards ischaemia. Another study showed an increased incidence of PGD early on, but similar rates at 6 h onwards between DCD and DBD lungs[106]. The Harefield group had a similar finding with an increased PGD incidence in their propensity-matched analysis in the DCD group[107]. One reason to explain this could be the lack of assessments and optimization in DCD donors compared to DBD donors[108]. A metanalysis from 2015 showed similar outcomes from DCD and DBD lung donations[109]. It should be noted that DCD lungs remain an underused resource and are still growing with preservation techniques for other organs such as the thoracoabdominal normothermic regional perfusion and ex-vivo lung perfusion (EVLP) postulated to increase its use[110].

Polytransfusion

A metanalysis highlighted polytransfusion of blood products to be a risk factor for PGD[62]. Although the exact relationship remains unclear, it is probably a combination of increased technical difficulty which invariably results in increased transfusion requirement[111], a degree of TRALI[112], a result of a significant IRI resulting in an ARDS type presentation or systemic inflammatory response (SIRS)[25]. Each of these has been implicated and may play a role in accentuating the severity of IRI. In addition, the need for transfusion shares some co-linearity with other risk factors such as primary pulmonary hypertension and the use of CPB[62]. Therefore, it is difficult to elucidate whether this occurs due to causality or as a response to the abovementioned insults. The transfusion of red blood cells (RBC) alone is associated with increased mortality in a study in Zurich[113]. RBC transfusion is also associated with an increased amount of soluble receptors for advanced glycation end products (sRAGE), which is a marker of alveolar epithelial injury[25]. On the other hand, intraoperative use of fresh frozen plasma has been shown to increase mortality[113], albeit these were more often used in sicker patients[114].

Timing of surgery

In 2018, a multicenter group published a unique study that highlighted an increased risk of PGD in lungs reperfused between 0400-0759[115]. Following the pilot study of 25 patients, a larger retrospective cohort study of 563 patients revealed a significantly increased risk of PGD (OR: 1.12, 95%CI: 1.03 to 1.21; P = 0.01) on univariate binary logistic regression and OR: 1.299, 95%CI: 1.004 to 1.681; P = 0.046 on multivariable binomial logistic regression. There were no differences in ischaemic times or operation lengths although they could not directly account for operator fatigue. The authors attributed the results to 'internal desynchrony between donor and recipient as a result of organ preservation' The circadian clock oscillations were thought to play a part in this and using a mouse model, the authors showed delayed oscillation for lungs that were kept in cold storage compared to lungs maintained at 37 °C. The authors highlighted the role of the clock protein, REV-ERBα which has previously been studied for its role in regulating neuroinflammation[116], and poorer outcomes following cardiac surgery[117]. We currently know that the nuclear receptor REV-ERBα is involved in the cell-autonomous mammalian circadian transcriptional/translational feedback loops as transcriptional repressors and hence indirectly mediates regulation of metabolic, neuronal, and inflammatory functions including bile acid metabolism, lipid metabolism, and production of inflammatory cytokines[118]. In an animal model, Cunningham *et al*[115] noted that in a panel of PGD biomarker gene expression was repressed by a synthetic REV-ERBα ligand. Conversely, 6 out of 7 biomarkers in this panel however demonstrated increased expression of macrophages in REV-ERBα knockout mice[115]. Though it is of interest, its current role remains limited to experimental research, although the introduction of normothermic ex-vivo perfusion devices may change the timing of the surgical aspect of transplantation.

Retransplantation

The association between PGD and re-transplantation is not well established with some centers highlighting no differences in the rates of PGD compared to primary transplants[119,120], but others

generally highlighting poorer survival outcomes especially if used in patients with severe PGD at the primary transplant[119,121,122]. Outcomes were also similar in single or bilateral lung transplantation during the re-transplant irrespective of the primary transplant[123]. The true incidence of PGD in the re-transplant setting is perhaps under-represented due to the higher incidence of secondary causes which include chest wall bleeding due to significant adhesions, coagulopathy, and infections, all of which preclude a diagnosis of PGD[119].

TREATMENT AND PREVENTION

Treatment of PGD is primarily supportive with the exception of severe PGD which requires circulatory support (ECMO). The challenge with PGD is usually establishing a diagnosis as mild and moderate PGD (Grade II and III) may often be mistaken for other conditions such as pulmonary oedema, TRALI, or superimposed infection. Treatment management is therefore directed at managing the ARDS-type picture.

Lung protective strategies and low tidal volume ventilation

The target tidal volume for low tidal volume ventilation (LTVV) is usually 4-8 mL/kg calculated based on predicted body weight (PBW)[124]. This is calculated using the following formula for

PBW males = 50 + 0.91 (centimeters of height - 152.4)

PBW females = 45.5 + 0.91 (centimeters of height - 152.4)

It is performed using a volume-limited assist control mode and the plateau pressure is usually kept below 30 cmH_2O with PEEP which usually starts at 5 cmH_2O and is titrated upwards. The ventilation should be set at ≤ 35 breaths/min to mimic the baseline minute. It is important to reassess the patient and increase or decrease tidal volume based on the plateau pressure. A summary of the Acute Respiratory Distress Syndrome Network trial on LTVV settings is included in Table 4.

The reasoning behind LTVV is lower tidal volumes may attenuate some of the alveolar overdistension and the release of inflammatory mediators induced by mechanical ventilation[124,125]. The ARDS network trial noted that patients randomized to the LTVV group had a lower mortality rate *vs* the control group (TV ≥ 12 mL/kg PBW) (31% *vs* 39.8%, $P = 0.007$) and more ventilator-free days within the initial 28 d (12 ± 11 d *vs* 10 ± 11 d, $P = 0.007$)[124]. A Cochrane review noted a reduction in 28-d mortality (27.4% *vs* 37%, RR: 0.74, 95%CI: 0.61 to 0.88) and in-hospital mortality using LTVV for ARDS compared to normal ventilation (34.5% *vs* 43.2%, RR: 0.80, 95%CI: 0.69 to 0.92)[126]. Evidence regarding volume-controlled *vs* pressure-controlled ventilation remains controversial in the management of patients with ARDS[127]. Protective lung ventilation strategies are advocated for PGD given its similarities with ARDS[125]. Its role may also be extended to donors with the group in Missouri identifying donor lung-protective ventilation with a tidal volume protocol of 6 to 8 mL/kg of donor ideal body weight and plateau pressure < 30 cmH_2O with lower incidence of PGD[128].

Reperfusion strategies

During reperfusion, the ischaemic lung is suddenly exposed to the recipient's circulation whereby there is rapid recruitment of neutrophils and ongoing propagation of ROS which as described above, results in a cascade of events heralding a viscous cycle of oxidative stress with increased vascular permeability and pulmonary hypertension[18]. Rapid reperfusion is also associated with mechanical stress failure of the alveolar/capillary barrier[129].

Hence altering the reperfusion process is a strategy to enervate PGD. The UCLA group utilized a modified reperfusion strategy by using buffered leukocyte-depleted blood and reperfused at the pressure of < 20 mmHg before cross-clamp release and noted a reduction in IRI in their cohort[130]. Leukocyte depletion has since been utilized with EVLP in several animal models with similar outcomes [131,132].

Diamond *et al*[9] noted that the odds ratio for PGD increased by 10% for every 10% increase in FiO_2 at the time of reperfusion. However, it should be noted that this may have been a response to poor oxygenation during reperfusion, hence implying an association rather than causality. However, to date, no studies have been conducted examining FiO_2 at reperfusion as a risk factor for PGD.

Inhaled NO usage

NO has been investigated as a therapeutic option for the prevention or treatment of PGD due to its pulmonary vasodilatory effects[133]. Given the effect of pulmonary hypertension, NO is believed to attenuate the effects of reperfusion. There is however a lack of randomized studies showing the survival benefit of the ubiquitous use of NO in treating PGD. Benefits noted from studies with ARDS did not result in improved mortality[134]. Moreno *et al*[135] published the only clinical study which elucidated a reduction in PGD by inhaled NO administration. The authors noted a significantly lower incidence of PGD in the iNO group *vs* the control group (17.2% *vs* 45%) ($P < 0.035$) alongside significant reductions in IL-6 (in blood at 12 h), IL-8 (in blood and BAL at 12 and 24 h), and IL-10 (in blood at 12 and 24 h and BAL at 24 h)[135]. In Moreno's study, iNO was commenced at the beginning of surgery and continued

Table 4 Oxyhemoglobin saturation and positive end-expiratory pressure combinations for low tidal volume ventilation in managing acute respiratory distress syndrome by the Acute Respiratory Distress Syndrome Network[124]

Arterial oxygenation and PEEP	
Target Oxygenation PaO_2 = 55-80 mmHg (7.35-10.7 kPa)or O_2 saturations (SpO_2) = 88%-95%	
FiO_2/PEEP combinations	
FiO_2 (%)	PEEP (H_2O)
30	5
40	5-8
50	8-10
60	10
70	10-14
80	14
90	14-18
100	18-24

PaO_2: Arterial oxygen tension; SpO_2: Oxyhemoglobin saturation; PEEP: Positive end-expiratory pressure; FiO_2: Fraction of inspired oxygen.

for 48 h postoperatively. Similar findings were noted by Yerebakan in their cohort with a similar length of iNO administration[136]. Other studies have not shown similar outcomes with the caveat that iNO was used either before reperfusion or at the beginning of the case and not as prolonged as Moreno's group[137]. The beneficial effects of NO may be transient and therefore not result in reductions in mortality[138]. Current evidence does not support the widespread routine use of NO for PGD prevention, although these studies were underpowered to detect minuscule differences in outcomes[12].

Prostaglandin E1

Prostaglandin E1 (PGE1) causes similar vasodilatory effects on pulmonary circulation and may therefore improve oxygenation. In addition, it may also play a role in attenuating IRI by reducing the expression of certain mediators such as IL-12 and TNF-α and increasing the expression of IL-10, an anti-inflammatory mediator[139]. The use of PGE1 has been proven in ARDS with improvements in oxygenation and reduction in PA pressures[12]. Hypotension was also a key feature in the metanalysis. Several studies have noted the benefits of using injected PGE1 during organ retrieval in transplantation. The Pittsburgh group noted an improvement in long-term survival following a change in their protocol in 1994 to include PGE1 addition to the graft preservation fluid[140]. Similarly, a group from Taipei noted that the addition of PGE1 to preservation fluid during pulmonary artery flushing resulted in the increased attenuation of IRI[141].

Inhaled prostacyclin analogue (PGI_2)

As with PGE1, iloprost is a prostacyclin analogue that primarily functions as a pulmonary vasodilator. In addition to the benefits of PGE1, PGI_2 also plays a role in inhibiting neutrophil adherence to improve endothelial integrity[142] and in reducing platelet aggregation[143]. Animal model studies have also shown some benefit in ameliorating IRI[144,145]. However, its use in the treatment and prevention of PGD is limited to a single retrospective study by Lee *et al*[143]. In a propensity-matched analysis, patients who were administered inhaled iloprost immediately after reperfusion of the grafted lung had significantly lower severity of pulmonary infiltration on postoperative days (PODs) 1 to 3 compared to the non-intervention arm. The PaO_2/FiO_2 ratio was also significantly higher in the treatment group compared to the control group (318.2 ± 74.2 mmHg *vs* 275.9 ± 65.3 mmHg, P = 0.022 on POD 1; 351.4 ± 58.2 mmHg *vs* 295.8 ± 53.7 mmHg, P = 0.017 on POD 2; and 378.8 ± 51.9 mmHg *vs* 320.2 ± 66.2 mmHg, P = 0.013 on POD 3, respectively). Finally, PGD3 prevalence was significantly lower on POD1 [2 (6.7%) *vs* 9 (30%), P = 0.042], POD2 [1 (3.3%) *vs* 8 (26.7%), P = 0.026] and POD3 [0 (0) *vs* 6 (20%), P = 0.024]. It should be noted however there was a higher rate of PGD1 (mild) in the iloprost arm of the study on all 3 d[143]. Larger prospective studies are needed to validate the above findings.

Surfactant

The surfactant depletion theory is another potential pathogenetic mechanism of PGD. In a prospective open-label randomized study, a study based in Israel investigated the role of surfactant therapy post bronchial anastomosis[146]. The authors noted that patients who received surfactant had improved mean PaO_2/FiO_2 (418.8 ± 123.8 mmHg *vs* 277.9 ± 165 mmHg, P = 0.004) post-operatively, lower PGD

grades (0.66 *vs* 1.86, $P = 0.005$), fewer cases of severe PGD (1 *vs* 12, $P < 0.05$)[146]. The same group then published a case series of 5 patients with severe PGD treated with surfactant instead of ECMO[147]. They noted a significant improvement in PaO_2/FiO_2 ratios within h of treatment (pretreatment mean PaO_2/FiO_2 *vs* post-treatment PaO_2/FiO_2 (98.8 ± 21.7 mmHg *vs* 236.8 ± 52.3 mmHg, $P = 0.0006$) who were still alive 6 mo post-treatment.

ECMO

ECMO is usually reserved for PGD grade 3 refractory to medical treatment. Outcomes post-ECMO are better with early initiation (< 24 h)[12,148]. The use of Veno-Venous ECMO (VV-ECMO) is currently preferred over Veno-Arterial ECMO (VA-ECMO) if the patient is haemodynamically stable due to the complications attributed to VA-ECMO[12]. The Pittsburgh group noted survival after both VV-ECMO and VA-ECMO were similar at 30 d, 1 year, and 5 years (58% *vs* 55%, $P = 0.7$; 42% *vs* 39%, $P = 0.8$; 29% *vs* 22%, $P = 0.6$)[149]. The Duke group noted that their VV-ECMO patients had better survival and medium-term outcomes, with all VV ECMO patients were successfully weaned from ECMO support, but only 50% (7 of 14) of the VA ECMO survived weaning ($P = 0.02$). The 30-d graft and patient survival for the VV ECMO group was 87.5% *vs* 0 in the VA-ECMO group[150]. In a subsequent study, the same group noted their VV-ECMO survival to be 82% at 30 d, 64% at 1 year, and 49% at 5 years which is arguably better compared to the previous report[151]. The poor outcomes for VA-ECMO are probably multifactorial, ranging from the severity of the SIRS response which necessitated VA-ECMO in the first place to the genuine complications attributed to VA-ECMO. Peripheral VA-ECMO has significant limb ischaemia complications reported to be around 16.9% (95%CI: 12.5% to 22.6%) with a 10.3% risk of fasciotomy or compartment syndrome (95%CI: 7.3% to 14.5%) and lower limb amputation rate of 4.7% (95%CI: 2.3% to 9.3%)[152].

The incidence of neurologic complications for VA-ECMO was 13.3% (95%CI: 9.9% to 17.7%), acute kidney injury, 55.6% (95%CI: 35.5% to 74.0%) with almost half requiring renal replacement therapy [95%CI: 46.0% (36.7% to 55.5%)][152]. The risk of bleeding complications in VA-ECMO is 46.0% (95%CI: 36.7% to 55.5%) with re-exploration for bleeding or tamponade reported around 41.9% (95%CI: 24.3% to 61.8%) alongside a significant infection rate of 30.4% (95%CI: 19.5% to 44.0%) in the post-cardiotomy cohort alone[152]. The risks of the above in the post-transplant setting have not been noted *via* a metanalysis but one can only assume the risks of renal impairment and infections to be higher with the administration of immunosuppressive medications.

Delayed chest closure

Delayed chest closure (DCC) was initially thought to be a marker for PGD with one study identifying patients with increased CXR changes as being at risk for DCC[153]. It is perhaps a surrogate marker for prolonged CPB usage, challenging intraoperative conditions, and polytransfusion. The Pittsburgh group showed no increased mortality in this group despite the increased PGD incidence, potentially indicating that DCC may be of benefit in these sub-select groups of patients as long as the skin closure method was applied[154]. They noted that acute lung oedema, oversized grafts, and coagulopathy were the most common reasons for DCC followed by haemodynamic instability. The authors noted that improved the haemodynamics and physiology of lung allografts especially when LPVV with high PEEP was utilized [154]. There is a delicate balance between the physiological and haemodynamic benefits *vs* the loss of the barrier function against infections, particularly in an immunosuppressed patient[154].

Aprotinin

Aprotinin is a nonspecific serine protease inhibitor that has shown evidence of attenuating ischemia-reperfusion lung injury by inhibiting the inflammatory response and suppressing NADPH oxidase [155]. Using a rat model, the team from Tokyo noted that by using aprotinin in the flush preservation solution during organ retrieval, and 18-h lung preservation at 4 ℃ followed by normothemic reperfusion with blood, the malondialdehyde (MDA) and IL-8 levels in the lung tissue after reperfusion were reduced in the aprotinin group. The aprotinin-treated lungs also showed significantly better oxygenation throughout the reperfusion period[155]. This preservative effect of aprotinin was also confirmed by the prevention of an increase in peak airway pressure in aprotinin group. They highlighted 2 key issues which were: cold ischemic preservation followed by reperfusion results in interstitial edema and neutrophil extravasation into alveoli, secondly, aprotinin prevented these pathological changes[155]. Similar outcomes were reproduced from 2 other animal model studies[156-158]. Bittner *et al* and the Leipzig group then translated this into a clinical study whereby 59 patients were managed perioperatively with aprotinin infusion using a historical cohort for comparison[159]. Despite advancing donor age in the aprotinin group and longer ischaemic times, the incidence of post-transplant reperfusion injury was markedly lower than in the historical cohort[159]. There were however several limitations to their study including the use of a historical cohort, alongside the multiple interventions used by the team during the aprotinin study, namely iNO usage, and controlled reperfusion.

Prone ventilation

Prove ventilation involves the delivery of mechanical ventilation with the patient in a prone position [160]. The oxygenation is improved due to improved lung perfusion and reduced lung compression [161]. It is a technique that is used as part of the lung-protective strategy to improve survival in severe cases of ARDS with some studies showing improvements, especially in the COVID-19 pandemic[162, 163]. Its role in lung transplantation however is slightly more limited due to the incision sites which tend to be *via* sternotomy or clamshell for bilateral lung transplants although posterolateral thoracotomies can also be performed. A team in Padua, Italy, utilized high-frequency percussive ventilation (HFPV) along with proning to good effect in 3 patients with infiltrates on CXR[164]. They noted a gradual improvement in the clearance of secretions without needing endotracheal intubation in all 3 of their patients. They also noted that HFPV accommodated volume distribution without overinflating compartments with low time constants thus potentially having a protective role against alveolar hyperinflation[164].

EVLP

Prior to EVLP, 4/5 of donor lungs expressed some degree of potential injury therefore not considered suitable for transplantation, limiting the donor pool[165]. Another major limitation of transplantation is prolonged cold storage during transport and its perceived effects on IRI[166]. Normothermic ex vivo lung perfusion is a novel way of organ preservation, evaluation, and potential reconditioning of donor lungs. EVLP allows for perfusion of the donor lungs using an ex vivo circuit (Figure 4).

There are currently 3 EVLP protocols that have been described, the Lund protocol, the Organ Care System protocol, and the Toronto protocol. The differences between the protocols are highlighted below in Table 5.

There are several EVLP kits available that differ in size, function, and portability. The specifics of these are outwith the remit of this review. EVLP was initially used by Steen *et al*[167] for the first human lung transplant using a DCD lung assessed by EVLP and the first successful lung transplant of an initially unacceptable donor lung reconditioned ex vivo in 2000. This proof of concept was then expanded to prolong the EVLP time up to 12 h[168] by the Toronto group. The usage of an acellular perfusate as per the Toronto Protocol is to mitigate the haemolysis of RBCs which may in itself precipitate IRI with the release of pro-inflammatory cytokines[169]. Haemolysis of RBCs also causes results in increased plasma volumes of AGEs (advanced glycation end-products), a finding noted in oxidative conditions and is associated with disease severity inflammatory conditions[170]. Since then, numerous trials have been conducted to show equivocal results to that of cold storage. This includes the NOVEL lung[171], HELP[165], and INSPIRE[172]. The HELP trial showed an increased rate of PGD at 72 h in lungs that underwent EVLP but this did not meet statistical significance (15% *vs* 30.1%; 95%CI: −2.6% to 32.8%; $P = 0.11$) although the study was not powered to calculate differences in PGD. Severe PGD rates were similar in both arms[165]. The NOVEL lung trial noted a higher number of severe PGD cases in the EVLP group [EVLP *vs* Control (21.4%, $n = 9$ *vs* 9.5%, $n = 4$), $P = 0.2$] although this study too was not powered for PGD outcomes[171]. Survival in both studies was similar between the groups. The UK-based DEVELOP-UK study indicated a higher rate of early severe PGD in the EVLP arm, but rates of PGD did not differ between groups after 72 h[173]. The requirement for ECMO support was higher in the EVLP arm than in the standard arm [(7/18, 38.8%) *vs* (6/184, 3.2%), $P < 0.001$][173]. The study however was concluded early and non-inferiority analysis of survival could not be performed. The EXPAND study was a single-arm trial that studied the role of EVLP using the Organ Care System Lung for procurement of extended-criteria donor lungs from brain-death donors, and donors after circulatory death, which are seldomly used for transplantation. The primary efficacy endpoint was a composite of patient survival at day 30 post-transplant and absence of primary graft dysfunction grade 3 (PGD3) within 72 h post-transplantation[174]. The authors chose a prespecified objective performance goal (OPG) of 65% based on a PGD3 within the initial 72 h post-transplant rate of 30.8% (95%CI: 28.2% to 33.3%) for standard-criteria donor lungs as noted by Diamond *et al*[9]. The primary effectiveness composite endpoint of patient survival at day 30 post-transplant and no PGD3 within the initial 72 h was achieved in 43/79 patients (54%) and did not meet the prespecified OPG[174]. When investigating this, they noted a perceptibly high rate of PGD3 of 44% (35/79 patients) within 72 h. At 72 h, post-transplantation, the severe PGD rate dropped to 6% (5/79) and moderate or severe PGD rate of 16% (13/79) which were comparable to the control group in INSPIRE[174]. These findings were also noted in the DEVELOP-UK study where the baseline severe PGD rate was 88.9% and dropped to 27.8% at 72 h [173].

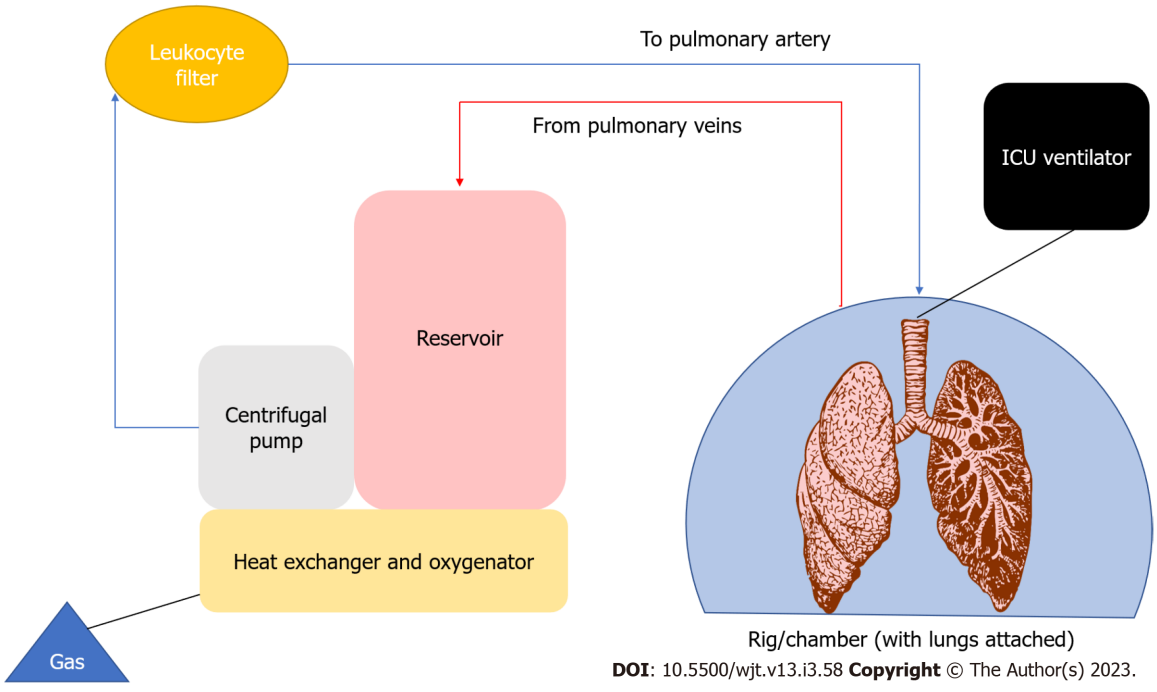
There is a disproportionate number of severe PGD cases following DCD procurement and EVLP. This could be a result of the prolonged functional warm ischaemic time as described above. Another explanation could be the 48% rate of CPB usage in the EXPAND trial (38/79 recipients).

It should be noted that despite the rate PGD associated with EVLP at the time of writing, these were lungs that were unlikely to be used. Given the 98.7% (78/79 patients) 30-d survival rate of lungs transplanted in the EXPAND study, EVLP has a major role to play in expanding the donor pool for lung

Table 5 Differences between the *ex-vivo* lung perfusion protocols

Description	Lund	OCS	Toronto
Year	2001[176]	2011[222]	2008[177]
Perfusion parameters			
Perfusate	CellularSteen solution + RBCs	CellularOCS proprietary solution + RBCs	AcellularSteen solution
Target haematocrit	14%	15%-25%	N/A
Target flow	100% cardiac output	2.0-2.5 L/min	40% cardiac output
PA pressure	≤ 20 mmHg	≤ 20 mmHg	Flow dictated (usually < 15 mmHg)
Left atrium	Open	Open	Closed
Flow type	Continuous	Pulsatile	Continuous
Ventilation			
Initial temperature	32 °C	34 °C	32 °C
Tidal volume	5-7 mL/kg	6 mL/kg	7 mL/kg
Respiratory rate	20/min	10/min	7/min
FiO_2	50%	12%	21%
PEEP	5 cmH_2O	5-7 cmH_2O	5 cmH_2O

FiO2: Fraction of inspired oxygen; RBCs: Red blood cells; PEEP: Positive end-expiratory pressure; OCS: Organ Care System.



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Figure 4 Example of an *ex vivo* lung perfusion circuit. ICU: Intensive care unit.

transplantation[174]. It remains a viable avenue for studies on preconditioning, attenuation, and mitigation of IRI in the near future.

FUTURE HORIZONS

Given our current understanding of PGD and the role of IRI in its pathogenesis, several experimental studies have been conducted to attenuate these. The search for a biomarker however remains elusive. Several biomarkers have been suggested including RAGE, plasminogen activator inhibitor-1 (PAI-1)

[175], IL-8[176], endothelin-1 (ET-1)[177], ICAM-1[27], proadrenomedullin (proADM)[178], and several others have been mooted but none have made the transition to routine clinical practice. A list of studied biomarkers is available in Table 6.

Shah *et al*[179] utilised a panel of biomarkers to improve the predictive value for PGD and survival by using a combination of biomarkers derived from the alveolar epithelium (sRAGE, SP-D), coagulation cascade proteins (PAI-1 and protein C), and vascular endothelium (ICAM-1). Ongoing research is needed to improve discriminatory value for PGD to allow better resource provision for these patients in the intensive care setting.

Stem cell therapy

EVLP has allowed therapeutic interventions to donor lungs prior to implantation. Using IL-8 as a biomarker for inflammation, the Toronto group created an animal model using porcine lungs preserved for 18 h followed by 12 h of EVLP conditioning[180]. In the treatment arm, mesenchymal stromal cells were used in the pulmonary artery. They noted a significant reduction in IL-8 levels in the perfusate in the intervention arm compared to the control group. A similar study had also been conducted where by McAuley *et al*[181] whereby lungs that were rejected for transplantation were reconditioned using mesenchymal stromal cell administration into the perfusate in the intervention group increased alveolar fluid clearance in the experimental group compared to the control group. A more recent study also showed using amnion-derived mesenchymal stem cells added to Steen Solution during EVLP resulted in further attenuation of IRI effects thus improving the efficacy of EVLP[182]. Mesenchymal stromal cells also demonstrated IL-10 attenuating properties in an animal model on sepsis[183]. Whilst still at an experimental stage, stem cell therapy may provide tangible treatment options in the near future.

Ischaemic preconditioning

Ischaemic preconditioning (IPC) is an intervention whereby brief intermittent ischaemic episodes are induced interspersed with reperfusion either at the site of interest (IPC) or at a distance from the site of interest (remote ischemic preconditioning, RIPC)[184]. The evidence for IPC or RIPC has resulted in mixed outcomes with favourable results in some studies[185-188] but with little clinical benefit in others [189-191]. Many animal models however have shown a reduction in acute lung injury following IPC or RIPC[192-195]. The Dutch group performed a series of lung transplants using rabbits and a variety of IPC strategies and noted that the lungs that underwent increasing bouts of ischaemic preconditioning had less oedema[196]. The authors hinted at an additional benefit for repeated cycles of IPC[196]. Randomised studies on RIPC in lung resections have shown a decreased incidence of acute lung injury in the intervention group[185,197]. A randomised pilot study was performed by Lin *et al*[198] on 52 patients to study the effects of RIPC using a tourniquet on the lower limb of the recipient and noted no statistically significant differences in PaO_2/FiO_2 ratios or panel of inflammatory markers at different time points. They concluded that there was no significant benefit of RIPC although the incidence of IRI/PGD was lower than expected[198]. In their subsequent publication, the Australian group however noted that RIPC is feasible and despite not reaching statistical significance, they noted a trend to improvements in P/F ratio and PGD grade seen at virtually all time points during the first 72 h after lung transplantation[199]. Given the negligible cost of the intervention, a multicenter randomized study could well highlight whether RIPC has a role in lung transplantation.

Pharmacology

Pharmacological interventions to attenuate IRI have been suggested in recent times.

Adenosine A_2A receptor agonist - regadenoson is a drug that was intended for use for its coronary vasodilatory effects during stress testing in myocardial perfusion scans[200]. Animal models have shown success in using Adenosine A_2A agonists with EVLP in reducing IRI[201-203]. A recently completed Phase I study was also published with no dose-limiting toxicities observed and no mortalities reported[204].

α1-antitrypsin (AAT)- is a plasma proteinase inhibitor that has a protective function for proteolytic enzymes produced by inflammatory cells[205]. In a rat model, lungs primed in AAT had decreased weight and allograft necrosis compared to the control group (primed in albumin highlighting a potential role in ameliorating IRI[205]. When used in addition to lung preservation fluid, reduced the extent of primary graft dysfunction and early neutrophil responses after extended storage for 18 h at 4 ℃ and 4-h reperfusion in another rat model study[206]. Interestingly, there were similar findings in proteinase 3/neutrophil elastase (PR3/NE) double-deficient mice, highlighting a potential pathogenetic pathway[206].

C1-esterase inhibitor (C1-INH) - In ARDS, the blood coagulation contact system and the complement system are activated, leading to capillary leakage and the pathognomic sequalae. Activation of the contact as well as the complement system is regulated by a common inhibitor, C1-INH[207]. A canine model study indicated that C1-INH administration prevented hypoxemia, activation of the complement system, and decreased expression of leukocyte adhesion molecules alongside inflammatory cell infiltrate[208].

Table 6 List of biomarkers that have been used in primary graft dysfunction

Biomarker	Donor/recipient	Timing	Type
RAGE[179]	Donor	Retrieval	Alveolar epithelium
	Recipient	Intraoperative, post-transplant	
PAI-1[175]	Recipient	Post-transplant	Vascular endothelium
Protein C[179]	Recipient	Post-transplant	Vascular endothelium
IL-8[176]	Donor	EVLP	Inflammatory marker
	Recipient	Pre-transplant	
		Post-transplant	
ET-1[171]	Donor	EVLP	Inflammatory marker
ICAM-1[27]	Recipient	Post-transplant	Vascular endothelium
IL-6[135]	Recipient	Pre-transplant	Inflammatory marker
		Post-transplant	
IL-10[135]	Recipient	Pre-transplant	Inflammatory marker
		Post-transplant	
proADM[178]	Recipient	Post-transplant	Vascular endothelium
TNF-α[139]	Recipient	Post-transplant	Inflammatory marker
P-selectin[26]	Recipient	Post-transplant	Vascular endothelium
SP-D[179]	Recipient	Post-transplant	Alveolar epithelium

EVLP: Ex-vivo lung perfusion; proADM: Proadrenomedullin; RAGE: Receptor for advanced glycation endproducts; PAI-1: Plasminogen activator inhibitor-1; ET-1: Endothelin-1; ICAM-1: Intercellular adhesion molecule-1; TNF-α: Tumor necrosis factor-alpha; SP-D: Surfactant protein-D.

The Hannover group initially reported 2 cases whereby C1-INH was used to good effect[207]. They reported their experience in using it in PGD3 patients whereby it was administered in the operating theatre once PGD3 was suspected[209]. When comparing the 3 groups (control *vs* C1-INH *vs* PGD3) ICU stay was longest in the PGD3 cohort and prolonged in C1-INH patients compared with the control group [29 (2-70) *vs* 9 (2-83) *vs* 3 (1-166) d, $P = 0.002$]. The C1-INH-treated-group had a one-year survival of 82.5% which was better than the PGD3 cohort (71.4%)[209].

Gene therapy

The Toronto group described one of the earliest attempts at using adenovirus-mediated gene therapy in 1999[210]. They then successfully demonstrated that the adenoviral-mediated human IL-10 (hIL-10) gene to donor rat lungs 24 h before lung retrieval reduced IRI and improved post-transplant graft function[211]. Following the development of EVLP, they were able to administer the adenoviral-mediated hIL-10 gene intrabronchially with 12 h of EVLP and noted significantly better gas exchange, lower histologic inflammation score, and less interferon-gamma production when compared with non-treatment groups[212]. This will perhaps be an avenue clinical application of gene therapy to optimise donor lungs and improve outcomes post-lung transplantation.

CONCLUSION

PGD remains a life-threatening complication post-transplantation. The pathophysiology is not fully understood but ischaemic-reperfusion injury is almost certainly implicated. Diagnostic criteria make classification easier, however, it is still lacking an encompassing biomarker. Animal models and preclinical studies have played vital roles in helping us understand the pathophysiology and engineer therapeutic options which will hopefully translate to clinical benefits in the near future. The role of EVLP is still in its infancy with multiple conditioning, treatment, and assessment options available for research opportunities to guide our ongoing understanding of this condition.

FOOTNOTES

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MINIREVIEWS

Transitioning of renal transplant pathology from allograft to xenograft and tissue engineering pathology: Are we prepared?

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Abstract

Currently, the most feasible and widely practiced option for patients with end-stage organ failure is the transplantation of part of or whole organs, either from deceased or living donors. However, organ shortage has posed and is still posing a big challenge in this field. Newer options being explored are xenografts and engineered/bioengineered tissues/organs. Already small steps have been taken in this direction and sooner or later, these will become a norm in this field. However, these developments will pose different challenges for the diagnosis and management of problems as compared with traditional allografts. The approach to pathologic diagnosis of dysfunction in these settings will likely be significantly different. Thus, there is a need to increase awareness and prepare transplant diagnosticians to meet this future challenge in the field of xenotransplantation/regenerative medicine. This review will focus on the current status of transplant pathology and how it will be changed in the future with the emerging scenario of routine xenotransplantation.

Key Words: Xenotransplantation; Bioengineered tissues; Pathology; Allograft; Xenograft

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Core Tip: End-stage organ failure is a significant public health problem worldwide. Currently, treatment options are limited and organ shortage for allotransplantation is one of the biggest challenges. Alternative options being explored are xenografts and engineered/bioengineered tissues/organs. These developments will pose different challenges for the diagnosis and management of transplant pathologies as compared with traditional allografts. The approach to pathologic diagnosis of dysfunction in these settings will likely be significantly different. Thus, there is a need to increase awareness and prepare transplant pathologists to meet this imminent challenge in the field of xenotransplantation/regenerative medicine.

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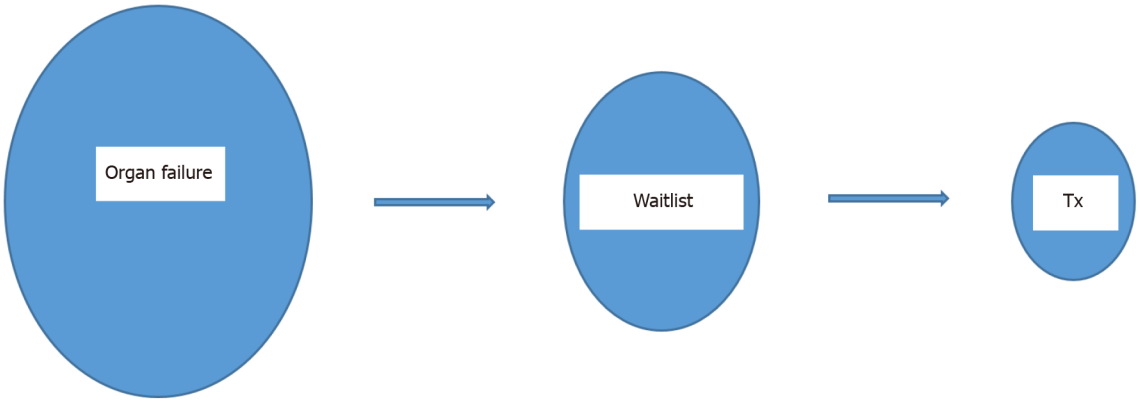
INTRODUCTION

End-stage organ failure of vital organs is one of the leading causes of morbidity and mortality worldwide. Currently, the only treatment or in the case of some organs, the treatment of choice for these patients is the transplantation of those organs. In the United States of America alone, more than 1.2 million people need transplantation for end-stage organ failure; the vast majority of these await kidney transplants. Currently, less than one-third of these succeed in getting transplants with varying rates in different countries, as shown in Figure 1[1-3].

The remarkable success in the progress of solid-organ transplantation in the last few decades of the preceding century is rightly considered a milestone in the history of modern medicine. However, it has not completely met the goals. Many challenges remain to be surpassed and unmet needs to be fulfilled. Currently, the main limitations to the field of transplantation include complications related to lifelong immunosuppression, chronic rejection, and shortage of organs. Among these, the latter is one of the biggest challenges facing the transplant community worldwide. The rejection of transplanted organs, particularly chronic rejection, represents another formidable challenge. Fortunately, the rate of acute rejection has been reduced drastically over the past few decades due chiefly to the development of more potent immunosuppressive agents. However, chronic rejection still poses a big challenge and it remains the leading cause of graft failure worldwide and the dominant indication for second or third transplants. Efforts to prevent or treat it effectively have not been successful till date[4,5].

Against the backdrop of the above facts and challenges, the scientific community has been striving hard to find alternative solutions. The use of animal cells or tissues (xenogeneic) is one of such solutions that could easily reduce the ever-increasing gap between the demand of organs and their supply[6-10]. Although non-human primates are closely related to humans phylogenetically, it is the pig that has been identified as the optimum donor species for xenotransplantation (XenoTx) into humans. The pig kidneys are suited for transplantation in humans on both anatomical and physiological grounds[11,12]. Pig breeding is easy and does not pose major ethical issues, and considerable progress has been made in genetically modifying the animal to improve the acceptance of swine organs. Xenografts from genetically modified pigs have become one of the most promising solutions to the shortage of human organs available for transplantation. The use of organs from such modified pigs together with different methods of inducing tolerance has paved the way to prolonged survival of xenografts, removing the early obstacles that cause hyperacute rejection (HAR) and immediate graft loss[13-17]. Transgenic modifications including knockout of carbohydrate epitopes and additions of the complement cascade and coagulation cascade regulatory proteins have extended the xenograft survival in pig-to-non-human primate transplants of kidneys, hearts, and livers. In addition, improvements in immunosuppressive drugs such as the introduction of mammalian target of rapamycin inhibitors and blockers of co-stimulatory pathways have resulted in better outcomes. However, delayed antibody-mediated rejection and thrombotic microangiopathy (TMA) continue to be the major challenges in the field and need further focused research[18-20].

Regenerative medicine/tissue engineering is another promising field to bridge the existing gaps in transplantation. It can be used to lengthen the lifespan and improve the function of suboptimal donor organs, thereby greatly augmenting the existing donor organ pool, and has the capability to save the remaining vast majority of patients waiting for transplants, by generating or repairing organs. The discipline of regenerative science is older than that of organ transplantation. The first textbook on regenerative medicine was written in 1901. Similarly, a major regenerative science conference was held in 1988, while first Banff renal transplant pathology meeting was held three years later[21]. Contrary to this, the subject of regenerative medicine/tissue engineering pathology (TEP) never received much attention till the recent past[21-25]. In the near future, the discipline of transplantation will expand manifold, through a combination of tissue engineering with the prevalent approaches to decrease the



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Figure 1 Schematic illustration of global estimates of patients with terminal organ failure, waitlist patients, and patients undergoing transplantation. This is only an approximation and not actual numbers. More patients are waiting for kidneys than any other organ.

organ shortage. These new options will bring along with them new challenges in related fields such as pathology and diagnostic fields.

The role of transplant pathology in the diagnosis and management of graft rejection, particularly in the allotransplant setting, cannot be overemphasized. Although it is easy to conceptualize and classify rejection in theory, its diagnosis and classification are not always easy or straightforward in practice. The Banff process was initiated more than 30 years back to standardize the criteria for diagnosing and classifying the rejection process in human allotransplants. Considerable refinements and improvements in the classification system have been made over the last three decades and there are still many unmet needs to be fulfilled[21-25]. However, the Banff group is not oblivious to the developments or progress in the related fields of regenerative medicine/tissue engineering and XenoTx. In fact, the Banff researchers have proposed to create a new Banff classification, tentatively named TEP, to address issues related to the success or dysfunction of engineered tissues/organs[25]. It is also hoped that the Banff group will also address the issues related to standardization of the diagnostic criteria and classification of XenoTx pathology.

Herein, we review the pathobiology of the rejection process in the XenoTx setting and the current status of histopathology in clinical xenoTx, and focus on current results in the pig-to-primate model, as this is thought as the most relevant to human xenoTx. We will briefly review the histological findings in the three recently performed pig-to-human kidney transplants. We will also explore the future challenges and prospects of XenoTx pathology in light of advancements in human transplant pathology. We will not discuss further the topic of TEP, as it is beyond the scope of the present review.

PATHOGENETIC BASIS OF REJECTION IN XENOTX

The major barriers to successful solid organ XenoTx are natural antibodies to carbohydrate antigens, present in pigs but absent in humans and non-human primates, mainly galactose-α-1,3-galactose (Gal), which is produced by the enzyme α-1,3-galactosyltransferase (GT). Bi-allelic GT knockout (GTKO) pigs were used in early protocols of solid organ XenoTx[26-29]. The lifespan of grafts improved, and immediate and accelerated injury to xenografts was overcome. GTKO pigs with further genetic modifications in the form of knockout of two other xenospecific antigens, expressed in pigs but not in humans, termed triple knockout (TKO) pigs, were also used in these experiments. Further multiple transgenic modifications including the addition of human complement regulatory proteins, such as CD46 and CD55, and regulatory molecules of human coagulation cascade have further lengthened the lifespans of xenografts. Suggestions to introduce other transgenes to provide multi-dimensional lines of safety for the xenograft have been put forward, with the aim of countering rejection, coagulopathy, or additional mechanisms of immediate or early xenograft injury[30,31].

Three recent cases of pig-to-human kidney xenoTx utilizing 10 gene modifications in genetically engineered (GE) pigs, termed 10-GE pigs, demonstrate the feasibility of the procedure with no HAR. These were performed in brain-dead human recipients and were terminated at 2 to 3 d post-transplant [32,33]. These have attracted considerable public interest and re-kindled the interest of the transplant scientific community. The pigs used as organ donors in both procedures were produced and supplied by Revivicor, Inc., United States. Revivicor (https://www.revivicor.com/), a subsidiary of United Therapeutics Corporation, uses precise gene editing tools to delete or insert genes in the pig genome. Gene editing is carried out *in vitro* in pig cells cultured in Petri dishes. The cells are screened and analyzed to make sure that the gene editing is accurate. Somatic cell nuclear transfer (SCNT) is then

used to produce pigs from the gene-edited cells. SCNT involves the transfer of a nucleus from a gene-edited pig cell into an enucleated pig egg from which the nucleus has been extruded. The eggs are then transferred to surrogate sows where they develop and grow until natural birth (Figure 2). Revivicor raises the organ donor pigs in a designated pathogen-free facility to eliminate infectious agents that could transmit disease to human transplant recipients. Revivicor received approval from the Food and Drug Administration in 2020 for use of the GalSafe™ pig as a source of food for human consumption, and as a source of human therapeutics (https://www.revivicor.com/).

PATHOLOGIC EVALUATION OF XENOGRAFT AND CURRENT STATUS OF HISTOPATHOLOGY

Histopathology is presently considered the gold standard in the diagnosis of solid organ graft rejection. However, this status of histopathology is subject to certain conditions which must be fulfilled, such as adequacy of sampling and the experience of pathologists. Banff schema of transplant pathology represents a significant scientific effort in the recent past in the field of transplantation diagnostics. Substantial progress has been made in improving the diagnostic criteria and rationalizing the classification of rejection processes in human allografts. This was made possible with continued and concerted efforts by the Banff team and researchers in the transplant field worldwide over the past three decades. However, there are still many unmet needs and challenges in the field, and the Banff process is poised to tackle these in near future[21-24].

The status of histopathology in XenoTx is less developed as compared to its status in allotransplantation (alloTx), principally because there is a lack of extensive literature on this topic. In contrast to alloTx, during the rejection process of a xenograft, the host is likely to use almost the entire armamentarium of its immune mechanisms, encompassing all elements of innate immunity, such as naturally occurring xenoreactive antibodies. In addition, xenograft damage may be caused by mechanisms such as TMA initiated by molecular incongruities in the processes of homeostasis at the surface of the endothelium of blood vessels. Thus, the pathology of xenoTx rejection represents a more complex process and presents a wide variety of histologic features than allograft rejection[32-39]. With multiple transgenic modifications and combinations leading to potentially heterogeneous data in the XenoTx field, systematic study of the xenograft at gross and microscopic levels is crucial. At present, the Banff classification for renal allograft rejection is used by some researchers in some experimental studies [39]. Although the utility of the Banff classification in alloTx is now well-established throughout the world, the pathogenic processes involved in XenoTx and hence the pathologic patterns may be dissimilar. Presently, xenograft pathology classification relates to the diagnostic aspects of rejection, and also reflects, to some extent, the pathomechanisms of rejection. On the other hand, the pathologic evaluation of alloTx rejection provides information not only limited to diagnosis but also on the prognosis and the reversibility of the rejection process with treatment. However, it should be noted that similar to alloTx, histopathology can not be practiced in isolation, but represents a supportive component in the multidisciplinary evaluation of a xenograft[22].

The main focus in earlier Banff classifications of human allograft pathology was on the cellular part of rejection, with the role of alloantibodies relegated to the now obsolete category of HAR[21]. In contrast, in XenoTx, humoral rejection is considered the most important. Accordingly, the classifications have differed in construct and weightage to different categories. More recently, the focus of human allograft pathology has also shifted to humoral rejection beyond immediate and early posttransplant periods[22].

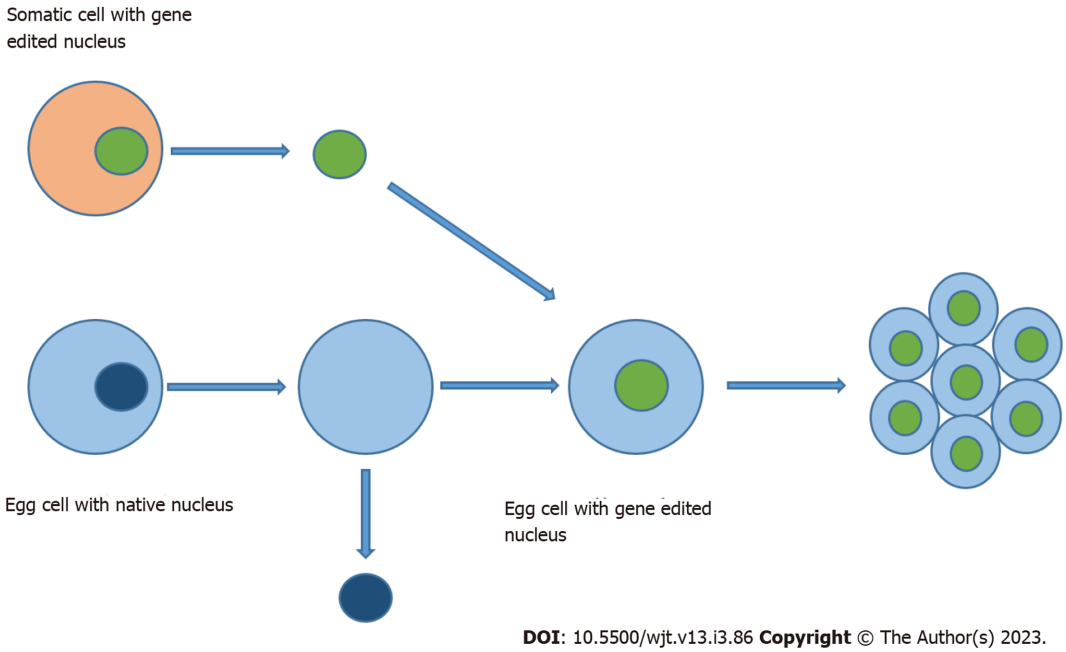
HISTOPATHOLOGIC CLASSIFICATION IN XENOTX

There are very limited studies that report specific morphological features of xenoTx rejection. Since most work on XenoTx has been done with pig-to-non-human primate models, the study of pathologic features has been reported in this setting[34-39]. Most researchers working with these XenoTx models have implemented a simple and mechanistic classification of rejection processes. The current xenograft pathology classification originated at Imutran, Cambridge, UK, in 2002 and has subsequently been used by other researchers as well[40]. Basically, three main diagnostic categories are distinguished: (1) Hyperacute rejection; (2) acute humoral xenograft rejection (AHXR); and (3) acute cellular xenograft rejection (ACXR), as shown in Table 1. As with Banff classification of human allograft pathology, this classification relies not only conventional morphology, but also needs immunofluorescence for immunoglobulin and complement proteins including C4d, and correlation with clinical information, including status of graft function for optimal evaluation and potential significance of pathological lesions[39,40].

Although the xenograft rejection pathology classification primarily relates to pathogenetic rejection mechanisms, each type of rejection incorporates a wide range of cellular and humoral elements of the specific immune system and innate inflammatory mechanisms. It is likely that different histopathologic

Table 1 Classification and diagnostic criteria used in pig-to-primate solid organ transplantation pathology

Hyperacute rejection	Acute humoral xenograft rejection	Acute cellular xenograft rejection
Time period		
Immediately after reperfusion of the graft (typically within 24 h)	Later after reperfusion (after 24 h)	After 3 d
Immediate graft function		
No (no urine since reperfusion)	Yes, urine formation initially	Yes, urine formation initially
Histopathologic features		
Massive hemorrhage; Immunoglobulin and fibrin deposition; Complement (C5b-9) deposition; Presence of neutrophils; Thrombosis, ±	Hemorrhage present; Immunoglobulin and fibrin deposition; Complement (C5b-9) deposition; Presence of neutrophils; Lymphocytes may be present; Necrosis and transmural infiltration by neutrophils in blood vessels can be present; Apoptosis may be present; Thrombosis present	No hemorrhage; Immunoglobulin and fibrin deposition, rare; Complement, ±; Presence of mononuclear (lymphoid) cells associated with tissue destruction (*e.g.*, tubulitis); No thrombosis



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Figure 2 Schematic diagram showing steps involved in somatic cell nuclear transfer. The process involves both *in vitro* and *in vivo* procedures under strict quality control mechanisms.

entities will emerge and the classification will evolve when additional genetically altered animal organs and novel immunosuppressive agents that subdue the immune system are made available. In expectation of this, the proponents of the above classification have kept the nomenclature of the classification schema relatively simple at this stage, leaving room for expansion or modification of the classification in the future, as more data accumulates on this subject[33].

HYPERACUTE REJECTION

HAR entails immediate destruction of the microvasculature and subsequently, the graft parenchyma following reperfusion, resulting in intravascular thrombosis and diffuse interstitial hemorrhage. HAR has, fortunately, become exceedingly rare in human alloTx. In the pig-to-primate model, HAR is mainly caused by the binding of naturally occurring xenospecific antibodies to Gal epitopes exposed on cell-surface glycoproteins and glycolipids of pig organs, followed by activation of the complement cascade. It can be prevented by the removal of naturally occurring anti-Gal antibodies or by chemical inhibition of complement activation. The removal of naturally occurring antibodies can be accomplished by extracorporeal immunoadsorption or these can be neutralized by the intravenous administration of soluble glycoconjugates. Many such conjugates have been tried with variable success rates. Similarly, many agents have been developed and tried that inhibit complement activation. Alternative options include the use of knockout or transgenic animal organs to circumvent this problem. Multi-transgenic

pigs by inserting multiple complement regulatory proteins have been developed in an attempt to augment complement inhibition. More recently, 10-GE pig kidneys have been used in clinical-grade xenotransplants in brain-dead human recipients with promising results[32,33]. However, there were some caveats in these trials, which need to be addressed in the future. Nevertheless, the reports have attracted public attention towards xenotransplantation which, if properly harnessed, should be of significant benefit to future progress. Although the above strategies have successfully overcome the barrier of HAR, a similar but less fulminant type of rejection still develops later and is called AHXR.

AHXR

AHXR, also known as ''acute vascular rejection'' or ''delayed xenograft rejection'', is an important form of antibody (Ab)-mediated rejection in xenoTx setting. The use of the AHXR term was adopted as it more closely represents the potential mechanism of Ab-induced rejection, mediated by the activation of complement pathway and/or infiltration by polymorphonuclear leucocytes. The other two terms either reflect the morphological aspect of rejection or the clinical aspect (delayed rejection) and hence, are better avoided.

The antibodies that cause AHXR can be both naturally occurring xenospecific antibodies, *e.g.*, anti-Gal antibodies in the pig-to-primate and pig-to-human situations, or they may be formed *de novo*. In the former case, AHXR is best considered a delayed form of HAR. In the latter situation, AHXR is due to induced antibodies after sensitization by the graft. The *de novo* antibodies may be directed against Gal or non-Gal antigens.

AHXR is the only type of humoral rejection to occur after Tx of organs between the concordant species, in which setting, HAR characteristically does not develop. The hamster-to-rat solid organ Tx model is the most commonly used such animal model, particularly in studies on immunosuppression or induction of immune tolerance in the presence of the development of sensitization. Among discordant species combinations, discrimination between the roles of pre-formed and *de novo* antibodies in the rejection process is vital for the development of plans to preclude or control the rejection. A few researchers have tried to address this topic but none has been completely successful in discriminating between the roles and significance of natural *vs de novo* antibodies in AHXR.

ACXR

ACXR has been studied to a much less extent than AHXR and hence, detailed accounts of this rejection type are scarcely reported[41]. This is mainly due to the fact these xenografts are usually lost as a result of HAR, which occurs before cellular rejection. In general, ACXR is more or less similar to that observed in human alloTx rejection. Cell-mediated rejection, in isolation, is a comparatively rare occurrence in pig-to-primate solid organ grafts. More commonly, it occurs in combination with AHXR but usually is of lesser intensity than AHXR. Morphologically, the entire range of mononuclear cells, including T lymphocytes (both CD4+ and CD8+ cells), B lymphocytes, and natural killer cells and macrophages, may be present in the interstitium and inside the tubules (tubulitis). Endothelialitis, and in severe forms, transmural vasculitis can be present in cellular rejection.

CHRONIC REJECTION

Chronic rejection is defined on theoretical grounds as the progressive and unremitting destruction of a transplant over months to many years. As one of the major causes of delayed graft failure from human donors, chronic rejection is currently considered as the major obstacle to the long-term success of alloTx. Chronic rejection has not been widely observed in xenoTx because of the generally short survival of xenotransplants and thus remains understudied. With recent developments resulting in prolonged graft survival in xenoTx, the challenge of chronic rejection is more likely to become prominent in the future as the initial barriers are surmounted and graft survival is extended. Currently, the literature on chronic vasculopathies and other chronic xenograft changes is scarce. In a GTKO porcine to baboon discordant xenoTx of hearts, morphological changes of chronic xenograft rejection were reported 78-179 d post-transplantation[42]. As is well described in the literature, in cardiac transplants, chronic rejection is mainly expressed by vascular changes. Hisashi *et al*[42] described four types of chronic xenograft vasculopathy in GTKO pig hearts transplanted into baboons, as shown in Table 2. Among these, fully developed and chronic antibody-mediated rejection-associated vasculopathy types were predominant in graftectomy specimens removed from the gradually weakened group between 78 and 179 d after transplantation. They hypothesized that fully developed vasculopathy was the end-result of combined chronic humoral and cell-mediated rejection-associated mechanisms, as the intimal fibrosis usually followed the infiltration of cells and deposition of fibrinoid material in the arterial intima. On the other

Table 2 Types of chronic xenograft vasculopathy

Type of vasculopathy	Histopathological features
Chronic humoral rejection-associated vasculopathy	Arterial intimal thickening; Presence of TUNEL+ cells; Deposits of fibrin, immunoglobulins (IgG and IgM), and complement components (C3, C4d, and C5b-9)
Chronic cellular rejection-associated vasculopathy	Mononuclear cell infiltration in the neointima; Active endothelialitis; TUNEL+ cells
Combined chronic humoral and cellular rejection-associated vasculopathy	Fibrinoid material deposition and cellular infiltration in the arterial neointima with immunoglobulin and complement deposition and infiltration of T cells, macrophages, and polymorphonuclear leukocytes
Fully developed vasculopathy	Narrowing of arteries with a fibrotic neointima, but without fibrinoid material, or cellular infiltration

TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling.

hand, evidence of chronic cell-mediated rejection-associated vasculopathy or a combination of both chronic humoral and cell-mediated rejection-associated vasculopathy was less frequent. Nevertheless, the precise mechanism by which chronic rejection and vasculopathy are mediated is still incompletely understood.

The relative roles of cellular and humoral immune components along with the roles of soluble serum inflammatory cytokines, such as tumor necrosis factor-alpha, interleukin-6, and interleukin-17, and their antagonists are yet to be fully explored in human recipients of xenografts[43-49]. Contemporary studies have focused on prolonging the graft survival and preventing the causes of early graft loss but future studies are likely to focus on detailed pathologic assessment of prolonged surviving grafts and protocol biopsies for elucidating the pathomechanisms of chronic rejection.

FUTURE PROSPECTS

Although extensive pig genome editing and recent pig-to-human kidney transplants in brain-dead recipients have opened the doors of clinical xenoTx in humans, much remains to be done before this becomes a routine activity. The potential advantages of kidney XenoTx are enormous if the immunological barriers are surmounted. Immunological tolerance to the graft may be easier to induce in models of xenoTx than in alloTx. It is hoped that eventually, XenoTx will compete favorably with alloTx. The recent cases of pig-to-human kidney transplants, albeit in brain-dead recipients, have also provided an opportunity to educate healthcare professionals and the public about xenoTx's potential, as well as its public health risks and logistic and economic implications. Increased public awareness and full transparency during clinical trial planning and execution will be required to generate support for xenoTx trials. Kidney xenoTx pathology will also evolve as the activity in clinical xenoTx increases and the xenograft survival is prolonged. There is abundant opportunity to learn from the evolution of the Banff process of human kidney allograft pathology.

CONCLUSION

Overall, XenoTx pathology is a comparatively new and evolving field of transplant diagnostics. The currently used classification is simple, mechanistic-cum-time based, and flexible. In general, humoral components of the specific immune system and innate immunity play important roles in the immediate and early post-transplant period. These are relatively well reported in the literature and now well controlled, resulting in improved xenograft survival. The transplant obstacles related to the regulation of complement and coagulation cascades due chiefly to species incompatibility and chronic rejection are yet to be investigated and understood. Obviously, with the prolongation of graft survival to years, there is more need of understanding the mechanisms of chronic rejection and to enrich the diagnostic armamentarium for pathologic evaluation. There is a need to increase awareness and train transplant pathologists in this emerging field of transplant diagnostics.

FOOTNOTES

Author contributions: Mubarak M is the sole author of the manuscript, and he conceived and designed the study, performed the research, participated in primary and final drafting, and has read and approved the final manuscript.

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Long-term outcomes of pediatric liver transplantation in acute liver failure *vs* end-stage chronic liver disease: A retrospective observational study

Amr M Alnagar, Abdul R Hakeem, Khaled Daradka, Eirini Kyrana, Marumbo Methga, Karthikeyan Palaniswamy, Sanjay Rajwal, Jamila Mulla, Moira O'meara, Vivek Upasani, Dhakshinamoorthy Vijayanand, Raj Prasad, Magdy S Attia

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Abstract

BACKGROUND

Children with acute liver failure (ALF) who meet the criteria are eligible for super-urgent transplantation, whereas children with end-stage chronic liver disease (ESCLD) are usually transplanted electively. Pediatric liver transplantation (PLT) in ALF and ESCLD settings has been well described in the literature, but there are no studies comparing the outcomes in these two groups.

AIM

To determine if there is a difference in post-operative complications and survival outcomes between ALF and ESCLD in PLT.

METHODS

This was a retrospective observational study of all primary PLTs performed at a single center between 2000 and 2019. ALF and ESCLD groups were compared for pretransplant recipient, donor and operative parameters, and post-operative outcomes including graft and patient survival.

RESULTS

Over a 20-year study period, 232 primary PLTs were performed at our center; 195

were transplanted for ESCLD and 37 were transplanted for ALF. The ALF recipients were significantly older (median 8 years *vs* 5.4 years; $P = 0.031$) and heavier (31 kg *vs* 21 kg; $P = 0.011$). Living donor grafts were used more in the ESCLD group (34 *vs* 0; $P = 0.006$). There was no difference between the two groups concerning vascular complications and rejection, but there were more bile leaks in the ESCLD group. Post-transplant patient survival was significantly higher in the ESCLD group: 1-, 5-, and 10-year survival rates were 97.9%, 93.9%, and 89.4%, respectively, compared to 78.3%, 78.3%, and 78.3% in the ALF group ($P = 0.007$). However, there was no difference in 1-, 5-, and 10-year graft survival between the ESCLD and ALF groups (90.7%, 82.9%, 77.3% *vs* 75.6%, 72.4%, and 66.9%; $P = 0.119$).

CONCLUSION

Patient survival is inferior in ALF compared to ESCLD recipients; the main reason is death in the 1st year post-PLT in ALF group. Once the ALF children overcome the 1st year after transplant, their survival stabilizes, and they have good long-term outcomes.

Key Words: Pediatric liver transplantation; Acute liver failure; End-stage chronic liver disease; Graft failure; Patient survival; Complications

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Core Tip: To the best of our knowledge, this is the first study to compare the complications and survival outcomes in acute liver failure (ALF) and end-stage chronic liver disease (ESCLD) children post-pediatric liver transplantation (PLT). This study not only showed that survival in the ALF group was significantly inferior post-PLT but also showed a different pattern of survival where ALF survival was mostly affected in the 1st year post-transplant and then stabilized, whereas ESCLD survival declined steadily over time.

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INTRODUCTION

Liver disease is a leading cause of morbidity and mortality in children. The spectrum of liver pathologies in this age group includes infectious, genetic, metabolic, and drug-induced disorders that may eventually progress to either acute liver failure (ALF) or end-stage chronic liver disease (ESCLD). Pediatric liver transplantation (PLT) is the only treatment option for children with ALF or ESCLD[1].

The diagnosis of ALF in children can be challenging, as hepatic encephalopathy in this age group is usually difficult to define, particularly in its early stages and sometimes it may not be clinically evident until the ALF becomes advanced[2-4]. Also in some cases, accurate diagnosis of the etiology of ALF may not be possible, primarily in candidates who present with unrecognized metabolic diseases shortly after birth or those who clinically deteriorate over a short period not allowing enough room for full biochemical and radiological testing[3].

Managing children suffering from ALF is a dynamic process, with the decision to list for PLT made in an emergent manner, when the probability of spontaneous recovery is low but also before any irreversible neurological or respiratory sequalae take place[2]. At times, the window from presentation to PLT may span from only few hours up to a small number of days, posing significant challenges for the clinical team[5]. Optimum clinical and logistical management is essential as successful PLT in this special group has a dramatic effect on their survival[4-6]. Hence at the national level, the graft allocation system gives ALF children the highest priority being labeled as "super-urgent."

In comparison, the clinical and logistic dynamics are completely different in the case of children with ESCLD because PLT is usually performed on an elective basis, as candidates are usually in less critical clinical condition and the transplant team has enough time for evaluation and planning, aiming for optimum timing and potentially improved outcomes.

Both groups were discussed among other categories in publications describing the experience of PLT centers, but to the best of our knowledge, no previous studies have directly compared the outcomes of PLT in ALF and ESCLD settings. This study was conducted to determine if there is a difference in post-

PLT complications between the ALF and ESCLD groups, and to describe any variance in survival between the two cohorts. The importance of this comparison is to provide insights for transplant centers and organ allocation systems dealing with these two divergent groups to make the best use of limited resources including a limited graft pool and to anticipate differences in behavior between candidates in each group to tailor their clinical care accordingly. This comparison also opens the door for future research to overcome obstacles and improve PLT outcomes, especially in the ALF group where the underlying cause of the liver failure remains unknown in a considerable number of children.

MATERIALS AND METHODS

This was a retrospective cross-sectional observational study of the long-term outcomes of PLT performed at Leeds Teaching Hospitals NHS Trust between 2000 and 2019. Hospital documents and electronic records were used to retrieve donor and recipient data. Ethical approval was not required for this retrospective analysis of already collected data, and the study was registered as a service improvement project within the hospital clinical governance department, with no patient identifiable information stored while collecting and analyzing the data for this project.

Eligibility

The inclusion criteria were all PLT recipients of the first liver transplant in our center ≤ 18 years with either ALF or ESCLD as the recorded indication for PLT. Exclusion criteria were retransplants, primary PLTs for liver tumors, or metabolic disorders without underlying liver disease. Retransplants were excluded as they represent a heterogenous group with well-reported inferior outcomes compared to primary transplants. Children with liver tumors are unique with a well-defined transplant indication, and their disease may be complicated by the burden of chemotherapy before undergoing a liver transplant, although they tend to be systemically well with no effects of acute or chronic liver disease. So, we think they should be ideally studied separately. PLT for metabolic diseases usually has excellent patient and graft survival than PLT for other indications. In addition to this, genotypic and phenotypic diversity in metabolic disorders complicate the possibility of forecasting long-term outcomes in this group of children; hence, they were excluded from the study.

Definitions

For the objective of this article, ALF was specified to match the Pediatric Acute Liver Failure Study Group[6] definition, as biochemical proof of liver injury, excluding records of recognized chronic liver illness, international normalized ratio > 1.5 if the patient had encephalopathy or > 2.0 if the patient did not have encephalopathy, and coagulopathy not rectified by vitamin K use.

ESCLD was specified as enduring hepatic inflammation identified by biochemical investigations and clinical examination, spanning more than 6 mo causing cirrhosis or permanent liver injury[7].

Data collected and outcomes studied

Data were collected through a retrospective case note review. We recorded 24 peritransplant parameters for this study, which were grouped into four classes: Pretransplant recipient as well as donor parameters, operative parameters, and post-transplant recipient observations. Pretransplant recipient variables were sex, age, weight, liver failure category (ALF and ESCLD), fundamental liver illness etiology, time on the transplant waiting list, and patient location when graft became available (an indirect marker of recipient sickness instantly pretransplant). Donor parameters were sex, age, weight, type of graft (living and deceased), and type of graft (whole or variant graft such as split or reduced). The intraoperative parameters studied were warm ischemia time and cold ischemia time. The post-operative outcomes studied were the incidence of vascular and biliary complications, post-transplant pediatric intensive care unit (PICU) and overall hospital stay, the incidence of biopsy-proven acute/chronic rejection, retransplantation, causes of graft and patient loss, and 1-, 5-, and 10-year graft as well as patient survival.

The primary outcome of this article was to determine if there is a difference in patient and graft survival in PLT recipients transplanted for ALF or ESCLD. The secondary outcome was to compare the incidence of vascular, biliary complications, and biopsy-proven rejection in PLT for both groups.

Statistical analyses of the data

Data were evaluated using IBM SPSS software version 20.0. (IBM Corp., Armonk, NY, United States). Kolmogorov-Smirnov was employed to validate the normality of variable allocation. Assessments for categorical variables were conducted using the χ^2 test (Fisher's exact adjustment). Student's *t*-test was applied to assess two normally distributed quantitative variables between two cohorts, whereas the Mann-Whitney test was applied to assess non-normally distributed quantitative data. Missing data were taken into account through statistical evaluation. The Kaplan-Meier survival curve was employed to examine the graft and patient survival. The significance of the recorded outcomes was determined at the 5% level.

RESULTS

Between November 2000 and August 2019, 322 PLTs were performed in our center. We excluded retransplants, transplants for children with liver tumors, or metabolic disorders without underlying liver disease (90 PLTs) from the final analysis. The remaining 232 PLTs were classified into 195 PLTs due to ESCLD and 37 PLTs as emergency management of ALF (Figure 1). The median follow-up for the ALF group was 8.3 years (1–19.3 years), while the median follow-up for the ESCLD group was 8.1 years (1–19.6 years).

During the study period, 232 children presented to our institute with ALF. Unfortunately, 58 (25.0%) of them did not survive to undergo transplantation, 37 (15.9%) underwent transplantation, and 137 (59.1%) recovered without transplantation.

Pretransplant recipient parameters

Both groups were homogenous in terms of recipients' sex (P = 0.312), whereas recipients' age and weight were significantly higher in the ALF group. Further analysis of the ALF group showed that 6 patients were transplanted at below 1 year of age, 10 patients were transplanted at 1 year to 4 years of age, 3 patients were transplanted at above 4 years to 10 years of age, and 18 patients were older than 10 years of age at the time of transplant. Biliary atresia and progressive familial intrahepatic cholestasis were the most common causes of liver failure in the ESCLD group, whereas seronegative hepatitis and autoimmune hepatitis were the most common causes in the ALF group (Table 1). There was a significant difference in waiting time on the transplant list between both groups; the median waiting time for the ALF group was 3 d (1–41 d), whereas the median waiting time for ESCLD patients was 60.5 d (1-560 d; P < 0.001). The location of the recipient when the liver graft became available also showed a significant difference as the home locality was greater in the ESCLD group, whereas in the ALF group, hospital, as well as PICU locality (with or without invasive ventilation), were significantly higher (Table 1).

Donor parameters

There was no statistically significant difference in terms of donor sex or weight; however, donors in the ALF group were significantly older than those in the ESCLD group (Table 1). Concerning the graft resource, living donors were used more commonly in the ESCLD cohort (34 donors) than in the ALF cohort, which did not receive any graft from living donors (P = 0.006).

Operative parameters

Technical variant (reduced and split) grafts were used significantly more in the ESCLD group (Table 1). There was no difference in cold ischemia time between the two groups, but warm ischemia time was significantly longer in the ALF group (median 55 min, 32–81 min) than in the ESCLD group (median 45.5 min, 29–81 min; P = 0.004).

Post-transplant recipient variables

Vascular complications occurrence: There was no distinction among the groups regarding vascular complications. Five patients in the ALF group and forty-one patients in the ESCLD group had at least one post-transplant vascular event (Table 2). Some patients in the ESCLD group had more than one vascular complication; two recipients had both hepatic artery thrombosis and portal vein thrombosis (PVT), two recipients developed both hepatic artery stenosis and portal vein stenosis (PVS), and one patient had PVS then PVT (Table 2).

Incidence of biliary complications: Bile leak was significantly higher in the ESCLD group, whereas biliary stricture and common hepatic duct sludge showed no significant difference between the two groups. It was also of note that three of the ESCLD recipients developed both bile leakage and biliary stricture (Table 2).

Incidence of rejection: There was no difference in biopsy-proven acute or chronic rejection between the two groups. Seventeen (45.9%) ALF patients had one or more episodes of rejection and sixty-two patients (31.8%) in the ESCLD group experienced rejection (P = 0.096).

Post-transplant stay

PICU stay post-PLT was longer in the ALF group by a median of half a day (2.5 *vs* 2 d), but this difference was not statistically significant (P = 0.112). In keeping with their sick status before the transplant, the ALF patients had a longer median hospital stay (29 *vs* 21 d) compared to ESCLD patients (P = 0.013).

Retransplantation rate

There was no difference among the studied groups in terms of the need for retransplantation; 5 (13.5%) in the ALF group and 27 (13.8%) in the ESCLD group (P = 0.957).

Table 1 Donors and recipients demographics

Demographics	ALF (*n* = 37), %	ESCLD (*n* = 195), %	*P* value
Donor demographics			
Sex			
Male	45.7	46.9	0.902
Female	54.3	53.1	
Weight, kg	66.2 (8–90)	65.8 (10–98)	0.912
Age, yr	35.2 (0.9–65)	29 (1–66)	0.039
Type of liver graft			
Whole liver	14 (37.8)	38 (19.7)	0.016
Variant graft including split, reduced, living donor	23 (62.2)	155 (80.3)	
Recipient demographics			
Sex			
Male	16 (43.2)	102 (52.3)	0.312
Female	21 (56.8)	93 (47.7)	
Age at transplant, yr	8 (0.1–16.7)	5.4 (0.3–17.2)	0.031
Weight, kg	31 (2.7–66.5)	21 (4.7–89)	0.011
Etiology of liver disease			
Alagille's syndrome	0 (0)	12 (6.2)	0.222
Alpha-1-AT deficiency	0 (0)	15 (7.7)	0.138
Autoimmune	4 (10.8)	13 (6.7)	0.487
Biliary atresia	0 (0)	92 (47.2)	< 0.001
Biliary cirrhosis	0 (0)	2 (1.0)	1.000
CF liver disease	0 (0)	13 (6.7)	0.232
Drug induced	2 (5.4)	0 (0)	0.025
Hepatitis A	2 (5.4)	0 (0)	0.025
HSV	2 (5.4)	0 (0)	0.025
Seronegative hepatitis	17 (45.9)	0 (0)	< 0.001
PFIC	0 (0)	29 (14.9)	0.006
Post-liver resection	2 (5.4)	0 (0)	0.025
PSC	0 (0)	8 (4.1)	0.361
Others	8 (21.6)	11 (5.6)	0.004
Location of the recipient when the graft is available			
Home	0 (0)	137 (71.4)	< 0.001
Hospital	15 (40.5)	47 (24.5)	0.044
PICU not ventilated	7 (18.9)	5 (2.6)	0.001
PICU ventilated	15 (40.5)	3 (1.6)	< 0.001

ALF: Acute liver failure; CF: Cystic fibrosis; ESCLD: End-stage chronic liver disease; HSV: Herpes simplex virus; PFIC: Progressive familial intrahepatic cholestasis; PICU: Pediatric intensive care unit; PSC: Primary sclerosing cholangitis.

Patient survival

During the follow-up period, 17 (8.7%) of the ESCLD recipients died while in the ALF group, and 9 (24.3%) recipients died (P = 0.011) (Figure 2A and Table 3). Sepsis and liver failure were the two most common causes of death in PLT recipients, but there was no statistically significant difference between the two groups (Table 2). Analysis of ALF group survival in conjunction with the age of transplant (less

Table 2 Post-transplant outcomes

Outcome	ALF among *n* = 37, *n* (%)	ESCLD among *n* = 195, *n* (%)	*P* value
Vascular complications			
AV malformation post-liver biopsy	0 (0)	1 (0.5)	1.000
Retroperitoneal hematoma, femoral vein bypass cannula	0 (0)	1 (0.5)	1.000
HAS	2 (5.4)	13 (6.7)	1.000
PVS	0 (0)	14 (7.2)	0.134
HAT	1 (2.7)	10 (5.1)	1.000
PVT	1 (2.7)	7 (3.6)	1.000
HVS	1 (2.7)	0 (0)	0.159
Biliary complications			
CHD sludge	0 (0)	2 (1)	1.000
Biliary stricture	3 (8.1)	21 (10.8)	0.775
Bile leak	0 (0)	23 (11.8)	0.031
Cause of graft loss	*n* = 5	*n* = 27	
HAT	0 (0)	9 (33.3)	0.288
PNF	2 (40)	5 (18.5)	0.296
Chronic rejection	3 (60)	6 (22.2)	0.121
Biliary tract complications	0 (0)	7 (25.9)	0.560
Cause of death	*n* = 9	*n* = 17	
Unknown	0 (0)	5 (29.4)	0.129
Cardiopulmonary	3 (33.3)	1 (5.9)	0.104
Cerebral oedema	1 (11.1)	0 (0)	0.346
Fungal infection	1 (11.1)	0 (0)	0.346
Gastrointestinal	0 (0)	1 (5.9)	1.000
Intracranial hemorrhage	1 (11.1)	0 (0)	0.346
Liver failure	1 (11.1)	4 (23.5)	0.628
Recurrence of disease	0 (0)	1 (5.9)	1.000
Sepsis	2 (22.2)	5 (29.4)	1.000

ALF: Acute liver failure; AV: Arteriovenous; CHD: Common hepatic duct; ESCLD: End-stage chronic liver disease; HAS: Hepatic artery stenosis; HAT: Hepatic artery thrombosis; HVS: Hepatic vein stenosis; PNF: Primary non-function; PVS: Portal vein stenosis; PVT: Portal vein thrombosis.

than 1 year, 1-4 years, 4-10 years, more than 10 years) showed 5-year patient survival of 50%, 90%, 100%, and 77.8%, respectively.

Graft survival

Median graft survival was longer in the ESCLD group (2412 d) compared to the ALF group (2292 d), but this difference was not statistically significant (P = 0.587) (Figure 2B and Table 3). Despite some causes of graft failure being more frequent in one group than the other, there was no statistically significant difference (Table 2).

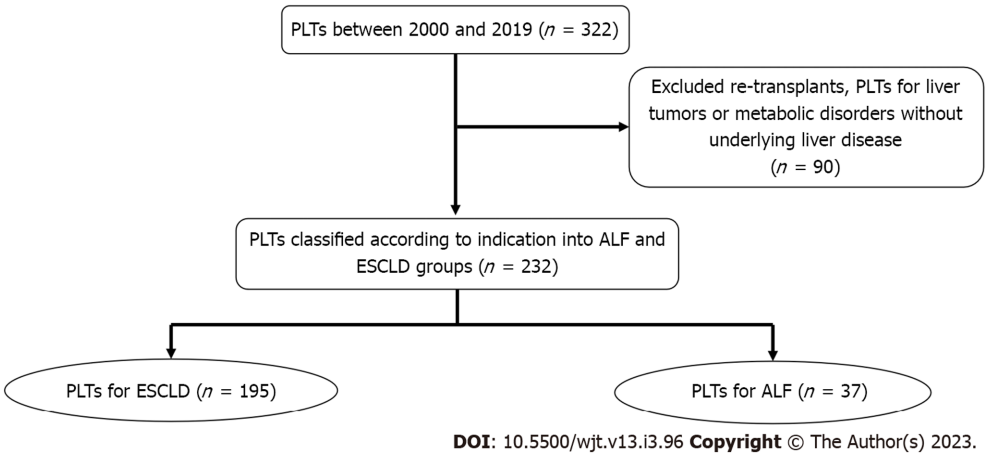
DISCUSSION

In the United Kingdom, children with ALF or ESCLD who are candidates for PLT are referred to one of the three centers in the country for evaluation, including our center. When the indication for PLT is established, patients are offered transplantation if there is more than 50% survival likelihood at 5 years

Table 3 Survival among category groups- 1-, 5-, 10-yr and end of study for patients and grafts

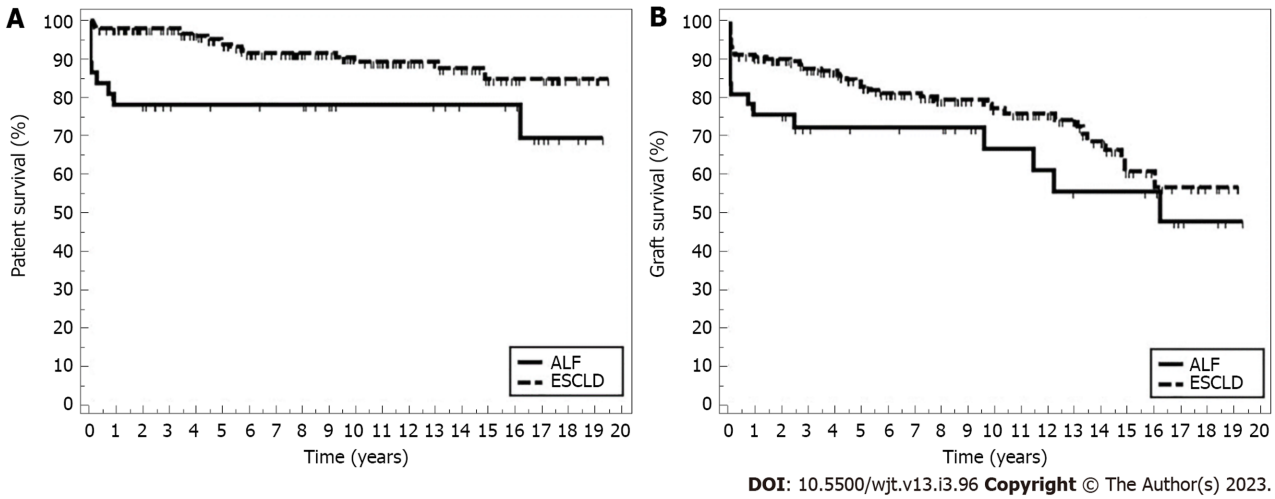
Survival outcome	Mean	%1 yr	%5 yr	%10 yr	%End of study	Log rank	
						χ^2	*P* value
Patient survival							
ALF	14.86	78.3	78.3	78.3	69.6	7.370	0.007
ESCLD	17.71	97.9	93.9	89.4	85.0		
Graft survival							
ALF	12.46	75.6	72.4	66.9	47.8	2.426	0.119
ESCLD	14.46	90.7	82.9	77.3	56.8		

ALF: Acute liver failure; ESCLD: End-stage chronic liver disease.



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Figure 1 Flow diagram of study participants. ALF: Acute liver failure; ESCLD: End-stage chronic liver disease; PLT: Pediatric liver transplantation.



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Figure 2 Kaplan-Meier survival curve for patient survival, and graft survival. A: Patient survival; B: Graft survival. ALF: Acute liver failure; ESCLD: End-stage chronic liver disease.

after PLT with an acceptable quality of life. But the dynamics of PLT are completely divergent between ALF and ESCLD settings, leading to separate selection criteria for candidates needing emergency transplantation compared to elective procedure.

The studied cohorts have diverse etiology with distinct differences in short-term prognosis. Similarly, graft allocation procedures are unique for elective and emergency transplantation, showing that those cohorts have a distinct probability of mortality without PLT. In our study, the percentage of PLTs

performed as emergency management for ALF was 11.5%, consistent with studies from other centers[8-10], whereas some other authors have reported higher rates of PLT in ALF patients that may reach up to 35%[11,12]; this difference reflects the absence of a reliable prognostic model for ALF patients that can accurately predict ALF candidates who would not survive without PLT.

Identifying ALF patients who would be saved by successful PLT and differentiating them from those who may recover spontaneously or those who will eventually die with or without PLT cannot be guided by currently available data[13-16]. Using isolated biomarkers such as ammonia, actin-free Gc-globulin, and lactate is not reliable and cannot be applied to all ALF patients without being sufficiently studied in the pediatric population[17-19]. Prognostic scoring models applying clinical and laboratory variables such as King's college criteria and liver injury unit score cannot be confidently used to anticipate ALF patient death[19-21].

In terms of the etiology of liver failure, biliary atresia was the most common indication for PLT in ESCLD patients in our study (47.2%), consistent with the literature[1,8,11,22,23]. On the other hand, the etiology of the underlying liver disease could not be identified in 45.9% of our ALF recipients. Most of the literature concerned with PLT in ALF patients has shown the same observation[3,12,24,25]. Failure to identify the etiology of ALF is probably multifactorial. First, most of the data concerned with ALF in children and infants are retrieved from case reports, exploration of adult data, individual practice, and retrospective studies of single centers[2]. Second, the rapid progression of liver failure to transplant or death does not give enough room for the extensive work-up required[4]. The inability to identify the cause of ALF is always stressful for the treating physicians as it may affect the outcome of this group of patients because of its effects on prognosis, therapy, and prevention.

Until 2008, we were using molecular adsorbent recirculating system as bridging therapy for ALF patients, but we did not find it helpful in terms of changing outcomes for patients. We use plasmapheresis in selected patients, as we used it in a paracetamol overdose patient in the last 3 years. Such bridging therapies are not commonly used in our program for ALF children, due to the lack of evidence for survival benefits. Time on the transplant waiting list was significantly shorter in the ALF group; this is the outcome of labeling such patients as "super-urgent," which puts them on top of the national waiting list. Receiving a timely PLT in this group is vital as prolonged waiting can lead to the development or progression of respiratory and neurological complications, which can eventually result in the de-listing of the child who becomes "too sick" for transplantation and eventually patient mortality.

The location of the recipient when the graft became available showed a significant difference between the two groups. ALF patients are mostly located in the hospital ward or PICU while ESCLD patients are usually admitted to our center from home. This is explained by the fact that ALF patients are usually sicker in the immediate pretransplant period; thus, they are usually hospitalized or even admitted to the PICU if multiple organ support is needed, while ESCLD patients are mostly less critical and thus usually followed up in outpatient clinics and admitted to the transplant center only when the graft becomes available. This was also reflected in the post-transplant hospital stay that was significantly longer in ALF patients who are expected to require a longer time to recover before discharge.

In contrast to the ESCLD group, ALF candidates in our study did not receive a living donor graft; this is possibly linked to a brief window that does not provide sufficient time for meticulous assessment of possible living donors. Living donation intended for ALF candidates has consistently been a matter of discussion[26]. Various studies have expressed concerns about the ultra-short period utilized for radiological and clinical assessment of the living donor along with the emotional element in PLT that might affect the outcomes[27]. Other reports claim that PLT using living donor grafts has a possibly better outcome due to a briefer waiting period as the sick child does not have to wait for the liver graft allocation system to receive a suitable graft in addition to the presumed better-quality graft due to limited cold ischemia time as shown by the inferior primary non-function incidence in grafts from living donors[28].

Technical variant grafts were used significantly higher in the ESCLD group; this is explained by the significantly lower age at transplant of this group compared to the ALF group, so smaller grafts were needed to match recipient size. This can also explain higher rates of bile leakage in the ESCLD group from the cut surface of reduced or split grafts.

ALF recipients in our study have a significantly lower survival rate than ESCLD recipients, which has been reported in multiple studies[11,22], while only one study to the best of our knowledge has reported similar patient survival in both groups[25]. This can be explained by multiple factors. First, the more critical condition of ALF patients in the pretransplant period that was reflected in our study by significantly higher PICU location of these patients when the graft becomes available and was linked in some reports to low post-transplant survival[11]. Second is the scarcity of suitable grafts for the pediatric population[29], which prolongs the waiting time of ALF patients and may put pressure on the transplant centers to accept marginal grafts, as survival of this critical group is largely dependent on receiving a PLT within a short window of opportunity[28]. The third is the fact that the etiology is unknown in most cases of ALF, and this will surely affect post-transplant disease management and progression.

Interestingly, we noticed that the recipient's survival in the ALF group is most affected in the 1st-year post-transplant and remained almost stable after that, while survival in the ESCLD group continued to decline gradually over the years. This observation is probably related to how unwell the ALF recipients were at the time of transplant (a considerable proportion was in intensive care), but after the 1st year, survival stabilizes. Whereas in ESCLD, the 1st-year outcomes are better, probably because most of these patients were stable and admitted for transplant from home. However, after that, there seems to be a steady decrease in their survival, possibly because of the effects of disease chronicity where ESCLD itself or its underlying etiology like cystic fibrosis or alpha-1-antitrypsin deficiency would have affected other systems such as the lungs and kidneys and this effect would reflect on patient survival over the years.

There were some limitations in this study. The larger study cohort, longer follow-up duration, single-center population with uniform pretransplant and post-transplant protocol, and careful retrieval of data allowed us to overcome the limitation of the retrospective nature of the study. More importantly, no such studies are comparing ALF with ESCLD in the paediatric transplant literature.

CONCLUSION

This was a retrospective study that compared the long-term outcomes of PLT in ALF and ESCLD settings. Survival of PLT recipients was significantly higher in the ESCLD group due to multiple factors such as the critical general condition of ALF patients in the peritransplant time, scarcity of suitable grafts for pediatric recipients, and obscure etiology of ALF in most of the cases. The rate of complications did not show a significant difference apart from higher rates of bile leak in the ESCLD group.

ARTICLE HIGHLIGHTS

Research background

Settings of pediatric liver transplantation (PLT) in end-stage chronic liver disease (ESCLD) and acute liver failure (ALF) are divergent. ALF recipients are transplanted within a narrow window of opportunity, whereas ESCLD recipients are usually transplanted electively.

Research motivation

Outcomes of PLT in ALF and ESCLD were previously described by different centers but to the best of our knowledge, they were not compared to establish if there is a difference in post-PLT survival and complication rates between these two groups.

Research objectives

To determine if there is a difference in post-operative complications and survival outcomes between the ALF and ESCLD in PLT.

Research methods

This was a retrospective observational study of all primary PLTs performed at a single center between 2000 and 2019. ALF and ESCLD groups were compared for the pretransplant recipient, donor and operative parameters, and post-operative outcomes including graft and patient survival.

Research results

During the 20-year study period, 232 primary PLTs were performed at our center; 195 were transplanted for ESCLD and 37 were transplanted for ALF. The ALF recipients were significantly older (median 8 years *vs* 5.4 years; $P = 0.031$) and heavier (31 *vs* 21 kg; $P = 0.011$). Living donor grafts were used more in the ESCLD group (34 *vs* 0; $P = 0.006$). There was no difference between the two groups concerning vascular complications and rejection, but there were more bile leaks in the ESCLD group. Post-transplant patient survival was considerably superior in the ESCLD group: 1-, 5-, and 10-year survival rates were 97.9%, 93.9%, and 89.4% correspondingly compared to 78.3%, 78.3%, and 78.3% in the ALF group ($P = 0.007$). However, there was no difference in 1-, 5-, and 10-year graft survival rates between the ESCLD and ALF groups - 90.7%, 82.9%, and 77.3% *vs* 75.6%, 72.4%, and 66.9% ($P = 0.119$).

Research conclusions

Post-PLT survival in ALF patients is inferior to ESCLD patients. This may be due to several factors including uncertainty of the underlying pathology in most ALF patients and the more critical clinical status of ALF candidates in the immediate pre-transplant period. Survival post-PLT in the ALF group was adversely affected in the 1st year and then stabilized, while post-PLT survival in the ESCLD group showed a gradual decline over the study period.

Research perspectives

Future research should address the dilemma of identifying the underlying pathology in a considerable portion of ALF candidates and should also try to overcome liver graft shortage by identifying methods to widen the graft pool.

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REVIEW

Islet transplantation-immunological challenges and current perspectives

Plamena Kabakchieva, Yavor Assyov, Stavros Gerasoudis, Georgi Vasilev, Monika Peshevska-Sekulovska, Metodija Sekulovski, Snezhina Lazova, Dimitrina Georgieva Miteva, Milena Gulinac, Latchezar Tomov, Tsvetelina Velikova

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Abstract

Pancreatic islet transplantation is a minimally invasive procedure aiming to reverse the effects of insulin deficiency in patients with type 1 diabetes (T1D) by transplanting pancreatic beta cells. Overall, pancreatic islet transplantation has improved to a great extent, and cellular replacement will likely become the mainstay treatment. We review pancreatic islet transplantation as a treatment for T1D and the immunological challenges faced. Published data demonstrated that the time for islet cell transfusion varied between 2 and 10 h. Approximately 54% of the patients gained insulin independence at the end of the first year, while only 20% remained insulin-free at the end of the second year. Eventually, most transplanted patients return to using some form of exogenous insulin within a few years after the transplantation, which imposed the need to improve immunological factors before transplantation. We also discuss the immunosuppressive regimens, apoptotic donor lymphocytes, anti-TIM-1 antibodies, mixed chimerism-based tolerance induction, induction of antigen-specific tolerance utilizing ethylene carbodiimide-fixed splenocytes, pretransplant infusions of donor apoptotic cells, B cell depletion, preconditioning of isolated islets, inducing local immunotolerance, cell encapsulation and immunoisolation, using of biomaterials, immunomodulatory cells, *etc.*

Key Words: Islet transplantation; Type 1 diabetes; Diabetes mellitus; Immune tolerance; Graft rejection; T regulatory cells; B regulatory cells

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Core Tip: Type 1 diabetes (T1D) is associated with loss of beta-cell mass and insulin secretion. Regardless of its nature, autoimmune or idiopathic, the loss of own insulin secretion is a hallmark dysfunction in T1D mellitus; thus, therapeutic options are aimed at either replacing the missing insulin or restoring physiological insulin secretion to achieve normoglycemia and postponing micro- and macrovascular complications. Nevertheless, the need to completely replace the depleted pancreatic secretion also leads to the emergence of new therapeutic horizons, including pancreas and islet cell transplantation. However, this approach also meets several immunological challenges-cellular and antibody-mediated rejection and loss of function. To improve the outcomes, several approaches are performed: Immunosuppression, apoptotic donor lymphocytes, anti-TIM-1 antibodies, mixed chimerism-based tolerance induction, induction of antigen-specific tolerance utilizing ethylene carbodiimide-fixed splenocytes, infusion of donor apoptotic cells before transplantation, combined with anti-CD40L antibodies and rapamycin, preconditioning of isolated islets, inducing local immunotolerance, cell encapsulation and immunoisolation, using of biomaterials, immunomodulatory cells, *etc.* mesenchymal stem cells, as an adjunct therapy to islet transplantation, can promote long-term graft survival, possibly by reducing inflammation and enhancing immune tolerance.

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INTRODUCTION

Pancreatic islet transplantation is a minimally invasive procedure aiming to reverse the effects of insulin deficiency by transplanting pancreatic beta cells[1]. Pancreatic islet transplantation can be done with autologous and allogeneic islets. While autologous islet transplantation has the advantage of being derived from the same patient, eliminating the risk of immune rejection, its widespread utilization is limited due to several drawbacks, including the need for pancreatectomy, which may have associated surgical risks, and the limited availability of functional islets from a single organ in patients with advanced disease. On the other hand, allogeneic islets are taken from different individuals of the same species, usually for treating type 1 diabetes (T1D), with followed immunological response complications [2].

Typical for T1D is the continuing pancreatic beta cell destruction, which could be autoimmune (Type 1A) or non-autoimmune (Type 1B), resulting in decreased or absent insulin production. As a result, it increases in incidence yearly and is associated with severe hypoglycemia, ketoacidosis, and vascular

complications[3]. Although exogenous insulin analogs are considered the primary treatment option for managing T1D in response to hyperglycemia, they cannot accurately resemble the timing and dosing of physiological insulin secretion. Moreover, exogenous insulin therapy is associated with an increased risk of severe side effects such as hypoglycemia, weight gain, lipodystrophy, *etc.*[4]. Therefore, there is an ongoing effort to improve the treatment options[5]. Among them, pancreatic islet transplantation is promising to become the mainstay in the treatment process[6].

As a minimally invasive procedure, islet transplantation is ideal for high-risk surgical patients burdened with cardiovascular disease[7]. It does not follow the significant complications of vascularized pancreas transplantation, and with minimal intra-operational complications, such as bleeding and portal vein thrombosis, the mortality is negligible. On the negative side, multiple donors for a single patient are needed, while the alternative whole pancreatic transplantation treatment needs 1 and rarely 2 pancreases. This makes it a rather wasteful procedure[8]. An adequate islet number must be transplanted for patients to become insulin-independent. A single transplantation is often insufficient; several sequential transplantations are needed for satisfactory glycaemic and insulin results[9]. Early attempts had been made as early as 1893. Still, the milestone that grabbed the scientific community's attention was the ground-breaking Edmonton protocol, with its non-corticosteroid immunosuppressive treatment[9] and the other studies regarding the benefits of islet transplantation on glucose metabolism improvement[10,11]. Studies have shown that 5-year insulin independence has increased manifold[12-14].

Overall, pancreatic islet transplantation has improved to a great extent, and cellular replacement will likely become the mainstay treatment. Our goal was to review pancreatic islet transplantation as a treatment for T1D and the immunological challenges faced. To prepare this narrative review, we search the main databases, Medline, PubMed, and Scopus, in conformity with the principles of writing a narrative review[15].

ISLET TRANSPLANTATION PROCEDURE

The main procedural steps are pre-transplant assessment, pancreas procurement, islet isolation, tissue culture, transplantation, and post-transplant evaluation[8].

In pre-transplant assessment, eligible patients are chosen. Strong indications include recurrent severe hypoglycemic shocks, impaired awareness of hypoglycemia, undetectable C-peptide, age between 18-65, and a diagnosis of more than five years[16]. Additionally, previous kidney transplantation has been shown to impact the outcomes of islet transplantation positively. Studies have reported that patients who have undergone a kidney transplant before islet transplantation have higher graft survival rates, improved glycemic control, and reduced insulin requirements compared to those without a prior kidney transplant. This may be attributed to the immunosuppressive regimen used for kidney transplantation, which may enhance the success of islet transplantation by preventing the rejection of the transplanted islets[17]. Exclusion criteria include poorly controlled hypertension, heart disease, macroalbuminuria, glomerular filtration rate < 80 mL/min/1.73 m^2 and potential contraindications for immunosuppression. Current indications do not include the pediatric population[18]. In the transplantation of allogeneic pancreatic beta cells, ABO and human leucocyte antigen histocompatibility have to be assessed. The number of islet donors is generally limited, but new xenografts with islets from other species, typically porcine islets, and stem cell technologies could tackle this critical problem[19].

In the stage of pancreas procurement, the pancreas is removed from donors and preserved in the University of Wisconsin solution for up to 24 h. Important in this stage is the capsule to be kept intact. The pancreas is delivered to the islet isolation center when procurement is ready[20]. The islet isolation process involves the preparation of the pancreas, which is carefully cleaned of surrounding tissues and dissected to expose the islets of Langerhans. The pancreas is then cannulated and perfused with a collagenase enzyme solution for 10 min, which distends the pancreas to facilitate the separation of the islets from the surrounding stroma. Next, the distended pancreas is cut and set into the Ricordi Chamber, an automated device designed to facilitate the islet isolation process. The chamber employs a series of automatic steps to separate the islets from the exocrine tissue, including filtration and density gradient centrifugation. Finally, the isolated islets are processed using a COBE 2991 cell processor, which further separates the islets from any residual exocrine tissue, and the purified islets are then cultured for transplantation[21,22].

In the hands of the proper expert, the tissue culture stage of islet isolation represents a critical step in preparing isolated islets for transplantation. This stage allows the islets to recover from the stress induced by the previous steps of the isolation procedure, during which they may have been subjected to mechanical and enzymatic stress. The tissue culture stage typically involves the placement of the purified islets into a nutrient-rich media in a controlled environment, where they are allowed to recover for several hours to several days. During this time, the islets are carefully monitored for signs of viability and function, including assessment of insulin secretion and glucose-stimulated insulin release. This stage also allows for flexibility in scheduling the subsequent transplant procedure, as the islets can be stored under optimal conditions until the transplant recipient is ready to receive them. The success of

the tissue culture stage is highly dependent on the expertise of the individual performing the procedure, as optimal conditions must be maintained to ensure the viability and function of the isolated islets[23].

Before transplantation begins, the final transplantation islet site has to be decided. The liver is considered preferable for transplantation, although different places are being tested for better islet survival and function[24]. Upon islet infusion, an "instant blood-mediated inflammatory reaction" is described with platelet consumption, activation of coagulation, and the complement system[25].

The post-transplant period following islet transplantation is characterized by a prolonged period of recovery during which insulin independence may not be immediately achieved. The transplanted islets may take months to years to fully integrate into the recipient's body[6] and establish a functional vascular supply. During this period, the transplanted islets are subject to immunological attacks from the recipient's immune system, which can compromise their function and survival. A combination of induction, maintenance, and antirejection immunosuppressive drugs are typically used to prevent rejection of the transplanted islets. However, a notable irony is that many of these immunosuppressive drugs have diabetogenic properties, which can exacerbate preexisting metabolic abnormalities in transplant recipients. As such, these drugs must be carefully balanced against the need to maintain optimal islet function and prevent rejection[26].

Recent advances in islet transplantation have focused on immunoisolation, which involves the encapsulation of transplanted islets in a protective membrane to prevent their recognition and subsequent destruction by the recipient's immune system. Encapsulation of islets for immunoisolation involves using biocompatible materials that allow for efficient nutrient and oxygen exchange while preventing immune cells from accessing the transplanted islets. Several biomaterials have been studied for this purpose, including alginate, agarose, and polyethylene glycol hydrogels[27,28]. The techniques for improving islet cell survival by encapsulation are presented in Figure 1A.

For example, alginate hydrogels are commonly used due to their biocompatibility, ease of fabrication, and ability to protect transplanted islets from the immune system. While early studies in small animal models have shown promising results, with sustained islet function and reduced immunosuppressive drug requirements, translation to larger animals and humans has been less successful, with limited long-term success and significant technical challenges in maintaining membrane integrity and permeability. Using traditional immunosuppressive regimens remains a crucial component of current islet transplantation protocols, albeit with the recognized risks of diabetogenicity and other adverse effects[11].

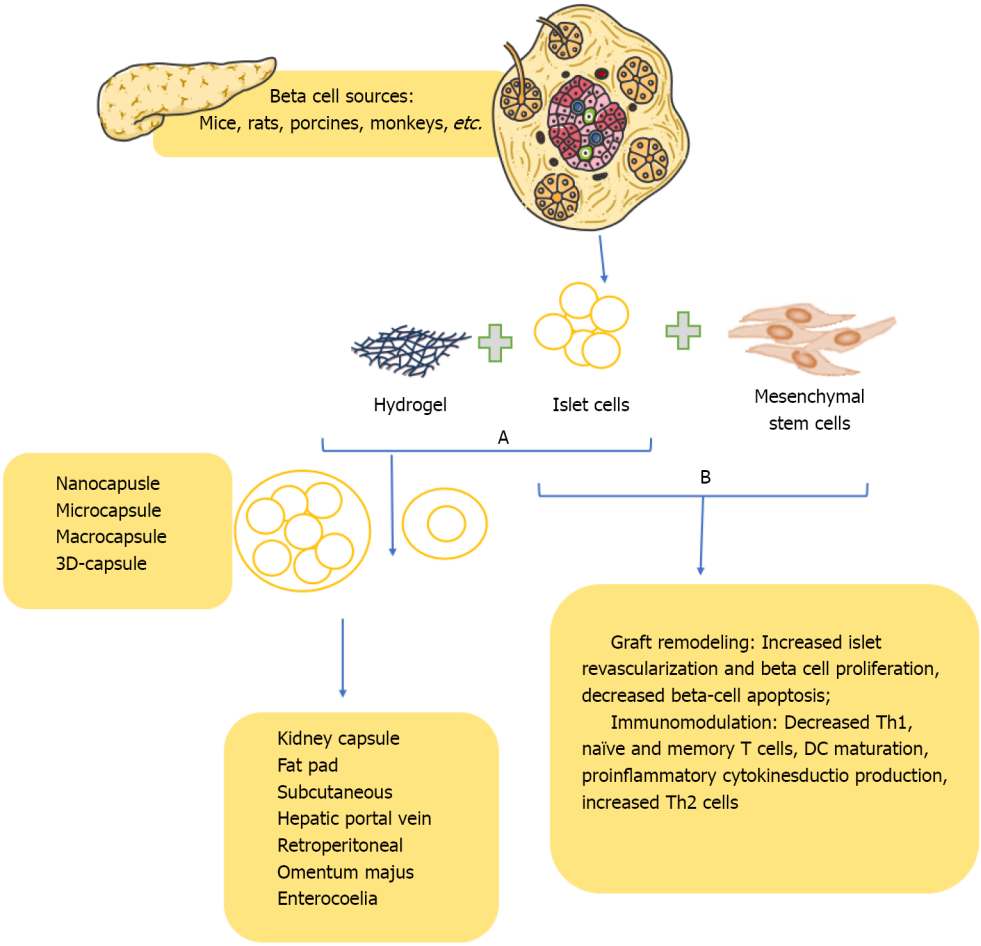
T1D AND THE NEED FOR ISLET TRANSPLANTATION

Type 1 diabetes mellitus (T1DM) is a metabolic disease distinct by hyperglycemia, insulin deficiency, and a lifelong need for exogenous insulin replacement treatment[3,29]. T1DM is an autoimmune disease that develops in genetically predisposed individuals under the influence of environmental factors, which triggers autoimmunity to pancreatic beta cells. Although it is defined as "diabetes of young age", T1DM can also affect adults[30]. In general, T1DM is divided into two subtypes, 1A and 1B[31]. While T1ADM is associated with autoantibodies against islet cells [glutamic acid decarboxylase (anti-GAD65), tyrosine phosphatases islet antigen 2 (IA-2), IA-2β insulin, or zinc transporter 8[32], also observed in patients with T2D[33], T1BDM, in turn, is a relatively small subtype that is not mediated by the immune system and has an unclear genesis.

T1DM is related to other autoimmune conditions such as celiac disease[34,35], Hashimoto thyroiditis, Addison's disease, pernicious anemia, *etc*.[36]. Moreover, patients with diabetes may have a compromised immune system, leading to a more complicated course of infections, including coronavirus disease 2019[37]. Some of the immune defects described in patients with diabetes are decreased cellular response *in vitro*, low complement factor 4, diminished cytokine response after stimulation, reduced chemotaxis, phagocytosis, and killing of polymorphonuclear cells and macrophages[38].

Regardless of the subtype, the loss of insulin secretion is a hallmark dysfunction in T1DM, and therapeutic options aim to replace the missing insulin or restore physiological insulin secretion to achieve normoglycemia and prevent micro- and macrovascular complications. Within the last few years, we have seen a rapid evolution in the therapy of T1DM[39]. First, tangible progress marked the discovery of insulin in 1921-22 by Banding and Macleod, saving from certain death children with diabetes. The subsequent development of new analog insulins with a better therapeutic and safety profile results in better control of hyperglycemia and a reduced risk of hypoglycemia, respectively. The introduction of insulin pumps with continuous subcutaneous insulin administration[40] and the implementation of modern technologies in diabetes control with continuous glucose monitoring systems combined with glucose prediction algorithms enabling the development of artificial pancreas delivery systems[41] marks extraordinary progress in managing T1DM.

Nevertheless, the need to completely replace the depleted pancreatic secretion also leads to the emergence of new therapeutic horizons, including pancreas and islet cell transplantation. They allow not only to achieve independence from exogenous insulin administration and the need to monitor blood sugar but also successfully to afford counterregulatory hormone secretion and pancreatic exocrine



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Figure 1 Techniques for improving graft survival. A: Islet cell encapsulation (after isolation of islets by density gradient centrifugation), islets are capsuled with different hydrogel types to obtain various sizes of capsules. Then the capsules are transplanted into the body; B: Mesenchymal stem cells modulate graft and immune responses and support the islet cell survival after transplantation. Parts of the figure were drawn using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/Licenses/by/3.0/).

function[42].

IMMUNOLOGICAL ALTERATIONS IN T1D

T1DM was thought to be a T cell-mediated autoimmune illness for many decades. This belief persists, but multiple recent discoveries hint at a role for beta cells beyond being a non-provoking victim of an autoimmune onslaught[38].

The interaction between genetic vulnerability and probable triggers is likely to begin at a young age, gradually leading to the loss of tolerance to self and, eventually, the development of clinical symptoms. The result is determined by genetic predisposition, decreased removal of the apoptotic cell remains, altered immune regulation, and environmental triggers (*i.e.*, viral infections). In addition, autoreactivity may exist under physiological settings, and illness may arise if the integrity of the complicated regulatory process is compromised[43].

The beta cells are destroyed by islet-infiltrating cells (*i.e.*, CD8+ cytotoxic lymphocytes and macrophages), resulting in insulitis. In addition, macrophages release cytokines that are harmful to beta cells. Secondary considerations are autoantibodies, which serve as the foundation for clinical diagnosis [43].

Initially, B lymphocytes are known to play a secondary role in T1DM that even occurs in severe congenital B-lymphocyte immunodeficiency[44]. Xiu *et al*[45] considerably delayed disease development in NOD mice by depleting B-lymphocytes using an anti-CD20 antibody. They concluded that this was not due to T effector cell reduction or T regulatory (Tregs) induction but rather to a decrease in the development of autoreactive T cells[45].

However, autoreactive T cells are part of the typical T cell repertoire. In T1D, beta cells live in an inflammatory environment and participate in their destruction. Additionally, metabolic activity is what causes beta cell malfunction and destruction. Insulitis is characterized by inflammation, associated with substantial metabolic, epigenetic, and autoantigenic alterations that expose beta cells to the immune system[46]. In line with this, immunotherapy may be insufficient to treat T1D, although beta cell therapy may help reduce beta cell immunogenicity and islet autoimmunity[47].

It was demonstrated recently that innate immunity components might play a role in T1D pathogenesis, such as pattern recognition receptors and proinflammatory cytokines[47]. Nevertheless, the accompanying inflammation of the islets leads to damaged beta cells and loss of insulin production.

Animal studies (*i.e.*, non-obese diabetic mice) and human studies in T1D revealed defects in thymic selection, expansion of effector T cells, impaired homeostasis and FoxP3+ Tregs[48]. However, even if we accept the immune system's role in the development of T1D, science cannot assume that the disease is entirely a result of dysfunctional immunity, *i.e.*, autoreactive T cells. Recent research focuses on the participation of the peripheral immune system in the targeted tissue and the role of beta cells in the autoimmune process[49,50].

Indeed, when we accept this conception, it was demonstrated that T1D is usually characterized by less beta-cell mass, functional capacity and inability to control glycemia. Usually, beta cells undergo metabolic stress, inflammatory environment and other factors that increase the expression of specific adhesion molecules and other receptors, making them prone to immune attacks[46].

Islet transplantation has been considered a potential cure for T1D by replacing the damaged beta cells. However, its effectiveness is dependent on the underlying cause of the disease. For example, if T1D results from a pancreatic dysfunction leading to the loss of beta cells, then islet transplantation may be a viable option. However, if T1D is viewed as an autoimmune disorder, the presence of autoreactive T and B cells can lead to the disease's recurrence and limit the transplantation's efficacy[47]. In such cases, alternative approaches such as immunomodulatory therapies, co-transplantation with immune cells, or encapsulation of islets can be explored to improve the success rate of islet transplantation.

RESULTS ON DIABETES CONTROL AND AVOIDING DIABETES COMPLICATIONS AFTER ISLET TRANSPLANTATION

Patients with T1D or pancreatogenic (type 3c) diabetes (also known as insulin-deficient) may benefit from islet isolation from a deceased donor followed by transplantation of allogeneic islets in the liver. This can help alleviate hypoglycemia while stabilizing glycemic lability, and maintaining glycemic control, ultimately improving quality of life and frequently eliminating the need for insulin therapy. Replacement of islet function by transplantation addresses the underlying pathophysiology of long-standing T1D with sub-total annihilation of islet alpha-cells and the associated loss of the alpha-cell response to hypoglycemia[19]. This allows for the avoidance of hypoglycemia and stabilization of glycemic lability, which would otherwise contribute to impaired awareness of hypoglycemic states. Patients with T1D uncontrolled hyperglycemia, demonstrated by the recurring episodes of diabetes-associated ketoacidosis or quickly progressing severe complications related to the disease, might also benefit from islet transplantation[51,52].

Patients with T1D complicated by an allergy or resistance to insulin that is administered subcutaneously are a rare but essential indication for this treatment[53]. Finally, alloislets (from a viable allograft pancreatectomy) re-transplantation has been successfully executed in a patient with T1D who was initially given the pancreas transplant for hypoglycemia unawareness. Similarly, a T1D patient received simultaneous pancreas/kidney transplantation complicated by pancreas graft arterial anastomosis bleeding[54]. Notably, the degree of glycemic control achieved within the first five days after surgery determines the chances of accomplishing long-term insulin independence[55].

We analyzed the literature data published on islet transplantation focusing on the clinical outcomes [55-60]. Our results have been summarized in Table 1. The total number of included patients was 372. We established that the time for islet cell transfusion varied between 2 and 10 h. Approximately 54% of the patients gained insulin independence at the end of the first year, while only 20% remained insulin-free at the end of the second year. Most patients have received islet cells in the liver, and only 38 patients have IC harvested in the spleen. Another interesting fact we discovered was the high percentage of opioid-free patients after this intervention.

Unfortunately, the Collaborative Islet Transplant Registry reported 71% insulin independence in the first year and 24% in the third from the islet transplant centers[61]. Eventually, most transplanted patients need exogenous insulin within a few years after the transplantation[62].

Some additional factors can also improve the outcomes after islet transplantation. For example, experiments in mice and rats with Vitamin D show promising results on glycemia and tumor necrosis factor-α (TNF-α) production in islet transplantation[63]. In addition, analogs of vitamin D3 are shown to prevent the autoimmune destruction of transplanted islets in non-obese mice[64]. This is a promising direction for research on humans due to the well-known anti-inflammatory effects of vitamin D3 *in vivo* [65,66].

Table 1 Islet transplantation protocols

Ref.	Patients (*n*)	Time of infusion of islets (h)	HbA1c, 1-yr, median (%)	HbA1c, 2-yr, median (%)	Insulin independence 1-yr, median (%)	Insulin independence 2-yr, median (%)	IEQ harvested/g pancreas, median (range)	IEQ transplanted/g pancreas, median (range)	Opioid and pain-relieving	Organ placement
Sutherland *et al*[56]	173	2-7	NR	NR	32	24	< 1000 IE/kg	(> 5000, 2500-5000 and < 2500 IE/kg)	NR	173 liver
Ahmad *et al*[57]	45	7-10	NR	NR	40	NR	NR	297889 ± 49480	72%	45 liver
Rodriguez Rilo *et al*[58]	22	9	NR	NR	41	NR	245457 (range 20850 to 607466-175234)	350428 (range 31500 to 1164000-299321	82%	22 liver
Webb *et al*[59]	46	NR	7	6.7	12	5	1876 (249-12271)	I130029 (24332-958078)	NR	42 liver; 2 spleen; 2 both
Garcea *et al*[60]	50	NR	Approximately 6	Approximately 6	24	10	NR	NR	60%	85 liver
Johnston *et al*[55]	36	8-9	NR	6.8	50	33	358959 (45000–672000)	4308 (769–9942)	30%	36 spleen

HbA1c: Hemoglobin A1c; IEQ: Indoor environmental quality. NR: Not reported.

IMMUNOLOGICAL CHALLENGES OF ISLET TRANSPLANTATION-CELLULAR IMMUNE RESPONSE, INDUCTION OF TOLERANCE, REJECTION

At this point, the main complication after allogeneic islet transplantation is the chronic rejection conducted by activated T cells. This is also the main barrier to accomplishing long-term engraftment. One of the ways to maintain immune tolerance to the allograft is to administer immunosuppression[67].

However, this could be toxic for the islet grafts, leading to worsening long-term function of the islets, increased risk of infections, development of cardiovascular and renal diseases, *de novo* diabetes, neurotoxicity and malignancies[68].

The ultimate goal of islet transplantation is to achieve donor-specific immune tolerance. A recently proposed method for tolerance induction using apoptotic donor lymphocytes (ADLs) in animal models (*i.e.*, non-human primates)[69]. ADLs employ clonal depletion, anergy, expansion of Treg cells, regulatory B cells (Bregs), *etc.* Usually, these mechanisms act together to induce and maintain tolerance. However, this approach also meets several challenges.

Initially, the immune rejection after transplantation starts with innate immune cells infiltration into the islet grafts (*i.e.*, macrophages), followed by donor-specific lymphocyte response, consisting of T cells (CD4+ and CD8+) and B cells. In line with this, the protocol comprised of T cell depletion and anti-TNF agents may enhance short-term graft survival[67]. However, this protocol has a significant drawback-it cannot modulate antibody-mediated rejection[70,71].

Targeting Bregs (*i.e.*, low-affinity antibodies against TIM-1, essential for Breg development) results in considerably longer islet cell survival (about 30% of mice attained engraftment over 3 mo)[72]. Surprisingly, anti-TIM-1 treatment of B cell-depleted recipients significantly increased interferon-γ and prevented the typically seen rise in Th2 cytokines[72].

Furthermore, in a mouse islet transplant model, a combination of anti-CD45RB and anti-TIM-1 antibodies synergized in establishing tolerance in all recipients. Depending on the presence of interleukin (IL)-10-producing B cells in the recipient, the combined antibody therapy significantly increased the regulatory lymphocytes[73]. Furthermore, the study implied that B cells expressing CD19 and TIM-1 are part of tolerance development and maintenance. These results might clarify why B cell reduction decreased the effectiveness of dual antibody therapy.

Cross-reactive memory T and B cells could substantially impede immunological tolerance in animals and humans after transplantation. However, tolerance development in non-human models or humans would be more complex than in rat models, owing to cross-reactive memory immune cells. Yet, a few hopeful treatments exist, such as mixed chimerism through hematopoietic cell transplantation[74,75] or ADL exposure[76], which have led us to anticipate that immune tolerance can eventually be attained in people.

Oura *et al*[77] published the results of a non-human islet transplantation model where a nonmyeloablative condition regimen induced the mixed chimerism-based tolerance. The latter consisted of total

body irradiation, and administration of horse anti-thymocyte globulin, monoclonal antibodies (*i.e.*, anti-CD154, anti-CD8, *etc*.), or cyclosporine (the so-called calcineurin inhibitor-free regimen)[77]. As a result, temporary chimerism did not prompt tolerance to increase the islet graft survival. Eventually, the islet stopped functioning shortly after chimerism disappeared[77]. Oura *et al*[77] also found that islet recipients had greater levels of inflammatory cytokines (*i.e.*, TNF-α and IL-17) in blood circulation than kidney recipients[77]. This study implies that excessive levels of inflammatory mediators following islet transplantation may impede islet graft tolerance induction. Since isolated islet grafts could induce a significant systemic inflammatory response, this should be the focus of future research to improve tolerance development and graft survival.

Induction of immune tolerance utilizing ethylene carbodiimide (ECDI)-fixed splenocytes in combination with particular antigens or peptides is a method used in transplantation models, including islet transplantation. Kheradmand *et al*[78] demonstrated various mechanisms (*i.e.*, anergy, clonal depletion, employment of Tregs, *etc*.) *via* donor ECDI-fixed splenocytes administration. These splenocytes possess direct and indirect allospecificities that target allogeneic host responses. These mechanisms act synergistically to cause tolerance after transplantation[78]. In addition, Tregs and myeloid-derived cells that exert immunosuppression are activated and increased in number in the case of ECDI-fixed splenocytes infusion[79].

Allotransplantation in sensitized patients with pre-formed donor-specific memory lymphocytes and antibodies increases the risk of allograft rejection. Dangi *et al*[80] showed that administration of donor apoptotic cells, anti-CD40L antibodies, and rapamycin before transplantation resulted in a considerable extension of islet graft in allosensitized patients (median survival time, 35 d)[80]. Sato and Marubashi [69] confirmed that invading B lymphocytes play an essential part in the chronic rejection of the islet graft by stimulating local T cells. Therefore, ECDI-fixed splenocytes from the donor infused into sensitized recipients efficiently reduced alloreactive B cells. However, the latter could be switched by contemporary B cell invasion into the graft. As a result, in B cell-depleted patients, a method to regulate concurrent B cell invasion is required[69].

Moreover, islet grafts might be more resistant to immunological tolerance induction. Compared to kidney grafts, the considerably increased immunogenicity of islet grafts may impede tolerance induction in islet transplantation[77]. Islet grafts have relatively strong cytokine secretion activity because pancreatic islets are endocrine cells. Furthermore, cell stressors during the isolation process cause islet inflammation, increasing the immunogenicity of the islet graft before transplantation.

These conclusions imply that the stress during the separation method activates the proinflammatory gene program. Islet isolation entails many steps, including pancreatic distention, digesting with collagenase, and purification. Therefore, the islets should be injured throughout each phase by hypoxia and heated ischemia, production of activated proteolytic enzymes by acinar cells, and oxidative and mechanical stress[69].

According to estimates, around half of the transplanted islets are irreparably destroyed around the transplantation period (from hours to days). In addition, more than a quarter of islet grafts are known to be lost shortly after the portal vein infusion[81]. Therefore, the initial inflammatory response is crucial in instant transplanted islet loss due to immediate blood-mediated inflammatory reaction (IBMIR). During IBMIR, coagulation pathways are activated, proinflammatory cytokines are produced, and innate immune cells infiltrate the graft[82], all contributing to the islet's acute cell-mediated damage. Additionally, IBMIR is distinguished by coagulation and complement systems activation, fast activation and binding of platelets and leukocyte recruitment and infiltration[83].

Preconditioning isolated islets with sublethal genotoxic stress may be a potential technique for lowering islet immunogenicity and extending islet transplant life. It is reasonable to believe that preconditioning therapy for reducing graft immunogenicity will synergistically impact tolerance induction therapy, including the ADL regimen[69].

Applying the cellular treatment is a novel approach to induce local immunotolerance and avoid islet rejection. In addition, the administration of stem cell-derived beta cells during islet transplantation improves graft performance while reducing the negative consequences of systemic immunosuppression. Recent advances in T1D cell replacement treatments (*i.e.*, non-encapsulation and local immunomodulatory techniques) are addressed in this concise review[84]. They include alteration of islet/cell, use of biomaterials that provide immunomodulation, and immunomodulatory cell co-transplantation.

Co-transplantation of pancreatic islets with mesenchymal stem cells (MSCs) is one such approach that has attracted attention. Studies have shown that using MSCs as an adjunct therapy to islet transplantation can promote long-term graft survival, possibly by reducing inflammation and enhancing immune tolerance[85]. For instance, co-transplantation of adipose tissue-derived MSCs and pancreatic islets improved glycemic control and regulation of the Th17/Treg function streptozotocin-induced diabetic mice model[86]. Encapsulation, on the other hand, is another technique that has been extensively studied for its potential to protect transplanted islets from immune rejection while allowing for efficient nutrient and oxygen exchange. In addition, Vegas *et al*[87] demonstrated that beta cells derived from human stem cells, when implanted into mice with preserved immune competence, resulted in long-term glycemic control[87]. Thus, further investigation into these novel strategies for T1D cell replacement therapies may provide new insights and solutions to the ongoing challenges in this field.

Therefore, methods for immunoisolation or beta cell encapsulation are one approach to improving graft performance. Still, it has its own set of obstacles, which causes a loss in cell viability over time (Figure 1B). Although altering human islets in clinical applications is implausible, creating universal cells from pluripotent stem cells that can elude immune identification offers enormous promise in diabetic cell treatments. However, despite these breakthroughs, critical problems like the persistence of genomic and epigenetic modifications and cell phenotypes stability remain unanswered. Additionally, although these cells are hypoimmunogenic, their safety should be carefully maintained because cells that elude the immune system are intrinsically dangerous.

Similarly, undifferentiated stem cells can potentially develop into teratomas *in vivo* because it is well-known that both embryonic and induced pluripotent stem cells can differentiate into all three germ layers. Therefore, they can form teratomas if not fully differentiated[88]. Theoretically, the presence of a few remaining undifferentiated pluripotent stem cells can cause undesirable teratomas after transplantation. Although "suicide genes" could be incorporated into stem cells for increased safety[89], it is still uncertain how these cells would behave in people over time, necessitating additional research.

Biomaterials combined with immunomodulation give multiple instruments for locally modulating immune responses and are an intriguing way to assist cell transplantation. This technique has apparent advantages, including safety as "nonliving" materials. Furthermore, biomaterials are generally simple to mass-produce. In contrast, cell modification or immunomodulatory cell preparation is sometimes difficult, in addition to the necessity of good manufacturing processes that must fulfill clinical requirements. Yet, given the restricted ligands and the eventual exhaustion of coated reagents, the long-term durability of biomaterials and delivery techniques remains challenging. Hence, there is a need for new approaches for the retention or restocking of the supplied reagents in the future[84].

Interestingly, immunomodulatory cells operate as "living" medicine repositories and, if engrafted, may boost functional stability by producing cytokines continuously or expressing surface markers to affect the immune system. Improvements in these immunoregulatory cells' acquisition, retention, stability, potency and localization are required to increase their effectiveness and safety. As we create T1D therapies and cures, a functioning resolution will likely need a multi-modal methodology involving several immuno-modalities and tissue engineering methods. The strategy for the 3D-engineered biomaterial tissue construct coupled with both invisible to the immune response cells and accessory cells that exert could be employed to provide long-term effective and safe cell treatments for T1D. Examining the disease's heterogeneity and customizing therapy procedures is critical to reaching the best possible outcomes[84].

Additionally, because transplanted islets are isolated from deceased donors who are not human leukocyte antigen (HLA)-matched to recipients, the use of multiple donors and the potential need to discontinue immunosuppression in the case of a clinically failed islet-alone graft increases the risk of HLA sensitization in islet transplant recipients. Most transplant patients currently have an unexplained slow loss of islet graft function may be partly caused by allograft rejection. However, discovering anti-HLA antibodies during graft deterioration remains uncommon[90].

FUTURE PERSPECTIVES ON ISLET TRANSPLANTATION

Future pathways for improving the outcomes of islet transplantation include obtaining alternative sources of insulin-secreting cells, attempts to improve the immune protection and revascularization of the transplanted tissue, and methods for enhancing viability[91].

Islets obtained from human embryonic stem cells (hESC) are in early-phase clinical trials[92]. hESC islets should theoretically not require immunosuppression or HLA silencing, which would allow the treatment of children. However, alternative strategies, such as xenogeneic sources of islets and human-induced pluripotent stem cells[93], are also being researched.

Several therapeutical approaches to improve islet survivability are currently in the preclinical phase of research. These include cellular therapies such as MSCs[94], regulatory T-cells[95], as well as modulators of the liver niche with anti-inflammatory agents[96] and growth factors[97]. MSCs appear promising as their anti-inflammatory and immunomodulatory properties have been used in humans for other conditions and could, in theory, enable them to reduce the immunosuppression dose[98]. In addition, improving vascularity through gene therapy[99] of the transplant has also been a sought-after strategy for future development.

Last but not least, various scaffolding methods, as well as alternative implant sites, are undergoing research to enhance the viability of the grafts. For example, dexamethasone-loaded microplate-enriched collagen-coated polydimethylsiloxane scaffolds have improved transplant outcomes and survival[100]. While the liver currently remains the localization of choice for islet transplantation, several other sites are being investigated, such as intramuscular[101], gastric submucosa[102], thymus, testes and the eyes [103].

CONCLUSION

T1DM is an immune-associated metabolic disease characterized by hyperglycemia, absolute insulin deficiency, and a lifelong need for exogenous insulin replacement treatment. The implementation of modern technologies in diabetes control with continuous glucose monitoring systems combined with glucose prediction algorithms enables the development of artificial pancreas delivery systems. Nevertheless, the need to completely replace the depleted pancreatic secretion also leads to the emergence of new therapeutic horizons, including pancreas and islet cell transplantation. They allow not only to achieve independence from exogenous insulin administration and the need to monitor blood sugar but also successfully to afford counterregulatory hormone secretion and pancreatic exocrine function. At this point, the main complication after allogeneic islet transplantation is the chronic rejection conducted by activated T cells and autobodies-mediated rejection, the main barrier to accomplishing long-term engraftment. To improve the outcomes, several approaches are performed: Immunosuppression, ADLs, anti-TIM-1 antibodies, mixed chimerism-based tolerance induction, induction of antigen-specific tolerance utilizing ECDI-fixed splenocytes, infusion of donor apoptotic cells before transplantation, therapy with anti-CD40L antibodies and rapamycin, preconditioning of isolated islets, inducing local immunotolerance, cell encapsulation and immunoisolation, using of biomaterials, immunomodulatory cells, *etc*.

FOOTNOTES

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MINIREVIEWS

Intracranial pressure monitoring in the perioperative period of patients with acute liver failure undergoing orthotopic liver transplantation

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Abstract

Acute liver failure (ALF) may result in severe neurological complications caused by cerebral edema and elevated intracranial pressure (ICP). Multiple pathogenic mechanisms explain the elevated ICP, and newer hypotheses have been described. While invasive ICP monitoring (ICPM) may have a role in ALF management, these patients are typically coagulopathic and at risk for intracranial hemorrhage. ICPM is the subject of much debate, and significant heterogeneity exists in clinical practice regarding its use. Contemporary ICPM techniques and coagulopathy reversal strategies may be associated with a lower risk of hemor-rhage; however, most of the evidence is limited by its retrospective nature and relatively small sample size.

Key Words: Acute liver failure; Liver transplant; Hepatic encephalopathy; Intracranial hypertension; Brain edema

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Core Tip: Despite its rare occurrence, acute liver failure generates academic interest from multiple disciplines because of its multiorgan involvement and high morbidity and mortality. Severe neurological complications may arise, requiring invasive monitoring with the potential risk of fatal intracranial bleeding. Newer strategies could decrease the risks while keeping the benefits.

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INTRODUCTION

Definition and incidence

Acute liver failure (ALF) is a rare syndrome caused by abrupt hepatocyte injury that can progress to a fatal outcome in days to weeks. The most widely accepted definition of ALF includes evidence of coagulopathy and any degree of mental alteration (*i.e.*, encephalopathy) within 26 wk in a patient without preexisting liver disease[1]. Classification according to etiology highlights associated prognostic value and disease-specific treatment. An alternative classification quantifies the interval between symptom onset and development of encephalopathy; hyperacute (0–7 d), acute (8–28 d), and subacute (1–3 mo)[2]. The incidence of ALF in the United States of America is thought to be close to 3000 cases per year[3].

Despite its rare occurrence, ALF generates academic interest from multiple disciplines because of its multiorgan involvement and high morbidity and mortality. The survival from ALF has improved in recent years through better knowledge of pathophysiology, advances in critical care management, and access to emergency liver transplantation (LT)[4].

Etiology, pathophysiology and multiorgan involvement

The pathophysiological process that leads to hepatocyte injury causes either direct toxic necrosis or immune apoptotic injury; the predominant cause for direct injury is acetaminophen toxicity, developing from hours to days[5]. The immune apoptotic injury is a slower injury process, led by hepatitis B infection/reactivation, autoimmune hepatitis, and drug-induced liver injury[6,7]. ALF is characterized by the development of hepatic encephalopathy (HE), and the loss of synthetic dysfunction in the form of coagulopathy. An elevated prothrombin time is a marker of synthetic dysfunction that occurs from the decrease in the vitamin K-dependent coagulation factors (II, VII, IX, X); prolongation of the INR more than 1.5 is considered a poor prognostic sign and a cornerstone of ALF diagnostic criteria.

The pathophysiology of ALF can be divided into primary liver injury specific to etiology and secondary multiorgan failure. The primary liver insult of acetaminophen-induced ALF has the best understood mechanism, namely glutathione depletion. The secondary multiorgan failure, severe systemic inflammation and microcirculatory alterations contribute to a clinical picture comparable to a distributive shock[8]. The vascular tone of the brain and kidneys are most vulnerable, leading to cerebral edema, encephalopathy, and functional renal failure[9].

NEUROLOGICAL DYSFUNCTION IN ALF

The central place of HE in the definition of ALF reflects its key prognostic impact, and its development reflects severely impaired liver function. A multiaxial definition of the syndromes of HE was developed for chronic liver disease by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism based on the type of underlying hepatic abnormality, the time course, and severity of neurological manifestations[10]. The American and European Associations for the Study of Liver Diseases practice guidelines highlights the distinct features of HE in ALF and the association of HE with increased intracranial pressure (ICP)[11].

Cerebral edema and resulting intracranial hypertension (ICH) are the most severe neurological clinical manifestations in patients with ALF. In the past, cerebral edema was presumed to occur in up to 80% of patients with ALF. However, recent data from developed countries estimates a drop in the incidence to 20%-30%, probably due to earlier diagnosis and improved management[12].

Pathogenesis of brain edema in ALF

The pathogenesis of cerebral edema in ALF is complex and only partially understood, and its occurrence is related to the severity of encephalopathy. Cerebral edema is occasionally observed in patients with grade I-II encephalopathy; moreover,the risk of edema increases to 25% to 35% with progression to grade III, and 65% to 75% or more in patients reaching grade IV coma[13].

Potential contributing factors include cytotoxicity due to osmotic effects of ammonia, glutamine, and proinflammatory cytokines, vasogenic edema due to disruption of the blood-brain barrier with the rapid accumulation of low molecular substances, and the loss of the cerebral blood flow autoregulation.

Multiple studies support astrocyte swelling and cytotoxic edema as major contributors to cerebral edema in ALF[12,14,15]; the evidence is most compelling in the central role of ammonia causing astrocyte swelling. The ammonia-glutamine hypothesis has persisted over years, describing an excess of ammonia in the brain which is converted to glutamine with resulting osmotic effects on astrocytes. New studies have challenged this hypothesis, concluding that astrocyte swelling may not be the result of glutamine's direct osmotic effect; instead, a "Trojan horse" hypothesis is proposed in which glutamine may function as a carrier of ammonia into the mitochondria where its accumulation can lead to oxidative stress and ultimately cellular swelling[16]. Oxidative stress has been implicated as an important factor in the pathophysiology of ammonia-induced neurotoxicity through the formation of free radicals which may result in mitochondrial permeability transition[17].

Other studies have suggested that neuroinflammatory mediators, particularly proinflammatory cytokines such as the interleukins (IL)-1β and IL-6 and tumor necrosis factor-α, play an essential role in the development of brain edema and ICH[18,19]. Neuroinflammation is now widely considered the result of a direct interaction between microglia and ammonia. The released proinflammatory cytokines from activated microglia cells and ammonia appear to act synergistically to induce cytotoxic cerebral edema in which the blood-brain barrier is preserved.

Research combining brain imaging in the context of ALF demonstrates evidence of interstitial brain edema in addition to cytotoxic brain edema, implying the presence of vasogenic edema, in which the blood-brain barrier would be compromised[20,21]. Although a generalized breakdown of the blood-brain barrier cannot be demonstrated, some studies propose the "leaky" theory, in which there are subtle changes in the integrity of the tight junctions of the blood-brain barrier. The exact mechanism of how cytotoxic, vasogenic, and neuroinflammation interact to bring brain edema in ALF remains unknown.

The role of ICP monitoring in ALF

The Brain Trauma Foundation guidelines explicitly recommend ICP monitoring (ICPM) for patients with severe traumatic brain injury to minimize mortality[22]; however, recommendations for ICPM in patients with non-traumatic brain injury are lacking. The rationale for using monitors to measure the pressure inside the cranium in ALF considers the potential benefit of early identification and management of ICH. In addition, continuous ICP measurements contribute to the decision-making process for emergency LT; intraoperative ICPM facilitates active neurological management in the setting of rapid fluid shifts and hemodynamic instability.

Invasive ICPM remains the gold standard for the measurement of ICP[23], which may reveal occult elevations in ICP in comatose patients with ALF[24]. Despite the proposed benefits, invasive ICPM in this unique patient population raises concern due to the risk of life-threatening intracranial hemorrhage in the setting of coagulopathy.

Noninvasive ICPMs offer an alternative solution in this specific group of patients, employing techniques of optic nerve ultrasound and transcranial doppler. However, current evidence does not support its use to accurately identify patients with ICH. One study evaluated noninvasive ICPM techniques in comparison to the gold standard of invasive ICPM; the authors concluded that neither optic nerve ultrasound nor transcranial doppler pulsatility index correlated with the gold standard[25]. Another standard noninvasive option is cerebral computerized tomography, yet, evidence demonstrates this method's failure to consistently detect brain edema in patients with elevated ICP[23]. In addition, the complexity of intrahospital transport for critically ill patients should not be underestimated.

With invasive ICPMs identified as the most accurate modality to identify ICH in patients with ALF, several invasive options exist. Transducers may be placed in the brain parenchyma, ventricular system, epidural or subdural spaces. Epidural devices have lower complication rates than subdural or intraparenchymal monitors[26]. A ventricular system has the potential to be diagnostic and therapeutic as cerebrovascular fluid can be drained; however, intraventricular placement may be associated with severe and potentially fatal hemorrhage.

LT in ALF

With high-grade HE identified as an independent predictor of mortality in patients with ALF, LT is a potentially life-saving intervention[27]. Access to emergency LT has improved survival rates for patients that fulfill criteria for a poor prognosis. The King's College Criteria remains the most clinically useful prediction tool, with disease-specific modeling for paracetamol and non-paracetamol categories[28]. Post-LT outcomes in this population are high with one- and three-year patient survival rates reported as 91% and 90% respectively[28].

Consensus guidelines for ICP monitor use

A review of the current literature highlights the lack of consensus regarding the use of ICPM in patients with ALF. The Acute Liver Failure Study Group guidelines does not recommend the use of external ventricular devices to monitor ICP for all patients with ALF; however, they recognize that most centers will place ICPM in patients with advanced encephalopathy[29,30]. A survey of 24 centers in the United States of America demonstrated that a minority (approximately 30%) of centers utilized ICPM[31].

Invasive ICPM use in Europe is more prevalent with 55% of centers surveyed reporting use of this monitoring modality[26]. In both surveys, invasive ICPM was reserved for patients with advanced encephalopathy according to The West Haven criteria; the type of invasive monitor use was not specified. The American Association for the Study of the Liver recommends invasive ICPM in patients with ALF awaiting LT and in centers with expertise[28]; The European Association for the Study of the Liver recommends monitoring only in a select group of patients including those with advanced encephalopathy at risk of ICH, hyperammonemia, and renal or vasopressor support[32]. Table 1 summarizes the current large-society recommendations.

Robust data regarding the impact on long-term neurological consequences of cerebral edema and ICH in patients with ALF is scarce. Similarly, evidence reporting outcomes associated with the use of ICPM in this patient population is also lacking. Karvellas *et al*[33] reported a multicenter retrospective cohort study involving 140 patients managed with ICPM *vs* 489 controls without ICPM; the mortality at 21 d was not significantly different[33].

The incidence of spontaneous intracranial hemorrhage in ALF

The estimated risk of spontaneous intracranial hemorrhage in overt encephalopathy grade III and IV is 25%-35% and 65%-75% respectively[34]. The incidence of intracranial hemorrhage has decreased over many years. Bernal *et al*[4] reported a series of 3300 patients, in which intracranial hemorrhage occurred in more than 70% of patients on initial analysis with a dramatic reduction in incidence to only 20%, with a corresponding reduction in mortality, 20 years later[4]. The same author reported 29% incidence of intracranial hemorrhage in a series of more than 160 patients with overt encephalopathy[14]. The risk factors for intracranial hemorrhage include hyperacute presentation, younger age, and requirements of vasopressors or renal replacement therapy[14,35].

Risk of bleeding and outcomes from the use of invasive ICPM in ALF

The general incidence of hemorrhagic complications from ICPM is approximately 10%-20% with fatal hemorrhage reported in 1%-5% of patients[31,36]. The risk of intracranial bleeding is related to the type of device and location of the ICPM placement. Some authors claim a reduction in bleeding risk by a meticulous insertion technique and targeted peri-procedural transfusion (*e.g.*, recombinant factor VIIa prior to the placement of the ICPM)[37]. A literature search from 1992 to 2017 shows eleven studies reporting the use of ICPM in ALF;only four of these studies described an institutional protocol to correct the coagulopathy prior to the insertion of ICPM. Variable use of peri-procedural blood product transfusion was observed.

Another potential complication associated with ICPM insertion is infection. The general risk of infection is approximately 1%-20%[38]. To our knowledge, ALF patients have no associated increase in infection risk; however, data is limited. Multiple small case series demonstrated a low incidence of ICPM-related infections[24,37,39]. Reported rates of infection ranged from 0%-7%. A common practice to reduce infection risk is the administration of prophylactic intravenous antibiotics to cover the typical skin flora prior to ICPM placement.

TECHNICAL ASPECTS FOR ICPM

It is important to acknowledge that regardless of the transducer selected, the management of ICP should be guided by the cerebral perfusion pressure. The cerebral perfusion is estimated by the difference between the mean cerebral arterial pressure and the ICP. To ensure accurate measurement of cerebral arterial pressure, it is recommended that the arterial line transducer should be positioned at the external auditory meatus, level with the middle cranial fossa[40].

Interventions for managing brain edema and ICH in ALF are out of the scope of this article. However, standard measures are to maintain adequate sedation, head elevation at 30 degrees, target plasma sodium levels of 145 to 155 mEq/L, maintain normocapnia with a CO_2 of 35 mmHg, a plasma osmolarity of 320 mOsml/L, a mean arterial blood pressure of 75-80 mmHg, and temperature between 32-34 °C for 10-14 h in candidates for LT[41].

SINGLE-CENTER EXPERIENCE

Using the limited evidence and large-society guidelines, a protocol was developed and implemented to guide management of severe neurological consequences of ALF in our center. Integral to this document is the recommendation for the use of invasive ICPM in carefully selected patients. Protocol development engaged representatives from all multidisciplinary stakeholders including hepatology, anesthesia, critical care, and surgery. Explicit clinical criteria outlined patients appropriate for invasive ICPM use.

As outlined in this protocol, patients with high-grade HE (grade III and IV) in the context of ALF, with the possibility of recovery from medical intervention and/or LT, warrant ICPM insertion.

Table 1 Summary of recommendations for intracranial pressure monitor in patients with acute liver failure

Society	Recommendation	Quality of evidence
AASLD 2005[1]	ICPM is mainly considered for patients who are listed for transplantation. In the absence of ICPM, frequent evaluation for signs of intracranial hypertension is needed to identify early evidence of uncal herniation	Evidence level III
AASLD Revised 2011[28]	The use of recombinant factor rVIIa may be considered	NA
ALSFG 2007[30]	Insufficient data to recommend ICPM placement in all patients with ALF. However, most members of the ALFSG place ICPM in patients with advanced (stage III/IV) hepatic encephalopathy	NA
EASL 2017 [32]	ICPM should be considered in a highly selected subgroup of patients, who have progressed to grade 3 or 4 coma, are intubated and ventilated and deemed at high risk of intracranial hemorrhage, based on the presence of more than one of the following variables: (1) Young patients with hyperacute or acute presentations; (2) ammonia level over 150–200 lmol/L that does not drop with initial treatment interventions (RRT and fluids); (3) renal impairment; and (4) vasopressor support (> 0.1 lg/kg/min)	(Evidence level II-3, grade of Recommendation 1)

AASLD: American Association for the Study of Liver Diseases; ALSFG: United States Acute Liver Failure Study Group; EASL: European Association for the study of the Liver; ICPM: Intracranial pressure monitor; RRT: Renal replacement therapy; ALF: Acute liver failure; rFVIIa: Recombinant factor VIIa; NA: Not available.

Due to the risk of severe brain edema, eventually obliterating the ventricles, our neurosurgical team is reluctant to use external ventricular devices, in addition to the increased risk of periprocedural hemorrhage. In our protocol, we use the Codman Microsensor™ intraparenchymal monitor, which measures ICP *via* a strain gauge microchipat the catheter's tip. Pressure is reflected as an electrical voltage transmitted to the proximal end of the catheter through nylon-encapsulated copper wires. The proximal end of the catheter is connected to the Codman Express™ monitor, which displays the ICP value. Following baseline brain imaging andbefore insertion, the ICPMis zeroed at atmospheric pressure; after insertion, opening pressure is determined, and real-time display and longitudinal recordings are obtained.

To minimize the risk of ICPM-associated hemorrhage, coagulation correction is frequently undertaken prior to device insertion. It is generally accepted that conventional coagulation tests (*e.g.*, INR and platelet count) provide a limited perspective of *in vivo* clot formation in patients with liver disease. With the growing popularity of viscoelastic testing (VET) to guide coagulation management during LT, VET has been proposed as a more comprehensive tool to facilitate invasive procedures such as ICPM insertion. Our protocol utilizes a combined approach of VET and conventional laboratory testing. In our early institutional experience, directed administration of recombinant factor VIIa, fibrinogen, platelets, and desmopressin has enabled intraparenchymal monitor insertion, maintenance, and removal without hemorrhagic complications.

CONCLUSION

Future prospective studies are necessary to address the existing gaps in knowledge outlined in this review. Given the rarity of ALF, and the broad spectrum of presentation, it is unlikely that single-center studies will provide robust evidence. Most of the protocols currently in place, including the one used in our center, are derived from retrospective observational and expert consensus statements. It is paramount to define the specific population of patients in which insertion of ICPMs changes outcomes and standardized transfusion protocols to minimize the associated risk of bleeding.

FOOTNOTES

Author contributions: All authors contribute to the review of literature, first author Mendoza Vasquez LE wrote the initial manuscript that was extensively reviewed and changed by the other two authors.

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MINIREVIEWS

Women's health issues in solid organ transplantation: Breast and gynecologic cancers in the post-transplant population

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Abstract

The success of solid organ transplant has steadily improved which has led to a unique set of post-transplant issues. The rates of *de novo* cancer in the solid organ transplant recipient population are higher than those in the general population. There is growing evidence that breast and gynecologic cancers may have a higher mortality rate in post-transplant patients. Cervical and vulvovaginal cancers specifically have a significantly higher mortality in this population. Despite this increased mortality risk, there is currently no consistent standard in screening and identifying these cancers in post-transplant patients. Breast, ovarian and endometrial cancers do not appear to have significantly increased incidence. However, the data on these cancers remains limited. Further studies are needed to determine if more aggressive screening strategies would be of benefit for these cancers. Here we review the cancer incidence, mortality risk and current screening methods associated with breast and gynecologic cancers in the post-solid organ transplant population.

Key Words: Cancer screening; Solid organ transplant; Female-specific cancer

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Core Tip: Survival after solid organ transplant is continually improving. Because of this, patients are living longer and are requiring long-term monitoring for malignancies. There is growing evidence that breast and gynecologic cancers (specifically cervical and vulvovaginal cancers) may have a higher mortality rate in post-transplant patients. Despite this increased mortality risk, there is currently no consistent standard among transplant societies for screening and identifying these cancers in post-transplant patients. Ultimately, data are not robust and further studies are needed to determine if more aggressive screening strategies would be of benefit for these cancers.

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INTRODUCTION

Overall, survival following solid organ transplant (SOT) has improved considerably since the first successful kidney transplant was performed in 1954. The female post-transplant population is growing as well; with women constituting 38% of liver transplant recipients in 2021 *vs* 35% in 2011[1]. Improvement in post-transplant survival, along with the growing female transplant recipient population presents unique concerns with regards to post-transplant sex-specific cancer screening. There are currently no American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL), Kidney Disease: Improving Global Outcomes (KDIGO) or International Society for Heart and Lung Transplantation (ISHLT) guidelines regarding post-transplant specific screening methods for gynecologic or breast cancers following liver, kidney, heart, or lung transplantation[2-6]. Here we will review the incidence and current screening standards for breast and gynecologic (particularly cervical, ovarian, uterine, and vulvovaginal) cancers following SOT. The data included in this paper is extracted from studies including solid organ transplant recipients (SOTRs). It is challenged to define the rates and true causality of *de novo* cancers in the post-SOT population. There is a growing body of evidence suggesting that cancer diagnosis and cancer-related mortality are increased in post-transplant patients as compared to the general population. Here, we will review the incidence and mortality data available for breast and gynecologic cancers as well as the current screening recommendations for the general population in comparison to the post-transplant population. Although these cancers affect a small proportion of all SOTRs, they bear significance as their mortality rates appear to be considerably higher than in the general population.

CANCER RISK FOLLOWING TRANSPLANTATION

Analysis from SOTRs registries suggests there is a higher incidence of cancers in the post-transplant population as compared to the general population[7]. Most studies analyze the incidence of cancer post-transplant utilizing the standardized incidence ratio (SIR), which depicts the relationship between the observed and expected cancer cases among post-transplant patients compared to the general population. A Swedish study conducted in 2003 demonstrated SIR of 4.0 for developing a first cancer post renal, hepatic or other organs from 1970 to 1997[8]. Watt *et al*[9] found that malignancy was responsible for 22% of deaths greater than one year after liver transplant in a population of 798 patients [9]. Although the cancer risk post-transplant remains high, incidence of *de novo* malignancy following transplantation is improving over time. In a Nordic cohort of greater than 4000 post-liver transplant patients followed over three decades, there was a noted era-dependent decrease in SIR[10]. The SIR for all cancers in this population decreased each decade from the 1980s to the early 2000s, however cancer incidence remained elevated compared to the general population. These findings were attributed to changes in immunosuppression regimens as well as changes in cancer screening protocols and patient follow up. The majority of *de novo* cancers following transplantation are cutaneous and lymphoid, and have been previously linked to the degree of immunosuppression[11-13]. However, there is also a large category of viral infection-related cancers, including cervical, vulvar and vaginal cancers which affect women in particular. 12805 kidney transplant recipients registered in the Netherlands Organ Transplant Registry were followed for a total of 89651 person-years with an incidence of cancer of 7.1 percent as well as a survival reduction of nearly 5 years despite 69 percent dying with a functioning renal graft. The authors also highlighted that 62% of patients diagnosed with *de novo* breast cancer and 64% of patients diagnosed with gynecologic cancers died from their respective cancer; both mortality rates are considerably higher than the general population[14]. This increase in cancer-related mortality is striking and begs the question of its true relationship to SOT or immunosuppression. But the mortality rates

urge those managing post-transplant patients to explore perhaps more aggressive cancer screening strategies.

Cervical cancer

Cervical cancer is primarily caused by the oncogenic human papillomavirus (HPV) infection[15,16]. Although the incidence and mortality of cervical cancer has decreased since the adoption of routine screening with Papanicolaou (Pap) smear, cervical cancer continues to have a considerable impact on the United States population[17]. Cervical cancer had an incidence rate of 7.5 in the general population in 2019[18]. There is varying data on the incidence of cervical cancer in post-transplant populations. However, several studies showed an increased risk of cervical cancer, particularly in the younger post-transplant population[8,19-21]. In a study published by Madeleine *et al*[19] in 2013, there was a SIR of 3.3 for *in situ* cervical carcinoma in SOTRs, and a SIR of 1.0 for invasive cervical cancer[19]. After adjustment for age, this study found that younger recipients (18–34 years old) had a higher incidence of *in situ* cervical cancer. Using incidence rate ratio (IRR), which compares between subgroups of the transplant population (in this case, age), an IRR of 4.7 for *in situ* cervical cancer and an IRR of 2.4 for invasive cervical cancer in the younger transplant recipients was noted compared to older transplant recipients. Another study found a statistically non-significant mild increase in cervical cancer post-SOT with SIR of 2.6 [95% confidence interval (CI): 0.1-15][20]. Adami *et al*[8] found cervical carcinoma *in situ* SIR of 1.3 (95%CI: 1.0-1.8) among patients transplanted with kidney, liver or other organs[8]. A separate study published from data utilizing Swedish and Danish SOTR registries discovered a significantly increased incidence of cervical cancer compared to the general population with SIR 2.6 (95%CI: 1.6–4.5) [21]. Although the rate of cervical cancers varied between these studies, they illustrate a concern for increased risk for cervical cancers in the SOTR. These studies again highlight the concern for a significant change in incidence of cancer post transplantation. These studies also do not clearly delineate the rates of cervical cancer screening in post-transplant patients. But given the incidence, continued diligence seems necessary. Particularly when considering the increased mortality risk related to gynecologic cancers.

Breast cancer

Breast cancer is the most commonly diagnosed cancer among women in the United States and was the second leading cause of cancer-related deaths in 2021[18,22]. The etiology is thought to be multifactorial due to the presence of proliferative breast disease, reproductive factors and genetics and is impacted by several factors such as demographics and environmental exposures[22]. Given the incidence of breast cancer in the general population, most transplant centers require breast cancer screening prior to transplant listing. Several studies have shown a decreased risk of breast cancer which is likely a consequence of pre-transplant screening methods[23-25]. In one study of 1000 post-liver transplant patients, 57 of whom developed cancer after transplantation, the SIR for breast cancer was 0.74 (95%CI: 0.15-2.16, $P > 0.05$)[23]. Another study by Oruc *et al*[24] found the incidence rates of *de novo* breast cancer following liver transplant at the University of Pittsburgh were similar to incidence of breast cancer in the general population with incidence rate of 523.6 per 100000 women in the post-transplant population. Though it is worth noting the incidence rate of breast cancer in the general population at the time was a bit lower than that observed in post-transplant patients, this was not found to be statistically significant [24]. Engels *et al*[25] found a significantly decreased SIR in breast cancer. Among 1700 SOTRs, there was a SIR of 0.85 (95%CI: 0.77-0.93). The authors attribute this significant decrease in risk to pre-transplant cancer screening[25].

Ovarian and endometrial cancer

Ovarian cancer is the second most common gynecologic cancer and the most common cause of gynecologic cancer-related death in the United States[26]. The most common histopathologic type is epithelial ovarian cancer. There are many risk factors for epithelial ovarian cancer; increased age, polycystic ovarian syndrome, endometriosis, infertility, and genetic predisposition (particularly presence of BRCA 1 or 2 mutation and Lynch Syndrome)[26]. Most studies in SOTRs found the SIR for ovarian cancer did not have a statistically significant increase compared to the general population, with a range of 1.2-2[8,9,21,27]. One study did find an increased incidence of *de novo* ovarian cancer arising in patients with a prior breast cancer diagnosis with an incidence of one in 6.5 women *vs* one in 385 for the rest of the study population[28]. Most studies show a statistically non-significant increase in SIR for ovarian cancer One study did show a very mildly decreased SIR of 0.95 for ovarian cancer following SOT, however this was not statistically significant (95%CI: 0.7-1.24)[25]. There is little evidence for ovarian cancer-related mortality within the SOTR population. However, one Korean study found the standardized mortality rate (a comparison in mortality due to the cancer between the transplant population and the general population) for ovarian cancer was 4.0 (95%CI: 2.1-6.5) in female kidney transplant recipients[29]. This study had a higher incidence of ovarian, gynecologic and breast cancer as compared to SOTR studies within North America. The reason for this difference is not clearly elucidated in this paper. The authors postulate the difference may be due to a focus on a later transplant epoch in the Korean population, higher proportion of female transplant recipients (43% *vs* 36%), genetic predis-

position, possible unique environmental exposure of the Korean population, different immunosuppression regimens or different screening and surveillance protocols[11,29].

Endometrial cancer develops in about 3 percent of females in the United States[30]. The more common type 1 endometrial cancer tends to present at an earlier stage and has a better prognosis than type 2 for the general population. Risk factors for type 1 endometrial cancer include excess estrogen unopposed by progestin, genetic predisposition (Lynch Syndrome), obesity, nulliparity, hypertension and diabetes[30]. In most post-SOT studies published, there does not seem to be a statistically significant increase in risk for development of endometrial cancer. Multiple studies have demonstrated SIR ranging from 0.86 to 1.4 without statistical significance[20,21,25]. However one study utilizing data from the Australian and New Zealand SOT registry did find a significant increase in uterine cancer with SIR 1.85 (95%CI: 1.16-2.93)[27,31]. The difference in incidence in this study appears to be anomalous compared to other post-SOT studies.

Vulvar and vaginal cancer

Vulvovaginal cancers are less common in the United States compared to the rest of the world. The incidence of vulvar cancer was 2.5 in 100000 women in 2019; the true incidence of vaginal cancer is unknown, however the estimated incidence of vaginal carcinoma *in situ* is 0.1 in 100000[18,32,33]. Most cases of vaginal cancer in the United States are linked to HPV infection, similar to cervical cancer. Risk factors include multiple lifetime sexual partners, current cigarette smoking, early age at first intercourse [32,33]. Vulvar cancer is less common than the other gynecologic malignancies in the United States, and tends to be diagnosed at earlier stages. Similar to cervical and vaginal cancer, it is also linked to HPV infection. Other risk factors include prior history of cervical cancer or intraepithelial neoplasia, current cigarette smoking, vulvar lichen sclerosis, immunodeficiency syndromes and northern European descent[32]. Most studies found a dramatic increase in rates of vulvar, vaginal or combination of the two malignancies in post-transplant patients which is postulated to be due to viral infection with HPV[34, 35]. In a retrospective study of female renal transplant patients over the age of 40 years, Meeuwis *et al* [36] found 92% of cervical and vulvovaginal cancers were associated with HPV, specifically HPV 16 in 53.8% of cases[36]. In most studies, there was a statistically significant increase in vulvar and vaginal cancers, with SIR ranging from two to forty-five-fold increase compared to the general population[8,19, 20,25,27]. One study found a higher incidence of *in situ* vulvar cancer in younger SOT patients (age 18-34 years) with an increase in IRR to 4.1 (95%CI: 3.0-5.6) for vulvar cancer compared to women transplanted over the age of 35. This study found that younger age at transplant, older immunosuppressive regimens containing azathioprine and cyclosporine, and increased time since transplant were associated with a higher incidence of *in situ* vulvar cancer. Additionally, they found higher incidence of *in situ* rather than invasive genital cancers; potentially due to diagnosis of cancer at earlier stages with screening, or owing to the nature of vulvovaginal cancers being symptomatic, even at early stages[19, 30]. There is sparse data regarding mortality specifically due to vulvar or vaginal cancer across SOTR studies. This may be due to diagnosis at earlier stages and consequently higher rates of remission after treatment.

CURRENT SCREENING STANDARDS

More aggressive cancer screening methods are known to improve detection of cancer and in to thus improve cancer-related mortality rates. Finkenstedt *et al*[37] introduced an intensified surveillance protocol in their post-liver transplant patients and were able to improve the detection of *de novo* cancers from 4.9% to 13%. They also observed more *de novo* malignancies diagnosed in earlier stages[37]. Despite studies such as this, there is no SOTR-specific guideline or guidance for breast or gynecologic cancers aside from cervical cancer surveillance. The ISHLT recommends employing the same general malignancy screening and surveillance methods used for the general population in pre- and post-heart and lung transplant patients with respect to breast and gynecologic cancers[5,38]. The American Society of Transplantation (AST) recommends annual pelvic exam with Pap smear for post-kidney transplant patients[39]. The KDIGO recommends age-appropriate cancer screening in pre- and post-transplant patients in their latest guidance statement, however no specific screening for ovarian, endometrial or vulvovaginal cancers[6,40]. Thusly, the screening strategies included below are those suggested for the general population and, if available, those recommended for the SOTR population (Table 1).

Breast cancer screening: Breast cancer screening, like many other cancer screenings relies heavily upon risk designation of the individual being screened. Screening modality, time at which to start screening and risk-reducing measures differ from the average risk population for women who are considered moderate or high risk. Currently, immunosuppression and transplant status are not considered to increase risk and thus average risk breast cancer screening strategies should be applied to these groups. Screening is recommended by most United States government-sponsored groups and medical societies for average risk women beginning at age 50 with mammography every 1-2 years, with interval frequency based on imaging findings. For women age 40-49 years, it is recommended a conversation

Table 1 Breast and gynecologic cancer screening recommendations and incidence rates as compared to the general population

Cancer type	Current standard guidelines	SOTR specific recommendations	Rates of malignancy in SOTR: Increased (+), Same (=), or Less (-) than general population
Breast cancer	Mammography every 1-2 yr in women > 50 years old (for average risk). Discussion for screening beginning at age 40 yr	Mammography prior to transplantation if > 50 yr; otherwise, same screening interval as the general population	-
Cervical cancer	Women 21 to 29 years old should have a Pap test alone every 3 yr. HPV testing alone can be considered for women who are 25 to 29 years old, but Pap tests are preferred	Pap if younger than 30 years old at transplant, co-testing with Pap and HPV is preferred beginning at age 30 yr but annual Pap is considered adequate	+
	Women who are 30 to 65 years old have three options for testing: Pap and HPV (co-testing) every 5 yr. Pap alone every 3 yr. Or they can have HPV testing alone every 5 yr	If performing co-testing with HPV and Pap: If results of baseline Pap and HPV testing are normal, co-testing can be performed every 3 yr. If the patient is transplanted prior to age 21, it is recommended screening begin within 1 yr of initial engagement of sexual activity	
Vulvar and vaginal cancer	No current screening strategy for the general population, however recommended annual pelvic exam in patients with HIV	AST recommends annual pelvic exam for kidney transplant patients; otherwise, no consistent guidance across societies	+
Endometrial cancer	No current screening strategy	No current screening strategy	=/-
Ovarian cancer	No current screening strategy	No current screening strategy	=/-

SOTR: Solid organ transplant recipient; Pap: Papanicolaou smear; HIV: Human immunodeficiency virus; AST: American Society of Transplantation.

regarding screening is initiated, but screening itself has not shown mortality benefit in this population [41,42].

Cervical cancer screening and prevention: There is considerable data for women post-transplant supporting a more aggressive screening approach than for the general population[13,19]. There is a consensus statement published in 2019 by the American Society for Colposcopy and Cervical Pathology recommending the following: Cervical cytology if the patient is younger than 30 years at transplant, co-testing with cytology and HPV is preferred beginning at age 30 years but cytology is considered adequate. If only performing cytology, annual cytology is recommended; if 3 consecutive cytology results are normal, the interval frequency may be increased to cytology every 3 years. If performing co-testing with HPV and cytology: If results of baseline cytology and HPV testing are normal, co-testing can be performed every 3 years. If the patient is transplanted prior to age 21, it is recommended screening begin within 1 year of initial engagement of sexual activity. Continuation of screening throughout the patient's lifetime is recommended. A discussion regarding quality and duration of life should be pursued prior to discontinuation of screening[43]. There is currently guidance regarding HPV vaccination in pre-transplant populations. Currently, it is recommended by the AASLD to administer the quadrivalent HPV vaccine prior to listing for transplant in women up to the age of 45 years[44]. There is evidence that the HPV vaccine is safe in the immunocompromised population, including SOTRs[45]. However, it is worth noting the immunogenicity of the vaccine is lower in certain circumstances: Lung transplant recipients (57.1% response rate 7 mo after vaccination), high doses of tacrolimus, and vaccination in the early post-transplant period[46]. Further studies are required to assess the benefit of repeating the vaccine series to improve response rates and the effect of this on decreasing vulvovaginal and cervical cancers in the SOTR population.

Vulvovaginal cancer screening: There are currently no screening strategies for vulvovaginal cancer other than pelvic exam. The AST recommends annual pelvic exam in post-kidney transplant patients, however most other SOT societies lack guidance in this area[39]. Diagnosis of vulvovaginal cancers rely upon visual assessment with histopathologic confirmation. The American College of Obstetricians and Gynecologists (ACOG) primarily focuses on methods of prevention including administration of the quadrivalent or nonavalent HPV vaccine[47]. There is growing evidence of increased risk for vulvovaginal cancers among HIV patients due to immunosuppression and concomitant HPV infection. Because of this, annual pelvic exam with close attention paid to visual inspection is recommended in this population[48]. Although the means of immunocompromise/immunosuppression differ between the HIV-infected population and the post-transplant population, the dramatic increased incidence of

vulvovaginal cancers in the HIV-infected population could serve as evidence for more aggressive screening methods in other immunocompromised (or immunosuppressed, in this case) populations. Although there are not specific recommendations regarding screening for vulvovaginal cancers, they are by default screened for by means of pelvic exam during cervical cancer screening-which does have recommendations by transplant societies and the ACOG[2,4-6,13,43]. In one recent review of gynecologic malignancies post-liver transplant, annual pelvic exam is recommended[49]. It is possible that as vulvovaginal cancers are diagnosed in early stages, the mortality rate is relatively low. However, treatment can potentially include chemotherapy, radiation and excision (depending on the stage); all of which have considerable risk and cost to the patient[50].

Ovarian cancer screening: There is currently no recommended screening strategy for ovarian cancer in women of low or average risk within the general population. Furthermore, there is no screening test leading to the early detection of ovarian cancer that reduces ovarian cancer mortality, regardless of risk [51]. One study found an incidence of 1 in 6.5 cases of ovarian cancer in pts with a prior history of breast cancer suggesting closer follow up/screening for this population[28]. Obtaining a detailed family history to identify high risk patients is essential. Patients with family history of breast or ovarian cancer, patients of Ashkenazi Jewish descent, and patients with known hereditary syndromes such a BRCA 1 or 2 mutation or Lynch Syndrome (among others) are identified as high-risk for developing ovarian cancer and should be considered for referral to genetic counseling. Patients with the presence of high-risk genes may benefit from risk-reducing techniques such as bilateral salpingo-oopherectomy[52].

Endometrial cancer screening: Current screening strategies for endometrial cancer rely upon presence of clinical signs/symptoms (such as uterine bleeding) in both average and high-risk patients. It is recommended patients with a genetic predisposition such as Lynch Syndrome or Cowden Syndrome potentially undergo endometrial tissue sampling every 1-2 years starting at age 30-35 years and risk-reducing hysterectomy[53,54].

CONCLUSION

While overall survival and incidence of cancer post-SOT are improving, cancer-related mortality across all cancers remains considerably higher in the post-transplant populations that have been studied as compared to the general population. Despite limited series, cervical and vulvovaginal cancers appear to be the highest risk of incidence of the gynecologic cancers following SOT. Breast cancer does not appear to have a higher incidence following transplantation, and screening methods used in the general population should be sufficient. Ovarian and endometrial cancer rates vary among post-SOT populations[8,9,21,27]. For the most part, they are not significantly increased with exception of patients with a genetic predisposition[28]. Careful history-taking with particular attention to familial cancer syndromes is key in identifying this population.

The lack of uniform gynecologic cancer screening recommendations post-SOT may be due to the small amount of existing evidence. Many studies either combine ovarian, uterine, cervical and vulvovaginal cancers together into a "gynecologic cancer" group or fail to mention vulvovaginal cancers entirely. The incidence of these cancers appears to be small when compared to other cancers. Data regarding mortality from breast and gynecologic cancers is also lacking in these patients. The existing data does appear to indicate a substantially higher mortality rate for SOTRs with breast and gynecologic cancers.

Despite these limitations, there are certain modifiable risk factors to which all Physicians managing the post-transplant population should be aware. As the most common risk factor for vulvovaginal and cervical cancer is infection with HPV, efforts should be focused on prevention (with HPV vaccination in those less than 45) as well as screening in order to decrease the associated morbidity and mortality of these malignancies.

Further studies regarding breast and gynecologic cancer in SOTRs is required to assess the respective incidence and mortality in order to direct screening and surveillance of these cancers. The decreasing age at transplant, growing female transplant population and improved survival post-transplant necessitate improved guidance regarding screening and surveillance of breast and gynecologic cancers among SOTRs.

FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Pre-Lung transplant reflux testing demonstrates high prevalence of gastroesophageal reflux in cystic fibrosis and reduces chronic rejection risk

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Abstract

BACKGROUND

Gastroesophageal reflux (GER) has been associated with poor outcomes after lung transplantation for chronic lung disease, including increased risk of chronic rejection. GER is common in cystic fibrosis (CF), but factors influencing the likelihood of pre-transplant pH testing, and the impact of testing on clinical management and transplant outcomes in patients with CF are unknown.

AIM

To evaluate the role of pre-transplant reflux testing in the evaluation of lung transplant candidates with CF.

METHODS

This was a retrospective study from 2007-2019 at a tertiary medical center that included all patients with CF undergoing lung transplant. Patients with pre-transplant anti-reflux surgery were excluded. Baseline characteristics (age at transplantation, gender, race, body mass index), self-reported GER symptoms prior to transplantation, and pre-transplant cardiopulmonary testing results, were recorded. Reflux testing consisted of either 24-h pH- or combined multichannel intraluminal impedance and pH monitoring. Post-transplant care included a standard immunosuppressive regimen, and regular surveillance bronchoscopy and pulmonary spirometry in accordance with institutional practice as well as in symptomatic patients. The primary outcome of chronic lung allograft dysfunction (CLAD) was defined clinically and histologically per International Society of

Heart and Lung Transplantation criteria. Statistical analysis was performed with Fisher's exact test to assess differences between cohorts, and time-to-event Cox proportional hazards modeling.

RESULTS

After applying inclusion and exclusion criteria, a total of 60 patients were included in the study. Among all CF patients, 41 (68.3%) completed reflux monitoring as part of pre-lung transplant evaluation. Objective evidence of pathologic reflux, defined as acid exposure time > 4%, was found in 24 subjects, representing 58% of the tested group. CF patients with pre-transplant reflux testing were older (35.8 *vs* 30.1 years, $P = 0.01$) and more commonly reported typical esophageal reflux symptoms (53.7% *vs* 26.3%, $P = 0.06$) compared to those without reflux testing. Other patient demographics and baseline cardiopulmonary function did not significantly differ between CF subjects with and without pre-transplant reflux testing. Patients with CF were less likely to undergo pre-transplant reflux testing compared to other pulmonary diagnoses (68% *vs* 85%, $P = 0.003$). There was a decreased risk of CLAD in patients with CF who underwent reflux testing compared to those who did not, after controlling for confounders (Cox Hazard Ratio 0.26; 95%CI: 0.08-0.92).

CONCLUSION

Pre-transplant reflux testing revealed high prevalence of pathologic reflux in CF patients and was associated with decreased risk of CLAD. Systematic reflux testing may enhance outcomes in this patient population.

Key Words: Cystic fibrosis; Gastroesophageal reflux; Lung transplantation; pH monitoring

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Core Tip: This study found that objective evidence of gastroesophageal reflux disease was present in > 50% of lung transplant candidates with cystic fibrosis (CF). However, CF patients were less likely than those with other pulmonary diagnoses to undergo pre-transplantation reflux testing. CF patients who underwent objective reflux testing were less likely to develop chronic lung allograft dysfunction, as those tested positive were more likely to undergo anti-reflux surgery. Our findings provided evidence for the association of routine peri-transplant reflux testing with improved lung transplant outcomes in CF patients, and the importance of timely identification of reflux to allow early intervention.

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INTRODUCTION

Gastroesophageal reflux (GER) has been associated with poor outcomes after lung transplantation including early rehospitalization[1], early allograft injury[2], and chronic allograft rejection[3]. The proposed mechanism for this involves the increased risk of post-transplant aspiration, which may lead to an inflammatory cascade resulting in recurrent allograft injury and ultimately rejection. GER has been recognized as a common condition associated with cystic fibrosis (CF), with a reported prevalence of 67%-90% in adult CF patients[4-8]. Since CF is a common indication for lung transplantation, the detection and treatment of GER in this population may potentially reduce multiple preventable post-lung transplant complications[9].

Unfortunately, despite the high prevalence of GER in CF patients and the association between GER and worse lung transplant outcomes, the testing and management of GER in these patients remain inconsistent across lung transplant centers. For instance, some centers have selectively pursued objective GER testing and treatment in patients with restrictive lung disorders such as idiopathic pulmonary fibrosis (IPF) rather than all chronic lung diseases, likely due to a correlation between GER and IPF in several early studies[10-13]. However, the factors that influence whether patients with CF undergo testing for GER prior to lung transplant are unknown. Additionally, the long-term outcomes and effects of pre-lung transplant GER testing and management for patients with CF have not been evaluated.

In this study, we aimed to assess the differences between CF patients with and without GER on reflux testing during pre-lung transplant assessment, as well as the relationship between reflux test performance and chronic rejection in this cohort. We hypothesized that GER symptoms and demographic factors would influence the likelihood of undergoing pre-transplant reflux testing, and that performance of pre-transplant reflux testing to identify candidates for reflux interventions would decrease the risk of post-transplant allograft rejection in this patient population.

MATERIALS AND METHODS

This was a retrospective cohort study of lung transplant recipients at a tertiary care center from 2007-2019. All patients above the age of 18 who underwent lung transplant for a primary indication of CF were included in the primary analysis; all transplant recipients of any indication were included to calculate differences in the rates of reflux test performance between CF and non-CF patients. Patients with pre-transplant anti-reflux surgery were excluded. Baseline characteristics [age at transplantation, gender, race, body mass index (BMI)], self-reported GER symptoms prior to transplantation, and pre-transplant cardiopulmonary testing results, including echocardiogram, right heart catheterization, and spirometry, were recorded. ABO compatibility was assured for all donors and recipients prior to transplantation.

Reflux testing consisted of either 24-h pH- or combined multichannel intraluminal impedance and pH monitoring (Sandhill Scientific Inc, Highland Ranch, CO, United States) performed off acid suppression medications prior to transplantation. The reflux monitoring systems included a catheter with one or two pH sensor(s) which was introduced transnasally and positioned in the esophagus with the distal sensor localized to 5 cm above the lower esophageal sphincter, as well as a portable electronic datalogger. During the 24-h study, subjects remained upright during the day and recumbent at night, maintaining their normal scheduled activities. Meal periods, as documented by the patients using the datalogger, were excluded from analysis. Reflux monitoring results were analyzed with the assistance of a dedicated software package (Bioview Analysis, version 5.6.3.0, Sandhill Scientific Inc, Highland Ranch, CO, United States). Parameters of interest included acid exposure time [(AET) percentage of total study time with pH < 4 at the distal pH sensor] and the DeMeester score, a composite measure of acid reflux severity[14]. Standard normative cutoffs were employed in determining abnormal reflux[15,16].

Following transplantation, patients were prescribed a standard immunosuppressive regimen with azathioprine or mycophenolate, a calcineurin inhibitor, and methylprednisolone[17]. Routine surveillance bronchoscopy and pulmonary spirometry were performed at regular intervals according to institutional practice, and reflexively in symptomatic patients to evaluate for complications. The primary outcome was chronic rejection manifesting as chronic lung allograft dysfunction (CLAD), which was defined clinically and histologically per International Society of Heart and Lung Transplantation criteria[18].

Of note, post-transplant proton pump inhibitor (PPI) use was not part of the established clinical protocol. However, the threshold to initiate such medication was low with any reflux-associated symptoms or based on evidence of objective reflux on pre-transplant testing.

Statistical analyses were performed using χ^2 test or student's *t*-test for comparison of baseline characteristics between patient groups. Time-to-event analysis was performed for chronic rejection outcome using Cox proportional hazards model. Subjects not meeting the outcome were censored at time of post-transplant anti-reflux surgery, last clinic visit, or death, whichever was earliest. Potential confounders adjusted for in the multivariable Cox regression model were selected based on univariate analyses, and included presence of typical GER symptoms pre-transplant, forced expiratory volume in 1 s on pulmonary function testing prior to transplant, BMI, and age at transplant. All statistical analysis was performed using SAS 9.4 statistical package (SAS Institute Inc., Cary, NC, United States).

The study was approved by the Mass General Brigham Healthcare Institutional Review Board (2011P001563) prior to inception.

RESULTS

Of the 368 patients who underwent lung transplant during the study period, 60 subjects with CF met inclusion criteria for the study, with 50% male, a mean age of 34 years, and a total follow-up of 254 person-years. Among all CF patients, 41 (68.3%) completed reflux monitoring as part of pre-lung transplant assessment. Overall, objective evidence of increased acid reflux, defined as AET > 4%, was found in 24 (58.4%) subjects. Of the subgroup of 22 (53.7%) patients reporting typical esophageal symptoms of GER, including heartburn, regurgitation, and chest pain, 14 (63.4%) demonstrated increased acid reflux on pH-monitoring.

Patients with CF were less likely to undergo reflux testing during pre-lung transplant assessment compared to those with other pulmonary diagnoses (68% *vs* 85%, $P = 0.003$). CF patients with pre-transplant reflux testing were older (35.8 years *vs* 30.1 years, $P = 0.01$) and more commonly reported

typical esophageal symptoms of GER (53.7% *vs* 26.3%, P = 0.06) compared to those without reflux testing. Conditions that may affect reflux, including major esophageal motility disorders (achalasia, absent contractility) and gastroparesis, were not noted in our study cohort during the pre-transplant period, likely because many patients with known history of these conditions were not transplanted. Other patient demographics and baseline cardiopulmonary function did not significantly differ between CF subjects with and without pre-transplant reflux testing. All CF patients underwent bilateral lung transplant, and none received lung allografts from donors with risk factors for blood-borne disease transmission. Post-transplant infection rates were similar between subjects who did and did not undergo pre-transplant reflux testing, and were relatively high across both groups as is commonly seen in this patient population (Table 1).

A significantly lower proportion of patients in the pre-transplant reflux testing group developed CLAD compared to the no reflux testing group (21.9% *vs* 63.1%, P = 0.02). The risk of acute rejection did not differ significantly between groups. Both all-cause and pulmonary mortality were higher among those who did not undergo pre-transplant reflux testing, although statistical significance was not reached (42.1% *vs* 19.5%, P = 0.11 and 31.6% *vs* 12.2%, P = 0.09, respectively). Post-transplant PPI use was very common in both groups, including 83.9% in the pre-transplant testing group compared with 89.5% in the no testing group (P = 0.70), and higher than pre-transplant PPI use in both groups. One third (8/24) of patients who were found to have objective evidence of acid reflux on pre-transplant testing proceeded to anti-reflux surgery in the post-transplant follow-up period, while none of the patients in the no reflux testing group underwent anti-reflux surgery.

Multivariable time-to-event analysis, summarized in Table 2, similarly demonstrated a decreased risk of CLAD in patients with CF who underwent reflux testing during pre-lung transplant assessment compared to those who did not, even after controlling for confounders [Cox Hazard Ratio (HR) 0.26; 95%CI: 0.08-0.92, P = 0.03]. In the Cox multivariable regression model, reports of typical reflux symptoms also significantly predicted development of CLAD (HR 3.13; 95%CI: 1.03-9.54, P = 0.04). On subgroup analysis of patients who underwent pre-transplant reflux testing, those with abnormal reflux had a trend of increased risk of CLAD compared to those with normal reflux burden, although statistical significance was not reached (HR 4.09; 95%CI: 0.74-35.2, P = 0.20).

DISCUSSION

GER has been suggested to represent a potentially modifiable risk-factor for the development of chronic allograft rejection in lung transplant patients, given the potential role of reflux and aspiration in the risk of allograft injury[2,3,19,20]. Moreover, both medical and surgical anti-reflux therapies have been associated with improved allograft function and transplantation outcome among those with GER[21-26]. The prevalence of GER in CF patients is particularly high as reported in prior studies as well as in our cohort, where 58.4% of patients tested showed objective acid reflux on pH testing. Despite these findings, reflux testing remains non-standardized in the evaluation of lung transplant candidates across transplant centers and in the management of chronic lung diseases including CF. Traditionally, objective reflux testing is more commonly obtained for patients with restrictive lung diseases, particularly those with IPF, as prior evidence suggests a higher prevalence of and more severe reflux among those with restrictive *vs* obstructive lung disease[27,28]. Data for lung transplant candidates with CF, characterized by both restrictive and obstructive features, remains more limited. Our study demonstrated that transplant patients with CF less likely underwent reflux testing as part of pre-transplant assessment. However, completing pre-transplant reflux testing was an independent predictor for lower risk of developing CLAD, after adjusting for severity of lung disease, possibly due to more timely GER treatment. Among the subgroup who underwent reflux testing, abnormal reflux was associated with a trend for increased risk for CLAD.

In addition to poor standardization of reflux evaluation and management in lung transplantation, there are several other reasons why CF patients may undergo reflux testing less frequently than patients with other chronic lung diseases. While GER can be present at any age, the risk of GER increases as one gets older[29]. Since most CF patients present for clinical evaluation at a younger age, clinicians may be less likely to consider GER as a contributor to clinical symptoms and pulmonary function decline. This may, in part, explain the finding in our data that CF patients without reflux testing were significantly younger than those who did undergo reflux testing.

Another possible explanation for why some CF patients were less likely to undergo reflux testing was that these patients may have had more severe clinical disease, requiring urgent transplantation without time for additional evaluation. In this scenario, these non-testing patients may have more severe pulmonary disease before transplant and may be at higher risk for complications and poor outcomes following transplant regardless of gastroesophageal reflux disease. Reassuringly, the pre-transplant pulmonary function test measures were similar between CF patients who did and did not undergo pre-transplant reflux testing, suggesting similar baseline lung function prior to transplantation between both groups, although this may not fully reflect the speed of pulmonary decline or clinical severity that may occasionally drive the urgency of lung transplantation.

Table 1 Differences in demographics, transplant risk, reflux parameters, and post-transplant management between cystic fibrosis subjects receiving and not receiving pre-transplant gastroesophageal reflux evaluation, *n* (%)

Covariate	CF patients with pre-transplant reflux testing (*n* = 41)	CF patients without pre-transplant reflux testing (*n* = 19)	*P* value
Male gender	21 (51.2)	9 (47.4)	1.00
Age at lung transplant	35.8 ± 8.21	30.1 ± 7.89	0.01
Body mass index	20.4 ± 2.51	19.4 ± 1.97	0.11
Caucasian race	41 (100)	19 (100)	1.00
FEV1 before transplant	0.84 ± 0.36)	0.75 ± 0.22	0.24
LVEF before transplant	0.60 ± 0.05	0.59 ± 0.05	0.52
Bilateral lung transplant	41 (100)	19 (100)	1.00
CMV mismatch	15 (36.6)	6 (31.6)	0.78
High-risk donor	0	0	1.00
GER symptoms before transplant	22 (53.7)	5 (26.3)	0.06
Pre-transplant PPI use	27 (65.8)	16 (84.2)	0.22
Abnormal testing/Acid reflux	24 (58.4)	-	
Post-transplant PPI use	34 (82.9)	17 (89.5)	0.70
Post-transplant Nissen fundoplication	8 (19.5)	0 (0)	**0.05**
Any infection	35 (85.4)	17 (89.5)	1.00
Acute rejection	12 (29.3)	7 (36.8)	0.56
Chronic rejection/CLAD	9 (21.9)	12 (63.1)	**0.02**
Death (All-cause)	8 (19.5)	8 (42.1)	0.11
Death (Pulmonary)	5 (12.2)	6 (31.6)	0.09

CF: Cystic fibrosis; FEV1: Forced expiratory volume in 1 second; LVEF: Left ventricular cardiac ejection volume; CMV: Cytomegalovirus; GER: Gastroesophageal reflux; PPI: Proton pump inhibitor; CLAD: Chronic lung allograft dysfunction.

Table 2 Cox multivariate time-to-event analysis demonstrating the association between pre-transplant reflux testing and reduction in chronic rejection (chronic lung allograft dysfunction) in cystic fibrosis patients, after controlling for confounders, suggesting that reflux testing and timely treatment may reduce rejection in this patient cohort

Covariate	Cox multivariate analysis hazard ratios for chronic lung allograft dysfunction	*P*
Pre-transplant reflux testing	0.26 (0.08-0.92)	0.03
Gastroesophageal reflux symptoms before transplant	3.13 (1.03-9.54)	0.04
Forced expiratory volume in 1 second before transplant	3.17 (0.61-16.4)	0.17
Body mass index	0.98 (0.75-1.28)	0.88
Age at transplant	0.98 (0.90-1.05)	0.54

In our study, reflux testing was also associated with a significantly reduced risk of chronic rejection, independent of baseline pulmonary function and patient-reported GER symptoms. The is notable as symptomatic patients may be more likely to get tested and our multivariable model also found GER symptoms to be associated with increased risk for CLAD, thereby potentially biasing the pre-transplant reflux testing group towards development of CLAD. Our observation that completing reflux testing correlated with lower risk of CLAD despite this potential selection bias further strengthens our results. The possible mechanism by which reflux testing reduced risk of CLAD was likely related to the increased early detection of pathologic acid reflux leading to consideration of anti-reflux therapy. In our cohort, one-third of patients with pre-transplant reflux testing eventually underwent anti-reflux surgery, compared to none in the no reflux testing group. Since most patients in both groups received

PPI therapy post-transplant, anti-reflux surgery represented the major difference in clinical anti-reflux management between patient cohorts. Thus, the difference in CLAD risk between groups could be due, in part, to increased and earlier diagnosis of GER with more timely and aggressive management, through appropriate application of anti-reflux surgery when indicated.

Despite prior evidence demonstrating the potential deleterious effect of GER on lung allografts[2,3,19,20,30,31] and the protective effect of both medical and surgical anti-reflux therapy[21,22,24-26,32-35], the value and optimal strategy for reflux assessment among lung transplant patients remain debated and inconsistent across centers. In particular, timely or early anti-reflux therapy, often defined in prior studies as within 6 mo of transplantation, has been associated with improved outcomes compared to late or no reflux treatment among lung transplant patients with GER[23,36]. Therefore, accurate and prompt detection of abnormal reflux among lung transplant patients may play a role in reducing allograft dysfunction and improving outcomes. Currently, testing strategies employed by lung transplant centers may include: No esophageal assessment; selective testing based on presence of esophageal symptoms; selective testing based on underlying lung disease diagnosis; routine testing for all patients. Furthermore, the testing modality obtained may include barium esophagram, upper endoscopy, or objective reflux testing such as pH-monitoring. However, prior studies have found that esophageal symptoms are often absent among chronic lung disease patients with abnormal reflux and may not be adequate in guiding reflux testing, and that barium esophagram may not be sufficiently sensitive for detection of abnormal reflux[37]. As discussed above, some centers routinely perform reflux testing for patients with restrictive lung disease due to the higher reflux burden often observed in this population. However, our study provides evidence that routine reflux testing should also be advocated for CF patients undergoing lung transplant, especially given the high prevalence of reflux and mixed restrictive and obstructive property of the condition.

The limitations of our study include its retrospective nature, which makes it difficult to assign causality. Another limitation is the modest sample size, which reduces the statistical power, particularly in subgroup analyses such as that of patients with reflux testing showing abnormal reflux. Additionally, the sample size and retrospective design also limit the ability to perform more comprehensive analyses of other potential factors that may be associated with performance of reflux testing. Despite these limitations, our study would add to the current scarce data on the impact of objective reflux testing on post-transplant outcomes in patients with CF.

CONCLUSION

Given that patients with CF have favorable outcomes compared to the general lung transplant population, the judicious use of pre-transplant pH testing and appropriate management of GER is crucial to reducing CLAD[38]. Our findings suggest that while lung transplant patients with CF are less likely to undergo reflux testing compared to patients with other chronic lung diseases, they would likely benefit from more routine use of reflux testing to inform prompt and effective management of GER, including anti-reflux surgery when indicated. Thus, standardized reflux testing followed by timely reflux management should be adopted systematically in the care of patients undergoing lung transplant to improve post-transplant outcomes, especially among patients with CF.

ARTICLE HIGHLIGHTS

Research background

Gastroesophageal reflux is prevalent in chronic lung disease and can negatively impact lung transplant outcomes. However, the impact of pre-transplant reflux testing is not established in the cystic fibrosis (CF) population.

Research motivation

Routine reflux evaluation remains poorly standardized in lung transplantation, and this work contributes to the growing literature on the utility of reflux testing and timely management in lung transplant patients, especially those with CF.

Research objectives

To evaluate the impact of pre-transplant reflux testing on transplant outcomes in CF, as well as determining the prevalence of reflux in this patient population.

Research methods

This was a retrospective cohort study of CF patients that underwent lung transplantation at a tertiary referral center.

Research results

Lung transplant candidates with CF were less likely than those with other chronic lung diseases to undergo reflux testing. Pre-transplant reflux testing identified high prevalence of pathologic reflux in CF. Reflux testing was associated with decreased risk of chronic rejection.

Research conclusions

Pre-transplant reflux testing revealed high prevalence of pathologic reflux in CF patients and was associated with decreased risk of chronic lung allograft dysfunction.

Research perspectives

Systemic reflux testing may improve lung transplant outcomes in the CF population. Future research should focus on the implementation of standardized reflux evaluation and timely reflux management in lung transplantation, and its impact on transplant outcomes, particularly in patients with CF.

FOOTNOTES

Author contributions: Chan WW and Lo WK initiated study concepts and design; Lo WK, Goldberg HJ, and Chan WW contributed to acquisition of data; Chan WW, Lo WK, Flanagan R, Goldberg HJ, and Sharma N performed analysis and interpretation of data; Lo WK, Flanagan R, and Chan WW drafted the manuscript; Chan WW, Lo WK, Flanagan R, Goldberg HJ, and Sharma N contributed to critical revision of manuscript for important intellectual content; Chan WW and Lo WK performed statistical analyses; and Chan WW provided administrative support and overall study supervision.

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ORIGINAL ARTICLE

Retrospective Study

Mortality assessment for pancreas transplants in the United States over the decade 2008-2018

Tambi Jarmi, Emily Brennan, Jacob Clendenon, Aaron C Spaulding

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Abstract

BACKGROUND

Pancreas transplant is the only treatment that establishes normal glucose levels for patients diagnosed with diabetes. However, since 2005, no comprehensive analysis has compared survival outcomes of: (1) Simultaneous pancreas-kidney (SPK) transplant; (2) Pancreas after kidney (PAK) transplant; and (3) Pancreas transplant alone (PTA) to waitlist survival.

AIM

To explore the outcomes of pancreas transplants in the United States during the decade 2008-2018.

METHODS

Our study utilized the United Network for Organ Sharing Standard Transplant Analysis and Research file. Pre- and post-transplant recipient and waitlist characteristics and the most recent recipient transplant and mortality status were used. We included all patients with type I diabetes listed for pancreas or kidney-pancreas transplant between May 31, 2008 and May 31, 2018. Patients were grouped into one of three transplant types: SPK, PAK, or PTA.

RESULTS

The adjusted Cox proportional hazards models comparing survival between transplanted and non-transplanted patients in each transplant type group showed that patients who underwent an SPK transplant exhibited a significantly reduced hazard of mortality [hazard ratio (HR) = 0.21, 95% confidence intervals (CI): 0.19-0.25] compared to those not transplanted. Neither PAK transplanted patients (HR = 1.68, 95%CI: 0.99-2.87) nor PTA patients (HR = 1.01, 95%CI: 0.53-1.95) experienced significantly different hazards of mortality compared to patients who did not receive a transplant.

CONCLUSION
When assessing each of the three transplant types, only SPK transplant offered a survival advantage compared to patients on the waiting list. PKA and PTA transplanted patients demonstrated no significant differences compared to patients who did not receive a transplant.

Key Words: Pancreas transplant; Simultaneous pancreas-kidney transplant; Pancreas after kidney transplant; Survival; Diabetes mellitus; Insulin

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Core Tip: The total number of pancreas transplants has been in the decline in United States since 2003/2004. This study aimed to show acceptable survival outcome for diabetic patients receiving pancreas transplant as a cure therapeutic approach.

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INTRODUCTION

The Diabetes Control and Complications Trial demonstrated the advantage of intensive diabetes therapy in delaying the development of macro/microvascular diabetic-related complications and decreasing the overall mortality rate of diabetic patients[1-4]. It is clear, however, from follow-up studies that the risk of developing secondary diabetic complications is not eliminated, and the incidence of hypoglycemic episodes increases over time[5,6]. As a result, pancreas transplant is the only treatment that restores normal glucose metabolism in insulin-dependent diabetic patients[7,8].

Pancreas transplants, in relation to kidney function, fall into three different categories: (1) Simultaneous pancreas-kidney (SPK) transplant in patients with end-stage kidney disease (ESKD); (2) Pancreas after kidney (PAK) transplant; and (3) Pancreas transplant alone (PTA) in patients with no kidney disease[9]. Recipient and graft survival rates and the total number of pancreas transplants had improved in all three categories since the introduction of the procedures. However, around 2003, the number of pancreas transplants started to decline[10]. Multiple events and factors could explain the paradoxical relationship between declining transplants despite improving outcomes[10]. One contributing factor was that during the period, two major studies conducted by Venstrom *et al*[11] in 2003 and Gruessner *et al*[12] in 2005 showed inconsistency in reported outcomes of patients and grafts after a pancreas transplant. Subsequently, the overall number of active pancreas transplant centers fell. By 2016, only 11 centers in the United States performed more than 20 pancreas transplants a year, and most centers performed less than 5 transplants annually[10,13]. Consequently, fewer surgeons are adequately trained in pancreas donor recovery and transplant[14,15]. Since the 2003 and 2005 studies, no comprehensive analysis has compared the outcomes of the three categories of pancreas transplant and waitlist survival. To remedy this gap in our understanding, the present study analyzed the mortality of transplanted *vs* wait-listed patients in all three pancreas recipient categories using United Network for Organ Sharing (UNOS)/IPTR data from May 31, 2008 through May 31, 2018. We hypothesized that since 2005, survival for each type of transplant will have improved. Specifically:

Hypothesis 1: PTA patients will have improved survival compared to those not transplanted.
Hypothesis 2: PAK patients will have improved survival compared to those not transplanted.
Hypothesis 3: SPK patients will have improved survival compared to those not transplanted.

MATERIALS AND METHODS

Data source and measures

Our study utilized the UNOS Standard Transplant Analysis and Research file[16]. This database contains clinical and follow-up data for all transplants in the United States. Pre- and post-transplant recipient and waitlist characteristics and the most recent recipient transplant and mortality status were used. We included all patients with type I diabetes listed for pancreas or kidney-pancreas transplant between May 31, 2008 and May 31, 2018. Any patients listed for pancreas or pancreas-kidney transplant for the first time before or after those dates were excluded. Patients listed for any organ other than a

pancreas, pancreas-kidney simultaneously, or were listed before May 31, 2008, were excluded. Patients under 18 years of age were also removed, as were patients with missing waitlist ID or registration dates.

Patients were grouped into one of three transplant types: SPK, PAK, or PTA. Patients listed for pancreas and kidney transplants at the same time (with overlapping waitlist times) or receiving a pancreas and kidney transplant together were included in the SPK group. Patients listed for their first pancreas transplant on or after May 31, 2008, and with a kidney or kidney-pancreas transplant record before their listing for a pancreas transplant and those receiving a pancreas transplant after having a kidney transplant were included in the PAK group. Finally, patients listed for or who received only a pancreas transplant, having never been listed for or received a kidney transplant, were considered in the PTA group. Patients were considered to have a pancreas transplant if they had a pancreas transplant ID code and date. Patient death was defined as having a death date in the UNOS record, and patients were censored at removal from the waiting list or at the date of the last follow-up unless a death date was present. Waitlist times were calculated as the difference between first registration (INIT_DATE) and waitlist removal date (END_DATE), death date (COMPOSITE_DEATH_DATE), or transplant date (TX_DATE). If a patient was listed at multiple locations or had multiple entries, we determined the unique days between first registration and the removal date, death date, or transplant date. If a candidate was removed for being too sick to undergo their transplant and had a death date after being removed, the time between removal and death was added to the waitlist time. Time from transplant to death or loss to follow-up was calculated as the difference between the transplant date and death or last follow-up date (PX_STAT_DATE).

Statistical analysis

Descriptive statistics were calculated for transplanted and non-transplanted waitlist patients for each transplant type group. Means, standard deviations, and ranges are used to describe continuous variables. Categorical variables are described by frequency and percentages. Cox regression models comparing transplanted to non-transplanted patients used transplant as a time-dependent covariate, with time on the waitlist as time interval one and time from transplant to death or last follow-up as time interval two for transplanted patients. Adjustment variables included age at waitlist registration, gender, race (white, black, or other), duration of diabetes (years from the date of diabetes onset to date of waitlist registration), body mass index (BMI), Karnofsky functional status score, and presence of peripheral vascular disease (yes or no). BMI and functional status were divided into common clinically relevant groups operationalized into categorical variables. Adjustment variables were not considered as time-varying. Adjusted Cox models comparing survival after transplant between transplant-type groups only included transplanted patients and time from transplant to death or censoring. Additional models for up to 90 d post-transplant, 91 to 365 d post-transplant, and over 1 year post-transplant were also performed to compare survival within each period between transplant-type groups. These models were adjusted for the same variables as the previous set of models, with the addition of years on the waitlist. Hazard ratio (HR) and 95% confidence interval (CI) are reported[17]. All statistical analyses were performed using R version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Demographic and clinical characteristics

There were 9498 patients listed for SPK transplant, 1111 Listed for PAK transplant, and 939 Listed for PTA between May 31, 2008 and May 31, 2018. Of those, 6883 (59.6%) were transplanted, and 926 (8.0%) died on the waitlist. The mean age at listing was 40.6 years (range: 18-73 years), and 6539 (56.6%) patients were male. The majority of patients (7695, 66.6%) were white, 2187 (18.9%) were black, and 1666 (14.4%) were of other races. Almost 12 percent of patients were of Hispanic/Latino ethnicity. Most patients (6931, 62.4%) had a high Karnofsky functional status score, 5347 (46.7%) had a normal BMI, 10217 (90.0%) did not have peripheral vascular disease, and the mean duration of diabetes before registration was 26.5 years (Table 1).

Survival

Kaplan-Meier curves for each transplant type *vs* the wait list over 8 years of follow-up are shown in Figure 1. When considering SPK transplant, there was a significant difference in the survival of the transplanted *vs* non-transplanted group, starting immediately and growing as time progressed. However, for PAK transplant and PTA, there was no separation between the groups over time, identifying no survival differences.

Results of adjusted Cox proportional hazards models comparing survival between transplanted and non-transplanted patients in each transplant type group are shown in Table 2. SPK transplanted patients exhibited a significantly reduced hazard of mortality (HR = 0.21, 95%CI: 0.19-0.25) compared to those not transplanted. Neither PAK transplanted patients (HR = 1.68, 95%CI: 0.99-2.87) nor PTA patients (HR = 1.01, 95%CI: 0.53-1.95) experienced significantly different hazards of mortality compared to patients who did not receive a transplant. Associations of adjustment variables with mortality varied by

Table 1 Demographic and clinical characteristics of patients listed for a pancreas transplant by transplant status and transplant type (May 31, 2008–May 31, 2018)

	SPK			PAK			PTA		
	Transplant (*n* = 5834)	Waitlist (*n* = 3664)	*P* value	Transplant (*n* = 430)	Waitlist (*n* = 681)	*P* value	Transplant (*n* = 619)	Waitlist (*n* = 320)	*P* value
Age at registration (yr)			< 0.001			0.04			0.68
mean (SD)	40.1 (8.7)	41.0 (9.3)		40.6 (8.9)	41.8 (9.5)		41.7 (10.6)	41.4 (10.8)	
Range	18.0 - 69.0	18.0 - 73.0		22.0 - 67.0	18.0 - 66.0		18.0 - 68.0	20.0 - 70.0	
Gender			< 0.001			0.026			0.49
Female	2284 (39.1%)	1663 (45.4%)		174 (40.5%)	322 (47.3%)		378 (61.1%)	188 (58.8%)	
Male	3550 (60.9%)	2001 (54.6%)		256 (59.5%)	359 (52.7%)		241 (38.9%)	132 (41.2%)	
Race			0.3			0.08			< 0.001
White	3732 (64.0%)	2295 (62.6%)		336 (78.1%)	502 (73.7%)		567 (91.6%)	263 (82.2%)	
Black	1229 (21.1%)	781 (21.3%)		37 (8.6%)	88 (12.9%)		25 (4.0%)	27 (8.4%)	
Other	873 (15.0%)	588 (16.0%)		57 (13.3%)	91 (13.4%)		27 (4.4%)	30 (9.4%)	
Ethnicity			0.22			0.7			0.012
Hispanic/Latino	714 (12.2%)	480 (13.1%)		46 (10.7%)	78 (11.5%)		23 (3.7%)	24 (7.5%)	
Non-Hispanic/Non-Latino	5120 (87.8%)	3184 (86.9%)		384 (89.3%)	603 (88.5%)		596 (96.3%)	296 (92.5%)	
Karnofsky score at registration			0.34			0.46			0.013
High	3441 (60.7%)	2151 (61.9%)		291 (70.3%)	427 (66.6%)		392 (64.9%)	229 (74.1%)	
Middle	2108 (37.2%)	1259 (36.3%)		114 (27.5%)	199 (31.0%)		195 (32.3%)	76 (24.6%)	
Low	121 (2.1%)	63 (1.8%)		9 (2.2%)	15 (2.3%)		17 (2.8%)	4 (1.3%)	
BMI at registration			< 0.001			0.038			0.82
Normal	2847 (49.1%)	1640 (45.2%)		200 (46.9%)	287 (42.5%)		240 (40.1%)	133 (41.8%)	
Underweight	95 (1.6%)	60 (1.7%)		5 (1.2%)	8 (1.2%)		11 (1.8%)	4 (1.3%)	
Overweight	2180 (37.6%)	1311 (36.2%)		172 (40.4%)	259 (38.4%)		231 (38.6%)	116 (36.5%)	
Obese	674 (11.6%)	615 (17.0%)		49 (11.5%)	121 (17.9%)		117 (19.5%)	65 (20.4%)	
Duration of diabetes (yr)			0.064			0.052			0.28
mean (SD)	26.3 (9.0)	26.6 (9.2)		26.9 (8.6)	28.0 (9.5)		26.6 (11.4)	25.8 (11.7)	
Range	0.0 - 59.0	0.0 - 60.0		3.0 - 49.0	2.0 - 55.0		0.0 - 58.0	1.0 - 57.0	
Peripheral vascular disease at registration			< 0.001			0.96			0.78
No	5253 (91.5%)	3136 (87.4%)		384 (91.0%)	613 (91.1%)		545 (89.1%)	286 (89.7%)	
Yes	488 (8.5%)	453 (12.6%)		38 (9.0%)	60 (8.9%)		67 (10.9%)	33 (10.3%)	
Time on waitlist (yr)			< 0.001			< 0.001			< 0.001
mean (SD)	0.9 (1.0)	1.8 (1.7)		1.2 (1.1)	2.5 (2.0)		0.6 (0.8)	1.9 (1.9)	
Range	0.0 - 7.4	0.0 - 10.3		0.0 - 5.9	0.0 - 9.9		0.0 - 6.7	0.0 - 10.0	
Follow-up time after transplant (yr)									
mean (SD)	3.7 (2.5)	NA		3.4 (2.6)	NA		3.3 (2.5)	NA	
Range	0.0 - 10.1	NA		0.0 - 9.1	NA		0.0 - 9.1	NA	

Continuous variables are presented as the mean and standard deviation (SD), and categorical variables are presented as frequency and percentage. SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone; NA: Not available.

Table 2 Adjusted Cox proportional hazards models comparing transplanted to non-transplanted patients within each transplant group

	SPK		PAK		PTA	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Transplanted (No)	Reference	Reference	Reference	Reference	Reference	Reference
Transplanted (Yes)	0.21 (0.19, 0.25)	< 0.001	1.68 (0.99, 2.87)	0.06	1.01 (0.53, 1.95)	0.97
Age at registration	1.01 (1.00, 1.02)	0.04	1.03 (1.00, 1.06)	0.02	1.03 (1.00, 1.06)	0.03
Gender (F)	Reference	Reference	Reference	Reference	Reference	Reference
Gender (M)	0.97 (0.86, 1.08)	0.55	0.55 (0.35, 0.88)	0.01	1.46 (0.90, 2.37)	0.13
Race (White)	Reference	Reference	Reference	Reference	Reference	Reference
Race (Black)	1.05 (0.91, 1.22)	0.47	1.82 (0.89, 3.71)	0.1	0.34 (0.05, 2.54)	0.29
Race (Other)	0.74 (0.62, 0.89)	0.001	0.77 (0.34, 1.74)	0.53	1.27 (0.45, 3.61)	0.66
BMI (Normal)	Reference	Reference	Reference	Reference	Reference	Reference
BMI (Obese)	0.76 (0.63, 0.90)	0	0.46 (0.21, 1.04)	0.06	0.80 (0.39, 1.65)	0.54
BMI (Overweight)	0.87 (0.77, 0.99)	0.03	0.66 (0.40, 1.10)	0.11	0.85 (0.50, 1.46)	0.57
BMI (Underweight)	1.16 (0.77, 1.75)	0.48	3.15 (0.90, 10.96)	0.07	1.76 (0.41, 7.64)	0.45
Duration of diabetes (yr)	1.00 (0.99, 1.01)	0.96	0.99 (0.96, 1.02)	0.62	0.98 (0.96, 1.01)	0.21
Karnofsky score (High)	Reference	Reference	Reference	Reference	Reference	Reference
Karnofsky score (Low)	0.98 (0.60, 1.60)	0.94	2.77 (0.96, 7.95)	0.06	3.07 (0.39, 24.14)	0.29
Karnofsky score (Middle)	1.42 (1.26, 1.60)	< 0.001	0.89 (0.52, 1.52)	0.66	2.22 (1.35, 3.64)	0
Peripheral vascular disease (No)	Reference	Reference	Reference	Reference	Reference	Reference
Peripheral vascular disease (Yes)	1.40 (1.19, 1.66)	< 0.001	0.98 (0.44, 2.16)	0.95	0.99 (0.47, 2.12)	0.99

SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; HR: Hazard ratios; CI: Confidence intervals; PTA: Pancreas transplant alone. Hazard ratios and 95% confidence intervals result from multivariate Cox proportional hazards models using transplant as a time-dependent covariate.

transplant type.

Results of adjusted Cox proportional hazards models comparing post-transplant survival between the transplant-type groups are shown in Table 3. In the model that utilized all post-transplant follow-up time, PAK transplant recipients showed a significantly increased mortality hazard compared to SPK transplant recipients (HR = 1.46, 95%CI: 1.07-2.01). In the model using only up to 90 d of follow-up, PTA recipients showed a significantly reduced hazard compared to SPK transplant recipients (HR = 0.21, 95%CI: 0.05-0.88). Patients in the PAK group also showed a reduced hazard in the 90 d after transplant compared to those in the SPK group, although the association was not significant (HR = 0.25, 95%CI: 0.06-1.03). In the model using 91-365 d of follow-up, no significant differences in mortality hazard were observed between the three groups. In the model using over one year of follow-up time, the PAK transplanted group exhibited a significantly increased hazard compared to the SPK group (HR = 1.59, 95%CI: 1.11-0.30), and the PTA group showed a higher hazard than the SPK group, though the association was not statistically significant (HR = 1.36, 95%CI: 0.96-1.92).

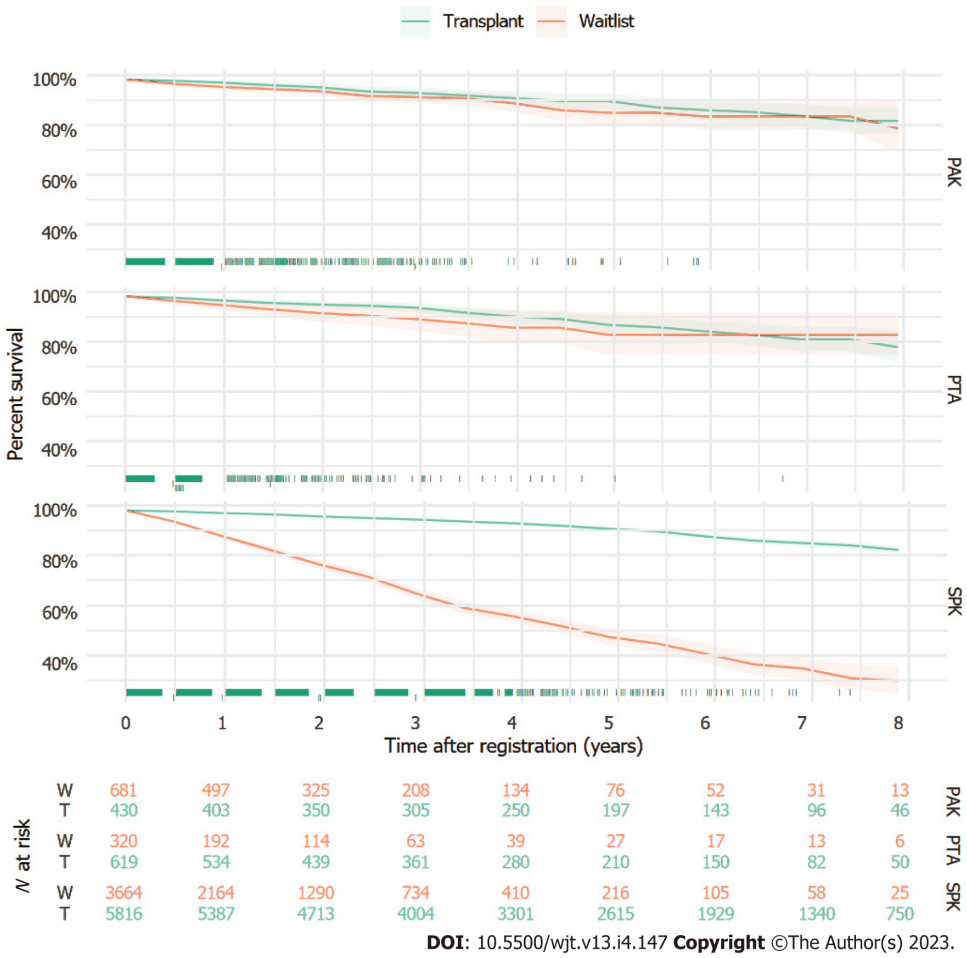
DISCUSSION

Solid organ pancreas transplant is a complex procedure for which significant progress, in terms of immunosuppressive and surgical advancement, has been made over the past 5 decades. However, despite the advancement in immunomodulatory medications and surgical techniques, the number of pancreas transplants in the United States has declined significantly since 2003/2004[18,19]. The current study found that simultaneous pancreas-kidney transplant offered a survival advantage compared to patients on the waiting list. PAK transplant and PTA patients demonstrated no significant differences compared to patients who did not receive a transplant. As mentioned, two milestone studies demonstrated divergent results regarding pancreas transplant outcomes that are important to consider in light of the current results. The 2005 study conducted by Gruessner *et al*[12] showed survival results to be improved, while the 2003 study conducted by Venstrom *et al*[11] showed negative survival

Table 3 Cox proportional hazards models comparing survival after transplant between transplant types

	Overall		Up to 90 d post-transplant		91-365 d post-transplant		Greater than 1 yr post-transplant	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Transplant type (SPK)	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Transplant type (PAK)	1.46 (1.07, 2.01)	0.02	0.25 (0.06, 1.03)	0.06	1.89 (0.89, 4.02)	0.1	1.59 (1.11, 2.30)	0.01
Transplant type (PTA)	1.22 (0.91, 1.65)	0.19	0.21 (0.05, 0.88)	0.03	1.31 (0.64, 2.68)	0.46	1.36 (0.96, 1.92)	0.08

SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone; CI: Confidence intervals; HR: Hazard ratios. Hazard ratios and 95% confidence intervals result from multivariate Cox proportional hazards models predicting survival after transplant among only transplanted patients and excluding time on the waiting list.



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Figure 1 Kaplan-Meier curves for each transplant type: Pancreas after kidney (PAK), pancreas transplant alone (PTA), and simultaneous pancreas and kidney transplant (SPK). The 8-year survival rate for PAK and PTA showed no separation between the transplanted and wait-listed groups over time. Simultaneous pancreas and kidney transplanted patients showed a significant difference in survival compared to the wait-listed group, starting immediately and growing as time progressed. PTA: Pancreas transplant alone; PAK: Pancreas after kidney; SPK: Simultaneous pancreas and kidney.

benefits.

In the category of PTA, the Gruessner study showed that the overall hazard ratio was 0.66 (95%CI: 0.39–1.12), favoring transplantation, while the Venstrom study showed the overall hazard ratio was 1.57 (95%CI: 0.98-2.53) favoring a no transplantation strategy. In our study, we analyzed data from the decade 2008-2018, and found recipients of PTA to have better survival results compared to the previous analysis conducted by Venstrom *et al*[11] and offered non-inferior outcomes when compared to patients on the waiting list (HR = 1.01, 95%CI: 0.53-1.95). As a result, there is mixed support for hypothesis 1, as

survival has improved compared to the Venstrom study but has not improved compared to the Grussner study. For PAK transplanted patients, Gruessner and colleagues found no overall difference for transplant (HR = 0.92, 95%CI: 0.69-1.12), but Venstrom *et al*[11] (HR = 1.42, 95%CI: 1.03-1.94) found a worse outcome. Our results, however, showed PAK transplanted patients to have an increased but not significant risk of death after transplant compared to waiting list patients (HR = 1.68, 95%CI: 0.99-2.87). As a result, there is also mixed support for hypothesis 2 as we found worse survival outcomes than Gruessner *et al*[12], but better survival than the Venstrom study. Finally, previous studies and ours favored transplantation in the SPK transplant category. Specifically, the Gruessner study identified an HR of 0.29 (95%CI: 0.27-0.33), and the Venstrom study identified an HR of 0.43 (95%CI: 0.39-0.48). Compared to patients on the waiting list, the mortality HR for SPK transplant recipients in the current study was 0.21 (95%CI: 0.19-0.25). As a result, there is support for hypothesis 3 as our results indicate improved survival compared to the previous studies.

When we considered the SPK transplant recipients' category as the analysis reference and broke down the follow-up period to: (1) Up to 90 d post-transplant; (2) 91 to 365 d post-transplant; and (3) Greater than 1 year post-transplant, we found an increased mortality risk among patients with PTA; however, the result was not significant (HR = 1.22, 95%CI: 0.91-1.65) (P = 0.19). The increased mortality risk was significant among patients in the PAK category (HR = 1.46, 95%CI: 1.07- 2.01) (P = 0.02). However, it is unclear why PAK transplant offers less survival benefit when compared to SPK transplant and the waiting list. This is more puzzling, especially if the expected sequence of PAK transplant is to receive a kidney from a living donor first, followed by a pancreas from a deceased donor. This sequence of events should offer a better survival than our results and previously published ones. Therefore, more analysis is needed to dissect all characteristics and conditions associated with the PAK category.

In relation to diseases that could influence poor outcomes, we also reviewed the impact of peripheral vascular disease (PVD) on the survival of the study patients. Patients diagnosed with PVD have a 3-fold increased risk of dying from all causes and a 6-fold increased risk of dying from cardiovascular disease within 10 years compared with patients without PVD[20-22]. Diabetic patients with PVD and those younger than 75 years have a 23% increase in mortality rate *vs* 7% among the control group[23]. We found patients from the SPK category group to have a lower incidence of PVD (8.5%) when compared to waitlist patients (12.6%) (P = 0.001). In the adjusted Cox proportional hazards models comparing transplanted to non-transplanted patients within each transplant category, SPK transplanted patients with PVD showed a significantly increased mortality risk compared to wait-listed patients (HR = 1.40, 95%CI: 1.19-1.66, P = 0.001). This could add a biased survival advantage when patients with less PVD are selected to proceed with SKP transplants after bypassing patients with more PVD on the waiting list. When reviewing the impact of BMI on the survival of the study patients, we found a paradoxical benefit of obesity among transplanted patients compared to wait-listed patients. This association was significant in the SPK category (HR = 0.76, 95%CI: 0.63-0.90) (P = 0.00) but was not significant in the PAK and PTA categories. The controversial advantage of obesity among patients with ESKD was shown before. Abbott *et al*[24] performed a retrospective analysis of the United States Renal Data System (USRDS) Dialysis Morbidity and Mortality Wave II Study patients who started dialysis in 1996 and were followed until October 31, 2001. They concluded that BMI ≥ 30 kg/m^2 was associated with improved survival in hemodialysis patients.

These results, in total, could be seen as an advancement in the field of transplantation and diabetic care in general. When we consider the consensus of the previous two studies and ours in favoring survival among patients who received SPK transplant, we are likely seeing a result of the remarkably high mortality rate among patients with end-stage kidney disease[25]. As a result, the benefit after an SPK transplant would appear to be more a consequence of resolving the kidney disease[25]. On the other hand, the lack of differences identified in the PAK and PTA groups, despite improved surgical and medical management techniques, likely points to similar progress in diabetic care in terms of medical technology, which improved the survival of diabetic patients with standard insulin therapy [26]. Patients with advanced diabetic disease may most benefit from PAK transplant or PTA. Previous studies have shown improved cost-effectiveness and quality of life for these groups compared to diabetic management through insulin alone[27].

CONCLUSION

Our study showed the survival advantage of SKP transplants compared to patients on the waiting list over the last decade. However, PAK transplant and PTA demonstrated no significant differences compared to patients who did not receive a transplant.

ARTICLE HIGHLIGHTS

Research background

Pancreas transplant is the only treatment that establishes normal glucose levels for patients diagnosed with diabetes. A significant advancement in management of diabetes associated with significant improvement in diabetic patients outcome has been achieved within the last decade. During the same period of time, there has been a noticeable decline in pancreas transplant procedures in the United States. In order to outline the importance of pancreas transplant as the only incurable treatment available for diabetes that could lead to normal glycemic status of these patients, we analyzed the outcome of pancreas transplant *vs* diabetic standard of care in the United States from 2008 to 2018.

Research motivation

A noticeable and significant decline of pancreas transplantation in the United States since 2004 has led to a decrease in the number of transplant centers that perform such procedure. This decline has led to a significant limitation among transplant surgeons and transplant physicians that are caring for patients receiving pancreas transplant. This study was to highlight the benefit of pancreas transplant in curing diabetes and to emphasize the potential benefit of pancreas transplantation in order to increase the number of diabetic patients that could receive this curative therapy.

Research objectives

The objective of this study was to bring pancreas transplant as a curative treatment, that could achieve glycemic control among diabetic patients, to the attention of transplant and endocrinology stakeholders. With the current technological advancement in treatment of diabetes, still a significant number of patients suffer from acute hyper and hypoglycemic events in addition to the chronic complications of diabetes. We hope that our research will at the current body of knowledge that supports pancreas transplant as a definitive treatment for diabetes and will encourage more clinical trials to compare standard of care for diabetes *vs* organ transplantation.

Research methods

Our study utilized the United Network for Organ Sharing Standard Transplant Analysis and Research file. This database contains clinical and follow-up data for all transplants in the United States since 1988. We included all patients with type I diabetes listed for pancreas or kidney-pancreas transplant between May 31, 2008 and May 31, 2018 and compared their outcome with the patients that had type 1 diabetes and were being listed and waiting for an organ transplant.

Research results

The adjusted Cox proportional hazards models comparing survival between transplanted and non-transplanted patients in each transplant type group showed simultaneous pancreas and kidney transplant patients to exhibit a significantly reduced hazard of mortality [hazard ratio (HR) = 0.21, 95% confidence interval (CI): 0.19-0.25] compared to those not transplanted. Neither transplanted patients (HR = 8, 95%CI: 0.99-2.87) nor pancreas transplant alone patients (HR = 1.01, 95%CI: 0.53-1.95) experienced significantly different hazards of mortality compared to patients who did not receive a transplant.

Research conclusions

Our study showed the survival advantage of simultaneous kidney and pancreas transplants compared to patients on the waiting list over the last decade. Patients who underwent pancreas transplant alone demonstrated no significant differences compared to patients who did not receive a transplant, which could highlight the importance of pancreas transplant alone despite the advancement in the technology of insulin delivery and diabetic management over the last decade.

Research perspectives

We hope that our study will encourage future clinical trials to randomize patients between diabetic standard of care *vs* transplantation. Meanwhile, we are conducting further studies to address disparities among patients who are receiving pancreas transplant *vs* remaining on the waiting list. We are aiming to identify any barriers among minorities that could prevent their access to transplant evaluation and to receive an organ transplantation.

FOOTNOTES

Author contributions: Jarmi T and Spaulding A designed the study and wrote the paper; Clendenon J wrote the paper; Brennan ER and Spaulding A collected and analyzed the data and wrote the paper.

Institutional review board statement: This study was reviewed and approved by Mayo Clinic institutional review board (IRB application number 20-004621).

Informed consent statement: Informed consent from the patients was not required.

Conflict-of-interest statement: Sample wording: The authors of this study have nothing to disclose. All authors are employed by Mayo Clinic.

Data sharing statement: Statistical code and dataset are available from the corresponding author at jarmi.tambi@mayo.edu.

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ORIGINAL ARTICLE

Retrospective Study

Is peri-transplant blood transfusion associated with worse transplant outcomes? A retrospective study

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Abstract

BACKGROUND

Blood transfusion is common during the peri-transplantation period. The incidence of immunological reactions to blood transfusion after kidney transplantation and their consequences on graft outcomes have not been extensively studied.

AIM

To examine the risk of graft rejection and loss in patients who received blood transfusion in the immediate peri-transplantation period.

METHODS

We conducted a single-center retrospective cohort study of 105 kidney recipients, among them 54 patients received leukodepleted blood transfusion at our center between January 2017 and March 2020.

RESULTS

This study included 105 kidney recipients, of which 80% kidneys were from living-related donors, 14% from living-unrelated donors, and 6% from deceased donors. Living-related donors were mostly first-degree relatives (74.5%), while the rest were second-degree relatives. The patients were divided into transfusion (

n = 54) and non-transfusion (*n* = 51) groups. The average hemoglobin level at which blood transfusion was commenced was 7.4 ± 0.9 mg/dL. There were no differences between the groups in terms of rejection rates, graft loss, or death. During the study period, there was no significant difference in creatinine level progression between the two groups. Delayed graft function was higher in the transfusion group; however, this finding was not statistically significant. A high number of transfused packed red blood cells was significantly associated with increased creatinine levels at the end of the study.

CONCLUSION
Leukodepleted blood transfusion was not associated with a higher risk of rejection, graft loss, or death in kidney transplant recipients.

Key Words: Transplantation; Transfusion; Rejection; Graft survival

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Core Tip: Blood transpfusion in patient undergoing kidney transplantation has long been avoided for the fear for the potential risk of reciepient's immunization and potential rejection. This study addresses the risks of peri-transplantation outcomes of blood transfusion.

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INTRODUCTION

Anemia is common in the early post-kidney transplant period[1-3]. The causes of this anemia are multiple and may include blood loss during the surgical operation, erythropoietin deficiency, iron deficiency as a result of previous end-stage renal disease along with delayed graft function (DGF), and adverse reactions to immunosuppressive agents. In some cases, blood transfusion is an essential life-saving practice. Blood transfusion is widely used in the early post-transplantation period following surgery[2].

However, blood transfusion is not without risks. Exposure to non-self human leukocyte antigens (HLAs) can lead to the formation of anti-HLA antibodies or allosensitization[2-4]. Donor-specific antibodies (DSAs) can develop in kidney recipients after receiving a blood transfusion[2]. HLA sensitization may have negative clinical impacts, including, an increased risk of rejection, and graft loss. Despite these risks, clinical guidelines do not provide specific recommendations for blood transfusion during the perioperative period[4]. This uncertainty could be due to the assumption that post-kidney transplant patients receive immunosuppressive agents, which could reduce the possibility of allosensitization[4,5].

The incidence of immunological reactions to blood transfusion after kidney transplantation and their consequences on graft outcomes have not been extensively studied. Our study aimed to examine the risk of graft rejection and graft loss in patients who receive a blood transfusion in the immediate post-transplantation period and those who were on immunosuppressive therapy.

MATERIALS AND METHODS

Study design

This was a single-center retrospective cohort study of kidney transplantation recipients who received either deceased or living-donor kidneys at Al-Hada Armed Forces Hospital, Taif, Saudi Arabia between January 2017 and March 2020. No other solid-organ transplantation or spontaneous kidney-pancreas transplantation was performed at our center during the study period.

We surveyed kidney transplant recipients who received a blood transfusion in the peri-transplant period (one week prior to transplantation and one month after the surgery). The control group included patients who underwent kidney transplantation during the same period but did not require blood transfusion. At our institution, only leukodepleted blood products are administered to kidney

transplant candidates and kidney transplant recipients; this applied to the kidney recipients enrolled in this study. Data were obtained from the patients' electronic files in the hospital. However, blood product type (leuko-depleted *vs* non-leuko-depleted) was confirmed from the blood bank records. We excluded recipients who were < 18 years of age, those with previous organ transplantation, those who required desensitization prior to transplantation, those on a calcineurin inhibitors (CNIs) avoidance protocol, and those who required permanent withdrawal of one or more of their immunosuppressive therapies.

During the study period, Immunosuppression protocol in our hospital consisted of induction therapy with either antithymocyte globulin (cumulative dose of 4-6 mg/kg) or basiliximab (two intravenous doses of 20 mg on post-op days 0 and 4) and maintenance immunosuppression with tacrolimus (targeting a tacrolimus level of 8-10 ng/mL in the first three months then 4-6 ng/mL), an antimetabolite (mycophenolate mofetil 1 gm twice daily) and prednisone (tapered to a maintenance dose of 5 mg daily).

Outcomes

Primary outcomes were biopsy-proven rejection, DGF, graft loss within the first 18 mo post-transplantation and death of any cause during the same time period. Post-transplant kidney biopsy and DSA identification were not performed routinely in this cohort but rather on a for-cause basis. Secondary outcomes were changes in creatinine levels during the study period, infections, and urological complications. Both cellular and antibody-mediated rejections were accounted for. Graft loss was defined as the need for another renal replacement therapy. Identification of DSAs was performed using a Luminex single-bead antigen solid-phase assay with a cutoff of 1000 mean fluorescence intensity.

Statistical analysis

All analyses were performed using SPSS version 26 (IBM, Armonk, NY, United States). Continuous variables are denoted as mean ± SD for normally distributed variables or median (interquartile range) for non-normally distributed variables. The Shapiro-Wilk test was used to assess the normality of continuous variables to guide the selection of a parametric or nonparametric test for the comparison of variables. The variables were compared using the Welch's *t*-test, Student's *t*-test, and Mann-Whitney-U test. Categorical variables were presented as frequencies and percentages and were compared using the χ^2 or Fisher's exact tests as appropriate. All independent variables from the univariate linear regression analysis with $P < 0.05$ were entered into a multivariate linear regression model to examine their association with creatinine changes. All reported P values were two-sided and P values < 0.05 were considered to indicate a statistical significance.

RESULTS

A total of 124 kidney transplant surgeries were performed at Al-Hada Armed Forces Hospital during the study period (between January 2017 and March 2020). Nineteen patients were excluded they were < 18 years (three recipients), had a previous kidney transplant (five recipients), required desensitization prior to surgery (nine recipients), had ABO incompatibility (1 recipient), and lacked sufficient information (one recipient). The final analysis included data from 105 recipients. The patients were divided into two groups: Blood transfusion (54 recipients) and non-transfusion (51 recipients) groups (Table 1). The transplant recipients in our cohort had a higher prevalence of male sex (77 recipients: 73%), and most kidney transplantations were from living-related (84 recipients, 80%) than living-unrelated (15 recipients, 14%) donors or from deceased-donor kidney transplantation (six recipients; 6%). The median number of HLA mismatches was three in both groups. Basiliximab was the most commonly used agent for induction (62 recipients; 59%). All the recipients in our cohort received a tacrolimus-based regimen with an average tacrolimus level during the study time of 7 ng/mL (6-8 ng/mL).

Approximately 85 (69%) recipients in our cohort had anemia [hemoglobin (Hb) of < 12 g/dL]; however, only 57 (54%) recipients received blood transfusions. Among the 57 recipients who received blood transfusion 31 recipients (54%) received only 1 unit, 15 (26%) received two units, 7 (12%) received three units, 3 (5%) received four units, and only 1 (2%) received nine units of blood. The average Hb at the time of transplantation was significantly higher in the non-transfusion group (11.2 mg/dL *vs* 9.8 mg/dL, $P < 0.001$) (Table 2). In the transfusion group, the average Hb level at which blood transfusion was initiated was 7.4 ± 0.9 mg/dL. There were no significant differences in infectious and non-infectious complications between the two groups (Table 3). Additionally, there was no significant difference in graft loss or all-cause death between the two groups (Table 4, Figures 1 and 2). There was no significant difference in creatinine level progression between the two groups during the study period (Figure 3).

Rejection occurred in five recipients in our cohort; three had cellular rejection and two had antibody-mediated rejections (Table 5). All rejection episodes were biopsy-proven, and three occurred in the transfusion group; nevertheless, there was no significant difference in the rate of rejection between the

Table 1 Baseline characteristics of both the transfusion and non-transfusion groups, *n* (%)

	Total cohort, 105	Non-transfusion, 51 (48.6%)	Transfusion, 54 (51.4%)	*P* value
Age (mean ± SD)	39.7 ± 14.5	40.5 ± 13.9	38.9 ± 15.1	0.583
Gender				
Female	28 (26.7)	10 (19.6)	18 (33.3)	0.127
Male	77 (73.3)	41 (80.4)	36 (66.7)	
Type of transplantation				
LRKTx	84 (80)	43 (84.3)	41 (75.9)	0.566
LURKTx	15 (14.3)	6 (11.8)	9 (16.7)	
DDKTx	6 (5.7)	2 (3.9)	4 (7.4)	
HLA mismatch	3 (1-4)	3 (0-4)	3 (2-4)	0.152
Cause of ESRD				
Diabetes	18 (17.1)	7 (13.7)	11 (20.4)	0.331
GN	26 (24.8)	11 (21.6)	15 (27.8)	
Hypertension	18 (17.1)	12 (23.5)	6 (11.1)	
PCKD	1 (1)	1 (2)	0 (0)	
Urological	7 (6.7)	2 (3.9)	5 (9.3)	
Other	35 (33.3)	18 (35.3)	17 (31.5)	
Donor's age	33 ± 8.6	32.4 ± 8.4	33.5 ± 8.8	0.562
Induction therapy				
ATG	42 (40)	21 (41.2)	21 (38.9)	1
Basiliximab	62 (59)	30 (58.8)	32 (59.3)	
No induction	1 (1)	0 (0)	1 (1.9)	
Maintenance immunosuppression				
CNI used tacrolimus	105 (100)	51 (100)	54 (100)	
Average CNI level	7 (6-8)	7 (6-8)	7 (6-8)	0.743
Antimetabolite used (MMF)	105 (100)	51 (100)	54 (100)	

LRKTX: Living-related kidney transplantation; LURKTx: Living non-related kidney transplantation; DDKTX: Deceased-donor kidney transplantation; HLA: Human leucocyte antigen; ESRD: End-stage renal disease; GN: Glomerulonephritis; PCKD: Polycystic kidney disease; ATG: Antithymocyte globulin; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil.

Table 2 Blood transfusion information

	Total, 105	Non-transfused, 51 (48.6%)	Transfused, 54 (51.4%)	*P* value
Hemoglobin at transplantation	10.5 ± 1.7	11.2 ± 1.6	9.8 ± 1.6	< 0.001
Hemoglobin at blood transfusion			7.4 ± 0.9	
Hemoglobin after transfusion			9.2 ± 1.1	
Number of blood transfusion units given	1 (0-1.5)		1 (0-1.5)	

two groups. Additionally, during the study period, there was an improvement in serum creatinine levels in all the patients with rejection in both groups. None of the recipients with allograft rejection lost their grafts during the study period. However, one of the recipients died due to coronavirus disease 2019 pneumonia with a functioning graft. There were no statistically significant differences in age, sex, type of transplantation, HLA mismatch, induction therapy, or CNI levels between patients who developed rejection and those who did not.

Table 3 Infectious and non-infectious complications among the two groups, *n* (%)

	Total, 105	Non-transfusion, 51 (48.6%)	Transfusion, 54 (51.4%)	*P* value
No. of infections	0 (0-1)	1 (0-1)	0 (0-1.25)	0.554
Types of infections				
none	55 (52.4)	25 (49)	30 (55.6)	0.745
UTI	30 (28.6)	14 (27.5)	16 (29.6)	0.832
Pnemonia	1 (1)	1 (2)	0 (0)	0.486
TB	1 (1)	0 (0)	1 (1.9)	1
BK	7 (6.7)	5 (9.8)	2 (3.7)	0.261
Bactremia	4 (3.8)	1 (2)	3 (5.6)	0.618
Epidediymo-orchitis	2 (1.9)	1 (2)	1 (1.9)	1
Gastroenteritis	2 (1.9)	2 (3.9)	0 (0)	0.234
Herpes zoster	1 (1)	0 (0)	1 (1.9)	1
Infected AVF	1 (1)	1 (2)	0 (0)	0.486
Perianal abcess	1 (1)	1 (2)	0 (0)	0.486
COVID-19	9 (8.6)	6 (11.8)	3 (5.6)	0.311
URTI	2 (1.9)	1 (2)	1 (1.9)	1
CMV	12 (11.4)	6 (11.8)	6 (11.1)	1
Urological complications				
None	95 (90.5)	49 (96.1)	46 (85.2)	0.484
Allograft artery stenosis	1 (1)	0 (0)	1 (1.9)	
Collection	3 (2.9)	1 (2)	2 (3.7)	
Lymphocele	1 (1)	0 (0)	1 (1.9)	
Obstrctive uropathy	1 (1)	0 (0)	1 (1.9)	
Perinephric collection and ureteric stricture	2 (1.9)	0 (0)	2 (3.7)	
Unrogenic bladder	1 (1)	0 (0)	1 (1.9)	
Urinary leak	1 (1)	1 (2)	0 (0)	
Urological complications				
No	95 (90.5)	49 (96.1)	46 (85.2)	0.094
Yes	10 (9.5)	2 (3.9)	8 (14.8)	
CNI withdrawal	1 (1)	0 (0)	1 (1.9)	1
Duration from Tx	3 d			
MMF withdrawal	1 (1)	0 (0)	1 (1.9)	1
Duration from Tx	3 d			
Steroids withdrawal	0 (0)	0 (0)	0 (0)	

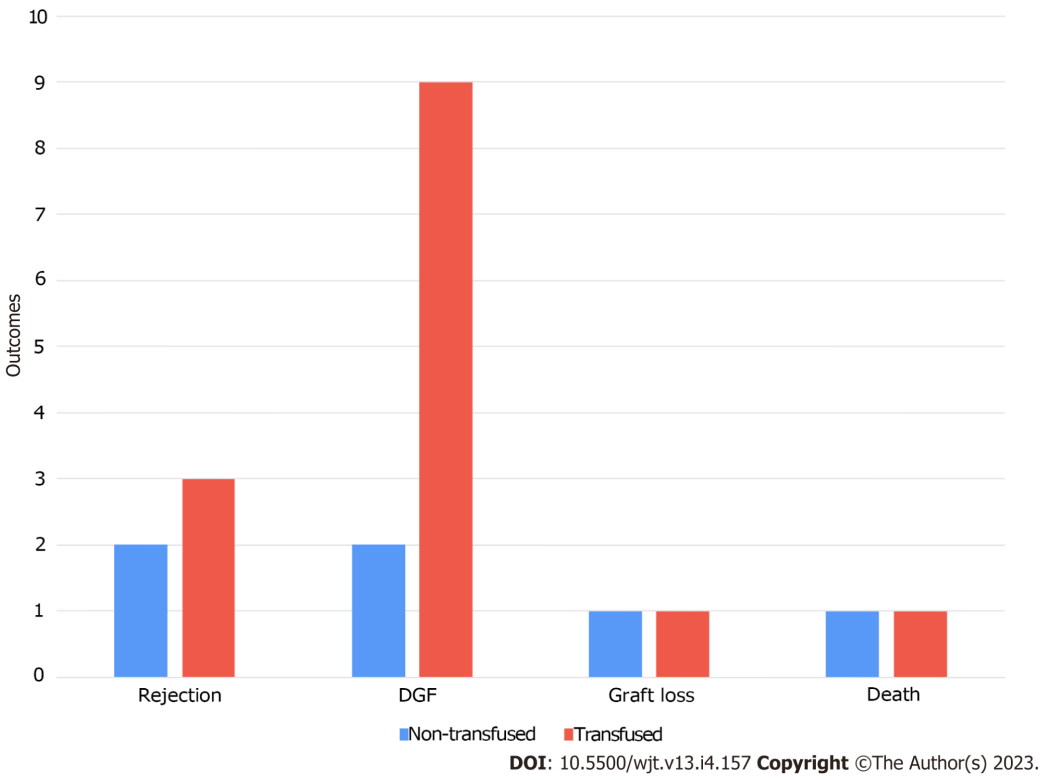
UTI: Urinary tract infection; TB: Tuberculosis; AVF: Arterio-venous fistula; COVID-19: Coronavirus disease 2019; URTI: Upper respiratory tract infection; CMV: Cytomegalovirus; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil.

The incidence of DGF was higher in the transfusion group; however, this difference was not statistically significant. In contrast, analysis of the predictors of DGF using multivariate logistic regression showed that age [adjusted odds ratio, 1.06, 95% confidence interval (CI): 1.012-1.111; P = 0.014] and blood transfusion (adjusted odds ratio 5.649, 95%CI: 1.106-28.848; P = 0.037) were significant independent risk factors for DGF. There were no significant differences in graft loss or all-cause death mortality between the two groups.

Table 4 Comparison in Outcomes of transplantation between the two groups, *n* (%)

	Total, 105	Non-transfusion, 51 (48.6%)	Transfusion, 54 (51.4%)	*P* value
Rejection	5 (4.8)	2 (3.9)	3 (5.6)	1
Rejection type				
ABMR	2 (40)	1 (50)	1 (33.3)	1
Cellular	3 (60)	1 (50)	2 (66.7)	
Graft loss	4 (3.8)	1 (2)	3 (5.6)	0.618
Death	2 (1.9)	1 (2)	1 (1.9)	1
DGF	11 (10.5)	2 (3.9)	9 (16.7)	0.053
Serum creatinine				
At discharge	141 ± 124.1	123 ± 56.7	158 ± 163	0.770
6 mo	108 ± 40.7	107.1 ± 28	108.9 ± 50.4	0.825
12 mo	109.1 ± 51.3	101.9 ± 22.9	117 ± 69.8	0.182
18 mo	126 ± 168.7	106.2 ± 26.5	147.4 ± 241.5	0.735
Creatinine difference: At 18 mo-at discharge		-19.4 ± 61.5	12.3 ± 253.8	0.439

ABMR: Antibody-mediated rejection; DGF: Delayed-graft function.



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Figure 1 Comparison in the outcomes between the blood transfusion *vs* non-blood transfusion groups. DGF: Delayed graft function.

We conducted a multiple linear regression analysis to examine the association between creatinine change (the difference between creatinine at the end of the study and baseline creatinine) as a dependent variable and eligible study variables as independent variables. We found that a higher number of transfused packed red blood cells was significantly associated with increased creatinine levels at the end of the study (B = 20.14; SE = 6.99; P = 0.004), whereas a higher creatinine level at discharge was associated with milder creatinine increase over the study period (B = -0.79; SE = 0.12; P < 0.001) (Table 6).

Table 5 Characteristics of rejection developers *vs* non-rejection developers among the study cohort, *n* (%)

	Non-rejection, 100	Rejection, 5	*P* value
Age (mean ± SD)	36.5 (28.25-51.75)	36 (21-46.5)	0.383
Gender			
Female	28 (28)	0 (0)	0.321
Male	72 (72)	5 (100)	
Type of transplantation			
LRKTx	81 (81)	3 (60)	0.172
LURKTx	13 (13)	2 (40)	
DDKTx	6 (6)	0 (0)	
HLA mismatch	3 (1-4)	3 (1-4)	0.729
Cause of ESRD			
Diabetes	18 (18)	0 (0)	0.199
GN	23 (23)	3 (60)	
Hypertension	18 (18)	0 (0)	
PCKD	1 (1)	0 (0)	
Urological	6 (6)	1 (20)	
Other	34 (34)	1 (20)	
Donor's age	32 (26-39)	28 (25.5-43.5)	0.981
Induction therapy			
ATG	41 (41)	1 (20)	0.438
Basiliximab	58 (58)	4 (80)	
No induction	1 (1)	0 (0)	
Average CNI level	7 (6-8)	8 (6.5-9)	0.311
Hb at transplantation	10.65 (9.025-11.3)	10.7 (9.05-12.45)	0.792
Hb at blood transfusion	7.4 (6.8-8)	7.8[1]	0.138
Hb after transfusion	8.9 (8.4-10)	10[1]	0.382
No of blood transfusion unites given	1 (0-1)	1 (0-3)	0.491
Serum creatinine			
At discharge	111 (83.25-142.75)	151 (113.5-222.5)	0.096
6 mo	102.5 (80.5-123)	120 (80-156)	0.420
12 mo	99.5 (81.75-119.25)	124.5 (92.5-140.75)	0.201
18 mo	105 (84.25-119)	107 (72-)	0.894
Death	1 (1)	1 (20)	0.093
DGF	9 (9)	2 (40)	0.084
No. of infections	0 (0-1)	1 (0-2)	0.651
Types of infections			
None	53 (53)	2 (40)	0.188
UTI	30 (28.6)	29 (29)	1
Pnemonia	1 (1)	1 (1)	1
TB	1 (1)	1 (1)	1
BK	7 (6.7)	7 (7)	1
Bactremia	4 (3.8)	4 (4)	1

Epidediymo-orchitis	2 (1.9)	2 (2)	1
Gastroenteritis	2 (1.9)	1 (1)	0.093
Herpes zoster	1 (1)	1 (1)	1
Infected AVF	1 (1)	1 (1)	1
Perianal abcess	1 (1)	1 (1)	1
COVID-19	9 (8.6)	8 (8)	0.367
URTI	2 (1.9)	1 (1)	0.093
CMV	11 (11)	1 (20)	0.462
Urological complications			
None	90 (90)	5 (100)	1
Allograft artery stenosis	1 (1)	0 (0)	
Collection	3 (3)	0 (0)	
Lymphocele	1 (1)	0 (0)	
Obstrctive uropathy	1 (1)	0 (0)	
Perinephric collection and ureteric stricture	2 (2)	0 (0)	
Unrogenic bladder	1 (1)	0 (0)	
Urinary leak	1 (1)	0 (0)	
Urological complications			
No	90 (90)	5 (100)	1
Yes	10 (10)	0 (0)	

[1]Interquartile range could not be calculated due to small number of patients for this outcome.
COVID-19: Coronavirus disease 2019; LRKTX: Living-related kidney transplantation; LURKTx: Living non-related kidney transplantation; DDKTX: Deceased-donor kidney transplantation; HLA: Human leucocyte antigen; ESRD: End-stage renal disease; GN: Glomerulonephritis; PCKD: polycystic kidney disease; ATG: Antithymocyte globulin; CNI: Calcineurin inhibitor; MMF: Mycophenolate mofetil; Hb: Hemoglobin; DGF: Delayed-graft function; UTI: Urinary tract infection; TB: Tuberculosis; AVF: Arterio-venous fistula; URTI: Upper respiratory tract infection; CMV: Cytomegalovirus.

Table 6 Multiple linear regression analysis of the association between creatinine change and eligible study variables

	B	SE	95%CI	*P* value
(Intercept)	70.23	18.72	33.54 to 106.92	< 0.001
Male *vs* female	-1.74	18.59	-38.17 to 34.69	0.925
No. of PRBCs	20.14	6.99	6.45 to 33.84	0.004
Creatinine at discharge	-0.79	0.12	-1.03 to -0.54	< 0.001

CI: Confidence interval; PRBC: Packed red blood cell.

DISCUSSION

Anemia is a common condition during the peri-transplantation period. The rate of anemia during this period varies significantly. In a retrospective cohort study, Vanrenterghem *et al*[1] reported an anemia rate of 38% in a transplant population[1]. However, in a recent prospective study, 64% of the study cohort had anemia that requiring blood transfusion in the first month after transplantation[2]. The transfusion rate post-transplantation has been repeatedly reported to be between 37%-75%[4,6-8]. This high prevalence of transfusion has also been observed in pediatric populations. For instance, Richards *et al*[7] reported that the prevalence of transfusion was approximately 50% with a higher prevalence in younger children[7]. In our study, the anemia rate was toward the higher end of the above mentioned range at 69% however, only 54% of our cohort required blood transfusion.

Anemia carries significant risk in kidney transplant recipients. A drop of Hb level > 30% of its pre-transplant level was reported to be associated with higher all-cause graft failure and longer length of hospital stay, with a greater risk in those who required blood transfusion of > 3 units and those with

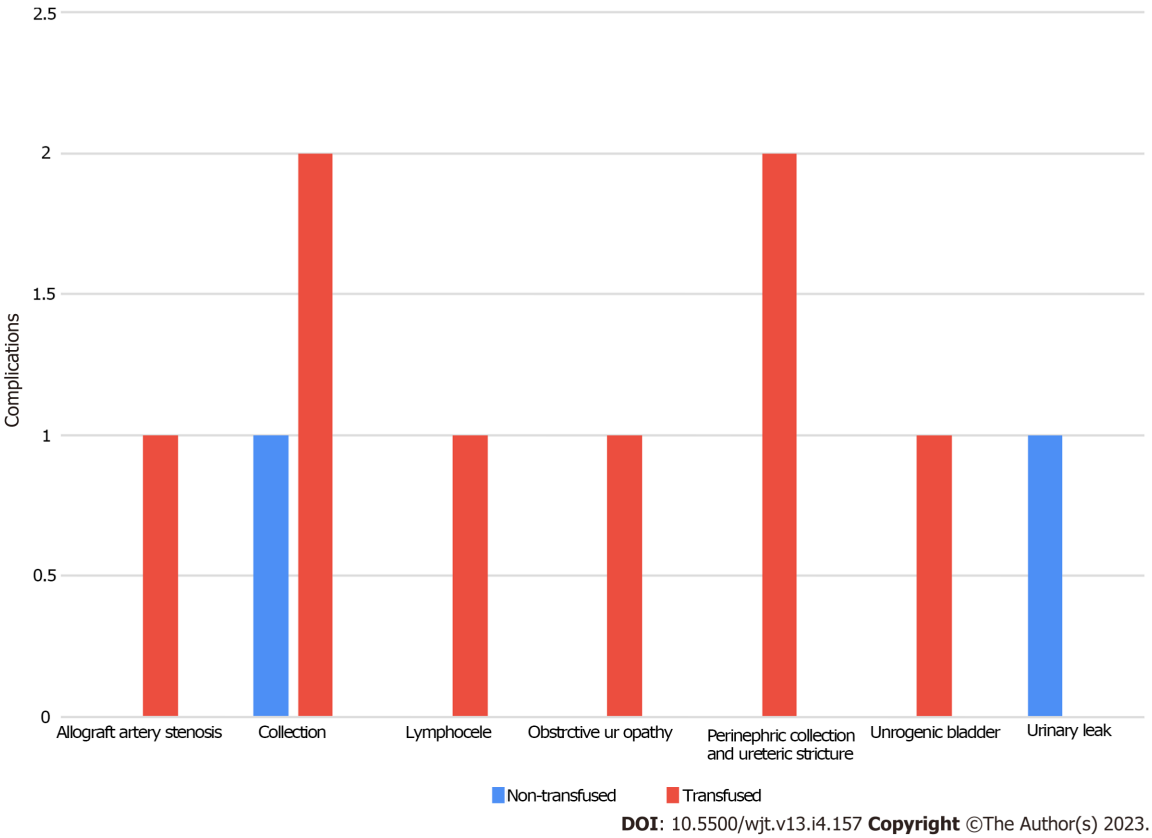


Figure 2 Progression of the mean creatinine between the blood transfusion *vs* non-blood transfusion groups.

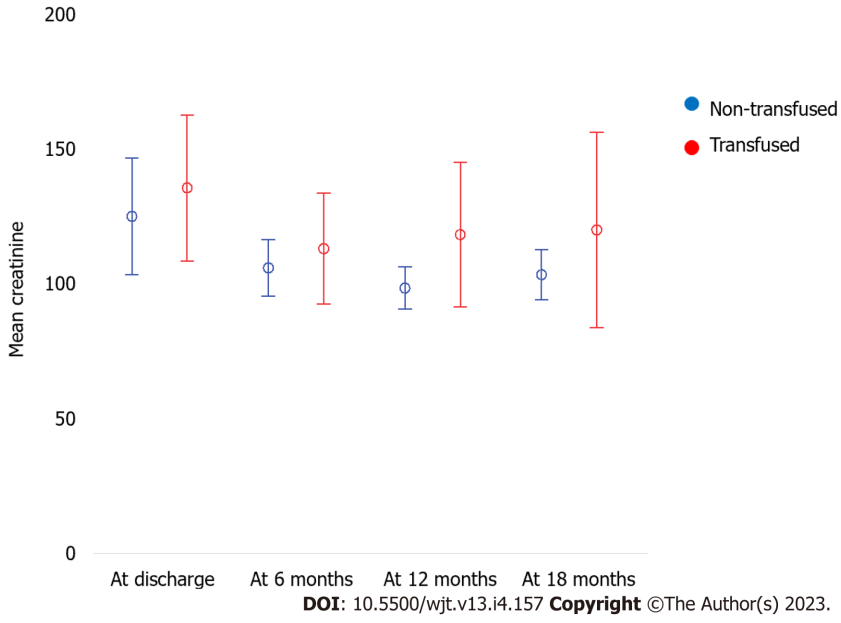


Figure 3 Progression of the mean creatinine between the blood transfusion *vs* non-blood transfusion groups. Total patients in non-transplantation group are 51. Total patients in transplantation group are 54 patients.

longer cold ischemia time[9]. However, the effect of peri-transplantation blood transfusion on graft outcome have not been well established. For instance, in a study by Daloul *et al*[4], blood transfusion was not associated with a greater risk of worse graft outcomes[4]; however, Massicotte-Azarniouch *et al*[6] revealed that blood transfusion is associated with a greater risk of graft loss[6]. This is also supported by the findings form a recent study that included more than 1000 recipients, which showed that early blood transfusion post-transplantation didn't lead to de novo DSAs formation[10]. Our study did not find any association between blood transfusion and graft loss or mortality. The link between blood

transfusion and graft or patient loss might be a cofounding factor because patients with advanced allograft dysfunction are commonly anemic. Similarly, sick patients with multiple comorbidities are usually anemic and may require blood transfusions.

HLA molecules in the blood products are known to cause HLA allosensitization for blood transfusion recipients[11-13]. Various strategies have been attempted to avoid HLA allosensitization after blood transfusion, including leuko-reduced (leuko-depleted) blood products[11,14], HLA-selected blood products[15], and autologous blood transfusion[16]. However, the protective effects of these strategies are not well established[11,14-19]. In our study, we decided to account only for leuko-depleted blood products because this is a widely used technique in our blood bank.

The effect of blood transfusion on DSA formation and antibody-mediated rejection are not well understood. Few studies have examined the development of de-novo HLA antibodies after blood transfusions in transplant populations. While some studies found that *de-novo* HLA antibodies and DSAs have a negative impact on the transplant[2,20], other studies have doubted the significance of HLA antibody development in the setting of immunosuppression therapy[3,8,11]. For instance, In Ferrandiz *et al*[2] reported that antibody-mediated rejection occurred in 6% of kidney transplant recipients who required blood transfusion post-surgery compared with 1.4% in a non-transfusion group (P = 0.04)[2]. In contrast, in a study by Jalalonmuhali *et al*[3] involving 699 patients, there was no differences in the development of HLA antibodies or de-novo HLA-DSA and rejection between the transfusion and none transfusion groups[3]. Similarly in our study, the rejection rate in the transfusion group was approximately 5%, with no difference between the two groups.

Multiple factors are associated with an increased risk of poor transplant outcomes after blood transfusion. In a previous prospective observational study, worse transplantation outcomes were linked to the number of transfusion episodes (pre and post-transplantation), regardless of the total number of transfusion units[20]. In another study, poor transplantation outcomes were linked to the number of transfusion units (> 3 units)[9]. In our study, creatinine levels tended to increase toward the end of the follow-up period in the transfusion group, but this finding was not statistically significant.

It is noteworthy that maintenance immunosuppression therapy in studies that found a significant increase in rejection risk after transfusion was cyclosporine-based[2,20] while studies in which the maintenance immunosuppression regimen was tacrolimus-based showed no significant increase in rejection rate between transfusion and non-transfusion groups[3,8]. Our study is consistent with this observation as rejection rate was not significantly different between the two groups in our tacrolimus-based study cohort.

Although blood transfusion after kidney transplantation did not have an impact on patient survival, a cross-sectional study of 1198 liver transplant recipients showed a significant increase in mortality rate in patients who received a large number of blood transfusion units. Average blood transfusion units in expired patients was 5.92 ± 5.91 compared to 3.74 ± 4.23 in alive patients (95%CI: 1.47–2.88)[21].

In this study, there was a tendency toward higher DGF rates in the transfusion group. Although this finding was not statistically significant, it was in line with that of MacIsaac *et al*[9], in which the rate of DGF in transplant patients was up to 26%[9]. Similarly, in a retrospective cohort study on 1258 kidney transplant recipients who were followed for a median of 1405 d, DGF was as high as 41% in a transfusion group *vs* 15% in a non-transfusion group (P < 0.0001)[6]. In a study by Fidler *et al*[20], DGF was associated with a higher risk of combined patient and graft loss at a hazard ratio of 2.5 (1.5-4.5) on univariate analysis; However, this difference disappeared on multivariate analysis. It's difficult to determine whether DGF is a cause, or a result of blood transfusion based on the available literature.

This study has limitations. This was a single-center retrospective cohort study. The lack of routine DSA and allograft biopsy restricted the inclusion of clinically insignificant DSAs and non-apparent rejections. Moreover, our cohort was predominantly males, which limits the generalizability of our findings.

CONCLUSION

Leukodepleted blood transfusion in the peri-transplantation period was not associated with a higher risk of rejection, graft loss, or patient loss. Further investigations are needed to address the link between peri-transplantation blood transfusions, DGF and DSA formation.

ARTICLE HIGHLIGHTS

Research background

Blood transfusion is common during the peri-transplantation period. The incidence of immunological reactions to blood transfusion after kidney transplantation and their consequences on graft outcomes have not been extensively studied.

Research motivation
Blood transfusion during the peri-transplantation period is very common and its safety need to be studied.

Research objectives
To examine the risk of graft rejection and loss in patients who received blood transfusion in the immediate peri-transplantation period.

Research methods
A retrospective cohort study of 105 kidney recipients who received leukodepleted blood transfusions at our center between January 2017 and March 2020.

Research results
Of 105 kidney recipients were divided into transfusion (n = 54) and non-transfusion (n = 51) groups. There were no differences between the two groups in terms of rejection rates, graft loss, or death. There was no significant difference in creatinine level progression between the two groups. A high number of transfused packed red blood cells was significantly associated with increased creatinine levels at the end of the study.

Research conclusions
Leukodepleted blood transfusion was not associated with a higher risk of rejection, graft loss, or death in kidney transplant recipients.

Research perspectives
Leukodepleted blood transfusion in the peri-transplantation period is likely safe.

FOOTNOTES

Author contributions: All the co-authors contributed in data collection, writing, editing, literature review and designing the study.

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ORIGINAL ARTICLE

Retrospective Study

Delayed referral for liver transplant evaluation worsens outcomes in chronic liver disease patients requiring inpatient transplant evaluation

Katherine M Cooper, Alessandro Colletta, Nicholas J Hathaway, Diana Liu, Daniella Gonzalez, Arslan Talat, Curtis Barry, Anita Krishnarao, Savant Mehta, Babak Movahedi, Paulo N Martins, Deepika Devuni

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Abstract

BACKGROUND

Indications to refer patients with cirrhosis for liver transplant evaluation (LTE) include hepatic decompensation or a model for end stage liver disease (MELD-Na) score ≥ 15. Few studies have evaluated how delaying referral beyond these criteria affects patient outcomes.

AIM

To evaluate clinical characteristics of patients undergoing inpatient LTE and to assess the effects of delayed LTE on patient outcomes (death, transplantation).

METHODS

This is a single center retrospective cohort study assessing all patients undergoing inpatient LTE (n = 159) at a large quaternary care and liver transplant center between 10/23/2017-7/31/2021. Delayed referral was defined as having prior indication (decompensation, MELD-Na ≥ 15) for LTE without referral. Early referral was defined as referrals made within 3 mo of having an indication based on practice guidelines. Logistic regression and Cox Hazard Regression were used to evaluate the relationship between delayed referral and patient outcomes.

RESULTS

Many patients who require expedited inpatient LTE had delayed referrals. Misconceptions regarding transplant candidacy were a leading cause of delayed referral. Ultimately, delayed referrals negatively affected overall patient outcome and an independent predictor of both death and not receiving a transplant. Delayed referral was associated with a 2.5 hazard risk of death.

CONCLUSION
Beyond initial access to an liver transplant (LT) center, delaying LTE increases risk of death and reduces risk of LT in patients with chronic liver disease. There is substantial opportunity to increase the percentage of patients undergoing LTE when first clinically indicated. It is crucial for providers to remain informed about the latest guidelines on liver transplant candidacy and the transplant referral process.

Key Words: Liver transplantation; Liver transplant evaluation; Liver transplant referral; Patient access; Equity; Patient outcomes

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Core Tip: There are many system and provider-level barriers to liver transplant evaluation. However, the effect of late transplant evaluations remains unclear. We demonstrate delayed liver transplant evaluation is independently associated with death prior to transplant in patients undergoing liver transplant evaluation.

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INTRODUCTION

The global impact of chronic liver disease is increasing. Liver transplantation is the only definitive treatment for decompensated cirrhosis. Guideline recommended indications to refer patients with cirrhosis for liver transplant evaluation (LTE) include hepatic decompensation or a Model for End Stage Liver Disease score (MELD) ≥ 15[1,2]. While the progression cirrhosis usually occurs over multiple years [3], many patients go un-diagnosed prior to overt hepatic decompensation[3,4]. Thus, many patients have progressed disease when they begin receiving care[5]. Further delays entering the transplant care pathway can result in delayed referral and need for expedited LTE in the setting of acute decompensation. While there is emerging literature on what qualifies as late referral or urgent transplant evaluation[6,7], there is little data regarding the influence of delayed transplant evaluation on outcomes. In this retrospective analysis, we evaluate clinical characteristics of patients undergoing inpatient LTE to identify risk factors for delayed LTE and assess the effect of delayed LTE on patient outcomes.

MATERIALS AND METHODS

Study design and definitions

This is a single center retrospective cohort study analyzing patients undergoing LTE at a large quaternary care and liver transplant center. Medical records were obtained for patients with a transplant evaluation encounter between October 2017 and July 2021 using our center's liver transplant database. Patients with diagnosis of cirrhosis who underwent LTE for chronic liver disease (CLD) as an inpatient in this time period were identified as potential subjects. Patients were excluded if they: (1) Were undergoing re-transplantation; (2) being evaluated for acute liver failure; and (3) were completing evaluation in the outpatient setting. Patients with hepatocellular carcinoma were also excluded due to differences in candidacy and referral criteria[8]. Study data were collected and managed using a 255-field form with an electronic data capture tool hosted at UMass Chan Medical School. Research Electronic Data Capture (REDCap) is a secure, web-based software platform designed to support data capture for research studies, providing: (1) An intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources[9,10].

All clinical and laboratory data including Model for End Stage Liver Disease -Sodium (MELD-Na) score were collected at the time of LTE. Available clinical documentation collected during LTE was closely reviewed and evaluated. Cirrhosis etiologies included chronic alcohol (ETOH) associated liver disease, non-alcoholic steatohepatitis (NASH), Hepatitis C (HCV), cholestatic liver disease (primary sclerosing cholangitis, primary biliary cirrhosis), inherited/genetic disease (hereditary hemochromatosis, alpha-1 anti-trypsin deficiency), and cryptogenic/other. Clinical decompensations included hepatic encephalopathy, jaundice, ascites, hepato-renal syndrome, spontaneous bacterial peritonitis (SBP), and variceal bleed[2,11]. Patients were considered to have a cardiac diagnosis if their past medical history included diagnosis or treatment of a cardiac arrhythmia, coronary artery disease, or cardiomyopathy with heart failure. Malnutrition was diagnosed by registered dieticians on the multidisciplinary transplant team using the ASPEN criteria[12]. Cause of death was recorded when available.

Transplant evaluation indications were defined using the American Association for the Study of Liver Disease (AASLD) guidelines and included: (1) Hepatic decompensation OR; and (2) MELD ≥ 15 AND (3) absence of active alcohol or illicit drug use[13]. Time for sobriety required for evaluation at our institution is 3 mo. Subjects were dichotomized to either "delayed referral" or "early referral." "Delayed referral" indicated that subjects had an indication for transplant evaluation but were not referred within three months, while "early referral" meant that subjects were referred within three months of having an indication for transplant evaluation. Three months was chosen as this is the timeline of clinical improvement in patients expected to recover once cirrhosis trigger is withdrawn (*e.g.*, alcohol cessation) [14]. In terms of transplant outcomes, there are multiple potential outcomes of LTE and many of these can occur interchangeably. For example, patients can be approved but not yet listed, or listed but inactive on the wait list. For analytical simplicity, our selected outcomes included: not approved, died on waitlist, off list, on list, and transplanted. For statistical analysis, subjects were further dichotomized as "approved" or "not approved, "dead" or "not dead," and "transplanted" or "not transplanted" at the time of data collection.

Endpoints and data analysis

Normally distributed continuous data is reported as "mean (standard deviation)" and were compared with two-sample *t*-test. Non-normally distributed continuous data is reported as "median [inter-quartile range]" and were compared using Wilcoxon rank sum tests. Categorical variables are reported as "percentage" and were compared using pair-wise z testing. Correlations are reported using Pearson's bivariate correlation coefficient. Associations are reported as odds ratios with 95% confidence intervals and were evaluated with logistic regression.

Demographic, psychosocial, and clinical variables were compared between delayed and early referral (Tables 1-3). Comparisons were also made between: (1) Dead and not dead; and (2) transplanted and not transplanted within the delayed referral group to identify potential markers of mortality within this cohort (Supplementary Table 1).

Backward logistic regression modeling was used to identify risk factors for delayed referral with the following starting variables: Age, race, sex, ethnicity, time since diagnosis (months), malnutrition (as defined by ASPEN guidelines), depression, trauma history, number of prior hospitalizations, sobriety period, smoking history, lives with family, married/stable partner, stable housing, employed within 1 year, military service history, non-English first language, education, proximity to transplant center, regular outside gastroenterologist, regular outpatient labs.

Backward logistic regression was also used to evaluate if delayed referral was an independent predictor of transplant status and death amongst other relevant clinical markers (for full list see Tables 4 and 5, respectively). We created a multi-variable logistic regression model utilizing this data and other variables known to affect outcomes in the liver transplantation pathway including but not limited to sex [15], age[16], height[17], acute on chronic liver failure (ACLF) grade[18], and laboratory markers that comprise MELD-Na and represent hepatic function. The final model was created to optimize goodness of fit using the Hosmer and Lemeshow test.

Cox proportional hazard regression modeling was used to evaluate the impact of delayed referral on risk of dead in patients undergoing inpatient LTE. Participants were censored on the day of transplant and the last known well if lost to follow up. An unadjusted model was performed using "delayed" as the sole independent variable; the adjusted model incorporated the following additional variables: age, sex, ethnicity, etiology, MELD-Na, and blood type. Data is reported as hazard ratios (HRs) with 95% confidence intervals.

The threshold for statistical significance was set at $P < 0.05$. For all backward logistic regression model threshold to enter was 0.05 and threshold to remove was 0.10. All statistical analysis was conducted using SPSS version 29. This study was reviewed and approved by the institutional review board at our medical center.

RESULTS

We identified 160 patients undergoing inpatient LTE for cirrhosis (49% delayed referral and 51% early

Table 1 Baseline and demographics, %

Characteristic	Delayed referral (*n* = 78)	Early referral (*n* = 82)	*P* value
Portion of sample	49	51	-
Age (yr)	59 (10)	57 (9)	0.19
Distance to center (miles)	43.0 [20.5–59.5]	43.5 [19.3–67.3]	0.74
Time since diagnosis (mo)	30 [12.3–60]	11 [3.75–55.5]	< 0.01
Gender			0.59
Female	39.7	43.9	
Male	60.3	56.1	
Race			0.49
Asian	1.3	3.7	
Black or African American	1.3	1.2	
Other/Unknown	17.9	12.2	
White	79.5	82.9	
Ethnicity			0.11
Hispanic/other	19.2	9.8	
Non-Hispanic	80.8	90.1	
Etiology			0.88
Autoimmune	5.1	4.9	
Alcohol	43.6	53.7	
Cryptogenic/cholestatic	5.1	6.1	
Genetic	7.7	4.9	
Hepatitis C	11.5	9.8	
NASH	26.9	20.7	
Blood type			0.36
A	37.2	27.2	
B	16.7	19.8	
AB	1.3	4.9	
O	44.9	48.1	

Demographic and clinical data for delayed referral (left) versus early referral (right) patients undergoing inpatient liver transplant evaluation. Data reported as percentages of total group for categorical data; as average (standard deviation) for normally distributed continuous data, and as median [IQR] for non-normally distributed continuous data. NASH: Non-alcoholic steatohepatitis.

referral). Participants were predominately a male, white, and non-Hispanic with a mean age of 58 +/- 10. Over half of subjects had a high school level education or less (50.7% early *vs* 62.7% delayed, P = 0.14). The most common etiologies of cirrhosis were ETOH, NASH, and HCV. Subjects with delayed referral had been diagnosed with liver disease more months on average than those with early referral (P < 0.01). Subjects with early referral were diagnosed within the preceding year more often than subjects with delayed referral (50.7% *vs* 30.8%, P = 0.02) (See Table 1 for summary of demographics).

Laboratory evaluation collected at time of LTE did not differ between groups (Supplementary Table 2). Most subjects had MELD-Na scores between 25-34 with an average score of 27 in each group (P = 0.91). A similar proportion of subjects had Grade 1, Grade 2, and Grade 3 ACLF (P = 0.56). The mean number clinical decompensations present during LTE was 4 and the number decompensations positively correlated with MELD-Na score (r(157) = 0.390, P < 0.01). One third of subjects were diagnosed with malnutrition during LTE (23.1% delayed referral *vs* 43.9% early referral, $P \leq 0.001$). Infection was recorded 40% of patients (42.3% delayed *vs* 35.4% early, P = 0.39) and blood pressure support occurred in 30% of patients (34.6% delayed *vs* 26.8% early, P = 0.29). About half the subjects in each group (48%) required an intensive care unit (ICU) stay during LTE with no differences in days of ICU stay (P = 0.44). Trans-jugular intrahepatic portosystemic shunt during admission was 2.3 times

Table 2 Liver transplant evaluation data, %

	Delayed	Early	*P* value
Transferred to center	48.7	51.2	0.75
MELD-Na (points)	27.2 (7)	27.0 (9)	0.87
TIPS placed	15.4	7.3	0.22
ICU stay	51.3	43.9	0.35
ICU d (#)	10 (9)	8 (7)	0.44
Pressor support	34.6	26.8	0.29
Declined for LT listing	17.9	15.9	0.72
Reasons declined			
Psychosocial	30.0	12.5	0.38
Medical	20.0	25.0	
Death	30.0	12.5	
Other	20.0	50.0	
Decompensations			
Ascites	94.9	96.3	0.65
Jaundice	64.1	72.0	0.29
EVB	21.8	24.4	0.70
HE	70.7	70.5	0.98
HRS	59.8	62.8	0.69
HHT	21.8	14.6	0.24
SBP	21.8	18.3	0.58
ACLF grade			
Grade 1	34.6	42.7	0.56
Grade 2	50.0	42.7	
Grade 3	15.4	14.6	
ACLF bilirubin			
< 15 mg/dL	82.1	76.8	0.28
15-25 mg/dL	9.0	17.1	
> 25 mg/dL	9.0	6.1	
ACLF INR			
< 1.8	62.8	62.2	0.78
1.8-2.5	28.2	25.6	
> 2.5	9	12.2	
ACLF lactate			
< 1.5 mmol/L	73.1	80.5	0.16
1.5-2.5 mmol/L	15.4	6.1	
> 2.5 mmol/L	11.5	13.4	
ACLF creatinine			
< 0.7 mg/dL	7.3	7.3	0.64
0.7-1.5 mg/dL	32.9	32.9	
> 1.5 mg/dL	52.6	59.8	

Clinical data from index admission and liver transplant evaluation. Data reported as percentages of group for categorical data; as average (standard deviation) for normally distributed continuous data. Comparisons were made using students T tests and comparison of proportions test. ACLF: Acute on chronic liver failure; LT: Liver transplant; ICU: Intensive care unit; MELD: Model for end stage liver disease; TIPS: Trans-jugular intrahepatic portosystemic shunt; EVB: Esophagogastric variceal bleeding; HRS: Hepatorenal syndrome; HHT: Hepatic hydrothorax; SBP: Spontaneous bacterial peritonitis; LTE: Liver transplant evaluation; INR: International normalized ratio; HE: Hepatic encephalopathy.

more common in delayed referrals (95%CI: 0.92-8.25, P = 0.11). Most subjects (83%) were accepted as candidates for liver transplant with no differences between groups (P = 0.78). However, it took 6-8 d longer to complete LTE for subjects with delayed referral compared to early referral (P = 0.07) (See Table 2 for summary of clinical data).

Pre-LTE: Identifying risk factors for delayed referral

Psychosocial factors: A similar proportion of participants resided with family (P = 0.75) and had stable housing in each group (P = 0.68). Interestingly more subjects with delayed referral had an established partner compared to early referral (P = 0.05). Slightly more subjects with a delayed referral reported English as a second language, though this failed to meet statistical significance 20.5% *vs* 13.6%, P = 0.24). In terms of education, almost two thirds of the delayed referral group had a high school education or less compared to one half of the early referral group (P = 0.14) Employment within the last year (P < 0.01) and having an identifiable source of income (P = 0.01) were more common in subjects with early referral. Smoking history (P = 0.15) and alcohol use history was similar in each group (P = 0.12). However, for those patients who reported prior regular alcohol consumption, early referral subjects were closer to their last drink compared to delayed referral (P < 0.01). Specifically, more patients in the early group were evaluated with sobriety of 3-6 mo (39.3% early *vs* 22.4% delayed, P = 0.05) while more patents in the delayed group were referred with sobriety of 1-2 years (30.6% delayed *vs* 8.2% early, P < 0.01) (See Table 3 for summary of psychosocial factors).

Clinical care- outpatient providers, medication, and gastrointestinal provider notes: There were no significant differences in pre-LTE hepatic decompensations between groups (Table 3). Average body mass index was slightly higher in missed group (32.5 +/-10 *vs* 30.1 +/- 8; P = 0.09). Malnutrition was more common amongst early referrals and was associated with a 2/3 Lower chance of having a delayed referral (OR: 0.34, CI: 0.14-0.78, P = 0.01). The number of patients receiving routine medications for ascites and hepatic encephalopathy when applicable based on decompensation history did not differ between groups. Interestingly, of the 35.6% of patients with known diabetes, insulin use was more common in delayed referrals, but not to a statistically significant degree (33.3% delayed *vs* 16.7%, P = 0.15). Of patients with regular laboratory evaluation available, previously documented hypercoagulability and transaminitis was noted between groups; hypoalbuminemia was slightly more common amongst those with delayed referral (Table 3). Considering only patients with outside documentation from gastroenterologist, there were no differences in proportion of patients with low albumin, elevated international normalized ratio, or abnormal liver enzymes between early and delayed referral (data not shown) (See Table 3 for summary of outpatient care factors).

Risk factors for delayed referrals: Backward logistic regression model using 20 psychosocial or demographical variables identified female sex and trauma history to be predictors of delayed referral while malnutrition, work within the prior year, and prior smoking history were predictors of early referral (Supplementary Table 3). The most common theme identified in clinical documentation leading to delayed referral was poor understanding about indications for transplant referral, which was identified in 20% of the subjects with delayed referrals. Specifically, outpatient providers cited inaccurate contraindications to transplant, such as age or weight, or incorrect sobriety periods required for referral. Other frequently identified themes included failure to obtain or calculate MELD-Na labs (10%), lack of care continuity (18%), insurance or financial barriers (9%), or patient reluctance to pursue transplant (10%). However, one in three patients had no clear reason for lack of referral.

Effects of referral time on patient outcomes

Primary outcome measures differed between those with delayed compared to early referral. Delayed referrals were transplanted less often (28% *vs* 48%) and died prior to transplant more often those with early referral (42% *vs* 21%). Predictors of transplant identified on backward logistic regression include age, ACLF grade, platelets, neutrophil-lymphocyte ratio, albumin, sex, months since diagnosis, weight, blood type, and delayed referral. On a multivariable regression model created using clinical data optimized for goodness of fit, early referral was associated with 2.3 increased odds of receiving a transplant (95%CI: 1.02-4.57; P = 0.045) (Supplementary Table 4). Of those transplanted, over 80% of each group was one year post transplant at the time of data collection, and about 50% were two years post-transplant. There were no differences in survival at either the one-year (P = 0.650), or two-year (P = 1.000) time points (data not shown).

Table 3 Pre-transplant clinical and demographic factors, %

	Delayed	Early	*P* value
Education			0.14
Highschool or less	62.6	50.7	
College degree or more	14.7	23.4	
Substance use			
Smoking history	55.1	57.3	0.15
Drinking history	62.8	74.3	0.12
Sobriety period			< 0.01
< 6 mo	22.4	59.0	
6 mo – 2 yrs	53.0	26.2	
> 2 yrs	23.6	14.8	
Psychosocial factors			
Depression history	39.7	28.0	0.12
Trauma history	9.0	2.4	0.07
Public insurance	50.0	50.0	1.00
Non-English first language	20.5	13.6	0.24
Lives with family	78.2	80.2	0.75
Married/stable partner	67.5	52.4	0.05
Unstable housing	6.4	4.9	0.68
Military service history	3.8	8.6	0.21
Worked within 1 mo	7.7	22.2	<0.01
Worked within 1 yr	24.4	49.4	<0.01
Clinical care			
Outpatient GI documentation	83.3	78.0%	
Ascites on diuretics	90.7	90.3	0.94
Ascites with regular paracentesis	32.0	25.0	0.35
On lactulose/rifaximin	85.0	90.5	0.39
Midodrine	42.9	46.0	0.81
Regular labs	*n* = 59	*n* = 40	
Low albumin	89.8	77.5	0.09
High ALT/AST	93.2	87.5	0.31
High INR	84.7	72.5	0.14
Prior decompensations			
Ascites	96.2	87.8	0.05
Jaundice	66.7	68.3	0.83
Variceal bleed	35.9	29.3	0.37
Hepatic encephalopathy	78.2	64.2	0.06
Hepatorenal syndrome	35.9	31.7	0.58
Hepatic hydrothorax	11.5	9.8	0.72
Spontaneous bacterial peritonitis	21.8	24.4	0.68

Comparison of psychosocial and clinical data from prior to liver transplant evaluation (LTE) in patients with delayed compared to early LTE. Psychiatric

comorbidities including depression and trauma occurred more in delayed LTE. Working history was strongly associated with timely referral. Data reported as percentages of group for categorical data; as average (standard deviation) for normally distributed continuous data. Comparisons were made using students T tests and comparison of proportions test. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GI: Gastrointestinal; INR: International normalized ratio.

Predictors of death on backward logistic regression include Age, hematocrit, neutrophil to lymphocyte ratio, albumin, months since diagnosis, weight, decompensation number, and delayed referral (Table 5). Within the delayed LTE cohort patients who died were older (P = 0.04), had an outpatient gastrointestinal (GI) provider less often (P = 0.03), had SBP more often (P = 0.04) and required an ICU stay and blood pressure support more often (< 0.01) (Supplementary Table 1). On univariable Cox Regression, the HR of death was 2.2 (95%CI: 1.2–2.9) in for delayed referral compared to early referral over average follow up period of 269 d. When adjusting for age, sex, ethnicity etiology, and MELD-Na, the HR for increased to 2.5 (95%CI: 1.3–4.7) for delayed referral compared to early referral (Figure 1).

DISCUSSION

Our study assessed clinical characteristics of patients with decompensated cirrhosis undergoing inpatient LTE and examined the effect of delayed referral on patient outcomes. We observed that a significant proportion of patients could have been referred earlier and built on this notion by demonstrated delayed LTE was associated with worse patient outcomes in patients already undergoing urgent LTE. These relationships persisted when controlling for key variables and backward logistic regression identified delayed referral as an independent risk factor for death and not receiving a liver transplant. We identified risk factors for death within the patients who had a delayed LTE to identify the most vulnerable cohorts and found death to be most common in patients with delayed referral and (1) Had no regular documentation from an outside GI provider; and (2) were critically ill in the ICU with SBP and requiring blood pressor support.

The high proportion of patients with delayed referrals is consistent with previous studies that report poor adherence to liver transplant referral guidelines in patients with cirrhosis[19]. We sought to identify demographical risk factors for delayed LTE but observed no differences in basic demographics between cohorts in our study. Patients in our study resided within similar proximity to the transplant center, which is inconsistent with previous literature reporting that increased distance from a transplant site is a barrier to transplant related care[20]. However, we believe this suggests distance may be more related to the ability to attend health care appointments and not play a role in the referral decision itself. For example, a recent study that identified LTE within 30 d of LT referral was associated with better outcomes and that distance from the transplant center reduced odds of completing LTE within the 30-d window[21]. While we anticipated group differences in health insurance[6,22,23], we observed approximately 50% of each cohort having publicly funding insurance. It is possible that this is due to the robust public health and insurance funding in Massachusetts.

There were notable psychosocial differences between cohorts including education and employment status. Lower education attainment and lack of employment within the preceding year were more common in patients with delayed referral. This data supports that lower degrees of financial stability and health literacy may act as barriers to early evaluation. Identifying patients with limited health literacy could reduce the number of delayed evaluations by improving patients' understanding of their disease[24]. In addition, we found that being married or having a stable partner was more common in patients with delayed referrals but did not affect transplant or death. We found this point interesting as typically psychosocial support is associated with improved outcomes in the transplant pathway; it remains unclear the role of having a spouse or stable partner on referral and care seeking in this population.

We utilized clinical history and provider written medical documentation to inform understanding of barriers to access to liver transplantation referral and evaluation. First, specific hepatic decompensations did not differ between groups, which is consistent with recent research reporting that clinical manifestations of CLD may be poor markers of the timeliness of transplant evaluation[7]. Conversely, malnutrition was protective against of delayed evaluation which may suggest that frailty is a conspicuous manifestation of CLD that is more readily recognized compared to more obscure manifestations of CLD, such as mild hepatic encephalopathy, or that physicians associate frailty with poor outcomes and are more likely to refer. Differences in time from diagnosis to transplant evaluation may reflect this as well, as data suggests providers have different thresholds for referral. Conversely it may be explained by lack of care continuity amongst patients with delayed referrals. Care continuity may reflect poor understanding of disease severity, and it is possible that targeting patient understanding of liver disease may improve the follow up rate in this cohort.

Table 4 Predictors of transplant

	Initial multivariate regression				Backward logistic regression			
	Wald	*P* value	OR	95%CI	Wald	*P* value	OR	95%CI
Age (yr)	3.45	0.06	0.94	0.9-1.0	4.62	0.03	0.95	0.9-1.0
Education (HS)	2.41	0.12	1.49	0.9-2.5	-	-	-	-
ICU stay (+)	1.12	0.29	0.38	0.1-2.3	-	-	-	-
ACLF grade (G3)	2.67	0.10	2.76	0.8-9.3	4.75	0.03	2.13	1.1-4.2
MELD (points)	0.58	0.45	1.07	0.9-1.3	-	-	-	-
Creatinine (mg/dL)	0.08	0.78	0.90	0.4-1.9	-	-	-	-
Sodium (mmol/L)	1.28	0.26	0.90	0.8-1.0	-	-	-	-
Bilirubin (mg/dL)	1.06	0.30	1.05	1.1-1.1	-	-	-	-
INR	1.28	0.26	0.42	0.1-1.9	-	-	-	-
WBC ($\times 10^9$/L)	0.03	0.86	0.99	0.8-1.2	-	-	-	-
Hematocrit (%)	1.34	0.25	0.94	0.9-1.0	-	-	-	-
Platelets ($\times 10^9$/L)	1.73	0.19	0.99	1.0-1.0	5.50	0.02	0.99	1.0-1.0
N-L ratio	3.65	0.06	0.89	0.8-1.0	5.15	0.02	0.90	0.8-1.0
Albumin (g/dL)	6.79	< 0.01	3.58	1.4-9.4	9.04	< 0.01	3.32	1.5-7.3
Malnutrition (+)	0.30	0.59	1.39	0.4-4.6	-	-	-	-
Cardiac dx (+)	0.06	0.82	0.83	0.2-3.9	-	-	-	-
Sex (Male)	7.29	< 0.01	14.8	2.1-105	3.02	0.08	2.38	0.9-6.3
Race (White)	1.24	0.27	0.42	0.1-1.9	-	-	-	-
Depression (+)	4.17	0.04	4.24	1.1-17	-	-	-	-
Time since dx (mo)	2.44	0.12	1.01	1.0-1.0	2.69	0.10	1.01	1.0-1.0
Pressor need (+)	0.28	0.60	0.56	0.1-4.8	-	-	-	-
Height (cm)	2.37	0.12	0.94	0.9-1.0	-	-	-	-
Weight (kg)	1.22	0.27	0.99	1.0-1.0	4.72	0.03	0.98	1.0-1.0
Transferred (+)	0.00	1.0	1.00	0.3-3.5	-	-	-	-
Refer to LTE (d)	0.04	0.85	1.00	1.0-1.0	-	-	-	-
Delayed referral (+)	2.67	0.10	0.32	0.1-1.2	3.51	0.06	0.40	0.2-1.0
Decompensations (#)	0.11	0.73	0.91	0.5-1.6	-	-	-	-
Etiology (ETOH)	0.00	0.98	1.00	0.7-1.5	-	-	-	-
TIPS (+)	1.36	0.24	0.52	0.2-1.6	-	-	-	-
Blood type (A)	2.50	0.11	0.62	0.3-1.1	2.71	0.01	0.65	0.4-1.1
Constant	3.26	0.07	5000	-	0.745	0.38	6.54	-

Multivariable logistic model with backward logistic regression to identify predictors of receiving transplant in patients undergoing inpatient liver transplant evaluation (LTE). Starting with 30 potential variables that may predict hepatic encephalopathy, backward regression identified 10 potential independent predictors for transplant including age, ACLF grade, platelets, N-L ratio, serum albumin, sex, time since diagnosis, weight blood type, and having a delayed LTE. Regression complete din SPSS using backward regression conditional model; probability to enter 0.05 and probability to remove 0.10. Units recorded in parenthesis for continuous variables; reference variable recorded in parenthesis for categorical variables where "+" indicates the variable is present in the patient. ACLF: Acute on chronic liver failure; ICU: Intensive care unit; WBC: White blood cell count; MELD: Model for end stage liver disease; INR: International normalized ratio; N-L ratio: Neutrophil to lymphocyte ratio; dx: Diagnosis; TIPS: Trans-jugular intrahepatic portosystemic shunt.

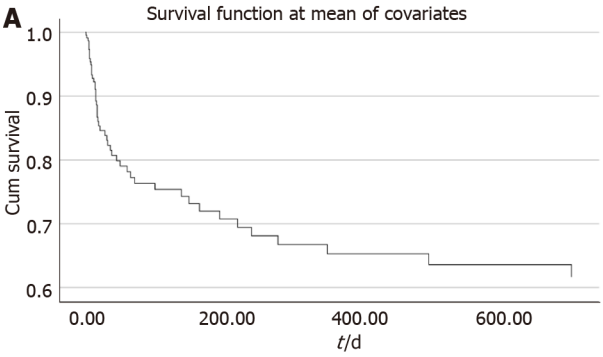
Documentation for 1 in 5 patients with delayed referral included misconceptions about candidacy and referenced inaccurate contraindications to transplant. This was especially evident in subjects with alcohol use disorder, where providers noted longer sobriety periods than truly required to enter the transplant care pathway. These findings are consistent with literature showing provider level factors

Table 5 Predictors of death

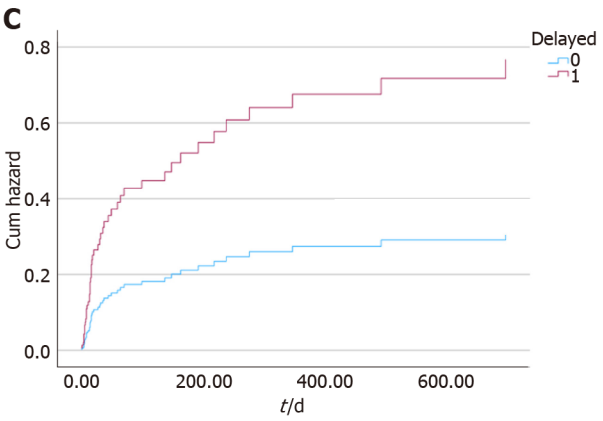
	Initial multivariate regression				Backward logistic regression			
	Wald	*P* value	OR	95%CI	Wald	*P* value	OR	95%CI
Age (yrs)	5.51	0.02	1.12	1.0-1.2	6.24	0.01	1.10	1.0-1.1
Education (HS)	0.72	0.40	0.75	0.4-1.5	-	-	-	-
ICU stay (+)	0.03	0.86	0.84	0.1-5.8	-	-	-	-
ACLF grade (G3)	0.06	0.81	1.19	0.3-4.9	-	-	-	-
MELD (points)	4.58	0.03	0.73	0.5-1.0	-	-	-	-
Creatinine (mg/dL)	2.85	0.09	2.46	0.9-7.0	-	-	-	-
Sodium (mmol/L)	5.25	0.02	0.82	0.7-1.0	-	-	-	-
Bilirubin (mg/dL)	0.04	0.84	0.99	0.9-1.1	-	-	-	-
INR	3.06	0.08	8.85	0.8-101	-	-	-	-
WBC ($\times 10^9$/L)	0.02	0.88	1.02	0.8-1.3	-	-	-	-
Hematocrit (%)	1.57	0.21	1.11	0.9-1.3	2.67	0.10	1.09	1.0-1.2
Platelets ($\times 10^9$/L)	0.09	0.76	1.00	1.0-1.0	-	-	-	-
N-L ratio	5.90	0.02	1.22	1.0-1.4	5.47	0.02	1.11	1.0-1.2
Albumin (g/dL)	5.07	0.02	0.18	0.0-0.8	2.67	0.10	0.49	0.2-1.2
Malnutrition (+)	0.04	0.85	0.84	0.1-5.1	-	-	-	-
Cardiac dx (+)	1.71	0.19	3.53	0.5-23	-	-	-	-
Sex (Male)	4.43	0.04	0.08	0.0-0.8	-	-	-	-
Race (White)	1.06	0.30	0.32	0.0-2.8	-	-	-	-
Depression (+)	1.72	0.19	3.07	0.6-16	-	-	-	-
Time since dx (mo)	5.84	0.02	0.97	1.0-1.0	3.52	0.06	0.99	1.0-1.0
Pressor need (+)	0.36	0.55	0.44	0.0-6.5	-	-	-	-
Height (cm)	4.04	0.05	1.13	1.0-1.3	-	-	-	-
Weight (kg)	3.83	0.05	1.04	1.0-1.1	7.01	< 0.01	1.02	1.0-1.0
Transferred (+)	1.53	0.22	0.36	0.1-1.8	-	-	-	-
Refer to LTE (d)	0.65	0.42	0.99	1.0-1.0	-	-	-	-
Delayed referral (+)	6.75	0.01	8.40	1.7- 42	7.27	< 0.01	4.51	1.5-14
Decompensations (#)	3.61	0.06	2.08	1.0-4.4	6.33	0.01	1.49	1.1-2.0
Etiology (ETOH)	1.22	0.27	1.30	0.8-2.1	-	-	-	-
Blood type (A)	4.98	0.03	3.01	1.1-7.9	-	-	-	-
TIPS (+)	0.44	0.51	1.45	0.5-4.4	-	-	-	-
Constant	0.09	0.76	0.02	-	0.75	0.38	6.54	-

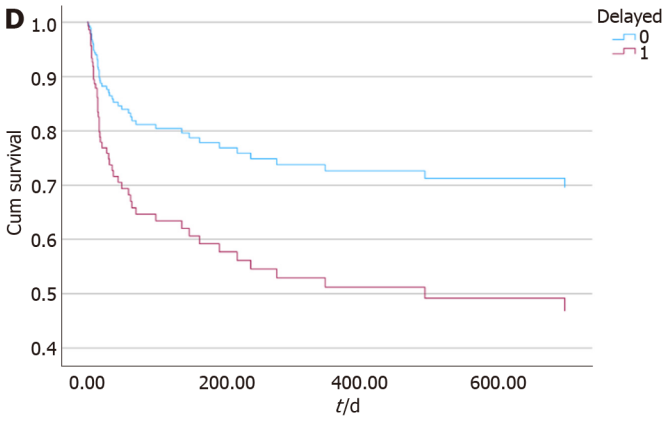
Multivariable logistic model with backward logistic regression to identify predictors of receiving transplant in patients undergoing inpatient liver transplant evaluation (LTE). Starting with 30 potential variables that may predict hepatic encephalopathy, backward regression identified 8 potential independent predictors for transplant including age, Hematocrit, N-L ratio, serum albumin, sex, time since diagnosis, weight, number of decompensations, and having a delayed LTE. Regression complete din SPSS using backward regression conditional model; probability to enter 0.05 and probability to remove 0.10. Units recorded in parenthesis for continuous variables; reference variable recorded in parenthesis for categorical variables where "+" indicates the variable is present in the patient. ACLF: Acute on chronic liver failure; ICU: Intensive care unit; WBC: White blood cell count; MELD: Model for end stage liver disease; INR: International normalized ratio; N-L ratio: Neutrophil to lymphocyte ratio; dx: Diagnosis; TIPS: Trans-jugular intrahepatic portosystemic shunt.

affect LT access[19,25] and may suggest bias has a negative impact on referral. Patients in our study who were referred within the first year of sobriety had improved outcomes. Patients in the delayed evaluation were more likely to have 1-2 years of sobriety than early referral. Patients who have continued hepatic decompensation after 3 mo of sobriety are less likely to recompensate and our data



B	Exp (B)	95%CI	*P* value
***Delayed**	2.46	1.30-4.66	0.005
***Age**	1.04	1.01-1.08	0.017
Ethnicity	1.36	0.58-3.21	0.479
Sex	1.20	0.64-2.26	0.576
***MELD**	1.07	1.03-1.12	0.002
Blood type	1.21	0.87-1.67	0.263
Etiology			0.601
ETOH	0.62	0.12-3.21	0.565
NASH	0.88	0.17-4.64	0.876
HCV	1.25	0.21-7.42	0.804
AIH	2.18	0.17-27.8	0.548
Genetic	1.60	0.21-12.0	0.647
Cholestatic	0.74	0.11-5.10	0.756





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Figure 1 Multivariable Cox regression model assessing the effect of delayed referral on death when accounting for age, ethnicity, patient sex, MELD score, and disease etiology. Patients were censored if lost to follow up or at the time of transplant. A: Total survival curve for patients undergoing inpatient liver transplant evaluation (LTE); B: Cox hazard regression output with hazard ratio (HR) with 95% CI and p values are reported from multivariate analysis. (*) indicates variables that are significant with $P < 0.05$; C: Hazard function plotted for risk of death since time of LTE start where "0" is early LTE and "1" is delayed LTE; D: Cumulative survival function since time of LTE start where "0" is early LTE and "1" is delayed LTE. Delayed LTE was associated with increased mortality amongst patients undergoing inpatient LTE.

supports the growing trend for early LTE referral in patients with alcohol liver disease. Our results demonstrate that providers need have increased awareness of patients who have not been referred to a transplant center at this point in sobriety as they may be at increased risk of precipitous decompensation and require urgent LTE. Beyond alcohol, reducing bias toward cirrhosis in general may help as almost one-third of patients did not have an identifiable reason for delayed referral. Further research is needed to characterize referral patterns for LTE. While nationwide and database research can help improve this, there is also the need for regionally based research given practices and attitudes likely vary by geographic location.

We believe our paper has multiple strengths. To our knowledge, this is the first study stratifying inpatient liver transplant candidates based on presence or absence of previously missed opportunities for transplant evaluation and compared outcomes. Study staff had full access to the electronic medical record and were able to conduct a comprehensive chart review that included both discrete/categorical data and more qualitative information from clinical documentation. This offers advantages compared to large databases studies which can analyze large amounts of data, but do not consider the clinical context in which medical decisions are taken. Statistically, we used a variety of modeling methods and used backward logistic regression to demonstrate delayed LTE is an independent predictor of death. This was further supported with Cox regression to demonstrate the strength of this relationship over time.

There are also limitations to our study. Its retrospective and single center nature with a small sample limits the elimination of biases and statistical analysis. Our study population is predominantly white and non-Hispanic which limited our ability to control for the effect of race and ethnicity[26] without disrupting the statistical strength of our models. In effort to account for this, we incorporated language status into the model which improved overall representation of our data. This study included evaluations performed during the SARS-2 Coronavirus pandemic, which universally impacted organ transplantation. However, overall patient outcomes did not differ before and after the onset of the pandemic in our study population (data not shown).

In this paper we build on existing literature that demonstrates many patients experience delays in access to LTE care and demonstrate that delayed referral for LTE has a negative impact on patient survival and transplant outcomes even in patients receiving expedited and high-level care at a tertiary

liver transplant center. There is substantial opportunity to increase the percentage of patients undergoing transplant evaluation when first clinically indicated. Providers should aim to consistently adhering to referral guidelines to limit provider bias and allow determinations about candidacy to be made by dedicated transplant center. For this to occur, providers need to remain up to date on guidelines regarding liver transplant candidacy, the transplant referral process, and routine work up in patients with CLD. Efforts to increase awareness of this information is critical in general gastroenterology and primary care providers. In future studies, we hope to strengthen the understanding of these phenomena by studying patients who are evaluated through routine outpatient visits.

CONCLUSION

Delayed LTE negatively impacts patient care. There are both provider and patient level factors that contribute to delayed LTE and may act as actionable targets to improve patient outcomes.

ARTICLE HIGHLIGHTS

Research background

Liver transplantation is the only definitive treatment for end stage liver disease, which has an increasing prevalence world wide. Despite this, there are many barriers to accessing liver transplant related care.

Research motivation

Barriers to timely liver transplant evaluation (LTE) are poorly understood and likely differ by geographic location.

Research objectives

We sought to perform a granular assessment of patients who completed inpatient LTE at our center and to identify risk factors for delayed LTE.

Research methods

We performed a single center retrospective cohort study analyzing patients with cirrhosis who completed LTE over 4 years. Patients were categorized as early or delayed LTE based on their clinical history. The electronic medical record was extensively reviewed to identify risk factors for delayed evaluation. Logistic regression was utilized to determine the effect of delayed evaluation on patient outcomes and to identify risk factors for delayed LTE.

Research results

Delayed referral increased the risk of death and decreased the odds of receiving a liver transplant. Female sex and trauma history to be predictors of delayed referral while malnutrition, work within the prior year, and prior smoking history were predictors of early referral. Documentation for 1 in 5 patients with delayed referral included misconceptions about candidacy and referenced inaccurate contraindications to transplant.

Research conclusions

Many patients undergo delayed LT which is associated with poor patient outcomes. Provider bias and patient psycho-social circumstances are both affect the timeliness of LTE and are targets for interventions aiming to improve access to liver transplantation.

Research perspectives

The use of granular data may improve the ability to identify patients at risk at individual centers.

FOOTNOTES

Author contributions: Cooper KM, Colletta A, Hathaway NJ, and Devuni D contributed to analysis and interpretation of data; Cooper KM, Talat A, and Devuni D contributed to study concept and design; Cooper KM, Colletta A, Liu D, Gonzalez D, Barry C, Krishnarao A, Mehta S, Movahedi B, and Martins PN contributed to acquisition of data; Cooper KM and Colletta A contributed to drafting of the manuscript; Cooper KM, Martins PN, and Devuni D contributed to critical revision of the manuscript for important intellectual content; Cooper KM and Hathaway NJ contributed to statistical analysis; Barry C, Krishnarao A, Mehta S, Movahedi B, and Martins PN contributed to material support; Devuni D contributed to study supervision.

Institutional review board statement: This study was reviewed and approved by the institutional review board at our medical center (IRB Docket: Study00000016, approved 10/24/21).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed care with informed consent. This study received a Health Insurance Portability and Accountability Act (HIPAA) waiver for informed consent at our institution through the IRB review process.

Conflict-of-interest statement: All authors have no conflicts of interest related to this study to report.

Data sharing statement: This study was reviewed and approved by the institutional review board at our medical center with a waiver of consent due to the retrospective nature of this study.

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ORIGINAL ARTICLE

Observational Study

Haemodynamic management in brain death donors: Influence of aetiology of brain death

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Abstract

BACKGROUND

In brain death donors (BDDs), donor management is the key in the complex donation process. Donor management goals, which are standards of care or clinical parameters, have been considered an acceptable barometer of successful donor management.

AIM

To test the hypothesis that aetiology of brain death could influence haemodynamic management in BDDs.

METHODS

Haemodynamic data (blood pressure, heart rate, central venous pressure, lactate, urine output, and vasoactive drugs) of BDDs were recorded on intensive care unit (ICU) admission and during the 6-h observation period (Time 1 at the beginning; Time 2 at the end).

RESULTS

The study population was divided into three groups according to the aetiology of brain death: Stroke (n = 71), traumatic brain injury (n = 48), and postanoxic encephalopathy (n = 19). On ICU admission, BDDs with postanoxic encephalopathy showed the lowest values of systolic and diastolic blood pressure associated with higher values of heart rate and lactate and a higher need of norepinephrine and other vasoactive drugs. At the beginning of the 6-h period (Time 1), BDDs with postanoxic encephalopathy showed higher values of heart rate, lactate, and central venous pressure together with a higher need of other vasoactive drugs.

CONCLUSION

According to our data, haemodynamic management of BDDs is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy have higher requirements for norepinephrine and other vasoactive drugs.

Key Words: Brain death donor; Postanoxic encephalopathy; Stroke; Acute traumatic injury; Haemodynamic management; Utilization rate

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Core Tip: In our single centre observational study including 138 brain death donors (BDDs), haemodynamic management is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy had higher requirements for norepinephrine and other vasoactive drugs.

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INTRODUCTION

Management of potential organ donors is the key in the complex donation process, considering that haemodynamic instability may be responsible for the loss of organs of brain death donors (BDDs)[1-8]. Changes in epidemiologic characteristics of BDDs, becoming older and with more comorbidities[9], do make haemodynamic management more challenging[10].

Donor management goals, which are standards of care or clinical parameters, have been considered an acceptable barometer of successful donor management[9,10]. Meeting donor management goals has been associated with an increased number of retrieved organs per donor[1,11-13] and, more recently, a reduced incidence of delayed graft function[14,15].

We hypothesized that aetiology of brain death could influence haemodynamic management in BDDs. In the present study, we tested this hypothesis in 138 BDDs consecutively admitted to our intensive care unit (ICU).

MATERIALS AND METHODS

In the present single centre observational study, we enrolled 138 BDDs consecutively admitted to our ICU from January 1, 2018 to October 31, 2022. The study was approved by the Institutional Review Board of Regional Authority for Transplantation and performed in accordance with the Helsinki Declaration of 1975.

Study population

Diagnosis of death was confirmed by strict adherence to standardized clinical, neurologic, and electroencephalogram criteria in accordance with the Italian law and related guidelines. According to the Italian law, death by neurologic criteria is certificated after a 6-h observation period. Time 1 refers to the beginning of this period, and time 2 to the end of this period.

Clinical data included age, risk factors (hypertension, diabetes mellitus, and known previous coronary artery disease). Data were prospectively recorded and retrospectively analysed. The study population was divided into three groups according to the aetiology of brain death: Stroke (n = 71), traumatic brain injury (n = 48), and postanoxic encephalophy (n = 19).

Donor management

All potential donors were managed as previously described[8,10]. Management goals were as follows: Mean arterial pressure > 70 mmHg, central venous pressure of 6 to 10 mmHg, urine output of 1.2 mL/kg/h, and haemoglobin levels to ≥ 10 g/dL. Ventilatory management was aimed to reach the target partial pressure of oxygen ≥ 90 mmHg[6,8,13]. Haemodynamic management also included replacement therapy with cortisone and thyroid hormone (T3). Antidiuretic hormone and intravenous insulin (target glucose values < 180 mg/dL) were considered on a case-by-case basis.

The following parameters were recorded on ICU admission and during the 6-h observation period (Time 1 at the beginning; Time 2 at the end): Systolic (SBP) and diastolic (DBP) blood pressure (mmHg), heart rate (bpm), central venous pressure (CVP) (cmH_2O), lactate (mg/dL), and urine output (mL/h).

Statistical analysis

Data were analysed with the use of SPSS 20 statistical software (SPSS Inc, Chicago, IL, United States). A two-tailed *P* value < 0.05 was considered statistically significant. Categorical variables are reported as frequencies and percentages, and continuous variables are reported as the mean ± SD or median [and 25^{th}-75^{th} interquartile range (IQR)]. For continuous variables, between-group comparisons were made using analysis of variance (followed by Bonferroni posttests if the overall *P* value was significant) or by means of Kruskal-Wallis *H* test. Categorical variables were compared by chi-square tests.

RESULTS

The study population included 138 consecutive BDDs. Stroke was the most frequent aetiology (51%). Table 1 shows the comparisons between the three subgroups. BDDs with postanoxic encephalopathy were the youngest (aged 59 ± 19 yr). No differences were detectable among the three subgroups in risk factors and refusal rates. In BDDs with postanoxic encephalopathy, the utilization rate showed a trend towards lower values, which did not reach statistical significance.

Haemodynamic data are depicted in Table 2, recorded at ICU admission and Time 1 and Time 2, respectively.

On ICU admission, BDDs with postanoxic encephalopathy showed the lowest values of SBP and DBP (98 ± 33 and 77 ± 22 mmHg, respectively) associated with higher values of heart rate and lactate and a higher need of norepinephrine and other vasoactive drugs. Urine output and CVP were comparable among the three subgroups.

At the beginning of the 6-h period (Time 1), SBP and DBP were comparable among the three subgroups, as well as urine output and norepinephrine use. BDDs with postanoxic encephalopathy showed higher values of heart rate, lactate, and CVP together with a higher need of other vasoactive drugs.

At the end of the 6-h period (Time 2), no significant differences in haemodynamic data were detectable among the threegroups except higher value of CVP in BDDs with postanoxic encephalopathy.

Other vasoactive drugs were vasopressin in all cases except dobutamine used in one BDD.

DISCUSSION

Our investigation, performed in 138 consecutive BDDs managed with the same donor management protocol, documented that haemodynamic management in BDDs is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy require an aggressive treatment, that is, a higher need of norepinephrine and other vasoactive drugs. Utilization rates did not differ among the BDDs with different aetiologies of brain death, probably due to a strict haemodynamic monitoring and donor haemodynamic management.

Brain death has been reported to occur in about one-sixth of patients after successfully resuscitated cardiac arrest[16], thus creating opportunities for organ donation. In a recent review by Sandroni *et al* [17], kidneys, livers, hearts, and intestines retrieved from BDDs with postanoxic encephalopathy showed survival rates comparable to organs transplanted from BDDs from other aetiolgies. No data are so far available on haemodynamic management in these donors.

In our investigation, we specifically addressed haemodynamic management in BDDs from postanoxic encephalopathy upon ICU admission and after brain death developed. Haemodynamic management in these donors is more challenging since norepinephrine administration is more frequently needed to reach and maintain donor management goals and, in about one third of cases, another vasoactive drug is required. This phenomenon may be attributed to post-cardiac resuscitation syndrome. Higher values of heart rate can be related to reduced cardiac function (as a compensatory mechanism), as indicated by higher values of CVP. Despite the achievement of donor management goals, lactate values were the highest in BDDs from postanoxic encephalopathy but urine output (an indirect index of systemic perfusion) was maintained.

The utilization rate in BDDs with postanoxic encephalopathy did not differ from that of BDDs with stroke and traumatic brain injury. This may be related to the strict haemodynamic monitoring and haemodynamic donor management, performed at our centre.

Our data underscore the utility of the relevant data on potential organ donors being reported to a national registry and how this can be used to drive practice improvement and eventually to develop consensus statements.

Table 1 Study population, *n* (%)

	Stroke	Traumatic brain injury	Postanoxic encelophaphy	
Number	71	48	19	
Age (yr, mean ± SD)	79 ± 14	68 ± 20	59 ± 19	0.0007[a]
Males	34 (48)	31 (65)	10 (53)	0.197[b]
Risk factors				0.673[b]
Hypertension	51	10	24	
Diabetes	24	9	16	
Heart disease	6	2	5	
Refusals to donation	13	10	2	0.613[b]
Utilized donors (*n*)	54	35	15	0.808[b]
Utilization rate (%)	93	92	89	

[a]One way analysis of variance.
[b]χ^2.

Table 2 Haemodynamic data, *n* (%)

	Stroke	Traumatic brain injury	Postanoxic encephalopathy	
Number	71 (51)	48 (35)	19 (14)	
ICU admission				
SBP (mmHg), mean ± SD	112 ± 44	123 ± 34	98 ± 33	0.002[a]
DBP (mmHg), mean ± SD	74 ± 21	74 ± 18	77 ± 22	0.001[a]
HR (bpm), mean ± SD	75 ± 22	77 ± 34	82 ± 35	0.015[a]
CVP (cmH_2O), mean ± SD	10 ± 3	11 ± 4	10 ± 3	0.819[a]
Norepinephrine	31 (44)	29 (60)	14 (74)	0.03[b]
Other vasoactive drugs	5 (7)	9 (18)	6 (32)	0.015[b]
Urine output, median (IQR)	200 (125-393)	261 (124-408)	287 (186-440)	0.279[a]
Lactate (mg/dL), median (IQR)	1.5 (1-2.6)	2.1 (1.3-3.1)	1.8 (0.8-4.6)	0.033[a]
Time 1				
SBP (mmHg), mean ± SD	123 ± 19	125 ± 23	122 ± 21	0.818[a]
DBP (mmHg), mean ± SD	63 ± 13	65 ± 14	68 ± 17	0.497[a]
HR (bpm), mean ± SD	86 ± 16	92 ± 17	94 ± 22	0.037[a]
Norepinephrine	56 (78)	43 (89)	18 (95)	0.120[b]
CVP (cmH_2O), mean ± SD	10 ± 3	11 ± 5	12 ± 7	0.001[a]
Other vasoactive drugs	7 (9.8)	10 (20)	5 (26)	0.113[b]
Urine output, median (IQR)	113 (57-210)	115 (85-285)	110 (65 220)	0.374[a]
Lactate (mg/dL), median (IQR)	1.2 (0.9-1.7)	1.4 (1-3.1)	1.7 (1.3-3.1)	0.006[a]
Time 2				
SBP (mmHg), mean ± SD	133 ± 25	131 ± 22	126 ± 27	0.510[a]
DBP (mmHg), mean ± SD	66 ± 14	65 ± 12	70 ± 17	0.784[a]
HR (bpm), mean ± SD	94 ± 19	95 ± 15	99 ± 25	0.760[a]
Norepinephrine	57	43	18	0.172[b]
Other vasoactive drugs	8 (11)	6 (12)	5 (26)	0.227[b]

CVP (cmH_2O), mean ± SD	10 ± 4	12 ± 4 (12)	13 ± 4	0.040[a]
Urine output, median (IQR)	143 (79-240)	160 (95-250)	200 (92-250)	0.785[a]

[a]One-way analysis of variance.
[b]χ^2.
IQR: Interquartile range; ICU: Intensive care unit; CVP: Central venous pressure, SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate.

This study has several limitations. It is a single-centre study, and the number of enrolled BDDs is quite small. However, they were managed with the same donor management protocol.

CONCLUSION

According to our data, haemodynamic management in BDDs is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy have higher requirements for norepinephrine and other vasoactive drugs.

ARTICLE HIGHLIGHTS

Research background

In brain death donors (BDDs), donor management is the key in the complex donation process. Donor management goals, which are standards of care or clinical parameters, have been considered an acceptable barometer of successful donor management.

Research motivation

Meeting donor management goals has been associated with an increased number of retrieved organs per donor and, more recently, a reduced incidence of delayed graft function.

Research objectives

To test the hypothesis that aetiology of brain death could influence haemodynamic management in BDDs.

Research methods

Haemodynamic data (blood pressure, heart rate, central venous pressure, lactate, urine output, and vasoactive drugs) were recorded on intensive care unit (ICU) admission and during the 6-h observation period (Time 1 at the beginning; Time 2 at the end).

Research results

The study population was divided three groups according to aetiology of brain death: Stroke (n = 71), traumatic brain injury (n = 48), and postanoxic encephalopathy (n = 19). On ICU admission, BDDs with postanoxic encephalopathy showed the lowest values of SBP and DBP associated with higher values of heart rate and lactate and a higher need of norepinephrine and other vasoactive drugs. At the beginning of the 6-h period (Time 1), BDDs with postanoxic encephalopathy showed higher values of heart rate, lactate, and central venous pressure together with a higher need of other vasoactive drugs.

Research conclusions

According to our data, haemodynamic donor management is affected by the aetiology of brain death. BDDs with postanoxic encephalopathy have higher requirements for norepinephrine and other vasoactive drugs.

Research perspectives

Our data underscore the utility of the relevant data on potential organ donors being reported to a national registry and how this can be used to drive practice improvement and eventually to develop consensus statements.

FOOTNOTES

Author contributions: Lazzeri C, Bonizzoli M, and Peris A designed the research study; Guetti C, Batacchi S, and Ottaviano A performed the research; Valletta A and Vessella W analyzed the data and wrote the manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: The study protocol was approved by our Internal Editorial Board.

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ORIGINAL ARTICLE

Observational Study

Randomized intervention to assess the effectiveness of an educational video on organ donation intent among Hispanics in the New York metropolitan area

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Abstract

BACKGROUND

The Hispanic community has a high demand for organ donation but a shortage of donors. Studies investigating factors that could promote or hinder organ donation have examined emotional video interventions. Factors acting as barriers to organ donation registration have been classified as: (1) Bodily integrity; (2) medical mistrust; (3) "ick"-feelings of disgust towards organ donation; and (4) "jinx"-fear that registration may result in one dying due to premeditated plans. We predict that by providing necessary information and education about the donation process *via* a short video, individuals will be more willing to register as organ donors.

AIM

To determine perceptions and attitudes regarding barriers and facilitators to organ donation intention among Hispanic residents in the New York metropolitan area.

METHODS

This study was approved by the Institutional Review Board at Northwell Health. The approval reference number is No. 19-0009 (as presented in Supplementary material). Eligible participants included Hispanic New York City (NYC) residents, 18 years of age and above, who were recruited voluntarily through Cloud Research and participated in a larger randomized survey study of NYC residents.

The survey an 85-item Redcap survey measured participant demographics, attitudes, and knowledge of organ donation as well as the intention to register as an organ donor. Attention checks were implemented throughout the survey, and responses were excluded for those who did fail. Participants were randomly assigned two-between subject conditions: To view a short video on organ donation and then proceed to complete the survey (*i.e.*, video first) and view the same video at the end of the survey (video last). No intra-group activities were conducted. This study utilized an evidenced-based emotive educational intervention (video) which was previously utilized and was shown to increase organ donation registration rates at the Ohio Department of Motor Vehicles. Results were analyzed using Jamovi statistical software. Three hundred sixty-five Hispanic individuals were included in the analysis. Once consent was obtained and participants entered the survey (the survey sample is presented in Supplementary material), participants were asked to report on demographic variables and their general impression of organ donation after death. The video depicted stories regarding organ donation after death from various viewpoints, including from the loved ones of a deceased person who died waiting for a transplant; from the loved ones of a deceased person whose organs were donated upon death; and, from those who were currently waiting for a transplant.

RESULTS

Using a binomial logistic regression, the analysis provides information about the relationship between the effects of an emotive video and the intention to donate among Hispanic participants who were not already registered as donors. The willingness to go back and register was found to be significantly more probable for those who watched the emotive video before being asked about their organ donation opinions (odds ratio: 2.05, 95% confidence interval: 1.06-3.97). Motivations for participation in organ donation were also captured with many stating the importance of messages coming from "people like me" and a message that highlights "the welfare of those in need". Overall, the findings suggest that using an emotive video that addresses organ donation barriers to prompt organ donation intentions can be effective among the Hispanic populous. Future studies should explore using targeted messaging that resonates with specific cultural groups, highlighting the welfare of others.

CONCLUSION

This study suggests that an emotive educational intervention is likely to be effective in improving organ donation registration intent among the Hispanic population residing in NYC.

Key Words: Community engagement and health; Health equity; Diversity and inclusion; Health policy; Kidney donation; Minority health and disparities; Organ transplant

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Core Tip: The Hispanic community has a high demand for organ donation but a shortage of donors. A study conducted in New York City found that providing an emotive educational video on organ donation before taking a survey significantly increased the odds of organ donation intent among Hispanic individuals. By providing necessary information and education about the donation process, Hispanic residents can be just as willing to become organ donors as their non-Hispanic counterparts.

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INTRODUCTION

As of March 2022, more than 105800 men, women, and children were on the United States national transplant waiting list, while just over 40000 organ transplants were performed in 2021, creating a deficit in which 17 people die each day while waiting for an organ transplant[1]. This issue can be viewed from many different perspectives, such as allocation systems, registration processes, cultural barriers, and even geographic considerations. Our goal is to highlight barriers and possible solutions to the dearth of organ donation registration in the State of New York, which has the lowest organ donation

rate in the country[2]. Specifically, the primary objective of this study is to test the effectiveness of a best practice educational video intervention to improve registration amongst Hispanic residents of the New York metropolitan area. Specifically, we will examine a representative sample of Hispanic respondents randomized to this best practice intervention, a subset of a previously published large study of New York residents, to focus on the Hispanic population to elucidate possible solutions to this significant and unfortunate shortage of lifesaving organs.

The organ donation process has a long legislative history that is not common knowledge nor without controversy[3]. In 1968, the United States passed the Uniform Anatomical Gift Act, creating a national organ transplantation policy[4]. Currently, the United Network for Organ Sharing maintains the organ procurement and transplantation network, a system established by the National Organ Transplant Act of 1984[4]. The goal of nationalizing the organ donation process and creating supporting networks was to create an effective and efficient organ-sharing system organized into 11 geographic regions[4]. Following the nationalization in 1998, the Former DHHS Secretary Donna Shalala issued the Final Rule policy to process organs more equitably[4]. The purpose of the policy is to match donors and recipients based on statistical consideration of both clinical parameters and proximity to the location of the organ donor. Before these rulings, states with larger donation banks benefited from distribution systems that favored locality, but allocation systems have now incorporated national needs. New York has explicitly unique difficulties that benefit from such policies, as they make up for 10% of the national organ transplant waiting list, yet they have the lowest donation rates[2]. NYS organ donation rate is a meager 35%, compared to the national average of 58%, and the highest-ranking state of Colorado, with a donation rate of 69%[5,6]. As a result, nearly 10000 New Yorkers are currently waiting for an organ[7].

Legislative initiatives intended to improve transplant systems have been effective, but literature reviews on improving donation rates at the individual level have taken on a human factor approach[3, 8]. This angle is of critical importance given the donation rates among racial/ethnic minority populations. The national transplant waiting list stands at 105464 people; 60.0% of those waiting represent racial and ethnic minorities[9]. Hispanics alone comprise 20.5% of the transplant waiting list [10]. Targeting organ donation initiatives to populations that are most at risk is vitally important in NYS, as increased diversity in donor populations can lead to increased access to transplantation and a better chance of finding close matches in terms of shared genetic background[4]. Hence, increasing registration rates among immigrant populations, of which NYS currently holds the second-largest ranking in the country, is key[11]. Donation trends by underrepresented minorities have always been historically low when compared to white individuals[12]. There is some encouraging news regarding donation rates. Specifically, the standardized donation ratio for Hispanic/Latino groups increased from 1.92% in 1999 to 3.35% in 2017[12]. While this increase is noteworthy, it was not significantly different than the increase seen in non-Hispanic/Latino individuals. Despite the benefits of a more diverse donor pool, there is still much to be done to motivate efforts to increase donation rates among Hispanic communities.

Given the great need to improve organ donation in NYS, we seek to identify effective interventions in Hispanic communities. Research looking at hindering factors to donor rates among Hispanic communities identifies factors such as mistrust of healthcare systems, literacy rates, and cultural barriers. For example, Hispanic donors are more likely to develop Clavien grade IV or higher surgical complications (not limited to nervous system complications), conversion to open nephrectomy, intensive care unit stays, and death[13]. Coupled with already existing health disparities such as kidney disease, higher prevalence of incidence of type 2 diabetes, and development of end-stage kidney disease, may add to the negative experiences and mistrust of the healthcare system[14-21]. Other factors that have been reported include insufficient levels of health literacy which has been found to impact organ donation registration and consent from family members[22-26]. Therefore, targeted educational messaging about organ donation is crucial to increase awareness and understanding among individuals. This is especially true when considering individuals' willingness to disseminate sociocultural tailored content that is shared by existing social ties[27]. Hence, targeted messaging that resonates with specific cultural groups and is shared through existing social connections may be more effective in increasing donation rates.

Educational interventions may include different settings such as schools, departments of motor vehicle (DMV), primary care, and other local community locations[8]. Approaches have included educational sessions and videos, leveraging peer leaders in the community, DMV staff training, messaging, and priming[8]. Other interventions include testing "opt-out" policies, which is a presumed consent model as opposed to the standard "opt-in" policy that exists in the United States[28-32]. Although the "opt-out" model has reported positive results such a policy is not expected to become imminently approved in the United States, suggesting further research into motivations behind organ donation. Our larger study 33 was built around an existing video message directly addressing some of the documented barriers to organ donation. The video was found to be successful in improving registration rates by addressing barriers such as: (1) Bodily integrity; (2) medical skepticism; (3) "ick"-described as a discomfort towards the process; and (4) "jinx"-superstitious around the process of preparing for one's death[33].

Table 1 Methodology

	Video first condition	Video last condition
Participants	192	173
IV	5 min 25 s emotive video addressing common barriers to organ donation	
DV	An 85-item Redcap survey measured participant demographics, attitudes, and knowledge of organ donation as well as intention to register as an organ donor	
Procedure	A human intelligence task, informed consent was required, random assignment was implemented	

The emotional video messaging used in the Thornton study[34] (as presented in Supplementary material) was effective in increasing organ donation registrations at the Ohio Bureau of Motor Vehicles (BMV). Our previous study[32] was also successful in increasing organ donation intent in NYS. While Thornton's study was conducted at 12 branches of the Ohio BMV, our larger study used a Sample of Amazon MTurk participants located in NYS with randomized exposure to the emotional video. We observed a significant increase in the proportion of respondents who were motivated to register as organ donors among those who were exposed to the emotional movie (randomized to the movie First condition) compared to those randomized to the Video Last condition. Of note, the original video did not use content specific to any particular culture. This paper aims to build on the larger study 32 by focusing on the effects of the video on the Hispanic demographic who viewed the video before ("first" group) administration of a survey of attitudes toward and knowledge of organ donation *vs* those who did not view the video until after survey participation ("last" group).

MATERIALS AND METHODS

The study adheres to the principles outlined in the Declaration of Helsinki and all participants provided informed consent before they participated in the study. As described in Table 1, participants (n = 365) were enrolled in part of a larger randomized survey study conducted with New York City residents who were recruited *via* a crowdsourcing online platform and were randomized to one of two groups, with exposure to viewing: (1) An educational video before completing an 81-question survey on organ donation ("video first" condition); or (2) after completing the survey ("video last" condition). The survey instrument was investigator-developed in the absence of existing validated tools. Interviews with subject matter experts and a review of the literature were utilized to ensure the topic of the survey is relevant to the population of interest during item creation. Logistic regression analysis compared organ donation intent (*i.e.*, "How likely are you to become an organ donor") between the two groups. Additional variables related to organ donation (*e.g.*, religious beliefs, financial incentives) were also evaluated between the two groups. Analyses were adjusted for organ donation registration status. Data were analyzed using Jamovi (version 2.3.19), a software package that runs in tandem with R Statistical Software. Frequencies and percentages were used for categorical data. Summary statistics were utilized to describe sample characteristics. To determine parameters that might predict the likelihood of organ donation registration and to assess the effects of the video intervention, we used binomial logistic regression analysis. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the Declaration of Istanbul on Organ Trafficking and Transplant Tourism.

Participants

Table 2 presents Hispanic participant characteristics for the total sample by registration status (registered organ donor, non-registered organ donor, and those who did not specify). More than a quarter (35%) of participants identified as White or Caucasian, less than a quarter (15%) as Black or African American, and 18% as multiracial. The majority of participants were female. Seventy-two percent of the sample participants said they were between the ages of 19 and 39; 60% of them reported being single or never married; and 67% said they were employed either full- or part-time. Thirty-eight percent of the sample as a whole had organ donation records after passing away 40% and 38%, respectively, of those who described themselves as spiritual or religious had registered as organ donors. Additionally, 28% of participants with degrees of 2 years or less were registered as organ donors, compared to 45% of participants with graduate degrees or 4-year degrees.

Table 2 Hispanic participant characteristics and test of proportions, *n* (%)

Total (*n* = 365)		*n* = 1905	
		Registered (*n* = 137)	Not registered (*n* = 228)
Gender			
Female	236 (65)	87 (37)	149 (63)
Male	126 (34)	48 (38)	78 (62)
Other/prefer not to say	3 (1)	2 (67)	1 (33)
Age (yr)			
≤ 39	263 (72)	105 (40)	158 (60)
40-69	97 (27)	31 (32)	66 (68)
≥ 70	5 (1)	1 (20)	4 (80)
Race			
White/Caucasian	130 (36)	60 (46)	70 (54)
Black/African American	54 (15)	20 (37)	34 (63)
Asian	4 (1)	3 (75)	1 (25)
Multiracial	63 (17)	23 (37)	40 (63)
Other	101 (28)	29 (29)	72 (71)
Native American or Alaskan Native	5 (1)	1 (20)	4 (80)
Native Hawaiian or Other Pacific, Islander	3 (1)	0	3 (100)
Prefer not to say	5 (1)	1 (20)	4 (80)
Spirituality			
Yes	252 (69)	106 (42)	146 (58)
No	99 (27)	28 (28)	71 (72)
Prefer not to say	14 (4)	3 (21)	11 (79)
Religiosity			
Yes	162 (44)	64 (40)	98 (60)
No	189 (52)	70 (37)	119 (63)
Prefer not to say	14 (4)	3 (21)	11 (79)
Religious denomination			
Christian	198 (54)	77 (39)	121 (61)
Jewish	3 (1)	2 (67)	1 (33)
Muslim	6(2)	3 (50)	3 (50)
Buddhist	2 (1)	2 (100)	0
Non-religious	103 (28)	41 (40)	62 (60)
Other	41 (11)	10 (24)	31 (76)
Prefer not to say	12 (3)	2 (17)	10 (83)
Marital status			
Single/never married	219 (60)	77 (35)	142 (65)
Married/living as married	123 (34)	52 (42)	71 (58)
Divorced/separated	17 (5)	6 (35)	11 (65)
Widowed	4 (1)	1 (25)	3 (75)
Prefer not to say	2 (1)	1 (50)	1 (50)
Level of education			

2-year associate degree or less	216 (59)	63 (29)	153 (71)
4-year college degree (*e.g.*, Bachelor)	121 (33)	56 (46)	65 (54)
Graduate degree (*e.g.*, Master, MD, PhD)	28 (8)	18 (64)	10 (36)
Employment status			
Full time or part time	182 (50)	86 (47)	96 (53)
Unemployed	116 (32)	33 (28)	83 (72)
Prefer not to say	4 (1)	0	4 (100)
Self-employed			
Yes, *n* (%)	59 (16)	28 (47)	31 (53)
No, *n* (%)	306 (84)	109 (36)	197 (64)
Annual income			
< $30000	108 (30)	33 (31)	75 (69)
$30001-$60000	113 (31)	41 (36)	72 (64)
$60001-$100000	88 (24)	43 (49)	45 (51)
> $100000	36 (10)	19 (53)	17 (47)
Prefer not to say	20 (5)	1 (5)	19 (95)
Insurance			
Medicaid or medicare	167 (46)	43 (26)	124 (74)
Employer	139 (38)	71 (51)	68 (49)
	27 (7)	15 (56)	12 (44)
Out of pocket			
Other	15 (4)	5 (33)	10 (67)
Prefer not to say	15 (4)	2 (13)	13 (87)

Fifty participants did not indicate their registration status.

RESULTS

Impact of emotional video

In the current study of Hispanic participants who were randomly assigned to the Video First condition who had not yet registered as organ donors, were found to be significantly more inclined to do so than those in the Video Last condition [odds ratio (OR): 2.05, 95% confidence interval (CI): 1.06-3.97], according to the results (Table 3). In comparison to those in the Video Last condition, participants in the Video First condition were less likely to be swayed by the donor's health [OR: 0.53, 95%CI: 0.31-0.90], more likely to be aware that they could sign up at the DMV [OR: 2.21, 95%CI: 1.22-4.03], and less in favor of an opt-out system [OR: 0.49, 95%CI: 0.25-0.96]. Contrasted with the bigger sample, it was discovered that Hispanics in the Video First condition was just as likely as those in the overall sample to express a willingness to register as donors among non-registered donors [OR: 1.64, 95%CI: 1.22-2.20].

Driving factors for organ donation

Table 4 lists reasons for participating in organ donation among the entire sample of participants. According to the findings, 35% of participants thought the message needed to come from a person similar to them, while 11% disagreed and 54% said it made no difference. A majority of participants (58%) said they would be inspired by a message that focused on the welfare of less fortunate people. However, the majority of participants did not have a preference for the demographics of the speaker promoting organ donation, such as their ethnic background or notoriety (44% and 38%, respectively).

DISCUSSION

Previous studies have considered the many hindrances that impede registering to be an organ donor, specifically in minority communities. One of the main reasons identified is a lack of awareness and

Table 3 Effects of the video among Hispanic participants not registered as organ donors

OR		95%CI	*P* value
Outcome			
Willingness to go back	2.05	1.06-3.97	0.03
Factors associated with OD			
Religious beliefs	1.54	0.64-3.72	0.34
Bodily integrity	0.89	0.50-1.58	0.69
Impact funeral proceedings	0.89	0.46-1.72	0.72
Treated differently by doctor	1.03	0.60-1.77	0.91
Recipient	0.89	0.49-1.62	0.70
Ick factor	1.65	0.82-3.32	0.16
Jinx factor	0.82	0.48-1.40	0.47
Health of donor	0.53	0.31-0.90	0.02
Age limit of donor	0.79	0.47-1.34	0.38
Treated differently by race	0.58	0.31-1.11	0.10
Notify relatives	1.13	0.60-2.10	0.71
Association with pain	0.58	0.22-1.55	0.28
Legal to buy an organ	0.60	0.33-1.12	0.11
Known where to sign up	1.11	0.66-1.86	0.70
Know process to sign up	1.08	0.62-1.85	0.79
Know can sign up at DMV	2.21	1.22-4.03	0.01
Know can sign up on online	0.97	0.55-1.71	0.91
Appropriate to be asked at DMV	0.74	0.43-1.25	0.26
Receive compensation	1.09	0.62-1.92	0.76
Receive funeral payment	1.02	0.60-1.72	0.10
Opt-out system	0.49	0.25-0.96	0.04

"OR" represents odds of selecting "Yes" to respective question for those in the Video First condition compared to those in the Video Last condition. OR: Odds ratio; CI: Confidence interval; DMV: Department of motor vehicle.

understanding about organ donation among minority communities. Many people in these communities may not be aware of the need for organ donation or may have misconceptions about the process. Additionally, there may be cultural and religious barriers to organ donation in some minority communities. Hence the importance of analyzing this subset of Hispanic participants to highlight some possible avenues of approach to overcome these hindrances using an effective educational intervention.

This analysis found that a previously established intervention had a significant effect on respondent willingness to register as donors. Participants who were not registered and exposed to the Video First condition were more likely to report their intention to register compared to those who were exposed to the Video Last condition. Additionally, our analysis indicates that participants not registered as donors knew they could register at the DMV and favored an opt-out system. When comparing these results with the results of our larger study. We see a similar level of willingness to donate after participating in the Video First condition. This indicates that Hispanic individuals are just as willing to become organ donors as their non-Hispanic counterparts when provided with the necessary information and education about the donation process.

Moreover, most Hispanic participants who indicated a preference were inclined to register when the messaging emphasized the needs of others and originated from a relatable person rather than a public figure. This suggests that delivering the message and the message communicates are essential. Interestingly, there were no preferences for ethnicity or race. This may be because of the cited confusion among respondents, particularly among Hispanics, regarding the classification of ethnicity and race [35]. Specifically, although more participants reported that they did want the message to come from someone like them, they may not identify with the traditional concepts of race and ethnicity. Further,

Table 4 Motives for organ donation among Hispanics, *n* (%)

	Total (*n* = 365)			Registered organ donor (*n* = 137)			Not registered organ donor (*n* = 228)		
	Yes	No	Doesn't matter	Yes	No	Doesn't matter	Yes	No	Doesn't matter
Receiving message from									
Someone like you	127 (35)	40 (11)	198 (54)	43 (31)	16 (12)	78 (57)	84 (37)	24 (11)	120 (53)
Same gender as you?	44 (12)	65 (18)	256 (70)	17 (12)	27 (20)	93 (68)	27 (12)	38 (17)	163 (71)
Same race as you?	45 (12)	64 (18)	256 (70)	19 (14)	27 (20)	91 (66)	26 (11)	37 (16)	165 (72)
Your community?	53 (14)	61 (17)	251 (69)	29 (21)	25 (18)	83 (61)	24 (11)	36 (16)	168 (74)
Economic status as you?	59 (16)	66 (18)	240 (66)	28 (20)	25 (18)	84 (61)	31 (14)	41 (18)	156 (68)
Own ethnic background?	44 (12)	66 (18)	255 (70)	15 (11)	29 (21)	93 (68)	29 (13)	37 (16)	162 (71)
Message of those in need?	139 (38)	60 (16)	166 (46)	50 (36)	23 (17)	64 (47)	89 (39)	37 (16)	102 (45)
A public figure?	38 (10)	90 (25)	237 (65)	17 (12)	35 (26)	85 (62)	21 (9)	55 (24)	152 (67)
Motivated by hearing from									
Relatives of organ donor	214 (56)	-	-	94 (44)	-	-	120 (56)		
Recipient of organ donation	183 (48)	-	-	82 (45)	-	-	101 (55)		
Family of recipient who died waiting	209 (55)	-	-	81 (39)	-	-	128 (61)		
Physician or provider	120 (32)	-	-	61 (51)	-	-	59 (49)		
Other	10 (3)			5 (50)	-	-	5 (50)		

Frequency of responses regarding motivation to participation in an organ donor program.

some Hispanics may identify with more than one race or ethnic category, therefore participants may not agree with the defined constructs by the federal administrative guidelines. Our findings also suggest that future interventions could be effectively implemented at the DMV, in primary care settings, or with a trusts and estate lawyer, especially when the messaging is tailored to sociocultural content.

Limitations

The study that served as the foundation for the current analysis concentrated more on participants' intentions to give organs than on their actual registration as donors. The transtheoretical model, however, proposes that analyzing intention is a crucial first step in boosting donor registration rates [36]. Therefore, by examining how knowledge, motivations, and attitudes concerning organ donation change as a result of the intervention, we sought to address the first two stages of the model (awareness and reflection). A comparable video intervention should be studied in more detail to see how it affects actual donor registration rates. The use of an online poll in this study is another potential weakness. Although we used attention checks to guarantee data quality and contact a variety of potential donors in New York City, future studies should utilize alternate settings to replicate our findings.

CONCLUSION

Overall, disparities in organ donation among minority groups are a significant problem that needs to be addressed. Increasing awareness and understanding about organ donation in minority communities, improving access to healthcare, and increasing representation on organ transplant messaging materials

are all steps that can help reduce these disparities and improve access to life-saving organ transplantation for minority communities.

ARTICLE HIGHLIGHTS

Research background

Research has documented barriers to organ donation, including: (1) Bodily integrity; (2) medical skepticism; (3) "ick"-discomfort toward the process; and (4) "jinx"-superstitions regarding preparations toward death. Furthermore, emotional video messaging is impactful in increasing the intention to register. While the emotional video messaging used in the present study was found to increase the intention to register among the Hispanic population.

Research motivation

Given the backdrop of shortages of organ donations and the benefits of a more diverse donor pool. In New York City (NYC), a place renowned for its diverse population, our goal was to evaluate the effects of a brief educational intervention meant to increase organ donation intentions. Additionally, we wanted to learn more about the attitudes and beliefs of Hispanic inhabitants of NYC toward organ donation as well as the predictors of it.

Research objectives

We hypothesized that an educational video addressing commonly cited barriers to organ donation would help ease resistance and change attitudes regarding intentions to donate.

Research methods

Data were collected using the online crowdsourcing platform CloudResearch targeting NYC residents. This study was approved by our Institutional IRB. Once consent was obtained and participants entered the survey, respondents were asked to report on demographic variables and their general impression of organ donation after death. Participants were then assigned at random to the video First condition, in which they saw a brief movie on organ donation before responding to the survey questions, or the Video Last condition, in which they answered the survey questions first and then watched the video. The five-minute intervention implemented was originally developed, tested, and found to significantly increase donation rates in a general population. The video presented a dialogue among twenty ethnically diverse individuals in terms of age and their experiences regarding organ donation, including donors, recipients, and loved ones of those who died while waiting for organ donation. Furthermore, the video has been found to elicit emotional responses and address concerns that are common barriers to donor registration.

Research results

Using a binomial logistic regression, the analysis provides information about the relationship between the effects of an emotive video and the intention to donate among Hispanic participants who were not already registered as donors. The willingness to go back and register was found to be significantly more probable for those who watched the emotive video before being asked about their organ donation opinions [OR: 2.05, 95%CI: 1.06-3.97] (as presented in Table 3). Motivations for participation in organ donation were also captured in Table 4, with many stating the importance of messages coming from "people like me" and a message that highlights "the welfare of those in need". Overall, the findings suggest that using an emotive video that addresses organ donation barriers to prompt organ donation intentions can be effective among the Hispanic populous. Future studies should explore using targeted messaging that resonates with specific cultural groups, highlighting the welfare of others.

Research conclusions

The wide variations in organ donation rates across the United States present both a problem and a chance. Our analysis has demonstrated that future campaigns must concentrate on densely populated, diversified locations with low donor rates if they are to boost organ donation registration. Educational initiatives that elicit strong emotions, address donor concerns, and take into account potential donors' preferences must be conducted to increase the overall registration rate. By implementing these actions, we have the potential to significantly alter the situation and save the lives of thousands of people who pass away each year while awaiting organ transplants.

Research perspectives

Future research should examine how video intervention affects actual donor registration to have a more thorough understanding of its effects. Although we used attention checks to confirm the accuracy of the data, it is advised that future research replicate our findings in various contexts.

FOOTNOTES

Author contributions: Pekmezaris R, Patel V, and Molmenti E designed and supervised the study; Cigaran E conducted data analysis and interpretation, and drafted the manuscript; Pekmezaris R, Patel V, Molmenti E, and Cigaran E conducted a literature review; Clement D contributed to data analysis and interpretation; Sardo Molmenti CL revised the manuscript critically for intellectual content; Molmenti E and Pekmezaris R approved the final version of the paper.

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CASE REPORT

Efficacy and safety of local candida immunotherapy in recalcitrant warts in pediatric kidney transplantation: A case report

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Abstract

BACKGROUND

Warts are common in recipients of kidney transplantation (KT). Resistant warts which are not amenable to conventional therapies may lead to significant morbidity. Limited data exists on safety and efficacy of local immunotherapy among immunocompromised KT recipients.

CASE SUMMARY

We report a seven-year-old child who presented with recalcitrant plantar periungual warts in the early KT period. Immunosuppression consisted of tacrolimus, mycophenolate and steroid. Due to failure of conventional anti-wart therapies, he was treated with two sessions of intralesional (IL) candida immunotherapy along with liquid nitrogen cryotherapy leading to complete resolution of the warts. Interestingly, de novo BK viremia was seen about three weeks following the last candida immunotherapy. This required reduction of immunosuppression and other anti-BK viral therapies. Allograft function remained stable but there were donor specific antibodies detected. There also was elevated level of plasma donor derived cell-free DNA. A *pneumocystis jirovecii* pneumonia occurred ten months following completion of immunotherapy that was successfully treated with trimethoprim-sulfamethoxazole. During this ten-month follow-up period, there have been no recurrence of warts, and transplant kidney function has remained stable.

CONCLUSION

Stimulation of cell-mediated immunity against the human papilloma virus induced by the IL candida immunotherapy is thought to be a cause for wart resolution. With this therapy, whether it is necessary to augment the immunosuppression to prevent rejection is unclear as that may come with a risk of infectious complications. Larger, prospective studies in pediatric KT recipients are needed to

explore these important issues.

Key Words: Warts; Kidney transplantation; Candida; Immunotherapy; Pediatric; Case report

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Core Tip: Warts are common after pediatric kidney transplantation. Given immunosuppressed status, most children are unable to clear the warts with conventional anti-wart therapies. Local immunotherapy has emerged as an excellent treatment modality for treatment of resistant warts following kidney transplantation. However, the safety of such agents needs careful consideration with longitudinal studies. Here, we studied the efficacy and safety of local candida immunotherapy in an immunocompromised child with kidney transplantation and recalcitrant plantar warts.

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INTRODUCTION

Cutaneous common warts (verruca vulgaris) are commonly seen after kidney transplantation (KT)[1-3]. In one study of 60 children and adolescents with KT, the incidence of warts was 28% with increased prevalence with time since KT. Plantar warts are the most common warts following KT[4]. The most common immunosuppressive regimen in these patients was tacrolimus and prednisone, in combination with either azathioprine or mycophenolate mofetil (MMF). The most commonly seen human papillomavirus (HPV) strains responsible for common warts are HPV-2, 27, 29, 34 and 57[5]. Painful warts can impair the quality of life and cause significant morbidity[6]. Unlike in non-immunocompromised individuals, warts in KT recipients may not undergo spontaneous resolution. Although the risk of cancerous conversion is primarily seen with genital warts, multiple verrucae (> 10 verrucae) may be associated with the development of actinic keratoses, invasive squamous cell carcinoma and basal cell carcinoma[7]. Some of the treatment options are topical keratolytics such as salicylate, cryotherapy with liquid nitrogen, electrofulguration or radiofrequency ablation, duct tape, pulsed dye or CO_2 laser, intralesional (IL) bleomycin, surgical removal with curettage or cautery, and IL immunotherapy[8]. Here we describe a seven-year-old KT recipient with recalcitrant plantar warts who had an excellent response to the IL candida immunotherapy with no recurrence in the short-term follow-up of ten months.

CASE PRESENTATION

Chief complaints

A seven-year-old Caucasian male presented with multiple wart-like lesions in the plantar aspect of both foot after KT.

History of present illness

The patient had received a pre-emptive first living unrelated donor KT with bilateral native nephrectomies one month prior to the onset of the skin warts. He sustained early loss of renal allograft secondary to transplant renal artery thrombosis. Transplant kidney biopsy showed coagulative necrosis and he was transitioned to chronic hemodialysis until receiving a second deceased donor KT two months later with excellent allograft function. Induction immunosuppression (IS) for both first and second KT consisted of three doses of 1.5 mg/kg/dose Thymoglobulin^R with steroid. Low dose tacrolimus and MMF were continued after the first failed KT. The first allograft was removed during the second KT. Maintenance IS for second KT consisted of tacrolimus, MMF and steroid. Serum trough tacrolimus level was maintained at the goal range.

History of past illness

The past medical history consisted of end stage renal disease secondary to posterior urethral valve. He however did not require dialysis given stable electrolytes and normal urine output. He had been immunized fully as per the routine childhood immunization schedule.

Personal and family history

The patient's personal and family history was otherwise unremarkable.

Physical examination

Physical examination of the patient showed normal vital signs and examination except for the abdomen with scar marks from prior surgeries and positive skin findings. Skin examination showed multiple verrucous papules and plaques on the anterior aspect of the plantar surface of foot bilaterally (Figures 1A and B), and some papular lesions in the left thumb. There were no warts seen in the genital region or the oropharynx region. The warts were extremely painful and would wake him throughout the night. The patient had difficulty ambulating and had to be carried to the clinic visits.

Laboratory examinations

Complete blood count was normal. Renal allograft function remained stable after second KT with serum creatinine of 0.5-0.6 mg/dL. C-reactive protein was normal. Serum trough tacrolimus level was at the goal of 9-11 ng/mL in the first month post KT, then 8-10 ng/mL in the second month, followed by 6-8 ng/mL from three to six months post KT. Urinalysis showed no proteinuria, hematuria or urinary tract infections. Given cytomegalovirus (CMV) mismatch, he received oral valganciclovir for six months post-KT. CMV, Epstein-Barr virus and BK virus polymerase chain reaction (PCR)s were all negative until six months post KT. HPV genotyping of the warts was not done.

Imaging examinations

Chest X-ray was negative for pneumonia or other viral processes. Renal allograft sonogram was normal.

FINAL DIAGNOSIS

Plantar warts in a child with kidney transplantation.

TREATMENT

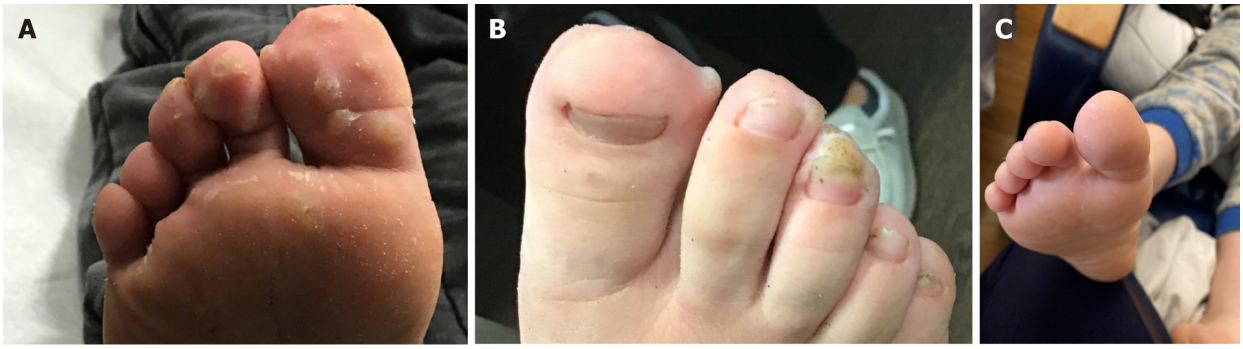
He was evaluated by dermatologist and was treated with lidocaine ointment, WartPEEL (17% salicylic acid and 2% 5-fluorouracil), WartSTICK (40% salicylic acid), and Differin (0.3% Adapalene gel) under occlusion for several weeks without any clinical improvement of the signs and symptoms. Six months after the first KT, he was treated with a first dose of Candin^{R} (IL *Candida albicans* antigen) to the largest wart paired with liquid nitrogen cryotherapy. Second dose of IL Candin^{R} and liquid nitrogen was administered four weeks later.

OUTCOME AND FOLLOW-UP

The patient had a significant improvement with almost complete resolution of the warts after two Candin^{R} paired with liquid nitrogen cryotherapy. Complete resolution was indicated by complete disappearance of the hyperkeratosis and thickening of the skin. Due to the presence of few scattered lesions only, a third dose of liquid nitrogen cryotherapy was administered two months later without IL Candin^{R}. There were no side effects observed such as blister, infection, post-inflammatory altered pigmentation, scarring or anaphylaxis. During a ten-month follow-up period since the second and last Candin^{R} therapy, there have been no recurrences of the warts (Figure 1C).

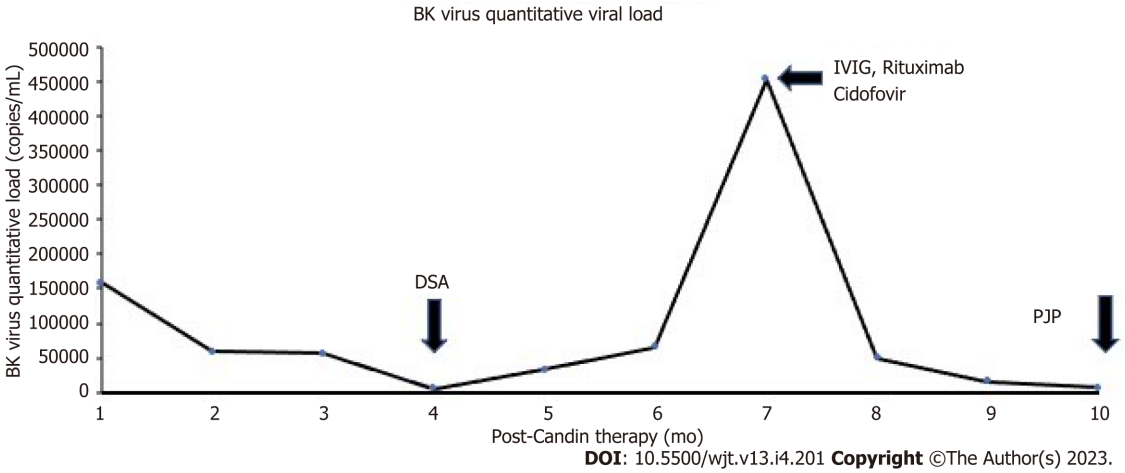
Three weeks after the first Candin^{R} injection, a follow-up whole blood BK virus deoxyribonuclease (DNA) PCR showed BK viral load of 159000 copies/mL (ARUP laboratories, Salt Lake City, UT, United States). His immunosuppression regimen had been same as before and his allograft function was stable. Following this, his tacrolimus dose was reduced with a lower trough goal level of 3-5 ng/mL, mycophenolate was discontinued and leflunomide was started. Over the next one year, his BK virus DNA PCR showed persistent positivity with a peak viral load of 453000 copies/mL seven months post last Candin^{R} therapy. He then received two monthly intravenous (IV) immunoglobulin therapies and a course of IV cidofovir with the most recent BK virus load of 6280 copies/mL ten months after the last Candin^{R} therapy (Figure 2). The most recent immunosuppression regimen consists of tacrolimus 2 mg twice daily, prednisone 10 mg daily and leflunomide 20 mg daily.

Donor specific antibodies (DSA) were obtained monthly as a part of the transplant center's protocol. Four months after the last Candin^{R} injection, weak DSA to class I antigens [B58, C12; 2500 mean fluorescent intensity (MFI) for both] were observed. Subsequently, strong DSAs against class II antigen (DQ6, 10000 MFI) also started appearing a month later. However, the serum creatinine remained stable around 0.6-0.7 mg/dL. He was treated with intravenous immunoglobulin and a dose of Rituximab 375



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Figure 1 Response to Candin^{R} treatment. A: Plantar warts before Candin^{R} treatment; B: Periungual plantar warts before Candin^{R} treatment; C: Resolution of plantar warts after Candin^{R} treatment.



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Figure 2 Association of Candin^{R} treatment with BK viremia, donor specific antibodies and *pneumocystic carinii* pneumonia. DSA: Donor specific antibodies; IVIG: Intravenous immunoglobulin; PJP: *Pneumocystic carinii* pneumonia.

mg/m^2. A kidney transplant biopsy could not be obtained due to parental hesitation. However, a plasma donor-derived cell-free DNA (dd-cfDNA) test showed elevated value of 1.21% (reference range: < 0.7% dd-cfDNA, Viracor TRAC kidney dd-cfDNA, Eurofins Transplant Genomics, Framingham, MA, United States). A decision was made to serially follow the dd-cfDNA and DSA closely given stable serum creatinine.

Ten months after the last Candin^{R} therapy, he presented with hypoxia and respiratory distress with chest X-ray showing ground-glass opacities in the lungs. He underwent bronchoscopy; the PCR of the bronchoalveolar lavage was positive for *pneumocystis jirovecii* and diagnosed with *pneumocystis jirovecii* pneumonia (PJP). He was treated with trimethoprim-sulfamethoxazole with complete resolution of respiratory symptoms. Immunosuppression was kept the same with a goal trough tacrolimus level of 3-5 ng/mL.

DISCUSSION

In patients with cutaneous warts with suboptimal or no response to conventional anti-wart therapies, IL immunotherapy may be useful[9,10]. Various IL immunotherapy regimen have been described such as candida antigen, mumps antigen, measles mumps rubella vaccine, purified protein derivative and bacilli calmette-guerin vaccine[10]. One systematic review showed 68% cure-rate of local immunotherapy in plantar warts, as opposed to low cure rate with topical salicylic acid and cryotherapy[11]. A randomized placebo-controlled trial by Horn *et al*[12] showed excellent efficacy of IL candida, mumps or trichophyton skin test antigens. The possible mechanism of action of immunotherapy is the proliferation of HPV-specific peripheral blood mononuclear cells that possibly mediate an immunologic attack against the wart tissue[13].

Data on efficacy of IL candida in children is scarce[14]. Alikhan *et al*[15] reported a retrospective study of 100 adults and children with verruca vulgaris who were treated with IL purified candida antigen therapy with 39% complete response and 41% partial response rate. In their study, six out of seven patients who were immunocompromised demonstrated partial or complete response rate. The proposed mechanism is *via* stimulation of a cell-mediated immune response. Phillips *et al*[13] retrospectively reviewed adults and children who received monthly IL candida antigen with 72% complete resolution rate. Another retrospective study of 220 children with multiple and recalcitrant warts who received IL candida injections showed 71% and 17% complete and partial response rates respectively. There were no side effects reported except for some discomfort at the time of injection[16]. IL *Candida* immunotherapy has also been shown to be efficacious in treating the distant non-injected warts[17]. Whether the similar results are expected in immunocompromised individuals needs to be studied on a larger scale.

With regards to immunosuppressed patients, the prevalence of warts corresponds with the duration of immunosuppressive therapy, increasing to 50%-92% in patients who are more than 4-5 years after transplantation[3]. Our report is unique in that the onset of warts was fairly rapid following KT. In most HPV infections in immunocompetent individuals, the cellular and cytotoxic immunity provided by T cells and natural killer cells are sufficient to control the warts[18]; however, in immunocompromised patients, due to lack of cell-mediated immunity, the proliferation of virus occurs causing warts, sometimes in unusual locations such as bladder[19,20]. Indeed, a few studies have reported clearance of the warts with reduction or cessation of immunosuppression only in KT recipients[21,22]. Conversion to another anti-rejection agent may be useful as well. Nguyen *et al*[23] reported 4 children with warts and molluscum contagiosum who benefited from conversion from tacrolimus/mycophenolate to tacrolimus/Leflunomide. Conversion to sirolimus has been shown to be effective for recalcitrant cutaneous viral warts in liver transplant recipients[24,25]. There is not much data on the efficacy of the IL immunotherapy. In patients who do undergo local immunotherapy, it is not known whether immunosuppression decreases the efficacy of local immunotherapy such as IL candida. Immunosuppression usually is at the maximal level during the first few months of KT and it will be interesting to study the efficacy of these immunotherapies during this period of maximal immunosuppression. On the other hand, there are also potential safety concerns with stimulating cell-mediated immunity with IL Candida therapy leading to rejection[26]. Few studies done in the children on warts have not looked at these longitudinal issues[4]. In our patient, there was a temporal relationship between the onset of BK viremia and Candin^{R} therapy along with observation of DSA, elevated dd-cfDNA, and PJP a few months following the completion of Candin^{R}. However, we could not establish a direct cause and relationship between IL candida and these findings. Since dd-cfDNA has been shown to diagnose subclinical rejection even in the absence of deranged renal function, this test may be important in children who have underwent IL candida therapy for establishing an early diagnosis of rejection and possibly close monitoring and treatment[27]. In those with concurrent viral infections and elevated dd-cfDNA, it is challenging to decide the amount of immunosuppression, as in our case. Also, since children with current BK viremia have been shown to have significantly higher median plasma dd-cfDNA, the importance of elevated dd-cfDNA in this subset of children is uncertain[28]. Also, as seen in this report, there may be as association between BK virus and HPV as both belong to the human papovavirus family. These are important topics of discussion that will need to be studied in further larger studies.

CONCLUSION

A decision of whether to treat with immunotherapy such as IL candida in immunocompromised transplant recipients is challenging due to concerns with efficacy and the possibility of rejection, and perhaps infections. Well-designed prospective studies are needed in the future to determine the efficacy and safety of this potentially curative treatment for the recalcitrant warts.

FOOTNOTES

Author contributions: All authors contributed to the study conception and design, writing; Acharya R, Bush R, and Johns F were involved in the acquisition of the clinical data, analysis, and interpretation; Upadhyay K was involved in the critical revision.

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EVIDENCE REVIEW

Simultaneous pancreas-kidney transplantation for end-stage renal failure in type 1 diabetes mellitus: Current perspectives

Lakshmi Nagendra, Cornelius James Fernandez, Joseph M Pappachan

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Abstract

Type 1 diabetes mellitus (T1DM) is one of the important causes of chronic kidney disease (CKD) and end-stage renal failure (ESRF). Even with the best available treatment options, management of T1DM poses significant challenges for clinicians across the world, especially when associated with CKD and ESRF. Substantial increases in morbidity and mortality along with marked rise in treatment costs and marked reduction of quality of life are the usual consequences of onset of CKD and progression to ESRF in patients with T1DM. Simultaneous pancreas-kidney transplant (SPK) is an attractive and promising treatment option for patients with advanced CKD/ESRF and T1DM for potential cure of these diseases and possibly several complications. However, limited availability of the organs for transplantation, the need for long-term immunosuppression to prevent rejection, peri- and post-operative complications of SPK, lack of resources and the expertise for the procedure in many centers, and the cost implications related to the surgery and postoperative care of these patients are major issues faced by clinicians across the globe. This clinical update review compiles the latest evidence and current recommendations of SPK for patients with T1DM and advanced CKD/ESRF to enable clinicians to care for these diseases.

Key Words: Type 1 diabetes mellitus; Chronic kidney disease; End-stage renal failure; Simultaneous pancreas-kidney transplantation; Perioperative complications; Immunosuppression

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Core Tip: Simultaneous pancreas-kidney transplant (SPKT) is a promising management option for patients with advanced chronic kidney disease or end-stage renal failure (CKD/ESRF) and type 1 diabetes mellitus (T1DM) for probable cure of these diseases and possibly some of their complications. However, limited availability of these organs, need for long-term immunosuppression, the surgical complications, lack of availability of this procedure in most centers, and the cost implications related to SPKT are major challenges across the world. This clinical update review is to enable clinicians with the best evidence and current recommendations of SPKT for managing their patients with T1DM and advanced CKD/ESRF.

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INTRODUCTION

Diabetes mellitus is one of the most common causes of chronic kidney disease (CKD) and end-stage renal failure (ESRF). Type 1 diabetes mellitus (T1DM), though less common when compared to type 2 diabetes, is associated with considerable morbidity and mortality secondary to microvascular and macrovascular complications including CKD. ESRF is a leading cause of death in patients with T1DM[1]. Although there has been considerable progress in the development of insulin delivery devices, newer insulin molecules, and glucose monitoring systems in recent years, there is still a significant negative impact on the quality of life in relation to disease management among T1DM patients[2]. Furthermore, these are not useful in reversing end-stage complications of diabetes such as ESRF. Despite extensive research, stem cell therapies in T1DM are still in the infantile stages[3]. Simultaneous pancreas-kidney transplant (SPK) is an attractive modality that fills this treatment gap in the management of T1DM and ESRF. Lack of wide availability, high cost, infections, and immunological problems following SPK have long been the challenges precluding the widespread use of SPK. However, advanced surgical techniques and newer immunosuppressive drug regimens in recent years have resulted in dramatic improvement in SPK outcomes. We describe the current perspectives on SPK for individuals with T1DM and ESRF, with the latest evidence on indications, perioperative care, immediate and long-term complications, and clinical outcomes through this comprehensive review.

HISTORY OF SIMULTANEOUS PANCREAS-KIDNEY TRANSPLANTATION

Kelly *et al*[4] from the University of Minnesota conducted the first pancreatic transplant in 1966 in combination with a kidney transplant to treat a 28-year-old uremic patient with T1DM. The patient was insulin-free for six days before needing exogenous insulin, which was brought on by the large dosages of steroids that were administered to avoid rejection. However, the patient developed graft pancreatitis, which was most likely caused by duct ligation and the transplantation procedure had to be reversed. Unfortunately, 13 days after the excision of the rejected pancreas and kidney transplant, the patient passed away from a pulmonary embolism[2]. Surgical difficulties, wound infections, and graft rejection were all prevalent issues with pancreatic transplantation in this initial example, which persisted for the next 20 years. Despite difficulties, the Minnesota team demonstrated the technical feasibility of SPK[4].

The first documented effective use of cyclosporine A in two pancreatic transplants was by Calne *et al*[5] in 1979. This heralded an exciting new era of effective immunosuppressive regimens which eventually led to the more widespread use of SPK. Triple immunosuppression (maintenance therapy with cyclosporine A, azathioprine, and steroids) soon gained popularity all over the world after the introduction of cyclosporine A[6]. In 1989 Starzl *et al*[7] used tacrolimus as an immunosuppressive agent. This was followed by the development of induction therapy initially using anti-thymocyte globulin such as thymoglobulin and later (1997) by a recombinant DNA-derived humanised anti-CD52 lymphocyte depleting monoclonal antibody known as Alemtuzumab. Certain centres explored steroid-free regimens in the late 1990s and early 2000s which showed improvement in metabolic outcomes[6].

The initial pancreas transplant was done with ligation of the pancreatic duct[7]. Montefiore used the pancreatic duct to ureter anastomosis as a method of exocrine secretion drainage; however, it was complicated with anastomosis leakage. Bewick developed the open pancreatic duct drainage of exocrine secretions; however, it was complicated by peritonitis and ascites. Sollinger *et al*[8] developed pancreas-to-bladder anastomosis for exocrine secretion drainage; however, it was complicated with urinary tract infections, chronic cystitis, reflux pancreatitis, metabolic acidosis, and haematuria. Currently, enteric drainage is widely used for exocrine drainage with anastomosis between transplanted duodenum and

recipient ileum, jejunum, and duodenum, with drainage into a jejunal loop being the most used technique using techniques including Roux-en-Y reconstruction[9].

There are many types of pancreas and islet transplantations as depicted in Figure 1. The number of pancreas transplants (especially SPK) increased steadily in the US and worldwide since 1984. However, the number of pancreas transplants has shown a 20% decline between 2005 and 2014, with a nadir reaching in 2015. This decline in pancreas transplants is due to various reasons including the availability of advanced alternative treatment options like sensors, pumps, and hybrid closed loops resulting in fewer referrals to the pancreas transplantation waiting list, diabetic complications like ESRF occurring at a later age group, worsening donor organ quality related to body mass index (BMI) among organ donors (BMI > 35 kg/m^2 associated with fatty infiltration of the pancreas), and high post-operative complication burden (> 50%) associated with the pancreas transplants[9].

Thereafter, though the pancreas transplant volume started to increase, there was a further decline to coincide with the beginning of the coronavirus disease 2019 (COVID-19) pandemic where the number of SPKs in the US dropped from 872 in 2019 to 827 in 2020[10]. The number of pancreas transplants and the trends in pancreas transplants in the US between 1966 and 2021 are shown in Figures 2 and 3[11,12]. This decline likely reflects the unwillingness of many transplant programs to move forward with pancreatic transplants due to COVID-19 limiting the resources. The pancreas after kidney (PAK) and pancreas transplant alone (PTA) increased marginally to compensate for the drop in SPK, as shown in Figure 3[10].

INDICATIONS FOR SPK

Typically, patients with T1DM who have low or absent C-peptide levels are eligible for the SPK. Candidates could also have severe nephropathy or ESRF, as well as comorbidities such as hypoglycemia unawareness, recurrent hospitalisation for diabetic ketoacidosis, progressive retinopathy, enteropathy, and neuropathy. The current indications for SPK in T1DM are outlined in the Table 1[13,14].

In patients with stage 4/5 chronic kidney disease, preemptive SPK is described as the transplantation of both the pancreas and kidney before the patient is initiated on dialysis. Preemptive SPK has been shown to be related to better results when compared to SPK carried out in patients undergoing dialysis, according to several retrospective investigations, including registry analysis. In SPK patients, time spent on dialysis also has a poor prognostic significance[15,16].

CONTRAINDICATIONS

The absolute and relative contraindications for SPK in patients with T1DM are given in Table 1[17].

Obesity alone is not an absolute contraindication to SPK, given that positive outcomes have been documented[18]. However, obese patients may experience a greater risk of early complications when compared to non-obese recipients [19]. Additionally, the significance of BMI < 18.5 kg/m^2 as a risk factor for long-term mortality needs to be emphasized [18].

Previous history of limb amputation and presence of coronary heart disease are risk factors for worse outcomes, but neither is considered an absolute contraindication to SPK[20]. Pre-SPK limb amputation often indicates worse transplant results because it raises the risk of cardiovascular disease[21]. The risk of serious adverse cardiovascular events following transplantation is further increased by a history of coronary artery disease before transplantation[22]. If medically treated and revascularized by accepted standards, coronary artery disease, however, does not pose a significantly higher risk for death.

SURGICAL TECHNIQUES

Most of the pancreas grafts are retrieved from heart-beating brain-dead donors, with an increasing number from non-heart-beating donors after circulatory death[17]. The retrieval involves the removal of the pancreas en-bloc with the donor duodenum and spleen, with the spleen removed before implantation. In SPK, both kidney and pancreas grafts are taken from the same deceased donor. The donor pancreas has two arteries (superior mesenteric artery and splenic artery), and these are joined with a 'Y' graft utilizing the donor common iliac artery and its bifurcation to create a single arterial inflow which is anastomosed to the recipient's right common iliac artery. The donor portal vein is anastomosed to the recipient's right common iliac vein or inferior vena cava. Finally, the donor duodenal conduit is anastomosed to the recipient's small bowel or urinary bladder. A pancreas transplant alone takes approximately 3-4 h, whereas a simultaneous pancreas and kidney transplant takes approximately 4-6 h[17,23].

Diverse and institution-specific procedures are employed for SPK. The intra-peritoneal technique is used by most transplant facilities for graft insertion. The kidney is transplanted to the left iliac fossa, the pancreas is generally placed in the right iliac fossa. The native pancreas and kidney remain in place. The peripancreatic fluid accumulations and wound complications are reduced because of this strategy. Extraperitoneal and ipsilateral insertion of both grafts constitute an alternate strategy[17,24].

Most pancreatic transplants use either enteric or bladder drainage. Comparing bladder and intestinal drainage of exocrine secretions in pancreas transplantation has been extensively studied. Compared to enteric drainage, bladder

Table 1 Current indications and contraindications for simultaneous pancreas-kidney in type 1 diabetes mellitus[11,12,15]

Current indications for SPK in T1DM
Confirmed diabetic nephropathy with low or absent C-peptide, on insulin treatment
Creatinine clearance < 15 mL/min or on dialysis
Presence of other microvascular or macrovascular complications of T1DM
Ability to withstand immunosuppression and surgery
History of compliance with medical advice and treatment
Absolute contraindications for SPK in T1DM
Significant cardiovascular disease with severe or non-correctable coronary artery disease
Cardiac ejection fraction < 50%
Recent myocardial infarction
Non-curable malignancy except localized skin cancer
Active sepsis
Active peptic ulcer disease
Severe mental health conditions that can lead to non-compliance
Inability to survive surgery or immunosuppression due to significant comorbidity
Relative contraindications for SPK in T1DM
Cerebrovascular event with long-standing impairment
Human immunodeficiency virus, hepatitis B and C virus infections
BMI > 30 kg/m^2
Age > 60 yrs
Extensive vascular, aortic, and renal artery disease (making surgery high-risk)
Excessive need for insulin > 1.5 U/kg/d
Continuous use of alcohol, smoking, and other drugs

T1DM: Type 1 diabetes mellitus; SPK: Simultaneous pancreas-kidney.

drainage increases late reintervention rates (primarily for enteric conversion), but it has no acute surgical risks[17]. In a recent study by Riad *et al*[25], at 10 years posttransplant, 44.3% of simultaneous pancreas-kidney transplant recipients had undergone enteric conversion. The enteric conversion was associated with an 85% increased risk of acute rejection but was not associated with graft loss or mortality. Additionally, bladder drainage is linked to long-term urologic problems such as bladder calculi, haemorrhagic cystitis, and recurrent urinary tract infections, as well as metabolic disturbances like acidosis and dehydration[26]. These factors have contributed to a drop in the use of bladder drainage over time.

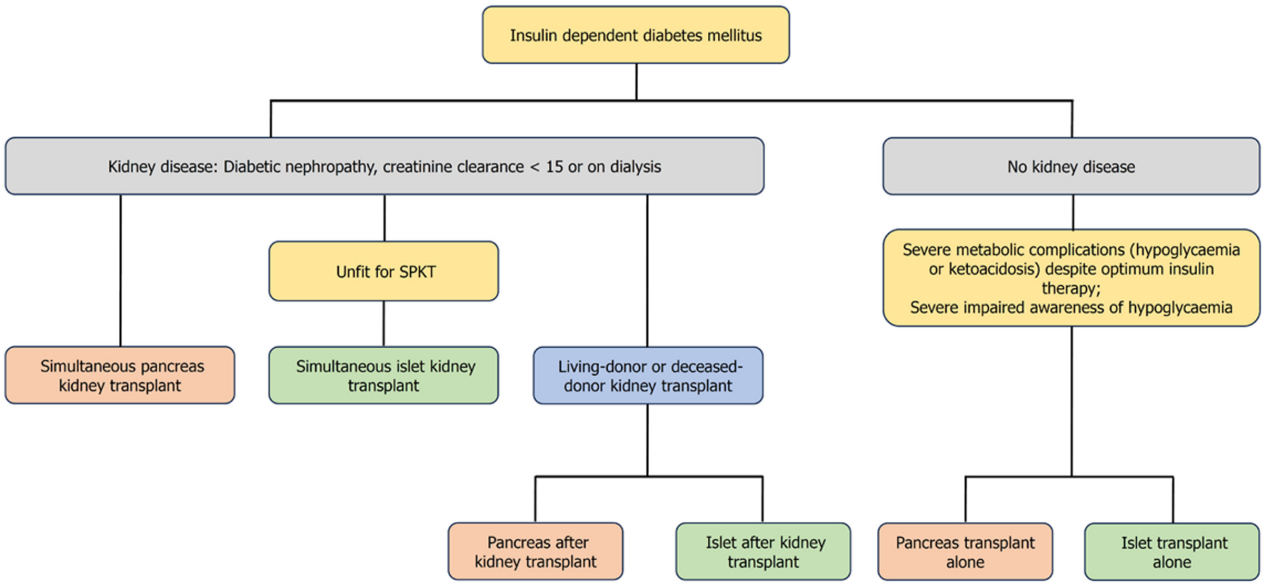
PERIOPERATIVE CARE

Insulin regimens

Perioperative plasma glucose monitoring is crucial. The metabolic reaction to stress and the impact of corticosteroids contribute to the frequent occurrence of intraoperative hyperglycemia. As uncontrolled glucose levels are linked to impaired immune function and an increased risk of infection, insulin infusion should be started before unclamping of the pancreas transplant. Plasma glucose must be closely monitored after unclamping since glucose levels might dangerously plummet[27].

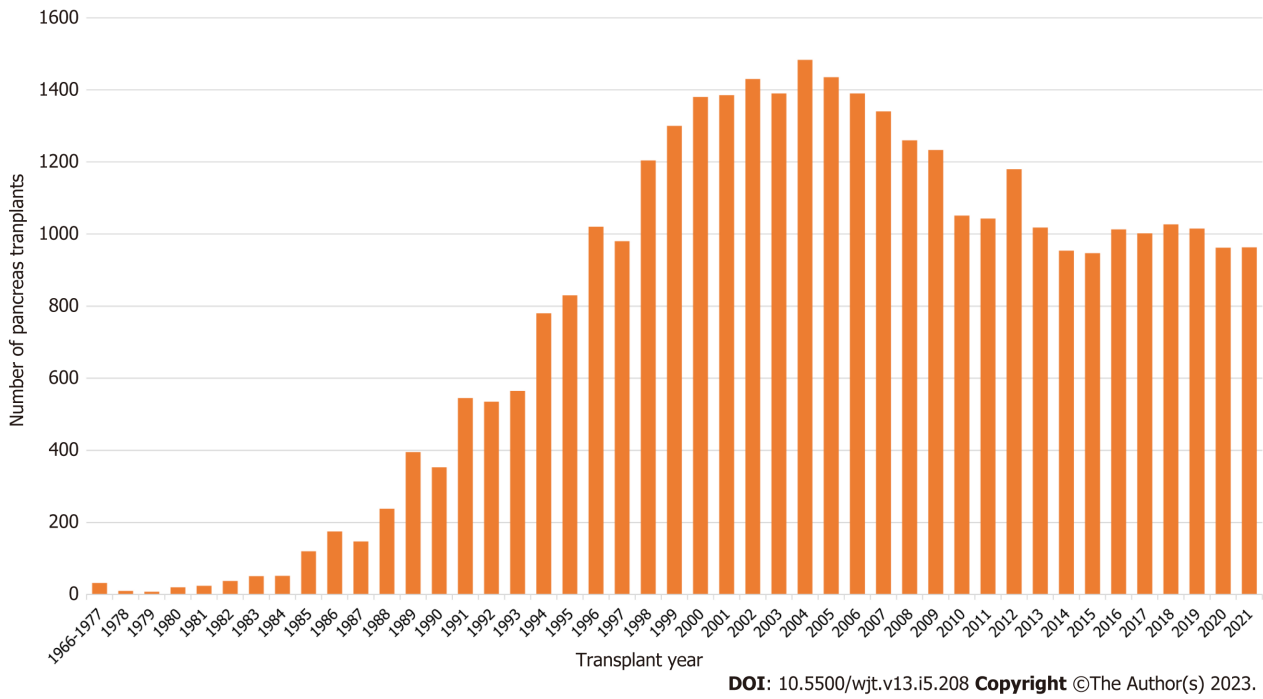
Heparin thromboprophylaxis

Thrombosis, which has a reported prevalence of 4%–20%, is a common complication associated with pancreatic transplantation. One of the main factors contributing to pancreatic transplant failure and graft loss has been identified as thrombosis. Despite this, the effectiveness of preventive anticoagulation is still debatable, with some trials finding positive results from anticoagulation and other trials reporting no benefit[28,29]. Pancreas transplant centers have various internal policies and practices, and there is still no standardised thromboprophylaxis approach for this procedure. According to a recent meta-analysis that included 11 studies and 1122 patients in the heparin group and 236 patients in



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Figure 1 Various types of pancreas (red box) and islet (green box) transplantation[7]. SPKT: Simultaneous pancreas-kidney transplant.



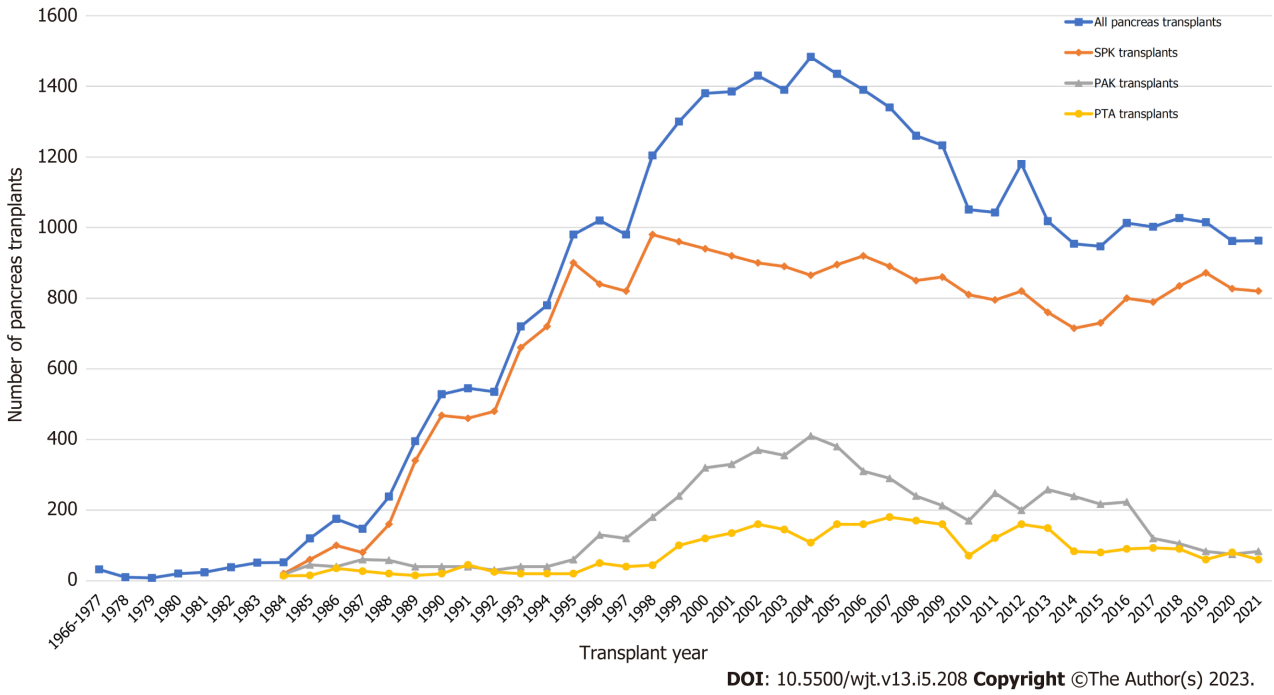
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Figure 2 Number of pancreas transplants in the United States between 1966 and 2021[9,10].

the no-heparin group, prophylactic heparinization significantly reduced the risk of early pancreas thrombosis and pancreas loss for SPK without increasing the incidence of bleeding or acute return to the operating room when compared to the no-heparin control[30]. In the included studies, intraoperative intravenous heparin 30-70 IU/kg was administered when heparin thromboprophylaxis was not contraindicated. Heparin was administered intravenously 200-1000 IU/h for 1-14 d or subcutaneously 3000-5000 IU 1-2 times daily during the postoperative period. Following this, aspirin 81-325 mg per day was used for maintenance[30].

IMMUNOSUPPRESSION

The accepted practice in modern immunosuppression is to combine numerous drugs with various mechanisms of action for maintenance therapy and to employ biologic medicines for induction. These regimens achieve the main objectives of



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Figure 3 Trends in pancreas transplants in the United States between 1966 and 2021[9,10]. SPK: Simultaneous pancreas-kidney; PAK: Pancreas after kidney; PTA: Pancreas transplant alone.

immunosuppression, which are to effectively manage acute rejection while reducing risks to the patient's safety and tolerability and damage to the allograft(s).

Induction immunosuppression

Early rejection and graft loss from combined pancreas-kidney transplants have been lower with the use of induction immunosuppression. Of the induction therapies, lymphocyte-depleting agents (alemtuzumab and anti-thymocyte globulin) and nondepleting agents [basiliximab and daclizumab (anti–interleukin 2 (anti–IL-2) receptor monoclonal antibody)] have been used in SPKs. Ninety percent of pancreatic transplant patients get a lympho-depleting drug during induction treatment, reflecting the widespread observation of greater rejection rates following pancreas transplant[10].

A recent meta-analysis studied 536 SPK participants in 7 randomised clinical trials that reported 5 induction methods. Antithymocyte globulin (97 patients), alemtuzumab (42 patients), 2 or 5 doses of daclizumab (113 patients), and no induction treatment (120 patients) were included in these regimens. A regimen containing 2 doses of daclizumab ranked highest for patient survival as well as kidney and pancreas transplant survival in the network meta-analysis. In contrast, alemtuzumab was ranked best for the prevention of acute renal and pancreatic rejection[31].

In patients at low immunologic risk, there isn't any conclusive proof that induction with depleting *vs* nondepleting antibodies leads to better immunologic outcomes. When compared with the use of nondepleting antibodies or no induction therapy, induction with depleting antibodies is associated with cytokine release syndrome requiring premedication and with an increased incidence of early posttransplant infections, especially cytomegalovirus (CMV) viremia (that do not result in inferior patient and graft survival). There is no conclusive evidence that induction treatment with depleting antibodies increases the risk of oncologic problems in pancreatic transplant patients, despite data on renal transplantation to the contrary[20].

Maintenance Immunosuppression

Modern immunosuppressive protocols for all types of pancreatic transplantation include tacrolimus, mycophenolate, and steroids for the purpose of maintenance of immunosuppression. Tacrolimus has been the preferred calcineurin inhibitor (CNI) for more than ten years, despite the risks of beta cell toxicity and renal damage linked to it. Results of a 3-year single-center, prospective, randomized comparison of the two calcineurin inhibitors in the setting of mycophenolate mofetil (MMF)-based immunosuppression in 47 SPK patients did not show superiority of tacrolimus over cyclosporin [32]. However, a larger study in 205 SPK recipients confirmed the superiority of tacrolimus over cyclosporine in preventing moderate or severe kidney or pancreas rejection and pancreatic thrombosis[33]. Tacrolimus is available as an immediate-release formulation (IR-Tac) which is traditionally given twice daily. Extended-release tacrolimus (ER-Tac) given once daily was later explored with the expectation of improved medication adherence. Falconer *et al*[34] reported that stable SPK recipients can safely be converted from IR-Tac to ER-Tac, with no clinical impact on the transplant function.

MMF continues to be the preferred antiproliferative drug for maintenance therapy. Following induction therapy, a review found that using mycophenolate mofetil in conjunction with CNI and steroids was linked to a 40% decrease in the risk of acute rejection one year following pancreatic transplantation[35]. When combined with tacrolimus or cyclosporine,

retrospective studies have shown that mycophenolate mofetil, as opposed to azathioprine, improves the immunologic outcome of pancreas transplantation, but at the cost of more gastrointestinal side effects that frequently necessitate dose reduction[36,37].

Total avoidance of steroid immunosuppression is referred to as "steroid avoidance." Early avoidance is defined as steroid therapy for fewer than 14 d following transplantation, while late avoidance is defined as steroid withdrawal after 14 d[38]. Though steroids form the cornerstone of immunosuppression therapy, steroid discontinuation is being explored and could lead to better metabolic outcomes over time. Although it fell from 27.2% in 2019 to 25.8% in 2020, the percentage of patients kept on a tacrolimus/MMF steroid-free therapy was mostly steady. Steroid withdrawal between 6-12 mo after transplantation was successful and safe in most patients without an increase in immune events. Additionally, the patients had a low prevalence of hypertension, dyslipidemia, and obesity[39].

Compared to the 12.4% reported in 2010, the percentage of pancreatic transplant patients in the "other" maintenance therapy regimens has reduced to 2.6%. This slow decline shows that co-stimulation blockade or mammalian target-of-rapamycin (mTOR) inhibitors have not been frequently used as alternate maintenance regimen components[9,20]. Though mTOR inhibitors show non-inferior immunological outcomes, the side effect profile of this group of drugs precludes its widespread use[40,41].

COMPLICATIONS

When compared to patients of kidney transplantation alone (KTA), those who received SPK typically have more severe and frequent complications in the first year after transplant. These complications are typically caused by either the more extensive surgical procedure or the necessary immunosuppression. Greater morbidity and early death are related to SPK than KTA because of perioperative problems. This difference is evidenced by longer initial hospital stays, higher rates of rehospitalization in the first 30 d, more serious infections necessitating rehospitalization, and higher perioperative mortality risk[42]. Khubutia *et al*[43] reported surgical complications in 37.5% of SPK patients. Asymptomatic para-pancreatic fluid collection (52.5%) was the most common surgical complication followed by superior mesenteric artery thrombosis (12.5%). Surgical site infections after pancreas transplantation in the Swiss Transplant Cohort Study were seen in 14% of patients[44].

Following a pancreatic transplant, technical failure rates might reach 8%. Graft thrombosis, graft pancreatitis, anastomotic leak, and infection are some causes of failure[45,46]. In a recent retrospective, single-center analysis, 114 adult patients who received an SPK between 2005 and 2018 were included. There was an 85.1% pancreas transplant survival rate at 3 mo. Early pancreatic transplant loss was mostly due to pancreatitis (2.6%), necrosis (2.6%), and thrombosis (6.1%). In contrast to patients with a functional pancreas, early pancreatic transplant loss was not linked to a lower chance of survival (P = 0.168) or severe adverse cerebral or cardiovascular events during a 10-year period[47]. Most postoperative problems in the SPK population that necessitate surgical re-exploration are pancreas-related. In a recent study on SPK patients, while 28.2% of patients experienced a major kidney complication, the rate for major pancreas-related complications was 43.6%[48].

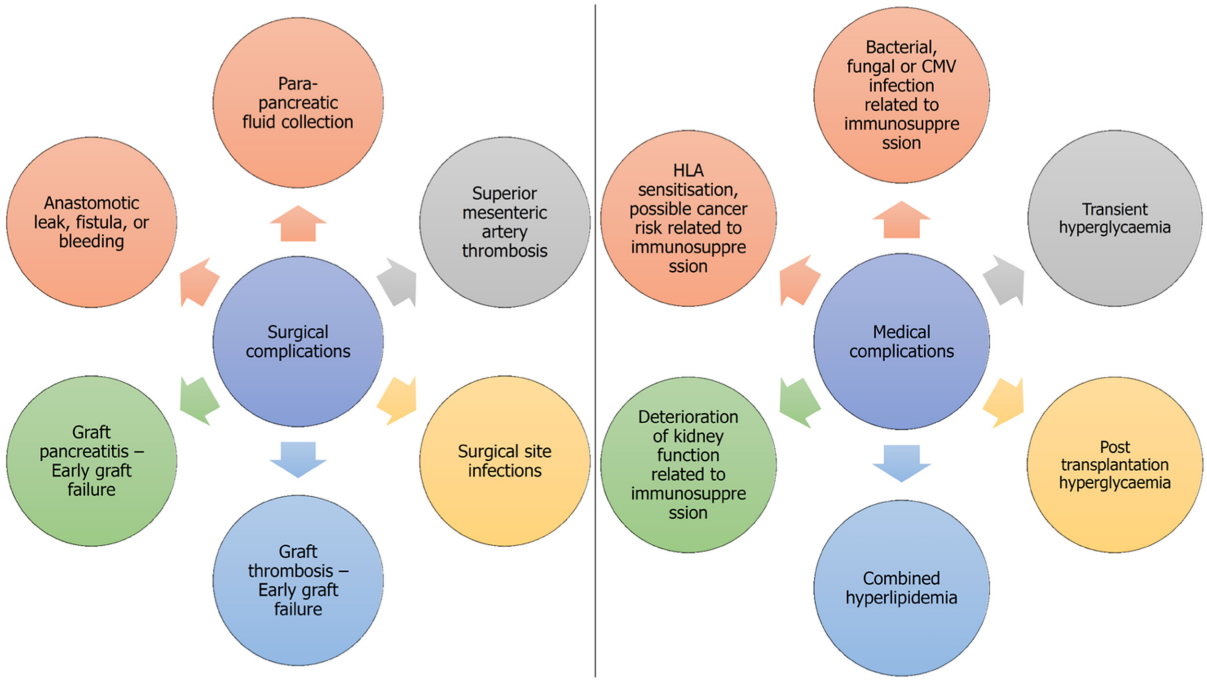
Even though SPK outcomes have improved dramatically, infectious complications continue to be the leading cause of morbidity and death. Michalak *et al*[49] reported 102 infections among 51 SPK patients during the posttransplant period. A total of 73 bacterial infections (systemic 13, pulmonary 13, intestinal 8, wound 23), 21 episodes of CMV infection (systemic 20, duodenal site 1), 73 fungal infections (central nervous system 5, gastrointestinal tract 3), and 8 bacterial infections (systemic 13, pulmonary 13, intestinal 8, wound 23) were reported. Some individuals had multiple infections. The overall mortality rate in the study cohort was 24.5%. Most deaths (77%) were due to infectious complications, which included systemic infection (38.5%) and CNS infection (38.5%). The majority of systemic illnesses had a bacterial aetiology and CNS infections had a fungal aetiology.

Metabolic complications are also a frequent cause of morbidity post-SPK. Within the first six months, transient hyperglycemia may develop because of acute or chronic rejection, pancreatitis, or a significant rise in insulin resistance brought on by weight gain. Post-transplant hyperglycemia has also been associated with immunosuppressant drug side effects, including steroids, calcineurin inhibitors (particularly tacrolimus), sirolimus, and mycophenolate. About 60 to 80% of patients receiving immunosuppressive medication develop hyperlipidemia following solid organ transplantation. Two of the most significant lipid abnormalities seen are high triglyceride levels and low-density lipoprotein cholesterol concentrations. Combined hyperlipidemia is also typical. Many risk factors, including advanced age, obesity, post-transplant weight gain, pre-transplant dyslipidemia, male gender, graft malfunction, proteinuria, newly diagnosed diabetes mellitus, prednisone dose, and the kind of immunosuppressive regimen, might contribute to the development of dyslipidemia following pancreatic transplant. Although tacrolimus and cyclosporine similarly negatively impact lipid metabolism, sirolimus has been linked to larger elevations in triglycerides and cholesterol[50]. The common complications of SPK are displayed in Figure 4.

OUTCOMES

Survival benefit

For transplants performed in 2018-2019, one-year patient mortality remained low at 2.6%. Ten-year mortality rates among 2010-11 transplant recipients were 20.9% likely reflecting cardiovascular comorbidities in the population. Five-year



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Figure 4 Common complications of simultaneous pancreas-kidney. CMV: Cytomegalovirus; HLA: Human leukocyte antigen.

survival rate was 92.7%[10].

Compared with living or deceased-donor kidney transplantation, SPK was associated with improved patient survival, especially in recipients with a long-term functioning pancreatic graft, and resulted in an almost 50% reduction 10-year mortality rate[51].

Glycemic control

Following a solid-organ pancreas transplant, the great majority of patients attain total insulin independence in both the short and long terms. Glycemic control outperforms that attained with insulin pumps or islet-cell transplants by a wide margin[52]. A recent study evaluated CGM-derived time in range and glucose variability in 43 patients with SPK. Time in range (TIR) at 5-12 years follow-up was 97.5%. Time above range (TAR) and time below range (TBR) were 2.5% and 3.5% respectively. Thus patients with functional pancreatic grafts exhibit very high TIR and low GV following SPK[53]. In the immediate post-transplant period at 6 wk, Dadlani *et al*[54] reported a TIR, TAR and TBR of 92%, 7.9% and 0.3% respectively in SPK patients.

Diabetes-related complications

Diabetic retinopathy: A feared side effect of pancreatic transplantation is the worsening of diabetic retinopathy brought on by abrupt glucose normalisation. There have been conflicting results on retinopathy outcomes after SPK. Chow *et al* [55] reported a high prevalence of severe proliferative diabetic retinopathy (DR) and blindness at the time of presentation for SPK. This was subsequently stabilised to inactive proliferative DR by appropriate laser therapy followed by metabolic control achieved by SPK. Voglová *et al*[56] studied 43 pancreatic and kidney recipients for a 12-mo composite endpoint that included the requirement for fresh laser therapy, newly discovered proliferation, macular edema, deteriorating vision, and blindness. This primary goal was attained by 37% of patients, however, the severity was only moderately high. Visual acuity remained constant. The absolute glycated haemoglobin, age, and duration of diabetes mellitus did not significantly differ between patients who met and did not achieve the primary goal, while a greater percentage of patients with deterioration had recently undergone laser therapy. 62.8% of individuals had stable retinal disease. In 26% of cases, visual acuity was noticeably improved. Even though retinal deterioration was observed in more than one-third of individuals, the progression of the condition was unrelated to the degree of metabolic alteration and instead followed the predicted normal course of retinopathy[56].

Diabetic neuropathy: Cardiac autonomic neuropathy is a dreaded complication of long-standing uncontrolled diabetes. Argente-Pla *et al*[57] reported improved cardiac autonomic neuropathy post SPK as evidenced by an improved Valsalva ratio. SPK is been shown to be beneficial for diabetic polyneuropathy in earlier studies. Kennedy *et al*[58] used muscle action potential and indices of nerve conduction velocity to examine how pancreatic transplantation affected peripheral motor, sensory, and autonomic nerve function. They discovered a notable improvement in motor and sensory indices during a 12-mo follow-up. Martinenghi *et al*[59] demonstrated that even in the presence of severe polyneuropathy, a persistent normoglycemic condition can enhance nerve function.

Diabetic nephropathy: For most patients with type 1 DM and ESRF, SPK restores normal renal function. According to Fioretto *et al*[60], characteristics of diabetic nephropathy were restored after 10 years of sustained normoglycemia post-transplant. It greatly decreased the thickness of the mesangial matrix and glomerular basement membrane, and it significantly improved glomerular and tubular lesions. Additionally, a decline in the rate of urine albumin excretion (20 mg/d *vs* 103 mg/d) was seen, demonstrating improved renal function. Diabetic nephropathy is reported to alter circulating long noncoding RNA levels that normalize following SPK[61].

Macrovascular complications: Microvascular diabetic problems are stabilised more frequently following effective SPK, although macrovascular diabetic sequelae and diabetic Charcot neuro-osteoarthropathy have been traditionally thought to progress. Duration of hemodialysis is an important risk factor for adverse cardiac events[62]. However, a recent study showed significant improvements in left ventricular systolic parameters during follow-up in SPK recipients[63]. Another recent study concluded that SPK favorably slows down the development and progression of peripheral vascular disease by maintaining a superior metabolic vascular risk profile[21].

Quality of life: When compared to KTA, it has been demonstrated that SPK improves quality of life (QoL). In addition to avoiding hypoglycemia spells and insulin injections, pancreas transplantation also lowers the risk of developing microvascular and macrovascular complications of diabetes and eliminates the need for glucose monitoring. After correcting for QoL, SPK outperformed KTA or dialysis in terms of cost-effectiveness over five years in a trial on individuals with T1DM and ESRF[64]. The outcomes of SPK are summarised in Figure 5.

Future perspectives of SPK in the context of islet transplantation

Pancreas transplantation is the best treatment to provide insulin-independence, excellent metabolic control, and an improvement in QoL. Additionally, it may be able to avoid, ameliorate, or even reverse most of the diabetic complications. The technique of pancreas transplantation has shown improvement over time. The factors playing their part in this improvement include intestinal drainage of pancreatic juices, the introduction of calcineurin inhibitors and T-cell depleting agents, and improvements in maintenance immunosuppression with tacrolimus and mycophenolate mofetil. Though the sirolimus-based protocols showed initial promise, their use subsequently declined significantly.

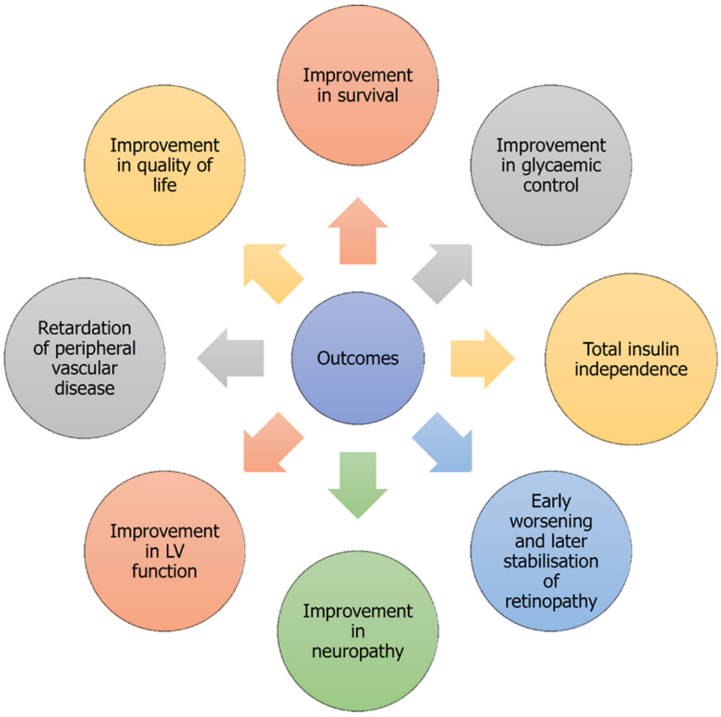
PTA and PAK are more difficult to monitor. Hence, they carry a high risk of immunological rejection and have less favourable outcomes in comparison to SPK. PAK is effective in those who have had KTA in the past and are now having trouble with achieving glycaemic control and/or management of diabetes-related complications. Thus, PAK is a therapeutic option as a life-preserving procedure that avoids long-term dialysis and mortality on the waitlist and provides the time to find a good pancreas graft after the kidney transplant. On the other hand, PTA is a treatment option for patients with brittle diabetes who suffer from hypoglycaemia unawareness impairing QoL or have difficulty adhering to insulin injection requirements, but with a normal or near-normal renal function. It provides the best one-year patient survival among all whole organ transplants[65].

Careful selection of recipients and donors, improvement in surgical techniques, and refinement in immunosuppressive protocols have provided excellent outcomes after pancreas transplantation. Additionally, early detection of postoperative complications through careful observation, and regular imaging, and prophylactic use of antimicrobial agents are possible strategies that would reduce postoperative morbidity/mortality and thereby favour the expansion of existing pancreas transplant programs. Islets constitute only 1%-2% of the pancreas. Therefore, a less invasive procedure with lower procedural morbidity, islet transplantation, involving percutaneous intra-portal infusion of the islets is considered another alternative[17].

No trials are comparing the outcomes of islet transplantation (SIK or IAK) *vs* SPK[17]. Pancreas transplantation is a more acceptable treatment option for patients with ESRF, who are already undergoing a kidney transplantation. On the other hand, islet transplantation is preferred in elderly, frail, and morbid patients who are unfit for pancreas transplantation and in patients with a preference for a less invasive procedure. These two procedures have comparable results in glucose control, avoidance of severe hypoglycaemia, and recovery from hypoglycaemia unawareness. However, the insulin independence rates are 'slow and low' with islet transplants in comparison to pancreas transplants depending on the number of islet transplants and the success of engraftments. Multiple donors are needed in islet transplantation, thereby increasing the waiting list. Contrary to pancreas transplantation, obesity in the donor is not a contraindication for islet transplantation[65].

CONCLUSION

For individuals with T1DM and ESRF, simultaneous pancreas and kidney transplantation has become the gold standard of care. In terms of patient survival, graft survival, diabetes complications, and QoL, there is a substantial body of evidence from clinical research that supports the procedure. Only carefully chosen individuals should undergo simultaneous pancreas and kidney transplantation since it is a technically challenging treatment that is linked with serious short-term and long-term complications. The wider adoption of this therapeutic paradigm can be made possible with patient education initiatives and public outreach to foster a charitable culture of organ donation.



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Figure 5 The outcomes of simultaneous pancreas-kidney. LV: Left ventricular.

FOOTNOTES

Author contributions: Nagendra L performed the literature search, interpreted the relevant literature, and drafted the initial manuscript; Pappachan JM and Fernandez CJ conceived the idea and provided additional input to design the paper; Fernandez CJ prepared the figures and with additional input from Pappachan JM, revised the article critically for important intellectual content after peer reviews; All authors have read and approved the final version of the manuscript.

Conflict-of-interest statement: All the authors declare that they have no conflict of interest.

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REVIEW

Evolution of human kidney allograft pathology diagnostics through 30 years of the Banff classification process

Muhammed Mubarak, Amber Raza, Rahma Rashid, Shaheera Shakeel

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Abstract

The second half of the previous century witnessed a tremendous rise in the number of clinical kidney transplants worldwide. This activity was, however, accompanied by many issues and challenges. An accurate diagnosis and appropriate management of causes of graft dysfunction were and still are, a big challenge. Kidney allograft biopsy played a vital role in addressing the above challenge. However, its interpretation was not standardized for many years until, in 1991, the Banff process was started to fill this void. Thereafter, regular Banff meetings took place every 2 years for the past 30 years. Marked changes have taken place in the interpretation of kidney allograft biopsies, diagnosis, and classification of rejection and other non-rejection pathologies from the original Banff 93 classification. This review attempts to summarize those changes for increasing the awareness and understanding of kidney allograft pathology through the eyes of the Banff process. It will interest the transplant surgeons, physicians, pathologists, and allied professionals associated with the care of kidney transplant patients.

Key Words: Banff process; Rejection; Kidney allograft biopsy; Transplant pathology; Review

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Core Tip: The efforts to standardize the nomenclature, classification, and reporting of kidney allograft biopsies were initiated in 1991 by a small group of renal pathologists, transplant physicians, and surgeons at a meeting in Banff, Alberta, Canada. Thereafter, regular meetings of the now ever-expanding, multidisciplinary, and international Banff community have been held every 2 years at different places around the world to revise, update and refine the classification. Major and frequent changes have occurred in the classification over the three decades of its evolution, making it extremely complex and difficult to comprehend, particularly for beginners in the field. The classification has essentially changed from pathology-based to pathogenesis-based classification and has become clinician-friendly and treatment-friendly. This review is an attempt to summarize the changes in the classification in an easily understandable manner and describe the rationale behind these changes for easy assimilation by both neophytes and practicing renal pathologists, transplant physicians, surgeons, and other relevant stakeholders.

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INTRODUCTION

Kidney transplantation is the preferred type of treatment for end-stage kidney disease patients throughout the world. Advancements in surgical techniques, immunosuppressive regimens, and infection control during the second half of the previous century markedly improved the short- and medium-term outcomes of kidney allografts. However, the long-term results are still poor and little progress has been made in this area[1,2]. Although highly effective, kidney transplantation is not completely immune to complications. Kidney allograft dysfunction can occur at any time after transplantation. It has been reported that kidney allograft dysfunction occurs in 50%-60% of cases after transplantation and there are many causes. Among the most important and prevalent causes of kidney allograft dysfunction are rejection, infection, and drug toxicity[3].

The Banff classification schema for kidney allograft pathology was developed in 1991 and is an ongoing process with an international approach[4-9]. The first Banff meeting was held at the small town of Banff in Alberta, Canada in August 1991, which was attended by a group of 12 nephropathologists and transplant clinicians with a common interest in kidney transplantation with the goal of standardizing the reporting of kidney allograft biopsies[10]. The objectives were two-fold: To guide therapy and to establish an objective endpoint for clinical trials. The first report in full paper form was published in 1993 after several cross-consultations and follow-up discussions[10]. These meetings have subsequently taken place biennially, initially at Banff and later on, in other parts of the world but have been named the Banff meetings after their original place of meeting to revisit, revise and update the Banff classification. Our understanding of kidney transplant pathology, and particularly, rejections has grown and improved with discourses and publications emerging out of these meetings[4-6,9]. At the same time, the classification has become more complex and difficult to assimilate, particularly for novices in the field.

The Banff schema is distinctive as the classification criteria are developed based on a consensus approach. Although the original Banff classification was developed based on expert opinion, its subsequent revisions and refinements have been made based on published sound scientific studies, multicenter studies by the Banff working groups (BWGs) on problematic areas, and consensus among the experts[6]. In this review, we summarize the major changes in the Banff classification and the rationale behind these changes. This will help the neophytes and practicing nephropathologists, nephrologists, and other stakeholders to better understand this classification.

TECHNICAL CONSIDERATIONS AND TISSUE ADEQUACY

For a kidney allograft biopsy to fulfill its role as the gold standard for accurate diagnosis, it needs to be adequate and as representative as possible of the whole kidney allograft and be prepared according to recommended protocols. With the evolution in the diagnostic criteria of the Banff categories, changes have also taken place in the tissue adequacy criteria, technical preparation guidelines, and the extent of the workup of kidney allograft biopsies (Table 1). In the first Banff meeting, the biopsy adequacy criteria were less stringent, particularly with regard to the number of blood vessels required. The first major change in adequacy criteria was made in 1997 when two cylinders of kidney allograft parenchyma including both cortex and medulla with 10 glomeruli and two arteries were recommended to fulfill adequacy criteria[11]. As the process of rejection is often focal and patchy in distribution, particularly during the early phase, a generous sampling of the kidney cortex from different areas is desirable for an accurate diagnosis, necessitating the recommendation for two cores of allograft tissue. During the first decade of the Banff process, the study of kidney allograft biopsy was based only on morphologic evaluation, *i.e.* light microscopy (LM). From the 2001 meeting onwards, a piece of frozen tissue for C4d was made mandatory for the complete evaluation of allograft pathologic lesions[12,13]. C4d staining should be done on all kidney allograft biopsies, preferably by immunofluorescence (IF), or by immunohisto-

Table 1 Adequacy criteria of renal allograft biopsies for an accurate pathologic diagnosis

Parameters/investigations	Requirements
Number of cores	Two (these should be divided to procure tissue for IF and EM studies, if necessary)
Components of graft parenchyma	Both cortex and medulla
For the light microscopic study	A significant amount of cortex containing up to: (1) 10 glomeruli; and (2) 2 arteries
For the immunofluorescence study	Cortex with up to 3 glomeruli
For the electron microscopic study	Cortex with 1 glomerulus

EM: Electron microscopy; IF: Immunofluorescence.

chemistry (IHC) technique, if the former is not available[13]. The threshold of C4d staining intensity is one grade level lower with the IHC technique. In the Banff 2013 meeting, conditional use of electron microscopy (EM) was recommended in certain situations[14-16]. EM study is not done routinely on all kidney allograft biopsies at all centers, but is performed in the case of suspected recurrent or *de novo* glomerulonephritis, persistent significant but unexplained proteinuria, and for the diagnosis of early chronic changes of allograft rejection such as transplant glomerulopathy and sometimes peritubular capillaries (PTCs). Tissue fixed in 2.5% glutaraldehyde provides optimum results for transmission EM. Standard techniques are employed for the preparation and interpretation of EM. For the above-mentioned ancillary investigations, the biopsy needs to be divided in such a manner that a minimum number of glomeruli and/or PTCs be present in specimens apportioned for IF and EM to maximize their utility. Ideally, this should be done in the biopsy suite under the dissection microscope while the specimen is fresh. Tissue samples should then be placed in appropriate fixatives for respective studies. Although not mandatory, IHC for polyomavirus is recommended on all renal allograft biopsies to help detect early viral lesions. In brief, the pathologic evaluation of kidney allograft biopsies has evolved from pure LM to ancillary techniques of IHC, IF, EM, and more recently, molecular studies to accurately diagnose transplant pathology lesions.

COMPONENTS OF THE BANFF CLASSIFICATION SYSTEM

The foundation of the Banff classification system is centered on the morphological evaluation of kidney allograft tissue comprising four basic components. Each of these components can be involved in either the acute or chronic disease processes, particularly the rejection process. The Banff process identified and defined the lesions of the allograft parenchyma in a systemic and semi-quantitative way (Table 2). Thus, the components of the Banff classification system can conveniently be grouped as: (1) Definitions of various components or lesions; (2) Diagnostic lesions; (3) Semi-quantitative scoring of the lesions; (4) Additional diagnostic features; and (5) The diagnostic categories (Figure 1). None of the individual lesions, in isolation, except possibly for intimal arteritis, is diagnostic of the rejection process. A combination of the lesions along with scores above some threshold value is needed to make a specific diagnosis. It is important to be thoroughly familiar with all these components of the Banff classification in order to reliably and precisely apply it in clinical or research settings[9]. Some important diagnostic lesions are illustrated in Figures 2-4.

TIMELINE OF THE EVOLUTIONARY CHANGES IN THE BANFF CLASSIFICATION

The year 2021 marked the 30th anniversary of the beginning of the Banff classification process for standardized reporting of renal allograft pathological lesions. However, XVth biennial Banff meeting that was to be held that year was postponed and held in 2022 due to the coronavirus disease 2019 situation[6]. It is befitting to review the evolution of the Banff classification, its strengths and limitations, future prospects, and opportunities. It will be more convenient if we divide the evolution of the Banff classification into three decade-wise eras, as below.

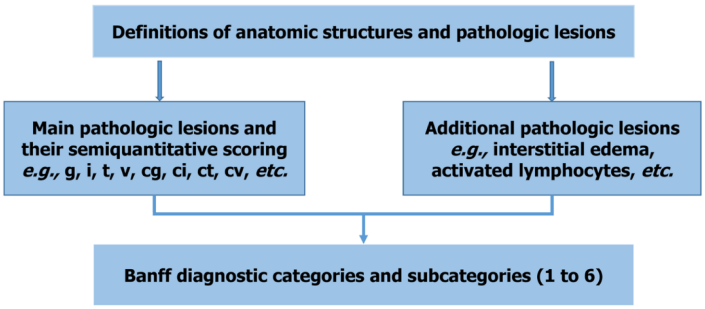
FIRST DECADE: DEVELOPMENT AND RECONCILIATION

The first decade may be called the decade of development and reconciliation/integration of the Banff classification, the latter with a rival classification developed in the United States called the Collaborative Clinical Trials in Transplantation (CCTT) modification of the classification[17]. This merger was the most significant achievement during the first decade as it paved the way for a single uniformly agreed-upon international classification for renal allograft pathology[6]. Three main and full papers on the classification were published during this decade, two of which became popular, the first was published in 1993 and the second in 1999. During this decade, the main focus of classification schema was on the cellular part of the rejection[18-20]. In fact, this category was named acute rejection without further qualification. Later on, it was changed to acute/active cellular and still later, acute/active T-cell mediated rejection (TCMR). The role of antibodies

Table 2 Banff reporting standardization template according to the Banff 2019 meeting

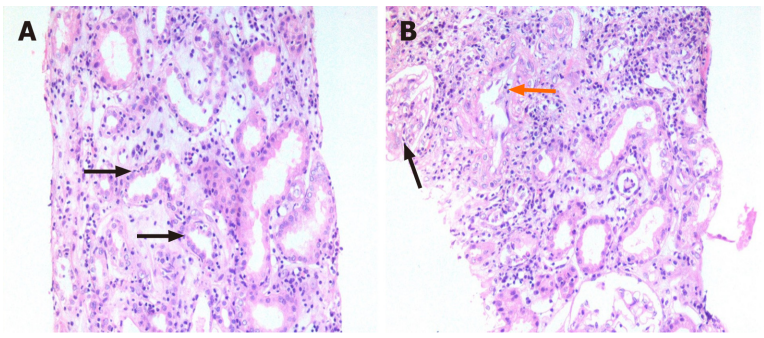
Components of the allograft	Acute lesions	Scoring as 0, 1, 2, 3	Chronic lesions	Scoring as 0, 1, 2, 3	Acute & chronic lesions	Scoring as 0, 1, 2, 3
Glomeruli	g	-	cg	-		
Interstitium	i	-	ci	-	ti, i-IFTA	-
Tubules	t	-	ct	-	t-IFTA	-
Vessels	v	-	cv	-		
Peritubular capillaries	ptc	-	ptcml	-		
C4d	C4d	-				

C4d: Linear staining in peritubular capillaries or medullary vasa recta either by immunofluorescence on frozen sections of fresh frozen tissue or immunohistochemistry on formalin-fixed, paraffin-embedded tissue; cg: Chronic glomerulopathy (transplant glomerulopathy); ci: Interstitial fibrosis involving the cortex; ct: Tubular atrophy in the cortex; cv: Arterial intimal fibrosis (fibrointimal thickening); g: Glomerulitis; i: Inflammation in the non-scarred cortex; i-IFTA: Inflammation in the scarred cortex; ptc: Peritubular capillaritis; ptcml: Peritubular capillary basement membrane multilayering (requires EM for detection); t: Tubulitis in cortical tubules within the non-scarred cortex; ti: Total cortical inflammation, including scarred and non-scarred cortex; t-IFTA: Tubulitis in mildly to moderately atrophic tubules within the scarred cortex; v: Arteritis (intimal to transmural arteritis).



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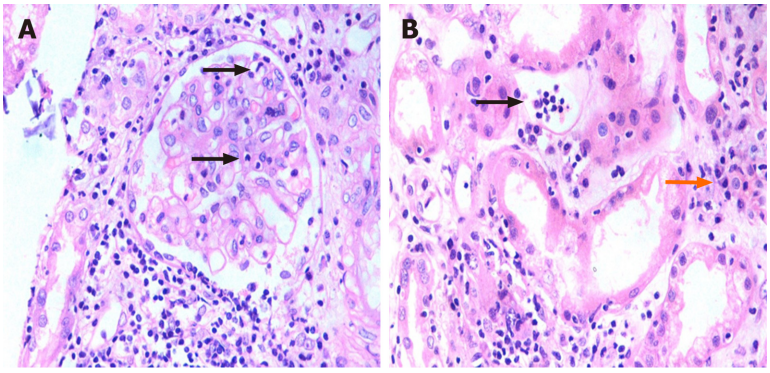
Figure 1 Basic components and construct of the Banff classification system. The content of the Banff classification can be cataloged into definitions, pathologic lesions, their semi-quantitative scoring, and a combination of these lesions to construct the diagnostic categories.



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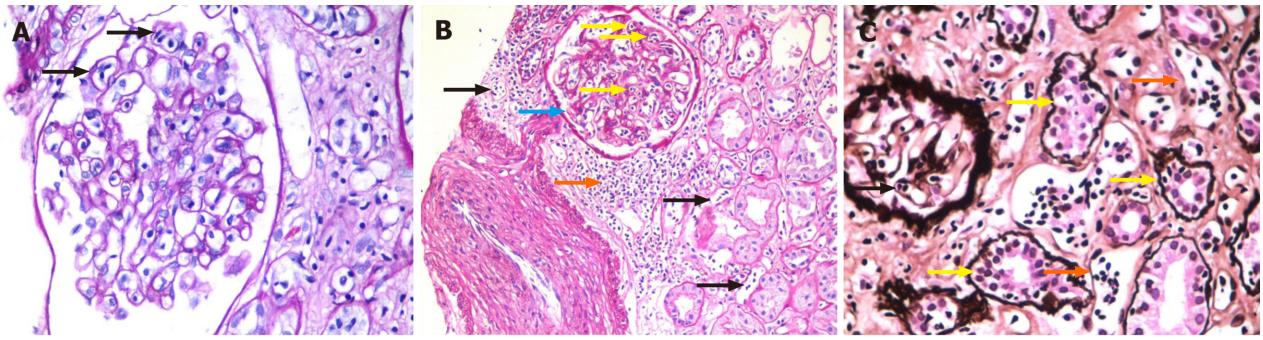
Figure 2 Representative acute Banff diagnostic lesions for rejection and their scores. A: There is diffuse interstitial inflammation (i3) along with interstitial edema. The later lesion, although important when present, is not formally included in the Banff classification system. Foci of mild tubulitis (t1) are also seen (arrows). These are better visualized on Period acid-Schiff stain [hematoxylin and eosin (H&E), × 200]; B: This field shows glomerulitis (g1) (black arrow) and intimal arteritis (v1) (orange arrow) in addition to i3 and interstitial edema. Such findings raise the suspicion of mixed antibody-mediated and T cell-mediated rejection (H&E, × 200).

beyond the immediate post-transplant period was not formally recognized during this decade, although studies were going on this subject. The workup of renal allograft biopsy was based on morphologic examination alone. The adequacy criteria for renal allograft biopsy were made more stringent in Banff 1997 classification but were still limited to the morphological study of the biopsy material.



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Figure 3 Acute Banff diagnostic lesions of microvascular inflammation. A: There is segmental glomerulitis (g1) (arrows) along with diffuse interstitial inflammation (i3) in the background [hematoxylin and eosin (H&E), × 400]; B: Peritubular capillaritis (ptc) score ptc 2 (black arrow). ptc is one of the key lesions of antibody-mediated rejection. Patchy interstitial edema, and inflammation with a few plasma cells (orange arrows) are seen in the background (H&E, × 400).



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Figure 4 Diagnostic lesions. A: Acute Banff lesion of glomerulitis. There is segmental glomerulitis (g1) (arrows) characterized by mononuclear inflammatory cell infiltration and endothelial cell enlargement resulting in partial to complete occlusion of capillary lumena. Glomerulitis is one of the key lesions of antibody-mediated rejection. (Period acid-Schiff, ×400); B Morphologic features of mixed antibody-mediated and T cell-mediated rejection with both acute and chronic lesions. There is almost global glomerulitis (yellow arrows) with segmental foci of glomerular basement membrane thickening (blue arrows) suggestive of early transplant glomerulopathy along with diffuse interstitial inflammation (i3) (orange arrows) and peritubular capillaritis (black arrows). An artery included shows severe intimal fibrous thickening (neo-intima formation) without duplication of elastica, (Period acid-Schiff, × 200); C: Mixed acute and chronic Banff diagnostic lesions of rejection. There is segmental glomerulitis (black arrow), peritubular capillaritis (orange arrows), and foci of tubulitis in mildly to moderately atrophic tubules within the scarred cortex (yellow arrows) (Jones Methenamine Silver, × 400).

SECOND DECADE: ANTIBODY-MEDIATED REJECTION

During this decade, the focus of the Banff classification was shifted to the development of the pathologic criteria and their refinement for a conclusive diagnosis of antibody-mediated rejection (AMR) beyond the immediate post-transplant period. Starting from the 2001 Banff meeting, the attention of the transplant community was shifted to the increasing recognition of the role of alloantibodies in causing allograft rejection. During the 2001 Banff meeting, pathologic criteria were formulated for the first time for a definitive diagnosis of AMR in the acute setting, *i.e.* beyond the immediate post-transplant period[12]. These included not only the morphologic criteria but also immunopathologic and serologic criteria. This led to the evolution of the Banff classification to a multidisciplinary schema. The adequacy of tissue was expanded to a portion of tissue for C4d staining and an optional tissue sample for EM study. In the 2005 Banff meeting, criteria for the diagnosis of chronic active AMR were formulated, thus recognizing the full spectrum of antibody-mediated injury[21]. With the widespread application of these criteria in clinical practice, it became obvious that not all forms of AMR are C4d positive. Hence, the need arose for a subtype of AMR to be introduced in the Banff classification, *i.e.* C4d-negative AMR, which was introduced in the Banff 2009 meeting[22]. From Banff 2001 to Banff 2011 meetings, only diffuse C4d staining (C4d3), involving more than 50% of PTCs, was recognized as fulfilling the immunopathologic criterion for AMR[23]. In the Banff 2013 meeting, focal (c4d2: 10%-50%) staining of PTCs for C4d was also accepted, as it was also associated with donor-specific antibodies (DSAs) and reduced allograft survival[14]. BWGs were also created during the 2009 Banff meeting for addressing the problematic areas of the Banff classification for evidence-based investigations and solutions [22].

THIRD DECADE: REFINEMENTS AND INTEGRATIONS

During this decade, further clarifications and refinements were made in the diagnostic criteria and classification of chronic active AMR and TCMR[14,24-27]. The thresholds of some of the lesions were re-defined[14]. Integrations of ancillary techniques of IHC, EM, and molecular studies were recommended for an accurate diagnosis and classification of rejection processes. Digital pathology (DP) and artificial intelligence (AI) tools were explored for their possible role in predicting, diagnosing, and prognosticating kidney allograft pathology[25,26].

Following a brief overview of the decade-wise evolution of the overall classification schema, it is now appropriate to discuss the evolutionary changes of the Banff classification according to individual diagnostic categories in some detail. The names of categories have changed many times. Here, we use the most representative name of the category, which may not be necessarily the same as in the latest Banff classification, the 2019 Banff classification.

Banff category 1: Normal biopsy or nonspecific changes

This is the first category of the original Banff construct and is still so. The definition of this category is self-explanatory. In fact, this category is a diagnosis of exclusion, which implies that not only the graft parenchyma should be free of inflammatory cell infiltration, but it should also show no features of acute tubular injury (ATI) or acute tubular necrosis. Taken at its face value, this category appears superfluous. The rationale behind using and retaining this category seems to be the unavoidable consequence of an overenthusiastic biopsy approach. In some centers, allograft biopsies are performed too quickly or for transient rises in serum creatinine, such that the morphological lesions are either not fully expressed or there is a cause of allograft dysfunction outside of the graft parenchyma. In some instances, sampling error may account for the normal appearances of the sampled cores, especially when the rise in serum creatinine is of an appreciable degree. This is the only category of the Banff classification that cannot be diagnosed in concurrence with any other category.

No significant changes have occurred in this category except for a name change from the "Normal" in the 1993 report through to the 2013 paper to the "Normal biopsy or nonspecific changes" in the 2015 Banff report[10,23,24]. The prevalence of this category in renal allograft biopsies should ideally be low.

Banff category 2: Antibody-mediated changes

Although the founders of the Banff classification recognized the importance of alloantibodies in causing allograft injury right from the beginning of the development of the classification and category 2 was devoted to alloantibodies in the original classification, their full scope was not fully known at that time[28-31]. The role of antibodies was initially thought to be limited only to the immediate post-transplant period[10,11]. With increasing experience and the resulting accumulating evidence, this notion proved to be incorrect and this category has undergone dramatic changes including its nomenclature during the three decades of the evolution of the Banff classification (Figure 5A).

A number of factors contributed to this increased focus on AMR: (1) Increased recognition of the condition as a result of identification of a highly sensitive and equally specific biomarker of AMR, *i.e.* C4d and subsequently some relatively specific pathological features of AMR; (2) A better understanding of the roles and techniques for the detection of anti-donor antibodies; (3) Increasing numbers of re-transplants, *i.e.* second or third transplants; and (4) Increased rates of transplantations across ABO and other immunologic barriers as a result of a shortage of donor organs.

Before discussing the changes in the Banff category of AMR at length, it seems prudent to discuss briefly the pathophysiology of AMR. The main target of AMR is the endothelial cell lining the vascular system, most notably those lining the microcirculation (glomeruli and PTCs in the kidney), but larger arteries may also be targeted. This is comprehensible as the alloantibodies are found in the bloodstream and they first encounter the endothelium of the blood vessels and interact with it. The intensity and nature of the subsequent pathological lesions are variable and depend on many factors including antibody type[32].

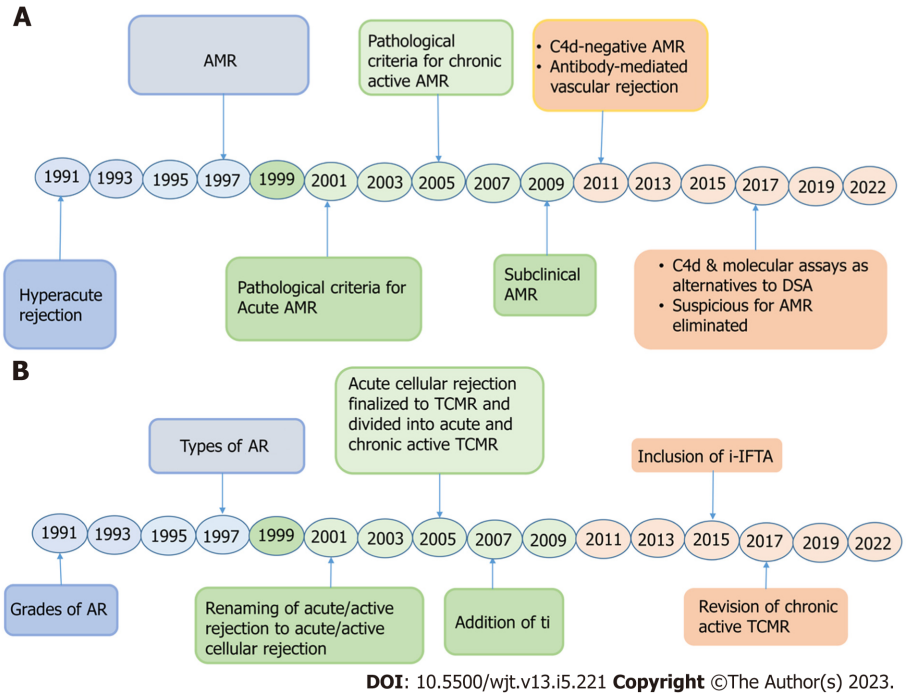
The terminology of the category has changed many times, as depicted in Table 3. These changes were necessitated by changing knowledge and accumulating evidence of the role of antibodies in causing allograft injury. In the Banff 93 classification, the category was named hyperacute rejection (HAR). The reason behind this was that, at that time, antibodies were thought to be responsible for causing only this particular type of rejection. In the Banff 97 classification, the category was renamed "antibody-mediated rejection" and divided on clinical grounds into two categories depending on their presentation, as shown in Table 3. HAR and accelerated acute rejections have fortunately become exceedingly rare nowadays. As a result, the Banff classification dropped these terms from the subsequent revised versions. In contrast to cellular rejection, antibodies themselves are not easily visualized in the kidney allograft biopsy tissue. Hence, identification of their role beyond the immediate post-transplant period required the discovery and use of some biomarkers of antibody action. The discovery of C4d in 1993 was such a transformative marker, which prompted research into the role of alloantibodies in allograft rejection[33-39]. In the Banff 2001 meeting, the role of antibodies was recognized in acute settings also, *i.e.* beyond the immediate post-transplant period[12]. In this meeting, for the first time, the pathological criteria were developed for the diagnosis of acute AMR and types of AMR were described. This marked the debut of not only the ancillary technique of C4d staining but also incorporated serology in the Banff classification system, making it a multidisciplinary classification[12]. In the Banff 2005 meeting, diagnostic criteria were developed for chronic AMR including the lesions of transplant glomerulopathy (cg), PTC basement membrane multilayering (ptcml), and transplant arteriopathy (cv)[21]. From the Banff 2007 meeting onwards, the name of this category was changed to antibody-mediated changes, instead of AMR, as it had been shown in experimental studies that not all antibodies cause rejection but some of the antibodies may be involved in accommodation and the full spectrum of antibody actions and outcome on graft tissue was being explored[40,41]. Thus, the present terminology reflects the broad spectrum of actions that can be mediated by antibodies in the graft, many of which still remain to be explored.

Table 3 Main changes in the nomenclature and classification of antibody-mediated rejection in the Banff classification over three decades of evolution (1991 to 2019)

Meeting reports, year	Category 2: Antibody-mediated rejection[1]
Banff, 1993	Hyperacute rejection
Banff, 1997	AMR[3]
	Hyperacute
	Accelerated acute[3]
Banff, 1997 update (2001)	Diagnostic criteria for acute antibody-mediated rejection were developed. Three types were described as: (1) Types I: ATN-like[3]; (2) Types II: Capillary[3]; and (3) Type III: Arterial[3]
Banff, 2005	Diagnostic criteria for chronic antibody-mediated rejection were developed
Banff, 2007	Antibody-mediated changes[2,3]
	C4d deposition without rejection[3]
	Acute antibody-mediated rejection
	Chronic active[3] antibody-mediated rejection
Banff, 2013	Antibody-mediated changes
	Acute/active antibody-mediated rejection
	Chronic active antibody-mediated rejection
	C4d-negative antibody[3]-mediated rejection
Banff, 2015	Antibody-mediated changes
	Acute/active[3] antibody-mediated rejection
	Chronic active antibody-mediated rejection
	C4d staining without evidence of rejection
	Transplant arteriopathy may be seen in chronic AMR
Banff, 2017	Antibody-mediated changes
	Active[3] AMR
	Chronic active AMR
	C4d staining without evidence of rejection
	3 criteria for AMR diagnosis remain but C4d can substitute for DSA
	DSA testing still advised
	Suspicious for AMR eliminated
Banff, 2019	Category 2: Antibody-mediated changes
	Active AMR
	Chronic active AMR
	Chronic (inactive) AMR[3]
	C4d staining without evidence of rejection

[1]May coincide with categories 3, 4 and 5 and 6;
[2]With the identification of c4d positivity without rejection, the category name was changed from rejection to changes);
[3]Changes in the nomenclature or criteria. AMR: Antibody-mediated rejection; ATN: Acute tubular necrosis; DSA: Donor-specific antibody.

With extensive use of c4d in clinical practice, particularly in the protocol biopsies, it was observed that a small number of graft biopsies show c4d positivity in the absence of morphological or clinical features of acute or chronic AMR. Thus, a new subcategory of "C4d deposition without morphologic evidence of active rejection" was added to the Banff classification in 2007[40,41]. Two new lesions of C4d and PTC were also introduced and presented at the 2007 Banff meeting for validation and future incorporation[42].



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Figure 5 Diagram depicting the main changes with the timeline. A: In the category of antibody-mediated rejection (AMR); B: In the category of T cell-mediated rejection (TCMR). DSA: Donor-specific antibody; i-IFTA: Inflammation in the scarred cortex.

From Banff 2001 to Banff 2011, only diffuse C4d staining (c4d3) on IF, involving more than 50% of PTCs, was recognized as fulfilling the immunopathologic requirement for AMR, which was amended in the Banff 2013 meeting to accept focal (c4d2: Staining 10%-50% of PTCs) PTC staining as it was shown to correlate with DSA and decreased allograft survival[14].

The second major modification in the AMR category took place in the Banff 2013 meeting[13]. Any degree of v (v > 0) was incorporated in the morphologic criteria for active AMR in contrast to the previous requirement of v3 in light of new studies[43,44]. The absolute condition (criterion 2) for PTC C4d staining for the definite diagnosis of active and chronic active AMR, was supplanted by the criterion of "Evidence of the recent/current interaction of alloantibody with the microvascular endothelium", the latter including C4d but alternatively a minimum of moderate microvascular inflammation (g + ptc ≥ 2) or amplified expression of validated gene transcripts in the biopsy material suggestive of endothelial injury[45-50]. This signaled the first incorporation of molecular diagnostics into the Banff classification[13]. With these additional criteria, many studies showed that a substantial number of AMR cases were C4d negative[51,52]. Thus, the subcategory of C4d-negative AMR was included in the classification at this meeting. The significance of this change can be judged by the fact that this inclusion was incorporated in the title of the paper of the 2013 Banff meeting[13]. In addition, at the Banff 2013 meeting, the minimum thresholds for glomerulitis score (g1) and chronic glomerulopathy by LM (cg1) were revisited based on results of BWG data showing better interobserver reproducibility with the revised criteria. The potential role of EM in the diagnostic evaluation of kidney allograft biopsies was also emphasized, with the inclusion of precise criteria for ptcml to augment the specificity of this pattern for chronic AMR and the inclusion of a new subtype of cg by EM exclusively (cg1a)[53,54].

In the Banff 2019 meeting, a subtype of chronic AMR, *i.e.* chronic inactive AMR was also introduced, as it could be diagnosed on kidney allograft biopsies[26]. Of note, there is no category of chronic (inactive) in TCMR. There is no provision for borderline changes (BCs) in the AMR category, but diagnostic thresholds do apply. The diagnosis of "suspicious for AMR (sAMR)" was finally removed from the Banff 2017 classification.

In summary, considerable progress has been made in the category of AMR. Molecular studies have been officially incorporated in the Banff classification for diagnosis of this category only. The absolute requirement for C4d its diagnosis has been eliminated. The requirement of DSA is also not absolute. sAMR has been removed from the classification.

Banff category 3: BCs

The original Banff classification recognized a category of BCs in reporting the renal allograft pathological lesions and the category is still there even after 30 years of refinements and evolution of the classification. This category encompasses only the tubulointerstitial type of rejection and is used when there is mild (i1) to severe (i3) interstitial inflammation but the tubulitis is of mild degree only (t1) or vice versa and no arteritis is present (v0). The true clinical significance of this lesion is still contentious and is largely determined by the clinical context of the case[55-62]. Some of the factors that may determine its clinical relevance include the source of the donor organ, time post-transplant, and the indication and timing of kidney allograft biopsies. Most of the studies on this category have been carried out in deceased donor transplantation programs[56-62]. Only a few studies are available on the clinical relevance of this finding in the live-related renal transplant setting[63,64].

The criteria for the diagnosis of BCs have changed little over time and essentially consist of any combination of interstitial inflammation (i) and tubulitis (t) scores below the threshold level required for the diagnosis of rejection, *i.e.* "i2, t2". The original criteria for the borderline category were developed at the Banff 1991 meeting, describing it as a "very mild" form of acute rejection lacking intimal arteritis (v0) and having only mild to moderate patchy mononuclear interstitial inflammatory cell infiltration (i1 or i2) with foci of mild tubulitis (t1; 1 to 4 mononuclear cells per tubular cross-section). In this initial classification, "no treatment" was suggested[10]. In 2005, the Banff group suggested the expansion of the "BC" category to include lesions with minimal interstitial inflammatory cell infiltration (i0) to i3 with t0 or t1 or t2, t3 with i0, i1[21]. This was further confirmed in the Banff 2007 meeting[42]. However, the minimum threshold of BC was restored to "i1, t1" in the Banff 2019 meeting, as longitudinal studies by Nankivell *et al*[65] showed no effect of isolated "t" on allograft survival.

The reported frequency of this category varies widely and ranges from 46% to 74 % on dysfunctional kidney allograft biopsies performed at different time points after transplantation[66,67]. This category is also most problematic from the point of view of the treatment. In reality, this category does not represent a true pathophysiological phenomenon. It represents a heterogeneous category of lesions encompassing pathophysiological processes with minimal, nonspecific, insignificant inflammation to clinically important TCMR, capable of immune-mediated allograft injury resulting in poor immunological, functional, and histological outcomes if not treated[55-58]. This category has been created primarily because of varying clinical criteria and the timing of kidney allograft biopsies. In an ideal world, an allograft biopsy should be categorized as rejection or no rejection, but in practice, it is not always so clear-cut. As the biological process of rejection is a gradual and patchy process, it takes time to develop full-blown features of rejection. If a biopsy is performed very early during the development of rejection, the pathological lesions will not have reached the threshold of diagnosis of rejection, and will inevitably be classified as a BC category. It is hoped that in near future this category will be eliminated with the incorporation of better diagnostic markers, particularly, molecular markers.

Banff category 4: Acute rejection (acute/active TCMR)

The spectrum of TCMR, as it is now officially called, was defined from the origin of the classification as the Banff diagnostic category 4 and now includes acute TCMR, grades IA, IB, IIA, IIB, and III, and chronic active TCMR (CA TCMR), grades IA, IB and II. There are no subgrades of grade II and no grade III in CA TCMR[26]. In addition, there is no subtype of chronic (inactive) in the category of TCMR, as is true for AMR. Category 4 is separated from category 3 by a threshold of i2, t2 and any v. Banff diagnostic categories 3 and 4 are mutually exclusive but can be diagnosed concurrently with other lesions from categories 2, 5, and 6.

In the previous iterations of the Banff schema, the main emphasis was on the diagnosis and classification of acute rejection, which essentially implied TCMR. This focus on cellular rejection dominated the transplant pathology field and subdued the recognition and characterization of AMR for quite some time during the earlier period of the Banff classification. On the other contrary, the category of cellular rejection lagged behind AMR in undergoing modifications till the very recent past. The most important changes in this category took place during the 1997 Banff meeting (Table 4). Thereafter, this category remained fairly stable and immune to changes except for minor nomenclature changes. More recent Banff updates have made some modifications to the morphological criteria and subdivision of this category (Figure 5B).

As alluded to earlier, the main emphasis of the first Banff classification was on the accurate diagnosis and classification of acute rejection, which essentially included acute cellular rejection. As this type of rejection is characterized by the infiltration of mononuclear cells into the allograft parenchyma, its diagnosis was relatively easy and obvious in most cases. The main targets of cellular rejection are the tubules, interstitium, and larger blood vessels. Microcirculation inflammation is rarely observed in this type of rejection[10,11,68-75]. The Banff classification introduced for the first time a minimum threshold (*i.e.* i2, t2) for the definitive diagnosis of acute cellular rejection of tubulointerstitial type or type I rejection. This separated it from the category of BCs in the cellular alloimmune lesions. There is no BC category for vascular or type II and type III rejections and the presence of even one lymphocyte in the intima is sufficient to diagnose vascular rejection. Early Banff classifications also emphasized the importance of the topographic location of the inflammatory cell infiltrate in the biopsy[10,11].

The nomenclature of this category has changed from acute rejection to acute cellular rejection to TCMR over the years reciprocating the changes in category 2 of AMR, as shown in Table 4 and Figure 3. With regard to the classification of TCMR, the first Banff classification divided acute rejection into three "grades" based on the increasing severity of the allograft damage, as shown in Table 4. These were: Grade I (mild), grade II (moderate), and grade III (severe) (Table 4). This classification lumped together both the tubulointerstitial and vascular rejections in grade II. It may be noted that this subdivision was based purely on a morphological or pathological basis with little consideration of the underlying pathogenetic basis of rejection. As mentioned earlier, the first main change in this category was effected in the Banff 97 meeting, when pathologists using the original Banff 93 classification and its CCTT modification got together and merged the two classifications to develop a unified and international consensus-based Banff 97 classification with substantial input from the CCTT classification, which stressed the pathogenetic foundation for the categorization of cellular rejection [4,5,10,11]. The Banff 97 classification divided acute/active rejection into "types" and subtypes rather than grades (Table 4). The main modifications in the Banff 97 classification included the segregation of type I (tubulointerstitial) rejection from vascular (type II) rejection. Type III rejection was categorized separately as in the Banff 93 classification (Table 4). This merger signified the adaptability of the Banff group to incorporate the observations of pathologists using CCTT modification and also embrace the emerging evidence from newer investigations showing that vasculitis per se has significant consequences for the response to treatment and/or graft survival[35,36].

Table 4 Main changes in the nomenclature and classification of T cell-mediated rejection in the Banff classification over three decades of evolution (1991 to 2019)

Meeting reports, year	Category 4: T cell-mediated rejection[1]
Banff, 1993	Acute rejection, grades I, II, III
Banff, 1997	Acute/ active cellular rejection
	Types[2] I A/B, II A/B, III
Banff, 1997 update (2001)	Acute/ active cellular rejection
	Types I A/B, II A/B, III
Banff, 2005	TCMR[2]
	Acute, types[2] I A/B, II A/B, III
	Chronic active[2] (includes only transplant arteriopathy)
Banff, 2007	TCMR
	Acute
	Chronic active (includes only transplant arteriopathy)
Banff, 2013	TCMR
	Acute
	Chronic active (includes only transplant arteriopathy)
Banff, 2015	TCMR
	Acute
	Chronic active TCMR may have tubulointerstitial changes[2]
Banff, 2017	TCMR
	Acute
	Chronic active TCMR grades I A/B and II defined
Banff, 2019	i-IF/TA and t-IF/TA included in criteria[2] (inflammation and tubulitis in areas of scarring)
	In chronic active TCMR with i >1, diagnosis to be combined chronic active and acute TCMR[2]

[1]May coincide with categories 3, 4 and 5 and 6;
[2]Changes in the nomenclature or criteria. i-IFTA: Inflammation in the scarred cortex; TCMR: T cell mediated rejection; t-IFTA: Tubulitis in mildly to moderately atrophic tubules within the scarred cortex.

In the Banff 97-update published in 2003 (from the Banff 2001 meeting), with profound and far-reaching changes in the category of AMR, the category of acute/active rejection was rechristened as acute/active cellular rejection (ACR), to underscore its distinction from AMR. Its types and subtypes, however, remained unchanged from the Banff 97 classification. The name of the category was again changed to TCMR in the Banff 2005 update (Table 4). On this occasion, it was further categorized into acute TCMR, which now encompassed all the subtypes of ACR of the Banff 97-update, and CA TCMR. The latter was diagnosed by the presence of chronic allograft arteriopathy only till the 2017 Banff meeting, characterized by new-onset arterial fibrointimal thickening with mononuclear cell infiltration in fibrosis, and the creation of neo-intima. Compared to previous iterations of the Banff classification, the Banff 2007 classification added a new "i" lesion score, labeled as "ti" (total interstitial inflammation score) to the schema[34,76-81]. Not much was changed in the criteria for diagnosis or classification of cellular rejection during the Banff 2009, Banff 2011, and Banff 2013 meetings. In the Banff meeting of 2015, it was realized and acknowledged that CA TCMR may manifest itself with tubulointerstitial inflammation in the form of inflammation in areas of scarred cortex (i-IFTA) in addition to arterial lesions[24]. However, detailed criteria and formal inclusion of CA TCMR were not affected till the 2017 meeting[25]. In the 2019 meeting, tubulitis in mildly to moderately atrophic tubules within the scarred cortex (t-IFTA) was also added as the diagnostic criterion for CA TCMR in addition to i-IFTA and ti scores. Thus, CA TCMR was divided into two types, in contrast to three types in acute TCMR. These types were: Types IA and IB and type II. A provision was also made for the diagnosis of borderline CA TCMR if the diagnostic criteria of CA TCMR types IA and IB were not fulfilled[26]. Banff 2019 also allows concurrent diagnosis of acute and CA TCMR, especially in the presence of intimal arteritis in association with acute TCMR types IA and IB[6,26].

It is obvious from the above deliberations that the mainstay for the diagnosis and classification of cellular rejection has remained and is still so the LM evaluation of allograft biopsy material with little help from the ancillary techniques of IHC or EM. More recently, molecular markers have shown promising results for a conclusive diagnosis of acute cellular

rejection in single-center studies[82-84]. These need to be validated in large, multicenter trials and the methodology needs to be standardized before they can be used widely in clinical practice. These represent the current challenges for the Banff classification system. The molecular information may be integrated with the histomorphological findings in the Banff classification in the future to improve the accuracy of diagnosis and classification of rejection, particularly borderline and CA TCMR cases[85-93].

Banff category 5: Interstitial fibrosis and tubular atrophy, no evidence of any specific etiology

This category of Banff classification of kidney allograft pathology was created to diagnose, classify, and grade (or stage) chronic fibrosing changes of kidney allografts resulting from a variety of causes[94]. Historically, many important changes took place in this category over the past three decades of the evolution of the Banff classification process. In the Banff 2019 meeting, this category has been replaced by polyomavirus nephropathy[26]. The rationale behind this change is that this category seems to be redundant in the absence of a plausible cause. The Banff schema stresses the need to determine the etiology of chronic changes whenever possible[21]. Moreover, chronic subtypes have been added to both types of rejection over the last two decades of evolution.

It seems appropriate to briefly summarize the evolution of the nomenclature and classification of chronic sclerosing lesions in the Banff schema, which are reflective of a continued and improved understanding of the pathophysiology of these lesions (Table 5). During the pre-Banff era, the term "chronic rejection" was utilized for all forms of chronic allograft dysfunction. This approach was an oversimplification, in that chronic changes in the allograft parenchyma are caused not only by alloimmune factors but also by non-immune factors and a distinction among these is important for tailored treatment. The Banff system put forward the nomenclature of "chronic allograft nephropathy (CAN)" in 1991 as a non-committal alternative to the then prevalent and confusing designation of "chronic rejection". The Banff 93 schema categorized CAN into three grades of increasing severity based on the degree of interstitial fibrosis and tubular atrophy (IFTA)[10]. No subdivision of the CAN grades was made and all etiologies of chronic changes were combined together in this unified category. In addition, many histomorphological patterns of, for example, chronic AMR, were not discovered at that time. In the Banff 1995 meeting, the chronic allograft damage index was merged with the CAN group to grade the severity of chronic changes. However, no subdivision of CAN was made in this update of the classification. In the Banff 97 meeting, an effort was made toward subclassifying chronic changes in the allograft and identifying and documenting the changes caused by the rejection processes. A subclassification of each of the grades of chronic changes into "a" and "b" categories was attempted depending on the absence or presence of obvious features associated with "chronic rejection", respectively. The 3-tier grading of the CAN entity remained the same as in previous classifications[11]. No modifications in the terminology or grading of CAN were attempted in the 97-update classification (Banff 2001 meeting) or the Banff 2003 meeting reports[12].

A significant modification in the category of chronic sclerosing changes was effected in the Banff 2005 meeting when the terminology of CAN was abolished and substituted by the term "interstitial fibrosis/tubular atrophy (IFTA)", with no evidence of specific etiology[21]. The etiologic groups of "a" subcategory of CAN in the previous classifications were relocated to the "other" category, while the chronic allo-immune causes were moved to the respective categories of AMR and TCMR as chronic active or chronic (inactive) types. Thus, category 5 in the Banff 2005 report and all succeeding updates (till 2019), included only those forms of chronic changes for which no specific etiological findings were found on the biopsy (Table 5). In the 2019 Banff classification, the category of IFTA has been eliminated and replaced by polyomavirus nephropathy, as shown in Table 5.

It is worth highlighting here that category 5 of the Banff classification can co-exist with any other types of renal allograft pathology, except category 1, which is normal. It is important to record and report both the acute and chronic pathological changes on the biopsies to guide therapy and determine the prognosis.

In summary, the nomenclature, categorization, and subcategorization of chronic changes have undergone substantial alterations over the past three decades of the Banff consensus classification. Of late, the focus was on identifying the early specific features relevant to causes of chronic allograft damage, so that their progression may be halted with intervention. This was somewhat facilitated by the ancillary techniques of IHC and EM. In the latest published 2019 Banff meeting report, this category has been eliminated altogether.

IMPLICATIONS OF ALLOGRAFT BIOPSY FOR CLINICIANS AND OTHER TRANSPLANT CARE TEAM MEMBERS

Renal allograft biopsy is a valuable diagnostic and prognostic tool in the hands of clinicians for evaluating the structural and functional status of the kidney allograft. It can provide important information about the underlying cause of graft dysfunction or rejection. Studies have shown that renal allograft biopsies change the clinical diagnosis in an average of 36% (24%-47%) of cases and treatment in 59% of cases. However, because only a tiny amount of kidney tissue is obtained during the biopsy, several limitations and shortcomings exist in the extent to which renal allograft biopsies can prove useful. A close liaison between the clinicians and nephropathology laboratory will go a long way in overcoming many of these shortcomings[13]. According to studies, the sensitivity of diagnosis of rejection is 90% with one core of tissue and it increases to 99% when two cores are obtained[95-102]. Apart from the above-mentioned inherent sampling error, it is well known that there can be interobserver variability among nephropathologists in interpreting renal allograft biopsies. It can arise due to variations in individual expertise, experience, training, and personal judgment. Many studies have documented the occurrence of interobserver variability in renal pathology, including the interpretation of allograft biopsies[103-112]. Sometimes, the biopsy has to be repeated in view of the above considerations, particularly when the

Table 5 Main changes in the nomenclature and classification of chronic changes of the allograft in the Banff classification over three decades of evolution (1991 to 2019)

Meeting reports, year	Category 5: Chronic allograft nephropathy
Banff, 1993	CAN, grades, I, II, III
Banff, 1997	CAN, grades, I, II, III, each divided into a and b subcategories[1]
Banff, 1997 update (2001)	CAN, grades, I, II, III, a and b
Banff, 2005	IFTA, of no specific etiology[1], grades I, II, III
Banff, 2007	IFTA of no specific etiology, grades I, II, III
Banff, 2013	IFTA of no specific etiology, grades I, II, III
Banff, 2015	IFTA of no specific etiology, grades I, II, III
Banff, 2017	IFTA of no specific etiology, grades I, II, III
Banff, 2019	Grading of polyoma viral nephropathy into classes 1, 2 and 3 (adequate sampling for scoring should include 2 cores with medulla)[1]

[1]Changes in the nomenclature or criteria. CAN: Chronic allograft nephropathy; IFTA: Interstitial fibrosis/tubular atrophy.

biopsy findings do not match the clinical picture. Furthermore, it is to be noted that the interobserver variability is not uniform for all the pathological lesions observed on renal allograft biopsies. For some lesions, the interobserver agreement is good, *e.g.*, ATI, interstitial fibrosis, and vascular changes are often more easily recognized and agreed upon by pathologists, leading to higher concordance in their interpretation. On the other hand, certain pathological patterns may be more challenging and prone to interobserver variability. For instance, the diagnosis and grading of TCMR, AMR, or BCs can sometimes be subjective and require expert judgment. These categories of pathological lesions often involve evaluating subtle changes in cellular infiltrates, glomerular lesions, or peritubular capillaritis, which can lead to differences in interpretation among pathologists.

It is important to recognize that considerable efforts have been made to minimize this variability. Quality control measures such as consensus conferences, panel discussions, and standardized reporting systems have been implemented to improve agreement among pathologists. For instance, the Banff classification system is widely used to grade and classify various pathological findings in renal allograft biopsies. This standardized approach helps in enhancing the reproducibility and consistency of pathological interpretations. In addition, advancements in ancillary diagnostic tests, morphometry, DP, and telepathology have allowed for remote consultation and collaboration among experts, further reducing the impact of interobserver variability[113,114].

While interobserver variability remains a consideration, renal allograft biopsy continues to be an essential diagnostic tool in clinical practice. It provides valuable information for guiding treatment decisions, assessing the severity of graft dysfunction, monitoring for rejection, and identifying other causes of kidney dysfunction. Collaborative efforts, standardized criteria, and ongoing advancements in the field aim to improve the reliability and credibility of renal allograft biopsy interpretations.

The turnaround time for reporting a renal allograft biopsy varies depending on several factors, including the urgency of the clinical situation, the workload of the pathology laboratory, and the complexity of the biopsy specimen. In general, the time frame for reporting renal allograft biopsies can range from a few hours to a few days. However, it's important to note that this is a general estimate and the actual turnaround time varies among different institutions and laboratories. In urgent or critical cases, such as suspected acute rejection or severe graft dysfunction, the pathology laboratory may prioritize the processing and reporting of the biopsy to expedite the diagnosis and facilitate prompt clinical decision-making. In such situations, the reporting time is typically shorter, ranging from a few hours (as short as 2-3 h) to 24-48 h, and is based on LM interpretation alone. In the authors' laboratory, LM findings of all renal allograft biopsies are reported within 4-8 h' time. For those cases, where there is no immediate need for urgent intervention, the reporting time is typically longer. This allows pathologists to carefully evaluate the biopsy specimen, conduct any necessary additional testing or staining such as IF, IHC, or EM, and provide a detailed and accurate report.

It is important to note that the clinical decision-making process based on renal allograft biopsy requires a multidisciplinary approach, involving nephrologists, transplant surgeons, pathologists, and other healthcare professionals. In particular, making a clinical decision based on renal allograft biopsy involves a comprehensive evaluation that integrates the pathological findings with clinical information and other relevant diagnostic tests such as imaging studies, drug levels, urine culture, and other laboratory tests. Collaboration and communication among the healthcare team members is the key to providing optimal patient care.

FUTURE DIRECTIONS

Although major advances have been made in understanding and categorizing kidney allograft pathology during the last

three decades, there are still many problematic areas that remain to be addressed. Issues of sampling errors, reproducibility, borderline category, subclinical rejection, global training and competence, and lack of sensitivity and specificity of morphological features are some such areas[115-118]. Many gaps remain from the diagnostic accuracy and precision point of view, *e.g.*, diagnostic thresholds and BCs. Focused research on molecular diagnostics, DP, AI, machine learning, and deep learning are some of the tools being actively investigated to address these problems[119-123]. Non-invasive serum and urinary molecular markers are also being actively sought for early and reliable identification of the rejection process right from the inception of the injury[124-127]. Integration of these with clinical, laboratory, and biopsy-based investigations may lead to a multimodal diagnostic algorithm for quick and accurate diagnosis for optimal treatment outcomes. Translation of the advancements in pathology diagnostics has yet not been realized into improved long-term graft outcomes.

CONCLUSION

The first 30 years of the Banff classification system have witnessed tremendous progress in understanding, streamlining, and classifying kidney allograft pathology, particularly the rejection. Essentially, the classification has changed from pathology-based to pathogenesis-based and has become clinician-friendly and treatment-friendly. However, many gaps remain from the diagnostic sensitivity point of view, *e.g.*, diagnostic thresholds and BCs. More sophisticated techniques and digital and computational approaches are being actively researched at present to further improve diagnostic accuracy and precision of the classification.

FOOTNOTES

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MINIREVIEWS

Sodium-glucose cotransporter-2 inhibitor use in kidney transplant recipients

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Abstract

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are novel oral hypoglycemic agents garnering much attention for their substantial benefits. These recent data have positioned SGLT2i at the forefront of diabetic chronic kidney disease (CKD) and heart failure management. SGLT2i use post-kidney transplant is an emerging area of research. Highlights from this mini review include the following: Empagliflozin is the most prescribed SGLT2i in kidney transplant recipients (KTRs), median time from transplant to initiation was 3 years (range: 0.88-9.6 years). Median baseline estimated glomerular filtration rate (eGFR) was 66.7 mL/min/1.73 m^2 (range: 50.4-75.8). Median glycohemoglobin (HgbA1c) at initiation was 7.7% (range: 6.9-9.3). SGLT2i were demonstrated to be effective short-term impacting HgbA1c, eGFR, hemoglobin/hematocrit, serum uric acid, and serum magnesium levels. They are shown to be safe in KTRs with low rates of infections, hypoglycemia, euglycemic diabetic ketoacidosis, and stable tacrolimus levels. More data is needed to demonstrate long-term outcomes. SGLT2i appear to be safe, effective medications for select KTRs. Our present literature, though limited, is founded on precedent robust research in CKD patients with diabetes. Concurrent research/utilization of SGLT2i is vital to not only identify long-term patient, graft and cardiovascular outcomes of these agents, but also to augment management in KTRs.

Key Words: Sodium glucose cotransporter-2; Sodium glucose cotransporter-2 inhibitor; Kidney transplantation; Diabetes; Post-transplant diabetes mellitus; New onset diabetes after transplant

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Core Tip: Multiple large trials have demonstrated sodium-glucose cotransporter-2 inhibitors (SGLT2i) associated kidney and cardiovascular benefits for chronic kidney disease patients with diabetes. Important considerations are critical to determine safety and efficacy of these medications after kidney transplantation. While evidence is limited, SGLT2i appear to be both safe and effective short-term. More robust research is needed to determine the long-term impacts of their use in kidney transplant recipients. Appropriate patient selection and monitoring are vital to clinical use and future research efforts of SGLT2i in kidney transplantation.

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INTRODUCTION

Sodium-glucose cotransporter-2 inhibitors (SGLT2i) or "gliflozins", are oral hypoglycemics that work by inducing glucosuria. They are derived from phlorizin, a glucosuric compound found in apple tree root bark. As described by van Bommel *et al*[1], there are 2 clinically significant sodium-glucose transporters found in humans: SGLT1 Low-affinity high-capacity transport in the distal convoluted tubule and SGLT1 high-affinity low-capacity transporter in proximal convoluted tubule. As noted by Salvatore *et al*[2] and Sawaf *et al*[3], SGLT2i reduces the glucose excretion threshold to 2.2 mmol/L (40 mg/dL) from 10 mmol/L (180 mg/dL).Consequently, they have been shown to reduce glycohemoglobin (HgbA1c) by 0.6%-0.9% with glomerular filtration rate (GFR) > 60 mL/min and 0.3%-0.4% with GFR 30-59 mL/min[1]. SGLT2i also block the sodium/glucose symport channel in the proximal convoluted tubule leading to osmotic diuresis and natriuresis[3]. This excess sodium excretion is thought to induce afferent vasoconstriction through glomerular feedback thereby reducing hyperfiltration[1].

Data on SGLT2i have demonstrated great promise for their use in chronic kidney disease (CKD) patients with diabetes. In a recent meta-analysis, Zelniker *et al*[4] synthesized the findings of multiple landmark trials (EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI). They showed that SGLT2i reduced the risk of renal disease progression by 45% [hazard ratio (HR) = 0.55, 95% confidence interval (CI): 0.48-0.64, $P < 0.0001$], and cardiovascular death or heart failure hospitalization by 23% (HR = 0.77, 95%CI: 0.71-0.84, $P < 0.0001$) in patients with and without atherosclerotic heart disease.

These renoprotective benefits have been observed in patients with, as well as without, diabetes. Heerspink *et al*[5], *via* dapagliflozin (DAPA)-CKD, showed that DAPA in CKD patients with or without diabetes reduced the risk of a composite outcome of estimated GFR (eGFR) decline of at least 50%, end stage kidney disease (ESKD), or death from renal/cardiovascular cause (HR = 0.56, 95%CI: 0.45-0.68, $P < 0.001$) with a number needed to treat of 19 (95%CI: 15-27).

As shown by adoption of SGLT2i as first line therapies for CKD patients with diabetes by the 2022 Kidney Disease Improving Global Outcomes guidelines by Rossing *et al*[6], evidence for these agents is promising. Favorable outcomes owing to SGLT2is have led the transplant community to investigate their broader application.

Many dependent diabetic kidney transplant recipients (KTR) appear to be likely beneficiaries of SGLT2i therapy. As described by Chewcharat *et al*[7], 40% of waitlisted patients have diabetes mellitus (DM) and 15%-30% of non-diabetic patients develop post-transplant DM (PTDM)[7]. PTDM is associated with high rates of graft loss, cardiovascular disease, infectious complications, and mortality[7]. Inherent risks of kidney transplantation *e.g.*, urinary tract infection, concern for drug interactions *i.e.*, immunosuppression, and acute kidney injury/CKD risk, have raised safety and efficacy concerns of SGLT2i.

In this mini review, we aim to summarize recent literature describing SGLT2i usage in KTRs to: (1) Provide guidance for clinical use; (2) identify current limitations; and (3) highlight future directions. We hope this mini review will act as a reference for clinicians and researchers alike to advance clinical/translational research and characterize SGLT2i's role in diabetes management after kidney transplantation.

SEARCH STRATEGY

We conducted literature searches in PubMed, Cochrane, Google Scholar from January 2019 to January 2023 and reference lists of relevant studies and reviews. Key words utilized in our search included the following: "SGLT2 inhibitors, SGLT2i, KTRs, type 2 diabetes mellitus, post-transplant diabetes mellitus."

We limited our search to studies with available full text and English language. In this mini review, we selected studies of SGLT2i use in type 2 DM (T2DM) and/or PTDM in KTRs that were either: (1) Prospective randomized control trials; (2) prospective case series; and/or (3) retrospective case series with comparison groups. We limited study inclusion to those occurring in the last 4 years to highlight recent research.

For our analysis of the following outcomes: HgbA1c, eGFR, weight, blood pressure, Immunosuppression drug interactions, adverse events, we pooled studies that reported these data together. As descriptions of cost, novel findings, and long-term outcomes were limited to one or a few studies, these were simply discussed in context of specific studies.

Nine studies met our search criteria: 1 randomized controlled trial, 2 prospective observational studies, and 5 retrospective analyses, of which 2 had comparison groups. All nine studies occurred in the last 4 years.

FINDINGS

In this sample, empagliflozin (n = 241) was the most prescribed SGLT2i followed by DAPA (n = 85) and canagliflozin (n = 74). The median time from transplant for initiating SGLT2i was 3 years (range: 0.88-9.6 years post-transplant). Median baseline eGFR was 66.7 mL/min/1.73 m^2 (range: 50.4-75.8). Median HgbA1c at initiation was 7.7% (range: 6.9-9.3). The following results were seen and are summarized in Table 1.

HgbA1c

HgbA1c generally improved with changes between 0.2%-1% in the reported studies. Notably, in the study by AlKindi *et al*[8], which included a cohort with a mean HgbA1c of 9.3% at initiation as well as excellent allograft function, HgbA1c decreased by 2.3% at 12 mo. As is described by Halden *et al*[9], more robust impacts on glycemic control were observed in those with higher HgbA1c and eGFR.

eGFR

eGFR was preserved in most studies over a period of 6-12 mo[8-13]. Lim *et al*[13] observed a 10% eGFR dip in 15.6% of their cohort with SGLT2i initiation, though eGFR did recover from this and stabilize. After month 5, there was no significant difference in eGFR between dippers and non-dippers. At last follow up (8 mo post-SGLT2i initiation), eGFR in the dippers (67.9 ± 13.9, n = 24) was comparable to that of the non-dippers [67.9 ± 13.9 mL/min/1.73 m^2 (n = 24) *vs* 69.8 ± 19.0 mL/min/1.73 m^2 (n = 106), P = 0.358].

Though specific data on long term eGFR are lacking, Lim *et al*[13] did report a significant reduction in terms of SCr doubling in the SGLT2i cohort *vs* non-SGLT2i users in both unadjusted (HR = 0.49, 95%CI: 0.29-0.85) , adjusted (across multiple models: Adjusted HR (aHR) = 0.37-0.41, 95%CI: 0.22-0.90, all P < 0.05) , and propensity-score matching (aHR = 0.45, 95%CI: 0.23-0.88, P = 0.019) at 72 mo of follow up.

Proteinuria

Proteinuria was not assessed in these studies. As proteinuria is a major risk factor for and driver of progressive CKD, this is certainly an area that needs further studying.

Weight

Weight decreased in 8 studies with a median weight decrease of 1.95 kg (range: 0.7-3.2 kg)[8-10,12,14].

Blood pressure

Blood pressure changes were reported in 4 studies, with mixed results[8,9,11,12]. The magnitude of these changes was on the order of 7-9 mmHg, which are likely clinically significant. This is reaffirmed by findings in the ADVANCE trial, whereby Heerspink *et al*[15] showed that randomization to perindopril-indapamide compared to placebo in CKD ≥ 3 patients with diabetes for 5 years prevented 12 cardiovascular events with reductions in systolic blood pressure on the order of 4.5 mmHg.

Immunosuppression drug interactions

Though data on drug interactions with immunosuppression were limited, four studies did not observe clinically nor statistically significantly differences in drug trough levels after SGLT2i initiation[9-12].

Adverse events

Urinary tract infections (UTI) were the most common adverse event observed across the various studies. When reported, these ranged from none observed up to 36%. 4 studies reported rates between 13%-15%[8-10,14].

Genital infections (GI) occurred but less commonly than UTI in KTRs with only a few GI occurring in studies where it was distinctly described[9,14,16].

Graft function remained stable throughout these studies despite high angiotensin converting enzyme inhibitors (ACEi)/aldosterone receptor blockers (ARB) utilization and the observed eGFR dip at the 4-6 wk mark[10,12,13].

Leg amputation was not observed in any of the studies described. Schwaiger *et al*[16] reported on this in their study with empagliflozin. As is aptly described by Heyward *et al*[17] in their systematic review and meta-analysis, the risk for lower extremity amputation for SGLT2i use in the non-transplant population has only been observed with canagliflozin.

In these small studies, no episodes of euglycemic diabetic ketoacidosis were reported. Song *et al*[14] noted a wide range of insulin dose reductions post-SGLT2i incorporation. Hypoglycemia was noted infrequently in these studies (n = 2 per Lemke *et al*[10]). This risk for hypoglycemia is highest for those with well controlled diabetes (HgbA1c < 8) as well as those on insulin and/or sulfonylurea-class medications, as was the case in the Lemke *et al*'s study[10].

Cost

Lemke *et al*[10] identified cost as the highest reported reason for SGLT2i discontinuation (35%, n = 6). Over time, SGLT2i have become more affordable. Aggarwal *et al*[18] recently described out-of-pocket expenses for SGLT2i, noting that for

Table 1 Summary of studies on sodium-glucose cotransporter-2 inhibitor use in kidney transplant recipients

Ref.	Type, location	Follow up	Treatment arms	Inclusion/exclusion criteria	Baseline eGFR (mL/min/1.73 m^2), HgbA1c (%)	Time from transplant	Result	Adverse events/treatment discontinuation	Comments
Lemke *et al*[10], 2022	Retrospective, United States	12 mo; 27 pts ≥ 12 mo	Cana (*n* = 12); Dapa (*n* = 3); Empa (*n* = 24)	T2DM or PTDM; SGLT2i; 4/2013 to 10/2020; care solely in health system	eGFR, median (IQR) 69 (54-76); HgbA1c Median (IQR) 8.4 (7.8-9.2)	Median (IQR) 28 mo (16-60)	HbA1c↓ (8.4-7.5 at 3 mo; 7.5 at 12 mo; eGFR ↔/Cr ↔ at 3/12 mo; Wt ↓1.6 kg	UTI (*n* = 6; 3 required hospital stay; 1 ICU). Diabetic foot ulcer (*n* = 2). Hypoglycemia (*n* = 2; insulin *n* = 1, glipizide *n* = 1). No DKA, AKI dehydration requiring IVF, Fournier gangrene, Genital infection, fractures. Discontinued tx: *n* = 17 [d/c after a median (IQR) 244d (117-401)], *n* = 6 for cost, *n* = 4, eGFR, *n* = 3 infection, *n* = 1 poor wound healing, *n* = 1, hypoglycemia, *n* = 1 self d/c, *n* = 1, death unrelated to SGLT2i	38% on ACEi/ARB at initiation. Insufficient proteinuria data; Tac levels stable. 5/6 had prior UTI, 4/6 continued SGLT2i w/o recurrence
Lim *et al* [13], 2022	Retrospective, South Korea	62 mo ± 42 mo	Empa (*n* = 150). Dapa (*n* = 76) *vs* non-SGLT2i (*n* = 1857)	T2DM or PTDM Pancreas Transplant Prescribed SGLT2i < 90 from transplant	eGFR at 3 mo post-transplant 66.9 ± 17.7 *vs* 68.4 ± 20.1. HgbA1c at 3 mo post-transplant. Both 7.3 ± 1.4	Mean 3.8 yr ± 4.5	A risk primary outcome = composite outcome of all-cause mortality, DCGF, and SCr doubling: Multivariate [aHR (0.43; 95%CI = 0.24-0.78, *P* = 0.006) propensity score-matched; aHR (0.45; 95%CI = 0.24-0.85, *P* = 0.013)]. HbA1c = NR. eGFR stable at 8 mo. ↓SCr doubling significantly in unadjusted and adjusted models. Wt = NR	UTI/genital mycotic infection: (SGLT2i 4.5 events/100 patient-year *vs* non-SGLT2i 6.2/100 patient-year). No DKA. Discontinued txt: NR	15.6% eGFR dip over 10% during first month. eGFR recovered thereafter. 48.7% of the SGLT2i cohort was on ACEi/ARB. Composite all-cause mortality, DCGF, or SCr doubling in KTRs
Hisadome *et al*[12], 2021	Retrospective observational study, Japan	48 wk	SGLT2i (*n* = 29); Cana (*n* = 9); Empa (*n* = 4); Dapa (*n* = 3); Luseo (*n* = 5); Ipra (*n* = 7); Tofo (*n* = 1) *vs* Other oral glycemic agent (*n* = 60); DDP4i (*n* = 42); meglitinides (*n* = 9); metformin (*n* = 4); SU (*n* = 4) α-glucosidase	ESRD patients w/T2DM nephropathy pre-transplant PO hypoglycemic. Follow up at outside centers < 1 yr follow up. Missing data	eGFR mean ± SD: 50.4 ± 13.9; 47.5 ± 13.1. HgbA1c mean ± SD: 7.7 ± 0.9; 7.6 ± 1.1	NR	HgbA1c 7.7 -> 7.6 (same) *vs* 7.6 to 7.5. Wt -0.7 ± 5.1 kg *vs* 1.6 ± 4.5 kg. eGFR 50.4 -> 51.4 *vs* 47.5 to 46.3. BP went up (7 mmHg ± 20 *vs* -3 ± 24)	UTI 2:0; CV disease 0:2. BPAR 1:1. Discontinued txt: NR	71.2% of the SGLT2i group was also on ACEi/ARB. Stable tac levels (*P* = 0.755)
Song *et al* [14], 2021	Retrospective, United States	101 d	Empa (*n* = 43); Cana (*n* =6); Dapa (*n* = 1)	PTDM eGFR ≥ 30. AKI in prior ≤ 30 d. UTI in prior 6 mo	eGFR at initiation: Mean 66.7; 30-45 (*n* = 7; 14%) HbA1c mean ± SD: 7.1 ± 0.1	Median (IQR): 319.5 d (122-696). 40% within 200 d	ΔeGFR 3 mo: -1 mL/min; 6 mo: 1 mL/min. ΔHgbA1c 0.53%. Treated UTI 7 (14%). Approximately 20% typical rate. Change in insulin (-3.7 units ± 22.8). Wt (-2.95 kg ± 3.54, 95%CI 3.53-1.5). HgbA1c ↔; eGFR ↔; Wt↓. ΔMag2+ ↑ by 0.13	UTI (*n* = 7). D/C txt: *n* = 9 (5, UTI; 1 genital infection, 1; native disease; recurrence, 1 PTDM; resolution, 1; physician preference)	80% T2DM; 98% on prednisone; UTI rate comparable to KT population (14%)

AlKindi *et al*[8], 2020	Retrospective case series, United Arab Emirates	Range: 3 mo to 2 yr	Empa 10 mg *n* = 5; 25 mg *n* = 1. Dapa 25 mg *n* = 2	Diabetic KTRs; SGLT2i between 06/16-01/19	eGFR mean ± SD: 75.8 ± 13.4; HbA1c mean ± SD: 9.3 ± 1.4	mean ± SD: 9.6 yr ± 6.41	HgbA1c↓ (9.0 at 3 mo; 8.6 at 6 mo; 7.7 at 9 mo; 7.4 at 12 mo; eGFR ↔ median eGFR 72 (range 62-76) at 12 mo. Wt (mean wt 84.82 kg -> 82.87 at 3 mo -> 82.75 at 6 mo). BP not statistically significant though 9 pt difference	UTI + hospitalization (*n* = 1); pt w hx of UTI no UTI w ppx. Discontinuation rate: NR	2/8 T2DM; 6/8 PTDM; all LURKTx
Halden *et al*[9], 2019	Prospective, double blind, RCT Norway	6 mo	Cana 10 mg (*n* = 22). Placebo (*n* = 22)	≥ 18 yr; ≥ 1 yr post-transplant. PTDM only < 20% SCr deviation in last 2 mo. ≥ 3 mo stable immunosuppression. eGFR ≤ 30; Pregnant or nursing	eGFR Median (IQR) 66(57-68): 59 (52-72). HbA1c Median (IQR) 6.9 (6.5-8.2): 6.8 (6.1-7.2)	Median (IQR) 3 yr (1-16): 3 yr (1-15)	HbA1c↓ (6.9 to 6.7 *vs* 6.6 to 6.9); eGFR↓ (2 mo), ↔ (6 mo)-66 to 61 *vs* 59 to 59. Weight↓ (92 kg to 88.8 kg *vs* 84 to 85 kg). No real impact on BP. Hgb increase 13.9 to 14.5. ↓Uric acid. Tac/CSA/Siro levels stable	Urosepsis 1:0 (hx of recurrent UTI), UTI 3:3, genital infection 1:0, dizziness 2:0, hematuria 1:0. Discontinued txt: *n* = 2 (recurrent UTI, urosepsis): 3 (withdrew consent, colon cancer, no longer PTDM)	High DPP-4i use; most were not on additional therapy
Schwaiger *et al*[16], 2019	Prospective	1 mo (*n* = 14); 12 mo (*n* = 8)	Empagliflozin (*n* = 14). Reference (*n* = 24)	eGFR > 30; < 40 IU/d insulin. HgbA1c < 8.5. Adequately diagnosed PTDM	Baseline. eGFR 55.6. Baseline HgbA1c 6.5	Median 69.4 ± 57.2 mo	HgbA1c 6.5-> 6.6 at 4 wk (*P* > 0.05). eGFR 55.6 -> 47.5 at 4 wk (*P* > 0.05). Average TBW↓ 1.6 kg; Waist circ ↓4 cm. ECV/TBFV decreased	UTIs: 5:9. Genital infection: 1. AKI, DKA, Fournier's-NR	100% on steroids. Median onset of PTDM was 0.5 months. 100% on insulin
Shah *et al*[11], 2019	Prospective	6 mo	Canagliflozin (*n* = 25)	≥ 18 years old. CrCl (ml/min) > 60; HgbA1c > 6.5; T2DM; PTDM. Unstable Cr. ALT > 2 × ULN; TBili > 2 × ULN; Recent UTI/genital mycotic infection	Baseline Cr (mg/dL): 1.1 ± 0.2; Baseline HgbA1c: 8.5 ± 1.5	Mean duration of transplant = 2.7 yr (0.2-13.2)	HgbA1c: 8.5 ± 1.5 -> 7.6 ± 1. Cr: 1.1 ± 0.2 -> 1.1 ± 0.3. Weight: 78.6 ± 12.1 -> 76.1 ± 11.2 (*P* < 0.05). SBP (mmHg): 142 ± 21 -> 134 ± 17 (*P* < 0.05)	No increase in UTI/genital infections. No hypoglycemia or DKA. Fatigue (*n* = 3). Discontinued treatment (*n* = 1)	20 T2DM; 5 PTDM. Reduction of other hypoglycemics needed. 1 KTR self d/ced. Used fixed 100 mg dose. Stable tac doses

eGFR: Estimated glomerular filtration rate; pts: Patients; Cana: Canagliflozin; Dapa: Dapagliflozin; Empa: Empagliflozin; T2DM: Type 2 diabetes mellitus; PTDM: Post-transplant diabetes mellitus; SGLT2i: Sodium-glucose cotransporter-2 inhibitor; IQR: Interquartile range; HgbA1c: Glycohemoglobin; Cr: Creatinine; Wt: Weight; UTI: Urinary tract infection; ICU: Intensive care unit; DKA: Diabetic ketoacidosis; AKI: Acute kidney injury; IVF: Intravenous fluids; txt: Treatment: d/c: Discontinued; ACEi: Angiotensin converting enzyme inhibitors; ARB: Aldosterone receptor blockers; tac: Tacrolimus; SCr: Serum creatinine; DCGF: Death censored graft failure; aHR: Adjusted hazard ratio; CI: Confidence interval; NR: Not reported; KTR: Kidney transplant recipient; Luseo: Luseogliflozin; Ipra: Ipragliflozin; Tofo: Tofogliflozin; DDP4i: Dipeptidyl peptidase 4 inhibitors; ESRD: End stage renal disease; PO: Oral; SD: Standard deviation; BP: Blood pressure; CV: Cardiovascular; BPAR: Biopsy proven acute rejection; Δ: Change in; Mag2+: Magnesium; KT: Kidney transplant; hx: History; ppx: Prophylaxis: LURKTx: Living unrelated kidney transplant; Hgb: Hemoglobin; CSA: Cyclosporine; siro: Sirolimus; IU: International units; TBW: Total body weight; circ: Circumference; ECV: Extracellular volume; TBFV: Total body fluid volume; CrCl: Creatinine clearance; ALT: Alanine transaminase; ULN: Upper limit of normal; TBili: Total bilirubin; SBP: Systolic blood pressure.

most insured patients, median cost for 30 d of SGLT2i therapy cost around $38.43 (range: $3.87-$49.42)[18].

Novel findings

In their comprehensive randomized controlled trial, Halden *et al*[9] observed increased hemoglobin/hematocrit and decreased uric acid levels with SGLT2i use. Song *et al*[14] observed an improvement in serum magnesium levels after SGLT2i initiation.

Long term outcomes

Lim *et al*[13] showed a significant reduction at five years in their composite outcome of all-cause mortality, death-

censored graft failure (DCGF), and serum creatinine doubling with SGLT2i use in both multivariate (aHR = 0.43; 95%CI: 0.24-0.78, *P* = 0.006] and propensity score-matched aHR (0.45; 95%CI: 0.24-0.85, *P* = 0.013). Otherwise, these studies lacked long term outcome data.

ANALYSIS

Though these studies are heterogenous and limited in terms of design and size, short term safety and efficacy outcomes of SGLT2i use in diabetic KTRs appear comparable to those observed in CKD patients with diabetes.

Glycemic control paralleled that seen in the non-transplant DM population with modest HgbA1c improvements. Though most studies included KTRs with adequate allograft function, Hisadome *et al*[12] and Song *et al*[14] included a substantial number of individuals with eGFR in the 30-45 range, which approximates to CKD stage 3b. Though there are potential differences between CKD and CKD after transplant as described by Djamali *et al*[19], evidence supporting safe, effective use of SGLT2i in KTRs with decreased allograft function is encouraging.

Remarkably, the eGFR decline, recovery and stabilization of kidney function that occurs in non-transplant diabetics was also observed in some KTRs without significant unfavorable impacts on long term graft function. This was in the setting of high reported concurrent ACEi/ARB use which are recommended as first line agents in diabetic kidney disease. This is exciting, as renin-angiotensin-aldosterone system (RAAS) blockade plays a vital role in diabetic CKD/cardiovascular management. Moreover, the major trials for SGLT2i, such as EMPA-REG OUTCOME by Wanner *et al*[20] reported RAAS blockade use between 80%-85% of those studied. In summary, the illustration of eGFR stability with simultaneous use of SGLT2i/RAAS blockade in KTRs across multiple studies will hopefully quell clinician fears regarding their concurrent use.

It is unfortunate that proteinuria was not an endpoint in any of the included studies. Results of studies in the general population, namely those by Jongs *et al*[21], Cherney *et al*[22], and Trujillo *et al*[23], in terms of SGLT2i effect on proteinuria, are both limited and mixed[21-23]. EMPA-REG OUTCOME by Wanner *et al*[20], CANVAS by Neal *et al*[24] and CREDENCE by Perkovic *et al*[25] and DAPA-CKD by Heerspink *et al*[5], suggested utility for these agents in reducing the geometric mean urinary albumin creatinine ratio, increasing the likelihood of regression in albuminuria stage and reducing the risk of macroalbuminuria progression[20,21]. Further investigations into whether or not SGLT2i impact proteinuria in KTRs will be important not only to better understand these medications, but also to help with agent selection if a difference *e.g.*, empagliflozin and canagliflozin *vs* DAPA, is observed between them in KTRs.

Weight loss occurred in almost every study, likely due to the osmotic diuresis caused by SGLT2i use. This is also occurring due to fat loss from caloric wasting *via* glucose. As the weight loss demonstrated for most patients is less than 5% total body weight, this likely has little bearing clinically.

That being said, perhaps weight loss can underscore future studies examining impacts on truncal obesity, waist size (as Schwaiger *et al*[16] remarked), cholesterol, uric acid levels, and other markers of obesity/metabolic syndrome and their impacts on kidney and cardiovascular outcomes.

Blood pressure outcomes were less clear across these studies, which is at least partly explained by the different mechanisms and influences on blood pressure in KTRs compared to CKD patients as described by Kasiske *et al*[26]. It is unlikely due to weight loss alone given the magnitude of weight loss as previously noted. As these medications are studied further in KTRs, perhaps novel mechanisms for how SGLT2i influence blood pressure will be elucidated.

While UTIs were observed in these studies, they did not appear to occur significantly more than in KTRs not on SGTL2i. As described by Brune *et al*[27], the prevalence of UTI after transplant varies significantly based on several factors (namely *via* definition, study, population, length of follow up). However, they state that a reasonable benchmark based on larger studies is a 1-year incidence rate around 30%. Lemke *et al*[10] reported continued use of SGLT2i after UTI, with one of those patients requiring hospitalization for treatment, but without recurrent disease. Long term impacts of SGLT2i use/glucosuria not only on UTI risk, but also asymptomatic bacteriuria, antibiotic use and associated complications are ongoing uncertainties. GI were observed but at a fairly low rate compared to UTI as described above.

Though limited, drug level data suggest that SGLT2i have little to no impact on calcineurin inhibitor (CNI) trough levels, nor were increased episodes of rejection observed. As Scheen[28] describes in his excellent review on the subject, SGLT2i metabolism minimally involves cytochrome CYP3A4, making SGLT2i-CNI drug interactions slight at best.

As described by Song *et al*[14], hypomagnesemia was improved in KTRs on SGLT2i. As hypomagnesemia is associated with increased risk of cardiovascular and infection-related mortality as noted by Panthofer *et al*[29] and Odler *et al*[30] and this is an important management target. Per Huang *et al*[31], there may be a role for pre-emptive SGLT2i use as hypomagnesemia itself has been shown to increase the risk of PTDM in KTRs. Additionally, hypomagnesemia treatment can be challenging as most magnesium formulations cause diarrhea. Therefore, SGLT2i may play a role obviate/minimize high magnesium supplementation needs.

Though not discussed thoroughly in the literature, Bilezikian *et al*[32] and Kohan *et al*[33] note that there are some concerns for SGLT2i and their impacts on bone health. Lemke *et al*[10] reported on fractures in their study, noting none occurred. Though this is a nascent area of research, Blau and Taylor[34] demonstrated a possible mechanism *via* the FGF23–1,25-dihydroxyvitamin D–parathyroid hormone axis. As impaired bone health is common in KTRs, seeing how this relationship bears out in longer, more robust studies will be important for patient selection and ongoing management. At the moment, there is insufficient data to attribute substantial fracture risk to SGLT2i use.

With SGLT2i being relatively new agents, there is a paucity of data on long-term kidney, cardiovascular, and survival outcomes. Determination of their impact on long-term outcomes will require larger, protracted investigations. This is illustrated in the EMPA-REG trial by Wanner *et al*[35], in which SGLT2i-mediated eGFR preservation was first seen

around 80 wk of therapy *vs* placebo.

Ideally, future retrospective studies, like that by Lim *et al*[13] and/or prospective analyses can describe these relationships going forward. These would be best achieved by multi-center, large trials analogous to their landmark predecessors.

In their comprehensive study review on the management of PTDM, Hecking *et al*[36] aptly summarize direct and indirect potential benefits of SGLT2i in kidney transplantation. Though some of this is extrapolated from non-KT research, novel impacts such as reduction in vascular rigidity as well as hypoxia-inducible factor-1, could be impactful in the kidney transplant population regarding cardio-/reno-/vascular health, anti-inflammatory properties and perhaps anemia management as described by Hecking *et al*[36], Gupta and Wish[37].

A key limitation of these studies is that they evaluated KTRs with diabetes alone. As this is a logical starting place for investigating the efficacy of SGLT2i, to suggest that these medications are limited only to KTRs with diabetes is too narrow a view. With kidney transplantation existing as a state of CKD as well as ESKD itself portending significant cardiovascular risk, we surmise (and hope) that the benefits of SGLT2i will extend to KTRs without diabetes as well. As was demonstrated in DAPA-CKD, a multicenter randomized controlled trial of 4304 patients in which 32.5% of the patients were non-diabetic, SGLT2i increased the likelihood of albuminuria regression and reduced the likelihood of progression to more severe stages of albuminuria in CKD patients with and without diabetes[5]. Therefore, KTRs without diabetes warrant investigation into the utility of SGLT2i use.

CLINICAL RECOMMENDATIONS

Though more research is needed, there appears to be a subset of non-insulin dependent diabetic KTRs who ought to benefit from SGLT2i therapy.

Identifying appropriate candidates is a critical step for implementing SGLT2i therapy routinely. Though questions remain presently regarding long term safety, the stalwart evidence from the CKD literature is compelling for the transplant community to press forward.

In their recent review, Patel *et al*[38] proposed an "ideal" KTR SGLT2i candidate. While this provides a nice general framework, we have additional characteristics to build on this model for identifying SGLT2i candidates.

At present, there does not appear to be substantial evidence on when post-transplant to initiate SGLT2i therapy. Earlier initiation *i.e.*, prior to 6- or 12-mo post-transplant may be beneficial for at least 3 reasons: (1) PTDM appears to be an early post-transplant complication. This is shown by Jenssen and Hartmann[39], in their review on PTDM, where they cite Porrini *et al*[40]. In their study, 32% of the cohort developed PTDM (215/672). Of these 215, 187 (87%) of these KTRs developed PTDM prior to 12 mo; (2) major benefits of SGLT2i therapy such as eGFR preservation may require long term medication use, as EMPA-REG showed[35]; and (3) as is aptly described by Wolfe *et al*[41] in their seminal study on mortality after deceased donor kidney transplant (DDKT), there is increased risk of death in the early post-transplant time period. Perhaps this will promote studies of initiating SGLT2i at the time of transplantation in select patients *e.g.*, DDKT with immediate graft function.

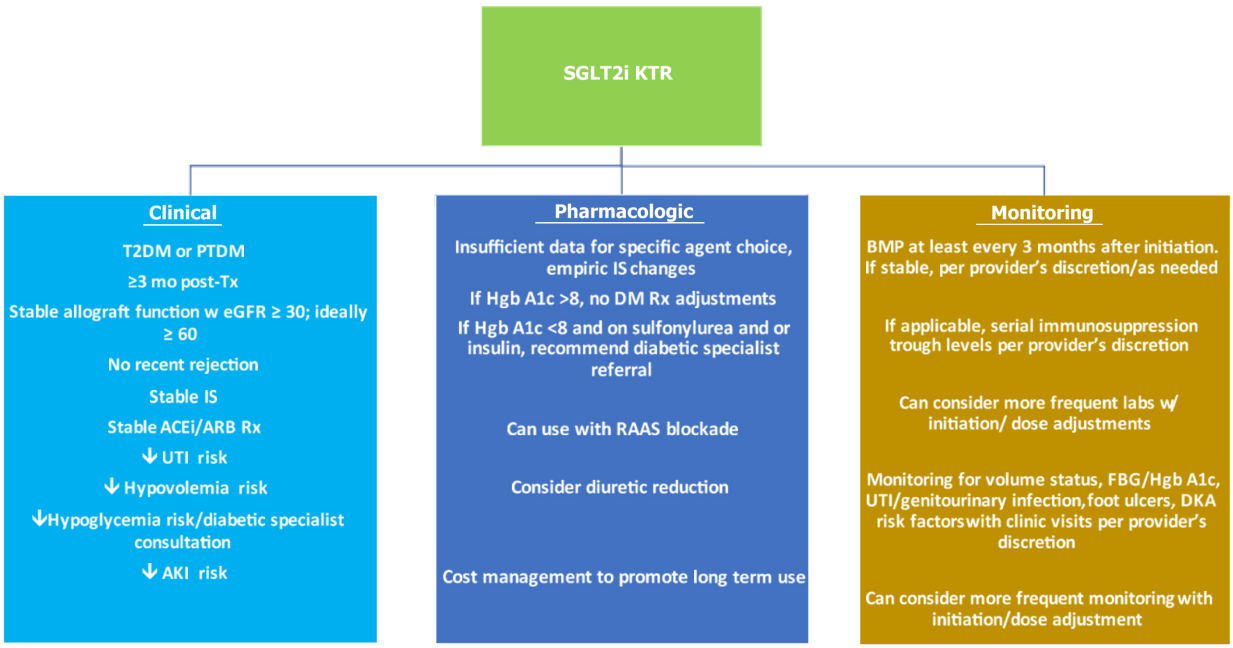
In the following section, we will put forth clinical recommendations for SGLT2i use in KTRs. These are based on the aforementioned results as well as inclusion/exclusion criteria in the studies reviewed. As this is an evolving science, these are solely recommendations *i.e.*, provider discretion remains crucial to using these medications. These are also summarized in Figure 1.

Based on the literature reviewed, we propose the following as good candidates for SGLT2i use: (1) KTRs with pre-transplant T2DM or PTDM; (2) at least 3 mo post-transplant; (3) stable allograft function preferably with eGFR of at ≥ 30 mL/min/1.73 m^2, ideally ≥ 60 mL/min/1.73 m^2 for the past 2 mo; (4) no rejection episodes within the past 3 mo; (5) at least 3 mo of stable immunosuppression; (6) stable ACEi/ARB doses; (7) patients at low risk for volume depletion *e.g.*, low risk for unstable diarrhea, vomiting; (8) patients at low risk for hypoglycemia *e.g.*, HgbA1c > 8 or < 8 and not on a sulfonylurea or insulin. If at risk for hypoglycemia, would consult diabetic specialist for regimen titration; (9) patients without significant UTI history or diabetic foot ulcers; (10) patients with low risk for acute kidney injury; and (11) patients who may benefit from novel aspects of SGLT2i: Hypomagnesemia, hyperuricemia, anemia.

In terms of pharmacologic therapy titration in the context of SGLT2i initiation, we recommend the following: (1) Insufficient data to support empiric adjustments to maintenance immunosuppression or to diabetic prescriptions; (2) can consider reducing diuretic doses; (3) advise diabetic specialist consultation for KTRs with well controlled diabetes (HgbA1c < 8) and other diabetic agents, particularly insulin or sulfonylureas, to help titrate their diabetic regimen to minimize the risk of hypo-glycemia; and (4) continued drug trough and blood glucose monitoring are key to titrate further.

In terms of monitoring parameters, we recommend the following: (1) Renal function assessment at least every 3 mo at a minimum. Can consider more frequent monitoring with initiation/dose adjustments; (2) if applicable (on CNI or mammalian target of rapamycin inhibitor therapy), serial immunosuppression trough levels per provider's discretion. Can consider more frequent monitoring with initiation/dose adjustments; (3) routine monitoring for volume status, risk factors for diabetic ketoacidosis, hypoglycemia; and (4) routine monitoring for signs and symptoms of UTI, diabetic foot ulcers.

It is somewhat challenging to put forth contraindications to use at this time, particularly when the evidence for use is so persuasive. Assuredly there are patients in whom SGLT2i use poses greater risk of harm than benefit *e.g.*, a KTR with a history of DKA, at risk for or experiencing recurrent transplant pyelonephritis, and/or chronic osteomyelitis and/or active diabetic foot wounds. Ultimately, the determination of benefit *vs* risk requires clinical reasoning, evaluation and



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Figure 1 Clinical, pharmacologic and monitoring parameters for sodium glucose cotransporter-2 inhibitor use in a kidney transplant recipient. Clinical criteria, pharmacologic and monitoring strategies are essential to selecting and managing kidney transplant recipient (KTRs) for sodium-glucose cotransporter-2 inhibitor (SGLT2i) use. Stable KTRs with an appropriate diabetes diagnosis, clinical stability and low risk for adverse events is key. Little data exists for empiric medication changes, though diuretic dose reduction ought to be considered. Strategies for cost management beyond insurance ought to be explored to maximize possible long-term benefit from SGLT2i administration. Laboratory and clinical monitoring more frequently with initiation/dose adjustments is critical to identifying adverse events. SGLT2i: Sodium-glucose cotransporter-2 inhibitors; KTR: Kidney transplant recipient; T2DM: Type 2 diabetes mellitus; PTDM: Post-transplant diabetes mellitus; Tx: Transplant; w: With; eGFR: Estimated glomerular filtration rate; IS: Immunosuppression; ACEi: Angiotensin converting enzyme inhibitor; ARB: Aldosterone receptor blocker; Rx: Prescription; UTI: Urinary tract infection; AKI: Acute kidney injury; Hgb: Hemoglobin; DM: Diabetes mellitus; RAAS: Renin-angiotensin-aldosterone system; FBG: Fasting blood glucose; DKA: Diabetic ketoacidosis.

patient-provider dialogue on whether SGLT2i use is in the patient's best interest.

Notably, guidance exists in the literature regarding patient handout communications when initiating SGLT2i therapy. Lam *et al*[42] provide an excellent version that is generally applicable to KTRs.

LIMITATIONS

Though early data on SGLT2i implementation in KTRs is promising, it is albeit limited.

There are 3 main limitations in the data on the use of SGLT2i in KTRs. Longitudinal studies with large enrollment volume are absent. The longest follow up was around 8.5 years with most having far less. This leaves cardiovascular, graft and mortality outcomes unexplored. Rare adverse events like euglycemic DKA or osteoporosis are also not explored. RCTs are necessary to establish causality and bolster clinical practice recommendations. Most of the studies in SGLT2i are limited to retrospective, observational design or case series.

The SGLT2i story is one that is well underway. There appears to be substantial evidence supporting their use in terms of safety and short-term efficacy based on the studies we described and their antecedents. What lies ahead regarding long-term SGLT2i therapy is unknown. With SGLT2i, we are not working *ab initio* (from the beginning). Rather, as is precedent in some of the greatest epics and sagas (*i.e.*, the *Mahābhārata,* Homer's *Iliad* and *Odyssey*, Virgil's *Aeneid,* Dante's *Divine Comedy*) as noted by Lochtefeld[43], Murray[44] and Raffa[45], we can and ought to forge ahead into the unknown *in medias res*-into the middle of things.

FUTURE DIRECTIONS

While the current literature gives insight into short-term outcomes of SGLT2i use in KTRs, more research is needed to identify the long-term impacts of SGLT2i use in this population.

Currently, there are 2 actively recruiting clinical trials (NCT04965935 aka INFINITI2019 and NCT04906213 aka CREST-KT).

INFINITI2019 is a double-blind, placebo-controlled trial aimed at comparing DAPA to placebo in 52 KTRs. The primary outcome is blood pressure reduction in addition to fasting blood glucose, HgbA1c, continuous home glucose

monitoring, arterial stiffness, systemic vascular resistance, change in baseline measured GFR, change in eGFR, proximal tubular natriuresis, albuminuria, change in baseline urinary and plasma oxidative stress markers, change in tubule interstitial hypoxia, CNI levels, and adverse events.

CREST-KT is a single-center, double-blinded randomized controlled trial of empagliflozin therapy in 72 KTRS with (36) and without (36) diabetes. After dividing by diabetes diagnosis, the groups will be randomized 2:1 to empagliflozin 10 mg *vs* placebo *i.e.*, 48 KTRs will be on empagliflozin and 24 KTRS will be on placebo. Study time is planned to be 18 mo.

Primary outcomes include: Change in eGFR, change in albuminuria, change in cardiac structure by 3D echocardiogram, change in blood insulin level, change in fasting blood sugar, # of UTIs and # of GI.

Secondary outcomes include: Change in kidney biopsy from time zero to 6 mo and change in HgbA1c as well as AEs.

In addition to these studies, hopefully future randomized controlled trials examining long term renal outcomes as well as cardiovascular outcomes, particularly in patients with known heart failure, will help guide appropriate SGLT2i use and influence guidelines and practice patterns for SGLT2i in KTRs.

CONCLUSION

SGLT2i appear to be safe, effective medications in the arsenal of post-transplant therapies for select KTRs. Our present literature, though somewhat limited, is founded on preceding strong research in CKD patients with diabetes. Concurrent research and utilization of SGLT2i is vital to not only identify long-term patient, graft and cardiovascular outcomes of these agents, but also to augment diabetic, CKD, and cardiovascular management in KTRs *in media res*.

FOOTNOTES

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MINIREVIEWS

Renal allograft procurement from living unrelated donors in Iran: What falls under the eclipse

Saeed Taheri

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Abstract

Renal transplantation is the treatment of choice for end stage kidney disease. However, despite all the efforts to expand the donor pool, the shortage of donors is increasing and as a consequence, there has been a significant increase in the number of patients on transplant waiting lists globally. Societies worldwide have employed different methods to address this, each with specific ethical concerns surrounding them. Over three decades ago, a governmentally regulated program of kidney transplantation from living unrelated donors was introduced in Iran and since practiced which has been the subject of hot debate in the literature. Nevertheless, despite all these extensive discussions and publications, several key aspects of the program have still not been properly elucidated and addressed. In this article, the author aims to illuminate some dark corners related to this issue that have largely escaped the notice of ethicists.

Key Words: Allograft procurement; Renal transplantation; Living unrelated donor; Organ market; Iran

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Core Tip: Iran's living unrelated kidney transplantation program has several limitations by its definition, but what is already in practice goes far beyond that and is actually a government legislated and regulated kidney market in which the laws and supports all essentially best serve the interests of brokers and financial agencies, and result in exploitation of the poor on either the recipient or donor.

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INTRODUCTION

Conventionally called "the Iranian Model of Kidney Transplantation", the practice of kidney allograft transplantation procured from living unrelated (LUR) donors in Iran has been highly controversial, and for that reason as well as the unclear origins of the idea when it was introduced into the Iranian medical society, this terminology was avoided in this commentary. Although this topic has been widely tackled in the past by its proponents, opponents, and health-authorities [1-3], there are still several major aspects of the practice that have not been very well addressed. In this paper, I intend to discuss some of these complexities.

According to the latest report by the Iranian Society of Nephrology, 76.3% of all the kidney transplantations performed in Iran are from living donors[4], 86% of which has been reportedly from LUR donors[5]. With such a large share of the transplantation volume, rather extensive claims have been made in the literature as to the merits of LUR transplantation in eliminating the kidney transplant waiting lists; although in real practice, there are already two simultaneous waiting lists in Iran: One for recipients and the other for donors. To be precise, they are not actual waiting lists, as you do not need to wait a moment if you have enough money to pay.

KIDNEY FOR SALE

"Kidney for sale with the blood-group of AB from Tehran. Urgent need for money! Also ready to sell bone marrow, liver or any other part of the body that could be sold (for money) anyway!" This is one of the huge number of advertisements that have been submitted to the Iranian Online Associations for Kidney Donation website[6] which provides free rooms to people who would want to get to the market, as kidney sellers, buyers or even brokers. Examples of advertisements from this website and other unofficial websites are provided in Table 1. A look at the advertisements reveals that kidney sellers likely concentrate on the price, while the buyers usually focus on the age (usually < 30 years), gender (male), overall health and the readily available laboratory reports which are supposed to be primarily paid and provided by the kidney sellers, as a prerequisite for finding a potential recipient.

A BRIEF INTRODUCTION

Upon its introduction to the Iranian health system, the LUR renal transplantation program had implemented some legal measures that were supposed to eliminate ethical concerns. In brief, renal patients as well as the potential LUR donors would separately contact a governmental regulation center which identifies suitable donor-recipient couplets and introduces them to transplantation centers (without them knowing each other prior to transplantation). All the expenses associated with the transplantation procedure and hospital costs would be fully covered by the government. After the procedure, the LUR donors would receive government-funded financial compensation and health insurance for one year, and "a majority" of them would also receive a gift from the recipient or charitable organizations. There would be no role for brokers or agencies in the process, and the program runs under the close scrutiny and surveillance of the Iranian Society for Organ Transplantation[1].

Whether or not the above-mentioned model sounds ethical, there are large practical deviations from the pronounced guidelines. During the past decades, the governmental "rewarding gift" to the LUR donors has shrunk from about 3000 United States dollar (USD) equivalent in local currency to less than 800 USD, with expectations to plunge even more due to the ongoing economic decline. Therefore, the government's financial participation in donor compensation is rapidly becoming smaller, driving the recipients to provide the largest share of the payment. In other words, only wealthy patients could be sure of obtaining an allograft whenever they need to, and the less-resourceful individuals would be driven to sacrifice their last possessions (*e.g.*, selling their family home) for this purpose; and finally the poorest people would have no chance in this market, meaning that even the limited governmental support would inevitably escape those who could not manage to provide the (much larger) remaining bulk of the payment, and the graft would go exclusively to the relatively more resourceful patients.

PREREQUISITES AND CONSEQUENCES OF INSTITUTING SUCH A PROGRAM

According to the above-mentioned evidence, what had been initially proclaimed to be a governmentally regulated and compensated altruistic organ donation is a myth now, and the only thing that one needs to get to the kidney market is simply finding a partner (a donor or a recipient) who would fulfill his/her (mainly financial) expectations, with apparent roles for brokers and agencies and no authoritarian surveillance. The burden of such a market could go far beyond what was mentioned above. Recently there was news about a father who was trying to sell his 19 mo-old child's organs in Alborz Province and was arrested after the baby's demise due to methadone overdose. This is probably not an exception and similar events have supposedly been taking place without finding a way to the media. Even in the legal practice, almost no one gets to the market in this country and it is about gaining higher standards of living, for example, buying a better house or indulging in an extraordinary ambition or anything other than the urgency of escaping a catastrophic collapse or securing the least living requirements. However, all societies and governments are obligated to provide appropriate environments for people to achieve fruitful livelihoods and prospects through ethical and constructive

Table 1 Examples of advertisements from kidney sellers and buyers on an official website in Iran[6]

Buyers' advertisements	Sellers' advertisements
Kidney buyer; blood group O+; man or woman; please only people with HLA reports contact; otherwise let's not waste each other's time (Tehran)	Kidney for sale; 42 yr old; blood group B+; due to financial crisis; no tobacco; no alcohol; bicycling each day for hours; and body works as infallible as a watch (East Azerbaijan)
Kidney buyer; blood group O; our patient is under dialysis and medical conditions is rapidly deteriorating; unemployed; lives in a renting house; some people promised helping; let's help for God's sake and his wife and children (Markazi)	Kidney for sale; 35 yr old man; blood group O+; me and my wife (blood group B+) both are ready to sell our kidneys; HLA testing ready for both; only recipients contact not dealers (brokers) (Tehran)
Kidney buyer; blood group O; I am under dialysis with complications; for God's sake help me to get free of dialysis; I also have financial problems; the seller preferably a man less than 35 (West Azerbaijan)	Kidney for sale; 39 yr old man; HLA and ultrasonography tests are ready; no history of any disease; family consent ready; I need money for my kid's illness; price would be fair and just (Kurdistan)
Kidney buyer; blood group AB; please don't give "mind blowing" price so I can prepare it (East Azerbaijan)	Kidney for sale; 24 yr old woman; married; family consent ready; all tests and HLA report ready; ultrasonography report ready; weight; no tobacco; healthy in every aspect (Tehran)
Kidney buyer; blood group O+; applicants must have HLA report and family consent ready; age less than 30; I'd pay the hospital costs and tests would be paid after the procedure; (Mazandaran)	Kidney for sale; 32 yr old; all tests (HLA, CTA, United States, & cardiologist letter) ready; hospital costs and labs should be covered by the buyer; price fair & with mutual consent (Mazandaran)
Kidney buyer; blood group A+; urgent need for a kidney; seller should have all the tests ready; age less than 30; powerful body; no user of tobacco; alcohol or other junks; preferably from Tehran (Khuzestan)	Kidney, liver and all other purchasable organs for sale; 40 yr old man; blood group A+; HLA test ready; at service wherever on the earth for the procedure; people with financial problems please don't contact! (Tehran)
I am highly experienced in kidney transplantation; ready to give consultation services to both buyers and sellers; contact me! (Tehran)	Kidney for sale; blood group AB; 31 yr old; I am in debt and can't pay for my house renting; please contact (West Azerbaijan)

Although in the introduction of the living unrelated kidney transplantation in Iran it is declared that all the hospital costs would be totally paid by the government[1], yet in the advertisements, the kidney sellers and buyers are talking about who should pay for the hospital costs. HLA: Human leukocyte antigen; CTA: Computed tomography angiography.

endeavors.

Such an organ procurement program as is already underway in Iran would not survive if the country managed to provide stable, productive and predictable economic conditions that offer people acceptable levels of livelihood in reasonable ways and time. In other words, there should be a constant state of "struggle for existence" to save the current organ market in Iran from collapse, and therefore any attempt at improving the country's economy could be considered a threat to the practice that betrays the donor pool. This would definitely not be good news, but the solution is certainly not to sustain the country in a collapsing state: *i.e.*, to force people into the organ market, *e.g.*, to rent a house for a while or pay for a life-saving medical procedure.

The penetration of brokers and agencies into the practice has further complicated the already-controversial program exponentially. As conventionally only people with high political connections can intervene in such businesses, any attempt to change the existing order into states that sound more ethical would be expected to receive serious backlashes. They even seem to consider renal graft procurement from deceased donors as a threat to their business. In a popular TV show, a person who happened to be a member of the health care system told his story of being in coma (for several weeks), and claimed that his family were under pressure to permit the donation of his organs for transplantation. However, it was only due to his father's heroic resistance against all the pressures that saved his life. It is not only in Iran but also in other parts of the world, that only brain-dead subjects, and not the comatose, who would be considered for organ donation.

SAFETY DATA AND RESEARCH

Despite decades of LUR kidney transplantation practice in Iran, some key aspects of concern have been hidden from the public and scientific literature. In fact there seems to be some undeclared red-lines that nobody could manage to cross. For example, despite overwhelming studies indicating the advantages of LUR transplantations, there are no data on the (particularly long-term) physical and/or psychological burden of the procedure on the donors. I had a not-so-good experience in a research attempt on donors' motivations and psychological burdens associated with LUR kidney transplantation, which was blocked suddenly and prematurely[7]. Moreover, the rationale behind some of the laboratory tests that are legally required for the procedure is unclear. For example, the introduction of potent immunosuppressive drugs and the shortage of available organs has eliminated the necessity for human leukocyte antigen (HLA) matching between the donors and recipients[1]. Actually the transplantation teams in Iran do not even look at the HLA test reports, yet it is still a mandatory part of the practice. Theoretically at least, the HLA reports could be used to find the best HLA matched donors only in exceptional cases, which offers no foundation to the large majority of donors or recipients to pay for this very important person service.

CONCLUSION

In conclusion, the LUR transplantation practice in Iran is associated with profound ethical concerns including discrimination, abuse, withholding information, and potential safety concerns. Should the practice persist, there would be a need for a major revision of the program in almost every aspect, in order to properly address all the issues of concern. Attempts at renovation of the practice should also warrant development of the country towards a more fruitful and prosperous economy and would not adversely affect transplantation.

FOOTNOTES

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Impact of tacrolimus intra-patient variability in adverse outcomes after organ transplantation

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Abstract

Tacrolimus (Tac) is currently the most common calcineurin-inhibitor employed in solid organ transplantation. High intra-patient variability (IPV) of Tac (Tac IPV) has been associated with an increased risk of immune-mediated rejection and poor outcomes after kidney transplantation. Few data are available concerning the impact of high Tac IPV in non-kidney transplants. However, even in kidney transplantation, there is still a controversy whether high Tac IPV is indeed detrimental in respect to graft and/or patient survival. This may be due to different methods employed to evaluate IPV and distinct time frames adopted to assess graft and patient survival in those reports published up to now in the literature. Little is also known about the influence of high Tac IPV in the development of other untoward adverse events, update of the current knowledge regarding the impact of Tac IPV in different outcomes following kidney, liver, heart, lung, and pancreas tran-splantation to better evaluate its use in clinical practice.

Key Words: Tacrolimus; Intra-patient variability; Rejection; Organ transplantation; Graft survival; Outcomes

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Core Tip: Tacrolimus is widely used after solid organ transplantation. High intra-patient variability of tacrolimus (Tac IPV) has been associated with poor graft and patient survival. This review summarizes current evidence regarding the impact of high Tac IPV in several outcomes after kidney, liver, heart, lung and pancreas transplantation.

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INTRODUCTION

Tacrolimus (Tac) is nowadays the most common immunosuppressive drug employed in solid organ transplantation and has replaced cyclosporin as the most common calcineurin inhibitor used worldwide in immunosuppressive regimens[1, 2]. Tac exhibits a peculiar pharmacokinetic profile with large inter-patient and intra-patient variability (IPV) of whole blood drug levels over time, even when doses remain unchanged. This is usually ascribed to overlapping factors, such as ethnicity, pharmacogenomics, food-drug and drug-drug interactions, non-adherence, enhanced Tac absorption or impaired drug excretion due to either diarrhea or cholestasis, assays variability for Tac levels determinations or even alternate use of Tac compounds or its generic formulations[3-5]. Due to its narrow therapeutic window, therapeutic drug monitoring of trough levels (Cmin) is required to attain target levels of immunosuppression over time, as well as avoidance of undesired Tac side effects such as infections, neurotoxicity and nephrotoxicity, which are usually related to higher drug exposure[1].

High Tac IPV or time in the therapeutic range (TTR) of Tac has been associated with an increased risk of immune-mediated rejection and poor outcomes after kidney transplantation (KT)[5,6]. Few data are available concerning the impact of high Tac IPV in non-kidney transplants[7]. However, even in KT, there is still a controversy whether high Tac IPV is indeed detrimental in respect to graft and/or patient survival[5,6]. This may be due to different methods employed to evaluate IPV and distinct time frames adopted to assess graft and patient survival in the reports published up to now. Little is also known about the influence of high Tac IPV in the development of other harmful adverse events associated with immunosuppression, such as infections, chronic kidney disease, type 2 diabetes, metabolic syndrome and *de novo* or recurrent cancer. The purpose of this review is to provide an update of current knowledge regarding the impact of Tac IPV in different outcomes following KT, liver (LT), heart (HT), lung, kidney/pancreas and bone marrow (BMT) transplantation to better evaluate its use in clinical practice.

STUDY SELECTION

To identify and select studies for this review, research was made in the MedLine/PubMed database, using the following terms: Tacrolimus; intra-patient; variability; transplant; transplantation; rejection; and graft loss. These terms were obtained from Medical Subject Headings (MeSH), using the Booleans "AND" and "OR", from various search algorithms in PubMed.

Search 1: ((“tacrolimus”[MeSH Terms] OR “tacrolimus”[All Fields]) AND “intra”[All Fields] AND (“patient s”[All Fields] OR “patients”[MeSH Terms] OR “patients”[All Fields] OR “patient”[All Fields] OR “patients s”[All Fields]) AND (“variabilities”[All Fields] OR “variability”[All Fields] OR “variable”[All Fields] OR “variable s”[All Fields] OR “variables”[All Fields] OR “variably”[All Fields])) AND (y_10[Filter]). Search 2: ((((((tacrolimus[Title/Abstract]) AND (variability[Title/Abstract])) OR (intrapatient variability[Title/Abstract])) AND (transplant[Title/Abstract])) OR (transplantation[Title/Abstract])) AND (rejection[Title/Abstract])) OR (graft loss[Title/Abstract]).

Subsequently, an active manual search of studies was carried out through carefully selected articles in gray literature.

The research was completed on May 17th, 2023. A total of 43 articles were included in the present study, 376 studies were found in PubMed database, and after careful reading of abstracts, 15 were included in our final review (references No. 3, 7, 24, 31, 33, 37, 38, 57, 60, 62, 65-67, 69, and 70). The excluded works did not satisfactorily meet the theme proposed for the present work. Furthermore, 28 studies different from the ones previously selected in PubMed database were identified in our active manual research in gray literature, all of which were included in this review.

METHODS USED TO ASSESS TAC IPV

Intra-patient variability of Tac over time has been calculated using different methods, particularly[5-7]: Mean levels and standard deviation (SD) of Tac whole-blood Cmin levels, also expressed as the medication level variability index (MLVI).

Mean absolute deviation (MAD), based on the formula MAD (%) = {[(Xmean - X1) + (Xmean - X2)… + (Xmean - Xn)]/n of Cmin results}, where X is the Tac Cmin level.

Coefficient of variation (CV), calculated according to the formula CV (%) = σ/μ, where σ is the standard deviation, and μ is the mean Tac Cmin levels of all available samples of the individual. CV may be corrected or not by the corresponding Tac dose (C0/D) or defined as time-weighted coefficient of variability using time-weighted standard deviation divided by the mean drug levels.

Tac TTR, calculated by the Rosendaal method[8]. Standard deviation or MLVI are expressed as numbers, classes, or dichotomized intervals, whereas CV and TTR are expressed as percentages, tertiles and dichotomized intervals usually at the median split. There are no universally accepted recommended target levels for each one of those parameters used to assess Tac IPV. It is important to highlight that target levels of Tac Cmin usually vary over time according to the type of organ transplant, donor and recipient risk factors for rejection, comorbidity, occurrence of side effects and local immunosuppression protocols. The TTR may also vary sharply according to adopted Tac Cmin thresholds used by distinct centers in different time frames after organ transplantation[5-7].

FACTORS INFLUENCING TAC IPV

Interpatient variability of Tac has been attributed to interindividual pharmacokinetics variability which may be induced by several factors including drug-food and drug-drug interactions, concurrent clinical events such as diarrhea, cholestasis or liver dysfunction, ethnicity and pharmacogenetics[3,9-13]. In this regard, polymorphisms in CYP3A5, CYP3A4, and SLC and ABC transporter encoding genes have been shown to influence the area under the curve of tacrolimus, leading either to rejection or even toxicity in transplant recipients[4,13].

Tac IPV, on the other hand, has been additionally ascribed to non-adherence after organ transplantation, pre-analytical and analytical variables to measure Cmin in different commercially available biochemical assays and administration of different Tac formulations, including generic substitutions[3,5-7]. However, non-adherence is a common reason reported in medical literature to explain the observed deleterious effect of Tac IPV on patient and graft survival in organ transplantation by some[14-19], but not all authors[20,21].

Several approaches have been proposed to assess IPV, with most studies being retrospective, with different methodologies, considering pediatric and adult populations, with no organ-specific approach. Despite these limitations, IPV provides a sign that patients are at risk.

TAC IPV IN HEART TRANSPLANTATION

Four studies evaluating the influence of Tac IPV on HT outcomes were performed in adult patients using Tac CV[22-24] and Tac TTR[25], and in pediatric subjects using Tac SD/MLVI[26,27].

Concerning pediatric LT, Pollock-Barziv *et al*[26] associated Tac IPV with late rejection as well as worse patient and graft survival, but it is worth to mention that few heart transplant recipients were included in this study. Sirota *et al*[27] found similar results for rejection, but the authors also linked Tac SD/MLVI, particularly when higher than 3, to cardiac allograft vasculopathy and patient survival. In adults, Gueta *et al*[22] described an association of Tac IPV in the first year after HT with rejection after 12 but not between three and 12 mo after HT. On the other hand, Shuker *et al*[23] found no increase in the frequency of either early or late acute rejection or even cardiac allograft vasculopathy in heart transplant recipients. Both authors ascribed the lack of association of Tac IPV with early acute rejection[20] and overall rejection[23] to a higher immunosuppression exposure frequently observed in those heart transplant recipients. González-Vílchez *et al*[24] studied the largest cohort up to now. The authors found an effect of Tac IPV, assessed between four to 12 mo after HT, on the frequency of rejection after one year. Using Tac TTR, Baker *et al*[25] found no effect of Tac IPV on acute rejection within the first 30 d after HT. None of those studies in adults reported other outcomes such as mortality or Tac-related adverse events in association with Tac IPV[22-25]. The main findings related to HT are depicted in Table 1[22-27].

TAC IPV IN LUNG TRANSPLANTATION

Four studies have investigated the impact of Tac IPV in the frequency of acute and chronic rejection or chronic lung allograft dysfunction (CLAD) after lung transplantation in adults using Tac SD/MLVI[28], Tac CV[29] and Tac TTR[29-31]. Gallagher *et al*[28] demonstrated that higher Tac SD/MLVI between 6-12 mo after lung transplantation was associated with development of CLAD with an adverse impact on survival. Acute rejection, on the other hand was not associated with Tac SD/MLVI[28]. Ensor *et al*[30] evaluated retrospectively the role of Tac TTR in 292 Lung transplant recipients the development of acute and chronic rejection. Tac TTR was measured in the first year after lung transplantation. The authors observed a lower likelihood for acute rejection and CLAD whenever Tac TTR was increased by 10%. Lower rates of infection and mortality was also linked to high Tac TTR. Other authors failed to demonstrate higher frequency of acute rejection after lung transplantation when Tac IPV was assessed by either Tac CV or Tac TTR in the first 6 mo after surgery[29]. On the other hand, more recently Japanese investigators disclosed an association of acute rejection with Tac TTR calculated in the first six month after lung transplantation[31]. The main findings related to lung transplantation are depicted in Table 2.

Table 1 Tacrolimus intra-patient variability in heart transplantation: Main findings

Heart transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV, assessment**	**Outcome**
Gueta *et al*[22], 2018	72	Deceased	CV	High trough level variability is associated with higher rates of graft rejection, and trough level variability during the first year is associated with increased risk of rejection after HT
Shuker *et al*[23], 2018	86	Deceased	MAD	A high IPV was not associated with the development and progression of cardiac allograft vasculopathy or development of acute cellular rejection
González-Vílchez *et al*[24], 2022	1581	Deceased	CV	IPV levels had limited influence on mid-term outcomes in heart transplant, however high IPV may predispose to rejection in initially stable patients
Baker *et al*[25], 2019	67	Deceased	TTR	Higher TTR was not associated with a lower rate of Acute Cellular Rejection within the first 30 d after heart transplant
Pollock-Barziv *et al*[26], 2010	144	Deceased	SD	Associated Tac IPV with late rejection as well as worse patient and graft survival, but it is worth to mention that few heart transplant recipients were included in this study
Sirota *et al*[27], 2021	118	Deceased	SD	SD ≥ 3 is associated with increased risk of poor outcomes

CV: Coefficient of variability; HT: Heart transplant; MAD: Mean absolute deviation; TTR: Time in therapeutic range; SD: Standard deviation.

Table 2 Tacrolimus intra-patient variability in lung transplantation: main findings

Lung transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV assessment**	**Outcome**
Gallagher *et al*[28], 2015	110	Non specified	SD	Patients with highly variable trough tacrolimus levels in the second half of the first post-transplant year will likely have similar variability in the second year and are at high risk for subsequent chronic lung allograft dysfunction and death
Kao *et al*[29], 2021	157	Non specified	CV and TTR	The results suggest that tacrolimus TTR, time in therapeutic range, and variability are not related to the presence of ACR in LTRs
Ensor *et al*[30], 2018	292	Non specified	TTR	Tacrolimus TTR was predictive of clinical outcomes of ACR, CLAD, infection, and death in lung transplant recipients at 1 yr in this investigation after adjusting for potential confounders
Katada *et al*[31], 2022	90	Living and deceased	TTR	A lower tacrolimus TTR is a predictor of late acute rejection

SD: Standard deviation; TTR: Time in therapeutic range; ACR: Acute cellular rejection; LTR: Lung transplant rejection; CLAD: Chronic lung allograft dysfunction.

TAC IPV IN LIVER TRANSPLANTATION

Impact of Tac IPV on different outcomes after LT, including allograft rejection, postoperative complications and survival was evaluated in pediatric[26,32-35] and adult[36-42] transplant recipients using SD/MLVI[26,32-34], CV[35-41], and TTR [42].

Most studies performed in children associated higher SD/MLVI to biopsy-proven acute rejection (BPAR) at least six months after LT[42-34]. Defrancq *et al*[35] found similar results in another cohort of children using Tac CV one year after surgery. The authors reported an association between high Tac CV and BPAR and correlated Tac CV with albumin and bilirubin levels in different time frames after LT as well as with missed outpatient consultations, possibly reflecting immunosuppression adherence[33]. Decreased survival was also related to high Tac IPV in just one of those reports including few patients submitted to LT[26].

Up to now, seven reports were published in the medical literature concerning the effect of Tac IPV on post-LT outcomes in adults. In this regard, Christina *et al*[36] disclosed an association between Tac SD/MLVI and BPAR in patients submitted to LT. Similar findings were reported by Del Bello *et al*[37] who reported higher Tac CV measured just after LT discharge with BPAR, as well as with the occurrence of *de novo* anti-donor specific antibodies (*dn*DSA). No impact was seen in patient survival[37]. Van der Veer *et al*[39] evaluated the influence of Tac CV measured between six to 18 mo after LT in adult subjects. The authors were unable to disclose any association between Tac CV and immune mediated graft injury. Rayar *et al*[38] investigated the influence of Tac CV measured in the first 30 d after LT on postoperative outcomes. The authors found an increased frequency of acute kidney injury as well as cardiovascular and

Table 3 Tacrolimus intra-patient variability and liver transplantation: Main findings

Liver transplantation				
Ref.	**Sample size**	**Donor**	**Tac-IPV assessment**	**Outcome**
Lieber *et al*[18], 2013	988	Not specified	SD	Non-adherence among liver transplant recipients is associated with increased risk of graft failure
Stuber *et al*[19], 2008	96	Not specified	SD	The SD has utility of monitoring routine tac blood levels in pediatric recipients for detecting non-adherence prior to clinical rejection
Venkat *et al*[32], 2008	101	Not specified	SD	Variations in tac blood levels is associated with an increased risk of late allograft rejection in pediatric recipients
Shemesh *et al* [33], 2017	400	Both living and deceased donor	SD; MLVI	MLVI predicts late acute rejection in pediatric liver transplantation recipients
de Oliveira *et al* [34], 2017	50	Both living and deceased donor	SD; MLVI	MLVI may be a nice indicator of the risk of medication non-adherence in child-age
Defrancq *et al* [35], 2019	41	Both living and deceased donor	CV	High Tac IPV may be associated with adverse patient outcomes. Also, there is some impact of biological factors on IPV and therapy adherence
Christina *et al* [36], 2014	150	Not specified	SD; MLVI	The MLVI is associated with and can predict rejection, possibly related to non-adherence in adult recipients
Del Bello *et al* [37], 2018	116	Deceased donor only	CV	Tac IPV could be useful to identify patients with a greater risk of graft rejection and pf developing *de novo* DSA after liver transplantation
Rayar *et al*[38], 2018	812	Deceased donor only	CV	High CV of Tac concentrations was found to be predictive of Tac-related toxicity and poorer survival
van der Veer *et al* [39], 2019	326	Both living and deceased donor	CV	High IPV in Tac exposure beyond 6 mo after liver transplantation was not associated with imune-mediated graft injury
Dopazo *et al*[40], 2022	140	Deceased donor only	CV	High IPV between the third and sixth months appears to be an early and independent predictor of poorer liver transplant outcomes
Kim *et al*[41], 2022	636	Both living and deceased donor	CV	High Tac IPV was associated with increased risks of overall mortality and HCC recurrence in liver transplantation recipients with HCC

SD: Standard deviation; CV: Coefficient of variation; MLVI: Medication level variability index; DSA: Donor-specific antibodies; HCC: Hepatocellular carcinoma.

neurologic complications in patients with higher Tac CV. Most importantly, shortened graft and patient survival rates were also associated with Tac IPV[38]. Other authors investigated whether Tac CV, assessed between three to six months after LT, could be associated with worse graft and patient long-term outcomes[40]. In this study, lower long-term survival and poorer renal function were similarly observed in those subjects with high Tac CV. Another group of investigators also linked higher Tac IPV using CV with hepatocellular carcinoma (HCC) recurrence after LT[41]. Only one study up to now assessed the impact of Tac IPV after LT employing TTR[42]. The authors found that lower TTR in those subjects, irrespectively of Tac CV, was associated with a higher risk for *dn*DSA and long-term death-censored graft loss. The main findings related to LT are depicted in Table 3.

TAC IPV IN KIDNEY TRANSPLANTATION

Most of the studies published thus far demonstrated an adverse impact of Tac IPV on KT outcomes (Table 4)[43-68]. Most of them were performed in adult recipients using MLVI/SD[44], MAD[45-48,62,66], CV[49-60,63,64,67-68], TTR[61] or other methods[65]. In this regard, several authors have associated higher Tac IPV, usually measured more than 6 mo after KT, with BPAR[44-46], long-term graft loss or dysfunction[47-55,58,59,68] as well as with lower survival[50,51]. In some, but not all reports[62], higher Tac IPV was associated with the development of *dn*DSA[53,67], chronic active antibody mediated rejection[47] and chronic histological lesions in kidney grafts[54,56]. Most authors attributed those Tac IPV-related outcomes to non-adherence[43] and some[57-59] but not others[60] to genetic predisposition. Two other reports compared TTR[61] and a novel Tac variability score (TVS)[64] to conventional IPV measures and found that both were more reliable in their ability to predict worse outcomes after KT.

Concerning pediatric transplant recipients, Pollock-Barziv *et al*[26] were one of the first authors to show a significant association of higher Tac IPV and late graft rejection or loss. Similar findings were subsequently reported by other investigators who reported and association of higher Tac IPV with BPAR and graft loss beyond one year in children and adolescents submitted to KT[66-68].

Table 4 Tacrolimus intra-patient variability and kidney transplantation: Main findings

Kidney transplantation				
Ref.	**Sample size**	**Donor type**	**Tac-IPV assessment**	**Outcomes**
Borra *et al*[47], 2010	297	Both living and deceased donor	MAD	Significant relationship between high Tac-IPV and long-term graft failure
Ro *et al*[45], 2012	249	Both living and deceased donor	MAD	TAC IPV had a significant impact on rejection-free survival. The effect was influenced by CYP3A5 polymorphism
Sapir-Pichhadze *et al*[44], 2014	356	Both living and deceased donor	MLVI/SD	Increased time-dependent TAC SD may be an independent risk factor for adverse kidney transplant outcomes
O'Regan *et al*[49], 2016	394	Both living and deceased donor	CV	Inferior renal allograft survival was observed in recipients with higher Tac-IPV
Rodrigo *et al*[53], 2016	310	Deceased donor only	CV	Tacrolimus level variability is a strong risk factor for dnDSA development and death-censored graft loss
Whalen *et al*[46], 2017	376	Both living and deceased donor	MAD	Highly variable tacrolimus levels predict worse out- comes postrenal transplantation
Shuker *et al*[48], 2016	808	Both living and deceased donor	MAD	A high tacrolimus IPV is an independent risk factor for adverse kidney transplant outcomes that can be used as an easy monitoring tool to help identify high-risk RTRs
Vanhove *et al*[56], 2016	220	Both living and deceased donor	CV	High IPV is related to accelerated progression of chronic histologic lesions before any evidence of renal dysfunction
Rozen-Zvi *et al*[51], 2017	803	Both living and deceased donor	CV	The combination of high CV and exposure to low drug levels might identify high-risk patients in the early post-transplantation period
Goodall *et al*[50], 2017	688	Both living and deceased donor	CV	High tacrolimus IPV and clinic nonattendance are associated with inferior allograft survival
Sablik *et al*[62], 2018	248	Both living and deceased donor	MAD	A high Tac IPV per se does not predispose to the development of chronic active antibody mediated rejection (c-aABMR) but is associated with inferior graft survival once c-aABMR is diagnosed
Seibert *et al*[57], 2018	1472	Both living and deceased donor	CV	High variability of TAC dose increases risk of acute rejection. High variability of TAC trough increases risk of graft failure
Mo *et al*[54], 2019	671	Both living and deceased donor	CV	High IPV of Tac is associated with early deterioration of chronic histologic lesions as well as poorer long-term outcomes
Song *et al*[61], 2019	1241	Living donor only	TTR	Increasing the TTR of tacrolimus in the first year was associated with improved long-term outcomes in living kidney transplants, and TTR may be a novel valuable strategy to monitor tacrolimus exposure
Süsal *et al*[55], 2019	6638	Deceased donor only	CV	Even in patients with good outcome during the first 3 post-transplant years, a high IPV was associated with inferior graft survival, indicating that a fluctuating tacrolimus trough level at years 1, 2 and 3 post-transplant is a major problem in kidney transplantation
Rahamimov *et al*[52], 2019	878	Both living and deceased donor	CV	Monitoring CV can help detect the high-risk patients
Gold *et al*[66], 2020	1419	Deceased donor only	MAD	A more intense and less variable exposure to tacrolimus could improve graft survival strongly in patients with high TAC IPV
Stefanović *et al*[58], 2020	104	Both living and deceased donor	CV	Combined assessment of tacrolimus IPV and tacrolimus C0/D may categorize patients towards risk of graft deterioration in the long-term post-transplantation period
Stefanović *et al*[59], 2021	103	Both living and deceased donor	CV	Simultaneous assessment of Tac IPV, C0/D, and CYP3A5 genotype may identify patients at risk of deterioration of graft function in the long-term post-transplantation period
Kim *et al*[65], 2021	1080	Both living and deceased donor	CV	High tacrolimus IPV significantly increases the risk of graft failure and antibody mediated rejection in patients with high immunological risk
Park *et al*[63], 2021	1143	Both living and deceased donor	CV	TAC-IPV can significantly affect allograft outcomes even with a high mean TAC-C0
Yin *et al*[64], 2022	1343	Living donor only	CV	Tac variability score is a novel measure of Tac IPV with higher correlation with graft survival and more convenience in clinical use than CV after kidney transplantation
Baghai Arassi *et al*[67], 2022	48	Both living and deceased donor	CV	High Tac IPV is associated with an increased risk of dnDSA development and rejection episodes > year 1 posttransplant even in patients with low immunological risk profile

Nuchjumroon *et al* [60], 2022	188	Both living and deceased donor	CV	No evidence that the CYP3A5 polymorphisms significantly influence tacrolimus IPV during the 6 to 12 mo after kidney transplantation

SD: Standard deviation; CV: Coefficient of variation; MLVI: Medication level variability index; DSA: Donor-specific antibodies; TTR: Time in therapeutic range.

TAC IPV IN KIDNEY AND PANCREAS, AND BONE MARROW TRANSPLANTATION

Two studies have evaluated the impact of Tac IPV in the frequency of *dn*DSA, BPAR and graft loss in adult kidney and pancreas recipients[69,70] and in the occurrence of graft *vs* host disease after bone marrow transplantation[70]. The first report failed to disclose an association of Tac IPV with BPAR in adult recipients of kidney and pancreas transplants, but the main purpose of the study was to compare Tac IPV and graft function in groups of patients receiving two different Tac formulations[69]. Davis *et al*[38] on the other hand, demonstrated that Tac TTR was associated to a very high risk of *dn*DSA and a 4-fold risk of graft loss by five years, independently of Tac CV.

In respect to bone marrow transplant recipients, Marco *et al*[70] correlated high Tac IPV, measured by CV, with the occurrence of acute graft *vs* host disease in the first month after BMT (Table 5).

CONCLUSION

Altogether, available data up to now suggest that Tac IPV, possibly due to non-adherence and/or genetic, pharmacologic, or clinically significant factors, is associated with adverse outcomes after organ transplantation, particularly KT. The heterogeneity observed in the results obtained in the reports thus far are probably due to the retrospective design of most studies, the distinct methods used to assess Tac IPV, utilization of different immunosuppression protocols, distinct observation time frames and endpoints. Refinement or combination of different scores may improve usage of Tac IPV in clinical practice in the future.

Table 5 Tacrolimus intra-patient variability in pancreas and bone marrow transplantation: Main findings

Kidney and pancreas, and bone marrow transplant				
Ref.	**Sample size**	**Donor type**	**Tac-IPV Assessment**	**Outcome**
Torabi *et al* [69], 2020	39	Both living and deceased donor	CV	The once daily LCPT dosing may facilitate medication adherence and result in improved long-term outcomes
Marco *et al* [70], 2022	128	Living donor only	CV	Determination of Tac IPV soon after alloHSCT could be useful in identifying greater risks of aGVHD

CV: Coefficient of variation; LCPT: LCP-tacrolimus; alloHSCT: Allogeneic stem cell transplantation; aGVHD: Acute graft-vesus-host disease.

FOOTNOTES

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ORIGINAL ARTICLE

Case Control Study

Invasive aspergillosis in liver transplant recipients, an infectious complication with low incidence but significant mortality

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Abstract

BACKGROUND

Infections, including invasive fungal infections (IFIs), are among the leading causes of mortality in liver transplant recipients during the first year post-transplantation.

AIM

To investigate the epidemiology, clinical manifestations, risk factors, treatment outcomes, and mortality rate of post-liver transplantation invasive aspergillosis (IA).

METHODS

In this case-control study, 22 patients with IA were identified by reviewing the archived and electronic medical records of 850 patients who received liver transplants at the Imam Khomeini Hospital complex in Tehran, Iran, between 2014 and 2019. The control group comprised 38 patients without IA infection matched for age and sex. The information obtained included the baseline characteristics of liver transplant patients, operative reports, post-transplantation characteristics of both groups and information about the fungal infection of the patient group.

RESULTS

The prevalence rate of IA among liver transplant recipients at Imam Khomeini Hospital was 2.7%. The risk factors of IA among studied patients included high serum creatinine levels before and post-transplant, renal replacement therapy, antithymocyte globulin induction therapy, post-transplant bile leakage, post-transplant hepatic artery thrombosis, repeated surgery within 30 d after the

transplant, bacterial pneumonia before the aspergillosis diagnosis, receiving systemic antibiotics before the aspergillus infection, cytomegalovirus infection, and duration of post-transplant hospitalization in the intensive care unit. The most prevalent form of infection was invasive pulmonary aspergillosis, and the most common chest computed tomography scan findings were nodules, pleural effusion, and the halo sign. In the case group, prophylactic antifungal therapy was administered more frequently than in the control group. The antifungal therapy response rate at 12 wk was 63.7%. The 3- and 12- mo mortality rates of the patients with IA were 36.4% and 45.4%, respectively (compared with the mortality rate of the control group in 12 mo, which was zero).

CONCLUSION

In this study, the prevalence of IA among liver transplant recipients was relatively low. However, it was one of the leading causes of mortality following liver transplantation. Targeted antifungal therapy may be a factor in the low incidence of infections at our facility. Identifying the risk factors of IFIs, maintaining an elevated level of clinical suspicion, and initiating early antifungal treatment may significantly improve the prognosis and reduce the mortality rate of liver transplant recipients.

Key Words: Aspergillosis; Cytomegalovirus infection; Immunosuppression therapy; Liver transplantation; Risk factors; Fungal infections; Fungal pneumonia

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Core Tip: In our center, invasive aspergillosis had a low incidence but a high mortality rate among liver transplant recipients. Invasive pulmonary aspergillosis was the most prevalent form of infection. Nodules, pleural effusion, and halo signs were the most commonly observed findings on chest computed tomography scans. Antifungal prophylaxis was more prevalent in the case group than in the control group. At week 6 of antifungal treatment, more than 60% of patients experienced complete recovery or relative response to therapy.

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INTRODUCTION

Invasive aspergillosis (IA) is one of the most common invasive fungal infections (IFIs) following solid organ transplants (SOT) and the leading cause of mortality and morbidity among transplant recipients. Several studies have reported rates of IA in organ transplant recipients between 1% and 15%[1-4]. In the TRANSNET study, an extensive cohort study on the prevalence of IFI in SOT recipients, the annual incidence rate of IA was 0.65%, second only to candidiasis[5].

IA typically develops 1 to 3 mo after a transplant[6]. However, delayed IA (6 mo after transplant) has recently been reported[7]. In a Swiss Transplant cohort study, the incidence of IA among liver transplant recipients was significantly lower than among recipients of other organ transplants[8]. In immunocompromised hosts, Aspergillus can infect every organ; however, sinopulmonary involvements are more common. Involvement of the central nervous system (CNS) and multiple organs is more prevalent in liver transplants than in other SOT[9].

The mortality rate of IA among recipients of liver transplants has not fallen over the past 15 years (compared with other SOTs). The 90-day mortality rate of liver transplant recipients with IA is higher than that of recipients of other organ transplants (85.7% *vs* 15.9%)[8,10].

Early diagnosis and proper treatment of IA are associated with a more favorable prognosis. Noninvasive modalities (such as imaging and antigen detection) aid in antifungal treatment initiation and duration. However, aggressive diagnostic approaches, such as bronchoalveolar lavage (BAL), should be considered for patients with imaging findings suggestive of IA[11,12].

Investigations revealed that BAL culture has a sensitivity of 50% in focal pulmonary lesions[13]. In such instances, a definitive diagnosis necessitates aggressive procedures, such as a thoracoscopic biopsy. Invasive diseases are strongly predicted by isolating Aspergillus species from sputum or BAL samples[14]. In the early stages of IA, single or multiple nodules are the most frequent finding on computed tomography (CT) scans[15]. Halo sign with peri-nodular haziness is a reliable indicator of IA[16]. In serial CT scan studies, the halo sign decreases during the first week, while the air crescent sign (another radiologic marker of pulmonary IA) increases[17]. Despite the clinical response to antifungal therapy, pulmonary lesions increase in size during the first week of treatment.

Positive serum and BAL galactomannan (GM), in conjunction with IA predisposing factors of the host, clinical and imaging findings consistent with IA, eliminate the need for invasive procedures in diagnosing IA[18]. The GM sensitivity decreases in the case of simultaneous use of active antimold agents[19]. Historically, Piperacillin-Tazobactam has been

linked to false positive GM results[20]. Blood[21,22] and BAL[23,24] Aspergillus PCR are used for initial IA diagnosis. However, further prospective studies are required to investigate the combination of diagnostic modalities in the early IA stages.

Voriconazole is more effective than amphotericin B in the early treatment of IA and significantly improves survival (71% *vs* 58%)[25]. Voriconazole improved the prognosis of CNS involvements[26], which in most cases resulted in high mortality rates[27]. Accordingly, it is recommended as the treatment of choice for IA. There are no clinical trials involving echinocandins as a first-line treatment for IA. Recent attention has been drawn to a combination of echinocandin and amphotericin B or azoles, and *in vitro*, studies have confirmed the synergistic effect of this combination[28,29].

In probable aspergillus cases, a combination of echinocandin with amphotericin B was associated with 40%-60% prognosis improvement[30,31]. Marr *et al*[32] reported survival improvement by combining voriconazole and echinocandin (compared with voriconazole alone). However, further studies are required to investigate the advantages of combination therapy in IA. Patients who recovered a single episode of IA are at higher risk of re-infection during immunosuppressive therapy. Therefore, effective antifungal prophylaxis is recommended, particularly in the hematopoietic stem cell transplant (HSCT) group[33,34].

This study examined the prevalence, epidemiology, clinical manifestations, risk factors, antifungal therapy response, and prognosis of IA infection in liver transplant recipients.

MATERIALS AND METHODS

The study population consisted of liver transplant recipients in the Imam Khomeini Hospital complex between 2014 and 2019. This hospital is a major referral and educational hospital and the second-largest center of liver transplants in Iran, with over 100 transplants per year.

Inclusion criteria

The study included all patients who received a liver transplant between 2014 and 2019 and were diagnosed with probable/proven IA.

Exclusion criteria

Multi-organ transplant recipients were excluded from the study.

Control group

Patients without IFI after the liver transplant. The following formula was utilized to determine the sample size of the control group:

Z tests-Correlations: Two independent Pearson r's; Analysis: A priori: Compute required sample size; Input: Tail (s) = One; Effect size q = 0.84; α err probability = 0.05; Power (1-β err probability) = 0.90; Allocation ratio N2/N1 = 2.

Output

Critical z = 1.6448536; Sample size group 1 (case) = 21; Sample size group 2 (control) = 42; Total sample size = 63; Actual power = 0.9037178.

A questionnaire containing the necessary information was created and filled out using data from liver transplant recipients' electronic and non-electronic medical records. The pre-transplant information included: Age, sex, underlying diseases, the Model for End-Stage Liver Disease (MELD) score, intensive care unit (ICU) hospitalization before the transplant, ventilator support during the week before the transplant, fungal colonization or infection within three months before the transplant, dialysis within the month before the transplant, diabetes mellitus, bacteremia within a month before the transplant, bacterial peritonitis before the transplant, cytomegalovirus (CMV) serology, and creatinine level before the transplant.

The peri-transplant information included: The date of transplant, transplant type (from deceased or living donor), type of anastomosis (duct to duct or Roux-en-Y), cold ischemia time (measured by minutes), and the number of transfused blood units (packed cells) during the operation.

The post-transplant information of the patients included: Induction therapy, type of antifungal prophylaxis after transplant, repeated surgery within 30 d after the transplant, ICU admission duration, mechanical ventilation after the transplant, bacteremia and pneumonia within 2 wk before IA diagnosis, creatinine level at the time of diagnosis, CMV viremia or disease within one month before the diagnosis, transplant rejection requiring treatment within three months before the diagnosis of IA.

Aspergillus information included: The time of infection, proven or probable diagnosis, the involved organ, the result of fungus culture, GM, pathology, PCR, radiologic findings, type of antifungal treatment, response to treatment at weeks 6 and 12, death within 12 mo of diagnosis, repeated transplant within 3 mo of diagnosis, and transplant rejection requiring treatment within three months of diagnosis. Proven and probable diagnoses of IA were defined according to the European Organisation for Research and Treatment of Cancer (EORTC) criteria[35].

The surgical methods, preventative measures, and immunosuppressive regimen utilized at our center are described in another article[36]. However, since 2018, the antifungal prophylaxis method has been changed from universal to targeted prophylaxis, and since 2020, the diagnosis of CMV infection has been based on PCR rather than CMVPP65 Ag detection.

Ethical considerations

The Institutional Review Board of the Tehran University of Medical Sciences approved the study with the file number (IR.TUMS.MEDICINE.REC.1399.874). The patients' information was registered anonymously in questionnaires. Due to the study's retrospective nature, no written consent was obtained from the patients.

Data analysis

The data was analyzed using SPSS version 26. The data was expressed as mean ± standard deviation (SD) to present quantitative variables with normal distribution and frequency (%) for qualitative variables. The qualitative variables were analyzed by chi-squared test, and continuous quantitative variables with normal distribution were analyzed with Student's *t*-test. *P* values < 0.05 were considered statistically significant. Multiple logistic regression analyses (both multivariate and bivariate) were performed.

RESULTS

Between 2014 and 2019, 850 patients received a liver transplant at the Imam Khomeini Hospital Complex in Tehran, Iran. Investigations of these patients' medical records revealed 22 cases of IA. To examine the risk factors of IA, 38 liver transplant recipients without a history of IA who matched the case group regarding age and sex were selected as the control group and enrolled in the study. Table 1 summarizes both groups' demographic and pretransplant information (cases and controls).

Of 22 patients with IA infection, 18 (81.8%) were male, and 4 (18.2%) were female. The mean ± SD age of the patients was 45.27 ± 14.85 years. In the control group, 31 (81.6%) were male, and the mean age of the control group was 47.21 (SD = 12.03). The mean number of MELD scores in the case and control groups was similar (21.05 *vs* 20.24). The blood creatinine level in the case group before the transplant was significantly higher than in the control group [1.74 mg/dL *vs* 1.22 mg/dL, *P* value 0.04, odds ratio (OR): 0.34; confidence interval (CI): 0.13-0.87)]. There were no statistically significant differences between the proportions of fulminant hepatic failure (FHF) patients in the patient and control groups [*P* value = 0.18; 27.3% (*n* = 6) and 5.3% (*n* = 2), respectively]. A higher percentage of IA patients were re-transplants [22.7% (*n* = 5) *vs* 7.9% (*n* = 3), *P* = 0.13], but the difference was not statistically significant. The mean time between liver transplantation and occurrence of IA was 313 ± 337.64 d (range 15-1350 d).

The most prevalent symptom of IA was pulmonary aspergillosis. Of the 22 cases of IA, nine patients had confirmed IA, and 13 had probable IA. Amphotericin B was the primary antifungal treatment (empirical therapy) for 72.6% of the patients. Nodular lesions and halo signs were the most common radiographic findings among the patients (50% and 45.5%, respectively). At week 6 of antifungal therapy, complete recovery and response to treatment were observed in 10 patients (45.5%), and relative response to treatment was observed in 4 patients (18.2%). The mortality rate after the study period was 36.4%. (8 patients). Table 2 presents the patients' information regarding IA.

Among the variables related to the peritransplant period, four variables, including induction therapy with antithymocyte globulin (ATG) [case no = 8 (36.4%), control no = 6 (15.8%), *P* value < 0.001, OR: 0.08, CI: 0.02-0.41] biliary leakage (case no = 9 [40.9%], control no = 0, *P* value < 0.001]), reoperation within 30 d of the transplant [case no = 12 (54.5%), control no = 5 (13.2%), *P* value < 0.001, OR = 7.92, CI: 2.25-27.94], and hepatic artery thrombosis [case no = 8 (36.4%), control no = 1 (2.6%), OR = 21.14, CI: 2.42-184.79], were significantly higher among patients with IA (Table 3).

Within 2 wk before the IA diagnosis, the immunosuppressive regimen included tacrolimus and mycophenolate in over 80% of patients and the control group. Nineteen patients in the case group (86.4%) and 18 patients in the control group (47.4%) received antifungal prophylaxis (40.9% of the patients' group and 13.1% of the control group received voriconazole). Bacterial pneumonia was diagnosed in 13 individuals in the case group (59.1%) and four individuals in the control group (10.5%) within 2 wk of the fungal infection diagnosis (*P* value < 0.001).

During the 2 wk preceding the infection, 16 patients (72.7%) received antibiotics, whereas 39% (no = 15) of patients in the control group received antibiotics during the same period (*P* value < 0.01). The maximum creatinine level at the time of IA diagnosis was 1.87 mg/dL (SD = 1.1) in the case group *vs* 1.21 (SD = 1.43) in the control group. CMV viremia was significantly higher in IA patients [case no = 9 (40.9%), control no = 4 (10.5%), *P* value=0.009]. Transplant rejection requiring treatment within 3 mo before the IA diagnosis occurred in 13 patients in the case group (59.1%) and 10 patients in the control group (26.3%) (*P* value = 0.01; OR: 4.04; CI: 1.33-12.34).

The mean lengths of stay in the ICU at the time of transplantation were 4.1 d for the case group and 1.8 d for the control group (*P* value = 0.008). The number of patients in the IA group who underwent dialysis was greater [7 (31.8%) cases *vs* 4 (10.5%)] controls; *P* value = 0.08), but the difference was not statistically significant. The results pertaining to post-transplant factors are summarized in Tables 4 and 5.

The case group had a significantly lower 12-month survival rate than the control group (56.4% *vs* 100%) (*P* value < 0.001) (Tables 1 and 2).

DISCUSSION

The epidemiology of IFIs (including aspergillosis) among transplant recipients has changed during the last two decades. The incidence rate of IA has significantly reduced (from 40% to less than 10%), and most cases now occur more than 90 d after the transplant[37].

Table 1 Demographic information and background factors before transplantation of the study population

Covariate	Case	Control	*P* value	OR (95%CI)
Gender (Male)	18 (81.8%)	31 (81.6%)	0.9	-
Gender (Female)	4 (18.2%)	7 (18.4%)	0.9	-
Age mean (SD)	45.27 (14.85)	47.21 (12.03)	0.58	-
MELD score (SD)	21.05 (6.78)	20.24 (5.54)	0.62	-
Pretransplant ICU stay	1.95 (0.22)	1.97 (0.16)	0.9	-
Duration of pretransplant ICU stay	2 (1)	1 (0)	0.27	-
Pretransplant creatinine	1.74 (1.03)	1.22 (0.47)	0.04	0.34 (0.13-0.87)
Pretransplant ventilator within 1 wk	-	1 (2.6%)	0.9	-
Pretransplant dialysis within 1 mo	-	1 (2.6%)	0.9	-
Pretransplant diabetes mellitus	12 (54.5%)	15 (39.5%)	0.26	-
Fulminant hepatic failure	6 (27.3%)	2 (5.3%)	0.18	-
Immunosuppressive agents (steroids)	2 (9.1%)	6 (15.8%)	0.08	-
Immunosuppressive agent (antimetabolites)	1 (4.5%)	1 (2.6%)	0.08	-
Immunosuppressive agent (steroids & antimetabolites)	1 (4.5%)	0	0.08	-
Immunosuppressive agent (steroids & calcineurin inhibitors)	1 (4.5%)	0	0.08	-
Immunosuppressive agent (no)	12 (54.5%)	31 (81.6%)	0.08	-
The pretransplant episode of documented bacterial peritonitis	3 (13.6%)	5 (13.2%)	0.9	-
Previous systemic antibiotic use of more than 14 consecutive days	5 (22.7%)	6 (15.8%)	0.51	-
Re transplantation	5 (22.7%)	3 (7.9%)	0.13	-

CI: Confidence interval; ICU: Intensive care unit; OR: Odds ratio; SD: Standard deviation.

The prevalence of IA in liver transplant recipients was 2.7% in the present study. Other studies have reported incidence rates between 1% and 8%[4,38]. The lower incidence of IA is attributable to several factors, including improvements in surgical techniques, immunosuppressive regimens, and targeted antifungal prophylaxis in patients at moderate to high risk for fungal infection[37]. There was no significant difference between the two groups' underlying liver disease and MELD scores (case and control groups). In earlier studies, however, a MELD score greater than 30 was associated with an increased risk of fungal infection[38].

Several studies have investigated the risk factors associated with IA in transplant recipients. Among the identified risk factors are longer duration of surgery, severe blood loss during the operation, reoperation, steroid-resistant rejection, renal failure (especially when dialysis is required), CMV infection, diabetes, and long-term use of broad-spectrum antibiotics[39-41]. Fortún *et al*[40] (2002) found that positive GM, in addition to reoperation and post-transplant dialysis, was a risk factor for aspergillus infection in 13 patients with IA and 38 patients without IA (control group).

Due to epidemiological changes in IFIs among liver transplant recipients, antifungal prophylaxis for the low-risk group is no longer recommended. The American Society of Transplantation and Infectious Diseases Society of America (IDSA) reserves antifungal prophylaxis against candidiasis in moderate-risk patients (patients with complicated surgeries, anastomosis of choledochojejunostomy and candida colonization before transplantation), and anti-mold prophylaxis for high-risk patients (repeated liver transplant, repeating the surgery, and post-transplant renal replacement therapy)[42-44].

Our facility has also implemented a targeted prevention strategy since 2018. In our study, over 80% of patients with IA received antifungal prophylaxis, compared to less than 50% of patients in the control group.

ATG induction therapy was more common among patients with IA than the control group. Given that administering this medication as induction therapy in our facility is primarily reserved for patients with renal dysfunction, renal function may influence this relationship. However, the immunosuppressive therapy type is a known risk factor for IA[45, 46]. CMV reactivation, an additional risk factor for delayed IA, is one of the most common side effects of anti-thymocyte globulin therapy. In addition, an increased dose of immunosuppressives for the treatment of rejection episodes (such as administration of corticosteroid pulses) was more prevalent in the case group than in the control group (59.1% *vs* 26.3%)[46-49].

In the case group, post-transplant ICU stays were significantly longer than in the control group (4.1 *vs* 1.8). This statistically significant difference in ICU admission length reflects the critical illness of the case group (which requires intensive care) and their increased susceptibility to opportunistic infections[45].

Table 2 Clinical and laboratory information of patients with invasive aspergillus infection[1]

Covariate	Number (percent)
Diagnosis (proven)	9 (40.9%)
Diagnosis (probable)	13 (59.1%)
Site of diagnosis (isolated pulmonary)	19 (86.4%)
Site of diagnosis (isolated sinusitis)	2 (9.1%)
Site of diagnosis (peritonitis)	1 (4.5%)
Positive galactomannan (serum)	5 (22.7%)
Positive galactomannan (BAL)	8 (36.4%)
Positive galactomannan (N/A)	9 (40.9%)
PCR (positive)	8 (36.4%)
PCR (negative)	3 (13.6%)
PCR (N/A)	11 (50%)
Pathology (positive)	2 (9.1%)
Pathology (negative)	4 (18.2%)
Pathology (N/A)	16 (72.7%)
Fungal culture (positive)	10 (45.5%)
Fungal culture (negative)	2 (9.1%)
Fungal culture (N/A)	10 (45.5%)
Site of positive culture (sputum)	2 (9.1%)
Site of positive culture (BAL)	6 (27.3%)
Site of positive culture (sinus biopsy)	4 (18.2%)
Site of positive culture (pulmonary biopsy)	1 (4.5%)
Site of positive culture (peritonitis)	1 (4.5%)
CT scan findings (nodules)	11 (50%)
CT scan findings (ground glass opacity)	2 (9.1%)
CT scan findings (halo sign)	10 (45.5%)
CT scan findings (consolidation)	5 (22.7%)
CT scan findings (cavity)	3 (13.6%)
CT scan findings (pleural effusion)	7 (31.8%)
Treatment response at 6 & 12 wk (cure)	10 (45.5%)
Treatment response at 6 & 12 wk (partial response)	4 (18.2%)
Treatment response at 6 & 12 wk (stable)	-
Treatment response at 6 & 12 wk (progression)	-
Treatment response at 6 & 12 wk (death)	8 (36.4%)
12- month mortality	10 (4.45%)

[1]Cases information are attached.
BAL: Bronchoalveolar lavage; CT: Computed tomography; PCR: Polymerase chain reaction; N/A: Not applicable.

A creatinine level equal to or higher than 2 mg/dL is suggested as a risk factor for IA[5]. Renal dysfunction, renal replacement therapy, and dialysis after transplantation are known factors associated with the incidence of IFIs in organ transplant recipients[2,8,40,46]. In the current study, most patients with IA underwent dialysis; however, the difference was not statistically significant, which may be due to the low sample size and lower mean creatinine level before IA diagnosis.

Table 3 Comparison of factors related to the transplant of the study population

Covariate	Case	Control	*P* value	OR (95%CI)
Type of anastomosis (duct to duct)	16 (72.7%)	30 (78.9%)	0.53	-
Type of anastomosis (Roux-en-Y)	6 (27.3%)	8 (21.1%)	0.53	-
Cold ischemic time (h)	283.95 (66.58)	300.37 (58.39)	0.32	-
Underlying disease (NASH)	6 (27.3%)	6 (15.8%)	0.74	-
Underlying disease (PSC)	3 (13.6%)	8 (21.1%)	0.74	-
Underlying disease (HBV)	3 (13.6%)	5 (13.2%)	0.74	-
Underlying disease (HCV)	2 (9.1%)	1 (2.6%)	0.74	-
Underlying disease (AIH)	1 (4.5%)	3 (7.9%)	0.74	-
Underlying disease (AIH & HCC)	1 (4.5%)	1 (2.6%)	0.74	-
Underlying disease (HCV & NASH)	1 (4.5%)	-	0.74	-
Underlying disease (PBC)	1 (4.5%)	-	0.74	-
Underlying disease (Others)	4 (18.1%)	5 (13.2%)	0.74	-
Underlying disease (ASH)	-	2 (5.3%)	0.74	-
Underlying disease (HCV & HCC)	-	2 (5.3%)	0.74	-
Underlying disease (NASH & HCC)	-	2 (5.3%)	0.74	-
Underlying disease (NASH & PSC)	-	1 (2.6%)	-	-
Underlying disease (HBV & HCC)	-	1 (2.6%)	-	-
Underlying disease (Wilson)	-	1 (2.6%)	-	-
Intraoperative blood transfusion	3.45 (3.05)	2.5 (2.57)	0.2	-
Induction therapy (ATG)	8 (36.4%)	6 (15.8%)	< 0.001	0.08 (0.02-0.41)
Induction therapy (methyl prednisolon)	14 (63.6%)	32 (84.2%)	< 0.001	0.05 (0.01-0.25)
Biliary leak post-transplant	9 (40.9%)	-	< 0.001	-
Reoperation within 30 d of transplant	12 (54.5%)	5 (13.2%)	< 0.001	7.92 (2.25-27.94)
Hepatic artery thrombosis post-transplant	8 (36.4%)	1 (2.6%)	< 0.001	21.14 (2.42-184.79)

AIH: Autoimmune Hepatitis; ASH: Alcoholic Steatohepatitis; ATG: Antithymocyte Globulin; HBV: Hepatitis B Virus; HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; NASH: Nonalcoholic Steatohepatitis; PBC: Primary Biliary Cirrhosis; PSC: Primary Sclerosing Cholangitis; CI: Confidence interval; OR: Odds ratio.

According to previous studies[8,46] and the current investigation, any local or systemic infection requiring IV antibiotics for more than 3-14 d is associated with further disruption of the normal microbial flora, the predominance of opportunistic pathogens, and an increased risk of IA. The incidence of bacterial pneumonia was significantly higher in IA cases two weeks before diagnosis (59.1% in the case group compared with 10.5% in the control group). The proportion of IA patients receiving systemic antibiotics two weeks before diagnosis was also greater than that of the control group (P = 0.01).

CMV is one of the immunosuppressive viruses known to cause various complications in organ transplant recipients due to cytokine dysregulation. CMV infection has been associated with increased susceptibility to IFIs due to dysfunction of the host's neutrophils and macrophages, which play a crucial role in aspergillosis defense. According to our study, CMV viremia was four times higher in IA patients than in the control group (40.9% *vs* 10.5%). Previous research shows CMV viremia is one of the most prominent predictors of IA (mostly the late form of IA)[10,40].

According to previous studies[47,49,50], type of anastomosis (Roux-en-y choledochojejunostomy), repeated transplant, FHF, antibiotics, and immunosuppressive medications before the transplant are among the reported risk factors for post-liver transplant aspergillosis. However, our study did not observe a significant difference between the two groups regarding these factors, which may be due to the low sample size of the present study.

In the past two decades, the rate of late IA (more than 90 d after transplant) has increased with intervals ranging from 22 to 1117 d[9,10,40,46]. An average of 313 d elapsed between the time of liver transplantation and the occurrence of IA, according to the present study (range 15-810 d). This shift in the onset of IA infection may be attributable to improvements in the early management of high-risk patients, advances in surgical techniques, or delayed risk factors (including CMV infection).

Table 4 Comparison of the post-transplant factors in the study population

Covariate	Case	Control	*P* value	OR (95%CI)
Antifungal prophylaxis after transplant (Fluconazole)	10 (45.5%)	13 (34.2%)	0.003	0.20 (0.05-0.85)
Antifungal prophylaxis after transplant (voriconazole)	9 (40.9%)	5 (13.1%)		0.08 (0.02-0.43)
Antifungal prophylaxis after transplant (no)	3 (13.6%)	20 (52.7%)		-
Bacteremia within 2 wk before diagnosis	3 (13.6%)	4 (10.5%)	0.70	-
Pneumonia within 2 wk before diagnosis	13 (59.1%)	4 (10.5%)	< 0.001	0.08 (0.02-0.31)
Systemic antibacterial within 2 wk before diagnosis	16 (72.7%)	15 (39.5%)	< 0.001	4.09 (1.31-12.81)
Dialysis requirement	7 (31.8%)	4 (10.5%)	0.08	
CMV viremia before diagnosis	9 (40.9%)	4 (10.5%)	0.009	5.89 (1.54-22.47)
CMV diseases before diagnosis	3 (13.6%)	2 (5.3%)	0.35	
Length of ICU stay at the time of transplant	4.05 (3.59)	1.75 (1.20)	0.008	0.56 (0.38-0.82)
Duration of mechanical ventilation at the time of transplant	1.25 (0.55)	1.12 (0.41)	0.34	
Creatinine at the day of diagnosis (highest value)	1/87 (SD:1/1)	1/21 (SD:1/43)	-	-

CI: Confidence interval; CMV: Cytomegalovirus; ICU: Intensive care unit; OR: Odds ratio; SD: Standard deviation.

Table 5 Rejection before and after diagnosis of invasive aspergillosis

Covariate	Case	Control	*P* value	OR (95%CI)
Rejection requiring treatment within 3 mo before diagnosis	13 (59.1%)	10 (26.3%)	0.01	4.04 (1.33-12.34)
Rejection required treatment after diagnosis	4 (18.2%)	4 (10.5%)	0.45	-

CI: Confidence interval; OR: Odds ratio.

Statistically significant differences were also observed between patients with IA and controls regarding biliary leakage after transplant (40.9% *vs* 0%) and hepatic artery thrombosis (36.4% *vs* 2.6%). It is necessary to consider these factors when determining the risk of IFIs. However, no similar findings were reported in the published literature.

Lungs were this study's most common site of IA (86.4%). This finding was consistent with other studies, which indicated that pulmonary aspergillosis (66% to 79%) was the most prevalent form of IA[4,46]. Environmental exposure to Aspergillus and inhalation of spores will result in airway colonization, which can progress to infection and disease development following transplant-induced immunodeficiency[4,46]. Elevated GM levels at any time after transplantation are an independent factor associated with aspergillosis, which may be a suitable predictor of IA prognosis[40]. In addition to a positive culture or positive PCR of secretions, GM serum antigen > 0.5 or BAL GM > 1 with a sensitivity of 22% and specificity of 84% aids in the diagnosis of IA[51].

In our study, GM was detected in 59.1% of cases, most of which were in the BAL. This finding is consistent with previous research indicating that BAL GM is more sensitive[18,52]. Due to the absence of GM measurement in the control group, the sensitivity and specificity of this test for IA diagnosis cannot be calculated.

In the present study, the most common CT scan findings were lung nodules (50%), halo sign (45.5%), and pleural effusion (31.8%). According to previous research, imaging-specific findings are ground glass opacities, cavities, and the nodule (with or without a halo sign)[15-17]. Halo sign, a typical and early finding of IA in HSCT and neutropenic patients, is rarely observed in SOT patients[53,54]. The high frequency of halo signs in the present study may be due to early diagnosis of this infection and conducting lung CT scan in our center as a primary diagnostic action for each patient with changes in general conditions, with or without pulmonary symptoms.

According to the most recent IDSA guidelines, voriconazole is the drug of choice for IA[55]. Isavuconazole and liposomal amphotericin B are alternatives. In our study, liposomal amphotericin B was administered to most patients with a high probability of fungal infection. After the diagnosis was confirmed, the treatment was changed to voriconazole. Those who received voriconazole had a higher recovery and survival rate than those who received amphotericin B[25]. In our study, the response to treatment, defined as complete and partial recovery within 12 wk of initiating antifungal treatment, was 45.5% and 18.2%, respectively. The overall treatment response rate of 63.7% was consistent with previous studies[9,42].

Overall, 16.9% of the mortality during the first year post-transplant is due to IA. The highest mortality rate is observed in CNS involvements and disseminated aspergillosis[10]. However, due to the increased rate of late-onset IA, the mortality has been reduced from 65%-92% to 22% (the higher mortality rate was related to the studies before 2000)[56].

Nevertheless, the mortality rate of IA in liver transplant patients remains high[8]. According to our study, the 12-week mortality rate was 36.4%. A study by Nagao *et al*[7] (2016) on five IA patients reported a mortality rate of 80%. The one-year survival rate of aspergillosis patients in this study was 54.6%. In contrast, the entire control group population survived one year after the transplant. A study by Barchiesi *et al*[4] revealed a 35% one-year survival rate. After the year 2000, the survival of patients who received voriconazole improved in the absence of renal failure.

Considering the study's retrospective nature, it was impossible to investigate several factors (including the role of GM and β-d-glucan in the IA diagnosis). In addition, due to the absence of invasive diagnostic procedures, most IA patients were not diagnosed.

CONCLUSION

Despite the significant decline in the incidence of IA at our center, this disease has a negative impact on the survival of transplant recipients. Early diagnosis based on clinical symptoms and imaging modalities, as well as identification of factors related to the incidence of IA, is of significant importance. The imaging findings of aspergillosis, including nodule and halo signs, continue to play a crucial role in diagnosing this lethal invasive infection.

Furthermore, according to our study, the level of creatinine before the transplant, the creatinine level after the transplant, or patients who require renal replacement therapies after transplantation, induction therapy with ATG, ICU length of stay after the transplant, pneumonia 2 wk before the IA diagnosis, CMV viremia within one month before the IA diagnosis, receiving systemic antibiotics more than three days within the two weeks before the IA diagnosis, treatment-required transplant rejection within three months before the IA diagnosis, repeated surgery within 30 d after the transplant were the risk factors associated with increased risk of IA. We also hypothesize that biliary leakage and hepatic artery thrombosis after the transplant are two potential risk factors for IA.

ARTICLE HIGHLIGHTS

Research background

During the past two decades, the incidence rate and onset time of invasive fungal infections (IFIs), such as aspergillosis, have changed in liver transplant recipients.

Research motivation

Determining the new risk factors and treatment outcomes of early and late-onset invasive aspergillosis (IA) in high-volume centers for liver transplants is essential. It may have a key role in improving the prognosis of these patients.

Research objectives

This study sought to determine the prevalence, risk factors, treatment outcomes, and prognosis of IA infection among liver transplant recipients at our institution. We also investigated the study patients' major clinical, laboratory, and radiologic manifestations of IA.

Research methods

To determine the prevalence of IA, we analyzed the data of 850 patients who received a liver transplant at the Imam Khomeini Hospital Complex in Tehran, Iran, between 2014 and 2019, and recorded the study variables for patients with an IA diagnosis. In addition, we devised a case-control study to identify the risk factors for IA and compare the prognoses of patients with and without IA.

Research results

Our center's IA rate was 2.7%. Pulmonary aspergillosis was the most common presentation of the patients with IA. In most of our patients, imaging findings indicative of aspergillosis, including nodule and halo signs, were detected. The high level of creatinine before and after the transplant, renal replacement therapy after transplantation, induction therapy with antithymocyte globulin, longer duration of intensive care unit admission after the transplant, pneumonia 2 wk before the IA diagnosis, cytomegalovirus viremia within 1 mo before the IA diagnosis, receiving systemic antibiotics for more than three days within the 2 wk before the IA diagnosis, treatment-required transplant rejection within three months before the IA diagnosis, receiving systemic antibiotics for longer than three months before the IA diagnosis, repeated surgery within 30 d after the transplant, biliary leakage after the transplant and hepatic artery thrombosis were the risk factors associated with increased risk of IA.

Research conclusions

In this study, the prevalence of IA among liver transplant recipients was relatively low. However, it was one of the leading causes of mortality following liver transplantation. Identifying and addressing risk factors for IA, early diagnosis and prompt treatment of this fatal disease may improve the prognosis and decrease the mortality rate of liver transplant recipients.

Research perspectives

The primary risk factors of IA in liver transplant recipients should be determined through a large, multicenter study. Moreover, we must investigate the role of noninvasive and rapid diagnostic tests in diagnosing patients suspected of IFI early.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Reasons and effects of the decline of willing related potential living kidney donors

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Abstract

BACKGROUND

Although the availability of related living donors (LDs) provides a better chance for receiving kidney transplantation (KT), the evaluation protocols for LD selection remain a safeguard for the LD's safety. These protocols are variable from one center to another, resulting in variable rates of decline of the potential LDs (PLDs). The decline of willing PLDs may occur at any stage of evaluation, starting from the initial contact and counseling to the day of operation.

AIM

To identify the causes of the decline of PLDs, the predictors of PLD candidacy, and the effect on achieving LDKT.

METHODS

A retrospective study was performed on the willing PLDs who attended our outpatient clinic for kidney donation to their related potential recipients between October 2015 and December 2022. The variables influencing their candidacy rate and the fate of their potential recipients were studied. Two groups of PLDs were compared: Candidate PLDs after a completed evaluation *vs* non-candidate PLDs with a complete or incomplete evaluation. A multivariate logistic regression was performed to assess the factors contributing to the achievement of PLD candidacy.

RESULTS

Of 321 willing PLDs, 257 PLDs (80.1%) accessed the evaluation to variable extents for 212 potential recipients, with a mean age (range) of 40.5 ± 10.4 (18-65) years,

including 169 females (65.8%). The remaining 64 PLDs (19.9%) did not access the evaluation. Only 58 PLDs (18.1%) succeeded in donating, but 199 PDLs (62.0%) were declined; exclusion occurred in 144 PLDs (56.0%) for immunological causes (37.5%), medical causes (54.9%), combined causes (9.7%), and financial causes (2.1%). Regression and release occurred in 55 PLDs (17.1%). The potential recipients with candidate PLDs were not significantly different from those with non-candidate PLDs, except in age (P = 0.041), rates of completed evaluation, and exclusion of PLDs (P < 0.001). There were no factors that independently influenced the rate of PLD candidacy. Most patients who failed to have KT after the decline of their PLDs remained on hemodialysis for 6 mo to 6 years.

CONCLUSION

The rate of decline of willing related PLDs was high due to medical or immunological contraindications, release, or regression of PLDs. It reduced the chances of high percentages of potential recipients in LDKT.

Key Words: Donor decline; Donor evaluation; Donor exclusion; Kidney transplantation; Living kidney donors; Related living donors

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Core Tip: The rate of decline of willing related potential living kidney donors (PLDs) was high (82%). The causes of decline included exclusion by the transplant team due to contraindications of donation, release after disqualification of the potential recipients, and regression due to withdrawal of the decision by the PLD. PLD exclusion was the commonest form of decline due to medical or immunological contraindications. The high rate of PLD decline resulted in the loss of chances of kidney transplantation for high percentages of potential recipients who were left on dialysis for variably long periods, who died, or who were lost to an unknown fate.

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INTRODUCTION

Living donor kidney transplantation (LDKT) is the optimal form of renal replacement therapy. It shortens the waiting times and provides better survival rates. Hence, it is recommended as the first choice of treatment for each candidate patient with end-stage renal disease (ESRD), especially with the availability of related potential LDs (PLDs)[1,2]. However, it is not easy to find a willing and suitable LD. In addition, the preparation of a potential donor-recipient pair for KT is a complex sequential process[3,4]. Relative to the variability of assessment protocols, the reported acceptance rate of LDs is variable at 8.0%-18.4%[4,5]. This variability in acceptance of LDs is significant among countries, medical societies, health organizations, and KT units[3,6].

A large proportion of those PLDs may initially be declined for demographic issues, such as unsuitable age and genetic unrelatedness, or excluded later during preparation due to different medical reasons[5,7,8]. Although the exclusion of a willing potential LD may negatively reflect on the potential recipients by reducing their chances of transplantation, it is still a paramount principle not to violate the donor's safety for the recipient's benefit[3-5]. In our center, the maintenance of this narrow-margin principle between the donor's safety and the recipient's benefit through the assessment process was the motivator for the conduct of the current study. The aim was to assess the reasons for the decline of PLDs and their effects on the fate of potential recipients.

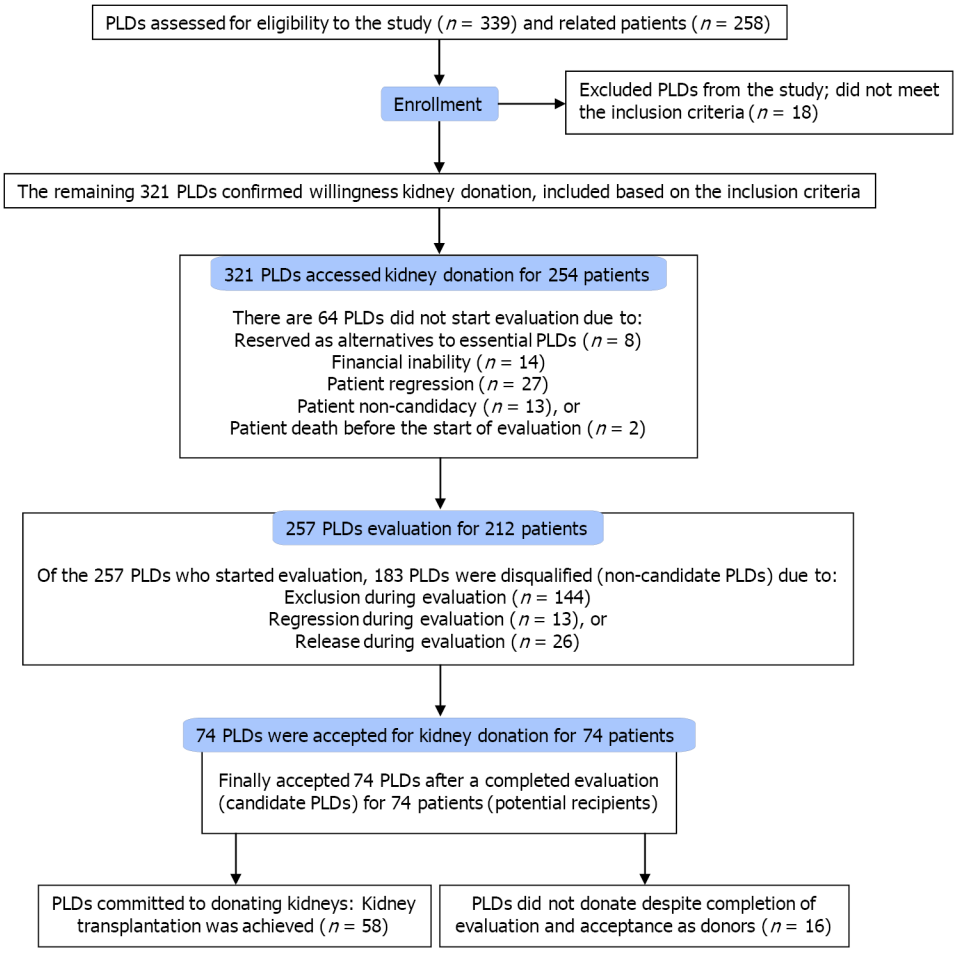
MATERIALS AND METHODS

Study design

A retrospective study was carried out by reviewing the data of the PLDs of ESRD patients who presented to our center seeking KT from October 2015 to December 2022. The inclusion criteria were a related PLD presenting to our center for donation to a related, intended patient with ESRD. Exclusion criteria included an initial failure to confirm the willingness to donate a kidney (Figure 1).

The flow of PLD evaluation

In our policy, the process of PLD evaluation is differentiated into six phases, from the initial contact to the achievement of a donation (Figure 2). Owing to the unavailability of a national waitlisting program and the nature of related living



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Figure 1 Flowchart of the potential living kidney donors and their intended recipients showing the levels of decline of the potential donors from the stage of access to the kidney transplantation center to the achievement of kidney transplantation. PLD: Protentional living donor.

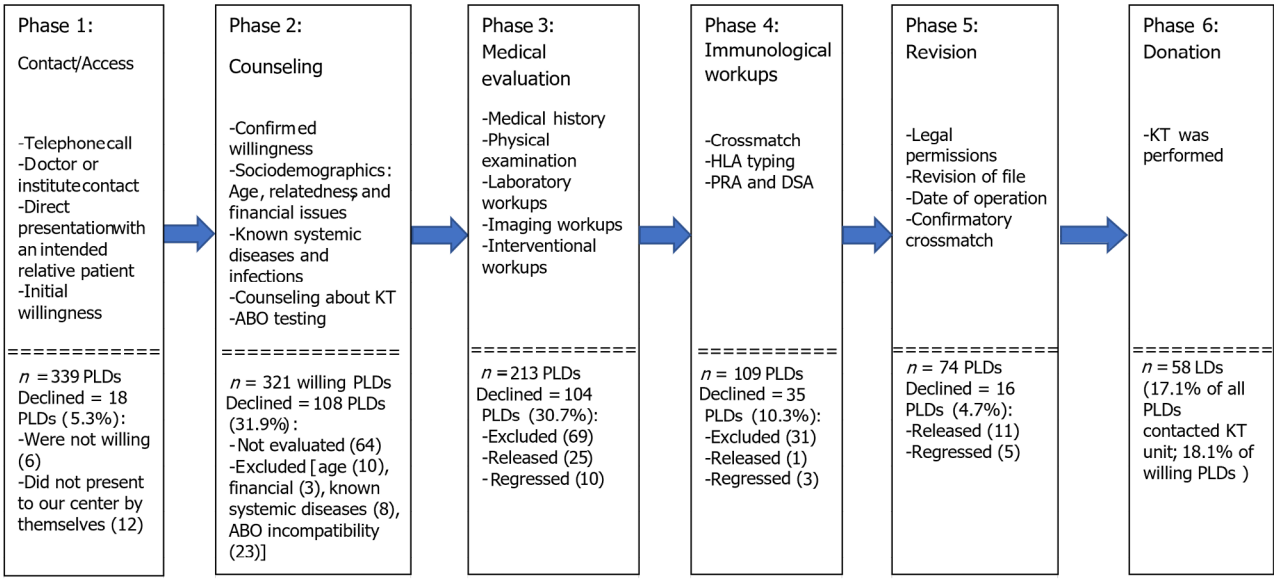
kidney donation (LKD), PLDs directly present with their intended recipients at the KT center. The initial two phases consist of contact with the KT center, confirmation of willingness to donate a kidney to an intended related potential recipient, counseling about KT, sociodemographic evaluation (age, familial relationships, and financial issues), and blood group matching. Initial history taking is usually performed at the first contact or counseling session, excluding previously known systemic diseases, financial issues, and factors violating the integrity of volunteer donation.

The third and fourth phases are multidisciplinary steps, including medical and immunological evaluations. The medical evaluation consists of detailed medical history, physical examinations, laboratory workups, and imaging workups. Kidney function was evaluated using the Technetium 99-diethylenetriamine pentaacetate renography for measurement of the total and split glomerular filtration rates in all PLDs. However, the anatomical features were evaluated by abdominal ultrasonography and contrast-enhanced computed tomography with renal angiography. In addition, psychosocial assessment was a routine workup to evaluate the mental status of the PLDs, motives for donation, cognitive capacity, expectations after donation, and exclude any psychogenic drive for self-harm. Furthermore, evaluation and exclusion of drug addiction was performed. The immunological workups include crossmatching, human leukocytic antigen (HLA) typing, and panel reactive antibody tests.

The fifth phase includes medicolegal permissions, determination of the date of surgery, and revision of the important tests. The sixth phase is the donation achievement.

Study outcomes and variables

The primary outcome of this study was the rate of PLD candidacy. It was defined as the percentage of PLDs with complete preparation for LKD and acceptance for donation, either when the transplantation was performed or it was cancelled due to causes related to the patient. Because the relevant characteristics of the intended patients were significant for the identification of the causes of decline of PLDs and their fates, these characteristics of those intended patients and their distribution per the outcomes of evaluation of their PLDs were studied. Each patient's file was examined for relevant demographic and clinical characteristics and related PLDs. The studied characteristics included the number, age, relatedness form and degree, decline form (exclusion, release, or regression), and causes of the decline of PLDs. In addition, the fate of PLDs and patients with declined PLDs was studied. Here, the relatedness was presented relative to



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Figure 2 Diagram of the different phases of the evaluation of the potential living kidney donors, showing the essential workups, percentages of declined donors, and causes of decline in each phase. DSA: Donor-specific antigens test; HLA: Human leukocytic antigen; KT: Kidney transplantation; PLD: Protentional living donor; PRA: Panel reactive antibodies test.

the genetic relatedness degrees (ABO-relatedness).

According to the primary outcome, the PLDs were differentiated into two groups. The first group was the candidate donors, including the finally accepted donors with a completed evaluation and preparation for donation. The second group was the non-candidate donors, including the remaining donors who were disqualified as PLDs, either with or without initial acceptance or a completed evaluation. The characteristics of both groups were compared with each other. The secondary outcomes were the rate of PLD decline in each phase of evaluation and the fate of patients with declined PLDs.

Sociodemographic definitions and documentation of donor-recipient relatedness

Throughout the process of LKD, the different statuses of the PLD were distinguished from each other as well-defined clinical events. They were defined to describe the events of PLD evaluation, from access to the achievement of LKD (Table 1). Based on these definitions, the outcomes of the study were estimated.

Official documents from the Civil Registry Office were requested to document the degree of genetic relatedness between the PLD and the intended recipient. Routinely, the birth certificates and national identity numbers for all PLDs and their intended recipients were the basic documents. In our center, the first and second degrees of genetic relatedness of PLDs were routinely allowed, based on these routine documents. If there was difficulty finding a PLD, the third and fourth degrees were allowed after investigations, and they were mostly processed similarly to the unrelated PLDs. In the latter instances, further documentation was warranted, such as a family genealogy tree from the Civil Registry Office and consent registered in the Real Estate Publicity Department and Documentation Office.

The processes employed to investigate the transparency of kidney donation

The transparency of the donation as an unpaid act was verified *via* multiple processes to identify and exclude any financial agreements in these cases: (1) Direct confrontation of the PLD and intended recipient with this issue during counseling and warning them that KT would not be done if there was any violation to the moral donation principle; (2) The KT ethical committee, which is composed of three medical professors who do not belong to the KT team, has the authority to investigate and revise the process of preparation, including the soundness of donation principles; (3) Each patient with a PLD of more than the second degree genetic relatedness had to introduce the proofs (official papers or documents) of the relatedness to his PLD from the Civil Registry Office; (4) As mentioned above, each PLD accepted for donation of his kidney had to sign a consent that the donation was for free without any financial or non-financial rewards from the intended recipient or from other relatives. This consent was documented by the Real Estate Publicity Department and Documentation Office; and (5) The Egyptian Supreme Committee of Organ Transplantation revises all these files and documents to prove the family tree and degree of relatedness between each candidate PLD and the intended recipient, with a special attention to exclude any financial agreements.

Ethical approval

This study was conducted as part of a research project on the outcomes of LDKT performed in our center. The institutional review board number is 17200148/2017.

Table 1 Definitions of terms used to describe the living donors at different stages of kidney donation including access, counseling, evaluation, acceptance, candidacy, and donation with kidney transplantation of related intended patients

Term	Definition
PLD	An individual who confirmed his willingness to donate a kidney to an intended patient at the initial counseling settings and was ready to start the evaluation for kidney donation, regardless of the commencement of the evaluation
Related PLD	PLD who had a relative intended patient with end-stage renal disease up to the 4th degree of genetic relatedness. Regardless of their genetic relatedness, the wife or husband of a recipient was considered a related PLD
Excluded PLD	PLD who was disqualified as a kidney donor and excluded from the process of kidney donation by KT team due to causes that disqualify candidacy to donate a kidney, such as medical, immunological, or financial causes
Regressed PLD	PLD who withdrew his decision of kidney donation at any stage after an initial confirmation of the donation decision and before the operation
Released PLD[1]	PLD who was still willing and completed or was still continuing the evaluation, but the related intended patient was withdrawn from KT preparation due to any cause
Candidate PLD	PLD who completed all the steps of evaluation and was finally accepted by the KT team for kidney donation, regardless of the later regression or release from donation
Accepted PLD	PLD who completed the evaluation without exclusion from kidney donation and was accepted for donation without release or regression from his willingness
LD	PLD becomes a LD when he succeeds in donating a kidney to his/her intended patient, which also means KT was achieved
Relatedness degrees and forms[2]	First degree: father, mother, son, daughter, wife, and husband. Second degree: brother, sister, grandfather, grandmother, grandson, and granddaughter. Third degree: nephew, uncle and aunt. Fourth degree: cousins

[1]In this study, release of the donor meant that the donor became free from any commitment to donating a kidney because his relative intended patient was excluded, regressed, or died. In addition, the donor would not be allocated to another patient, as he/she was willing to donate to his intended relative only.
[2]Husband-wife couples were processed as first-degree related potential living donors when donations were planned between each couple. However, they may be genetically related or unrelated, relative to their premarriage relatedness. KT: Kidney transplantation; LD: Living donor; PLD: Potential living donor.

Statistical analysis

Statistical analysis was performed with EasyMedStat software (version 3.21.4; www.easymedstat.com). The continuous data were presented as mean ± standard deviation and range. The categorical data were presented as frequency and percentage for each category. Two groups of PLDs were compared: candidate PLDs after a completed evaluation *vs* non-candidate PLDs with a complete or incomplete evaluation. Normality and hetereoskedasticity of continuous data were assessed with the White test (or Shapiro-Wilk in multivariate analysis) and Levene's test, respectively. Continuous outcomes were compared with the unpaired Student *t*-test, Welch *t*-test, or Mann-Whitney *U* test according to the data distribution. Categorical outcomes were compared with the *chi-squared* or Fisher's exact test. A multivariate logistic regression was performed to assess the factors contributing to the achievement of PLD candidacy. The data were checked for multicollinearity with the Belsley-Kuh-Welsch technique. A P value < 0.05 was considered statistically significant.

RESULTS

A total of 302 patients were referred to our center for related LDKT during the time frame of this study. The mean age (range) was 32.0 ± 11.7 (12-66) years. Of them, 44 patients (14.6%) did not have PLDs at presentation. The remaining 258 patients (85.4%) had 1-3 PLDs, constituting a total of 339 related PLDs. Eighteen PLDs (5.3%) were considered unwilling to donate a kidney as they could not confirm their willingness at the initial contact and presentation and were excluded from the study. However, the remaining 321 PLDs (94.7%) confirmed their initial willingness to donate to 254 relative patients and were included in the study (Figures 1 and 2). The mean (range) age of all the willing PLDs was 39.7 ± 10.4 (18-65) years, and they included 116 males (36.1%) and 205 females (63.9%).

Despite the confirmed willingness, 64 of 321 PLDs (19.9%) did not start the evaluation. The causes included financial inability in 14 PLDs (21.9%), serving as reserve donors in 8 PLDs (12.5%), patient non-candidacy to KT in 13 PLDs (20.3%), patient regression from KT in 27 PLDs (42.2%), and patient death in 2 PLDs (3.1%).

The remaining 257 PLDs (80.1%) were relatives of 212 patients (83.5%) (Tables 2-5). At the different levels of evaluation and preparation for the final acceptance as LDs (Figure 2), these 257 PLDs variably passed these levels of evaluation with two main outcomes. The first outcome was the completion of the evaluation with candidacy in 74 PLDs (28.8%). The second outcome was the failure to achieve the candidacy outcome in 183 PLDs (71.8%) (Table 5). The causes of the latter outcome were PLD exclusion in 144 PLDs (72.4%), regression from the donation decision in 18 PLDs (9%), and release after the disqualification of their potential recipients in 37 PLDs (18.6%) (Tables 3 and 4). In PLDs with candidacy for donation, 16 PLDs (21.6%) did not commit to donation. Accordingly, only 58 LDs (78.4%) succeeded in committing to

Table 2 Demographic and clinical characteristics of patients and related potential living donors presented as total patients (*n* = 212) and as a comparison between patients with candidate (*n* = 74) and patients with non-candidate (*n* = 138) potential living donors

Characteristics	Total patients, *n* = 212	Patients with candidate PLDs, *n* = 74	Patients with non-candidate PLDs, *n* = 138	*P* value
	mean ± SD (range)/number (%)			
Mean age in yr	31.2 ± 10.6 (13-66)	29.1 ± 9.6 (13-57)	32.9 ± 12.0 (14-66)	0.041
Sex, *n* = 212				
Males	173 (81.6%)	67 (90.5%)	106 (76.8%)	0.087
Females	39 (18.4%)	7 (9.5%)	32 (23.2%)	
Status of dialysis at presentation, *n* = 212				
Preemptive	19 (9.0%)	5 (6.8%)	14 (10.1%)	0.462
On regular hemodialysis	193 (91.0%)	69 (93.2%)	124 (89.9%)	
Primary kidney disease, *n* = 212				
Unknown	167 (78.8%)	56 (75.7%)	111 (80.4%)	0.088
Systemic disease	14 (6.6%)	3 (2.7%)	11 (8.0%)	
Glomerulonephritis	6 (2.8%)	3 (4.0%)	3 (2.2%)	
Hereditary renal disease	5 (3.8%)	2 (2.7%)	3 (2.2%)	
Obstructive uropathy	11 (5.2%)	8 (10.8%)	3 (2.2%)	
Urolithiasis	9 (4.2%)	2 (2.7%)	7 (5.1%)	
Categories of primary kidney disease, *n* = 212				
Unknown	167 (78.8%)	56 (75.7%)	111 (80.4%)	0.154
Systemic disease	14 (6.6%)	3 (4.0%)	11 (8.0%)	
Local, renal/urinary	31 (14.6%)	15 (20.3%)	16 (11.6%)	
Patients per number of PLDs, *n* = 212				
Patients with one PLD	165 (77.8%)	53 (71.6%)	112 (81.2%)	0.265
Patients with two PLDs	39 (18.4%)	17 (23.0%)	22 (15.9%)	
Patients with three PLDs	8 (3.8%)	4 (5.4%)	4 (2.9%)	

PLD: Potential living donor; SD: Standard deviation.

donating a kidney to their related recipients, representing 18.1% of the total 321 PLDs (Figures 1 and 2; Table 4). Single and multiple PLDs were found to be related to 165 patients (77.8%) and 47 patients (22.2%), respectively. The respective percentages of achieved donations (26.7% *vs* 29.8%) were not significantly different ($P = 0.674$).

In the 144 excluded PLDs, the causes of exclusion were immunological incompatibilities in 54 PLDs (37.5%), medical abnormalities in 79 PLDs (54.9%), and financial inability in 3 PLDs (2.1%). Combined immunological and medical causes occurred in 14 PLDs (9.7%). In addition, the exclusion was distributed per intended patient (Tables 3 and 4). Exclusion occurred before or after completion of the evaluation in 109 PLDs (75.7%) and 35 PLDs (24.3%), respectively.

A comparison was performed between patients with candidate PLDs and patients with non-candidate PLDs. Their characteristics and PLD-related distributions were not significantly different, except in the mean age, which was lower in patients with candidate PLDs ($P = 0.041$). During a variable follow-up period, patients with declined PLDs mostly remained on dialysis for 6 mo to 6 years (Tables 2-4).

Also, a comparison was performed between the candidate and non-candidate PLDs. Their characteristics were not significantly different, except in the degree of relatedness to their potential recipients ($P = 0.020$) and the time spent in the evaluation of PLDs. The latter was lower in patients with non-candidate PLDs ($P < 0.001$) (Table 5).

A multivariate logistic regression analysis of factors influencing the candidacy of PLDs was carried out. It revealed that the on-dialysis potential recipient ($P = 0.451$), younger age PLDs ($P = 0.925$), male PLDs ($P = 0.940$), second or higher degrees of relatedness to the recipient *vs* the first degree ($P = 0.834$), and multiplicity of PLDs ($P = 0.123$) were not significantly associated with the rate of candidacy of PLDs for LKD after completion of preparation (Table 6).

Table 3 Patient characteristics distributed per extent and outcome of evaluation of their potential living donors presented as total patients (*n* = 212) and as a comparison between patients with candidate (*n* = 74) and patients with non-candidate (*n* = 138) potential living donors.

Characteristics	Total patients, *n* = 212	Patients with candidate PLDs, *n* = 74	Patients with non-candidate PLDs, *n* = 138	*P* value
	mean ± SD (range)/number (%)			
Patients per extent of evaluation of their PLDs[1], *n* = 212				
Completed 1	71 (33.5%)	54 (73%)	17 (12.3%)	< 0.001
Completed 1/incomplete 1	15 (7.1%)	7 (9.5%)	8 (5.8%)	
Completed 1/incomplete 2	2 (0.9%)	2 (2.7%)	0 (0%)	
Completed 1/not evaluated 1	7 (3.3%)	6 (8.1%)	1 (0.7%)	
Completed 2	3 (1.4%)	3 (4.1%)	0 (0%)	
Completed 2/incomplete 1	1 (0.5%)	0 (0%)	1 (0.7%)	
Completed 3	2 (0.9%)	2 (2.7%)	0 (0%)	
Incomplete 1	94 (44.3%)	0 (0%)	94 (68.1%)	
Incomplete 1/not evaluated 1	1 (0.5%)	0 (0%)	1 (0.7%)	
Incomplete 1/not evaluated 2	1 (0.5%)	0 (0%)	1 (0.7%)	
Incomplete 2	13 (6.1%)	0 (0%)	13 (9.4%)	
Incomplete 3	2 (0.9%)	0 (0%)	2 (1.5%)	
Patients per acceptance of their PLDs[1], *n* = 212				
Accepted 1	44 (20.6%)	44 (59.5%)	0 (0%)	< 0.001
Accepted 1/excluded 1	8 (3.8%)	8 (10.8%)	0 (0%)	
Accepted 1/excluded 2	2 (0.9%)	2 (2.7%)	0 (0%)	
Accepted 1/not evaluated 1	4 (1.9%)	4 (5.4%)	0 (0%)	
Excluded 1	81 (38.2%)	0 (0%)	81 (0%)	
Excluded 2	14 (6.6%)	0 (0%)	14 (10.1%)	
Excluded 3	2 (0.9%)	0 (0%)	2 (1.5%)	
Excluded 1/released 1	5 (2.4%)	1 (1.4%)	4 (2.9%)	
Excluded 1/regressed 1	3 (1.4%)	1 (1.4%)	2 (1.5%)	
Excluded 1/not evaluated 1	2 (0.9%)	0 (0%)	2 (1.5%)	
Excluded 1/not evaluated 2	1 (0.5%)	0 (0%)	1 (0.7%)	
Excluded 2/released 1	2 (0.9%)	1 (1.4%)	1 (0.7%)	
Excluded 2/regressed 1	1 (0.5%)	1 (1.4%)	0 (0%)	
Released 1	28 (13.2%)	7 (9.5%)	21 (15.2%)	
Released 1/not evaluated 1	2 (0.9%)	2 (2.7%)	0 (0%)	
Regressed 1	12 (5.7%)	3 (4.1%)	9 (6.5%)	
Regressed 2	1 (0.5%)	0 (0%)	1 (0.7%)	

[1]The numbers here refer to the number of potential living donors who had this characteristic. In addition, it included 10 potential donors who were not evaluated, and they presented here as part of the combined donors to the same patients with evaluated donors. PLD: Potential living donor; SD: Standard deviation.

DISCUSSION

The state of the decline of PLDs is related to the availability of PLDs, the balance between the donor's safety and the recipient's benefit, and the achievement of LDKT as the optimal outcome of all these issues[5,6,8]. The decline of PLDs is the backbone of the failure to maintain the availability of PLDs for the majority of patients[6]. Its burden extends between and reflects on the medical and psychosocial integrities of the PLDs and their intended recipients. However, the current literature is still insufficient to resolve this problem because the rates of acceptance of LDs are still variably low[5]. Hence, the current situation mandates further study of the two main aspects of the process of evaluating PLDs. First, the root causes of the failure of high proportions of those PLDs to achieve the task of donating a kidney represent a major topic, despite the limited current literature. Many studies addressed the identification of these causes to help reduce their effects on the process of LKD[5,6,8]. Second, the fate of the intended recipients who had their PLDs lost is the other aspect that may be more critical in the process because those potential recipients may have their all chances for KT permanently lost also[5,6,9,10].

The availability of a related LD provides a better chance for receiving KT, and it represents the only source of grafts in many countries and programs[2,9]. This fact may raise caution to try to decrease the rate of decline of PLDs in those programs to afford the needs of the increasing pool of potential recipients over time. However, the evaluation protocols for suitable LD selection remain a safeguard against violations of donor safety, implementing a complex evaluation process[2,9,10]. According to this process, KT centers usually evaluate LD acceptance and exclusion processes in the context of the principle of non-violation of the donor's safety[3,11]. Our center implements only the LDKT strategy; hence, we evaluated the rate of candidacy and acceptance of LDs, the causes of declined PLDs, and the fate of potential recipients with declined PLDs.

Although the current rate of successful candidacy of PLDs is similar to other reported values from other centers, it is relatively hard to expect the exact percentage of PLDs who ultimately succeed in committing to LKD. This uncertainty in the acceptance rates can be attributed to the variability in the assessment protocols and stages from one center to another and from one country to another[5,8]. The stages of evaluation in our center may be different from those in other centers, due to socioeconomic factors and different policies of donation[5,9]. We considered HLA-typing at the late stage of evaluation due to sociodemographic reasons. Immunological tests for HLA typing and crossmatching are costly. However, other routine and multidisciplinary laboratory evaluations can be individualized into separate steps to catch any abnormalities in medical and laboratory workups with relatively low costs. In addition, related PLDs have higher chances of being HLA-matched with their intended recipients. On the other hand, this latter characteristic may be the reason why the mean age of the potential recipients was significantly lower than that of the PLDs. First-degree and second-degree relatedness between the PLDs and their potential recipients provided high proportions of parents and older sisters or brothers as PLDs for their relatives.

The efficiency of the evaluation of PLDs should consider the needs of the PLD, the intended recipient, and the qualifications of the healthcare system. The timing of the evaluation of multiple PLDs is an important issue[12]. In the current study, only the early stages of evaluation, including counseling and blood group (ABO) compatibility testing, can be carried out simultaneously due to financial causes. In addition, high proportions of PLD decline occur in the early stages of evaluation[5]. Similarly, the current results showed that more than two-thirds of PLDs were declined during the early evaluation phases.

The causes of the decline of PLDs are various and can be classified into PLD-related and patient-related causes[13]. In the current study, the major PLD-related causes included medical, immunological, and sociodemographic factors or combinations of them. ABO and HLA incompatibilities were responsible for high percentages of excluded PLDs. Trials to expand the pool of LDs may need novel strategies, such as accepting LDs with abnormalities that are not accepted in the standard criteria for LDs. The variability of the causes of decline mandates the variability of these strategies. Hence, this practice should be implemented under strict control in LDKT programs because it may have impacts on preserving full safety issues[3,4,11]. On the same principle, such policies have not been permitted in our center protocols to avoid the violation of donor safety.

About half of the evaluated PLDs in the current study were excluded due to immunological causes, including both ABO and HLA incompatibilities. These immunological barriers can be managed by strategies such as incompatible LDKT and paired or exchange LKD (PKD)[14]. The former strategy is certainly not acceptable due to the relatively inferior outcomes compared to the matched ABO-compatible or HLA-compatible patients and the potential higher costs for desensitization[15]. However, PKD or kidney-sharing programs seem to be more effective for the KT programs that are based on the LDKT strategy due to their low costs and high efficiency. They are currently recommended to reduce the decline rate of PLDs, which may increase the acceptance rate of PLDs to more than 50% and provide better chances of finding high-quality donors for those who already have matched PLDs. They overcome considerable proportions of ABO-incompatible and HLA-incompatible PLDs. Unfortunately, these programs have not been established in our country so far, allowing a high rate of PLD loss. However, it has gradually become the focus of some interested researchers in our KT community[16,17].

The PLDs could be disqualified from donation for different medical contraindications. These reasons vary from one program to another program[3,5]. In the current study, medical contraindications were found in more than 60% of the causes of the decline of PLDs, similar to previously reported experiences[5]. They included several clinical forms, such as systemic diseases, infections, urolithiasis, and primary kidney diseases with hereditary or familial patterns. These reasons may benefit from the relaxation of the standard criteria for donation, such as accepting those PLDs with mild hypertension, obesity, proteinuria, sporadic urolithiasis, or microscopic hematuria[3,18].

Table 4 Patients distributed per characteristics of exclusion of their potential living donors presented as total patients (*n* = 212) and as a comparison between patients with candidate (*n* = 74) and patients with non-candidate (*n* = 138) potential living donors.

Characteristics	Total patients, *n* = 212	Patients with candidate PLDs, *n* = 74	Patients with non-candidate PLDs, *n* = 138	*P* value
	mean ± SD (range)/number (%)			
Patients per number of excluded PLDs, *n* = 121				
Patients with one excluded PLD	100 (82.6%)	10 (71.4%)	90 (84.1%)	0.764
Patients with two excluded PLDs	19 (15.7%)	4 (28.6%)	15 (14.0%)	
Patients with three excluded PLDs	2 (1.7%)	0 (0%)	2 (1.9%)	
Patients per causes of exclusion of their PLDs, *n* = 121[1]				
Combined immunological and medical causes	14 (11.6%)	3 (21.4%)	11 (10.3%)	0.680
HLA-incompatibility	24 (19.8%)	3 (21.4%)	21 (19.6%)	
ABO-incompatibility	20 (16.5%)	1 (7.1%)	19 (17.8%)	
ABO and HLA-incompatibility	2 (1.7%)	0 (0%)	2 (1.9%)	
Age	8 (6.6%)	0 (0%)	8 (7.5%)	
Diabetes mellitus	4 (3.3%)	0 (0%)	4 (3.7%)	
HCV positive	5 (4.1%)	2 (14.3%)	3 (2.8%)	
Hypertension	11 (9.1%)	4 (28.6%)	7 (6.5%)	
Leprosy	1 (0.8%)	0 (0%)	1 (0.9%)	
Low GFR	4 (3.3%)	1 (7.1%)	3 (2.8%)	
High potential recurrence of primary kidney disease	6 (5.0%)	0 (0%)	6 (5.6%)	
Proteinuria	12 (9.9%)	0 (0%)	12 (11.2%)	
Psoriasis	1 (0.8%)	0 (0%)	1 (0.9%)	
Rheumatoid arthritis	1 (0.8%)	0 (0%)	1 (0.9%)	
Urolithiasis	5 (4.1%)	0 (0%)	5 (4.7%)	
Financial causes	3 (2.5%)	0 (0%)	3 (2.8%)	
Patients per main category of causes of exclusion of their PLDs, *n* = 121				
Combined immunological and medical causes	14 (11.6%)	3 (21.4%)	11 (10.3%)	0.866
Immunologic mismatches	46 (38%)	4 (28.6%)	42 (39.3%)	
Medical causes	58 (47.9%)	7 (50.0%)	51 (47.7%)	
Financial causes	3 (2.5%)	0 (0%)	3 (2.8%)	
Patients per timing of PLDs regression, *n* = 18				
During evaluation	13 (72.2%)	0 (0%)	13 (100.0%)	NA
After evaluation	5 (27.8%)	5 (100.0%)	0 (0%)	
Patients per cause of release of PLDs, *n* = 37				
Patient death	4 (10.8%)	3 (27.3%)	1 (3.9%)	0.186
Patient regression	22 (59.5%)	6 (54.5%)	16 (61.5%)	
Patient non-candidacy	11 (29.7%)	2 (18.2%)	9 (34.6%)	
Patients per timing of release of PLDs,				

n = 37				
During evaluation	26 (70.3%)	0 (0%)	26 (100.0%)	NA
After evaluation	11 (29.7%)	11 (100.0%)	0 (0%)	
Fate of patients with evaluated PLDs, *n* = 212				
Transplantation in our center	58 (27.4%)	58 (78.4%)	0 (0%)	NA
Transplantation in another center	14 (6.6%)	1 (1.4%)	13 (9.4%)	0.024
On hemodialysis	122 (57.6%)	12 (16.2%)	110 (79.7%)	< 0.001
Death	9 (4.2%)	3 (4.1%)	6 (4.4%)	0.920
Unknown	9 (4.2%)	0 (0%)	9 (6.5%)	0.024

[1]Regarding the exclusion due to anatomical abnormalities, they included ectopic pelvic kidney, solitary kidney, and hypoplastic kidney in 3 patients. They were included in donors with a low split glomerular filtration rate. However, kidneys with unilateral simple cysts in 2 patients and three renal arteries in 2 patients were not the cause of exclusion. In the former, the cysts were treated by marsupialization after perfusion and before implantation in the recipients. In the latter, the contralateral kidneys were donated. GFR: Glomerular filtration rate; HCV: Hepatitis C virus; HLA: Human leukocytic antigen; NA: Not available; PLD: Potential living donor; SD: Standard deviation.

Another right for PLD is autonomy, which provides the full capacity to preserve the ability to withdraw at any stage of preparation up to the date of surgery[19]. This right may contribute to the decline of PLDs due to withdrawal or regression from the decision to donate. In our study, 18 PLDs (7%) regressed from donation after confirmed initial willingness due to fear of health concerns, and 5 PLDs withdrew their decision after completion of the evaluation. Their potential recipients failed to find other suitable donors and remained on hemodialysis. Although it is disappointing to the potential recipients, PLD regression usually occurs in a small percentage of PLDs. However, it warrants the help of the team to support the PLDs in their decision and communicate with the potential recipient to deliver the decision[19]. Connaughton *et al*[5] reported that 15.5% of PLDs withdrew from donation during evaluation. A study by Liu *et al*[20] reported self-ranking health conditions, insufficient support in decision-making, value clarity, and conflicts in the decisions as factors of withdrawal.

For a PLD, withdrawal or being withdrawn indicates more time for finding another PLD. In our study, some patients found suitable donors after many trials among relatives. There is no doubt that this process was time-consuming, and the patients waited on dialysis for years. Also, some of them died while they were waiting for a donor. Moreover, the majority of the potential recipients are now still waiting on regular dialysis or have been transplanted in other places that mostly adopt the unrelated LDKT. The latter policy may predispose to such an unfavorable act of paid LKD. Hence, we preserved this policy for limited indications, such as cases of hereditary or familial primary renal diseases, including polycystic kidney disease. However, the in-depth discussion of the point of paid LKD is beyond the scope of this study.

Patient-related causes of the decline of PLDs included patient withdrawal from KT, non-candidacy, and death during preparation. We defined those PLDs as released because the intended recipients were disqualified. In an interview study by Pronk *et al*[21], patients expressed moral causes for regression from accepting related PLDs, such as reluctance to accept a kidney from close relatives and fear of being considered selfish.

The duration of PLD evaluation is variable and may be lengthy for repeating or confirmatory workups. Understanding the reasons that may prolong the evaluation may help reduce unnecessary delays[12]. The duration of evaluation in this study varied from 2 wk to 6 mo, with an average of 2.2 mo. This variation was due to the consideration of all PLDs with incomplete or complete evaluations.

Most of the potential recipients with declined PLDs remained on hemodialysis for variable periods ranging from 6 mo to 6 years. This means that the chances of achieving LDKT were reduced for those potential recipients when their PLDs were declined. Only 14 patients (6.6%) with declined PLDs succeeded in having LDKT in other centers, representing low chances of having LDKT similar to the results of previous studies[5,8,13]. In addition, patients with multiple PLDs did not significantly have higher chances of achieving KT. This might be attributed to the healthcare system implemented in our country, where most patients sought medical consultations in private clinics, and their PLDs had initial evaluations with their private physicians before the presentation to our center. PLDs with known systemic diseases and ABO typing can easily be excluded. In turn, this may be an explanation for the presentation of a single PLD in 77.8% of patients.

The outcomes of the current study should attract attention to the formulation of efficient plans to reduce the rates of decline of PLDs and promote LKD through the introduction of strategies such as PKD to our national program. Also, national initiatives for the education of the public, patients, and general practitioners about the advantages of LDKT and LKD may help reduce the decline of PLDs caused by the reluctance and low medical literacy of those individuals.

To the best of our knowledge, the current study is the first from Egypt that specifically addressed the topic of the decline of PLDs among related PLDs and recipients. This is a very important step in the development of an integrated national KT program, which has only been dependent on LKD until now. The current study may encourage other centers to conduct similar studies to provide better evidence of the problem and formulate a plan to overcome the causes of the decline of PLDs. In addition, the aim, rationale, and outcomes of this study were parallel to many studies from different countries[3,5,6,8,13], which may strengthen the effect of its outcomes on the improvement of our practice and healthcare

Table 5 Characteristics of potential living donors presented as total (*n* = 257) and as a comparison between the candidate (*n* = 74) and non-candidate (*n* = 183) groups of donors

Characteristics	Total PLDs, *n* = 257	Candidate PLDs, *n* = 74	Non-candidate PLDs, *n* = 183	*P* value
	mean ± SD (range)/number (%)			
Mean age in yr	40.5 ± 10.4 (18-65)	41.0 ± 10.5 (21-60)	40.4 ± 10.5 (18-65)	0.498
Sex				
Female	169 (65.8%)	49 (66.2%)	120 (65.6%)	> 0.999
Male	88 (34.2%)	25 (33.8%)	63 (34.4%)	
Form of relatedness[1]				
Aunt	4 (1.6%)	4 (5.4%)	0 (0%)	0.286
Brother	51 (19.8%)	14 (18.9%)	37 (20.2%)	
Cousin	4 (1.6%)	0 (0%)	4 (2.2%)	
Daughter	4 (1.6%)	1 (1.4%)	3 (1.6%)	
Father	23 (8.9%)	7 (9.5%)	16 (8.7%)	
Husband	6 (2.3%)	2 (2.7%)	4 (2.2%)	
Mother	76 (29.6%)	23 (31.1%)	53 (29%)	
Nephew	1 (0.4%)	0 (0%)	1 (0.6%)	
Sister	53 (20.6%)	13 (17.6%)	40 (21.9%)	
Son	4 (1.6%)	1 (1.4%)	3 (1.6%)	
Uncle	1 (0.4%)	1 (1.4%)	0 (0%)	
Wife	30 (11.7%)	8 (10.8%)	22 (12.0%)	
Degree of relatedness				
First	143 (55.6%)	42 (56.8%)	101 (55.2%)	0.020
Second	104 (40.5%)	27 (36.5%)	77 (42.1%)	
Third	6 (2.3%)	5 (6.8%)	1 (0.6%)	
Fourth	4 (1.6%)	0 (0%)	4 (2.2%)	
Extent of evaluation				
Complete	109 (42.4%)	74 (100.0%)	35 (19.1%)	NA
Incomplete	148 (57.6%)	0 (0%)	148 (80.9%)	
Fate of PLDs				
Donated	58 (22.6%)	58 (78.4%)	0 (0%)	NA
Excluded	144 (56.0%)	0 (0%)	144 (78.7%)	NA
Regressed[2]	18 (7.0%)	5 (6.8%)	13 (31.6%)	
During evaluation	13 (72.2%)	0 (0%)	13 (100.0%)	NA
After evaluation	5 (27.8%)	5 (100%)	0 (0%)	
Released	37 (14.4%)	11 (14.9%)	26 (68.4%)	
Causes of donor release				
Patient death	4 (10.8%)	3 (27.3%)	1 (3.9%)	0.186
Patient regression	22 (59.5%)	6 (54.5%)	16 (61.5%)	
Patient non-candidacy	11 (29.7%)	2 (18.2%)	9 (34.6%)	
Timing of PLDs release				
During evaluation	26 (70.3%)	0 (0%)	26 (100.0%)	NA
After evaluation	11 (29.7%)	11 (100.0%)	0 (0%)	

Time spent in PLDs evaluation in mo	2.2 ± 1.5 (0.5-6.0)	4.0 ± 0.9 (1-6)	1.5 ± 1.2 (0.5-5.0)	< 0.001

[1]Among the 6 husband and 30 wife potential living donors (PLDs), only 13 of them were genetically related PLDs to their intended recipients (due to consanguineous marriage);
[2]The reason of regression was the fear of health drawbacks from donation in all PLDs. NA: Not available; PLD: Potential living donor; SD: Standard deviation.

Table 6 Multivariate logistic regression of the potential variables influencing the candidacy of potential living donors with a completed preparation

Variables	Modality	Odds ratio	*P* value
Dialysis status	Preemptive *vs* on dialysis	0.66 (0.23-1.94)	0.451
Number of potential donors	Single *vs* multiple	1.69 (0.87-3.28)	0.123
Donor age	Increasing age	1.0 (0.97-1.03)	0.925
Donor sex	Men *vs* women	1.02 (0.55-1.92)	0.940
Relatedness degree	First *vs* more than first	1.07 (0.55-2.1)	0.834

system management.

The limitations of this study included the retrospective nature of the methods. The retrospective nature may be the reason that the regression of PLDs and their recipients was not reported in detail. It is unknown whether these events were due to improper counseling, sociodemographic characteristics, or the low integrity of the healthcare system. In addition, a relatively short follow-up period limited the evaluation of the long-term effect of the decline of PLDs on the fate of some intended recipients. Moreover, it was a single-center experience, which warrants further national or multicenter studies for the generalizability of these results. However, most of the available literature comes from retrospective single-center studies[3,5,8,13].

CONCLUSION

The willing, related PLDs have a mean age higher than their potential recipients due to relatedness; most of them were parents or older relatives. Also, their potential recipients had primary kidney diseases that typically affect young people. The rate of decline of the willing, related PLDs was high, reaching about 82%. The causes could be classified as PLD-related or potential recipient-related, depending on the side of the cause. In addition, they could be differentiated into exclusion due to contraindications, release after disqualification of the potential recipients, and regression due to withdrawal of the decision by the PLDs, based on the autonomy of decision-making. PLD exclusion was the commonest form during or after the completion of the evaluation due to medical or immunological contraindications. These high percentages of PLD decline resulted in the loss of the chance to obtain LDKT for a high percentage of potential recipients who were left on dialysis for variably long periods, who died, or who were lost to an unknown fate. In our country, this study represents an initial scientific step in the evidence-based evaluation of the situation of LD selection and its deficits. The high rate of decline of PLDs reported here may draw attention to implementing more research on this topic.

ARTICLE HIGHLIGHTS

Research background

The evaluation protocols for living kidney donor (LD) selection are usually strict but remain a safeguard against violations of LD safety. Hence, the decline of willing potential living donors (PLDs) may occur at any stage of evaluation due to different causes, resulting in variable rates of decline of PLDs.

Research motivation

The rate of decline of willing related LDs seems to be a modifiable variable for improving LD kidney transplantation (LDKT).

Research objectives

To identify the causes of the decline of PLDs, the predictors of PLD candidacy, and the effect on achieving LDKT.

Research methods
A retrospective study was performed on willing PLDs who attended our outpatient clinic for kidney donation to their related potential recipients between October 2015 and December 2022. Two groups of PLDs were compared: Candidate PLDs after a completed evaluation *vs* non-candidate PLDs with a complete or incomplete evaluation. A multivariate logistic regression was performed to assess the factors contributing to the achievement of PLD candidacy.

Research results
Of 321 willing PLDs, 257 (80.1%) accessed the evaluation to variable extents for 212 potential recipients, with a mean age (range) of 40.5 ± 10.4 (18-65) years. The remaining 64 PLDs (19.9%) did not access the evaluation due to serving as alternatives to essential PLDs, financial causes, and patient-related factors. Only 58 PLDs (18.1%) achieved donation, but 199 PDLs (62.0%) were declined. Exclusion occurred in 144 PLDs (56%) for immunological causes (37.5%), medical causes (54.9%), combined causes (9.7%), and financial causes (2.1%), but regression and release occurred in 55 PLDs (17.1%). The number of potential recipients with candidate PLDs was not significantly different from that with non-candidate PLDs, except in age ($P = 0.041$), rates of completed evaluation, and exclusion of PLDs ($P < 0.001$). In the multivariate analysis, there were no independent factors that influenced the rate of PLD candidacy. Most patients who failed to have KT after the decline of their PLDs remained on hemodialysis for 6 mo to 6 years.

Research conclusions
Despite the availability of willing related PLDs for most potential recipients, their rate of decline was high. The causes were various, including medical or immunological contraindications, release, and regression of PLDs. Hence, the chances of LDKT were reduced or lost in a high percentage of potential recipients.

Research perspectives
Trials to reduce the rate of decline of PLDs should not be at the expense of LD safety. However, revision and identification of the causes of PLD decline may help increase the chances of patients for KT, especially with the application of strategies that overcome the immunological barriers of LDKT and low medical literacy.

FOOTNOTES

Author contributions: Gadelkareem RA, Abdelgawad AM, and Mohammed N designed the research, collected the data, and wrote the paper; Reda A, Azoz NM, and Zarzour MA contributed to statistical analysis, literature review, writing, and revision; Hammouda HM and Khalil M contributed to the literature review, writing, revision, and supervision of the work; All authors approved the paper.

Institutional review board statement: This study was conducted as part of a research project on the outcomes of living donor kidney transplantation performed in our center (Approval No. 17200148/2017).

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Abstract

The shortage of deceased donor organs has prompted the development of alternative liver grafts for transplantation. Living-donor liver transplantation (LDLT) has emerged as a viable option, expanding the donor pool and enabling timely transplantation with favorable graft function and improved long-term outcomes. An accurate evaluation of the donor liver's volumetry (LV) and anatomical study is crucial to ensure adequate future liver remnant, graft volume and precise liver resection. Thus, ensuring donor safety and an appropriate graft-to-recipient weight ratio. Manual LV (MLV) using computed tomography has traditionally been considered the gold standard for assessing liver volume. However, the method has been limited by cost, subjectivity, and variability. Automated LV techniques employing advanced segmentation algorithms offer improved reproducibility, reduced variability, and enhanced efficiency compared to manual measurements. However, the accuracy of automated LV requires further investigation. The study provides a comprehensive review of traditional and emerging LV methods, including semi-automated image processing, automated LV techniques, and machine learning-based approaches. Additionally, the study discusses the respective strengths and weaknesses of each of the aforementioned techniques. The use of artificial intelligence (AI) technologies, including machine learning and deep learning, is expected to become a routine part of surgical planning in the near future. The implementation of AI is expected to enable faster and more accurate image study interpretations, improve workflow efficiency, and enhance the safety, speed, and cost-effectiveness of the procedures. Accurate preoperative assessment of the liver plays a crucial role in

ensuring safe donor selection and improved outcomes in LDLT. MLV has inherent limitations that have led to the adoption of semi-automated and automated software solutions. Moreover, AI has tremendous potential for LV and segmentation; however, its widespread use is hindered by cost and availability. Therefore, the integration of multiple specialties is necessary to embrace technology and explore its possibilities, ranging from patient counseling to intraoperative decision-making through automation and AI.

Key Words: Liver transplantation; Living-donor; Diagnostic imaging; Artificial intelligence; Machine learning; Deep learning

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Core Tip: Accurate liver's volumetry (LV) is imperative for successful living-donor liver transplantation to ensure adequate future liver remnant and graft volumes. Manual computed tomography scan delineation conventionally serves as the standard approach; however, it is constrained by factors such as cost, subjectivity, and variability. In contrast, automated LV techniques utilizing advanced segmentation algorithms present superior reproducibility, reduced variability, and enhanced efficiency compared with manual measurements. However, the accuracy of automated LV requires further investigation. The study comprehensively reviewed both traditional and emerging LV methods, including semi-automated image processing, automated LV techniques, and machine learning-based approaches, while analyzing their respective strengths and weaknesses.

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INTRODUCTION

Liver transplantation is the first-line treatment for patients with terminal liver disease. Deceased donor organ shortage and cultural barriers have led to the development of alternative graft types. Living-donor liver transplantation (LDLT) has emerged as an extension of the *ex-situ* graft transection concept, encompassing reduced-size and split-liver techniques. By enabling the expansion of the donor pool, LDLT offers the advantage of timely transplantation and holds the potential for excellent graft function and improved long-term outcomes[1-6]. Moreover, LDLT reduces waiting list mortality.

An adequate preoperative evaluation of the donor is essential for successful LDLT. Sufficient future liver remnant (FLR) and graft volume must be ensured through liver's volumetry (LV) studies[7,8]. An FLR of 30% to 35% of the original liver volume is required for donor safety, whereas at least 4% of the standard liver volume or more than 0.8 and less than 3–3.5 of the graft recipient weight ratio (estimated before the surgery through imaging and confirmed after the graft is weighted) is required to meet the recipient's needs[9,10]. Small grafts are associated with cellular damage due to excessive portal flow, leading to "small-for-size syndrome," whereas large grafts may receive inadequate portal flow, resulting in "large-for-size syndrome"[11-17].

Manual liver volumetry (MLV) conducted on portal venous phase multidetector computed tomography (CT) scans with intravenous contrast is conventionally considered the standard method for measuring LV[7,18,19]. However, it can be costly, time-consuming, subjective, and prone to inter- and intra-observer variabilities. The process entails manual tracing of the liver borders using specialized software, necessitating the expertise of an experienced radiologist, often without the input of the surgeon. The percentage of error (PE) may vary significantly, ranging from 2% to 20%, which can have a dramatic effect on the final graft volume and transplantation outcomes[20-24].

Advancements in medical imaging, computational algorithms, and artificial intelligence (AI) have set the stage for the development and application of automated LV techniques. Automated LV holds significant promise in the evaluation of LDLT, as it utilizes sophisticated segmentation algorithms to delineate liver boundaries from CT or magnetic resonance imaging (MRI) scans. Therefore, enabling volumetric calculations and comprehensive volumetric analysis and allowing for the assessment of lobe-specific volumes, segmental volumes, and overall liver volume. Such automated approaches offer advantages over manual measurements, including enhanced reproducibility, reduced intra- and interobserver variability, and improved efficiency. However, the accuracy of automated LV techniques is yet to be conclusively determined[25-28].

The study aimed to provide a comprehensive review of the literature, presenting both traditional and emerging methods of LV and anatomical liver assessment, while discussing their respective strengths and weaknesses. By examining the current state of LV techniques, the review aimed to contribute to the advancement and optimization of liver transplantation outcomes.

MANUAL LIVER VOLUMETRY

The introduction of multiphasic CT and MRI techniques has led to the widespread adoption of MLV as the standard practice in liver transplant centers to estimate liver volume before accepting a living-donor as a suitable candidate. During the donor evaluation, a complete anatomical analysis of the hepatic veins, portal vein and hepatic arteries is provided by multiphasic CT and MRI. Bile duct anatomy is evaluated in cholangio MRI studies, specially, in left lobe and right lobe donors.

If the donor´s anatomy is suitable for the planned procedure, LV is carried out. The procedure involves manual delineation of the liver borders using sequential image slices to determine the overall liver volume. Subsequently, a transection plane is selected based on the specific type of liver graft and the inclusion of the middle hepatic vein (MHV) [25,29-31] (Figure 1).

Limitations include reliance on operator expertise and medical specialty, leading to discrepancies between the analyses performed by radiologists and surgeons, potentially related to the transection line. Furthermore, the inclusion of blood vessels and bile ducts in the final volume calculation can lead to overestimations[32]. Additionally, the LV procedure itself is time-consuming, typically requiring approximately 20-40 min to complete, which significantly affects the daily workflow of both radiologists and surgeons[19,33]. In terms of accuracy, PE ranges from 5% to 36% when comparing the estimated volume with the actual graft weight (AGW)[34]. It is important to note that errors can occur in both directions, resulting in overestimation and underestimations[8].

It is routinely considered that the density of the liver is equivalent to the density of water; therefore, the AGW is representative of the graft volume[35]. However, studies measuring AGW have identified the necessity of correction factors when estimating graft volume, as highlighted in Table 1. Recently, Lemke *et al*[36], measured the mean physical density of 16 transplanted liver lobes to be 1.1157 g/mL, asserting that the conversion factor was, on average, 12% higher than expected. Tongyoo *et al*[32] demonstrated that the AGW of a right lobe donor liver graft (RLDG) was approximately 91% of the estimated right lobe liver volume. The 9% volume reduction was attributed to intrahepatic blood flushed out of the liver by the preservation solution during back-table preparation[9,31,37]. Other inaccuracies may have been due to the inclusion of the MHV and/or the caudate lobe[38].

SEMI-AUTOMATED IMAGE PROCESSING

Semi-automated methods have been developed to address observer-related issues associated with manual measurements and to enhance the efficiency of LV and hepatic segmentation. An example of such a method is the MeVis Liver Analyzer (MeVis Medical Solutions AG, Bremen, Germany), which is a computer-assisted software that operates on CT images. Moreover, the software employs a modified live-wire algorithm to automatically determine the contours between user-defined boundary points based on the CT values and gradients. The algorithm parameters were tailored to each CT phase, including the venous (V), arterial (HA), and native (N) phases. To ensure accurate liver segmentation, manual correction of automatically delineated contours and manual drawing of the contour parts were performed. Live-wire contours were interactively determined on 3 mm axial two-dimensional (2D) CT slices. The software automatically interpolates and optimizes the contours of intermediate slices, with final adjustments made by the operator through manual corrections, if necessary (Figure 2).

Volumetric calculations, expressed in milliliters (mL), were performed by adding the areas of all segmented regions. Surrounding structures such as major extrahepatic vessels (portal vein, hepatic artery, and inferior vena cava) and the gallbladder fossa were excluded from the volume calculations (Figure 3).

Goja *et al*[39] discovered that semiautomated software tools exhibited the highest correlation (r = 0.82) for measuring right lobe grafts. However, left lobe grafts tend to be overestimated, whereas left lateral segment (LLS) grafts are often underestimated, with an underestimation of approximately 66% of the total LLS grafts. One possible explanation for the underestimation of LLS grafts is that CT scans typically underestimate the volume because the actual surgical plane of transection is approximately 1 cm to the right of the falciform ligament, whereas the radiological plane of transection is exactly at the falciform ligament. Other studies have addressed the accuracy of semi-automated image processing (SAIP), and their results are presented in Table 2.

AUTOMATED LIVER VOLUMETRY TECHNIQUES

Automated LV relies on advanced image-processing techniques and algorithms to accurately segment the liver from CT or MRI scans. The principles and algorithms vary depending on the approach employed. However, some common techniques and concepts are involved.

Image preprocessing

Before liver segmentation, image preprocessing techniques may be applied to enhance the image quality, reduce noise, and improve the contrast between the liver and surrounding structures. These techniques include filtering, intensity normalization, and image enhancement methods.

Table 1 Formulas to estimate liver volumetry by computerized tomography

Ref.	Formula	Research place
Poovathumkadavil *et al*[22], 2010	LV = 12.26 × BW(kg) + 555.65	Saudi Arabia
Noda *et al*[21], 1997	LV = 0.05012 × $BW^{0.78}$	Japan
Johnson *et al*[20], 2005	LV = 0.722 × $BSA^{1.176}$	North America
Yuan *et al*[24], 2008	LV = 949.7 × BSA (m^2) - 48.3 × age - 247.4	China
Yoshizumi *et al*[23], 2003	LV = (0.772 × BSA)/1.08	North America

LV: Liver volume; BW: Body weight; BSA: Body surface area.

Table 2 Results of semi-automated image processing in different analysis

Ref.	Software and comparison	Reports
Pomposelli *et al*[47], 2012	Software MeVis Compared right lobe graft volumes estimated by SAIP with actual graft weights measured during LDLT	A nonsignificant volume difference of approximately 17.5 mL and a low percentage error of approximately 2.8%
Çelik *et al*[34], 2023	CT Liver Analysis, Philips Healthcare-RLDG volumes by manual and SA were compared to AGW	Both manual and SA overestimated the graft weight (manual: 893 ± 155 mL *vs* AGW: 787 ± 128 g, $P < 0.001$, SA: 879 ± 143 mL *vs* AGW, $P < 0.001$). The mean interaction time was 27.3 ± 14.2 min for manual and 6.8 ± 1.4 min for SAIP ($P < 0.001$)
Mohapatra *et al*[31], 2020	Myrian XP Liver 3D software (France)-RLDG, LLDG and LLSDG volumes by manual and SA were compared to AGW	Both manual and SA showed strong correlation with AGW ($r = 0.834$ and 0.856, respectively). The mean percentage error for manual and SA was 14.2 ± 12.5% and 12.2 ± 11.8%, respectively. The overall accuracy improved using SA ($P = 0.015$)
Kalshabay *et al*[25], 2023	Vitrea software, including two different applications for manual segmentation (Volume analysis) and automated segmentation (CT liver analysis) SA software (OsiriX MD) RLDG	The manual method correlated better with AGW ($r = 0.730$) in comparison with the SA ($r = 0.685$) and the automated ($r = 0.699$) methods ($P < 0.001$). The mean error ratio in volume estimation by each application was 12.7 ± 16.6% for manual, 17.1 ± 17.3% for SA, 14.7 ± 16.8% for automated methods
Goja *et al*[39], 2018	AW Volume share 6 (GE Healthcare; Chicago, Illinois, United States) RLDG, LLDG and LLSDG volumes by SA were compared to AGW	RLDGt: There was no statistically significant difference between mean SA and AGW in RL (722 ± 134 *vs* 717 ± 126 gm; $P = 0.06$). LLDG: Correlated strongly ($r = 0.81$, $P < 0.001$), mean SA was significantly high as compared to mean of AGW (460 ± 118 *vs* 433 ± 102 gm; $P = 0.003$). LLSDG: Mean SA was significantly low as compared to mean of AGW (203 ± 48 *vs* 254 ± 49 gm; $P < 0.001$)

CT: Computerized tomography; SA: Semi-automated; AGW: Actual graft weight, RLDG: Right lobe donor graft; LLDG: Left lobe donor graft; LLSDG: Left lateral segment donor graft.

Segmentation algorithms

Segmentation algorithms were used to delineate the liver region of interest from the remaining images. Additionally, such algorithms aim to accurately identify the liver boundaries. Commonly used algorithms include threshold-based methods, region growing, active contours (or snakes), level sets, graph cuts, and machine-learning-based techniques.

Threshold-based methods

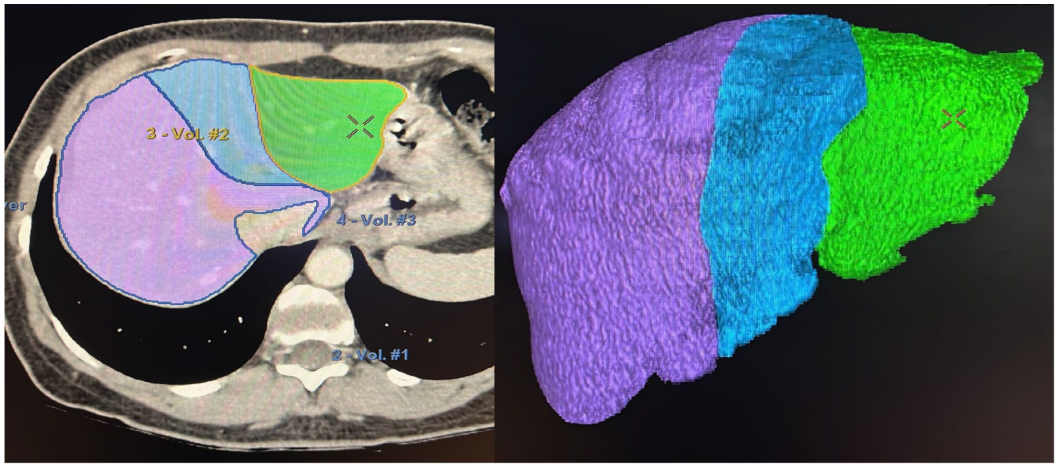
Threshold-based methods involve setting intensity thresholds to separate the liver from the background or other organs. The liver is segmented based on predefined intensity ranges or statistical measures such as the mean intensity or intensity distribution.

Region growing

Region-growing algorithms start from a seed point within the liver and iteratively develop the region by including pixels with similar characteristics (*e.g.*, intensity, texture, or gradient) until a stopping criterion is met. The method is particularly useful when the liver has a distinct intensity pattern compared to the surrounding tissues.

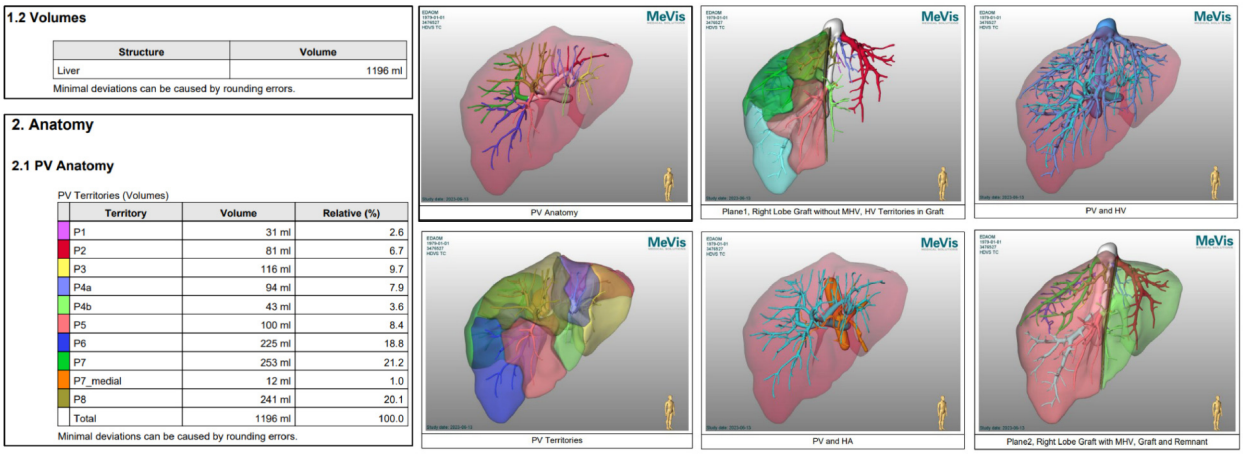
Active contours (snakes)

Active contour models, also known as snakes, use an energy-optimization approach to iteratively deform a contour to fit the liver boundary. The contour was attracted to the image edges or intensity gradients, ensuring accurate delineation of the liver boundaries.



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Figure 1 Manual volumetric study performed in our institution for pre-operative living-donor evaluation (Hepatic VCAR-GE Healthcare).



1.2 Volumes

Structure	Volume
Liver	1196 ml

Minimal deviations can be caused by rounding errors.

2. Anatomy

2.1 PV Anatomy

PV Territories (Volumes)

Territory	Volume	Relative (%)
P1	31 ml	2.6
P2	81 ml	6.7
P3	116 ml	9.7
P4a	94 ml	7.9
P4b	43 ml	3.6
P5	100 ml	8.4
P6	225 ml	18.8
P7	253 ml	21.2
P7_medial	12 ml	1.0
P8	241 ml	20.1
Total	1196 ml	100.0

Minimal deviations can be caused by rounding errors.

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Figure 2 MeVis software images and tables output: The software returns multiple images and tables. PV: Peripheral vein; MHV: Middle hepatic vein; HA: Hepatic artery.

Level sets

Level-set methods are mathematical techniques used to evolve a curve or surface over time to delineate the liver boundaries. The methods use the concept of level sets, which represent the evolving contour as a zero-level set of a higher-dimensional function.

Graph cuts

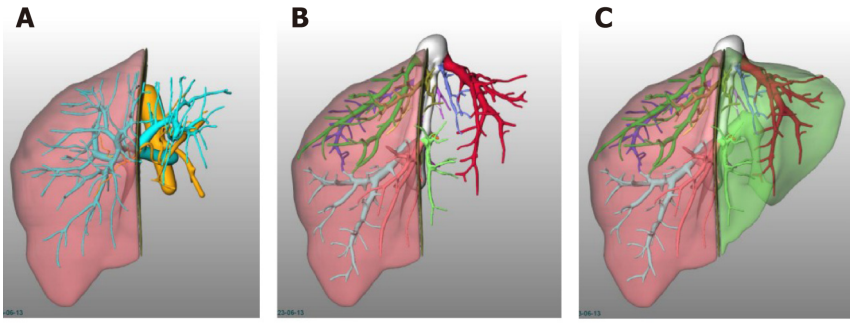
Graph cut algorithms model the liver segmentation problem as an optimization task in a graph framework. The graph is constructed using image features, and the segmentation is achieved by identifying the minimum energy cut that separates the liver from the background.

Machine learning-based techniques and deep learning

Machine learning algorithms, such as random forests, support vector machines, and deep learning models, can be trained on annotated liver images to automatically segment the liver. Such algorithms learn the patterns and features that distinguish the liver from other structures and can provide accurate and robust segmentation results[40].

Most software tools employ a combination of techniques or advanced algorithms that are specific to their methodology. The choice of algorithm depends on factors such as image quality, complexity of liver structures, computational efficiency, and specific requirements of the application. Each algorithm has its advantages, limitations, and parameter settings, which must be carefully considered and optimized for accurate LV. A combination of techniques can be used to improve accuracy and robustness[41].

For example, the initial segmentation can be obtained using thresholding or region growth, followed by refinement using active contours or graph cuts. Hybrid approaches that combine multiple algorithms can leverage the strength of each technique to achieve more accurate LV. Additionally, the validation and evaluation of the automated LV results against the ground truth or manual segmentations are critical for assessing the algorithm's performance and reliability



D

Plane1, Right Lobe Graft without MHV (Volumes)

	Territory	Volume	Relative (%)
	Plane	15 ml	1.3
	Graft	769 ml	64.3
	Remnant	412 ml	34.4
	Total	1196 ml	100.0

Minimal deviations can be caused by rounding errors.

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Figure 3 Resection planes volumetric estimation using MeVis. A: Right Lobe Graft without middle hepatic vein (MHV), peripheral vein and hepatic artery; B: Right Lobe Graft without MHV, HV; C: Right Lobe Graft without MHV, Graft and Remnant; D: Table showing total, plane, graft and remnant liver volumes. MHV: Middle hepatic vein.

[42].

Most computer aided diagnostics used in clinical practice use conventional machine learning approaches, in which the effectiveness depends on the domain expertise of the developers. So, the limitations of conventional learning are linked to the limitations of the human developer. Manual and semi-automated volumetry is dependent on conventional machine learning. Deep learning has emerged as a state-of-the-art machine-learning method for many applications. Deep learning is a type of representation learning method in which a complex multilayer neural network architecture learns representations of data automatically by transforming the input information into multiple levels of abstraction[43].

Deep convolutional neural networks (DCNN) are widely used in image pattern recognition. They can automatically extract relevant features from training samples by adjusting their weights through backpropagation. In contrast to manual feature design, the DCNN learns feature representations during training. When trained with a large and representative dataset, the DCNN features outperformed the hand-engineered features by being highly selective and invariant. The automated deep learning process enables the analysis of numerous cases, surpassing human capabilities. Deep learning proves robust in handling variations across different classes, as long as the training set is diverse and extensive [40-43].

ACCURACY AND RELIABILITY

Automated LV and deep machine learning for LDLT has gained attention in recent years. There has been an increase in the number and quality of AI and machine learning studies in the medical field, mainly those focused on automating the interpretation of 2D image tests (MRI, CT, and radiographs), assembling three-dimensional models of organs and tissues, and volumetric calculations, including virtual segmentation of the liver. In liver resection and liver transplantation, most studies have a small number of cases, focusing on adult liver transplantation and RLDG, with very few studies on left lobe donor graft and left lateral segment donor graft[26-28,42-44]. The higher risk of the small-for-size syndrome in adult liver transplantation justifies the intense volumetric and anatomical studies on RLDG. Usually, for pediatric recipients (< 10 kg), an inaccurate volumetric assessment will rarely lead to insufficient liver volume; in contrast, the risk of the large-for-size syndrome is higher compared to the small-for-size syndrome. In such cases, the surgeon usually reduces the graft on the back table or converts it into a mono-segmental graft before implantation[45].

Automated software allows the surgeon to choose the transection plane; some studies have compared the correlation of these measurements for RLDG when performed by the surgeon using automated software with the manual measurements performed by radiologists. Moreover, both measurements had a good correlation with the AGW (r > 0.80), along with no significant difference between measurements by the surgeon and the radiologist[29].

As it is of paramount importance that the surgeon who is going to perform the procedure to perform the anatomical assessment and to choose the adequate liver segmentation plane, new softwares, focusing on the surgeon's interaction are being developed. A more user-friendly automated platform was developed by a group from the Republic of Korea[46], which they referred to as Dr. Liver. They validated the method in 50 RLDG and compared it to MLV. The correlation with AGW was better for the automated Dr. Liver (r = 0.98) than for the MLV (r = 0.92), although they were both good correlations. However, the percentage of absolute difference (%AD) from AGW of Dr. Liver (3.1% ± 2.8%) was significantly

smaller than that of the MLV (10.2% ± 7.5%). None of the Dr. Liver measurements percentages of %AD was > 10%, while they were 46% for MLV measurements. Evaluation of %AD is very important in clinical practice because an error percentage of more than 10% can result in a small-for-size boundary graft volume. Also, the total time for task completion was shorter for Dr. Liver *vs* MLV (7.3 ± 1.4 min *vs* 37.9 ± 7.0 min).

CONCLUSION

Accurate preoperative assessment of the liver plays a critical role in ensuring the selection of suitable donors and improving recipient outcomes after LDLT. MLV initially emerged as the gold standard for accurate assessment. However, the time-consuming nature of the manual analysis, reliance on operator expertise, and high variability in PE have prompted the adoption of SAIP software tools, and more recently, automated software solutions. AI represents the future of LV and segmentation and offers immense potential in the field, leading to a future fully automated liver segmentation and volumetry based on deep-learning. However, the widespread adoption and daily application of AI are hindered by cost and accessibility limitations. We are responsible for embracing technology and fostering interdisciplinary collaborations in the fields of radiology, engineering, informatics, and surgery. The possibilities afforded by AI are limitless, ranging from patient counseling and education to intraoperative decision-making facilitated by automation and AI assistance.

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FOOTNOTES

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MINIREVIEWS

Anti-thymocyte globulin for treatment of T-cell-mediated allograft rejection

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Abstract

Anti-thymocyte globulin (ATG) is a pivotal immunosuppressive therapy utilized in the management of T-cell-mediated rejection and steroid-resistant rejection among renal transplant recipients. Commercially available as Thymoglobulin (rabbit-derived, Sanofi, United States), ATG-Fresenius S (rabbit-derived), and ATGAM (equine-derived, Pfizer, United States), these formulations share a common mechanism of action centered on their interaction with cell surface markers of immune cells, imparting immunosuppressive effects. Although the prevailing mechanism predominantly involves T-cell depletion *via* the complement-mediated pathway, alternate mechanisms have been elucidated. Optimal dosing and treatment duration of ATG have exhibited variance across randomised trials and clinical reports, rendering the establishment of standardized guidelines a challenge. The spectrum of risks associated with ATG administration spans from transient adverse effects such as fever, chills, and skin rash in the acute phase to long-term concerns related to immunosuppression, including susceptibility to infections and malignancies. This comprehensive review aims to provide a thorough exploration of the current understanding of ATG, encompassing its mechanism of action, clinical utility in the treatment of acute renal graft rejections, specifically steroid-resistant cases, efficacy in rejection episode reversal, and a synthesis of findings from different eras of maintenance immunosuppression. Additionally, it delves into the adverse effects associated with ATG therapy and its impact on long-term graft function. Furthermore, the review underscores the existing gaps in evidence, particularly in the context of the Banff classification of rejections, and highlights the challenges faced by clinicians when navigating the available literature to strike the optimal balance between the risks and benefits of ATG utilization in renal transplantation.

Key Words: Anti-thymocyte globulin; T-cell-mediated rejection; Steroid-resistant

rejection; Biopsy confirmed acute rejection

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Core Tip: Anti-thymocyte globulin is a highly efficient induction agent that can prevent acute rejection and delayed graft function. It is widely used for biopsy confirmed acute rejection reversal and steroid-resistant rejection.

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INTRODUCTION

Rejection is one of the common complications after kidney transplantation. About 10%-20% of kidney transplant recipients experience acute rejection (AR) in the first year post-transplant[1,2]. AR can be defined clinically as a rise in serum creatinine in the absence of other pathology, and verified by allograft biopsy using the Banff classification system [3]. AR is associated with an increased risk of long-term graft loss, morbidity, and mortality[4]. Therefore, timely treatment of AR is crucial in improving long-term outcomes in kidney transplantation. A proportion of AR can be resistant to steroids (25%-30% of AR episodes)[2]. Anti-thymocyte globulin (ATG) is a polyclonal antibody used as an induction agent to reduce rejection rates and treat rejections following a kidney transplant. It is available in rabbit-derived (rATG; Thymoglobulin), ATG-Fresenius, and equine-derived forms (eATG; ATGAM). During the early use of ATG, its role in treating steroid-resistant allograft rejection was established[5]. The Kidney Disease Improving Global Outcomes (KDIGO) and British Transplant Society guidelines advise using ATG at induction in high-risk individuals and as an option to manage steroid-resistant acute rejection[6,7]. For this review, we studied peer-reviewed research articles published in PubMed-indexed journals. We reviewed the various clinical trials of ATG, its use in the treatment of acute rejection, steroid-resistant rejection, recurrent rejections, and clinical studies published in similar journals. We excluded reports presented as conference abstracts and those published in languages other than English. We aimed to evaluate the risks and benefits of ATG treatment in rejections and its implications in clinical practice. We envisage that such analysis of the literature will help clinicians and patients evaluate the role of ATG holistically in current transplantation protocols and aid in clinical decision-making at an individual patient level. Lastly, we identify gaps in evidence and outline potential strategies that could help bridge these gaps to improve post-transplant patient and allograft survival.

MECHANISM OF ACTION

ATG predominantly targets T cell antigens (although some of these antigens are present in other cell types) like TCR/CD3, CD2, CD4, CD5, CD6, CD8, CD25, CD28, CD45, and HLA (Human Leukocyte Antigen) class I to induce the immunosuppressive effects. The complement-dependent T cell lysis in the intravascular compartment (*i.e.*, blood) and the phagocytosis of T cells by macrophages in peripheral and secondary lymph nodes are regarded as the primary mechanism of action of ATG. The pre-activated T cells present in blood or peripheral tissues are depleted through antibody-dependent cell-mediated cytotoxicity and Fas-ligand-dependent apoptosis pathways[5,8,9]. The pharmacokinetics of ATG depends on the dose and schedule of administration as well as the number of 'targeted' immune effectors[9]. A lower concentration of thymoglobulin in the 0.1–1 μg/mL range induces lysis of preactivated T cells. A higher concentration (10–100 μg/mL) triggers CD178 (CD95-L) expression by resting T cells and apoptosis of preactivated T cells through pathways mostly involving Fas/Fas-L interactions[10,11]. ATG also modulates cell surface expression of adhesion molecules (ICAM-1, -2, and -3), integrins (LPAM-1 and VLA-4), and chemokine receptors (CXCR4, CCR5, and CCR7), thus interfering with leukocyte-endothelial interactions that play a role in ischemia/reperfusion injury, graft *vs* host disease, and rejection[10,12]. The modulation, particularly in this setting, is the process of internalization of the ATG-antigen complex by endothelial cells. This results in decreased surface antigen which ultimately decreases the interaction of leucocytes with the endothelium and their trans-migration into tissue. ATG has been shown to contain antibodies against a few B-cell antigens, including B-cell-specific and non-specific surface proteins CD19, CD20, CD40, CD80, CD30, CD38, CD95, and HLA-DR. ATG crosslinks with these surface proteins and induces apoptosis (*in vitro*) in naïve and activated B cells at clinically relevant concentrations (1–100 ng/mL). ATG can also bind with Syndecan-1 (CD138), a plasma-cell-specific molecule; however, *in vivo* ATG treatment is not associated with a reduction in either splenic or bone marrow plasma cells[5,9].

ATG interferes with the functional properties of dendritic cells (DCs) including maturation and migration and influences the balance between solid organ rejection and tolerance. Several *in vitro* studies showed the tolerogenic effect of ATG. ATG attaches to Toll-like receptors present on the surface of DCs. The common mechanism is the induction of

complement-mediated DC lysis hampering lymphocyte proliferation[13-15].

Finally, ATG is also known to produce dominant tolerance by the expansion of CD4+CD25high Foxp3+ T-regulatory cells which inhibits the action of CD4+CD25- T cells, CD8+ T cells, B cells, DCs, and natural killer (NK) cells[16-18]. It also associates with the increase of NK-T cells (CD4-/CD8- subset of T cells), which seems to decrease the incidence and severity of acute rejection[19]. Figure 1 summarizes the five documented mechanisms of ATG.

TREATMENT OF T-CELL-MEDIATED REJECTION

T-cell-mediated rejection (TCMR) is a process initiated by the interaction of T-cells with donor antigens predominantly presented by macrophages. The interaction of these biomolecules leads to local inflammation (infiltration of T cells and macrophages) that further leads to recruitment of effector T cells, tubulitis, nephron response to injury including differentiation of the epithelium, and if untreated, nephron loss that will be irreversible. Acute rejection is clinically suspected in patients experiencing an increase in serum creatinine, after the exclusion of other causes of graft dysfunction. Subclinical acute rejection is defined by the presence of histological changes specific for acute rejection on screening or protocol biopsy, in the absence of clinical symptoms or signs. Kidney biopsy remains the gold standard test to diagnose acute rejection, with characteristic infiltration of donor tissue interstitium with host T cells, cells in the monocyte-macrophage lineage, and nephron injury[20]. Treatment of TCMR has changed little over time and sparse data exist comparing one strategy to another.

AR requires a short course of more intensive immunosuppression in addition to baseline immunosuppression therapy. Options include treatments with steroids, antibody preparations, alteration of maintenance immunosuppression, or a combination of these options. Corticosteroid therapy is the most commonly used first-line treatment for acute cellular rejection episodes. Although most patients respond to corticosteroids, the dose and duration of treatment have not been well defined by randomised controlled trials. Table 1 lists the published clinical trials and Table 2 lists published cohort studies, the majority of which are retrospective single centre studies. Treatment of acute cellular rejection with T-cell depleting antibody can be more effective in improving kidney function and preventing graft loss than treatment with corticosteroids alone[21]. However, all these trials were published more than 20 years ago, with the majority between 1970s and 1990s, when Banff classification was yet to be incorporated into clinical practice or clinical trials/studies. In clinical practice, treatment is guided by biopsy features as longer-term graft survival varies with the type of TCMR[22]. The majority of Banff class I lesions respond to methylprednisolone alone; conventionally pulse methylprednisolone at 250–500 mg daily for 3–5 d is recommended by international guidelines[6]. TCMR involving lymphocytic infiltrate of the vasculature (Banff II and III lesions) may necessitate T cell–depleting therapy. Polyclonal antibodies include horse-derived (anti-lymphocyte globulin, ALG) and rabbit-derived (ATG) antibodies against the human lymphocyte or thymocyte, respectively. Most commonly rATG dosed at 1.5 mg/kg for 7-14 doses was used (Tables 1 and 2)[8,21-24]. Reversal of rejections was seen in 50%-90% in clinical trials. Intravenous immunoglobulin (IVIG) and anti-thymocyte serum were also used in the past[25]. Recently, Alemtuzumab had been put forward as a possible treatment option for rejection[26].

STEROID-RESISTANT REJECTIONS

In approximately 25% to 30% of the patients, rejections are not reversed with steroid therapy alone. In these recipients, more intensive immunosuppressive therapy is required to reverse the AR episode. When serum creatinine levels do not recover to within 120% of the pre-rejection baseline value following corticosteroid pulse therapy within 14 d of the steroid medication's initiation, the episode is deemed steroid-resistant[27]. Up until day 5, patients with steroid-responsive and steroid-resistant AR experienced similar changes in their serum creatinine levels. However, at that point, the responders' creatinine levels significantly decreased, while the non-responders' levels stayed high. Therefore, conventionally, physicians typically wait 5 d for classifying a rejection as steroid-resistant[28].

ADVERSE EFFECTS

Infusion of ATG may be complicated by immediate toxicity in the form of fever, chills, or skin rash which are considered self-limiting and managed by symptomatic therapy (paracetamol, antihistamines, and bolus steroids) and reducing rates of infusion. Lymphopenia, neutropenia, and thrombocytopenia can occur, but these are amenable to dosage adjustment. Medium- to longer-term effects include cytopenia, higher rates of infection, and malignancy. Serum sickness is a rare complication caused by the deposition of immune complexes in tissues. Characteristic symptoms include fever, jaw pain, arthralgia, lymphadenopathy, and rash[10,22]. Registry studies have tried to determine whether ATG induction therapy is associated with a greater risk of developing post-transplant lymphoproliferative disease, but results are mixed and remain inconclusive[10]. Tables 1 and 2 outline the frequency of these adverse effects published in the randomised controlled studies and cohort studies, respectively.

Table 1 Summary of randomized clinical trial studies

No.	Ref.	Study design	ATG – dose & duration	Graft outcome	Death	Other adverse events
1	Shield *et al* [50], 1979	Prospective, randomised, single centre, United States; First rejection	eATG 15 mg/kg daily for 14 d (n = 10) *vs* MP 1 g/d for 5 d (n = 10)	Reversal – 8/10 (ATG) *vs* 6/10 (MP); Recurrent rejection 1/10 (ATG) *vs* 5/10 (MP); Graft loss at 12 mo – 1/10 (ATG) *vs* 1/10 (MP)	At 12 mo – 0/10 (ATG) *vs* 1/10 (MP)	Infection – 3/10 (ATG) *vs* 0/10 (MP); AVN – 1/10 (ATG) *vs* 0/10 (MP)
2	Filo *et al*[51], 1980	Prospective, randomised, single centre, United States; First rejection	eATG 10 mg/kg/d for 15 d (n = 35) *vs* MP 30 mg/kg every other day up to 5 doses (n = 43)	Reversal – 32/35 (ATG) *vs* 29/43 (MP); Recurrent rejection – 16/35 (ATG) *vs* 15/43 (MP); Graft survival (91% *vs* 62%); Faster recovery (6.9 d *vs* 8.9 d); Graft loss – 15/35 *vs* 25/43 (MP)	At 12 mo – 1/24 (ATG) *vs* 0/29 (MP)	
3	Hoitsma *et al* [52], 1982	Prospective, randomised, single centre, Netherlands; First rejection	rATG initially 4 mg/kg followed by 2-7 mg/kg for 21 d (n = 20) *vs* prednisolone 200 mg/d, tapered to 25 mg/d in 2 wk (n = 20)	Reversal – 43/50 (ATG) *vs* 35/50 (Prednisolone); Recurrent rejection – 28/50 (ATG) *vs* 35/50 (Prednisolone); Graft loss – 15/50 (ATG) *vs* 28/50 (Prednisolone)	At 12 mo – 0/20 (ATG) *vs* 1/20 (Prednisolone)	Infection – 9/20 (ATG) *vs* 15/20 (Prednisolone)
4	Toledo-Pereyra *et al* [53], 1985	Prospective, randomised, single centre, United States; First rejection	ALG 10 to 20 mg/kg for 10 d (n = 20) *vs* ATG 10 to 20 mg/kg for 10 d (n = 20)	Reversal – 15/20 (ALG) *vs* 16/20 (ATG)		
6	Alamartine *et al*[54], 1994	Prospective randomised, single centre, France; Steroid-resistant rejection	Muromonab-CD3 5 mg/d for 10 d (n = 27) *vs* rATG: 1.5 mg/kg/d for 10 d (n = 32)	Reversal – 25/26 (Muromonab-CD3) *vs* 27/32 (ATG); Recurrent rejection – 25/32 (ATG) *vs* 24/27 (Muromonab-CD3); Graft loss at 12 mo – 11/32 (ATG) *vs* 4/26 (Muromonab-CD3)		CMV infection – 8/27 (Muromonab-CD3) *vs* 18/32 (ATG)
7	Tesi *et al*[55], 1997	Prospective, randomised, multi-centre n = 163 (82 Thymoglobulin, 81 ATGAM); First rejection	rATG 1.5 mg/kg *vs* ATGAM 15 mg/kg (both for 7 to 14 d)	65% treated with THYMO had histology grade improvement (*vs* 50% in ATGAM)	Overall – 3/82 (rATG) *vs* 1/81 (eATG)	CMV infection 20/82 in both groups
8	Mariat *et al* [31], 1998	Prospective, randomised, single centre, France; First rejection	Muromonab-CD3 5 mg/kg for 3 d followed by 2.5 mg/kg for 7 d (n = 29) *vs* rATG 25 mg/d if < 40 kg, 50 mg/d if 40-70 kg & 75 mg/d if > 70 kg; 10 d (n = 31)	Reversal – 25/29 (Muromonab-CD3) *vs* 30/31 (ATG); Recurrent rejection – 11/29 (Muromonab-CD3) *vs* 9/31 (ATG); Graft loss at 12 mo – 6/29 (Muromonab-CD3) *vs* 4/31 (ATG)	At 12 mo – 3/31 (ATG) *vs* 1/29 (Muromonab-CD3)	CMV infection – 12/31 (ATG) *vs* 13/29 (Muromonab-CD3); Malignancy – 0/31 (ATG) *vs* 2/29 (Muromonab-CD3)
9	Gaber *et al* [56], 1998	Prospective, randomised, multi centre, United States; First rejection	Thymoglobulin (rATG) 1.5 mg/kg/d for 7-14 d (n = 82) *vs* ATGam (eATG) 15 mg/kg/d, for 7-14 d (n = 81)	Reversal – 88% (Thymoglobulin) *vs* 76% (ATGAM); Recurrent rejection; 28/82 (rATG) *vs* 50/81 (eATG)	Total 6/82 (rATG) *vs* 3/81 (eATG)	Leukopenia – 57% (rATG) *vs* 30% (eATG); Bacterial infection – 29% (rATG) *vs* 37% e(ATG); Viral infection – 21% (rATG) *vs* 11% (eATG)
10	Theodorakis *et al*[57], 1998	Prospective, randomised, single centre, Germany; First rejection	ATG 4 mg/kg for 7 d (n = 25) *vs* MP 250 mg/d for 3 d (n = 25)	Recurrent rejection – 4/25 (ATG) *vs* 18/25 (MP); Graft loss – 5/25 (ATG) *vs* 3/25 (MP)		
11	Baldi *et al* [58], 2000	Prospective, randomised, single center, Belgium; First rejection	rATG 4 mg/kg day for 10 d (n = 28) *vs* Muromonab-CD3: 5 mg/d for 10 d (n = 28); MP for both groups: 500 mg/d for 3 d	Reversal – 21/28 (rATG) *vs* 14/28 (Muromonab-CD3); Recurrent rejection – 9/28 (ATG) *vs* 10/25 (Muromonab-CD3)	Irreversible rejection in 3/28 OKT3, 2nd rejection in 33% ATG, 39% OKT3	Fever – 21.4% (ATG) *vs* 92.8% (Muromonab-CD3); Headache – 3.5% (ATG) *vs* 46.4% (Muromonab-CD3); Infection – 9/28 (ATG) *vs* 10/28 (Muromonab-CD3); Malignancy 2/28 (ATG) *vs* 0/28 (Muromonab-CD3)
12	Midtvedt *et al*[59], 2003	Prospective, randomised, single centre, Norway; First rejection	ATG 2 mg/kg followed by 1 mg/kg if & when T cells > 50 (n = 27) *vs* muromonab-CD3: 5 mg, then 2.5 mg (n = 28)	Reversal – 26/27 (ATG) *vs* 27/28 (Muromonab-CD3); Recurrent rejection – 12/27 (ATG) *vs* 14/28 (Muromonab-CD3); Grafts loss at 12 mo – 3/27 (ATG)	At 12 mo – 2/27 (ATG) *vs* 1/28 (Muromonab-CD3)	CMV infection – 14/27 (ATG) *vs* 11/28 (Muromonab-CD3); Malignancy – 1/27 (ATG) *vs* 1/28 (muromonab-CD3); Bacterial pneumonia – 3/27

			vs 4/28 (Muromonab-CD3)			(ATG) *vs* 3/28 (Muromonab-CD3)

ATG: Anti-thymocyte globulin; rATG: Rabbit Anti-thymocyte globulin, eATG: Equine Anti-thymocyte globulin; MP: Methylprednisone.

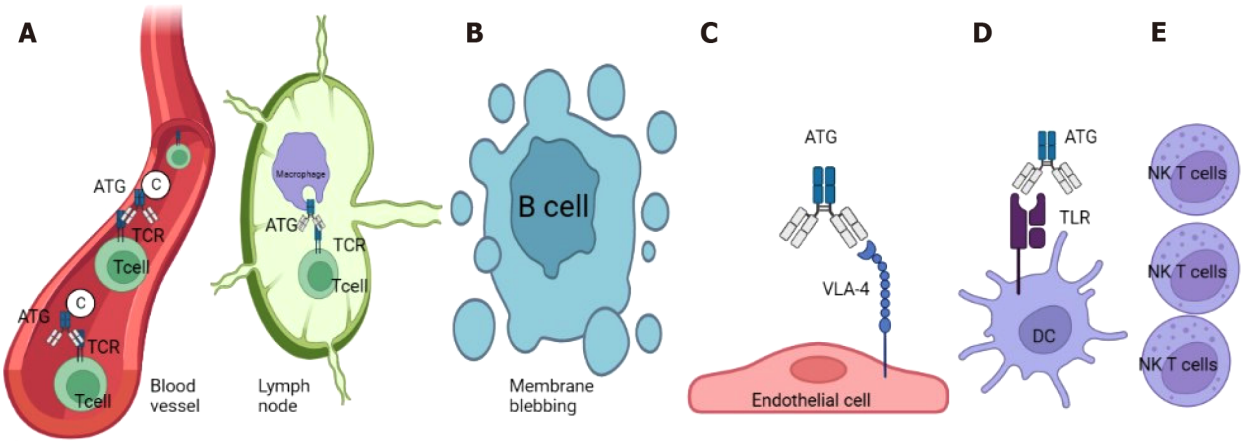
Table 2 Summary of non-randomized clinical studies

No	Ref.	Study design	ATG -dose/duration	Graft outcome	Death	Adverse events
1	Hardy *et al* [60], 1980	Prospective, non-randomised, single centre , United States, *n* = 20 (10 ATG)	eATG – 15 mg/kg (max 750 mg) for 21 d + MP (750, 200 & 150 mg for 3 d) (*n* = 10) *vs* MP (750, 200 & 150 mg for 3 d) (*n* = 10)	Reversal – 9/10 (ATG) vs 8/10 (control); Recurrent rejection 2/10 (ATG) *vs* 4/10 (control); Graft loss at 12 mo – 4/10 (ATG) *vs* 5/10 (control)	0 in both groups	3 serious complications in control group and 1 in ATG
2	Richardson *et al*[30], 1989	Prospective, non-randomised, single centre, United Kingdom	rATG (2-3 mg/kg for 5-10 d) reduced to 1-2 mg/kg if leukopenia or thrombocyt-openia (*n* = 27)	70.3% graft survival with mean follow-up time of 13.3 mo; 8 out of 27 failed (6 due to rejection, 1 death, and 1 renal artery stenosis)	1 death	6 UTIs, 1 pseudomembranous colitis, 8 CMV and 5 HSV, 2 deaths
3	Clark *et al* [45], 1993	Prospective, non-randomised, single centre, United Kingdom	Group 1: rATG, 2.5-5 mg/kg/d) for 10-14 d (*n* = 10); Group 2: As per T cell count for 10-14 d (*n* = 17)	76% graft survival at 1 year group 2 (*vs* 60% in group 1); Group 1 – (4 rejections); Group 2 – (4 rejections)	2 deaths (group 1) *vs* 0 deaths (group 2)	Group 1: 3 serious viral infection, 6 minor infections; Group 2: 11 minor infections
4	Uslu *et al* [61], 1997	Retrospective, non-randomised, single centre, Turkey	rATG 5 mg/kg for 13.7 ± 3.7 d (*n* = 9) OKT3 5 mg/d for 11.4 ± 1.9 d (*n* = 5)	Graft survival: 78% ATG *vs* 20% OKT3 with median f/u 405 d		OKT3 – 1 CMV, Fever > 38 in 80% pts in both groups, Leukopenia (35% ATG *vs* 0 in OKT3)
5	Sharma *et al* [46], 2003	Prospective, non-randomized, single centre, India	ATG 1.5-1.8 mg/kg alternate d, mean duration 5 doses (*n* = 33)	90% graft survival in first year and 73% at 20 mo. Graft loss in 4; Recurrent rejection in 8/33 at 3 mo	1 death	11 pneumonia, 3 UTI, 1 peritonitis, 2 CMV, 5 leukopenia
6	Colak *et al* [62], 2008	Retrospective, non-randomised, single-centre, Turkey	ATG 3-5 mg/kg/d 10-14 d (Dose adjusted with other parameters) (*n* = 23)	Graft function improved in 19 cases (83%)	1 death	9 infections (3 pulmonary aspergillosis, 2 CMV, 4 pulmonary/urinary bacterial infections)
7	Kainz *et al* [33], 2009	Retrospective, non-randomised, multi centre, Austria	N/A *n* = 399 (368 ATG, 31 OKT3)	Median actual graft survival 9.5 yr ATG *vs* 4.5 yr OKT3	N/A	N/A
8	van der Zwan *et al* [38], 2018	Retrospective, non-randomised, single centre, Netherlands	rATG – 4 mg/kg repeated after 4 d if CD3 > 200, for 2 wk (*n* = 103)	Median allograft survival 7.0 yr. At one yr 78.2% had functioning graft; At 5 yr 55.6% functioning graft; 49 lost graft in median f/u 6.8 yr	17 deaths	97 bacterial, 8 fungal, 27 CMV reactivation, 4 EBV reactivation, 6 BK viraemia), 14 malignancy (12 solid, 2 lymphoma)

ATG: Anti-thymocyte globulin; EBV: Epstein-Bar virus, CMV: Cytomegalovirus, rATG: Rabbit anti-thymocyte globulin; OKT3: Muromonab CD3, UTI: Urinary tract infection; N/A: Not applicable.

DISCUSSION

Despite the advancement of immunosuppressant therapy, AR remains one of the major problems in the field of clinical renal transplantation. The current approach in the management of acute kidney rejection in adults and children is based on the 2009 KDIGO guidelines[29]. These guidelines recommend corticosteroids for the initial treatment of acute cellular rejection. They advise adding or restoring maintenance prednisone in patients with rejection episodes who are not on steroids. They also recommend using lymphocyte-depleting agent or muromonab-CD3 (OKT3) for TCMR that does not respond to corticosteroids and for recurrent acute cellular rejections. The lymphocyte-depleting agent ATG has been used extensively for treating and preventing AR in kidney transplant recipients[21]. ATG has also been used as first-line therapy for those with severe acute TCMR including vascular lesions (Banff II or higher categories), and as rescue therapy for steroid-resistant acute TCMR (Tables 1 and 2). It has been shown that steroid-resistant rejection can be a significant problem in patients immunosuppressed with triple therapy (combination of tacrolimus [Tac], mycophenolate mofetil [MMF], and steroids) and 70% of such rejections can be reversed following ATG treatment[30]. A systemic review by Webster *et al*[23] was one of the comprehensive studies describing the advantages of using ATG over steroids for the treatment of steroid-resistant rejection. They studied 21 trials (49 reports, 1394 randomised participants) and concluded that in treating first rejection, ATG was superior to steroids in reversing rejection (relative risk [RR] = 0.57; 95% confidence interval [CI]: 0.38-0.87) and preventing graft loss (death-censored RR = 0.74; 95%CI: 0.58-0.95). However, there



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Figure 1 Mechanisms of action of anti-thymocyte globulin. A: T-cell depletion in blood through complement-mediated lysis and in secondary lymphoid tissue by T cell apoptosis; B: B-cell apoptosis by anti-thymocyte globulin (ATG); C: ATG-VLA-4 complex leading to decreased adhesion proteins in endothelial cells required by leukocyte/endothelium interaction; D: Dendritic cell maturation by HLA1/ATG interaction; E: Increased natural killer T cells.

was no difference in preventing subsequent rejections (RR = 0.67; 95%CI: 0.43-1.04) or death (RR = 1.16; 95%CI: 0.57-2.33) at 1 year between ATG and steroids. Additionally, they also found no benefits with the use of muromonab-CD3 over ATG or ALG in reversing rejection, preventing subsequent rejection, or preventing graft loss or death. A decade later, in 2017[21], Webster *et al*[23] updated the review with 11 new trials (76 reports, 1680 participants). The updated meta-review concluded that antibody therapy was still better than steroid therapy (RR = 0.50; 95%CI: 0.30 to 0.82) for reversing the first acute rejection and preventing subsequent rejections (RR = 0.70; 95%CI: 0.50 to 0.99) and tended to help prevent graft loss (death-censored RR = 0.80; 95%CI: 0.57 to 1.12). There was no benefit of muromonab-CD3 over ATG in reversing rejection, preventing subsequent rejection, or preventing graft loss or death[29].

Muromonab-CD3 (Orthoclone, OKT3) is the first monoclonal antibody used clinically for immunosuppression. It eliminates CD3+ T cells from the peripheral circulation to produce the immunosuppressive effects. A few noticeable studies compared muromonab-CD3 with monoclonal and polyclonal antibodies in the treatment of steroid-resistant rejection[31,32]. Using clinical records stored in the Austrian Dialysis and Transplant Registry, Kainz *et al*[33] conducted a retrospective descriptive analysis of 399 (368 ATG treated *vs* 31 OKT3 treated) patients diagnosed with biopsy-confirmed acute rejection between 1990 to 2005. Their study suggested that ATG treatment for rejecting allograft exhibited longer graft survival over OKT3 treatment (median graft survival 9.5 years in ATG group *vs* 4.6 years in OKT3 group) and increased risk of graft loss in OKT3 group (hazard ratio = 1.73; 95%CI: 1.09-2.74; P = 0.019). ATG was better tolerated compared to OKT3, with a lower frequency of cytokine release syndrome.

Clinicians all around the world have backed studies to find a better alternative or newer, safer but more effective immunosuppressive regimen. Due to cost-effectiveness, adverse infusion reaction, prolonged duration of inpatient stay, and need for central venous access for ATG, Alemtuzumab (CD52-specific monoclonal antibody), which can be given subcutaneously in a single dose, has been put forward with some promising results. A propensity-matched controlled study of 116 patients treated with Alemtuzumab, in comparison to 108 patients treated with ATG, showed similar patient and allograft survival[26] whilst having superior infection-free survival with Alemtuzumab. The authors suggested that Alemtuzumab therapy may therefore be an alternative therapy for glucocorticoid-resistant, recurrent, or severe acute kidney transplant rejection.Registry data show that the incidence of AR has been steadily falling. The rate of AR used to be more than 50% in the 1970s, which has markedly dropped to 10%-20% today as per the United States, Australian, and New Zealand registries[2]. This can be attributed to the improvement of induction and maintenance of the immunosuppressive regimen. During the 1980s, the triple therapy regimen, which was the combination of low-dose cyclosporine, azathioprine, and prednisolone, was prescribed for maintenance immunosuppression[34,35]. Over the years, various combinations have been tried to find the optimal regimes. As of today, the best results overall are achieved with Tac, MMF, and steroids. A randomised trial conducted by Gonwa *et al*[36] demonstrated that this triple therapy regimen showed overall better outcomes in terms of graft and patient survival compared to other drug combinations. The study also showed that this combination provided particular benefits to kidney allograft recipients who develop delayed graft function/acute tubular necrosis. The landmark Symphony trial consolidated evidence for reduced exposure to calcineurin inhibitors in kidney transplantation, in conjunction with induction with daclizumab, MMF, and corticosteroids[37]. van der Zwan *et al*[38] recently showed the long-term outcome of the use of rATG with the combination of Tac + MMF + steroids for the treatment of AR. They concluded that early detection of AR followed by Tac + MMF + steroids with ATG provides better allograft functioning and survival. Survival after rATG was comparable to the overall survival of all kidney transplantation patients (P = 0.10).

However, there is a paucity of studies using ATG in current immunosuppression era and contemporary classification of AR. Only few studies in Tables 1 and 2 used Banff classification in the description of AR and when used, was from earlier classifications[39], at which point the role of antibody mediated component was less well understood.

The ATG dosage and duration varied widely among randomised studies as well as cohort studies described in Tables 1 and 2. The optimal dosing schedule in patients at high or low immunological risk has yet to be determined. Préville *et al* [40] derived data from a non-human primate model (cynomolgus monkey) which suggested that T-cell depletion with rATG is dose-dependent and that the optimal total dose required to achieve lymphocyte depletion in both peripheral blood and secondary lymphoid tissues (spleen and lymph nodes) is approximately 6.4 mg/kg. About 40% of patients treated with Thymoglobulin (mean of 6 doses at 1.5 mg/kg/d) have a recovery of > 50% of the initial lymphocyte count at 3 mo. Yet, time to immune reconstitution is characterized by not only a high intra-individual variability in the immune cell subpopulations (T and B cells, NK cells, DCs) but also an interindividual variability leading to prolonged lymphopenia for some patients up to 5 years[8]. When used as induction agent, a significant difference in infection rates was reported with rATG dose of < 7 mg/kg compared to use of > 7 mg/kg[41,42]. Since then, other studies have attempted to use the lower dose while optimizing the immunosuppressive effects of ATG[43,44]. However, in the context of AR treatment, guidance for use of ATG at 1.5 mg/kg remains broad at 7-14 d. It is difficult to pre-determine precise duration based on published studies. Variation in effects with intermittent dosing and continuous dosing was also reported (Tables 1 and 2). For CD3 count (T cells) < 200, 4 mg/kg bolus dose was used followed by re-dosing after 4 d, and for CD-3 count < 50[45], ATG was limited to 5 doses[46].

There is a need for further studies to unravel implications of ATG in treatment of rejections. These include: (1) Identifying patients most likely to benefit from ATG therapy. Clinical risk factors and kidney biopsy findings will need to be tested as a multivariate prediction model in determining outcomes that would enable choice of right patients; (2) It is possible that some of the intra-graft mRNA expression profiles (immune and non-immune biomarkers) could predict response to pulse glucocorticoid therapy in transplant recipients and likewise additional therapy to ATG[47]; (3) Evaluating benefit of ATG in late rejections compared to its benefit in treating early rejections; (4) Finding the optimal balance of immunosuppression in renal allograft recipients. Suboptimal immunosuppression can lead to rejection while over-immunosuppression can lead to life-threatening post-transplant infections. There remains no precise way to monitor the intensity of immunosuppression to prevent infectious complications[21]. Reports of CMV infection (Tables 1 and 2) were considerably high in published studies and prophylactic treatment with Valganciclovir for 3-6 mo is common practice lately; (5) Role of Torque-Teno Virus measurement (as a biomarker of immunosuppression to predict over/under-immunosuppression) is still in an infantile state[48]; (6) Role of ATG treatment in rejections due to non-compliance with maintenance immunosuppression medications. Currently, outcomes of treatment of such rejections is unclear; and (7) Role of anti-ATG antibodies in negating therapeutic potency of ATG needs to be established[49].

CONCLUSION

In conclusion, ATG emerges as a valuable therapeutic option for managing acute T-cell-mediated rejections, particularly in cases refractory to steroid treatment or characterized by higher grade rejections, such as Banff II or III. While the established standard dosing regimen recommends 1.5 mg/kg for a duration spanning 7 to 14 d, it is imperative to underscore the complexity of tailoring ATG therapy to individual patients, where striking the optimal balance between risks and benefits remains a formidable clinical challenge. To further advance our comprehension of this crucial treatment approach, it is imperative that we embark on comprehensive investigations. Large-scale studies, ideally based on registries, should be conducted with meticulous phenotyping of transplant recipients and thorough analysis of renal transplant biopsy characteristics. Such endeavours are indispensable in augmenting the existing body of scientific knowledge, ultimately enabling us to address the pertinent questions surrounding the precise use of ATG in the management of acute T-cell mediated rejections.

FOOTNOTES

Author contributions: Acharya S, Lama S, and Kanigicherla DA performed the necessary article search and review, analyzed the paper, and wrote the manuscript; Acharya S made the figures and tables; all the authors have read and approved the final manuscript.

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MINIREVIEWS

BK viral infection: A review of management and treatment

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Abstract

BK viral infection remains to be a challenging post-transplant infection, which can result in kidney dysfunction. The mainstay approach to BK infection is reduction of immunosuppression. Alterations in immunosuppressive regimen with minimization of calcineurin inhibitors, use of mechanistic target of rapamycin inhibitors, and leflunomide have been attempted with variable outcomes. Over the past few years, investigators have explored potential therapeutic options for BK infection. Fluoroquinolone prophylaxis and treatment was found to have no benefit in kidney transplant recipients. The utility of cidofovir is limited by its nephrotoxicity. Intravenous immunoglobulin is becoming a popular option for treatment and prophylaxis for BK infection, as it increases the neutralizing antibody titers against the most common BK virus serotypes. Virus-specific T cell therapy is an emerging treatment option for BK viremia. In this review, we will explore management and therapeutic options for BK infection and recent evidence available in literature.

Key Words: BK infection; Kidney transplant; Treatment; Management

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Core Tip: BK viral infection is a significant post-transplant infection, which can result in kidney dysfunction if left unaddressed. The mainstay approach to BK infection is reduction of immunosuppression. Data on specific therapies have remained equivocal. In this article, we will review recent evidence available in literature on treatment approaches to BK viral infection.

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INTRODUCTION

BK virus is a DNA virus that belongs to the human polyomavirus family. It was first isolated in 1971 from the urine of a Sudanese kidney transplant recipient with initials B.K[1]. BK infection is common in the general population, approaching >90% seroprevalence by age 4[2]. It persists following primary infection and may reactivate following immunosuppression[1]. BK virus infection is a common and important post-transplant viral infection that can result in kidney dysfunction if left unaddressed. The evolution of BK infection often involves viruria, that progresses to viremia, and eventually leads to nephropathy. Severe BK virus-associated nephropathy (BKVAN) can result in loss of the kidney allograft. Effective treatment for the eradication of BK infection remains elusive. The most recent guidelines from the American Society of Transplantation Infectious Diseases Community of Practice (AST-IDCOP) recommends a stepwise approach in immunosuppression reduction as the primary intervention for BK viremia and nephropathy. The AST-IDCOP did acknowledge the lack of randomized controlled trials to provide evidence for using tacrolimus or cyclosporine, switching mycophenolate to mechanistic target of rapamycin (mTOR) inhibitor or leflunomide, and using intravenous immunoglobulin (IVIg) and cidofovir[2]. Studies that employed the use of fluoroquinolones in either prophylaxis or treatment have had varying outcomes. Finally, virus-specific T-cell therapy (VST) is a new emerging therapeutic option under current investigation. In this systematic review, we seek to present the most recent evidence surrounding management approaches and therapeutic options for BK infection following organ transplantation.

ALTERATIONS IN IMMUNOSUPPRESSIVE REGIMEN

BK virus infection poses a threat to the survival of kidney transplants, and a considerable proportion of infected patients face irreversible graft failure. The occurrence of this infection appears to be linked to the level of immunosuppression rather than any specific immunosuppressive agent. The optimal approach for treating BK infection is still uncertain, however, reducing immunosuppression is widely recognized as a primary therapy for BK infection. Although systematic studies in this area are lacking, several studies have shown that reduction in immunosuppression results in better viral clearance and preservation of graft function.

A retrospective study done in the Medical College of Wisconsin on 24 kidney transplant recipients with BK viremia (> 7000 copies/mL) showed that a 44% and 41% reduction in mycophenolate mofetil (MMF) and tacrolimus respectively, caused a significant decline in the BK DNA copies per milliliter of plasma ($P < 0.0001$) within a mean period of 5.8 mo. Only three patients (13%) developed acute cellular rejection, successfully treated with intravenous bolus steroids. After 43.5 mo, all except for one patient have a stable functioning graft[3]. In a similar study, post-transplant surveillance for BK DNA polymerase chain reaction and urinary cytology was done in 229 kidney transplant recipients. Patients found to have BK viremia and BKVAN received treatment with a 30%-50% reduction in tacrolimus and/or MMF dosages. After 5 years, overall patient survival and graft survival were 95.6% and 92.1% respectively. Following the reduction of immunosuppression, complete resolution of BK viremia was achieved in all patients and without any increase in acute rejection rates. Among the viremic patients without BKVAN, recurrent BK viremia did not occur. The seven patients diagnosed with BKVAN successfully cleared viremia within an average time of 5.9 mo, while having a stable glomerular filtration rates (GFR) in five years[4]. There have been several studies that compared reduction of immunosuppression *vs* other treatment approach in controlling BK virus infection. In 2010, Johnston *et al*[5] published a systemic review of 40 studies examining the effect of immunosuppression reduction alone or in combination with cidofovir, leflunomide, IVIg, or ciprofloxacin. Results showed a death-censored graft loss rate of 8/100 patient-years for immunosuppression reduction alone and 8 and 13/100 patient-years for the addition of cidofovir or leflunomide respectively, suggesting that there does not seem to be a graft survival benefit of adding cidofovir or leflunomide to immunosuppression reduction for the management of BKVAN. The same finding was seen in the study done by Halim *et al*[6] in 55 kidney transplant recipients where administration of three different anti-BK virus agents (leflunomide, IVIg, ciprofloxacin) added no benefit to long-term outcome in patients with BKVAN ($P = 0.32$). A recent retrospective study compared treatments for BK DNAemia in 43 kidney transplant recipients. The study evaluated immunosuppression reduction *vs* mTOR inhibitors plus IVIg. Results indicated that the immunosuppression reduction group experienced a significantly faster decrease in BK DNAemia compared to the mTORi±IVIg group ($P < 0.001$). Viral clearance was notably higher in the immunosuppression reduction group compared to the mTORi ± IVIg group ($P = 0.033$). There were no significant differences in death-censored graft loss, rejection rates, or graft function at 12 mo. This study further supports that standard BK virus (BKV) DNAemia treatment of reduction in immunosuppression as having superior outcomes compared to any other treatment approach[7].

LEFLUNOMIDE

Leflunomide, an immunosuppressive medication, has been explored as a potential treatment for BKVAN in kidney transplant recipients. The therapeutic benefit of using leflunomide in this context lies in its antiviral activity against various viruses such as herpes simplex (HSV-1) and cytomegalovirus (CMV). In vitro studies have shown that the active metabolite of leflunomide (A77 1726) has some anti-viral properties by a dose-dependent reduction in BK large T antigen expression. This reduction in antigen expression, however, did not translate to a reduction in BK virus DNA replication [8]. This finding was echoed by a retrospective single-center study done by Krisl *et al*[9] where 52 patients with BK viremia (with or without nephropathy) did not show any significant BK viral clearance after treatment with leflunomide compared to the control group. The rate of BK clearance was 30.8% in the leflunomide group *vs* 60.9% in the group that did not receive leflunomide (P = 0.02). Furthermore, graft failure occurred in 15% of patients in the leflunomide group and 7% in the no leflunomide group (P = 0.32).There are some studies that showed partial improvement in BK virus clearance and renal function. A prospective open-label study where 12 kidney transplant recipients diagnosed with BKVAN had MMF changed to leflunomide. Results showed that renal function improved in 50% of patients, remained stable in 16.6%, and deteriorated in 33.4%, with graft loss in 17% of cases. Clearance of BK viremia was observed in 42% of cases[10]. A similar study was done in 12 kidney transplant recipients whose MMF was changed to leflunomide upon diagnosis of BKVAN. Results showed that T-cell proliferation tend to be higher with leflunomide treatment compared to MMF therapy (8.4 ± 7.7% *vs* 12.4 ± 10%, P = 0.2). However, the difference was not statistically significant. BK viral clearance was observed in 41.6% of cases treated with leflunomide within 6 mo. Stable creatinine clearance was also noted in 50% of these patients within 6 mo of treatment. Of note, however, one patient in this study developed end-stage kidney disease because of concurrent acute antibody-mediated rejection and BKVAN[11].

Although these studies have shown dismal results, several case reports and studies have shown encouraging findings with the use of leflunomide in treating BK infection in kidney transplant recipients. One such study was done in 13 patients with biopsy-proven BKVAN treated with leflunomide in combination with a low-dose calcineurin inhibitors and prednisone after cessation of MMF therapy. Findings showed that 12 patients (93%) had undetectable viral load after mean treatment of 109 d. There was noted graft improvement in 13% of cases. However, overall graft function at follow-up was not significantly better than at diagnosis (P = 0.69). Leflunomide was well-tolerated and no serious adverse effects or episodes of graft rejection were reported[12]. Another study involving 26 patients with biopsy proven BKVAN investigated treated with either leflunomide alone or leflunomide plus a course of cidofovir and followed them for six to 40 mo. Results showed that 84% of cases had viral clearance in six months (P < 0.001). Follow-up after 12 mo or more showed creatinine levels not significantly changed compared to baseline in 16 patients. After follow-up of 40 mo, graft loss was at 15%[13].

The utilization of leflunomide in kidney transplant recipients with BK virus infection remains a topic of ongoing debate. A high-powered and robust randomized trial could prove essential in definitively establishing the relationship between this treatment and critical clinical outcomes such as effective viral clearance and the enduring maintenance of long-term graft function.

FLUOROQUINOLONES

Fluoroquinolones are often utilized in kidney transplant recipients due to their broad spectrum of activity. They have been demonstrated to inhibit BK replication in its natural host cells by blocking large T antigen helicase activity in polyomavirus, and possibly by inhibition of host cell proteins like topoisomerase II[14]. This perceived efficacy against the said virus was the impetus for several retrospective studies to investigate its role as prophylaxis for BK virus among kidney transplant recipients. One such study was performed by Gabardi *et al*[15] wherein they compared two groups of kidney transplant recipients with documented BK virus infection, one that used a fluoroquinolone (ciprofloxacin or levofloxacin adjusted according to renal function) for 30 d and another group that did not. In this study, sulfamethoxazole/trimethoprim was the primary antibiotic used for pneumocystis prophylaxis, whereas fluoroquinolone in combination with atovaquone use was used for those with sulfa allergy or G6PD deficiency. The results showed that there was lower BK viremia rate at one year post-transplant among those who received a fluoroquinolone compared to those who did not (4% *vs* 22.5%, respectively; P = 0.03). Another study retrospectively analyzed two groups of kidney transplant recipients, one with no BK virus prophylaxis (group I, n = 106), and another that used ciprofloxacin for 30 d to cover for BK virus prophylaxis (group 2, n = 130). The investigators evaluated the levels of BK viruria and viremia between the two groups over a period of 12 mo. On the third month after transplantation, there was a higher risk of developing BK viruria and viremia in group 1 *vs* group 2 (viremia: 0.161 *vs* 0.065, P = 0.0378; viruria: 0.303 *vs* 0.146, P = 0.0067). In the subsequent six, nine, and 12 mo though, there was no difference in the mean blood and urine BK viral load between the two groups, even after adjusting for corticosteroid regimen. This raised the possible benefit of increasing the duration of prophylactic treatment[16]. These studies were among those that inspired the randomized controlled trials that ensued.

Lee *et al*[17] conducted the first prospective, multicenter, double-blind, placebo-controlled trial that investigated the efficacy of levofloxacin in the treatment of BK viremia among adult kidney transplant recipients. A total of 43 patients were randomized to either receive levofloxacin 500 mg daily (with renal dose adjustment), or placebo for 30 d, with appropriate adjustment of immunosuppression according to the standard of practice at each institution. After three months of treatment, there was no significant difference in the percentage of BK viral load reduction between the levofloxacin-treated group and placebo (70.3% *vs* 69.1%, respectively, P = 0.93). Results were similar at one month (58% *vs*

67.1%; *P* = 0.47) and six months (82.1% *vs* 90.5%; *P* = 0.38). Hence, the use of levofloxacin did not improve BK viral load reduction, BK viral load clearance, or allograft function. Furthermore, those who used levofloxacin had a higher rate of Achilles tendonitis. Knoll *et al*[18] carried out a randomized clinical trial among 154 adult kidney transplant recipients looking into the efficacy of a three-month course of levofloxacin for the prevention of BK viruria within the first year of transplant. Apparently, levofloxacin administration showed no advantage as the rate of BK viruria was not significantly different between the two groups [29% in the levofloxacin group *vs* 33.3% in the placebo group; hazard ratio 0.91; 95% confidenceinterval (CI): 0.51-1.63; *P* = 0.58]. In addition, there was an increased risk of resistant infection among isolates usually sensitive to quinolones in the levofloxacin group *vs* placebo (58.3% *vs* 33.3%, respectively; risk ratio 1.75; 95%CI: 1.01-2.98), and increased risk of suspected tendinitis (7.9% *vs* 1.3%; risk ratio, 6.16; 95%CI: 0.76-49.95), albeit not statistically significant. Another point against the use of fluoroquinolone for the prevention of BK virus infection was noted in a trial that compared BK viremia between a group that received a three-month course of ciprofloxacin *vs* placebo. At six months post-transplant, more patients in the ciprofloxacin group had BK viremia compared to the placebo group (18.8% *vs* 7.5%, respectively, *P* = 0.03). Moreover, prolonged fluoroquinolone use resulted in a significantly higher rate of fluoroquinolone-resistant gram-negative urinary tract and bloodstream infections in the ciprofloxacin arm[19]. A meta-analysis that included two randomized controlled trials and six retrospective cohort studies reinforced that fluoroquinolones are not effective for prevention of BK viremia in kidney transplant recipients, and do not reduce the incidence of BKVAN or graft loss[20]. The latter studies constitute the evidence that fluoroquinolones have no role for the prevention of post-transplantation BK polyomavirus infection.

CIDOFOVIR

Cidofovir is a nucleotide analog of cytosine that is approved for the treatment of CMV in human immunodeficiency virus-positive patients, and has demonstrated *in vitro* activity against murine and simian polyomavirus strains[21,22], as well as a related human polyomavirus (JC virus) *in vivo*[23]. It decreases viral DNA synthesis upon incorporation with the nascent chain. Nephrotoxicity is its major adverse effect because it is taken up rapidly by proximal tubular cells by organic anion transporters at their basolateral membrane but secreted slowly into the lumen, resulting in high intracellular drug concentrations that can cause tubular necrosis. Hydration and co-administration with probenecid, a competitor of cidofovir for the transporter, can have a nephroprotective effect[24]. It is this adverse effect that precludes its recommendation for treatment of BK, such that its use should be weighed against the possible risk of worsening renal function.

In a cohort of 21 kidney transplant recipients with biopsy-proven BKV interstitial nephritis (BKVIN), Kuypers *et al*[25] investigated the effect of adjuvant low-dose cidofovir treatment *vs* no cidofovir, after lowering immunosuppressive drug therapy, on graft function, viral load, and graft outcome. Eight patients received cidofovir at 0.5-1.0 mg/kg at four to ten weekly courses. In the cidofovir-treated group, there was an improvement in creatinine clearance from 29.3 mL/min to 32.0 mL/min (range: 24-46) after a median follow up period of 24.8 mo (range 8-41) upon completion of treatment. Graft function did not acutely deteriorate during treatment except for one patient, but ultimately no graft loss occurred in this group. Blood viral load decreased in all patients treated with cidofovir. Once the BK viremia resolved, graft function improved but did not attain baseline levels. Adverse reactions noted include nausea in three patients, and development of pruritic maculopapular rashes in one patient. In contrast, nine of the 13 patients who did not receive cidofovir lost their graft after a median of eight (4-40) months. They also noted in this study that peak cidofovir concentrations were dose-dependent, and that probenecid treatment appeared to be unnecessary as it did not influence peak serum concentrations. This study was designed to be a preliminary report suggestive of the favorable effect of cidofovir on renal graft survival, function, and preservation, warranting a randomized controlled prospective study to follow suit. Another study by Kuypers done four years later investigated 41 kidney transplant patients with BKVIN, of whom 26 received cidofovir at 1 mg/kg to a maximum of ten weeks, without probenecid, and 15 did not receive cidofovir. Both groups had immunosuppression reduction. Similar to the previously mentioned study, there was a significantly higher occurrence of graft loss in the group that did not receive cidofovir (73.3% *vs* 15.4%, *P* = 0.0002). No renal toxicity was noted in the cidofovir group. The observed adverse effects include anterior uveitis in three patients, and skin rash during infusion with cidofovir[26].

A retrospective review of kidney and kidney-pancreas transplant recipients who received cidofovir combined with reduced immunosuppression for BKVAN or high-level viremia showed that adjunct cidofovir administration resulted in preserved renal function and no graft loss when viral clearance happened within six months of treatment. On the other hand, long term cases of BK infection (more than six months) were associated with a 15% decline in estimated glomerular filtration rate. Factors associated with long term BK infection include older age, delayed graft function, and higher peak BK viral load, suggesting that this subset of patients will not benefit as much from adjunctive cidofovir[27]. The course of cidofovir treatment among BK- infected individuals following bone marrow transplant manifesting as hemorrhagic cystitis have also been useful as the findings suggest applicability to kidney transplant recipients. In an open-label, non-randomized, single-dose pilot study done among hematopoietic stem cell transplant (HSCT) pediatric patients with symptomatic infection of adenovirus, nucleoside-resistant CMV, human polyomavirus (BK or JC virus), and/or nucleoside-resistant HSV, cidofovir was used to investigate virologic response, as well as safety and pharmacokinetics, with a focus on nephrotoxicity. Of the 12 patients in the study, four had BK viruria, and all four had unsuccessful viral clearance. One out of the four developed nephrotoxicity[28]. In a systematic review that compared intravesical *vs* intravenous route of cidofovir administration among stem cell transplant patients with BK polyomavirus hemorrhagic cystitis, there were more patients in the intravesical cidofovir group *vs* the intravenous cidofovir group who achieved a complete treatment response (88.2% *vs* 68%). Furthermore, no nephrotoxicity was observed in those that received the intravesical route,

whereas 9.3% had renal failure in those that received the drug intravenously. This better toxicity profile warrants more investigation due to its potential benefit[29]. All of the above mentioned studies are either preliminary or pilot studies done on a small population, or descriptive, retrospective ones. One randomized, double-blind, placebo-controlled, dose escalation study of cidofovir in kidney transplant patients with BKVAN was initiated in 2006 by the National Institute of Allergy and Infectious Diseases but closed early in 2013 due to failure to enroll in a timely manner.

Brincidofovir, a prodrug of cidofovir, which is less nephrotoxic due to its decreased accumulation in proximal tubules, is approved for the treatment of smallpox in pediatric and adult patients. Its use in BKVAN was described in a HSCT patient who had no reduction in immunosuppression. No drug-related adverse reactions occurred. Stable kidney function was maintained without the need for dialysis[30]. Another case was described in a pediatric kidney transplant recipient with BKVAN who was treated with brincidofovir after treatment failure with decreased immunosuppression, ciprofloxacin, and leflunomide. The treatment resulted in decrease in BK viral load, decrease in serum creatinine to baseline levels, and stabilization of renal function thereafter[31]. A phase 2, open-label, randomized, controlled, multiple ascending dose study on the safety and tolerability of IV brincidofovir in adult kidney transplant recipients with BK infection is currently underway in multiple study sites in Australia and Japan.To date, the role of cidofovir in the treatment of BK infection in kidney transplant recipients remains to be adjunctive at best, until a well-designed and high-grade study can better define its potential benefit.

IVIG

The effectiveness of IVIg against BK infection is still uncertain. IVIg is currently considered an additional treatment choice for patients with refractory BK infection despite aggressive adjustment in immunosuppressive medications. The proof of the effectiveness of IVIg is limited to case series, retrospective studies, and prospective cohort studies.

IVIg is believed to quell BKV-associated kidney disease by acting on various parts of the immune system, including dendritic cells, macrophages, and granulocytes. It is thought to demonstrate its effect by interacting with certain receptors like Fc gamma receptors[32]. Commercially available IVIg preparations contain strong antibodies that can counteract different strains of the BK[33].

In 2006, Sener *et al*[34] suggested that IVIg could be used as a treatment for BKVAN. A case report from 2009 demonstrated that IVIg helped restore kidney function, reduced BK levels, and improved histopathological findings in a pediatric kidney transplant recipient who did not respond adequately to immunosuppression reduction and cidofovir [35].

A study showed that 0.4 g/kg/d (n = 16) or 1 g/kg/d (n = 17) of IVIg administration resulted in increased BKV-neutralizing antibodies (NAbs), which persisted for 22 ± 7 days[36]. In one retrospective study involving 30 patients with BKVAN, 1 g/kg of IVIg was administered to patients who did not respond to eight weeks of the immunosuppression adjustment and leflunomide, with mean BKV loads of 205314 copies/mL. After one year of follow-up, 27 patients (90%) showed a positive response in clearing viremia, with decrease of BK viral loads to 697 copies/mL. It also showed a good graft survival in 12 mo[37].

Another retrospective, single-center cohort study involving 50 patients with BKVAN showed that 1g/kg of IVIg in addition to immunosuppression adjustment led to better clearance of viremia. It showed fewer graft losses with IVIg group (27.3% *vs* 53.6% for control, P = 0.06), although graft and patient survivals were not statistically different[38]. In contrast, a retrospective analysis by Naef *et al*[39] yielded conflicting outcomes. This study involved 860 kidney transplant recipients with BK viremia. A total of 52 out of 131 patients with high-level BK viremia received IVIg. At one year follow-up, the IVIg group exhibited lower estimated GFR compared to patients who did not receive IVIg (44 mL/min *vs* 52 mL/min) and failed to show advantages in shortening the duration of BK viremia or reducing rejections. On the other hand, IVIg might play a role in preventing BKVAN. In one study, 174 kidney transplant recipients were divided into the following three groups retrospectively based on their risk of BKV infection: patients with low NAbs (high-risk) with IVIg, high-risk patients without IVIg, and patients with high NAbs (low-risk) without IVIg. The IVIg group received 0.4 g/kg of IVIg every three weeks for one to three doses, for the first three months following transplant. At 12 mo post-transplant, the incidence of BK viremia in high-risk patients who received IVIg was significantly lower than untreated high-risk group (6.8 % *vs* 36.6%, P < 0.001), and similar to the low-risk group (10.1%)[40].

The AST-IDCOP states that these studies are difficult to evaluate given other concurrent antiviral intervention, widely variable empirical dosing, and initiation of treatment late in the course of the disease[2]. An ongoing randomized controlled trial (NCT 02659891), aims to shed more light on the potential benefits of IVIg in treating BKVAN.

MONOCLONAL ANTIBODIES

Efficacy and safety of first-in-class human IgG1 monoclonal high-affinity neutralizing antibody against BKVAN is currently under investigation (NCT 04294472). This phase 2, randomized, double-blind, placebo-controlled clinical trial evaluated the safety and efficacy of monoclonal antibody (MAU868) in kidney transplant recipients who had BK viremia within one year of enrolment. It involved 28 patients of whom 20 received MAU868 and eight received placebo. Results showed that the MAU868 group had more effective viral load clearance than the placebo group at week 16 through week 36. All patients tolerated MAU868 well. Further investigation regarding its safety and efficacy is warranted.

VST

VST is an emerging therapeutic option for BK infection. Pioneering work towards the development of T-cell therapy started in the early 1990s, mostly geared towards reconstitution of cellular immunity against CMV and isolation of antigen-specific T cells[41]. Over the recent few years, several trials have been conducted to test the clinical utility of VST for BK infection. In a study that included 16 HSCT recipients who developed BK infection, all achieved clinical benefit following VST. Viral load reduction of 85.5% and 96% were noted at week 6 and 12 post-infusion, respectively. Thirteen out of 14 patients who had hemorrhagic cystitis had resolution of hematuria. One of two patients with BKVAN had improvement in renal function[42]. In another study involving 59 HSCT patients with BK hemorrhagic cystitis who received BK-specific cytotoxic T-cell therapy, 67.7% mounted a response and had significant clinical improvement at day 14. Response rate increased to 81.6% at day 45 and was noted to be durable thereafter. Significant decrease in urine BK viral load was also noted among responders[43]. A phase II trial on Posoleucel, a multivirus-specific T-cell therapy derived from healthy, seropositive, third-party donors, was conducted among 59 HSCT recipients who developed CMV, epstein-barr virus (EBV), HHV-6, adenovirus, JC, and BK infection. Of the 27 patients who developed BK infection, all had partial response after 6 wk of treatment with Posoleucel. Of the 23 patients who had BK hemorrhagic cystitis, 74% had resolution of symptoms and macroscopic hematuria. Nine of 24 patients also had documented increase in IFN-γ ELISpot levels[44].

Multivirus-specific T-cell (MVST) lines that target CMV, EBV, Adenovirus, and BK were generated by Roubalová *et al*[45] and they found predominance of CD8+ phenotype in CMV-specific T cells and CD4+ phenotype in BK-specific T cells. The authors suggested modification of the protocol to prevent antigenic competition for MVST to be efficacious treatment of BK infection. Koukoulias *et al*[46] developed a glucocorticoid-resistant, multi-pathogen specific T cell product named Cerberus that targets Adenovirus, CMV, EBV, BK, and Aspergillus. This allows capture of common opportunistic infections among transplant recipients regardless of the intensity of immunosuppression.

In general, most trials conducted on VST claim potential widespread utility of this therapy against multiple post-transplant viral infections while avoiding the nephrotoxic and myelosuppressive effects of certain antivirals. VST is more widely utilized in HSCT recipients. Conceptually, since T-cell reconstitution is central to the management of viral infections, it seems intuitive that VST should have application in the management of BK infection in other solid organ transplant (SOT) recipients. Adenoviral vector-based multivirus-specific T-cell immunotherapy that targets CMV, EBV, Adenovirus, and BK has been developed and demonstrated rapid *in vitro* expansion of multivirus-specific T cells from SOT recipients and *in vivo* priming of antiviral T-cell immunity[47]. Autologous BK-specific T cell lines have been generated from viremic kidney transplant recipients[48]. BK-specific CD8+ T-cells have also been generated *in vitro* from peripheral mononuclear cells derived from healthy donors and pulsed with synthetic peptide pools[49]. These proofs of concept of T-cell therapy paved the way for a promising novel therapy for the prevention of BK infection before kidney and other solid organ transplantation and the treatment of BKVAN after transplantation[48,49]. Jahan *et al*[50] reported a case of a 54-year-old female kidney transplant recipient who developed BKVAN, necessitating reduction in mycophenolate and tacrolimus, administration of IVIg, leflunomide, cidofovir, and ciprofloxacin, but had worsening BKVAN and graft dysfunction. The patient eventually received BK-specific T-cell therapy derived from the patient's daughter and infused over ten sessions. Despite note of significant reduction in BK viral load, the kidney allograft eventually failed due to interstitial fibrosis and tubular atrophy. The authors proposed that early T-cell therapy might be more effective in treating BKVAN. Administration of VST in three SOT recipients, including kidney, heart, and heart-kidney transplants, elicited complete response in one and partial response in two patients[51]. Of the case reports that described the use of VST in kidney transplant recipients who developed BK infection, there were no reports of acute rejection, graft-versus-host disease (GVHD), or death with use of VST[52].

It is worth noting that rare but serious adverse effects of VST, including cytokine release syndrome, diffuse alveolar damage, hepatic sinusoidal obstruction syndrome, multi-organ failure[53], and GVHD[52] have been reported in literature. Other potential logistical limitations of VST include the need for donor immunity to the viral target, as well significant cost, labor, time, and regulatory burden for manufacturing the therapy[52,54]. Some investigators opted to utilize HLA-matched or partially matched T-cell donors, although this did not seem to affect the clinical outcome[43]. Other concerns involve antigenic competition between high and low frequency T-cells and multiple antigens[55] and the efficacy of VST in the setting of lifelong and more intense immunosuppression among SOT recipients[52].

BK VACCINE

An emerging preventative measure for BK infection is the administration of virus-like particle vaccines to induce high levels of neutralizing antibodies against BK even prior to transplantation. Peretti *et al*[56] immunized macaques and mice and were able to demonstrate broad neutralizing response to heterologous BK and JC virus genotypes following the priming dose in macaques and the booster dose in mice. The authors proposed the potential clinical value of BK vaccination among patients awaiting organ transplant to prevent kidney dysfunction and failure from BKVAN or potential transplant rejection following immunosuppression reduction.

DISCUSSION

BK viral infection poses a significant threat to SOT and HSCT recipients and may eventually lead to renal dysfunction and even loss of the renal allograft. Immunosuppression reduction is the mainstay approach to the management BK viral infection. This treatment, however, has a risk of acute rejection that may necessitate use of other anti-rejection therapy that can worsen the current BK virus infection. A cautious and stepwise approach in immunosuppression reduction coupled with close monitoring of renal function, have been found to be an effective approach to find the right balance between treating the BK virus and preserving graft function.

Changes in immunosuppressive regimen do not seem to have significantly different outcomes. Outcomes data on the use of leflunomide, fluoroquinolones, cidofovir, and brincidofovir remain equivocal. Leflunomide and fluoroquinolones are readily available and relatively well-tolerated. However, leflunomide has a potential risk of leukopenia, peripheral neuropathy, gastrointestinal effects, and liver dysfunction or damage[57]. Fluoroquinolones pose a risk of gastrointestinal effects, tendinitis, tendinopathy, tendon rupture, aortic aneurysm and dissection, neuropathy, arrhythmia, and labile blood sugars[58] and potentially higher rates of fluoroquinolone-resistant infections. Cidofovir may be nephrotoxic and myelosuppressive while brincidofovir may cause gastrointestinal effects, predominantly diarrhea[59]. IVIg and monoclonal antibodies are relatively well-tolerated but might carry the risk of headaches, flu-like symptoms, and rarely renal dysfunction, thrombosis, and hemolytic anemia[60]. Viral-specific T-cell therapy and vaccines are some of the emerging management approaches to BK viral infection. Viral-specific T-cell therapy may incur significant time, labor, and cost, while posing rare but potential risks of multi-organ failure and GVHD[52,53]. Certainly, the use of the above agents in addressing BK viral infection should be weighed against their potential adverse effects (Table 1).

Future perspectives

There are definite unmet needs in therapeutic options for BK viral infection. High quality ideally randomized controlled trials, on currently existing medications, as well agents in development, should be conducted. The value of viral-specific T-cell therapy and vaccines should be further investigated.

CONCLUSION

BK viral infection is an important post-transplant infection that can eventually lead to renal dysfunction. Mainstay for management is reduction in immunosuppression. However, this poses a risk for acute rejection. Over the years, alterations in immunosuppressive regimen, use of mTOR inhibitors and leflunomide, fluoroquinolones, cidofovir, and IVIg have been attempted and investigated, and resulted in variable outcomes. BK-specific T-cell therapy and vaccines are emerging options for the management and prevention of BK infection. Nevertheless, effective and durable treatment for BK infection remains elusive. In addition, there is paucity of randomized, controlled trials to provide high-level evidence to support certain management strategies. Indeed, there is a need to pursue studies that will provide evidence to support best management approaches for BK infection post-transplant. These studies might define the future landscape for BK management, while minimizing adverse effects of treatment and optimizing graft and patient survival.

Table 1 Summary table of studies on management of BK infection

Ref.	Study type/period	Subjects	Key findings (include *P* value if available)
Alterations in immunosuppression			
Vela *et al*[7], 2022	Retrospective study; Mar 2013-Oct 2020	43 kidney transplant recipients with BK DNAemia; 26 received mTORi + IVIg; 17 had immunosuppression reduction	BK DNAemia and viral clearance reduced faster and more significantly in subjects with reduced immunosuppression (P < 0.001 and P = 0.033 respectively). Death-censored graft loss, rejection rates, and kidney graft function at 12 mo did not differ significantly
Halim *et al*[6], 2016	Cohort study	55 kidney transplant recipients with BK viremia and/or BKVAN nephropathy; 22 received leflunomide + IVIg + ciprofloxaci; 33 had immunosuppression reduction alone	Administration of leflunomide, IVIg, and ciprofloxacin added no benefit to the long-term outcome of patients with established BKVAN. Treatment of BKVAN by reduction of immunosuppression alone appears to be more effective
Huang *et al*[4], 2015	Prospective study; Mar 2006-Oct 2008	229 kidney transplant recipients with BK viremia and BKVAN 30%-50% reduction in FK and/or MPA	BK viremia resolved in 100% of patients without increased acute rejection. All patients with BKVAN had viral clearance and showed no decline in GFR
Saad *et al*[3], 2008	Retrospective, single center study; Sept 2001-Dec 2003	24 kidney transplant recipients: 16 with BKVAN; 8 with BK viremia	Reduction in immunosuppression alone results in clearance of the BK viremia with good long-term outcome
Leflunomide			
Krisl *et al*[9], 2012	Retrospective, single center study; Jun 2001-Dec 2009	76 kidney transplant recipients with BK viremia with or without BKVAN; 52 received leflunomide; 24 did not receive	No difference in BK viral clearance. Multivariate analysis demonstrated that mycophenolate mofetil discontinuation, BK viremia without nephropathy, and mean BK viral load were

		leflunomide	significantly associated with BK viral clearance. Leflunomide use lacked this association
Canivet *et al* [11], 2009	Prospective study; Jan 2006-May 2008	12 kidney transplant recipients with BKVAN; MMF switched to leflunomide	Not statistically significant T cell markers, BK DNAemia clearance in 41.6%, creatinine clearance stable or improved in 50%, no significant adverse events
Teschner *et al* [12], 2009	Prospective study	13 kidney transplant recipients with BKVAN; MMF switched to leflunomide	12 had viral clearance at a mean of 109 d. Graft function stabilized or improved (mean [median] creatinine concentration at diagnosis, 2.39 [2.5] mg/mL, *vs* 2.27 [2.0] mg/dL at follow-up). 1 graft loss due to refractory rejection. Leflunomide concentration did not correlate with treatment efficiency
Faguer *et al* [10], 2007	Prospective study; Jul 2002-Apr 2006	12 kidney transplant recipients with BKVAN; MMF switched to leflunomide	42% had BK clearance. 66.6% had stable or improved renal allograft function
Josephson *et al* [13], 2006	Prospective study; Apr 2001-Apr 2004	26 kidney transplant recipients with BKVAN; 17 received leflunomide alone; 9 received leflunomide + cidofovir	84% of cases blood and urine viral load levels uniformly decreased over time ($P < 0.001$). Mean serum creatinine levels stabilized over the first 6 months of treatment, and with 12 mo or more of follow-up. 16 patients had fairly unchanged serum creatinine
Fluoroquinolones			
Patel *et al*[19], 2019	Prospective, randomized, placebo-controlled trial; Jan 2013 -Oct 2016	200 adult solitary kidney transplant recipients; 133 received ciprofloxacin as BK prophylaxis; 67 did not receive ciprofloxacin	BK viremia at 6 mo post-transplant occurred in 25 (18.8%) patients in the ciprofloxacin group and 5 (7.5%) in the placebo group ($P = 0.03$). Increased risk of fluoroquinolone-resistant infections in those who received ciprofloxacin
Knoll *et al*[18], 2014	Prospective, double-blind, placebo-controlled randomized trial; Dec 2011 -Jun 2013	154 adult kidney transplant recipients; 76 received a 3-mo course of levofloxacin; 78 received placebo	BK viruria occurred in 22 (29%) in the levofloxacin group *vs* 26 (33.3%) in the placebo group (HR 0.91, 95%CI: $P = 0.58$). Increased risk of resistant infection among isolates usually sensitive to quinolones in the levofloxacin group *vs* placebo (58.3% *vs* 33.3%, respectively); (RR 1.75; 95%CI: 1.01-2.98) as well as a nonsignificant increased risk of suspected tendinitis (7.9% *vs* 1.3%; RR 6.16; 95%CI: 0.76-49.95)
Lee *et al*[17], 2014	Prospective, multicenter, double-blinded, placebo-controlled trial; Jul 2009 -Mar 2012	43 adult kidney transplant recipients with documented BK viremia; 22 received levofloxacin for 30 d; 21 received placebo	At the 3-mo follow up, there was no significant difference in BK viral load reduction between the levofloxacin and placebo group (70.3% *vs* 69.1%, respectively, $P = 0.93$). The percentage reductions in BK viral load were also equivalent at 1 mo (58% *vs* 67.1%, $P = 0.47$), and 6 months (82.1% *vs* 90.5%, $P = 0.38$)
Wojciechowski *et al*[16], 2012	Retrospective study; First cohort (group 1): Jul-Dec 2009 Second cohort (group 2): Jan-Jun 2010	236 adult renal transplant recipients; Group 1: 106 did not receive BK virus prophylaxis; Group 2: 130 received ciprofloxacin as BK virus prophylaxis	At 3 mo post-transplant, the group that did not receive ciprofloxacin (group 1) had a higher risk of developing BK viremia than the group that received ciprofloxacin (group 2) (0.161 *vs* 0.065, $P = 0.0378$) and viruria (0.303 *vs* 0.146, $P = 0.0067$), but this difference progressively narrowed until there was no significant difference anymore at 12 mo for both viremia (0.297 *vs* 0.261, $P = 0.6061$) and viruria (0.437 *vs* 0.389, $P = 0.5363$)
Gabardi *et al* [15], 2010	Retrospective analysis; Jan 2004-Dec 2008	185 adult kidney transplant recipients; 25 received a 30-d course of ciprofloxacin; 160 did not receive a fluoroquinolone	Higher rate of BK viremia in those who did not receive a 1-mo course of levofloxacin 36 (22.5%) *vs* 1 (4%) who received levofloxacin; $P = 0.03$
Cidofovir			
Schneidewind *et al*[29], 2018	Systematic review	189 adult patients with BK virus associated hemorrhagic cystitis after allogenic stem cell transplant; 172 received intravenous cidofovir; 17 patients received intravesical cidofovir (2 patients received both routes of administration)	Complete response: 68% in intravenous cidofovir group, 88.2% in intravesical cidofovir. Kidney toxicity: 9.3% in intravenous cidofovir group, none in intravesical cidofovir group
Papanicolaou *et al*[30], 2015	Case report	58 yr old male post hematopoietic stem cell transplant; developed biopsy-proven polyomavirus associated nephropathy; received brincidofovir 100 mg twice weekly for 6 mo; no immunosuppression reduction	4-log decrease in BK virus viremia. No drug-related adverse events. Stable kidney function, and did not require dialysis
Caruso Brown *et al*[28], 2015	Open-label, non-randomized, single-dose, pilot study	12 pediatric patients (ages 6-18) with a hematopoietic stem cell transplant within 2 yr, with symptomatic infection of adenovirus, nucleoside-resistant CMV, human polyomavirus (BK or JC virus), and/or nucleoside-resistant HSV diagnosed by viral culture or PCR; all patients received cidofovir	2/12 acute kidney injury after the first dose 2/12 developed nephrotoxicity. Mean drug half-life 9.5 h (longer than documented half-life for adults based on other studies). No correlation between nephrotoxicity and plasma maximum concentration, clearance, or half-life. Cidofovir was well- tolerated in majority of patients
Kuten *et al*[27], 2014	Single-center, retrospective review; Jan 2007 to	75 kidney and kidney-pancreas transplant recipients who received cidofovir combined with reduced immunosuppression	32 (43%) had short-term BK (≤ 6 mo); 43 (57%) had long-term BK. 53 (71%) eventually cleared BK at a median of 4.2 mo (interquartile range 2.1-9.3 mo). Factors associated with long-term BK: older age

	Jun 2012		(OR 1.1, P = 0.02), Delayed graft function (OR 31.4, P = 0.01); higher peak BK (OR 12.8, P = 0.02. This group was associated with a 15% decline in estimated glomerular filtration rate. Factor associated with short-term BK: BK reduction by at least 1 $\log_{10}$copies/mL at 1 mo of treatment (OR 49.3, P < 0.01). This group maintained stable graft function and no graft loss was noted
Reisman, *et al* [31], 2014	Case report	pediatric patient who received kidney transplant for bilateral dysplastic kidneys, developed BKVAN; did not respond to decreased immunosuppression, ciprofloxacin, leflunomide; given brincidofovir	BK viral load decreased, but still detectable. Urine viral load declined but still elevated. Creatinine declined to baseline level and was stable for 2 yr. No drug-related adverse events
Kuypers *et al* [26], 2009	Single-center study	41 adult renal transplant recipients with biopsy-proven BKVIN; 26 received cidofovir at 1 mg/kg for a maximum duration of 10 wk and without probenecid; 15 did not receive cidofovir; All patients had immunosuppression reduction	Graft loss: 4/26 (15.4%) in cidofovir group, 11/15 (73.3%) in no cidofovir group (P = 0.0002). Percentage of patients who completely cleared the virus from the blood was not different between the 2 groups. 3 patients in the cidofovir group developed severe anterior uveitis at 6, 7 and 8 doses, respectively (later switched to leflunomide). No BM or renal toxicity was observed in the cidofovir group. One patient developed a skin rash during infusion of cidofovir
IVIg			
Naef *et al*[39], 2021	Retrospective analysis; Jan 2009-Mar 2019	Kidney transplant recipients with high level BK viremia; 79 transplanted before 2014 and had immunosuppression reduction alone; 52 transplanted after 2014 and had immunosuppression reduction + IVIg	IVIg group showed lower eGFR (44 mL/min *vs* 52 mL/min). IVIg did not shorten duration of BK viremia
Kable *et al*[38], 2017	Retrospective, single-center cohort study	50 BKVAN patients received IVIg 1 g/kg	Better clearance of BK viremia and fewer graft loss (not statistically significant)
Vu *et al*[37], 2015	Retrospective analysis; 2008-2012	30 kidney transplant recipients with BKVAN received IVIg 2 g/kg	90% of patients showed positive response in clearing viremia. Graft survival rate was 96.7% at 12 mo follow-up
Sener *et al*[34], 2006	Case series; Jul 2000-Jul 2003	8 kidney transplant recipients with IVIg 2 g/kg	88% of patients showed functioning graft at 15 mo follow-up
Monoclonal antibodies			
In the study	Ongoing RCT (NCT 04294472)	30 kidney transplant recipients with BK viremia; 22 received MAU868; 8 received placebo	Better BK viral clearance in MAU group
Virus-specific T-cell therapy			
Pfeiffer *et al* [44], 2023	Open-label, phase II trial; Apr 2014-Jul 2021	27 pediatric and adult HSCT recipients with BK infection; 25 with hemorrhagic cystitis; 2 with nephritis	100% had partial response at 6 weeks of treatment. 74% of patients who developed hemorrhagic cystitis had symptom resolution. 9/24 (37.5%) had increase in IFN-γ ELISpot counts
Koldehoff *et al* [1], 2023	Sequential analysis	17 HSCT recipients with BK hemorrhagic cystitis; 7 received VST; 10 did not receive VST (immunosuppression reduction or cidofovir)	6/7 from the VST group *vs* 6/10 from the non-VST group had T-specific cellular response, in most cases parallel to decrease in BK viral load
Olson *et al*[43], 2021	Single-arm, phase II clinical trial; Oct 2015-Sept 2019	59 HSCT recipients with BK hemorrhagic cystitis; received single IV infusion of partially HLA-matched BKV-CTL	Response rate and clinical improvement following the off-the-shelf BK-specific cytotoxic T-cells: 67.7% at day 14; 81.6% at day 45
Nelson *et al* [51], 2020	Phase II study; Jun 2017-Dec 2019	38 HSCT recipients; 3 solid organ transplant recipients: 1 kidney transplant recipient; 1 heart transplant recipient; 1 heart-kidney transplant recipient	Response rates: 86% in patients with BK viremia, 100% in patients with hemorrhagic cystitis, 87% in patients with BK viremia and hemorrhagic cystitis. Of the 3 solid organ transplant recipients, 1 had complete response and 2 had partial response
Tzannou *et al* [42], 2017	Phase II study	16 HSCT recipients; 14 with BK hemorrhagic cystitis; 2 with BKVAN	Decrease in urine BK viral load following VST: 85.5% at week 6, 96% at week 12. 13/14 with hemorrhagic cystitis had resolution of hematuria. 1/2 with BKVAN had improved renal function
Jahan *et al*[50], 2020	Case report; Sept 2018	1 kidney transplant recipient with BKVAN who failed other treatments	BK viral load decreased significantly following T-cell therapy, but allograft eventually failed due to interstitial fibrosis and tubular atrophy

BKVAN: BK virus-associated nephropathy; BKVIN: BK virus interstitial nephritis; CMV: Cytomegalovirus; eGFR: Estimated glomerular filtration rate; FK: Tacrolimus; GFR: Glomerular filtration rate; HLA: Human leukocyte antigen; HSCT: Hematopoietic stem cell transplant; IVIg: Intravenous immunoglobulin; MMF: Mycophenolate mofetil; MPA: Mycophenolic acid; mTOR: Mechanistic target of rapamycin; PCR: Polymerase chain reaction; RCT: Randomized controlled trial; VST: Virus-specific T-cell therapy.

FOOTNOTES

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MINIREVIEWS

Focus on limbal stem cell deficiency and limbal cell transplantation

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Abstract

Limbal stem cell deficiency (LSCD) causes severe vision impairment and can lead to blindness, representing one of the most challenging ocular surface disorders. Stem cell deficiency can be congenital or, more often, acquired. The categorization of ocular surface transplantation techniques is crucial to achieving treatment homogeneity and quality of care, according to the anatomic source of the tissue being transplanted, genetic source, autologous or allogenic transplantation (to reflect histocompatibility in the latter group), and cell culture and tissue engineering techniques. The aim of this minireview is to provide a summary of the management of LSCD, from clinical characteristics and therapeutic outcomes to the development of novel therapeutic approaches. The manuscript also briefly summarizes recent findings in the current literature and outlines the future challenges to overcome in the management of the major types of ocular surface failure.

Key Words: Limbal stem cell deficiency; Conjunctival limbal autograft; Conjunctival limbal allograft; Keratolimbal allograft; Cultivated limbal epithelial transplantation; Simple limbal epithelial transplantation

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Core Tip: Limbal cell transplantation has been developed for the management of limbal stem cell (LSC) deficiency, to improve this condition and related complications, ameliorating visual acuity and quality of life of affected patients. Some of the limitations include the lack of specific markers and standardized methods to identify LSCs, as well as the need to standardize the choice of therapeutic options which have diversified over the years and have evolved in terms of technology, efficacy, and safety. This clinical update review is to enable clinicians with the best evidence and current recommendations for managing their patients within the most advanced limbal cell transplant techniques.

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INTRODUCTION

The primary function of the cornea is to refract light, and its function directly depends on its transparency. One of the factors that is implied in the cornea's transparency is epithelium integrity. The corneal epithelium is a non-keratinized multilayer cuboid epithelium that covers the cornea starting from the limbus, where the junction between the conjunctiva and cornea is. It is capable of self-renewing thanks to the presence of stem cells. Corneal epithelial limbal stem cells (LSCs) reside preferentially in the basal layer of the peripheral cornea in the limbal zone[1,2]. There are no current specific markers for these cells. The research methods used for the identification of these cells tend to be indirect. The presence of stem cell-associated markers such as p63 and the absence of differentiated cell markers such as chemokine (CK) 12 (for corneal epithelium) or CK19 (for conjunctiva) indicate the putative stem cells[3,4].

With regards to the predominant theory about corneal epithelium regeneration, LSCs asymmetrically divide into transient amplifying cells that migrate centripetally and anteriorly and differentiate into squamous cells[5]. Several current studies suggest that, in experimental models, some stem cells could reside outside the limbus[5-7].

The presence of LSCs is crucial to inhibit the proliferation of the conjunctival epithelium on the corneal surface, and the reduction of their number leads to conjunctivalisation of the corneal surface, persistent and recurrent epithelial defects, scarring, and ulceration of the cornea. This condition is called LSC deficiency (LSCD). LSCD can be primary or secondary. Primary causes can occur for genetic pathologies or idiopathically, while the acquired ones can occur for traumas or autoimmune pathologies (Table 1)[8]. LSCD presents nonspecific symptoms such as discomfort, pain, photophobia, and decreased vision in more severe cases. The signs of LSCD depend upon pathology severity, starting from focal areas with a stippled staining pattern, loss of clarity, epithelium hyperreflectivity on Anterior Segment Optical Coherence Tomography (AS-OCT), and flattening of Vogt palisades. In severe cases, it is possible to have conjunctivalisation of the cornea, whorl pattern in fluorescein staining, superficial corneal neovascularization, persistent epithelium defect, stromal scarring, or sterile melts[9].

These signs can affect just some portion of the cornea with a clear demarcation between normal and abnormal areas, accordingly with the extension of LSC damage. In the cases of traumatic etiologies, LSCD is commonly asymmetrical. In autoimmune and congenital etiologies, LSC damage is commonly symmetrical. LSCD diagnosis is clinical in frank cases, but it can be confirmed by diagnostic investigation in subtle situations. There are several reliable tests in the diagnosis of LSCD. Understanding the underlying cause of LSC damage and starting adequate therapy are fundamental to ensuring good outcomes of LSCD treatments.

The aim of this minireview is to briefly summarize the important issues regarding the clinical characteristics and management of patients with LSCD, in addition to summarizing the therapeutic outcomes to the development of novel therapeutic approaches, future challenges, and recent findings in the current literature.

METHODS

We conducted a search of the literature published between January 1, 2002, to December 1, 2022, using MEDLINE (PubMed). The database was first searched using the following keywords: "Limbal Stem Cell Deficiency; Limbal Cell Transplantation; Limbal Stem Cell Deficiency and/or Limbal Cell Transplantation; LSCD, and/or Conjunctival limbal autograft (CLAU); LSCD and/or Conjunctival limbal allograft (CLAL); LSCD and/or Cultivated limbal epithelial transplantation (CLET); and, LSCD and/or Simple limbal epithelial transplantation (SLET)". We considered only studies in English and those referring to humans and with an abstract, thus reducing the count to 301 papers. The reference lists of all retrieved articles were assessed to identify additional relevant studies. The research of articles was performed using PubMed (https://pubmed.ncbi.nlm.nih.gov) and *Reference Citation Analysis* (https://www.referencecitationanalysis.com) Only articles with an abstract were considered. A quality score was calculated for each article using a checklist. Each study was independently assessed by at least two reviewers (Tonti E and Zeppieri M), and rating decisions were based on the consensus of the reviewing authors. The most common surgical techniques highlighted in the most relevant studies are shown in Table 1.

Table 1 Causes of limbal stem cell deficiency

Genetic disease	Acquired immune-mediated	Acquired nonimmune-mediated	Others
Congenital aniridia	Steven-Johnson syndrome	Chemical/thermal injury	Ocular surface tumors
Keratitis ichthyosis deafness syndrome	Toxic necrolysis	Radiation injury	Drug-induced LSCD
Xeroderma pigmentosum	Mucous membrane pemphigoid	Contact lens wear	Idiopathic
Ectrodactyly-ectodermal dysplasia-clefting syndrome	Vernal/atopic keratoconjunctivitis	Multiple limbal surgeries	
Dyskeratosis congenita	Graft-*vs*-host disease	Bullous keratopathy	
Peter's anomaly		Chronic lid diseases	
		Infectious ocular diseases	

LSCD: Limbal stem cell deficiency.

DIAGNOSIS AND STAGING OF LSCD

Impression cytology

A filter paper of nitrocellulose or acetate cellulose is applied over the cornea or the conjunctiva to obtain cells from the ocular surface. Repeating the sampling on the same area allows us to obtain cells from the deeper layers, and this makes the sampling more reliable. The specimens are processed with various stains searching for goblet cells[9-11]. The presence of these cells indicates the invasion of the conjunctival epithelium over the cornea, but their absence does not exclude LSCD. In fact, in some cases, such as Stevens-Johnson syndrome or chronic inflammatory diseases, the number of conjunctival goblet cells can be markedly reduced, and their identification can be difficult[11]. Differentiating corneal epithelial cells from conjunctival epithelial cells, instead, is possible only by immunohistochemistry. As mentioned before, CK2 and CK12 are specific for the mature corneal epithelium, CK3 for the conjunctiva and corneal epithelium, and CK7, CK13, and CK19 are specific for the conjunctival epithelium. Another used marker is mucin 5AC, but it has a low sensitivity. Impression cytology is also useful for analyzing the results of LSCD therapies[12].

In-vivo confocal microscopy (IVCM)

With this exam, it is possible to acquire pictures of the corneal microstructures without collecting specimens. The presence of goblet cells in a corneal IVCM, as seen in impression cytology, confirms the diagnosis of LSCD, but their absence cannot exclude the diagnosis because this exam scans just a small area and the morphology of goblet cells can be difficult to recognize in IVCM[13]. In LSCD, the density of the basal cells of the corneal epithelium is decreased and the mean size of cells is increased, and these findings correlate with the severity of the pathology[14]. Other findings are intraepithelial cystic lesions surrounded by goblet cells and the decrease in the density of the sub-basal nervous plexus [15].

AS-OCT

This is a non-invasive imaging tool with low operator dependence. LSCD has been associated with epithelial thinning at the cornea and limbus, but these signs are not specific to LSCD[16]. With volumetric scans, it is possible to study the status of Vogt palisades, and their thinning (or absence) is associated with areas with a thinned epithelium. The analysis of the reflectivity of the epithelium and stroma in LSCD shows that epithelial reflectivity varies more than stromal reflectivity, and the ratio between them could be a diagnostic tool for LSCD. Furthermore, this ratio tends to return to normal values after LSC transplantation, even if it does not return to normal values[11,17].

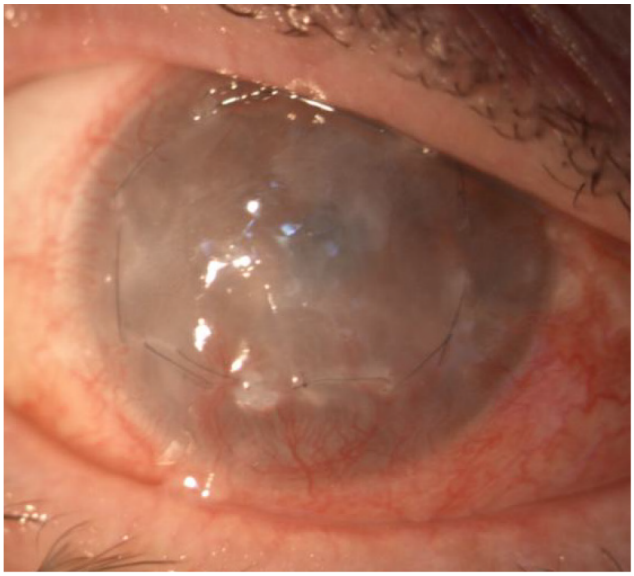
LSCD staging is based on the clinical presentation, and 5 mm central cornea involvement and limbal involvement are the two parameters evaluated (Table 2). The most important factor is corneal involvement; in the first stage central 5 mm is not involved, in the second it is partially affected, and in the final stage the entire corneal surface is involved. Every stage is divided into A when limbus involvement is less than 50%; B if it is more than 50% but non-complete; and C if the limbus is completely affected. Correct staging is useful for therapeutic decisions, but it is also important to evaluate palpebral and adnexa status and to control the underlying pathology if the LSCD is secondary to other pathologies[18]. Figures 1-3 show different stages of stem cell deficiency.

OCULAR SURFACE STEM CELL TRANSPLANTATION: CLINICAL OUTCOMES

Over the past two decades, a variety of ocular surface rehabilitation treatments have been developed. The ocular surface is rehabilitated by improving the ocular surface environment, ensuring control of inflammation, good lubrication, and lid closure, and eliminating keratinization and symblepharon. A favorable environment is crucial for restoring the normal corneal phenotype and proper corneal clarity[18]. Corneal transplantation can be considered for corneal clarity restoration in patients with LSCD, but results and visual outcomes tend to be limiting over time because of the inability of

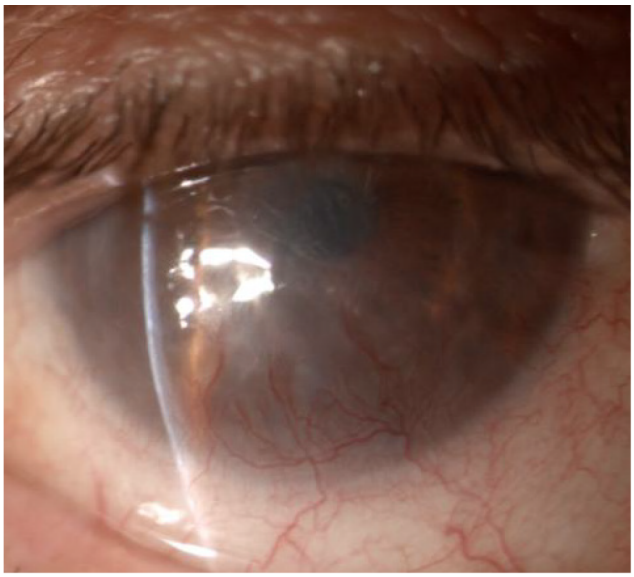
Table 2 Stages of limbal stem cell deficiency

Stage		A	B	C
I	Central 5 mm of cornea not involved	Limbus involvement < 50%	Limbus involvement > 50% but < 100%	Limbus entirely involved
II	Central 5 mm of cornea involved	Limbus involvement < 50%	Limbus involvement > 50% but < 100%	
III	The entire corneal surface involved			



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Figure 1 Limbal stem cell deficiency stage III, in which the entire corneal surface is involved.



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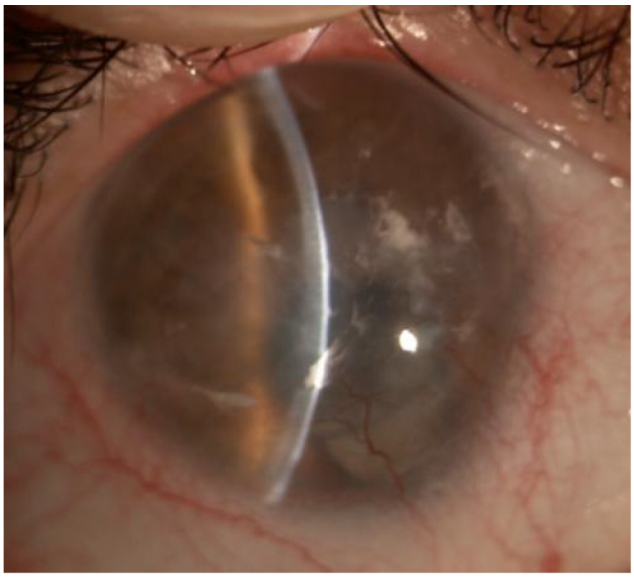
Figure 2 Partial stem cell deficiency (stage II-A).

the LSC to regenerate and maintain the transparency of the epithelium[19].

Several transplantation procedures have been used over the past years, and many of them have been labeled using different terminologies. These procedures include autologous and allograft conjunctival transplantation[20-22], keratoepithelioplasty[23], homotransplantation of limbal cells[24], limbal transplantation[25], homotransplantation of limbal cells [26], and autologous and allograft limbal transplantation (Table 3)[27-31].

Table 3 Common surgical techniques for limbal stem cell deficiency

Procedure	Abbreviation	Tissue origin
Direct transplantation		
Conjunctival limbal autograft	CLAU	Patient
Living-related conjunctival allograft	lr-CLAL	Relative donor
Keratolimbal allograft	KLAL	Cadaveric donor
Cincinnati procedure		Relative/cadaveric donor
Modified Cincinnati procedure		Patient/cadaveric donor
Stem cells transplantation		
Simple limbal epithelium transplantation	SLET	Patient
Tissue engineering		
Cultured limbal epithelial transplantation	CLET	Patient/living donor
Autologous conjunctival epithelial cells cultivated *ex vivo*	EVCAU	Patient
Cultivated oral mucosa epithelial transplantation	COMET	Patient



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Figure 3 Post-traumatic limbal stem cell deficiency with central corneal scarring.

CLAU

CLAU, first described by Tseng and Kenyon[26] in 1989, is one of the most used techniques for LSC transplantation in unilateral LSCD. It consists of taking a portion of limbal conjunctiva (usually from 3 to 6 o'clock) from the fellow eye and implanting it in the affected eye, with or without amniotic membrane (AM) transplantation. CLAU has been successfully used to treat different pathologies and LSCD of different etiologies and different severities, even in cases of total corneal involvement[26]. The donor eye should be examined with particular attention to exclude any sign of LSCD to avoid an iatrogenic LSCD, even if this represents a remote possibility[32,33].

The inflammatory status of the graft can reduce the transplantation success rate, so topical steroids could be useful before the graft harvesting[34]. There is not a universally accepted consensus about the size of limbal grafts, generally harvested at 12 and 6 o'clock, where Vogt palisades are more developed. The first technique used a wide graft (8 o'clock), but successful results have been achieved with smaller grafts and new promising techniques use two grafts each at about 1 o'clock combined with AM transplantation (AMT)[35-37].

AM could be transplanted even in the donor's eye when large grafts are taken to reduce the risk of LSCD due to its capacity to facilitate the *in-vivo* expansion of LSCs[38,39]. Generally, the recipient bed is prepared by doing a peritomy 4-5 mm from the limbus and dissecting the corneal pannus, the dissection of corneal layers should be avoided, and stromal opacities are better treated afterward by keratoplasty[40]. The limbal epithelial graft is fixed around the cornea and the posterior margin is sutured to the conjunctiva. Between the graft and the ocular surface could be interposed a layer of AM

that seems to increase the rates of success and the rapidity of the healing process, especially with little grafts, but a study with wide grafts showed no significant differences between the AMT group and the other without[41,42].

The great advantage of autologous transplantation is the immunosuppressive therapy sparing, so, generally, the only medication needed are topical antibiotics and topical corticosteroids. A scleral lens is applied to protect the graft from the mechanical stress of winking, and sometimes a temporary tarsorrhaphy can be considered[43]. A meta-analysis in 2020 found that the overall success rate of CLAU was 83.2%, with a 95%CI. In this study, "success" was defined as the reconstruction of an intact epithelium and a stable ocular surface. These data involved 16 articles, and 505 eyes, most of which had chemical or thermal injury[44].

Living-related (lr-CLAL) transplantation

In this technique, the surgical procedure is the same as CLAU, but the graft is harvested from a living related, and this makes it suitable even for severe bilateral LSCD. To decrease the chances of rejection, the donor must be the best human leukocyte antigen (HLA) matched available relative, generally a parent or a sibling. In 100% HLA compatibility cases, immunosuppressive therapy is not needed; in other cases, the administration of 6-12 mo of oral corticosteroids 10 mg/kg/d and oral cyclosporin A 10 mg/kg/d is required, subsequently tapered for maintenance dose during all the follow-up period. Some protocols added azathioprine to previous drugs and others used tacrolimus and mycophenolate mofetil [45,46]. Other authors administered oral cyclosporin for more than 6 mo and topical cyclosporin continued indefinitely unless toxic effects onset[47]. Patients under immunosuppressive therapy must be checked often for liver and kidney function.

Keratolimbal allograft (KLAL)

KLAL is an allogenic transplant from a cadaveric donor. The graft is prepared by dissecting and removing the limbus and a peripheral portion of the cornea of the donor eye, then the stromal portion is dissected carefully to preserve the conjunctival and limbal epithelium. The graft is then sutured to the peripheral cornea and a patch of AM is generally transplanted to ensure better outcomes[48-50]. Tissue from the youngest possible donor with an upper limit of 50 years is recommended. Surgery should be performed within 72 h as the cells are expected to be more active and vital[51-53]. The recipient bed is prepared the same way as CLAU and lr-CLAL. HLA matching is recommended, and an immunosuppressive therapy, similar to lr-CLAL, is generally needed.

Holland[29] developed the Cincinnati procedure combining lr-CLAL and KLAL. In this technique, two portions of healthy limbus conjunctiva are harvested from an HLA-matched living donor, and the corneoscleral rim is taken from a cadaveric donor. The conjunctival tissue is placed at 12 and 6 o'clock in the same anatomical orientation, and the corneoscleral tissue is placed at 3 and 9 o'clock. With this procedure, ocular surface stability was achieved in 54.2% and an improvement was achieved in 33.3%, and 75% had an improvement in the visual acuity[54]. The same authors described even the modified Cincinnati procedure that combines CLAU with KLAL, achieving ocular surface stability in 82% of patients and ocular surface improvement in 18%[55]. Both techniques require an immunosuppressive therapy like that for KLAL[54,55].

Tissue engineering for the reconstruction of the corneal epithelium

In this group of techniques, a small portion of the corneal epithelium is taken from a donor, cultivated to expand its surface, and then transplanted. The advantage of these techniques is that with a limited amount of harvested tissue, it is possible to generate a considerable amount of epithelium to transplant. Thus, even in severe bilateral LSCD, it is possible to conduct autologous transplantations. However, the cultivation process needs an advanced laboratory and a relevant amount of resources, so just a few centers perform these kinds of surgeries. The harvested corneal tissue can belong to a living donor (the patient itself, a living relative, or a living nonrelative person) or from a cadaveric donor, but some techniques use other epithelia such as the oral one (*ex vivo* oral mucosa autograft, also called cultivated oral mucosa epithelial transplantation).

However, most of the techniques are still experimental procedures non-suitable for routine application except for Holoclar (*ex vivo* expanded autologous human corneal epithelial cells containing stem cells), first described in 1997 by Pellegrini *et al*[56] that achieved EMA authorization for commercial purposes in 2015.

Holoclar is a CLET procedure that starts with the enzymatical dissociation of the sample and the seeding of the cells in a layer of irradiated mouse feeder cells with growth factors and antibiotics. After this step, cells are cryopreserved and samples are tested; some of them are stored in case of failure of the first graft. Primary cultures are then seeded into antibiotic-free fibrin matrix discs and cultivated again. Epithelized discs are then shipped to the clinic, shaped by the surgeon, and implanted like in the CLAU technique. There is no standard procedure for CLET, and in fact, the cultivation procedure in the literature varies for the substrate used.

AM and cultivating milieu are mostly used, but the overall success rate of this technique is 71.8%. When cultivated cells are autologous, the ocular surface stability is maintained for long follow-up periods[57-65]. Most patients are typically affected by LSCD for chemical injury, but this technology is used also to treat LSCD due to autoimmune and congenital pathologies.

Another technique is autologous conjunctival epithelial cells cultivated *ex vivo*, in which the cultivated tissue is fornical conjunctiva. The specimen is placed on a denuded human AM and submerged in a culture medium with grow factors and antibiotics. The cultivated tissue is then shaped and transplanted to the prepared corneal surface. A study with 12 eyes reported a success rate of 66.6% and 16.6% of partial success (conjunctival epithelial ingrowth recurred in 2 corneal quadrants), but we have no other data about the clinical outcomes in humans[66].

SLET

SLET is a recent procedure for unilateral disease and seeds donor stem cells directly on an AM placed on the recipient's ocular surface, completely obviating any need for laboratory conditions of expansion[67]. Although CLET reduced the complications of CLAU, cell expansion required a clinical-grade lab with regulatory approvals, which was and continues to be very expensive to build and maintain. SLET, introduced by Sangwan *et al*[67] in 2012, combining the benefits of CLAU and CLET while avoiding the limitations of both strategies.

Unilateral LSCD is the primary indication for autologous SLET. Ocular burns are the most common cause of unilateral LSCD, so it is not surprising that this indication is covered by almost all of the published literature on autologous SLET. More recently, the first case reports of allogenic SLET in cases of bilateral LSCD have been proposed and involved patients with severe chemical burns and dry eyes, respectively[68,69]. In the SLET technique, in the superior limbal district of the unaffected contralateral eye, a portion of 2 mm × 2 mm of limbal tissue is removed under topical anesthesia and placed in a balanced saline solution.

The corneal surface is exposed by removing the fibrovascular corneal pannus after 360-degree conjunctival peritomy and peribulbar anesthesia is induced. With the epithelial side up, human AM is grafted over the cornea and secured with fibrin glue, and the margins are trimmed to fit the external conjunctival borders. Eight to ten tiny pieces of the limbal sclerocorneal tissue are cut into pieces and adhered to the AM in a circular pattern using fibrin glue, sparing the optical zone[67]. In a study involving six patients with total unilateral LSCD, visual acuity improved in four of the recipients' eyes (66.6%), going from 20/200 or worse before SLET surgery to 20/60 or better afterward. None of the donor eyes experienced any complications. It took 9.2 mo on average to follow up[67].

CONCLUSION

Patients with severe ocular surface disease need to be treated in a methodical, step-by-step manner. To achieve the best results in the rehabilitation of the ocular surface, it is crucial to select the patient's most appropriate strategy of treatment. The underlying pathology, the extent, and severity of ocular surface disease, including the degree of stem cell damage, unilaterality or bilateralism of the condition, the presence or absence of conjunctival inflammation, and whether tear production is normal (significantly altered or absent), the patient's age, and systemic co-morbidities are important factors in the choice of regimen among the various surgical procedures proposed for the treatment of LSCD.

The development of xenobiotic-free culture systems and the standardization of culture conditions are two improvements that must be made in order to advance the therapeutic approach. Additionally, to guarantee the functionality and long-term regeneration of the transplants, tissue engineering strategies must incorporate a kind of quality control, verifying the preservation of stem cells during the culture process.

Clarifying the signaling pathways that control stem cell function and fate *in vivo* and *in vitro* is one of the remaining challenges. Future trends include the creation of biomimetic scaffolds that can deliver drugs, growth factors, or signaling molecules to help further promote cell function and tissue regeneration in addition to acting as structural supports for living cells.

FOOTNOTES

Author contributions: Tonti E wrote the outline, did the research, wrote the paper, and provided the final approval of the version of the article; Manco GA assisted in the editing and making critical revisions of the manuscript; Spadea L assisted in the writing, editing, and making critical revisions of the manuscript; Zeppieri M assisted in the conception and design of the study, and writing, outline, and final approval of the version of the article to be published and completed the English and scientific editing (a native English speaker).

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ORIGINAL ARTICLE

Retrospective Cohort Study

Predictors of graft function and survival in second kidney transplantation: A single center experience

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Abstract

BACKGROUND

The increasing kidney retransplantation rate has created a parallel field of research, including the risk factors and outcomes of this advanced form of renal replacement therapy. The presentation of experiences from different kidney transplantation centers may help enrich the literature on kidney retransplantation, as a specific topic in the field of kidney transplantation.

AIM

To identify the risk factors affecting primary graft function and graft survival rates after second kidney transplantation (SKT).

METHODS

The records of SKT cases performed between January 1977 and December 2014 at a European tertiary-level kidney transplantation center were retrospectively reviewed and analyzed. Beside the descriptive characteristics, the survivals of patients and both the first and second grafts were described using Kaplan-Meier curves. In addition, Kaplan-Meier analyses were also used to estimate the survival probabilities at 1, 3, 5, and 10 post-operative years, as well as at the longest follow-up duration available. Moreover, bivariate associations between various predictors and the categorical outcomes were assessed, using the suitable biostatistical tests, according to the predictor type.

RESULTS

Out of 1861 cases of kidney transplantation, only 48 cases with SKT were eligible for studying, including 33 men and 15 women with a mean age of 42.1 ± 13 years.

The primary non-function (PNF) graft occurred in five patients (10.4%). In bivariate analyses, a high body mass index (P = 0.009) and first graft loss due to acute rejection (P = 0.025) were the only significant predictors of PNF graft. The second graft survival was reduced by delayed graft function in the first (P = 0.008) and second (P < 0.001) grafts. However, the effect of acute rejection within the first year after the first transplant did not reach the threshold of significance (P = 0.053). The mean follow-up period was 59.8 ± 48.6 mo. Censored graft/patient survival rates at 1, 3, 5 and 10 years were 90.5%/97.9%, 79.9%/95.6%, 73.7%/91.9%, and 51.6%/83.0%, respectively.

CONCLUSION

Non-immediate recovery modes of the first and second graft functions were significantly associated with unfavorable second graft survival rates. Patient and graft survival rates of SKT were similar to those of the first kidney transplantation.

Key Words: Graft failure; Graft function; Kidney; Kidney retransplantation; Primary non-function graft; Second kidney transplantation

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Core Tip: Second kidney transplantation (SKT) is a viable option for patients with failed first kidney transplantation (FKT). Although the first primary nonfunction graft is a common contributor to SKT, it is also a potential outcome among a major proportion of those populations. Also, it is a significant risk factor for graft survival among those patients with functioning SKTs. Hence, the non-immediate recovery of the first graft function and delayed graft function in the second graft are significantly associated with unfavorable second graft survival rates. Inspite of this wide spectrum of risk factors, patient and graft survival rates in SKT seemed to be similar to those of FKT. SKT should be recommended for patients with failed FKT.

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INTRODUCTION

Kidney transplantation is the optimal treatment of end-stage renal disease (ESRD), because it provides better outcomes in survival rates, quality of life, and economic saving[1,2]. However, the expected survival of renal allografts is relatively lower than the patients' survival. This discrepancy between the patient and graft survival rates resulted in a progressively increasing number of patients who may need kidney retransplantation (KRT)[3-5]. Rates of KRT represent more than 15% of patients on the waiting lists[2,3,5], where the second kidney transplantation (SKT) is the most frequent form[5,6]. The numbers of KRT being still relatively far less than that of the first kidney transplantation (FKT) has resulted in persistent debates about the risk factors that may affect KRT and its controversial survival benefits. The magnitude of the reported outcomes of KRT has been shown to be either inferior or acceptable relative to those of FKT[5,7,8]. Beside the potential exposure to the same risk factors of FKT, recipients of KRT are prone to additional factors that may evolve from the repeated process such as sensitization and technical difficulties[5,6,9].

The unresolved debates about the risk factors and survival rates represented our rationale to present the current single center experience of SKT and explore the predictors for the graft function and survival of SKT.

MATERIALS AND METHODS

Study design

The electronic and manual records of the cases of KRT which were performed between January 1977 and December 2014 at Urology Department, Martin-Luther University, Halle (Saale), Germany were reviewed for the characteristics of the FKT and SKT processes. The effects of these variables on the primary graft function and the survival of both graft and patient were evaluated in SKT.

The target population was the adult patients who received SKT. Exclusion criteria were blood grouping or human leucocytic antigen (HLA) incompatible transplants; immunosuppression protocols other than basiliximab or anti-thymoglobulin for induction, and steroid, tacrolimus or cyclosporine, and mycophenolate mofetil for maintenance; missing data; and SKT within the year just before data collection.

Ethical approval

The authors confirm that all the experimental protocols of this study were approved by the Ethical Committee (Institutional Review Board; IRB) of the Faculty of Medicine, Assiut University, Egypt and Martin-Luther University, Germany (IRB approval number: 17200548/2015).

Statistical analysis

The statistical methods were implemented using IBM® SPSS® Statistics 23 and GraphPad Prism® 6. Two-tailed *P* values < 0.05 were considered significant.

After excluding primary non-function grafts, the survivals of both the first and second grafts were described using Kaplan-Meier curves. The same method was also used to describe patient survival after the second transplantation for the whole study sample. Moreover, regarding the graft and the patient survivals after SKT, Kaplan-Meier analyses were also used to estimate the survival probabilities at 1, 3, 5, and 10 post-operative years, as well as at the longest follow-up duration available.

Bivariate associations between various predictors and the categorical outcomes were assessed according to the predictor type. For quantitative predictors, the independent-samples *t* test was used when all outcome groups were normally distributed. Otherwise, the independent-samples Mann-Whitney *U* test and the Kruskal-Wallis test were used for binary and multinomial outcomes, respectively. For categorical predictors, Fisher's exact test was used.

As regards the second graft survival, associations with categorical predictors were evaluated by Kaplan-Meier curves for the strata of each predictor; the similarity between these curves for each predictor was tested by the log-rank test. On the other hand, associations with quantitative predictors were evaluated by Cox regression, where testing of the proportional hazards assumption was done by correlating ranked survival times with Schoenfeld residuals.

RESULTS

Between January 1977 and December 2014, a total of 1861 kidney transplants were done, of whom 176 cases had SKT. Only 48 cases were eligible for the current study. Characteristics of patients, donors, FKT, and SKT are summarized in Table 1. Twenty-three cases (47.9%) had primary non-function (PNF) first graft, while only five cases (10.4%) had PNF second graft. Patients with PNF grafts were excluded from the graft survival analyses. The median survival time for the first graft was 36 mo, while it was undefined for the graft and the patient after SKT (Figure 1). Survival probabilities of the graft and the patient after the SKT are shown in Table 2. The follow-up period ranged from 12 to 174 mo.

PNF graft occurred in five patients (10.4%). In bivariate analyses, a high body mass index (BMI) of the recipient was the only significant quantitative predictor of PNF graft ($P = 0.009$) (Tables 3 and 4). Also, first graft loss due to acute rejection was the only significant categorical predictor of PNF graft ($P = 0.025$) (Table 5).

The second graft survival was best in cases with a PNF first graft, while it was worst in cases with a delayed graft function (DGF) of the first graft ($P = 0.008$). Also, the second graft survival was better in cases with an immediate second graft function than in those with a delayed second graft function ($P < 0.001$) (Figure 2). Finally, the occurrence of acute rejection within the first year after the FKT decreased the survival of the second graft, but didn't reach the threshold of significance ($P = 0.053$) (Tables 6 and 7; Figures 3-5).

No significant associations were found between panel reactive antibodies (PRA) categories at SKT on one hand and first graft nephrectomy ($P = 0.784$), the duration before first graft nephrectomy ($P = 0.497$), or acute rejection of the second graft in the first year after SKT ($P = 0.223$) on the other hand. Also, no significant association was found between the number of second graft arteries and the vascular complications of SKT ($P = 0.382$).

DISCUSSION

Graft loss is always a potential outcome after variable periods of FKT[3,8-10]. This outcome created an imperative need for KRT[11]. Nowadays, there is a progressive rise in the numbers of patients receiving this line of treatment. KRT entails more risk factors for unfavorable outcomes than FKT[6,12]. Also, there are substantial controversies about the differences between FKT and SKT regarding patient and graft survival rates[7]. The current study targeted the potential risk factors affecting the second graft function in a large-volume kidney transplantation center.

In our study, the mean patient age at SKT was similar to that reported in other studies[5,13]. Also, our results resembled other studies regarding the gender distribution at SKT[5,13,14]. Causes of ESRD before kidney transplantation are not the same among the different world regions. Diabetic and hypertensive nephropathies represent the main causes in the United States. However, in the current series, glomerulonephritis was the leading cause, as in other countries[5,13].

It has been reported that occurrence of certain clinical outcomes after FKT is significantly associated with more likelihood of the same outcomes after KRT which increases the chances of graft loss[13]. In general, graft loss can be classified into three major categories: PNF grafts, patient death with a functioning graft, and loss of a previously functioning graft due to different medical and surgical causes[15,16].

PNF graft is defined as the permanent absence of functions of the transplanted kidney starting immediately after transplantation. It accounts for 0.6%-8% of all renal graft loss and it is significantly associated with poor patient survival [15,17]. In our series, a slightly higher rate was observed in SKT (10.4%), while the rate was much higher in FKT (47.9%). The major cause of PNF grafts has been reported to be venous or arterial thrombosis occurring within 1-2 d after

Table 1 Characteristics of recipients, donors, first kidney transplantation, and second kidney transplantation, *n* (%)

Variable		Value[1]
Recipient age at SKT (yr)		47.5 (41.3-56; 24-70)
Recipient sex	Male	33 (68.8)
	Female	15 (31.3)
Recipient BMI (kg/m^2) at SKT		24.7 (22.13-26.95; 19-33.5)
Causes of ESRD	Glomerulonephritis	16 (33.3)
	DM	1 (2.1)
	Hypertension	4 (8.3)
	PCKD	4 (8.3)
	Others	23 (47.9)
Overall duration of dialysis (mo.)		95 (76-121.8; 29-244)
Start of first graft function	PNF	23 (47.9)
	DGF	8 (16.7)
	Immediate	17 (35.4)
GFR one year after FKT (mL/min/1.73 m^2)		0 (0-29.3; 0-78.8)
Attacks of acute rejection in first year after FKT[2]		0 (0-1; 0-6)
First graft loss due to rejection		3 (6.3)
First graft nephrectomy		37 (77.1)
SKT donor type	Living	3 (6.3)
	Deceased	45 (93.8)
SKT donor age (yr)		50 (36.3-60.8; 16-74)
Recipient age minus donor age (yr) at SKT		0 (-10-7; -39-34)
SKT donor BMI (kg/m^2)		25 (23-27; 19-37.9)
Recipient BMI minus donor BMI (kg/m^2) at SKT		-0.45 (-3.8-3.15; -16.7-9.6)
SKT PRA level	0-30%	35 (72.9)
	31-80%	10 (20.8)
	> 80%	3 (6.3)
SKT HLA mismatches		2 (1.3-3.8; 0-6)
SKT laterality relative to FKT	Ipsilateral	1 (2.1)
	Contralateral	47 (97.9)
Number of renal arteries at SKT	Single	43 (89.6)
	Double	5 (10.4)
SKT operative time (min)		140 (113-170; 82-236)
SKT ischemia time (min)		708 (531-897; 74-1319)
SKT operative revision		24 (50)
SKT vascular complications		8 (16.7)
Start of second graft function	PNF	5 (10.4)
	DGF	10 (20.8)
	Immediate	33 (68.8)
Attacks of acute rejection in first year after SKT		0 (0-1; 0-3)
GFR one year after SKT (mL/min/1.73 m^2)		36 (22.8-52.8; 0-82.4)

[1]Quantitative variables are expressed as median (IQR; range), while categorical variables are expressed as count (percentage).
[2]Two missing cases.
BMI: Body mass index; DM: Diabetes mellitus; DGF: Delayed graft function; ESRD: End-stage renal disease; FKT: First kidney transplantation; GFR: Glomerular filtration rate; HLA: Human leucocytic antigen; PCKD: Polycystic kidney disease; PNF: Primary non-function; PRA: Panel reactive antibodies; SKT: Second kidney transplantation.

Table 2 Survival probabilities of the graft and the patient after the second kidney transplantation by Kaplan-Meier analyses

Follow-up time (months)	Second graft survival			Patient survival after second kidney transplantation		
	Survival probability (%)	Upper 95% confidence limit	Lower 95% confidence limit	Survival probability (%)	Upper 95% confidence limit	Lower 95% confidence limit
12	90.53	+5.81	-13.84	97.87	+1.83	-12.04
36	79.88	+9.55	-16.22	95.60	+3.29	-12.10
60	73.71	+11.31	-17.34	91.92	+5.51	-15.82
120	51.57	+21.01	-26.12	83.04	+9.90	-20.65
174 (study max.)	51.57	+21.01	-26.12	83.04	+9.90	-20.65

Table 3 Quantitative predictors (normally distributed over both outcome groups) of primary non-function second graft by the independent-samples *t* test

	Primary non-function (*n* = 5)		Primary function (*n* = 43)		*P* value[1]
	Mean	SE	Mean	SE	
Recipient age (yr)	47.8	5.4	47.9	1.8	0.98
Donor age (yr)	49.6	7.5	48.0	2.2	0.82
Recipient BMI (kg/m^2)	28.04	0.83	24.20	0.47	0.009
Total ischemia time (min)	655	98	711	48	0.70
Operative time (min)	150	20	142	6	0.66

[1]Since Levene's test yielded no significant differences between variances of outcome groups for the five tested predictors, equal variances were assumed.
BMI: Body mass index.

Table 4 Quantitative predictors (non-normally distributed over one or both outcome groups) of primary non-function second graft by the independent-samples Mann-Whitney U test

	Primary non-function (*n* = 5)		Primary function (*n* = 43)		*P* value
	Median	Mean rank	Median	Mean rank	
Duration of first graft function (mo)	0	17.6	4	25.3	0.26
Total duration of dialysis before second transplantation (including before first transplantation) (mo)	93	19.3	96	25.1	0.39

transplantation[15]. In our series, although the odds of PNF in cases with vascular complications was 4.1 times higher than in cases without these complications, the result was statistically insignificant probably due to the small sample. However, high recipients' BMI and first graft loss due to acute rejection were significantly associated with the occurrence of PNF after SKT. This might be attributable to the same mechanisms that decrease the second graft survival[15]. To our knowledge, it seems that these factors have not yet been studied relative to PNF graft after SKT.

The third category of kidney transplantation loss outcomes is the loss of the graft which functioned for a certain period before being permanently non-functioning. The risk factors of this outcome are multiple and have different tributaries. Regarding the elements of kidney transplantation process (recipient, donor, and process) and the previously proposed categorizations in the literature[5,14,18], the potential predictors or risk factors that affect the outcome of SKT could be classified into five classes: recipient-related, donor-related, FKT process-related, SKT process-related, and common factors.

Table 5 Categorical predictors of primary non-function second graft by Fisher's exact test

Variables		Primary non-function (n = 5)	Primary function (n = 43)[1]	Odds ratio[2]	P value
DM as a cause of ESRD	No	5	42	0	1
	Yes	0	1		
First graft function	No	3	20		0.84
	Delayed	1	7		
	Instant	1	16		
Acute rejection in first year after first transplantation	No	3	24	0.94	1
	Yes	2	17		
First graft loss by acute rejection	No	3	42	28	0.025
	Yes	2	1		
First graft nephrectomy	No	0	11	Not assessed[3]	0.58
	Yes	5	32		
Living donor	No	5	40	0	1
	Yes	0	3		
PRA grouping	0% to 30%	3	32		0.33
	31% to 80%	1	9		
	Over 80%	1	2		
Number of HLA mismatches	0	1	6		0.51
	1 to 3	2	27		
	4 to 6	2	10		
Over one artery	No	5	38	0	1
	Yes	0	5		
Vascular complications	No	3	37	4.1	0.19
	Yes	2	6		

[1]Except for acute rejection in first year after first transplantation, where n = 41 because two cases are missing.
[2]Odds of primary non-function in the presence of the predictor to odds of primary non-function in its absence.
[3]Not assessed, for the calculation entails division by zero.
DM: Diabetes mellitus; ESRD: End-stage renal disease; HLA: Human leukocytic antigens; PRA: Panel reactive antibodies.

The recipient-related risk factors include patient's age, sex, BMI, race, the cause of ESRD, and the associated comorbidities like diabetes mellitus and hypertension[5,13,19,20]. The second class risk factors are the donor-related factors either in FKT and SKT processes such as donor type (living or deceased), age, sex, and relatedness[5,13,14,21]. In the current series, the studied group of these factors showed no significant effects on SKT graft survival. We examined the effect of two further potential recipient-related variables; the differences between recipients' and donors' age and BMIs. Although they have been studied previously for their effect on FKT graft survival[22,23], they haven't been tested upon KRT survival so far. However, no significant association with the second graft survival could be found. It may be better demonstrated in larger studies.

The third class includes the factors from FKT process such as duration of FKT graft function and estimated glomerular filtration rate at one year after FKT[13,21,24-26]. The fourth class of risk factors includes factors that affect only SKT process such as sensitization due to previous transplantation represented by PRA level, first graft nephrectomy, and serum creatinine at one year after SKT[5,21,25].

The fifth class consists of the common variables between FKT and SKT processes and they represent the major proportion of risk factors. They involve all the phases of the process; factors in the preoperative phase such as number of HLA mismatches[4,5,18], and duration of dialysis[13,27]; factors in the operative and perioperative phases such as ischemia time, DGF[20,28], mode of recovery of graft function[13,27], and surgical complications[14]; factors in the postoperative phase such as acute rejection[13,27]; and factors involving the whole phases such as immunosuppressive regimens[5,12,29], and volume of transplantation center[18]. The reported incidence of DGF among KRTs ranged from 26.7%-39%[5,7,20]. In our study, the non-immediate mode of recovery of first graft function and DGF of second graft were

Table 6 Categorical predictors of second graft survival by the log-rank test for Kaplan-Meier curves

Variables		Events (*n* = 13)	Censored (*n* = 30)[1]	Log-rank statistic	*P* value
DM as a cause of ESRD	No	12	30	1.218	0.270
	Yes	1	0		
First graft function	No	2	18	9.684	0.008
	Delayed	4	3		
	Instant	7	9		
Acute rejection in first year after first transplantation	No	5	19	3.757	0.053
	Yes	8	9		
First graft loss by acute rejection	No	13	29	0.369	0.543
	Yes	0	1		
First graft nephrectomy	No	3	8	0.097	0.756
	Yes	10	22		
Living donor	No	12	28	0.002	0.965
	Yes	1	2		
PRA grouping	0% to 30%	11	21	0.693	0.707
	31% to 80%	2	7		
	Over 80%	0	2		
Number of HLA mismatches	0	2	4	0.106	0.948
	1 to 3	8	19		
	4 to 6	3	7		
Over one artery	No	10	28	1.584	0.208
	Yes	3	2		
Vascular complications	No	13	24	1.723	0.189
	Yes	0	6		
Delayed second graft function	No	7	26	12.238	0.0005
	Yes	6	4		

[1]Except for acute rejection in first year after first transplantation, where $n = 28$ because two cases are missing.

BMI: Body mass index; DM: Diabetes mellitus; ESRD: End-stage renal disease; HLA: Human leukocytic antigens; PRA: Panel reactive antibodies.

the only significant predictors for low second graft survival. It has been reported that occurrence of acute rejection during their first year post FKT is significantly associated with occurrence of acute rejection during KRT[13,21]. The current results showed that the incidence of acute rejection in FKT approached the threshold of significance in affection of the graft survival of SKT. This insignificant association could be attributed to the small sample size. The significant association of the mode of recovery of FKTs and the nearly significant association of the incidence of acute rejection among FKTs with the SKT graft survival, without the same effect on the SKT, could be attributed to the more stringent immunosuppression protocols and precise donor selection. This may improve the SKT graft function recovery and decrease the incidence of acute rejections. Thus, it may improve the short-term results to some extent but, it doesn't exterminate the inherent high risk of those patients[9,30].

With controversy, rates of graft and patient survivals of KRTs have been reported as inferior[3,14] or insignificantly different from those of FKT[4,5,21]. In the current study, the long-term graft survival rates were similar to FKT. This outcome is similar to the other studies[4,21].

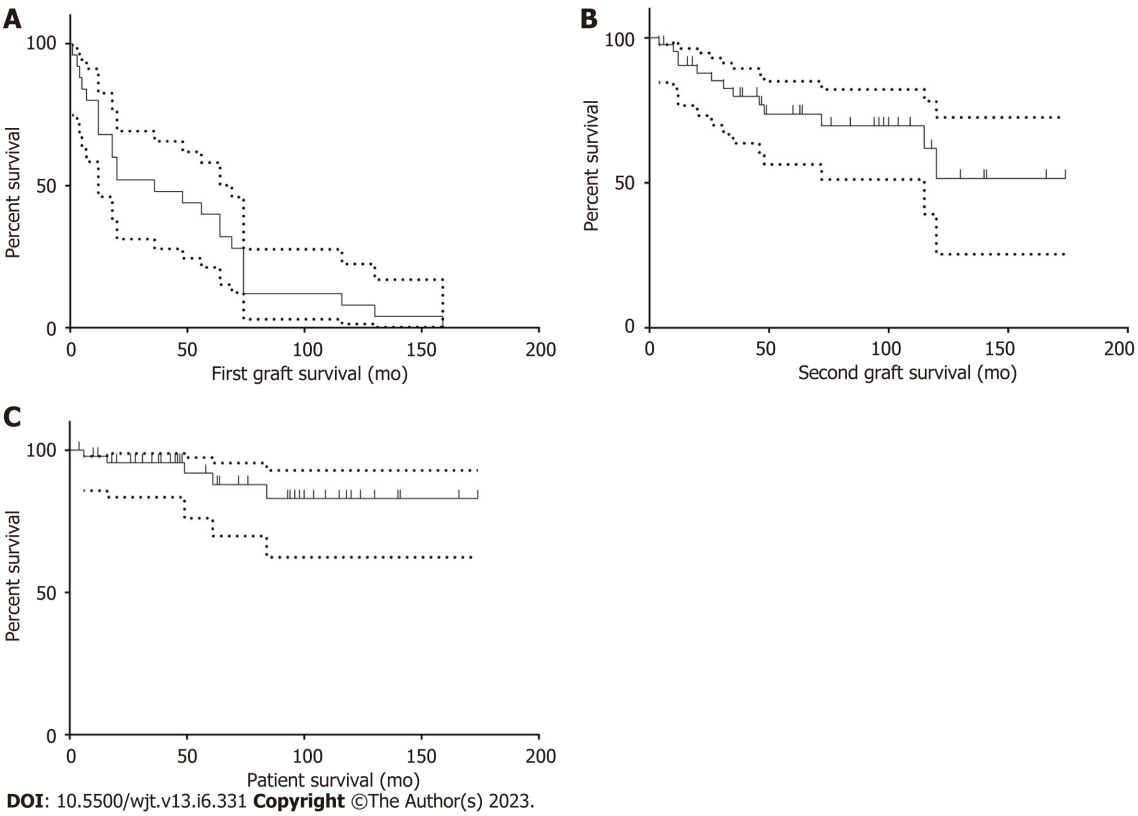
This study was conducted in a large-volume kidney transplantation center and extracted from a relatively large reviewed number of kidney transplantations. Also, new potential predictors including the differences in age and BMI between the recipients and donors were studied for their effect on graft survival.

Limitations of the current study were the relatively small sample size that didn't allow for adequate powerful statistical tests such as the multivariate analysis and lack of reporting of some complications as post-transplant neoplastic diseases and infections. Specifically, there were some missing data, such as the levels of the donor specific antibodies against the HLA alleles of the first graft and the pathological evaluation of the donors. In addition, the retrospective studying has its mere limitations of difficult implementation of comparison and randomization.

Table 7 Quantitative predictors of second graft survival by Cox regression

Variables	HR	95%CI for HR		*P* value	*P* value for PH testing[1]
		Lower bound	Upper bound		
Recipient age (yr)	0.976	0.930	1.023	0.306	0.074
Recipient BMI (kg/m^2)	0.980	0.810	1.185	0.833	0.787
Duration of first graft function (mo)	1.007	0.994	1.020	0.307	0.059
Total duration of dialysis before second transplantation (including before first transplantation) (mo)	1.006	0.995	1.017	0.295	0.061
Donor age (yr)	1.016	0.979	1.055	0.396	0.852
Recipient age minus donor age (yr)	0.972	0.937	1.009	0.140	0.306
Recipient BMI minus donor BMI (kg/m^2)	0.984	0.893	1.085	0.751	0.410
Total ischemia time (min)	1.001	0.999	1.003	0.284	0.579
Operative time (min)	0.995	0.979	1.010	0.497	0.363

[1]Testing of the proportional hazards assumption was done by correlating ranked survival times with Schoenfeld residuals.
BMI: Body mass index; HR: Hazard ratio; PH: Proportional hazards.

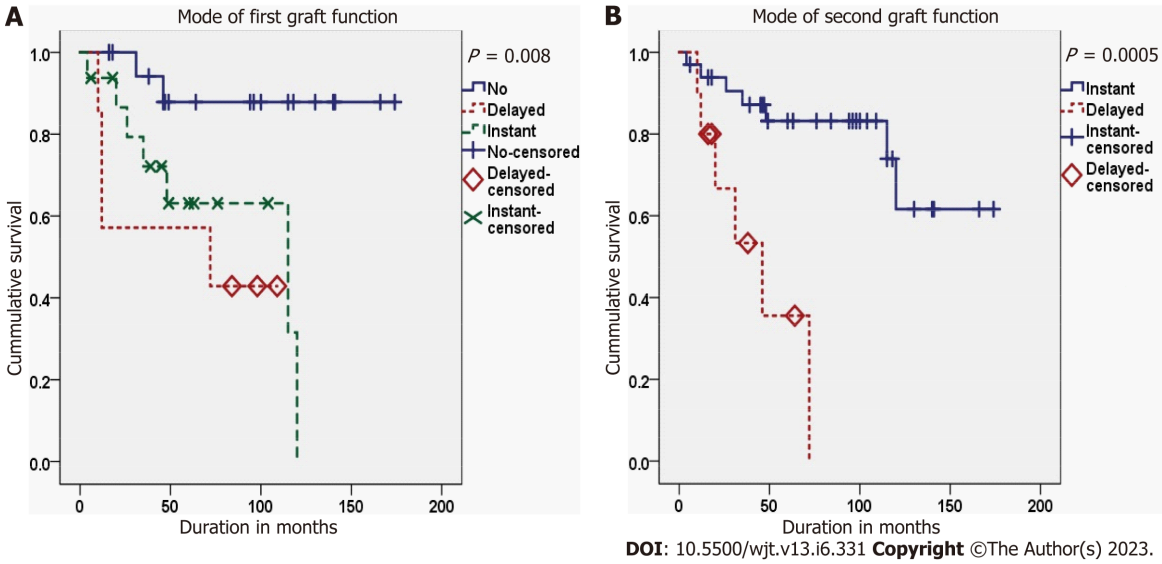


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Figure 1 Kaplan-Meier curve for overall survival rates. A: First graft survival with 95% confidence bands. Twenty-three cases were excluded from the analysis due to primary non-function grafts. All 25 cases had the event; B: Second graft survival with 95% confidence bands. Five cases were excluded from the analysis due to primary non-function grafts. Thirteen cases had the event, while 30 cases were censored; C: Patient survival after the second kidney transplantation with 95% confidence bands. Only five patients died, while 43 patients were censored.

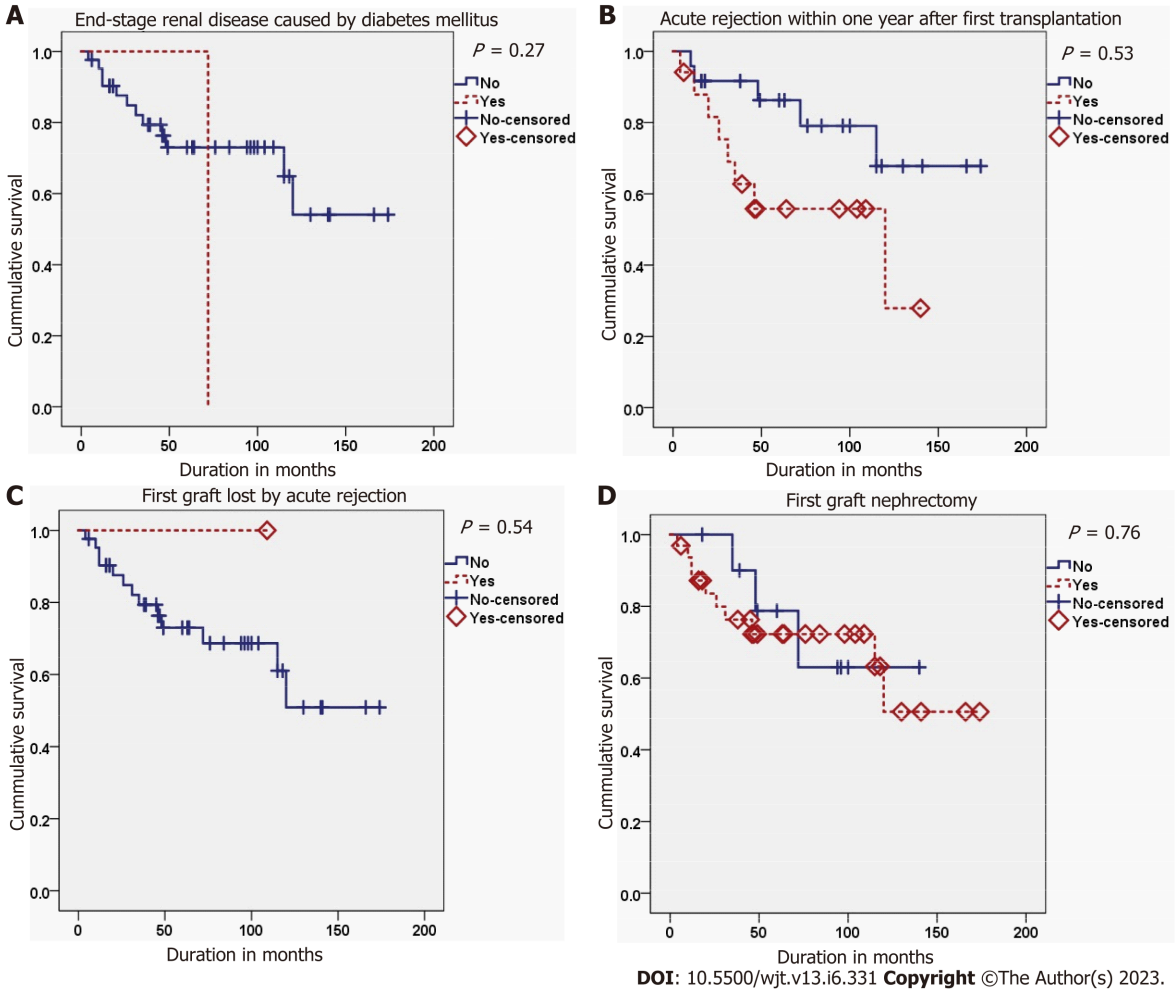
CONCLUSION

SKT is a viable option for patients with failed FKT. Demographics and clinical characteristics of the patients accessing SKT are not significantly different from those of FKT. There are multiple potential factors that may originate from the different components and phases of SKT and could affect the survival outcomes. Although the first PNF graft is a



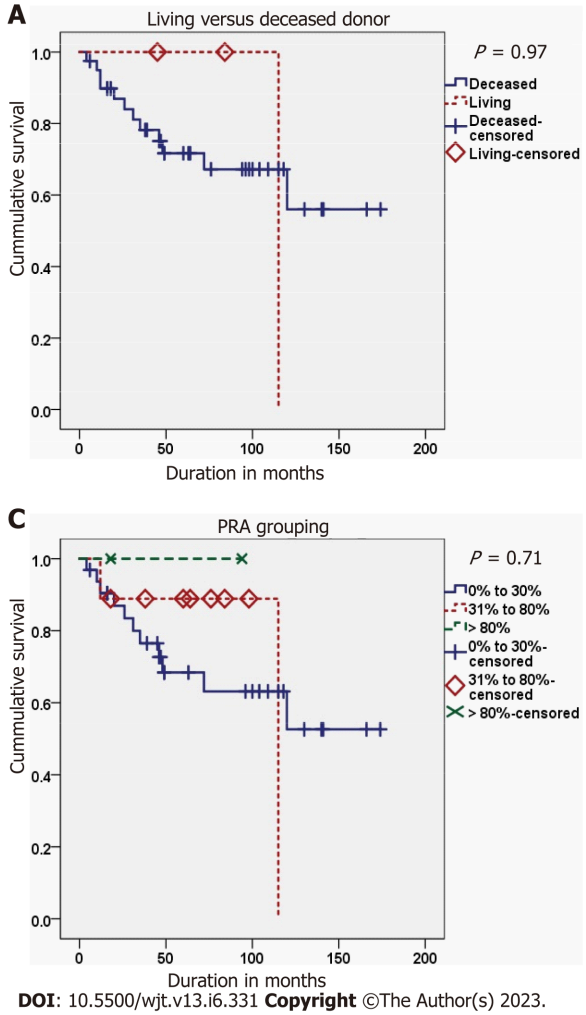
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Figure 2 Kaplan-Meier curves for the second graft survival stratified by the mode of graft function. A: In the first kidney transplantation; B: In the second kidney transplantation.



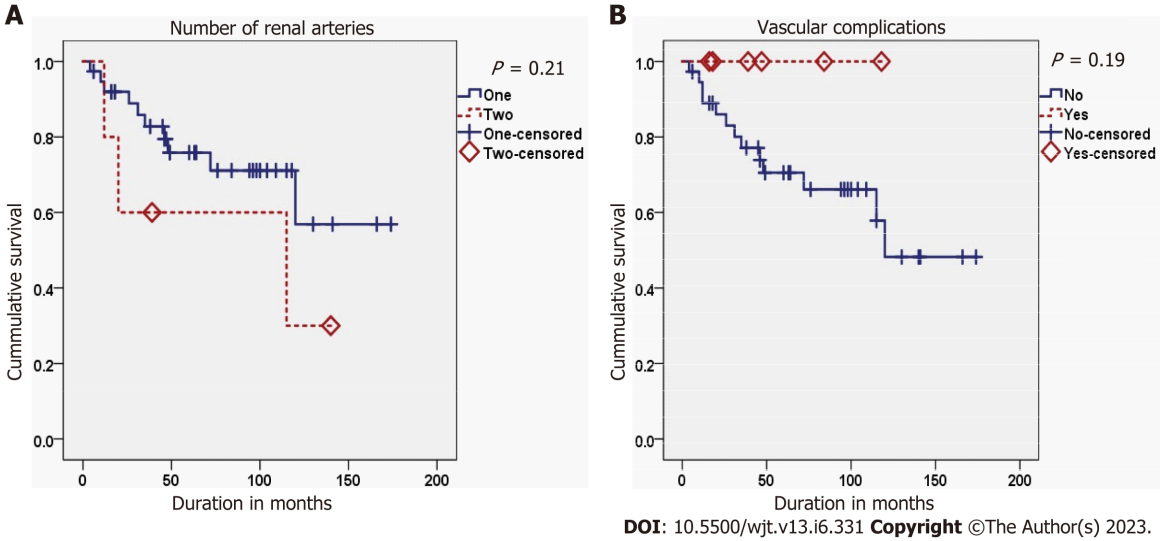
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Figure 3 Kaplan-Meier curves for the second graft survival stratified by four non-significant predictors related to the first kidney transplantation. A: End-stage renal disease caused by diabetes mellitus; B: Acute rejection within one year after first transplantation; C: First graft loss by acute rejection; D: First graft nephrectomy.



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Figure 4 Kaplan-Meier curves for the second graft survival stratified by three non-significant predictors related to the donor of second kidney transplantation. A: Living versus deceased donor; B: Number of human leukocytic antigens mismatches; C: Panel reactive antibodies. HLA: human leukocytic antigens; PRA: Panel reactive antibodies.



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Figure 5 Kaplan-Meier curves for the second graft survival stratified by second non-significant predictors related to the second kidney transplantation recipient. A: Number of renal arteries; B: Vascular complications.

common contributor to SKT, it is also a potential outcome among a major proportion of those populations. Also, it is a significant risk factor for graft survival among those patients with functioning SKTs. So, the non-immediate recovery of the first graft function and DGF in the second graft are significantly associated with unfavorable second graft survival rates. Inspite of this wide spectrum of risk factors, patient and graft survival rates in SKT seemed to be similar to those of FKT.

ARTICLE HIGHLIGHTS

Research background

The increasing kidney retransplantation rate has created a parallel field of research, including the risk factors and outcomes of this advanced form of renal replacement therapy. The presentation of experiences from different kidney transplantation (KT) centers may help enrich the literature on kidney retransplantation, as a specific topic in the field of KT.

Research motivation

Despite the potential high risks of repeated KT, increase of the rate of second KT (SKT) seems to be a modifiable variable and may provide better outcomes than return to dialysis in patients with failed first KT.

Research objectives

To identify the risk factors affecting primary graft function and graft survival rates after SKT.

Research methods

The records of SKT cases performed between January 1977 and December 2014 at a European tertiary-level kidney transplantation center were retrospectively reviewed and analyzed. Beside the descriptive characteristics, the survivals of patients and both the first and second grafts were described using Kaplan-Meier curves. In addition, Kaplan-Meier analyses were also used to estimate the survival probabilities at 1, 3, 5, and 10 post-operative years, as well as at the longest follow-up duration available. Moreover, bivariate associations between various predictors and the categorical outcomes were assessed, using the suitable biostatistical tests, according to the predictor type. However, associations with quantitative predictors were evaluated by Cox regression.

Research results

Out of 1861 cases of kidney transplantation, only 48 cases with SKT were eligible for studying, including 33 men and 15 women with a mean age of 42.1 ± 13 years. The primary non-function (PNF) graft occurred in five patients (10.4%). In bivariate analyses, a high body mass index (P = 0.009) and first graft loss due to acute rejection (P = 0.025) were the only significant predictors of PNF graft. The second graft survival was reduced by delayed graft function in the first (P = 0.008) and second (P < 0.001) grafts. However, the effect of acute rejection within the first year after the first transplant did not reach the threshold of significance (P = 0.053). The mean follow-up period was 59.8 ± 48.6 mo. Censored graft/patient survival rates at 1, 3, 5 and 10 years were 90.5%/97.9%, 79.9%/95.6%, 73.7%/91.9%, and 51.6%/83.0%, respectively.

Research conclusions

Non-immediate recovery modes of the first and second graft functions were significantly associated with unfavorable second graft survival rates. Patient and graft survival rates of SKT were similar to those of the first KT.

Research perspectives

Repeated kidney transplantation may provide better outcomes in patients with failed previous grafts. However, this approach may be associated with higher risks than the first time due to the surgical difficulties and immunological sensitization. Controlling of these risk factors can enhance the outcomes.

FOOTNOTES

Author contributions: Khalil M and Gadelkareem RA designed the research, collected the data, performed statistical analysis and wrote the paper; Abdallah MA, Mohammed N and Sayed MA contributed to data collection, literature review, writing and revision; and Elanany FG and Fornara P contributed to literature review, writing, revision and supervision of the work; All authors approved the paper.

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Informed consent statement: This article is a retrospective study. Hence, the patients were not required to give informed consent to the study, because the manipulated data were anonymous and were obtained after each patient, with his potential kidney donor(s), agreed

to the plan of management.

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ORIGINAL ARTICLE

Retrospective Study

Risk stratification of renal transplant recipients using routine parameters: Implication of learning from SARS-CoV-2 into transplant follow-up program

Abbas Ghazanfar, Madiha Abbas, Md Walid Hussain, Malik Kayal

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Abstract

BACKGROUND

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is a global pandemic that is associated with a high risk of morbidity and mortality among recipients of solid organ transplantation. In the course of acute SARS-CoV-2 infection, various laboratory markers have been identified as predictors for high risk of mortality.

AIM

To risk stratify renal transplant recipients (RTxR) using general demographic parameters, comorbidities and routine laboratory markers for the severity of the disease and its outcomes. We believe that learning about these routinely monitored parameters can help us plan better strategies for the RTxR follow-up program.

METHODS

This present study includes RTxR who acquired SARS-CoV-2 infection from March 2020 to February 2021. We recorded the basic demographics, comorbidities and routine laboratory markers. We investigated the impact of SARS-CoV-2 infection on RTxRs and risk-stratified the progression of disease severity and outcomes in terms of recovery or mortality.

RESULTS

From 505 RTxRs in our renal transplant follow-up program, 29 (7.75%) RTxRs had PCR-positive SARS-CoV-2 infection. We recorded 8 deaths from SARS-CoV-2 infection giving an overall mortality rate of 1.6% but a significant 27.6% mortality in SARS-CoV-2 positive recipients. Age more than 68 years, non-Caucasian ethnicity and male gender were associated with a significant drop in survival probability; $P \leq 0.001$. < 0.001 and < 0.0001 respectively. 87.5% of the deceased were diabetic; $P \leq 0.0.0001$. Estimated glomerular filtration rate of less than 26 mL/min/1.73 m^2, serum albumin less than 20 g/L, Hemoglobin less than 9.6 g/L and serum calcium less than 1.70 mmol/L were all associated with significantly increased risk of mortality; $P = 0.0128$, < 0.001, < 0.0001 and 0.0061 respectively.

CONCLUSION

This study has identified some routinely used modifiable parameters in predicting a higher risk of mortality and morbidity. This knowledge can be used in RTxR follow-up programs by addressing these parameters early to help reduce the morbidity and mortality in RTxRs.

Key Words: SARS-CoV-2 mortality; Renal transplant recipients; Glomerular filtration rate; Anemia; Albumin; Calcium; Reducing morbidity and mortality; Renal transplant follow-up program

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Core Tip: In this present study, we aim to risk stratify renal transplant recipients (RTxR) using general demographic parameters, comorbidities and routine laboratory markers for the severity of the disease and its outcomes. We believe that learning about these routinely monitored parameters can help us to plan better strategies for RTxR follow-up program.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first identified in December 2019[1] and subsequently declared a global pandemic on March 11, 2020[2]. So far it has resulted in more than 767 million cases worldwide with more than 6.9 million deaths[3]. The severity of the disease is related to various risk factors and associated comorbidities including older age, obesity, diabetes, pre-existing cardiac and pulmonary disease and conditions that affect the immune system[4-6].

The recipients of solid organ transplantation (SOT) are known to be more vulnerable to opportunistic infections[7] including several common respiratory virus infections[8], due to a weakened T-cell mediated immune response[9]. Globally, the recipients of SOT were included among patients at increased risk for severe illness from SARS-CoV-2[10, 11]. The reported mortality among Renal Transplant Recipients (RTxRs) from SARS-CoV-2 varied between 10% to 33%, in different studies across the world[12-17]. This increased risk of mortality is not only because of immunosuppression but also secondary to associated comorbidities[5,6]. In the course of acute SARS-CoV-2 infection, various laboratory markers have been identified as predictors for high risk of mortality including lymphopenia, high C-reactive protein levels, D-dimer, lactate dehydrogenase and ferritin[18-20]. However, some of the other routinely monitored parameters have not been studied in detail in RTxRs when compared with the general population. These include blood pressure control[21], Haemoglobin (Hb)[22], serum albumin[23], serum calcium levels[24] and function of the renal allograft, being measured as estimated glomerular filtration rate (eGFR)[25]. In this present study, we investigate these routine parameters with an aim to risk stratify RTxRs in high or low-risk groups using general demographic parameters, comorbidities and routine laboratory markers. The aim is to identify relevant routinely done parameters to identify high-risk RTxRs at an early stage. We believe that identification and correction of these parameters can significantly reduce long-term morbidity and mortality in RTxRs from SARS-CoV-2 as well as non-SARS-CoV-2 related infections.

MATERIALS AND METHODS

In this retrospective observational study, we analysed the data of our renal transplant follow-up program. At the time of the present study, we had 505 RTxRs registered under the follow-up program at St Georges University Hospitals NHS Foundation Trust, London, United Kingdom. Since the start of the pandemic in March 2020, on the advice of National Health Services England, National Health Services Blood and Transplant and the British Transplantation Society, we

recommended shielding for all our RTxRs in our follow-up program. In this present study, we included all RTxR who acquired SARS-CoV-2 infection from March 2020 to February 2021. It included both symptomatic and asymptomatic patients. There were 29 patients in our RTxRs follow-up program who acquired SARS-CoV-2 infection during this period which were included in study group cohort A; leaving 476 patients in the control group, cohort B. We recorded the basic demographics, comorbidities and routine laboratory markers. We compared these two groups to identify any significant factors responsible for predisposing RTxRs to the severity of SARS-CoV-2 infection. We then further investigated 29 RTxRs with SARS-CoV-2 infection to stratify the progression of disease severity and outcomes in terms of recovery or mortality. We subdivided patients in cohort A into A1 (n = 21) where they recovered from SARS-CoV-2 infection and A2 (n = 8) which resulted in mortality. We used Prism 9 and MedCalc statistical software programs for the data analyses. Baseline characteristics were compared using a t-test, Fisher exact test, Chi-square test or Mann-Whitney U-test where appropriate. Box-Whisker plots were used to describe means, standard deviations and standard error of means. Survival probabilities were recorded for individual risk factors. Univariate and multivariate analyses were performed to record the impact of various factors on each other. Survival analysis was carried out using Kaplan–Meier estimates and for differences in survival, a log-rank test was used.

RESULTS

From 505 RTxRs in our renal transplant follow-up program 29 (7.75%) RTxRs had PCR-positive SARS-CoV-2 infection (cohort A), leaving 476 patients in control cohort B. We recorded 8 deaths in cohort A giving a mortality rate of 1.6% for the overall follow-up population but a significant 27.6% mortality in SARS-CoV-2 positive patients. There was no death recorded in cohort B during the same period.

General demographic and risk of SARS-CoV-2

The patients who acquired SARS-CoV-2 infection were from a significantly older age group with a mean (SD) and median interquartile range (IQR) of 63.24 (12.57) and 65 (56-71.5) compared to rest of the group; $P \leq 0.001$ (Table 1, Figure 1). In intra-cohort A analysis, where all patients were exposed to SARS-CoV-2 infection, the mean (SD) and median (IQR) age in years in cohort A1 and A 2 were 60.85 (12.5) and 64 (64-69.5) compared with 69.5 (9.5) and 68 (68-77); $P = 0.0986$ (Figure 2). However, on further analysis of survival probability, a direct correlation was noted between older age and mortality (Figure 3). There was a significant drop in survival probability recorded once patients crossed 68 years of age; $P \leq 0.001$. When comparing gender distribution as a risk of SARS-CoV-2 infection there was no significance recorded between cohort A and B; $P = 0.3056$. However, when the risk of mortality was compared in the SARS-CoV-2 infection-positive group, there was a higher risk of mortality among male patients, with 75% of the deceased patients being male; $P \leq 0.0001$ (Table 1). Non-Caucasian ethnicity was associated with high mortality risk once infected with SARS-CoV-2; $P \leq 0.001$ (Figure 4). The survival probability was worst in older patients from Middle Eastern ethnicity followed by Black, Asian and White ethnicities (Figure 5).

Clinical comorbidities and SARS-CoV-2 risk analysis

The overall prevalence of diabetes in our RTxR follow-up patients was 20%. Of the patients who acquired SARS-CoV-2 infection, 55% were diabetic (Cohort A) with 87.5% among deceased (Cohort A2); $P \leq 0.0.0001$ (Figure 6). This suggests diabetes is a major risk factor for SARS-CoV-2-related mortality in renal transplant patients. We further analysed survival probability depending on the recipient's age and diabetic status and found a direct correlation between old age, diabetes and mortality (Figure 7). The mean (SD) body mass index (BMI) kg/m^2 of the overall RTxR population was 26.60 (4.81). There were no significant differences recorded in BMI across the RTxR population (Figure 8). There was no impact of BMI on mortality. In our RTxR follow-up cohort hypertension and history of ischemic heart disease were also not independently significant risk factors for mortality; $P = 0.8221$ and $P = 0.7622$ respectively.

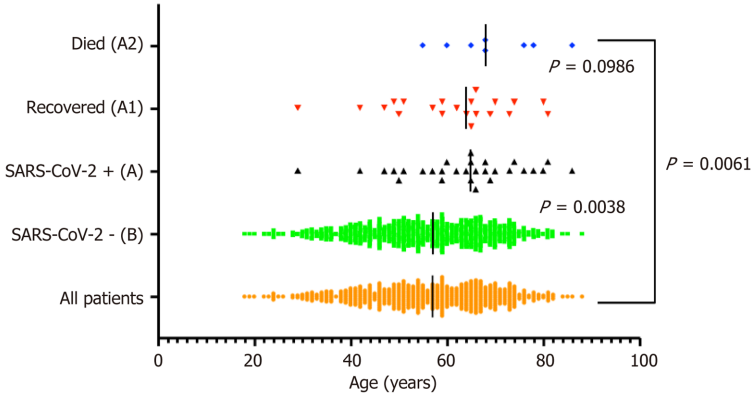
Common laboratory markers and SARS-CoV-2 risk analysis

We analysed some of the routinely monitored laboratory investigations to identify the severity of SARS-CoV-2 infection. We analysed the latest laboratory markers just prior to SARS-CoV-2 infection to avoid any impact of acute infection on these markers. We investigated the patient's renal allograft function recorded as an eGFR in mL/min/1.73 m^2). The mean (SD) and median (IQR) in cohort A1 and A2 were 47 (21) and 41 (41-56.5); and 25.75 (7.5) and 26.5 (26.5-30) respectively, $P = 0.0128$ (Figure 9). The poor functional quality of the renal allograft was directly related to a higher risk of mortality (Figure 10). The second marker we investigated was serum albumin level. The mean (SD) and median (IQR) of serum albumin in g/L of all RTxR patients was 36.81 (4.36) and 38 (35-39) which was within the normal range (Figure 11). On review, there was a significant difference between serum albumin levels of patients who recovered from SARS-CoV-2 infection as compared to those who died; $P \leq 0.0001$. There was also a significant relation noted between low albumin levels and a high risk of mortality, particularly when serum albumin was less than 20g/L $P \leq 0.001$. The mean (SD) and median (IQR) (Hb g/L) of overall RTxR were 126.9 (18.07) and 127 (115-140) compared to 106.4 (20.8) in group A and 101 (93-124) in group A2; $P \leq 0.001$ (Figure 12). On further comparison between patients who recovered (A1) with patients who died (A2), a significant difference was recorded; $P \leq 0.0001$. Looking at survival probability Hb less than 7 was associated with higher mortality. Finally, we looked at serum calcium levels across our RTxR. The mean (SD) and median (IQR) values of serum calcium in mmol/L of the overall RTxR cohort were 2.39 (0.14) and 2.41 (2.3-2.4). There was a significant difference in serum calcium recorded between all RTxR and SARS-CoV-2 positive; $P \leq 0.001$ and also between patients who recovered and those who died; $P = 0.0061$ (Figure 13). We found a significant correlation between low serum

Table 1 Demographic factors and risk of severe acute respiratory syndrome coronavirus 2 infection in renal transplant recipients, (%)

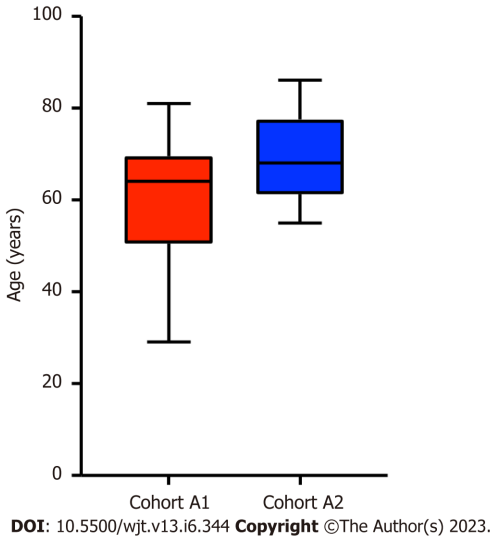
Demographic	Cohort A (*n* = 29), SARS-CoV-2 infection	Cohort B (*n* = 476), no infection	Significance
Age			
Mean (SD)	63.24 (12.57)	55.70 (13.63)	< 0.001
Median (IQR)	65 (56-71.5)	57 (46-66)	
Gender			
Male	14 (48.27)	276 (57.8)	0.3056
Female	15 (51.73)	200 (42.2)	
Ethnicity			
White	7 (24.13)	252 (52.94)	
Black	8 (27.58)	90 (18.9)	
Asian	13 (44.82)	126 (26.47)	< 0.001[a]
Others	1 (3.44)	8 (1.6)	
Cohort A1		Cohort A2	
(Recovered; *n* = 21)		(Died; *n* = 8)	
Age			
Mean (SD)	60.85 (12.5)	69.5 (9.5)	0.0986
Median (IQR)	64 (64-69.5)	68 (68-77)	
Gender			
Male	8 (38)	6 (75)	< 0.001
Female	13 (62)	2 (25)	
Ethnicity			
White	5 (23.8)	2 (25)	
Black	7 (33.33)	1 (12.5)	
Asian	9 (42.85)	4 (50)	< 0.001[b]
Others	0	1 (12.5)	

[a]Asian ethnicity is associated with a significant risk of severe acute respiratory syndrome coronavirus 2 infection.
[b]Non-Caucasian ethnicities are associated with a significant risk of severe acute respiratory syndrome coronavirus 2 mortality.



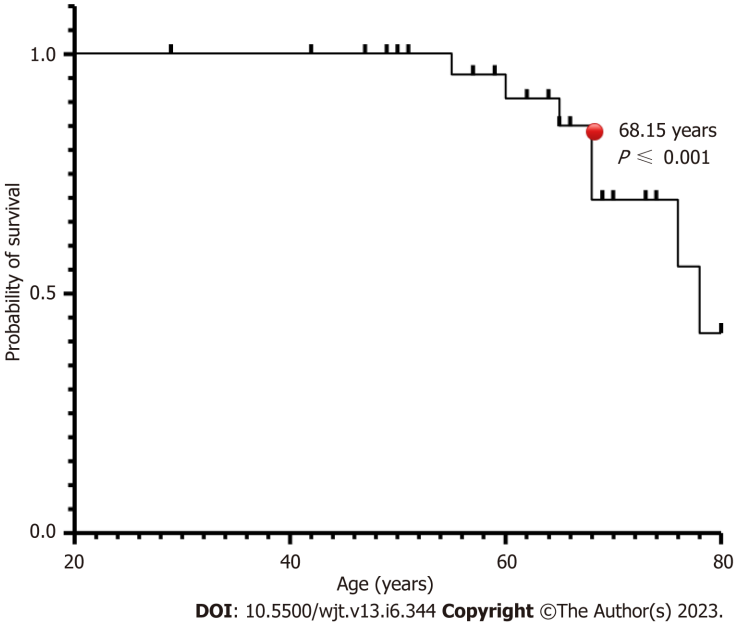
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Figure 1 Median age across various cohorts.



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Figure 2 Intra-group age analysis A1 *vs* A2.



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Figure 3 Age-related survival probability.

calcium levels and mortality once the level falls below 1.70 mmol/L < 0.001.

DISCUSSION

The recipients of solid organ transplantation are more vulnerable to opportunistic infections due to immunosuppressant medication. They demonstrate reduced resistance to infection, rapid progression of pathology, atypical clinical presentations and high risk of morbidity and mortality[26]. In addition to these factors, recovery from infection is dependent on various factors including the general well-being of the recipient and associated comorbidities. In renal transplant recipients, the functional status of the renal allograft also plays a vital part in the recovery phase, particularly when medication dosage is dependent on renal function. In addition to this, treatment regimens may be complicated by drug interactions and the need to maintain immunosuppression to prevent rejection. This complex interconnection between high-risk of infection, allograft function, limited treatment choices and associated comorbidities makes post-transplant infections the leading cause of morbidity and mortality[27]. During SARS-CoV-2 pandemic, the reported mortality among renal transplant recipients was as high as 33%[17]. In various general population studies, greater than 75 years of age, male gender and BMI greater than 40 are associated with significant mortality[28]. In our study, the mean (SD) age of recipient mortality was 69.5 (± 9.5) with a significantly increased risk of mortality after age 68 years and above. This

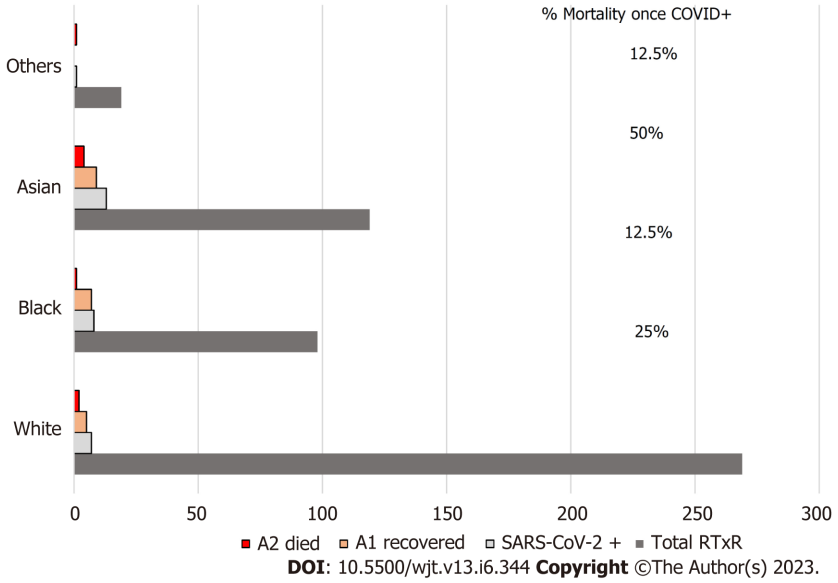


Figure 4 Ethnicity across various cohorts.

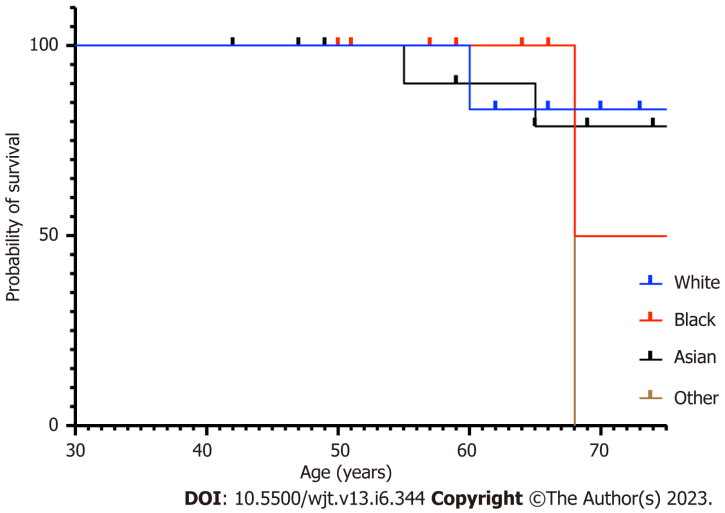


Figure 5 Survival probability with age and ethnicity.

finding is comparable to other studies in the renal transplant population[11,17,28] (Figure 14). These findings confirm that renal transplant recipients are at high risk of mortality at an earlier age when compared to the general population. We recorded a higher rate of mortality among male patients. This is also comparable with other published data[11,17,27,29]. Comparing BMI, there was no significant difference recorded in various groups in our study. The mean (SD) BMI in our mortality group was 27.20 (4.97) which is comparable to other published studies in the transplant population[11,17,29]. In general population studies, there was a high risk of mortality recorded in patients with a BMI greater than 40, but this BMI range is uncommon in renal transplant recipients. Surprisingly, we did not find any significant impact of hypertension and ischemic heart disease on mortality in our study population. This finding contrasts with general population studies[28,30,31] as well as other renal transplant studies[11,17,29] where there is a high risk of SARS-CoV-2-related mortality. The mean (SD) and median (IQR) systolic BP in our RTxR population were 130.8 (14.56) and 128 (120-139) with diastolic BP 79.22 (9.9) and 80 (71-87). This showed good BP control of our RTxR population. We had a higher number of patients with diabetes compared to other studies. This demonstrates that the demographics of renal transplant recipients vary widely across the globe and even within the United Kingdom. In contrast to other studies where acute inflammatory markers were studied in RTxR, we looked at routine laboratory parameters in predicting the outcome of RTxR after getting SARS-CoV-2 infection. We compared this to routine laboratory parameters when RTxR were free of SARS-CoV-2 infection. This helped to determine baseline parameters. There are limited studies of such parameters in the transplant population, so we compared our results with published data on the non-transplant population[14]. We noted that anaemia, hypercalcemia and hypoalbuminemia are associated with high-risk mortality in our study. These findings are similar to other published studies in non-transplant patients (Figure 15). We also noted that low GFR in RTxRs is also associated with high mortality risk. When we compared the impact of these parameters on mortality using multiple

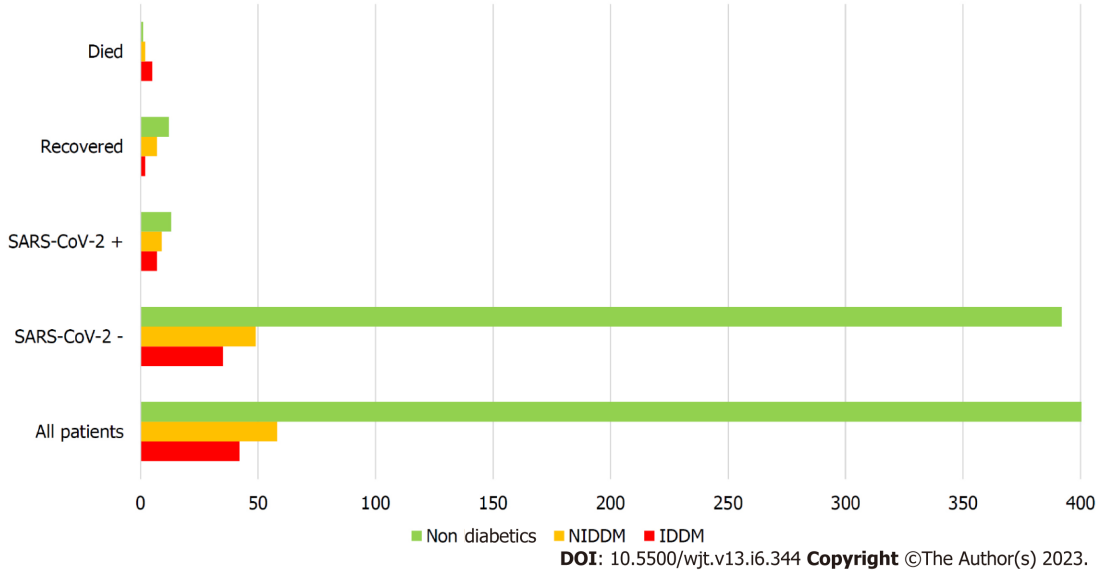


Figure 6 Diabetic status across various cohorts.

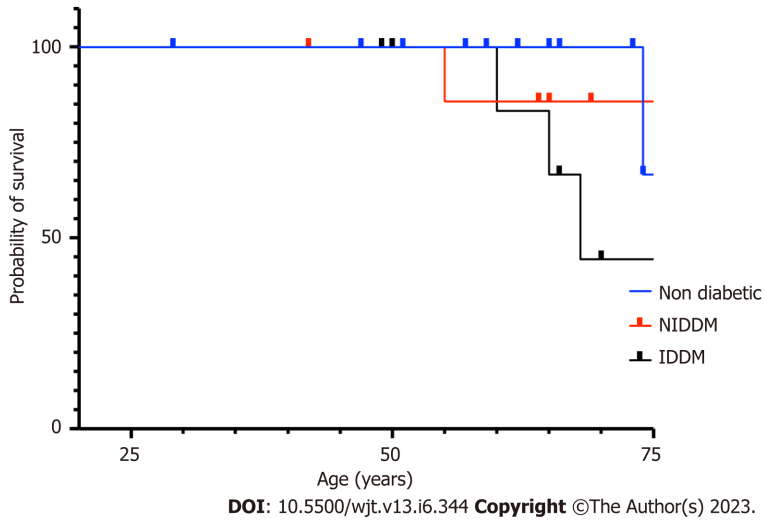


Figure 7 Survival probability with age and diabetic status.

logistic regression, we found a direct correlation (Figure 16). Identifying the impact of these parameters on mortality may be an important finding. The majority of these factors can be picked up on simple routine tests and do not require specialist investigations. Some of these factors are correctable with simple interventions. These can be addressed at an early stage during the RTxRs follow-up program with an aim to bring them to the normal range, where possible. This in return can significantly reduce morbidity and mortality in RTxRs.

CONCLUSION

It would be very easy and cost-effective to incorporate the findings of this study into any post-operative follow-up pathway and protocol for RTxRs. These simple parameters can help to risk stratify RTxRs into high and low-risk categories. In addition to this, despite having a failing renal transplant, early intervention to improve a patient's anaemia, hypercalcemia and hypoalbuminemia could reduce their risk of morbidity and mortality. Early identification of at-risk sub-groups within those already identified as being high-risk, can further reduce the risk of infection-associated mortality, with timely interventions.

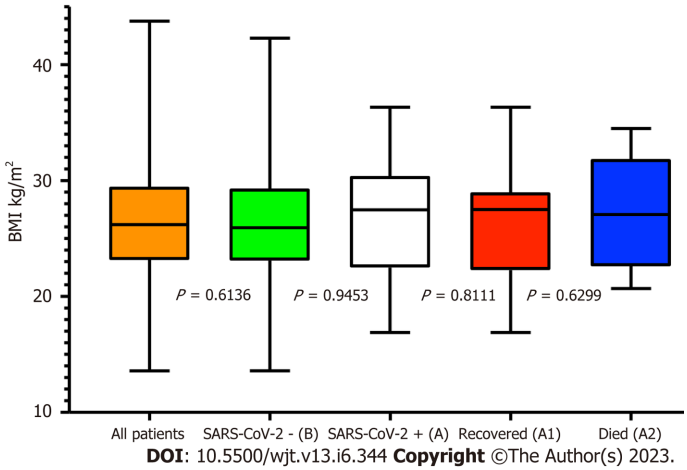


Figure 8 Body mass index range across various cohorts. BMI: Body mass index; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

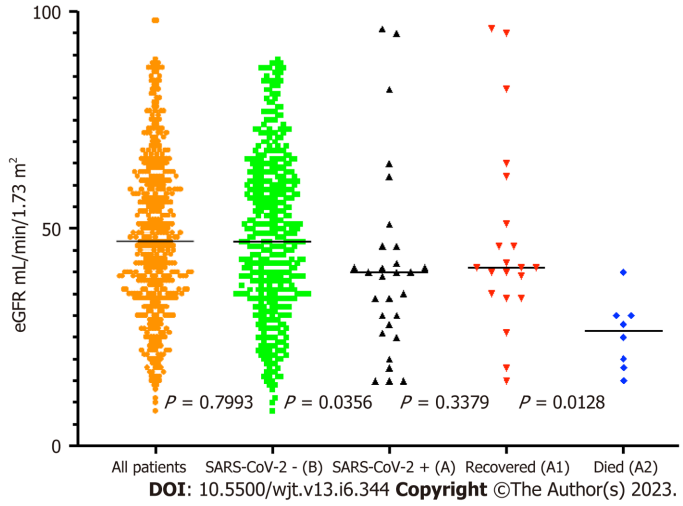


Figure 9 Median estimated glomerular filtration rate across various cohorts. eGFR: Estimated glomerular filtration rate; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

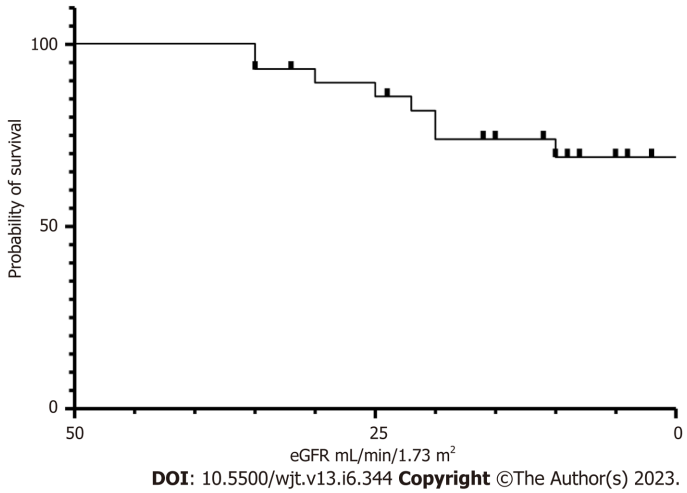


Figure 10 Survival probability dependent on graft estimated glomerular filtration rate. eGFR: Estimated glomerular filtration rate.

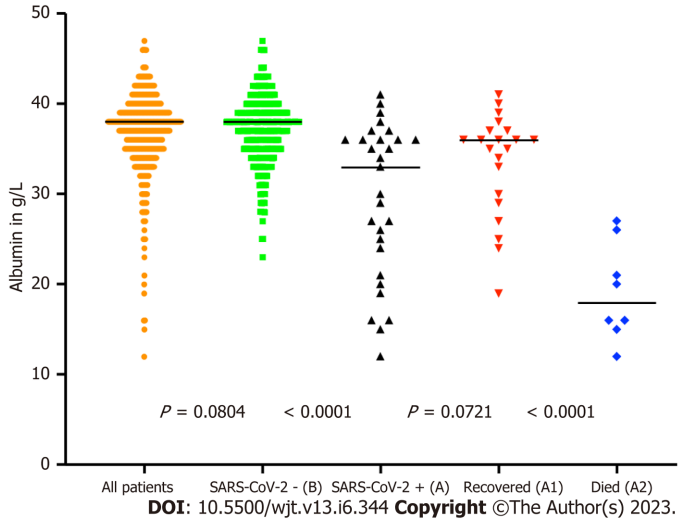


Figure 11 Albumin (g/L) across various cohorts. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

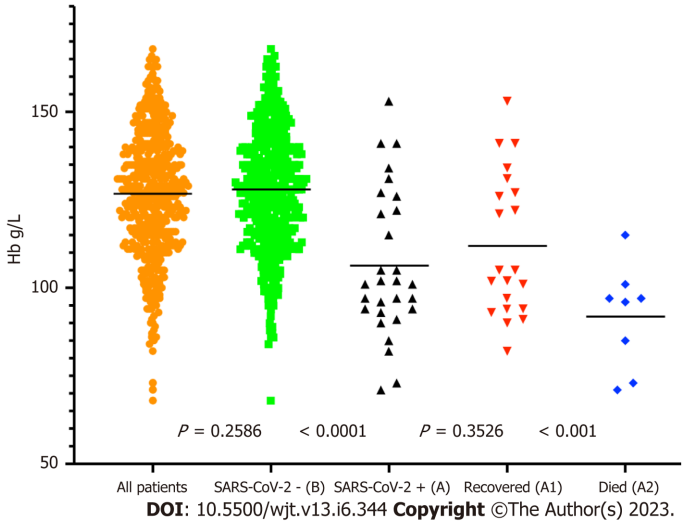


Figure 12 Hb distribution among various cohorts. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

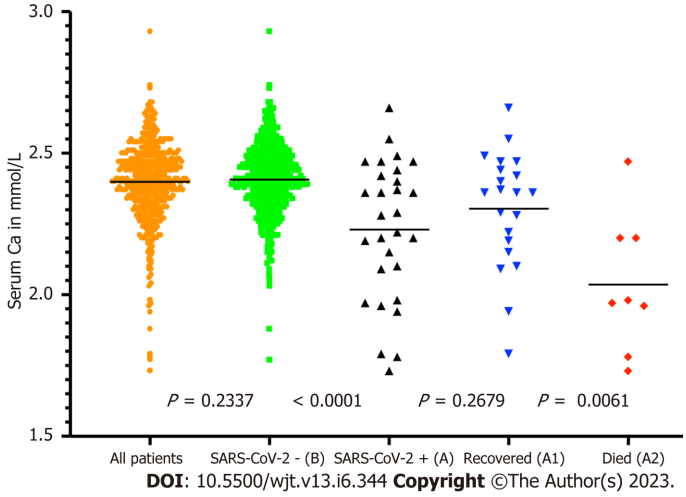


Figure 13 Serum Ca distribution across various cohorts. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

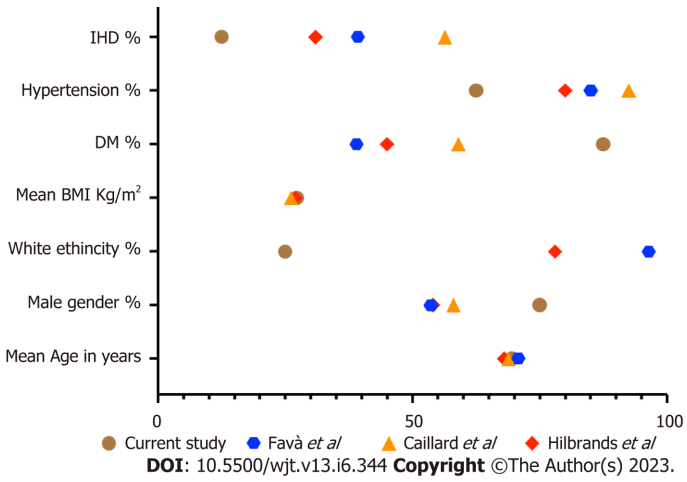


Figure 14 Comparison of current study demographics with published data. IHD: Ischemic heart disease; DM: Diabetes mellitus; BMI: Body mass index.

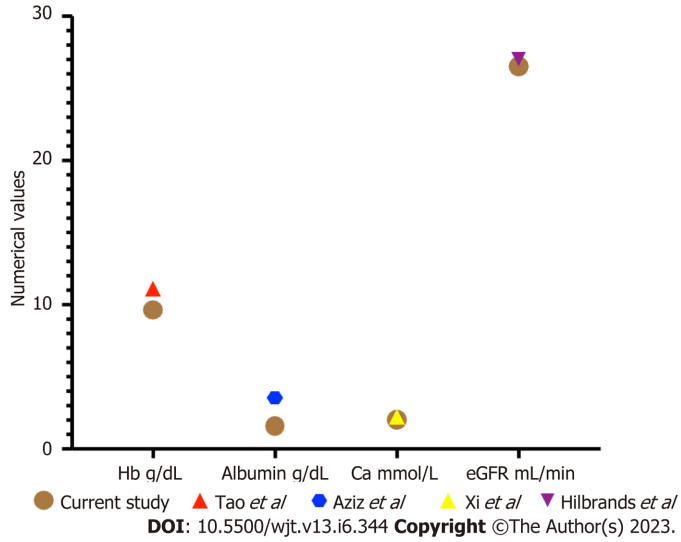


Figure 15 Comparison of current study routine lab parameters with published data. eGFR: Estimated glomerular filtration rate.

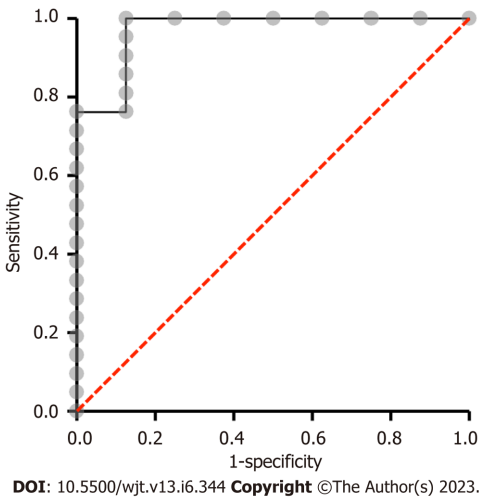


Figure 16 Multiple logistic regression: Mortality with Haemoglobin, Estimated glomerular filtration rate, Albumin and Ca.

ARTICLE HIGHLIGHTS

Research background

Various studies have been done to separately study routine laboratory markers to stratify patients with high risk of morbidity and mortality but very little is known in renal transplant patients.

Research motivation

This study provides a new way of looking at the significance of routine laboratory tests with an aim to risk stratify renal transplant recipients into high-risk sub-groups.

Research objectives

This study will help in shaping new policies and guidelines by providing individualized shielding advice, self-isolation guidance and booster coronavirus disease 2019 vaccination. Moreover, this will also help to plan better follow-up strategies for transplant patient. Addressing and correcting these parameters during a follow-up program can reduce the risk of morbidity and mortality in renal transplant recipients (RTxR).

Research methods

Retrospective observational study to analyze the data of our renal transplant follow-up program for various routine parameters and their impact of patient outcomes.

Research results

This study has identified some routinely used modifiable parameters in predicting a higher risk of mortality and morbidity.

Research conclusions

This knowledge can be used in RTxR follow-up programs by addressing these parameters early to help reduce the morbidity and mortality in RTxRs.

Research perspectives

This knowledge can be used in RTxR follow-up programs by addressing these parameters early to help reduce the morbidity and mortality in RTxRs.

FOOTNOTES

Author contributions: Ghazanfar A and Abbas M contributed to study design, data analysis, manuscript writing; Ghazanfar A and Hussain Md W contributed to data collection; Kayal M contributed to manuscript writing support.

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Informed consent statement: Online assessment confirmed that no patient consent or ethical approval from NHS HRA/REC was required.

Conflict-of-interest statement: Authors have no conflict of interest related to the content of this publication.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at email address a.ghazanfar@nhs.net.

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ORIGINAL ARTICLE

Observational Study

Outcomes of early hospital readmission after kidney transplantation: Perspectives from a Canadian transplant centre

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Abstract

BACKGROUND

Early hospital readmissions (EHRs) after kidney transplantation range in incidence from 18%-47% and are important and substantial healthcare quality indicators. EHR can adversely impact clinical outcomes such as graft function and patient mortality as well as healthcare costs. EHRs have been extensively studied in American healthcare systems, but these associations have not been explored within a Canadian setting. Due to significant differences in the delivery of healthcare and patient outcomes, results from American studies cannot be readily applicable to Canadian populations. A better understanding of EHR can facilitate improved discharge planning and long-term outpatient management post kidney transplant.

AIM

To explore the burden of EHR on kidney transplant recipients (KTRs) and the Canadian healthcare system in a large transplant centre.

METHODS

This single centre cohort study included 1564 KTRs recruited from January 1, 2009 to December 31, 2017, with a 1-year follow-up. We defined EHR as hospitalizations within 30 d or 90 d of transplant discharge, excluding elective procedures. Multivariable Cox and linear regression models were used to examine EHR, late hospital readmissions (defined as hospitalizations within 31-365 d for 30-d EHR and within 91-365 d for 90-d EHR), and outcomes including graft function and patient mortality.

RESULTS
In this study, 307 (22.4%) and 394 (29.6%) KTRs had 30-d and 90-d EHRs, respectively. Factors such as having previous cases of rejection, being transplanted in more recent years, having a longer duration of dialysis pretransplant, and having an expanded criteria donor were associated with EHR post-transplant. The cumulative probability of death censored graft failure, as well as total graft failure, was higher among the 90-d EHR group as compared to patients with no EHR. While multivariable models found no significant association between EHR and patient mortality, patients with EHR were at an increased risk of late hospital readmissions, poorer kidney function throughout the 1st year post-transplant, and higher hospital-based care costs within the 1st year of follow-up.

CONCLUSION
EHRs are associated with suboptimal outcomes after kidney transplant and increased financial burden on the healthcare system. The results warrant the need for effective strategies to reduce post-transplant EHR.

Key Words: Kidney; Transplantation; Early hospital readmissions; Incidence and trends; Post-transplant outcomes

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Core Tip: Early hospital readmissions post-transplant are associated with suboptimal patient outcomes and increased financial burden on the healthcare system. The 90-d window for defining early hospital readmissions, in addition to the frequently used 30-d period, provides a novel opportunity to evaluate the risks for kidney transplant recipients.

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INTRODUCTION

Kidney transplantation is widely accepted as the best treatment option for the majority of patients with end-stage renal disease[1]; however, it carries a risk of complications and subsequent hospital readmissions in the post-transplant period [2]. Early hospital readmissions (EHRs), commonly defined as any new hospitalization occurring within 30 d after initial transplant discharge, is an indicator of healthcare quality and an important outcome measure after transplantation[2,3]. In the United States, approximately 30% of kidney transplant recipients (KTRs) have EHR, with rates ranging from 18% to 47% between transplant centres[4,5]. More recently, a single-centre Brazilian study reported an EHR incidence of 27% among 1175 KTRs from 2011 to 2012[3], while a population-based Canadian study reported a cumulative EHR incidence of 21% among 5437 KTRs from 2002 to 2014[2].

The relatively high incidence of post-transplant EHR is concerning since EHRs have been associated with a severe reduction in health status and substantial healthcare costs. Several kidney transplant studies observed an increased risk of graft failure, patient mortality, and suboptimal graft function with EHR[6-10]. EHRs were also associated with more late hospital readmissions (LHRs), defined as subsequent readmissions within the 1st year of transplantation after the EHR time frame. Furthermore, EHRs had a mean cost of approximately 10000 USD per KTR, which can create a significant burden on healthcare delivery systems[2].

Factors that interfere with post-transplant recovery and increase the risk of EHR include patient demographics (*e.g.*, older age, African American race), pre-existing comorbidities (*e.g.*, obesity, diabetes, heart disease, chronic obstructive pulmonary disease), transplant characteristics (*e.g.*, expanded criteria donor transplants, lack of induction therapy, longer initial hospital stay, surgical complications), and frailty, a measure of physiologic reserve in aging populations[7,8,11-13]. Alternatively, EHR could potentially reflect deficits in discharge planning and outpatient management, calling for improvements in transplant care practices[8].

While EHRs have been studied extensively in American transplant settings, there is a paucity of EHR data collected in Canadian transplant populations. One Canadian study recently examined secular trends in post-transplant EHR incidence; however, it did not report on the impact of these findings on patients and healthcare delivery systems[2]. Due to significant differences in the delivery of healthcare services and patient outcomes between American and Canadian transplant centres[2], results from American studies cannot be readily extrapolated to Canadian populations[2].

The objectives of our study were to examine the impact of EHR on graft outcomes, patient mortality, LHR, and hospital costs in a Canadian transplant setting. We also considered how the impact on outcomes would change with an expanded EHR definition that included hospitalizations within 90-d of transplant discharge. With this information, we hoped to generate knowledge that may be useful in developing strategies to reduce post-transplant EHR.

MATERIALS AND METHODS

Design and setting

We conducted a single-centre observational cohort study at the University Health Network (UHN) in Toronto, Ontario. Approval was obtained from the institutional Research Ethics Board.

Population and sample

We included all adult (age ≥ 18 years) KTRs who received a kidney transplant from January 1, 2009 to December 31, 2017 (with follow-up until December 31, 2018) at the Toronto General Hospital, UHN. KTRs were excluded if they: (1) Were multiorgan transplant recipients; (2) Were transplanted at another transplant facility; (3) Experienced primary graft non-function; or (4) Experienced graft loss, death, or had their last follow-up before the study origin (*i.e.* 30 d after discharge from their transplant hospitalization).

Data collection

Patient data was obtained from electronic hospital health records in the Organ Transplant Tracking Record and subsequently stored in the in-centre research database, the Comprehensive Renal Transplant Information System (CoReTRIS)[14]. CoReTRIS consists of recipient, donor, transplant, treatment, and follow-up data for all KTRs at UHN since January 2000 and has been audited for completeness and accuracy. All participants provided informed written consent for their health record information to be stored, collected, and used in CoReTRIS.

Exposure and outcome classification and assessment

The main exposure of interest was EHR, defined as any hospitalization occurring within 30 d after discharge from the transplant hospitalization. We also examined an extended window of 90 d after discharge. The hospitalization must have been documented, either as an electronic summary in the Organ Transplant Tracking Record or as a paper discharge summary faxed from a non-UHN hospital. Hospitalization data was captured by a team of research assistants using a systematic review of medical records. Any discrepancies during data collection were later validated and resolved by a trained clinician.

The primary clinical outcome of interest was the composite of graft failure or death with graft function. Graft failure and death with graft function were also examined separately as our secondary outcomes. The time of origin for the analyses was defined as either 30 d or 90 d after transplant discharge. Therefore, we excluded KTRs who experienced death or graft failure or were lost to follow-up prior to this time. Other clinical outcomes included: (1) Graft function, which was measured using estimated glomerular filtration rate, calculated using the Chronic Kidney Disease Epidemiology Collaboration equation, at 6-mo and 1-year post-transplant; and (2) LHR, defined as any hospitalization occurring between 31 and 365 d for 30-d EHR or 91 to 365 d for 90-d EHR. The financial outcome of interest was the average cost of hospital-based care (inpatient and outpatient) per KTR over the 1st year of follow-up. This included all billed patient expenditures at each department of all hospitals that are part of UHN. Inpatient and outpatient cost data were provided by the UHN Accounting Centre and evaluated using a single-centre perspective.

Potential confounders

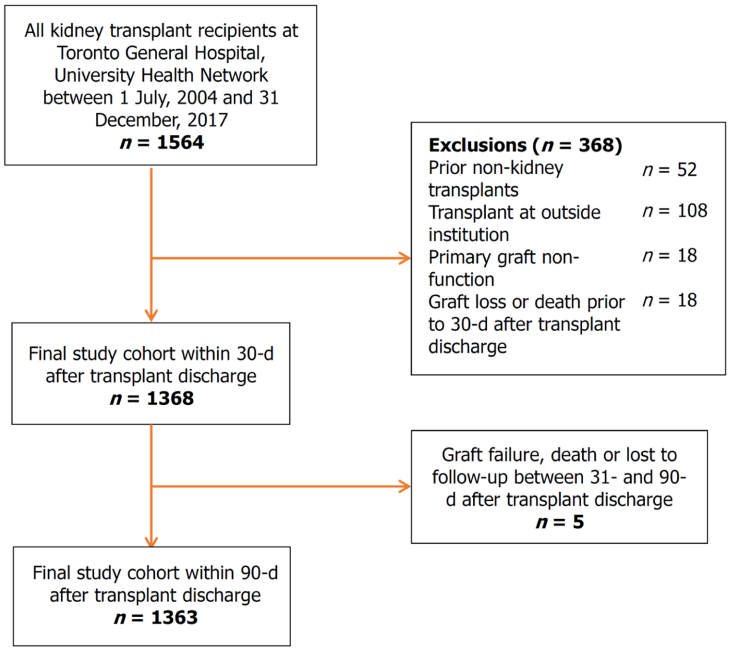
To assess the independent association between the exposure and outcomes, covariates were chosen based on the literature and clinical experience. Recipient factors (*i.e.* age, sex, race, body mass index at time of transplant discharge, smoking history, diabetes mellitus, chronic lung disease, cardiovascular disease, baseline estimated glomerular filtration rate, and time on dialysis), donor factors (*i.e.* donor age, body mass index at time of donation, donation type, and expanded-criteria status), and transplant factors (*i.e.* peak panel reactive antibody, delayed graft function, acute rejection within 30 d of discharge, and transplant era) were considered in multivariable analyses.

Statistical analysis

Categorical variables were described using frequencies and percentages. Continuous variables were described using mean ± standard deviation if normally distributed and median [interquartile range (IQR)] if skewed. Baseline characteristics were compared between patients who experienced EHR and patients who did not experience EHR, using the χ^2 test for categorical variables, the Student *t*-test for normally distributed continuous variables, and Wilcoxon rank-sum test for skewed continuous variables. The Kaplan-Meier product limit method was used to assess time from 30 d post-discharge to graft failure, death, or the composite by EHR status. Multivariable Cox proportional hazard models were used to estimate the independent association of EHR with graft failure, mortality, and LHR. Linear regression models were used to estimate the association between EHR and graft function during 1-year of post-transplant follow-up. Multiple imputation by chained equations method was used to address the degree of absence of all outcome variables[15]. Two-tailed *P* values < 0.05 were considered statistically significant. Data management and analyses were performed using Stata/MP 12.0 (StataCorp, College Station, TX, United States). Statistical review of the study was performed by a biomedical statistician (Li Y from Toronto General Hospital).

RESULTS

A total of 1564 KTRs were eligible for inclusion in the study cohort. Application of the prespecified exclusion criteria



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Figure 1 Study flow diagram.

resulted in a final study cohort of 1368 KTRs for 30-d EHR analyses (Figure 1). A final study cohort of 1333 KTRs was used for the 90-d EHR analyses, as 5 KTRs experienced death or graft failure or were lost to follow-up between 31-d and 90-d post-transplant. For the 30-d EHR analysis, the median follow-up time was 5.11 years (IQR: 3.16, 7.59), with 329 cases of graft failure, 145 cases of death, and 439 cases of LHR in the 1st year starting from 30 d after transplant discharge. For the 90-d EHR analysis, the median follow-up time was 5.05 years (IQR: 3.12, 7.52), with 324 cases of graft failure, 140 cases of death, and 368 cases of LHR in the 1st year starting from 90 d after transplant discharge.

Baseline recipient, donor, and transplant characteristics of both study cohorts are summarized in Table 1. The 30-d EHR study population was 60.0% male and 46.7% White. The 90-d EHR study population was 60.2% male and 47.4% White. A total of 307 (22.4%) and 394 (29.6%) KTRs experienced 30-d and 90-d EHRs, respectively. KTRs who experienced an EHR were more likely to have a longer duration of dialysis, an expanded donor criteria donor, and a previous case of biopsy-proven acute rejection and received transplantation between 2015-2017. Particularly, KTRs with 90-d EHR were older, more likely to have a history of diabetes, and more likely to have a previous case of rejection, spent a longer time on dialysis before transplant, had older donors, and received transplantation between 2015-2017. Other characteristics were similar between the EHR and non-EHR groups.

The 30-d EHR group did not have a higher cumulative probability of death-censored graft failure as compared to non-EHR KTR (Figure 2A); in contrast, the 90-d EHR group did show a greater probability of death-censored graft failure (log rank $P = 0.01$, Figure 2B). The 30-d and 90-d EHR groups had greater cumulative probabilities of LHR within 1 year (Log rank $P < 0.001$, Figure 2C and D) compared to the non-EHR group. The 30-d EHR group did not have a higher probability of death *vs* the non-EHR group (Figure 2E), whereas the 90-d EHR group displayed a higher probability of death (log rank $P = 0.02$, Figure 2F). Neither EHR group had a higher probability of the composite outcome of graft failure or death *vs* the non-EHR group (Figure 2G and H).

The 30-d and 90-d EHRs were independent predictors of LHR hazard ratio (HR): 1.73; 95% confidence interval (CI): 1.40, 2.13 for 30-d EHR and HR: 1.58; 95%CI: 1.27 to 1.97 for 90-d EHR (Table 2). Neither 30-d nor 90-d EHRs were associated with the other outcomes of interest in the multivariable Cox models. In multivariable linear regression models (Table 3), 30-d and 90-d EHRs were associated with lower graft function at 3 mo (HR: -2.60; 95%CI: -4.90 to -0.30) and 12 mo (HR: -3.11; 95%CI: -5.62 to -0.60) for 30-d EHR and lower function at 3 mo (HR: -3.08; 95%CI: -5.17 to -0.99), 9 mo (HR: -2.81; 95%CI: -5.24 to -0.39), and 12 mo (HR: -3.77; 95%CI: -6.15 to -1.38) for 90-d EHR.

The mean cost of hospital-based care per KTR in the 1st year post-transplant is shown in Figure 3. In the first 3 mo, the mean cost of care for KTR with an EHR was nearly three times higher than for those without EHR (Figure 3A). After 3 mo, the mean cost of care for the EHR group declined to levels comparable to the non-EHR group, with an exception at month 7. Similarly, the mean number of readmissions for the EHR group decreased after the first 3 mo post-transplant, though the EHR group had more readmissions than the non-EHR group overall (Supplementary Figure 1). When the cost of hospital-based care was examined cumulatively, the mean post-transplant cost was consistently higher for the EHR group than the non-EHR group (Figure 3B).

Table 1 Baseline recipient, donor, and transplant characteristics by early hospital readmission status

Variables	EHR within 30 d after transplant discharge				EHR within 90 d after transplant discharge			
	Number of patients, *n* = 1368	Yes, *n* = 307	No, *n* = 1061	*P* value	Number of patients, *n* = 1333	Yes, *n* = 394	No, *n* = 939	*P* value
Recipient characteristics								
Recipient age at transplant in yr, mean (± SD)	1368	52.4 (13.4)	51.4 (13.6)	0.26	1333	52.7 (13.4)	51.1 (13.6)	0.05
Recipient sex								
Male	821	185 (60.3%)	636 (59.9%)	0.92	802	235 (59.6%)	567 (60.4%)	0.80
Female	547	122 (39.7%)	425 (40.1%)		531	159 (40.4%)	372 (39.6%)	
Recipient race								
White	639	134 (56.3%)	505 (59.1%)	0.44	632	176 (57.1%)	456 (59.1%)	0.56
Non-white	454	104 (43.7%)	350 (40.9%)		448	132 (42.9%)	316 (40.9%)	
History of smoking								
Smoker	584	137 (44.8%)	447 (42.3%)	0.42	569	174 (44.5%)	395 (42.1%)	0.42
Non-smoker	780	169 (55.2%)	611 (57.8%)		760	217 (55.5%)	543 (57.9%)	
History of diabetes mellitus	467	111 (36.2%)	356 (33.6%)	0.40	455	151 (38.3%)	304 (32.4%)	0.04
History of chronic lung disease	57	14 (4.6%)	43 (4.1%)	0.70	56	21 (5.3%)	35 (3.7%)	0.19
History of cardiovascular disease	377	82 (26.7%)	295 (27.8%)	0.70	368	118 (30.0%)	250 (26.7%)	0.22
Recipient body mass index at transplant discharge in kg/m^2, mean (± SD)	1074	27.2 (6.0)	26.9 (5.9)	0.49	1333	52.7 (13.4)	51.1 (13.6)	0.05
Recipient eGFR at baseline in mL/min, mean (± SD)	1085	62.7 (26.5)	63.0 (28.0)	0.88	1072	60.7 (27.0)	64.0 (27.7)	0.08
Time on dialysis in yr, mean (± IQR)	1368	3.4 (1.2, 5.6)	3.2 (1.2, 5.3)	0.46	1333	3.5 (1.6, 5.8)	3.1 (1.1, 5.3)	0.02
Donor characteristics								
Donor age at donation in yr, mean (± SD)	1359	48.9 (14.2)	47.3 (15.0)	0.10	1325	49.3 (14.4)	47.0 (14.9)	0.01
Donor body mass index in kg/m^2, (mean ± SD)	1339	26.9 (5.6)	26.7 (5.4)	0.56	1305	26.7 (5.4)	26.8 (5.4)	0.70
Type of donation								
Deceased	766	178 (58.0%)	588 (55.4%)	0.43	742	234 (59.4%)	508 (54.1%)	0.08
Living	602	129 (42.0%)	473 (44.6%)		591	160 (40.6%)	431 (45.9%)	
Expanded criteria donor	256	70 (22.8%)	186 (17.5%)	0.04	249	94 (23.9%)	155 (16.5%)	0.002
Transplant characteristics								
Peak PRA								
0%	709	161 (52.6%)	548 (51.7%)	0.78	686	211 (53.7%)	475 (50.6%)	0.31
> 0%	657	145	512		645	182	463	

		(47.4%)	(48.3%)			(46.3%)	(49.4%)	
Delayed graft function	276	57 (18.6%)	219 (20.6%)	0.43	265	79 (20.1%)	186 (19.8%)	0.92
Biopsy-proven acute rejection	85	46 (15.0%)	39 (3.7%)	< 0.001	98	59 (15.0%)	39 (4.2%)	< 0.001
Transplant era								
2009-2011	429	94 (30.6%)	335 (31.6%)	0.002	429	131 (33.3%)	298 (31.7%)	< 0.001
2012-2014	431	75 (24.4%)	356 (33.6%)		430	96 (24.4%)	334 (35.6%)	
2015-2017	508	138 (45.0%)	370 (34.9%)		474	167 (42.4%)	307 (32.7%)	

Mean and median values were reported with standard deviation and interquartile range, respectively. IQR: Interquartile range; eGFR: Estimated glomerular filtration rate; EHR: Early hospital readmissions; PRA: Panel reactive antibody; SD: Standard deviation.

Table 2 Association of early hospital readmission with graft failure or death, graft failure, death, and late hospital admissions (within 1 yr after the first 30 d or 90 d post-transplant discharge)

Outcome	30-d EHR			90-d EHR		
	Number of outcomes	Full model[1]		Number of outcomes	Full model[1]	
		HR (95%CI)	*P* value		HR (95%CI)	*P* value
Graft failure or death	237	1.06 (0.77-1.45)	0.73	232	1.21 (0.91-1.61)	0.19
Graft failure	92	1.05 (0.62-1.77)	0.86	92	1.45 (0.92-2.29)	0.11
Death	145	1.08 (0.73-1.60)	0.71	140	1.09 (0.75-1.57)	0.66
LHR	439	1.73 (1.40-2.13)	< 0.001	368	1.58 (1.27-1.97)	< 0.001

[1]This Cox proportional hazard model for the association of 30-d early hospital readmissions on outcomes included early hospital readmission status, recipient characteristics (age, sex, race, body mass index at transplant discharge, history of smoking, diabetes, chronic lung disease and cardiovascular disease, estimated glomerular filtration rate at baseline, and time on dialysis), donor characteristics (age, body mass index at time of donation, donation type, and expanded-criteria status), and transplant characteristics (peak panel reactive antibodies, delayed graft function, acute rejection within 30 d of discharge, and transplant era). CI: Confidence interval; EHRs: Early hospital readmissions; HR: Hazard ratio; LHRs: Late hospital readmissions.

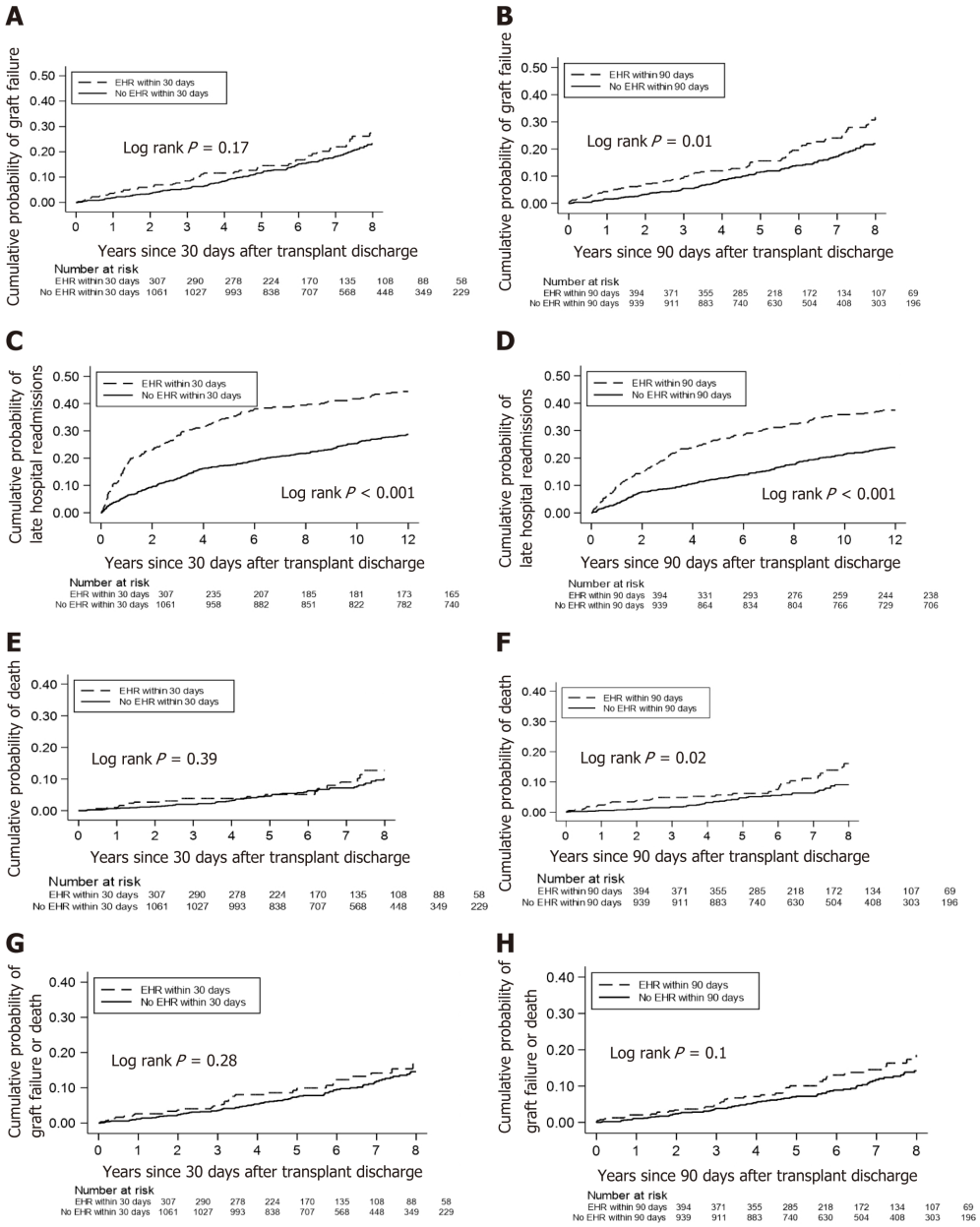
Table 3 Association of early hospital readmission with estimated glomerular filtration rate at 6-mo and 12-mo after transplant discharge

Outcomes	30-d HER, Full model[1]		90-d HER, Full model[1]	
	Coefficient (95%CI)	*P* value	Coefficient (95%CI)	*P* value
eGFR at 6 mo after transplant discharge	-1.38 (-3.87 to 1.12)	0.28	-2.18 (-4.40 to -0.03)	0.054
eGFR at 12 mo after transplant discharge	-3.11 (-5.62 to -0.60)	0.02	-3.77 (-6.15 to -1.38)	0.002

[1]The linear regression model for the association of 30-d early hospital readmissions on estimated glomerular filtration rate included early hospital readmissions status, recipient characteristics (age, sex, race, body mass index at transplant discharge, history of smoking, diabetes, chronic lung disease and cardiovascular disease, estimated glomerular filtration rate at baseline, and time on dialysis), donor characteristics (age, body mass index at time of donation, donation type, and expanded-criteria status), and transplant characteristics (peak panel reactive antibody, delayed graft function, acute rejection within 30 d of discharge, and transplant era). CI: Confidence interval; eGFR: Estimated glomerular filtration rate; EHR: Early hospital readmissions.

DISCUSSION

In our patient cohort, the incidence of 30-d and 90-d EHRs was 22.4% and 29.5%, respectively. The 30-d EHR incidence was lower than those reported in the American studies by Luan *et al*[8] (36%) and McAdams-DeMarco *et al*[9] (31%). This may be related to differences in the study population as well as specific threshold and institutional criteria for admitting KTRs rather than outpatient care. Our results were comparable with the 30-d EHR incidence of 21% that was reported in a recent population-based Canadian study[2]. However, Naylor *et al*[2] found that 30-d EHR rates can vary even across different transplant centres within the province of Ontario, ranging from 16% to 27%.

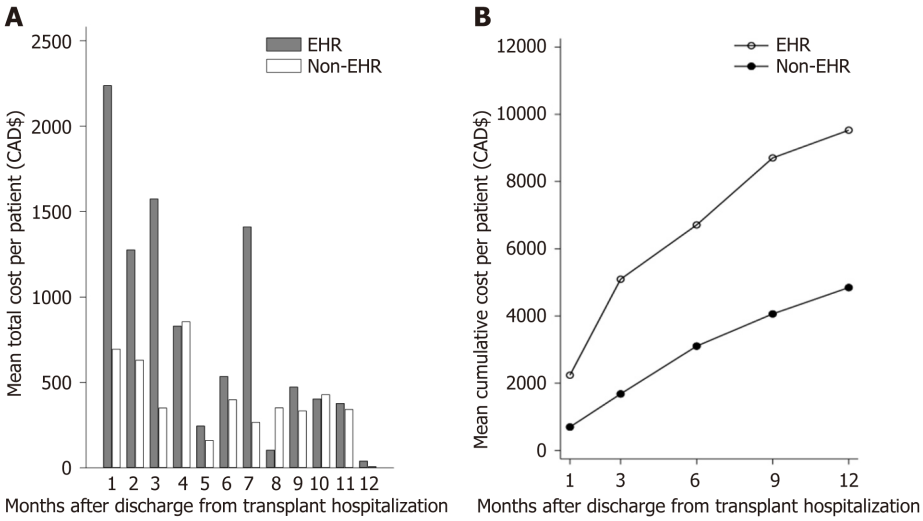


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Figure 2 Cumulative probability of clinical outcomes, separated by early hospital readmission status, over 5 years of follow up. A: Graft failure for 30-d early hospital readmission (EHR) group; B: Graft failure for 90-d EHR; C: Late hospital readmissions for 30-d EHR; D: Late hospital readmissions for 90-d EHR: E: Death for 30-d EHR; F: Death for 90-d EHR; G: Composite of graft failure and death for 30-d EHR; H: Composite of graft failure and death for 90-d EHR.

After accounting for potential confounders, 30-d and 90-d EHRs were shown to be an independent predictor of LHR at 1-year post-transplant and poorer graft function. Our results corroborated recent observational studies that associated EHR with negative clinical outcomes among KTRs and other high-risk patient populations[7,16-19,20]. More specifically, Luan *et al*[8] and McAdams-DeMarco *et al*[9] also demonstrated that EHRs are associated with a higher risk of LHR and graft failure in KTRs. However, contrary to these studies, we did not find a statistically significant association between EHR and patient mortality. Additionally, while most studies focused on the impact of 30-d EHR[9,21], we expanded our EHR definition and were able to demonstrate that hospitalizations occurring within the first 3 mo after transplantation discharge are also associated with rehospitalizations up to 1 year post-transplant.

The relationship between EHR and inferior patient outcomes can be explained in several ways. Post-transplant conditions or complications that necessitate EHR could directly result in clinical events like graft failure or frequent hospital readmissions[8]. Alternately, KTRs with EHR may already possess pre-existing medical comorbidities (*e.g.*, diabetes mellitus, cardiovascular disease) that increase the likelihood of adverse clinical events after transplantation. In our study, the patients in the EHR group were more likely to have an expanded criteria donor and a history of acute rejection, which have been previously linked with mortality, graft failure, and hospitalizations after kidney transplant[5,22]. EHRs are also associated with frailty, which is a marker of suboptimal transplant outcomes[12,23-26]. This factor may become increasingly important over time with an aging and subsequently a KTR population with more comorbidities[7].



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Figure 3 Costs of hospital-based care per kidney transplant recipient over 1-year after transplant discharge. A: Mean cost of hospital-based care per kidney transplant recipient per month; B: Cumulative cost of hospital-based care over 1-year after transplant discharge. EHR: Early hospital admission.

Moreover, patients transplanted in the more recent era (2015-2017) were more likely to have EHRs as compared to earlier transplant years. The transplant program at our centre has been expanding its pool of patients among both recipients and donors in more recent years to include more medically complicated patients such as expanded criteria donors.

EHR not only affects patient outcomes but is detrimental from a financial perspective. We observed that, on average, twice as much money was spent on EHR patients as compared to non-EHR patients. Hospital readmissions increase the financial burden on the healthcare system, costing 1.8 billion CAD annually (11% of annual inpatient costs)[27]. Moreover, the average cost of a second hospitalization is often greater than the first[27], which is particularly relevant to our finding that EHR increase the risk of LHR. Our analysis only focused on costs at a single transplant centre, thus the financial consequence might have been more significant if expenditure at other tertiary care centres and community-based hospitals were also taken into consideration.

Due to the risks and costs associated with EHR, there is considerable interest in clinical monitoring and prevention of EHR. However, despite the growing evidence in the literature, there are no specific clinical practice guidelines to manage and monitor KTRs with EHR. After transplant discharge, KTRs at the UHN Kidney Transplant Program are followed weekly for the 1st month, biweekly from months 2 to 3, monthly from months 4 to 6, bimonthly from months 7 to 12, every 3 to 4 mo from 13 to 24 mo, and then every 6 to 12 mo beyond 24 mo[28]. Like many other centres, a number of KTRs with stable kidney function from the UHN program are transferred from the hospital-based transplant unit to community-based general nephrology centres within the 1st year post-transplant. Thus, although there are standard practices in place for KTR management in general, there are no standardized strategies that are tailored specifically for those KTRs at risk of EHR.

KTRs who are at increased risk of EHR may benefit from multifaceted interventions that include: (1) Better educational strategies to improve medication knowledge and support capacity for self-care; (2) Collaborative care provided by transplant and general nephrologists; and (3) More frequent follow-up visits for an extended period of time[2,9,29]. Further investigation of these interventions would be required to determine the feasibility and efficiency of reducing EHR in KTRs. Previous studies have suggested that up to half of hospital readmissions for KTRs are preventable and can be reduced by early intervention[30]. Exploring the characteristics of KTRs with preventable EHR can inform the development and evaluation of prediction tools, which will aid clinicians in identifying high-risk patients[31].

With this study, we were able to extend the previous work on EHR and long-term outcomes of KTRs to a Canadian healthcare context. Our methodology involved a standardized and comprehensive collection of patient and hospitalization data for a relatively large study population of over 1000 KTRs[14]. Moreover, we benefited from exploring the use of 90-d EHR (in addition to the previously used 30-d EHR definition) for the assessment of outcomes. Nevertheless, some limitations to our study also warrant discussion. First, the generalizability of our findings may be limited by the single-centre study design. Second, this study was based on observational data. Therefore, we cannot confirm that changes in EHR would improve long-term outcomes. Third, non-UHN readmissions may have been missed since we relied on UHN clinical notes to determine readmissions within the 1st year. However, it is unlikely that many events were missed since patients are instructed to contact the transplant centre if they are admitted to any facilities outside of UHN, and hospitalization events are checked with each patient at every clinic visit. Finally, while patient and hospitalization data could be verified with patient charts and electronic records, our cost data was solely obtained from the UHN financial services and was difficult to verify independently. However, these cost data are used for hospital planning and budgeting and were sufficient for their intended purpose in our study.

CONCLUSION

In summary, EHR after kidney transplantation was associated with a greater risk of LHR at 1-year post-transplant, suboptimal kidney function, and higher hospital-based care costs. The 90-d window after discharge from transplant hospitalization, in addition to the frequently used 30-d post-transplant period, marks a novel opportunity to evaluate the risks for KTRs. Further studies are required to determine which EHRs are preventable and implement reliable tools that can reduce EHR after kidney transplantation.

ARTICLE HIGHLIGHTS

Research background

Early hospital readmissions (EHRs) post-kidney transplantation adversely impact clinical outcomes such as graft function and patient mortality as well as healthcare costs. A better understanding of EHR can facilitate improved discharge planning and long-term outpatient management post kidney transplant.

Research motivation

Associations between EHR and suboptimal clinical outcomes post kidney transplant have not been extensively studied in a Canadian healthcare setting. We sought to explore the burden of EHR on kidney transplant recipients (KTRs) and the Canadian healthcare system in a large transplant centre.

Research objectives

The objectives of our study were to examine the impact of EHR on graft outcomes, patient mortality, late hospital readmissions (LHRs), and hospital costs in a Canadian transplant setting.

Research methods

This was a single centre cohort study of 1564 KTRs transplanted between 2009-2017. Analyses were separated by patients with no EHRs, patients with EHRs within 30 d of transplant, and those with EHRs within 90 d of transplant. Multivariable Cox and linear regression models were used to examine EHR, LHR, and outcomes including graft function and patient mortality.

Research results

EHRs post kidney transplant were associated with subsequent LHRs, suboptimal kidney function, and a higher burden on the healthcare system.

Research conclusions

EHRs post kidney transplant are associated with suboptimal patient outcomes and higher burdens on the healthcare system. Expanding the window of readmissions to 90 d post-transplant revealed an important target for reducing the risk of suboptimal outcomes.

Research perspectives

A better understanding of EHR can contribute to the development of prediction tools to identify those KTRs at risk of EHR and thus a standardized approach to manage and target these patients.

FOOTNOTES

Author contributions: Famure O and Kim SJ formulated the research question; Famure O, Kim ED, Huang J, Zyla R, Au M, Chen PX, Sultan H, Ashwin M, and Kim SJ designed the study; Kim ED, Huang J, Zyla R, Au M, Chen PX, Sultan H, Ashwin M, and Minkovich M performed the research; Li Y analysed the data; Famure O, Kim ED, Li Y, Huang J, Zyla R, Au M, Chen PX, Sultan H, Ashwin M, Minkovich M, and Kim SJ interpreted the data; Famure O, Kim ED, Huang J, Zyla R, Au M, Chen PX, Sultan H, Ashwin M, Minkovich M, and Kim SJ wrote the paper.

Institutional review board statement: The study was reviewed and approved by the University Health Network Institutional Review Board.

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at michelleminkovich@gmail.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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ORIGINAL ARTICLE

Prospective Study

Dosing strategies for *de novo* once-daily extended release tacrolimus in kidney transplant recipients based on *CYP3A5* genotype

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Abstract

BACKGROUND

Tacrolimus extended-release tablets have been Food and Drug Administration-approved for use in the *de novo* kidney transplant population. Dosing requirements often vary for tacrolimus based on several factors including variation in metabolism based on *CYP3A5* expression. Patients who express *CYP3A5* often require higher dosing of immediate-release tacrolimus, but this has not been established for tacrolimus extended-release tablets in the *de novo* setting.

AIM

To obtain target trough concentrations of extended-release tacrolimus in *de novo* kidney transplant recipients according to *CYP3A5* genotype.

METHODS

Single-arm, prospective, single-center, open-label, observational study (Clinical-

Trials.gov: NCT037-13645). Life cycle pharma tacrolimus (LCPT) orally once daily at a starting dose of 0.13 mg/kg/day based on actual body weight. If weight is more than 120% of ideal body weight, an adjusted body weight was used. LCPT dose was adjusted to maintain tacrolimus trough concentrations of 8-10 ng/mL. Pharmacogenetic analysis of *CYP3A5* genotype was performed at study conclusion.

RESULTS

Mean time to therapeutic tacrolimus trough concentration was longer in *CYP3A5* intermediate and extensive metabolizers *vs* *CYP3A5* non-expressers (6 d *vs* 13.5 d *vs* 4.5 d; $P = 0.025$). Mean tacrolimus doses and weight-based doses to achieve therapeutic concentration were higher in *CYP3A5* intermediate and extensive metabolizers *vs* *CYP3A5* non-expressers (16 mg *vs* 16 mg *vs* 12 mg; $P = 0.010$) (0.20 mg/kg *vs* 0.19 mg/kg *vs* 0.13 mg/kg; $P = 0.018$). *CYP3A5* extensive metabolizers experienced lower mean tacrolimus trough concentrations throughout the study period compared to *CYP3A5* intermediate metabolizers and non-expressers (7.98 ng/mL *vs* 9.18 ng/mL *vs* 10.78 ng/mL; $P = 0$ 0.008). No differences were identified with regards to kidney graft function at 30-d post-transplant. Serious adverse events were reported for 13 (36%) patients.

CONCLUSION

Expression of *CYP3A5* leads to higher starting doses and incremental dosage titration of extended-release tacrolimus to achieve target trough concentrations. We suggest a higher starting dose of 0.2 mg/kg/d for *CYP3A5* expressers.

Key Words: Immunosuppression; Kidney transplant; Dosing; Tacrolimus; Therapeutic drug monitoring; Genotype

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Core Tip: In this single-arm, prospective, observational study we study once-daily, extended release tacrolimus dosing. Here we find that the expression of the cyctrochrome P450 enzyme, *CYP3A5*, is an important clinical factor to determine optimal dosage requirements after kidney transplantation. In kidney transplant recipients who express *CYP3A5* activity, higher doses of extended-release tacrolimus are required to attain therapeutic trough concentrations. Delays in achieving therapeutic trough concentrations has been linked to increase rates of acute rejection which highlights the importance of this research in identifying dosing considerations for extended-release tacrolimus in the *de novo* kidney transplant setting.

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INTRODUCTION

Outcomes after kidney transplantation have been significantly improved with advances in immunosuppressive therapies. Tacrolimus is currently marketed in various formulations that have proven to be highly effective in preventing acute rejection after kidney transplantation[1-3]. Compared to immediate release tacrolimus, once daily extended-release formulations have demonstrated similar efficacy and safety in the *de novo* kidney transplant setting leading to increased utilization[1,2,4,5]. Life cycle pharma tacrolimus (LCPT) (Envarsus®; Veloxis Pharmaceuticals) was designed to enhance the bioavailability of tacrolimus[6]. In published studies, utilization of LCPT has been shown to provide rapid achievement of target trough concentrations following kidney transplantation[1,2,7]. In addition, a once daily LCPT dosing regimen results in lower peak concentrations with equivalent overall exposure compared to immediate-release and other extended-release tacrolimus formulations[3]. Similar efficacy and safety profiles have been demonstrated when comparing LCPT to other available tacrolimus formulations[1-3,7,8].

The use of LCPT has been Food and Drug Administration (FDA)-approved for the prophylaxis of organ rejection in *de novo* kidney transplant patients and in kidney transplant patients converted from tacrolimus immediate-release formulations[6]. The recommended FDA-approved dosing for *de novo* kidney transplant recipients is 0.14 mg/kg/d, however various starting doses have been evaluated in clinical trials[1,2,6]. Some kidney transplant recipients are known to metabolize tacrolimus at a higher or lower rate due to the presence of genetic polymorphisms that affect its metabolism [9]. The metabolism of LCPT occurs primarily within the cytochrome P450 (CYP) system, of which approximately 55 different genes have been identified in the human genome[10]. A multitude of CYP enzymes exist, including *CYP3A5* which is known to be an integral component of tacrolimus metabolism. In addition, genetic variation affecting *CYP3A5* function is known to impact overall tacrolimus exposure as well as dosing requirements to attain therapeutic concentrations[11,12]. The most common genetic variants (*CYP3A5**3* and *CYP3A5**6*) of *CYP3A5* in the general population

produce non-functional versions of the enzyme[13,14]. On the other hand, the presence of at least one *CYP3A5*1* allele would confer activity to *CYP3A5* (commonly known as an expresser) which has been shown to lead to higher dosage requirements of tacrolimus to attain therapeutic concentrations[9]. Previous data has illustrated that *CYP3A5* expressers can require up to 2-fold higher tacrolimus doses to achieve similar trough concentrations compared to *CYP3A5* non-expressers[15]. *CYP3A5* genetic variation may also lead to delays in time to achievement of target trough concentrations, which has been linked to higher rates of acute rejection. Furthermore, knowledge of *CYP3A5* genetic variants in transplant patients may lead to prevention of subtherapeutic and supratherapeutic concentrations in the early post-transplant period potentially lowering the risks of acute rejection and drug toxicities[16,17].

The primary objective of this study was to identify the time to therapeutic trough concentration of *de novo* once-daily LCPT in kidney transplant recipients according to *CYP3A5* expresser status. Secondary objectives include the description of the distribution of common *CYP3A5* variants in our population and to identify the dose required (total and weight-based) to obtain target trough concentrations according to expresser status.

MATERIALS AND METHODS

Study design and patient population

We conducted a single-arm, prospective, open-label, single-center, observational study (ClinicalTrials.gov: NCT03-713645). Adult *de novo* recipients of a living or deceased donor kidney transplant capable of providing consent from November 15, 2018 to April 23, 2021 were consented for inclusion in the study. Patients who were scheduled for multiple organ transplants at enrollment, non-English speaking, pregnant, or diagnosed with moderate to severe hepatic impairment (Child Pugh > 10 or bilirubin > 2 mg/dL) were excluded from the study. In addition, patients who had existing contraindications to tacrolimus-based products including hypersensitivity to tacrolimus or any other component of the formulation or who were receiving concomitant medications known to have strong drug-drug interaction potential with tacrolimus were excluded from the study. The post-transplant observation period was 30 d.

Intervention

All patients received LCPT tablets orally once daily at a starting dose of 0.13 mg/kg/day based on actual body weight. If a patient weighed more than 120% of their ideal body weight, an adjusted body weight was calculated for initial drug dosing[18]. All doses were rounded to the nearest 1 mg increment and adjusted to maintain a tacrolimus trough concentration of 8-10 ng/mL for the first 30 d after kidney transplant. No dose adjustments were performed during the first 48 h after the initial dose or subsequent dose adjustments to allow steady state concentrations to be achieved. All patients received additional immunosuppression with antithymocyte globulin (Thymoglobulin®; Sanofi Pharmaceuticals) or basiliximab (Simulect®; Novartis Pharmaceuticals) induction and mycophenolate sodium 720 mg by mouth every 12 h. Antithymocyte globulin dosing ranged between 4-6 mg/kg based on immunologic risk and was dosed by actual body weight unless the patient was greater than 120% of their ideal body weight, for which an adjusted body weight was utilized. Adjustments to mycophenolate sodium dosing was at the discretion of the treating physician, based on adverse effects, lab abnormalities, and other clinical considerations. All patients received daily pulse-dose methylprednisolone for 5 d according to institutional protocol. Prednisone maintenance immunosuppression was utilized in some recipients based on immunologic risk and the presence of an automimmune kidney disease at the time of kidney transplant. Patients requiring prednisone received a maintenance dose of prednisone 5-10 mg by mouth daily.

CYP3A5 genotype sample collection and analysis

Two buccal swab samples were collected from each patient using DNA/RNA Shield™ collection tubes (Zymo Research Corporation). The samples were stored frozen at -20 °C until obtaining samples from all patients included in the study. The DNA extraction was performed with NucleoMag® DNA Swab extraction kit (Takara Bio Inc.) following the manufacturer's recommendations. A Tecan Spark Plate Reader was used to determine the DNA concentration using the NanoQuant Plate™. The DNA concentration was normalized at 5 ng/L for all the samples with molecular biology grade water for real-time PCR analysis.

We processed all the patient's DNA samples on the same day for DNA genotyping. We performed DNA single nucleotide polymorphism (SNP) analysis of these CYP3A5 variants: *CYP3A5*3* (rs776746), *CYP3A5*6* (rs10264272), and *CYP3A5*7* (rs41303343). We used three TaqMan™ probes for variant detection *via* real-time PCR (Catalog ID 4362691, 4362691, 4362691) following the manufacturer's recommendations (Thermo Fisher Scientific). As positive controls, we used nine commercially available DNA samples containing all possible combinations of the *CYP3A5* variants analyzed in this study. The positive control samples were obtained from the Coriell Institute with the following catalog numbers: *CYP3A5 *1*1* (HG01190), **1*3* (NA07000), **1*6* (NA19226) **1*7* (NA19035), **3*3* (NA17660), **3*6* (NA18855), **3*7* (NA19207), **6*7* (NA19143), **7*7* (NA19920). The real-time PCR assay was performed at the Genetics Core Facility of the University of Arizona. The variant detection data analysis was done single-blinded to corroborate the correct identification of the control samples' genotypes. Upon receipt of *CYP3A5* genotype results, patients were then classified by *CYP3A5* phenotype as a *CYP3A5* non-expresser (individual carries two non-functional alleles), *CYP3A5* intermediate metabolizer (individual carrying one functional allele and one non-functional allele), or *CYP3A5* extensive metabolizer (individual carrying two functional alleles)[19].

Clinical and safety endpoints

The primary efficacy endpoint was the time to therapeutic tacrolimus trough concentration during the first 30 d after kidney transplantation. Therapeutic tacrolimus trough concentration was defined as tacrolimus trough concentration 8 ng/mL. Secondary efficacy endpoints included the tacrolimus dose and weight-based tacrolimus dose required to achieve an initial therapeutic trough concentration. Safety outcomes measured included incidence of hyperkalemia (serum potassium > 5.5 mEq/L) and incidence of tremor. Tremor was assessed utilizing the quality of life in essential tremor (QUEST) questionnaire and was completed at 30 d post-kidney transplant[20]. Incidence of serious adverse events (SAEs) and drug discontinuation due to adverse events (AEs) were also reported.

Statistical methods and analysis

Descriptive statistics were used to characterize the baseline demographics of the entire cohort (intent to treat population). Continuous parametric data are presented as mean ± SD while continuous non-parametric data are presented as median (25%-75% interquartile range). Analysis of outcomes according to *CYP3A5* expresser status within the modified intent-to-treat (ITT) population were completed using the Kruskal-Wallis or ANOVA test for continuous data and the chi-squared test for categorical data. Tests were corrected for multiple comparisons as necessary utilizing the Bonferroni method. All tests were two-tailed, and $P < 0.05$ was used to represent statistical significance. Time to therapeutic tacrolimus trough concentration was analyzed using a Kaplan-Meier time-to-event analysis. All analyses were performed using SPSS, version 26 for windows (Armonk, NY; IBM Inc.).

RESULTS

A total of 36 patients (ITT population) were enrolled and 35 patients completed the entire 30-d treatment period. One patient withdrew prior to the end of the study time period due to neurologic toxicity and tremors. Patients who were able to complete genotype testing were included in the final analysis [$n = 34$; modified ITT (mITT) population]. All 34 patients were included in the mITT analysis and patients were stratified based on *CYP3A5* phenotype. Of the 34 total patients, 15 (44.1%) were found to be non-expressers of *CYP3A5*, while 13 (38.2%) and 6 (17.6%) were found to be intermediate and extensive metabolizers, respectively. The population was predominantly black (66.7%), male (55.6%), and recipients of a deceased donor kidney transplant (69.4%) with a mean age of 55.5 years (Table 1). Baseline characteristics were similar between groups except for a higher percentage of black patients (92.3% *vs* 83.3% *vs* 46.7%; $P = 0.026$) in the CYP3A5 intermediate and extensive metabolizer groups compared to *CYP3A5* non-expressers (Table 2).

Mean time to therapeutic tacrolimus trough concentration was longer in *CYP3A5* intermediate and extensive metabolizers compared to *CYP3A5* non-expressers ($P = 0.025$). A Kaplan Meier analysis demonstrated that the highest incidence of patients not achieving therapeutic tacrolimus trough concentration by 7 d post-transplant were *CYP3A5* extensive metabolizers followed by *CYP3A5* intermediate metabolizers. Only 13.3% of *CYP3A5* non-expressers failed to achieve a therapeutic tacrolimus trough by 7 d post-transplant compared to approximately 30.8% of *CYP3A5* intermediate metabolizers and 83.3% of *CYP3A5* extensive metabolizers (Figure 1). Mean tacrolimus doses to achieve therapeutic concentration were higher in *CYP3A5* intermediate and extensive metabolizers compared to *CYP3A5* non-expressers (16 mg *vs* 16 mg *vs* 12 mg; $P = 0.010$). Mean weight-based tacrolimus doses to achieve therapeutic tacrolimus trough concentrations were also higher in *CYP3A5* intermediate and extensive metabolizers compared to *CYP3A5* non-expressers (0.20 mg/kg *vs* 0.19 mg/kg *vs* 0.13 mg/kg; $P = 0.018$) (Table 3).

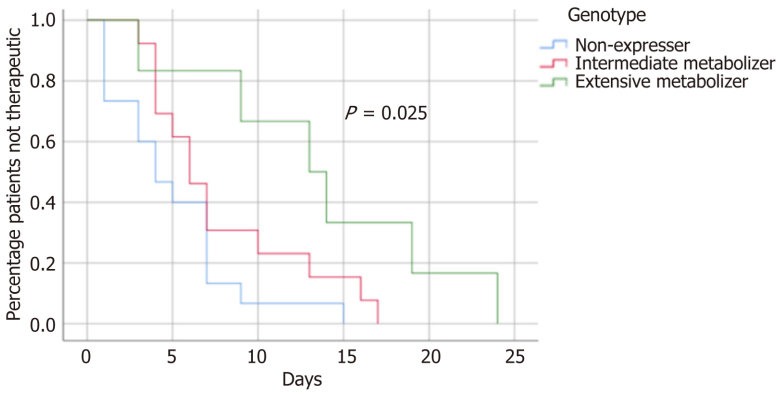
Mean daily tacrolimus dose, daily weight-based tacrolimus dose, and tacrolimus trough concentrations throughout the 30-d study period were compared amongst the three groups. A higher mean daily tacrolimus dose was seen in *CYP3A5* intermediate and extensive metabolizers compared to poor metabolizers (12.5 mg *vs* 13.8 mg *vs* 9.6 mg; $P = 0.011$). While not statistically significant, a higher daily weight-based tacrolimus dose was seen in *CYP3A5* intermediate and extensive metabolizers compared to *CYP3A5* non-expressers (0.136 mg/kg *vs* 0.176 mg/kg *vs* 0.128 mg/kg; $P = 0.074$). *CYP3A5* extensive metabolizers experienced lower mean tacrolimus trough concentrations throughout the study period compared to *CYP3A5* intermediate metabolizers and non-expressers (7.98 ng/mL *vs* 9.18 ng/mL *vs* 10.78 ng/mL; $P = 0.008$). No statistically significant differences in kidney graft function at 30-d post-transplant were observed between *CYP3A5* extensive metabolizers, intermediate metabolizers, and non-expressers measured by mean serum creatinine (1.94 mg/dL *vs* 1.76 mg/dL *vs* 1.76 mg/dL; $P = 0.906$) and mean estimated glomerular filtration rate (31.5 mL/min/1.73 m^2 *vs* 46 mL/min/1.73 m^2 *vs* 40 mL/min/1.73 m^2; $P = 0.701$) (Table 3).

Safety endpoints were evaluated as part of the ITT analysis. SAEs were reported for 13 (36%) patients with 1 SAE (2.8%) attributed to study drug. The one patient who experienced a SAE attributed to study drug resulted in neurotoxicity which led to study drug discontinuation. Assessment of tremor using the QUEST questionnaire revealed that the majority of patients experienced no significant impact of tremor on their quality of life. A further description of patient responses to the QUEST questionnaire are summarized in Figure 2. A total of 11 (31%) patients enrolled experienced at least one potassium value above 5.5 mEq/L. Mean potassium values did differ throughout the 30-d study period between extensive metabolizer, intermediate metabolizer, and non-expresser groups, but were not clinically significant (4.35 *vs* 4.68 *vs* 4.29; $P = 0.041$).

Table 1 Baseline Characteristics (intent to treat population)

All patients (*n* = 36)	
Age (yr), mean ± SD	55.5 ± 13.7
Male, *n* (%)	20 (55.6)
Race, *n* (%)	
White	9 (25.0)
Black	24 (66.7)
Hispanic	2 (5.6)
Transplant type, *n* (%)	
Deceased donor	25 (69.4)
Living donor	11 (30.6)
Hypertension, *n* (%)	28 (77.8)
Diabetes mellitus, *n* (%)	9 (25.0)
Focal segmental glomerulosclerosis, *n* (%)	1 (2.8)
Polycystic kidney disease, *n* (%)	1 (2.8)
HIV-associated nephropathy, *n* (%)	1 (2.8)
Lupus nephritis, *n* (%)	1 (2.8)
Transplant number, *n* (%)	
One	35 (97.2)
Two	1 (2.8)
cPRA (%), median (IQR)	0 (0-10.0)
Actual body weight (kg), mean ± SD	87.4 ± 18.4
Dosing weight, *n* (%)	
Actual	16 (44.4)
Adjusted	20 (55.6)
BMI (kg/m^2), mean ± SD	30.0 ± 5.5

BMI: Body mass index; cPRA: Calculated panel reactive antibody; IQR: Interquartile range; HIV: Human immunodeficiency virus.



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Figure 1 Time to therapeutic tacrolimus trough concentration (Kaplan Meier analysis).

Table 2 Baseline characteristics (modified intent to treat population)

	Non-expresser (*n* = 15)	Intermediate metabolizer (*n* = 13)	Extensive metabolizer (*n* = 6)	*P* value
Age (yr), mean ± SD	53.8 ± 12.6	49.0 ± 14.0	58.3 ± 14.1	0.354
Male, *n* (%)	9 (60.0)	8 (61.5)	2 (33.3)	0.470
Race, *n* (%)				0.026
White	7 (46.7)	1 (7.7)	0	
Black	7 (46.7)	12 (92.3)	5 (83.3)	
Hispanic	1 (6.7)	0	0	
Transplant type, *n* (%)				0.550
Deceased donor	12 (80.0)	8 (61.5)	4 (66.7)	
Living donor	3 (20.0)	5 (38.5)	2 (33.3)	
Hypertension, *n* (%)	12 (80.0)	9 (69.2)	6 (100.0)	0.304
Diabetes mellitus, *n* (%)	2 (13.3)	4 (30.8)	2 (33.3)	0.457
Focal segmental glomerulosclerosis, *n* (%)	1 (6.7)	0	0	0.521
Polycystic kidney disease, *n* (%)	0	1 (7.7)	0	0.435
HIV-associated nephropathy, *n* (%)	1 (6.7)	0	0	0.521
Lupus nephritis, *n* (%)	0	1 (7.7)	0	0.435
Transplant number, *n* (%)				0.435
One	15 (100.0)	12 (92.3)	6 (100.0)	
Two	0	1 (7.7)	0	
cPRA (%), median (IQR)	0 (0-20.8)	10.0 (0-10.0)	0 (0-20.8)	0.732
Actual body weight (kg), mean ± SD	85.5 ± 16.8	91.8 ± 22.2	77.4 ± 10.5	0.286
Dosing weight, *n* (%)				0.987
Actual	7 (53.3)	6 (53.8)	3 (50.0)	
Adjusted	8 (46.7)	7 (46.2)	3 (50.0)	
BMI (kg/m^2), mean ± SD	29.68 ± 5.0	30.68 ± 6.9	28.88 ± 4.5	0.805

BMI: Body mass index; cPRA: Calculated panel reactive antibody; IQR: Interquartile range; HIV: Human immunodeficiency virus.

DISCUSSION

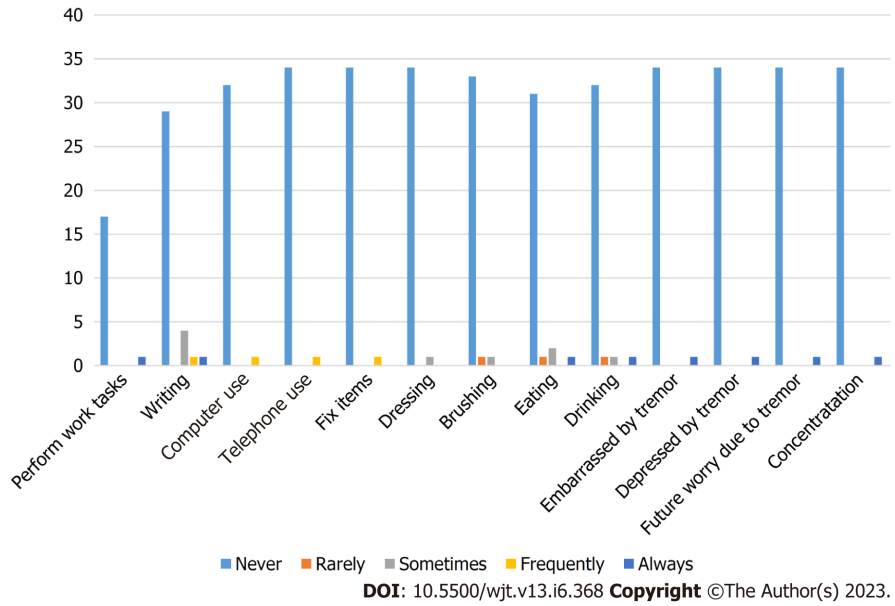
To our knowledge, this is the first prospective observational study to provide outcomes data for the *de novo* dosing of extended-release tacrolimus, LCPT, in a predominant *CYP3A5*1* expresser kidney transplant population. This research evaluates a lower initial LCPT dose of 0.13 mg/kg/d compared with the FDA-approved initial LCPT dosing of 0.14 mg/kg/d. A starting LCPT dose of 0.17 mg/kg/d was commonly evaluated in other *de novo* kidney transplant populations[1,2]. Genetic polymorphisms have been shown in numerous studies to directly affect dosage requirements of extended-release tacrolimus preparations, including LCPT[8,12]. In addition, several other patient specific factors may affect tacrolimus absorption including age, ethnicity, body weight, hepatic function, drug-drug interactions, and oral intake[15,21]. The incorporation of a *CYP3A5* genotype testing variable provides a clearer understanding of LCPT dosage requirements in this study given its significant impact on individual metabolism and tacrolimus interpatient variability[12,19].

Delayed time to therapeutic tacrolimus trough concentrations results in higher rates of acute cellular rejection[15-17]. The expression of at least one *CYP3A5*1* allele is associated with a delayed time to achieve initial therapeutic tacrolimus trough concentration as well as a decreased time within therapeutic tacrolimus trough concentration range after kidney transplantation[12,15]. The significant impact of *CYP3A5* activity on tacrolimus metabolism warrants investigation into dosing of once daily tacrolimus formulations in *CYP3A5* expressers. Participants in this study who expressed at least one *CYP3A5*1* allele or two *CYP3A5*1* alleles had significant increases in LCPT dosing requirements compared to those who did not express any *CYP3A5*1* alleles. Higher dosing requirements in *CYP3A5* expressers noted in this study leads to the consideration of a need for higher initial LCPT *de novo* dosing in this population to avoid delays in attainment of therapeutic tacrolimus trough concentrations.

Table 3 Primary and secondary efficacy endpoints

	Non-expressers (*n* = 15)	Intermediate metabolizer (*n* = 13)	Extensive metabolizer (*n* = 6)	*P* value
Time (d) to therapeutic tacrolimus concentration, median (IQR)	4.5 (1.0-7.0)	6.0 (4.0-11.5)	13.5 (7.5-20.25)	0.025
Tacrolimus dose (mg) at therapeutic concentration, median (IQR)	12 (10-14)	16 (13-20)	16 (11-20.5)	0.010
Weight-based tacrolimus dose (mg/kg) at therapeutic concentration, median (IQR)	0.13 (0.12-0.165)	0.20 (0.125-0.25)	0.19 (0.138-0.265)	0.018
Tacrolimus dose (mg), median (IQR)	9.6 (9.2-10.1)	12.5 (10.6-14.5)	13.8 (10.4-14.4)	0.011
Weight-based tacrolimus dose (mg/kg), median (IQR)	0.128 (0.102-0.142)	0.136 (0.108-0.169)	0.176 (0.128-0.217)	0.074
Tacrolimus trough concentration (ng/mL), mean ± SD	10.78 ± 2.1	9.18 ± 1.6	7.98 ± 1.3	0.008
Weight-based tacrolimus dose at day 30 (mg/kg), mean ± SD	0.103 ± 0.429	0.154 ± 0.620	0.167 ± 0.590	0.022
Potassium (mEq/L), mean ± SD	4.29 ± 0.36	4.68 ± 0.35	4.35 ± 0.59	0.041
Serum creatinine (mg/dL) at day 30, median (IQR)	1.76 (1.29-2.62)	1.75 (1.27-2.65)	1.94 (1.2-3.0)	0.906
eGFR (mL/min/1.73 m^2) at day 30, median (IQR)	40.0 (27.0-58.0)	46.0 (30.0-58.5)	31.5 (25.0-56.3)	0.701

eGFR: Estimated glomerular filtration rate; IQR: Interquartile range.



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Figure 2 Quality of life in essential tremor questionnaire lifestyle self-assessment.

Since LCPT dosing has not been evaluated in prior studies based on *CYP3A5* genotype, it is worthwhile to compare the results of our study to a different once daily tacrolimus formulation (Advagraf®, Astagraf®; Astellas Pharmaceuticals). De Meyer *et al*[12] showed that *CYP3A5* expressers, both intermediate and extensive metabolizers, required higher tacrolimus extended-release doses by day 30 compared to *CYP3A5* non-expressers (*CYP3A5* intermediate metabolizer: 0.30 mg/kg/d *vs* *CYP3A5* extensive metabolizer: 0.46 mg/kg/d *vs* *CYP3A5* non-expresser: 0.15 mg/kg/d; $P < 0.001$). We identified a similar trend as De Meyer *et al*[12] in which *CYP3A5* expressers regardless of intermediate or extensive metabolizer phenotype, require higher LCPT dosing than *CYP3A5* non-expressers. However, lower doses of LCPT appear to be required for *CYP3A5* expressers in our study compared to other available once daily tacrolimus formulations (Astagraf®) when comparing dosing at day 30 post-kidney transplant (*CYP3A5* intermediate metabolizer: 0.17 mg/kg/d *vs* 0.30 mg/kg/d; *CYP3A5* extensive metabolizer: 0.16 mg/kg/d *vs* 0.46 mg/kg/d). One limitation to this comparison is the goal tacrolimus trough concentration, since in De Meyer *et al*[12] it was 8-12 ng/mL at day 30 compared to our study goal of 8-10 ng/mL, although median trough concentrations were similar at day 30 for both studies.

Guidelines from the Clinical Pharmacogenetics Implementation Consortium for *CYP3A5* Genotype and Tacrolimus Dosing provide clinical recommendations for dosing based on *CYP3A5* genotype[19]. These guidelines provide clinical

evidence for dose adjustments required for immediate-release tacrolimus dosing, but do not discuss the implications for dose adjustments for tacrolimus extended-release formulations, such as LCPT. Recommendations for all *CYP3A5* expressers is to provide initial tacrolimus dosing of 1.5-2 times the recommended starting dose and to not exceed a starting dose of 0.3 mg/kg/d. *CYP3A5* expressers in our study required approximately 1.5 times the recommended FDA-approved 0.14 mg/kg/d starting dose for LCPT to achieve therapeutic tacrolimus trough concentrations[6]. The majority of *CYP3A5* expressers in this study required an approximate 20% reduction in the mean LCPT dose at day 30 from the time of attainment of therapeutic tacrolimus trough concentrations. The delayed time to achieve therapeutic tacrolimus trough concentration for *CYP3A5* expressers compared to *CYP3A5* non-expressers leads to *CYP3A5* expressers requiring higher initial starting doses of LCPT. However, patients may require dose reduction over time to maintain therapeutic tacrolimus concentrations. Patients in this study identified as *CYP3A5* intermediate metabolizers required a mean of 0.2 mg/kg/d to achieve therapeutic tacrolimus concentration *vs* 0.19 mg/kg/d for *CYP3A5* extensive metabolizers. Given the similarity in doses required to achieve therapeutic tacrolimus concentrations between these two groups, a similar dosing strategy for all *CYP3A5* expressers could be utilized. Two large sample size studies evaluated clinical outcomes associated with *de novo* use of LCPT in kidney transplant recipients. Budde *et al*[1] evaluated the incidence of biopsy-proven acute rejection, graft failure, patient survival, and AEs at 12 mo while Rostaing *et al*[2] evaluated similar outcomes at both 12 and 24 mo after kidney transplantation. Both of these studies evaluated an initial starting dose of 0.17 mg/kg/d, which is the maximum dose of LCPT evaluated in clinical studies with at least 12 mo efficacy and safety outcomes. *CYP3A5* genotype was not performed for these studies and our study provides additional data regarding initial *de novo* LCPT dosing based on *CYP3A5* genotype. Based on these findings, we suggest that *CYP3A5* expressers may require higher initial starting doses of approximately 0.2 mg/kg/d. In order to avoid delays in attaining therapeutic tacrolimus trough concentrations, 0.2 mg/kg/d may be used as an initial starting LCPT dose for *CYP3A5* expressers barring no other clinical barriers to higher starting doses.

This study has several limitations to the interpretation and generalizability of its findings. The single-center design of this study reflects the clinical approach of one institution which may not be applicable to all kidney transplant recipients. *CYP3A5* genotype may not be the only genetic consideration when determining an individual's genetic predisposition to the metabolism of tacrolimus. Genetic differences in *CYP3A4* activity and other SNPs within the *CYP* system could play a role in determining the metabolic rate of tacrolimus which is not captured in our study[12]. Our study evaluated dose requirements and other clinical outcomes through the first 30 d after kidney transplantation. This follow-up period only provides information on short-term LCPT dosing outcomes and future studies with long-term follow-up periods should be performed. This study is also limited by its open-label design and relatively smaller number of patients enrolled. In addition, the single-arm design of this study did not allow for a comparator arm and future randomized controlled studies should be performed to further evaluate dosing requirements of LCPT in the *de novo* kidney transplant population.

CONCLUSION

Expression of *CYP3A5* metabolic activity is an important clinical factor needed to determine optimal LCPT dosage requirements in the *de novo* kidney transplant recipient. It is expected that *CYP3A5* expressers would require a higher initial starting dose as well as higher incremental dosage titration to achieve therapeutic tacrolimus trough concentrations in a reasonable timeframe. Prospective identification of *CYP3A5* genotype may lead to optimized dosing of LCPT in the *de novo* kidney transplant setting. Future, randomized, larger-scale studies should be conducted to determine the optimal *de novo* dosing of LCPT after kidney transplantation.

ARTICLE HIGHLIGHTS

Research background

Tacrolimus has been extensively studied and shown to require significant dose adjustments in *CYP3A5* expressers compared to non-expressers. Data regarding the impact of *CYP35* expresser status on the dosing of tacrolimus extended-release tablets has not been published and is important to understand given the vastly different pharmacokinetic profile of this tacrolimus formulation. There is an increased use of tacrolimus extended-release tablets in the *de novo* setting warranting further investigation into this clinical question.

Research motivation

The main concerns when initiating tacrolimus in the *de novo* kidney transplant setting is to achieve therapeutic tacrolimus trough concentrations in a reasonable timeframe while also avoiding drug toxicity. The rationale behind this research is to identify dosing strategies that should be considered when initiating tacrolimus extended-release immediately after kidney transplant. Particular, research evaluating dosing strategies in patients known to have higher tacrolimus dose requirements (*i.e*. *CYP3A5* expressers) will provide data for transplant centers to make educated clinical decisions surrounding dosing and dosing adjustments for tacrolimus extended-release tablet formulations.

Research objectives

The main objectives of this research was to identify the time to therapeutic tacrolimus trough concentration as well as the dose required to obtain that trough concentration. These objectives were realized as well as the differences in dosing requirements amongst CYP3A5 expressers compared to non-expressers. The significance of these objectives warrant further investigation towards linking clinical outcomes such as acute rejection and graft function outside of the first month after transplant in patients receiving tacrolimus extended-release tablets in the *de novo* kidney transplant setting.

Research methods

Patients (n = 36) were consented to receive tacrolimus extended-release tablets at a dose of 0.13 mg/kg/d at the time of kidney transplantation. Dosing was adjusted to maintain therapeutic trough concentrations of 8-10 ng/mL which assisted in identifying the primary objective of time to therapeutic concentration. In addition, all patients that consented to *CYP3A5* genotype testing (n = 34) were included in additional data analysis to describe dosing requirements for tacrolimus extended-release tablets in patients that were *CYP3A5* expressers compared to *CYP3A5* non-expressers. These methods allowed the authors to describe initial dosing requirements as well as the impact of *CYP3A5* metabolism on tacrolimus extended-release dosing and attainment of target trough concentrations.

Research results

This research demonstrated that kidney transplant recipients who are expressers of *CYP3A5* exhibited higher dose requirements for tacrolimus extended-release tablets and also experienced delays in attaining therapeutic trough concentrations compared to *CYP3A5* non-expressers. These findings are pertinent to the field of solid organ transplant since transplant centers that utilize tacrolimus extended-release tablets in the *de novo* setting should be aware of the higher dosing needs in this patient population. In addition, transplant recipients suspected to or known to be *CYP3A5* expressers may require more aggressive dose titration to achieve and maintain target tacrolimus trough concentrations. Future research in this area should focus on clinical outcomes beyond our study period of 30 d to determine the impact on acute rejection and kidney graft function.

Research conclusions

Overall, this study provides additional clinical information regarding the dosing requirements of tacrolimus extended-release tablets in the *de novo* kidney transplant setting. To our knowledge, this is the first prospective observational study to provide outcomes data for the *de novo* dosing of tacrolimus extended-release tablets. The findings from this research validate that the impact of *CYP3A5* expression has a clinical impact on the pharmacokinetic profile of tacrolimus extended-release tablets similar to findings published with tacrolimus immediate-release. New approaches to dosing and dose titration for tacrolimus extended-release tablets have been proposed by this research in the *de novo* kidney transplant setting and can be used as a guide when making clinical decisions in this patient population.

Research perspectives

Future research should aim to randomize patients to various doses of tacrolimus extended-release tablets to offer a more advanced comparison of different initial dosing strategies. Conducting *CYP3A5* genotype analyses prior to study drug initiation would be beneficial in future studies in order to further assess the impact of pharmacokinetic variations in metabolism on tacrolimus extended-release tablets.

FOOTNOTES

Author contributions: Diamond A and Di Carlo A participated in design and oversight of the study, data collection, data analysis, and drafted and finalized the manuscript; Karhadkar S and Lau KN, participated in design and oversight of the study, and assisted with data analysis; Chavin K drafted the manuscript and assisted with data analysis; Constantinescu S participated in design and oversight of the study, drafted the manuscript, and assisted with data analysis; Mohrien K performed statistical analysis in conjunction with Temple University Center for Biostatistics & Epidemiology, participated in data analysis, and drafted the manuscript; Perez-Leal O conducted DNA analysis for genotype samples and analyzed genotype data, and drafted the manuscript; Sifontis N participated in design and oversight of the study, assisted with data analysis, and drafted the manuscript; all authors read and approved the final manuscript.

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ORIGINAL ARTICLE

Basic Study

Pathophysiology of acute graft-versus-host disease from the perspective of hemodynamics determined by dielectric analysis

Masayuki Nagasawa

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Abstract

BACKGROUND

Numerous reports have demonstrated that the pathophysiology of graft-versus-host disease (GVHD) during hematopoietic stem cell transplantation (HSCT) is closely related to vascular endothelial disorders and coagulation abnormalities. We previously presented the discovery of a principle and the development of a novel instrument for measuring whole blood coagulation. This was achieved by assessing the variations in the dielectric properties of whole blood.

AIM

To investigate how GVHD affects the changes of dielectric properties of whole blood in patients with HSCT.

METHODS

We examined the changes of dielectric properties of whole blood and erythrocyte proteins by sodium dodecyl sulfate-polyacrylamide gel electrophoresis sequentially in patients with HSCT and compared it with clinical symptoms and inflammatory parameters of GVHD.

RESULTS

During severe GVHD, the dielectric relaxation strength markedly increased and expression of band3 decreased. The dielectric relaxation strength normalized with the improvement of GVHD. *In vitro* analysis confirmed that the increase of relaxation strength was associated with severe erythrocyte aggregates, but not with decreased expression of band3.

CONCLUSION

Severe erythrocyte aggregates observed in GVHD may cause coagulation abnor-

malities and circulatory failure, which, together with the irreversible erythrocyte dysfunction we recently reported, could lead to organ failure.

Key Words: Graft-versus-host disease; Dielectric relaxation; Erythrocyte; Stem cell transplantation; Coagulation

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Core Tip: The pathophysiology of graft-versus-host disease (GVHD) is complex. Examination of changes in the dielectric properties of whole blood revealed that erythrocytes formed risky levels of rouleaux and aggregates in severe GVHD. In severe GVHD, oxidative stress causes degradation of erythrocyte band3 and truncation of the C-terminus of peroxiredoxin 2, resulting in decreased plasticity, increased fragility, and reduced oxygen-carrying capacity. These phenomena may underlie persistent refractory coagulopathy and circulation disorder, leading to organ damage in severe GVHD.

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INTRODUCTION

The graft-versus-host (GVH) reaction is the most serious complication of hematopoietic stem cell transplantation (HSCT) and the most important reaction that eradicates malignant cells[1,2]. When the GVH reaction is excessively induced leading to organ dysfunction, it is designated as graft-versus-host disease (GVHD) and is a target for treatment. Moreover, GVHD progresses in three phases[3]. The first is cell damage due to pretreatment with anticancer drugs and radiation, which induces inflammatory reactions and the production of inflammatory cytokines. The second mechanism involves the recognition and activation of host antigens by transplanted immune cells. Inflammatory cytokines produced in the first phase promote the response in phase 2 by inducing an increased expression of alloantigens. In phase 3, immunocompetent cells activated in phase 2 attack the host cells, induce new inflammation and initiate a vicious cycle of excessive inflammatory responses. The treatment for GVHD involves suppressing and controlling activated immunocompetent cells induced in phases 2 and 3[3]. Uncontrolled and persistent GVHD leads to the insidious progression of severe coagulation disorders and microcirculation disturbances, resulting in irreversible organ failure and tissue damage directly induced by the attack of activated immunocompetent cells[4]. Early and persistent coagulopathy has been reported to be associated with HSCT prognosis[4].

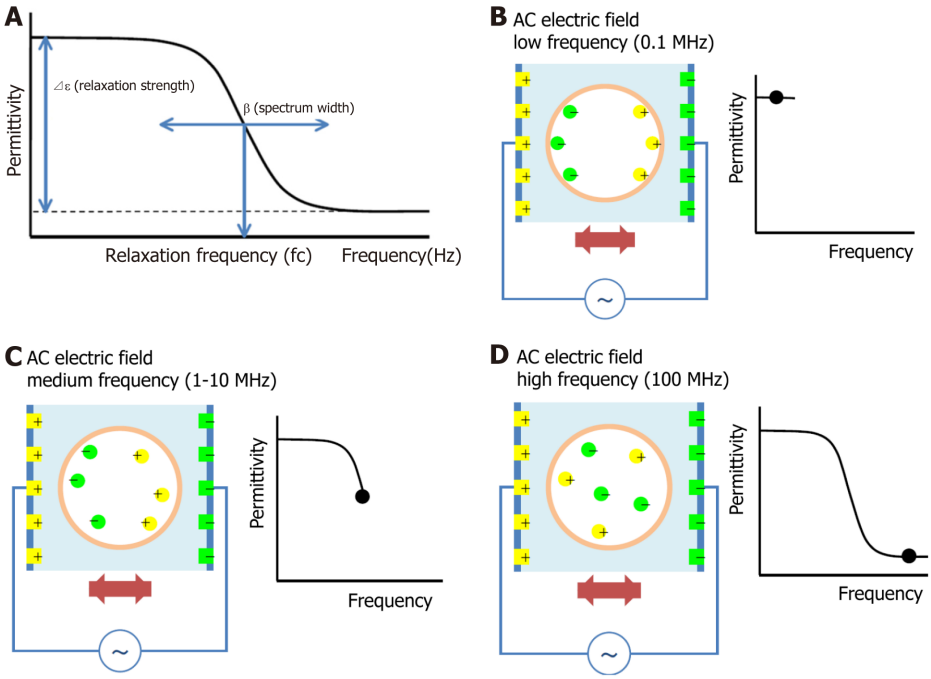
Coagulation abnormalities and circulatory failure in the peripheral circulation are not always caused by GVHD after HSCT. In some cases, the main causes of coagulation disturbances stem from treatment with anticancer drugs, radiation, or vascular endothelial damage caused by calcineurin inhibitors, which are used as immunosuppressants to prevent GVHD[1,5,6]. Furthermore, cytomegalovirus infection/reactivation induced in an immunodeficient state may also be involved in the aforementioned disturbances[7,8]. Additionally, clinically determining whether coagulation abnormalities and vascular endothelial disorders that develop after HSCT are caused by GVHD is often difficult[9,10]. The assessment of peripheral blood circulation abnormalities and coagulation disorders following HSCT, specifically concerning pathological alterations in erythrocytes, has received limited attention in the context of GVHD.

The measurement of the complex dielectric properties of biomaterials at radio frequency has gained increasing importance not only in material science, microwave circuit design, and absorber development but also in biological research[11-13]. Dielectric measurement is important for providing the electrical or magnetic characteristics of materials in a noninvasive manner and has proven useful in many research and development fields. We performed dielectric measurements of the coagulation process in whole human blood, clarified the principle, and reported its usefulness as a new whole-blood coagulation measurement method[14,15]. Moreover, we examined the changes in the dielectric properties of whole blood after HSCT in 16 patients and discussed the relationship between the changes in the dielectric properties of whole blood and GVHD.

MATERIALS AND METHODS

Principles of dielectric properties of whole blood

The principle of the dielectric measurement of whole blood is displayed in Figure 1A-D. Whole blood comprises plasma and blood cells (mainly erythrocytes), each of which is electrically charged. When an alternating electric field is applied to whole blood, sufficient ionization is achieved at low frequencies. However, as the frequency increases, ionization fails to keep pace sufficiently. Beyond a certain frequency, ionization is no longer possible and the dielectric constant does not change (Figure 1B-D). The dielectric properties of each material can be represented by the relaxation strength and



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Figure 1 The principle of the dielectric measurement of whole blood is displayed. A: Brief description of dielectric parameters; B: Sufficient ionization is achieved when a low frequency alternating voltage is applied; C: As the frequency of the AC voltage increases, the ionization cannot keep up with the frequency, and the dielectric strength gradually decreases; D: When the frequency of the AC voltage exceeds a certain level, no dielectric occurs and the dielectric strength stabilizes at a low value.

frequency, as displayed in Figure 1A. The dielectric constant of whole blood was determined as the sum of the plasma (solvent) and blood cell components. As the electrode polarization of the solution component had a strong effect in the low-frequency region, the interfacial polarization of the blood cell component was calculated by correcting for this effect. Theoretically, the dielectric properties of blood cell components are considered to be significantly affected in the high-frequency range (Figure 2).

Dielectric measurement of whole blood

Venous blood was drawn in a blood collection tube containing Ethylenediamine-N, N, N', N'-tetra acetic acid dipotassium salt dihydrate (EDTA-2K·2H_2O) and diluted to 10% hematocrit (Hct) with phosphate buffer saline (PBS). After 30 min of incubation at room temperature with gentle stirring, the dielectric properties were measured by our developed equipment. Diluted blood samples (200 L) were adjusted to 10% Hct using PBS and measured at 57 frequencies from 100 Hz to 40 MHz[14]. The measurement time for each frequency was < 0.2 s and the total frequency scan time for one dielectric relaxation measurement was 10 s. Measurements were performed within 1 h of blood sample collection.

Clinical samples

Clinical samples were obtained from 16 patients who underwent allogeneic HSCT. The clinical information for each patient is summarized in Table 1. A portion (1 mL) of blood collected during routine clinical examinations performed 2–3 times per week after HSCT was used for the research. Information such as clinical symptoms and blood data were collected as anonymized information from medical records.

Sodium dodecyl sulfate-polyacrylamide gel electrophoresis

Cells were washed with PBS and then lysed at 4 °C in a buffer containing 10 mmol/L Tris-hydrochloric acid, 50 mmol/L sodium chloride, 0.5% sodium deoxycholate, 0.2% SDS, 1% Nonidet P-40, 1 mmol/L phenylmethylsulfonyl fluoride, 50 mg/mL aprotinin, 50 mmol/L leupeptin, and 0.1 mmol/L sodium orthovanadate. After removing cellular debris by centrifugation, lysates were prepared for electrophoresis, and PAGE was performed as described previously[16]. Further, proteins separated on the gel were stained using silver staining.

RESULTS

Typical changes in dielectric relaxation strength and frequency are depicted in patients who developed acute GVHD of grade 3 or more (patient 4) and those who did not (patient 2). During GVHD, a sharp increase in the dielectric relaxation strength and a decrease in the relaxation frequency intensity were observed (Figures 3 and 4). Overall, the dielectric

Table 1 The clinical information for each patient

Patient No	Disease	Acute GVHD	Stage			Conditioning	Stem cell source	Decreased band3	Truncated PRDX2
			Skin	Gut	Liver				
1	AML	I	1	0	0	MAC	URCB	No	No
2	HIM	0	0	0	0	RIC	URBMT	No	No
3	SCID	III	2	3	1	RIC	URCB	Yes	Yes
4	SCID	III	1	3	1	RIC	URCB	Yes	Yes
5	AML	I	1	0	0	MAC	MSBMT	No	No
6	AML	II	3	0	0	MAC	URBMT	No	No
7	DKC	III	2	3	1	RIC	URBMT	Yes	Yes
8	ALL	0	0	0	0	MAC	URBMT	No	No
9	ALL	II	3	0	0	MAC	URCB	No	No
10	ALL	II	3	0	0	MAC	MSBMT	No	No
11	AML	I	1	0	0	MAC	MSBMT	No	No
12	AML	III	1	3	1	MAC	mis-RBMT	Yes	Yes
13	ALL	III	1	2	1	MAC	URBMT	Yes	Yes
14	ALL	III	1	2	1	MAC	URBMT	Yes	No
15	ALL	II	3	0	0	MAC	mis-RBMT	No	No
16	SCN	I	1	0	0	RIC	MSBMT	No	No

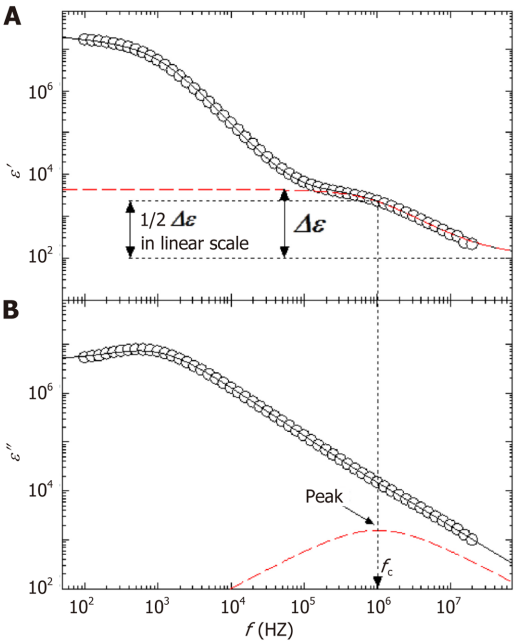
AML: Acute myeloid leukemia; HIM: Hyper IgM syndrome; SCID: Severe combined immunodeficiency; DKC: Dyskeratosis congenital; ALL: Acute lymphoblastic leukemia; SCN: Severe congenital neutropenia; MAC: Myeloablative conditioning; GVHD: Graft-versus-host disease; RIC: Reduced-intensity conditioning; URCB: Unrelated cord blood; URBMT: Unrelated bone marrow transplant; MSBMT: Matched sibling bone marrow transplant; mis-RBMT: Mismatched related bone marrow transplant.

relaxation strength and frequency changed in a complementary manner.

To investigate whether the change in dielectric properties was due to blood cells or plasma components, the expression of erythrocyte membrane proteins was analyzed using sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). As demonstrated in Figure 3, a decrease in band 3 expression was observed in line with GVHD onset (Figure 3). Decreased expression of band 3 is one of the mechanisms of hereditary spherocytosis, in which erythrocytes are not normally concave-discoid-shaped, however, they morphologically change into spherocytes, exhibiting osmotic fragility. However, our previous study on dielectric relaxation frequency intensity changes in various erythrocyte morphologies displayed that the relaxation frequency increased during spherocytosis[12,17]. No significant changes in the dielectric properties of the plasma components were observed with or without GVHD (data not displayed). Therefore, we conducted a replacement experiment for the blood cells and plasma components. As demonstrated in Figure 5, the relaxation strength depends on the plasma components (Figure 5A). Observation of erythrocyte states under each condition using a phase-contrast microscope revealed the formation of rouleaux or aggregates in the presence of plasma components during the progression of GVHD (Figure 5B). Although the data are not displayed, rouleaux formation of erythrocytes was observed at a high frequency in the blood, in which the dielectric relaxation strength increased after HSCT.

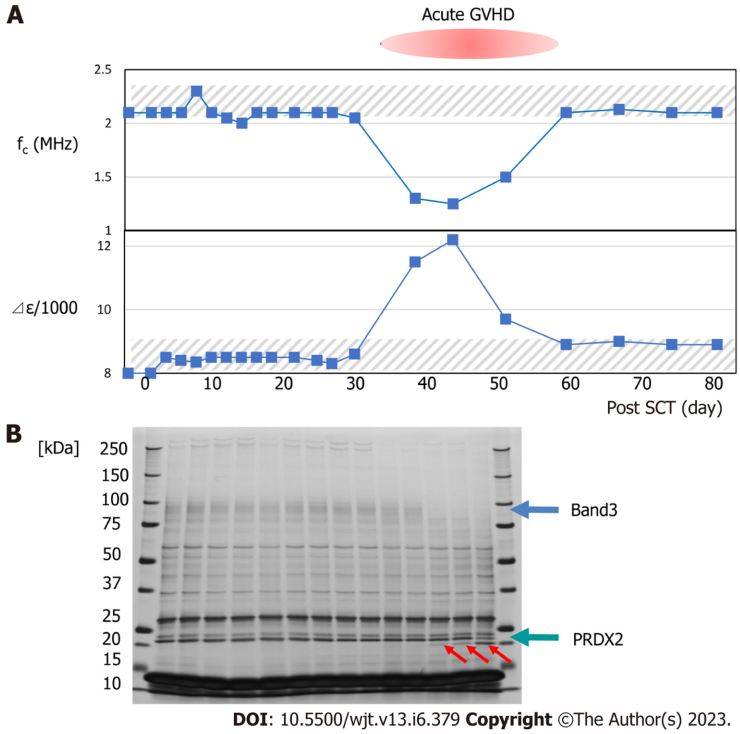
Next, to estimate the quantitative relationship between the dielectric relaxation strength change and the rouleaux formation of erythrocytes, experiments with the addition of gamma (γ)-globulin were carried out. Blood obtained from healthy individuals was washed with PBS, a 10% Hct erythrocyte suspension solution was created, and then γ-globulin was added to measure the dielectric properties and confirm the morphology at several concentration settings. The serum concentration of γ-globulin in healthy individuals is considered to be approximately 10 mg/mL, but little change was observed in dielectric relaxation strength and morphology under conditions between 0 mg/mL and 10 mg/mL of g-globulin. A rouleaux formation of erythrocytes was observed at a g-globulin concentration of 50 mg/mL, and large erythrocyte aggregates were observed at a concentration of 150 mg/mL. For dielectric relaxation measurement, the patient's whole blood was diluted to approximately 1/3 in PBS to match 10% Hct. The observed rate of change in the dielectric constant in our study suggests that the acute phase of grade 3 or more GVHD was comparable to a state where the γ-globulin concentration exceeded 100 mg/mL, which is ten-fold higher than the normal value (Figure 6) (comparing with the data displayed in Figure 5A).

Figure 7 displays the changes in the dielectric relaxation strength and C-reactive protein (CRP), a biomarker of inflammation, in patients who developed grade 3 or more of GVHD. The dielectric relaxation strength and CRP levels demonstrated a correlation in some cases, but they did not necessarily match. In addition, the dielectric relaxation



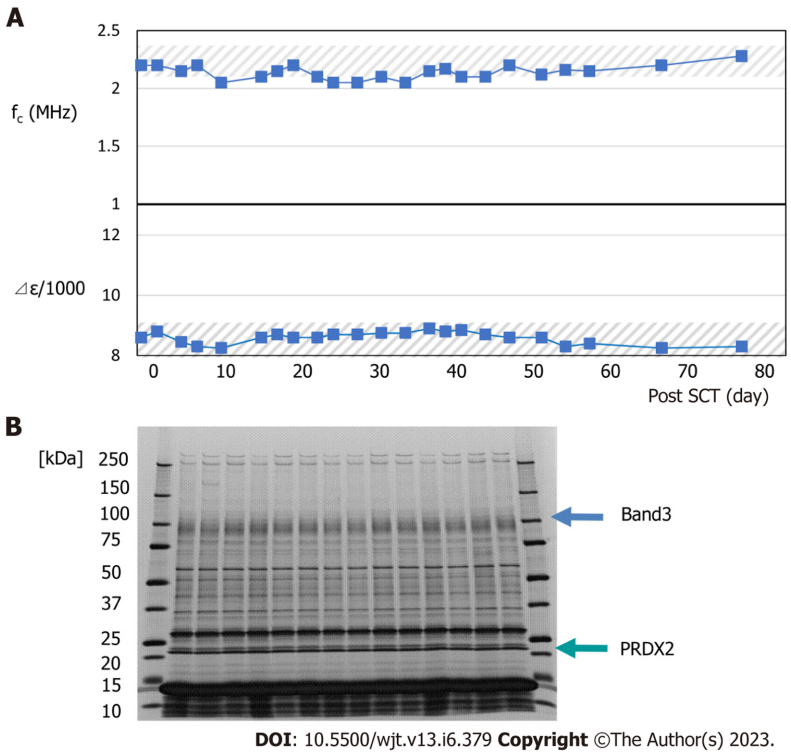
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Figure 2 Understanding of the dielectric relaxation of whole blood, which is consist of plasma and blood cells. A: Shows the real part; B: The imaginary part of the complex permittivity. The broken red lines are the result of an analysis of the interfacial polarization phenomenon according to a Cole−Cole type dielectric relaxation function. This function is characterized by the relaxation strength Δε corresponding to changes in ε' (A) and the relaxation frequency fc that corresponds to the peak of this function observed in the imaginary part of permittivity, ε" (B). The curved lines in the figure are the sum of all the assumed contributions in the analysis, and agree well with the experimental values.



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Figure 3 Changes in the relaxation frequency and relaxation intensity of whole blood after transplantation in a transplant patient who developed severe graft-versus-host disease during the course. A: The hatched area indicates the normal range of relaxation frequency and relaxation intensity; B: The figure below shows the results of sodium dodecyl sulfate-polyacrylamide gel electrophoresis of erythrocyte proteins over time. Consistent with graft-versus-host disease, there is a decrease in band3 and the appearance of a 20KDa band (red arrows). The 20KDa band was found to be the C-terminal deleted PRDX2[37]. GVHD: Graft-versus-host disease.



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Figure 4 Changes in the relaxation frequency and relaxation intensity of whole blood after transplantation in a transplant patient who developed no graft-versus-host disease during the course. A: The hatched area indicates the normal range of relaxation frequency and relaxation intensity; B: The figure below shows the results of sodium dodecyl sulfate-polyacrylamide gel electrophoresis of erythrocyte proteins over time. There was no significant change.

strength may fluctuate significantly, even with a slight change in the CRP. Interestingly, the dielectric relaxation strength increased gradually with minimal CRP changes in patient 3, who developed severe gastrointestinal GVHD. This indicates that the dielectric relaxation strength is affected by persistent or chronic inflammatory reactions even if the CRP level is elevated.

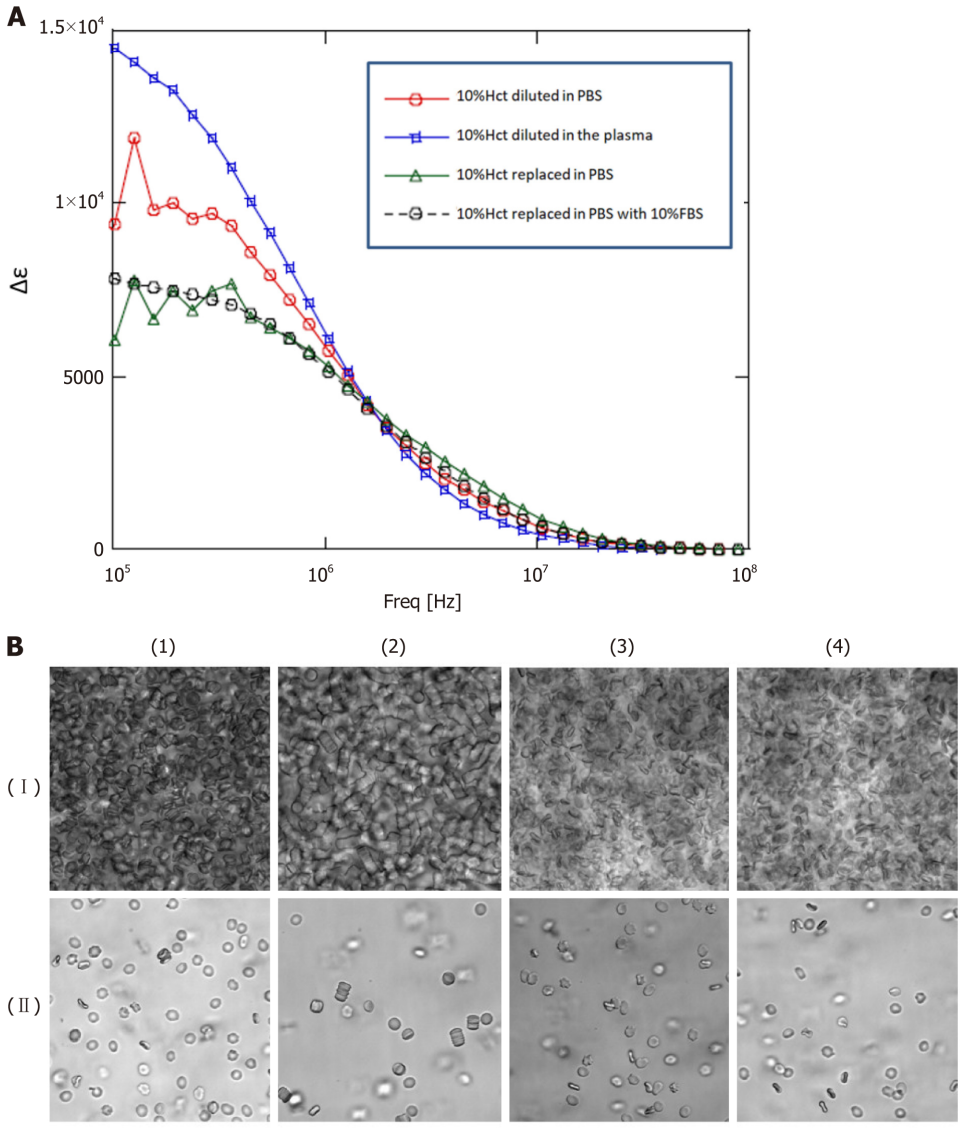
DISCUSSION

Erythrocytes account for two-thirds of all human cells. They are constantly produced in the bone marrow of hematopoietic stem cells and supplied to the blood[18]. The main role of erythrocytes is to transport oxygen to every corner of the body; therefore, the cell has an optimal structure for efficiently transporting oxygen. Erythrocytes are often subjected to oxidative stress due to their role in transporting high concentrations of oxygen and therefore have a strong scavenger function against reactive oxygen species[19-21]. A typical example is peroxiredoxin 2 (PRDX2), which is present in high concentrations in red blood cells and is maintained by the pentose phosphate pathway and glutathione system[22]. A concave discoid-like shape without a nucleus is the optimal structure that can efficiently take in oxygen and move inside the capillaries to every corner of the tissue with strong deformability[23]. Furthermore, erythrocytes have a strong buffering capacity to maintain the acid-base balance in body fluids[24] and abundant scavenger functions against oxidative stress[19-21].

On the other hand, the coagulation system is known to be phylogenetically closely related to inflammatory and immune responses[25,26]. The system is considered to have evolved as a biological defense mechanism that not only stops bleeding but also traps pathogens and prevents them from spreading to the surrounding area. In vivo, the coagulation system is initially considered to be activated on the cell surface[27], and evidence indicates that stagnation of blood flow can be a trigger[28].

Based on the principle of our newly developed *in vitro* whole blood coagulation measurement system utilizing whole blood permittivity measurements, this process can be divided into three stages[14]. First, an increase was observed in relaxation strength due to rouleaux formation, followed by a further increase in relaxation strength due to aggregation. Additionally, a rapid decrease in relaxation strength due to changes in erythrocyte morphology and tertiary structure caused by platelet secondary aggregation and clot retraction due to fibrin formation and polymerization was also observed. This result suggests the importance of erythrocyte rouleaux and aggregate formation as an initial reaction or precursor state for the activation of the coagulation system.

As is well known, hypergammaglobulinemia induces rouleaux formation by neutralizing the negative charge on the surface of erythrocytes. Venous thrombosis frequently occurs in multiple myeloma presenting with pathological

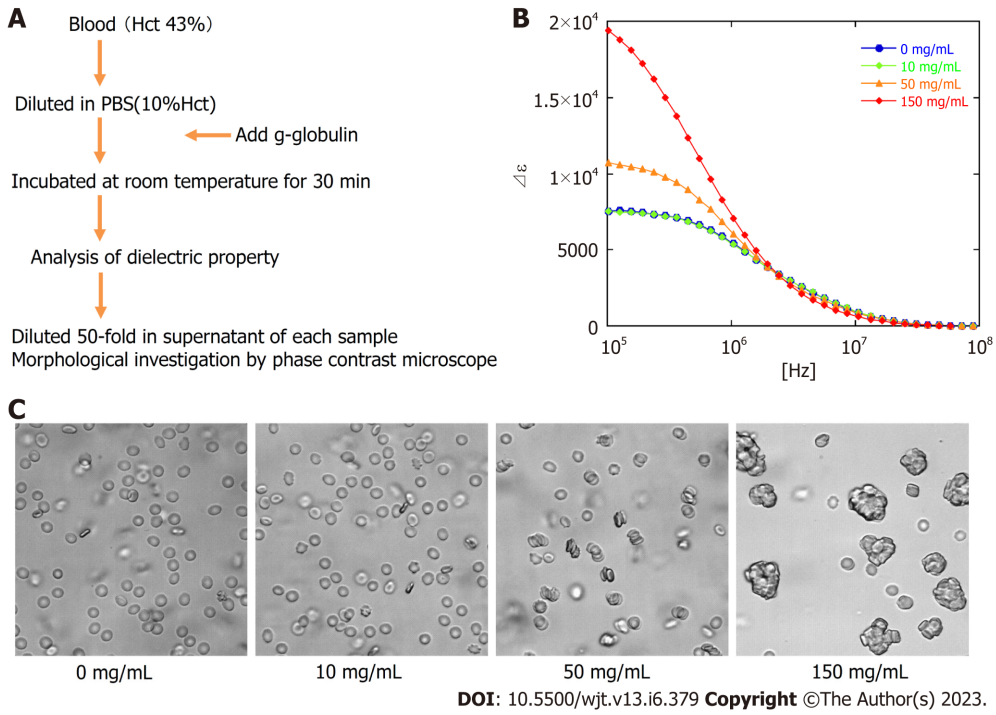


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Figure 5 We conducted a replacement experiment for the blood cells and plasma components. A: Blood sample (about 30%Hct) from the patient with graft-versus-host disease was diluted as 10%Hct diluted in phosphate buffer saline (PBS), 10%Hct diluted in the patient's plasma, 10%Hct replaced in PBS, and 10%Hct replaced in PBS with 10%FBS, and dielectric properties were measured; B: (I) Blood sample (about 30%Hct) from the patient with graft-versus-host disease was diluted as (1) 10%Hct diluted in PBS, (2) 10%Hct diluted in the patient's plasma, (3) 10%Hct replaced in PBS, and (4) 10%Hct replaced in PBS with 10%FBS, and observed by phase-contrast microscopy; (II) Sample of (I) was further diluted by 50-fold in the same way, and observed by phase-contrast microscopy. PBS: Phosphate buffer saline.

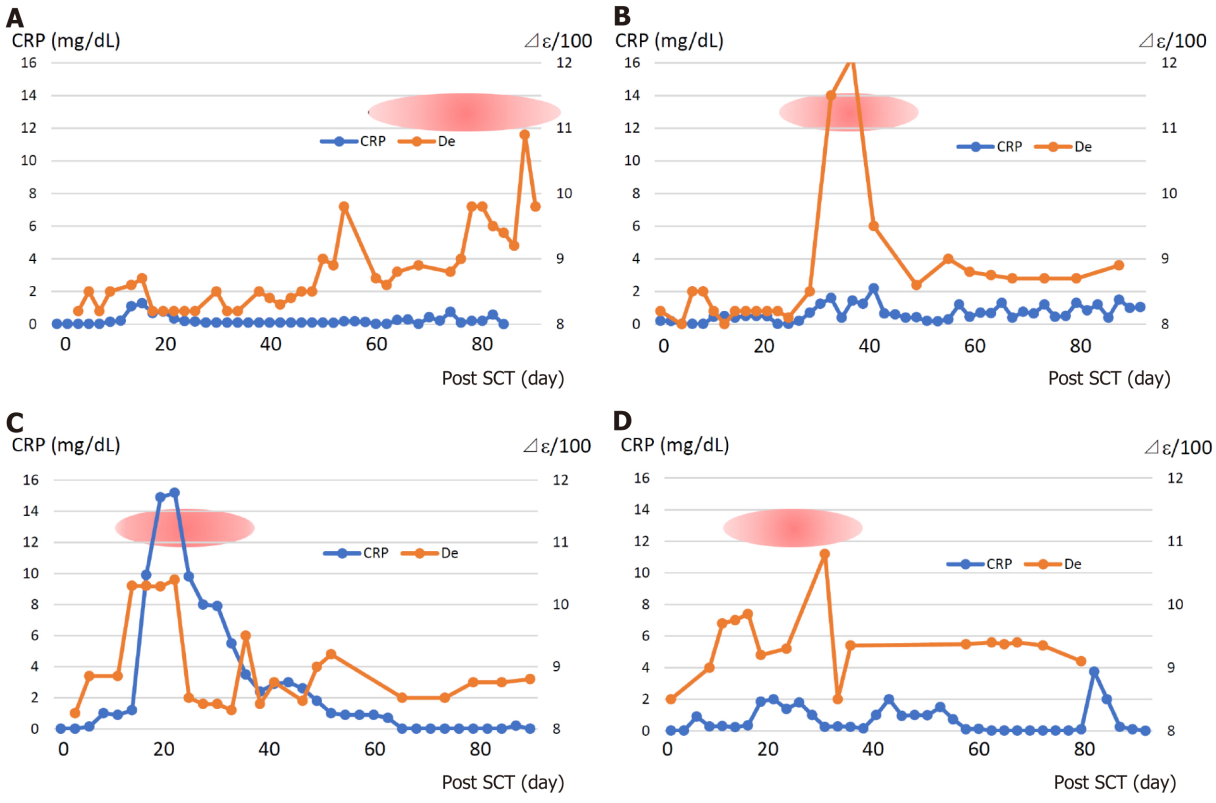
hypergammaglobulinemia[29,30]. Many reports of thrombosis, likely due to high-dose g-globulin therapy[31-33]. The high-viscosity state caused by rouleaux formation causes stagnation of blood flow and interacts with tissue factors produced by GVHD-induced inflammatory reactions to lower the threshold of initial coagulation activation. According to this study, the change in whole blood dielectric constant in acute GVHD was considered equivalent to the change in hypergammaglobulinemia from 10 to 15 mg/mL, which is a high-risk level that progresses to thrombus formation and renal failure when replaced with multiple myeloma patients.

On the other hand, oxidative stress has been reported to be enhanced in acute GVHD[34,35], in addition to the oxidative stress induced by conditioning chemotherapy and radiation therapy[36]. We recently reported that calpain activated by oxidative stress may cause the degradation of band 3 and PRDX2[37]. Degradation of band 3 causes a decrease in erythrocyte plasticity, making the cell more susceptible to hemolysis[38,39]. The degradation of PRDX2 irreversibly disrupts the scavenging function of erythrocytes and reduces the resistance of the cell against oxidative stress [40-42]. Phosphatidylserine, which appears on the cell surface due to abnormal erythrocyte membranes, acts as a procoagulant[43]. Free hemoglobin released by hemolysis scavenges nitrogen oxide (NO)[26], which has a vasodilatory effect, and the released erythrocyte arginase reduces NO production[44]. These pathological conditions overlap to form a vicious circle, and it is thought that the progression of microcirculatory failure and the accompanying organ failure result in an irreversible state leading to fatality.



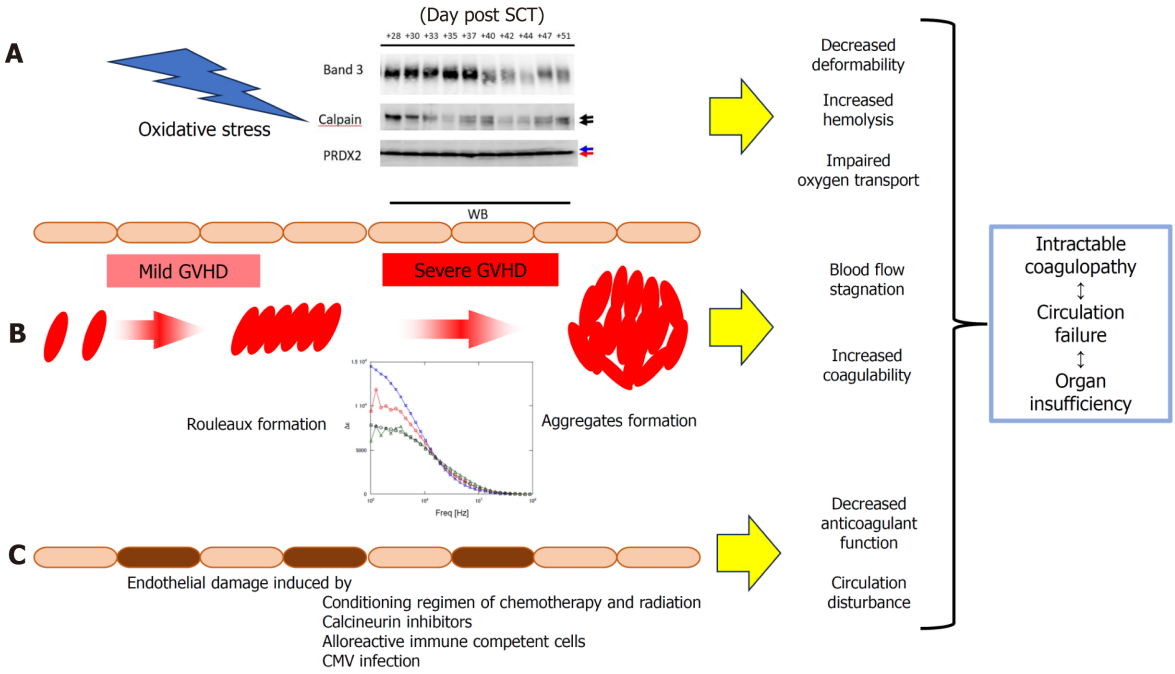
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Figure 6 The observed rate of change in the dielectric constant. A: Blood sample from a healthy volunteer (Hct 43%) was diluted in PBS to 10% Hct, and g-globulin was added to a final concentration of 0 mg/dL, 10 mg/dL, 50 mg/dL, and 150 mg/dL; B: After incubation for 30 min, dielectric properties of each sample were measured; C: Morphology of erythrocytes was investigated by phase-contrast microscopy after further dilution by 50-fold. PBS: Phosphate buffer saline.



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Figure 7 Transition and relationship between dielectric relaxation strength and C-reactive protein in patients who developed graft-versus-host disease grade 3 after transplantation. A: Patient 3; B: Patient 4; C: Patient 12; D: Patient 13. Red oval marks indicate the period of grade 3 and more acute graft-versus-host disease. CRP: C-reactive protein; SCT: Stem cell transplantation.



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Figure 8 Schematic illustration of graft-versus-host disease from the perspective of dielectric analysis of whole blood cells. A: In graft-versus-host disease (GVHD) of grade 3 or higher, oxidative stress-activated calpains lead to degradation of band3 and truncation of the C-terminus of PRDX2, leading to decreased erythrocyte plasticity, increased fragility, and impaired oxygen transport; B: Changes in plasma contents due to complex inflammation such as GVHD cause rouleaux formation and aggregation of erythrocytes, causing stasis in blood circulation and becoming more susceptible to coagulation activation; C: Vascular endothelial cell damage by pretreatment or calcineurin inhibitors is further prolonged and increased by alloimmune reactions and reactivation of cytomegalovirus virus, and the anticoagulant function of vascular endothelial cells is reduced. These phenomena are compounded and lead to refractory coagulopathy and subsequent organ circulatory failure and dysfunction. CMV: Cytomegalovirus; CRP: C-reactive protein; GVHD: Graft-versus-host disease; SCT: Stem cell transplantation.

The differences between rouleaux formation, which is indicated by changes in dielectric relaxation strength, and the erythrocyte sedimentation rate (ESR), which has been classically used as a biomarker of inflammation, could not be examined in detail in this study. Moreover, ESR requires 30–60 min or more for measurement, whereas dielectric properties can be measured within 10 s, and it is believed that the condition of erythrocytes can be accurately depicted with minimal external influences during the assay. Furthermore, ESR is considered to be affected by many factors other than changes in the dielectric relaxation strength and does not necessarily reflect the same factors. Additionally, ESR is also affected by anemia and polycythemia. In this regard, our previous study on Hct and dielectric relaxation strength identified an increase in dielectric relaxation strength with increasing Hct[45]. An increase in Hct results in a decrease in ESR, which indicates that the phenomena of an increase in the dielectric relaxation strength and enhancement of ESR are not necessarily the same.

As demonstrated in Figure 3, when the dielectric relaxation strength was higher than a certain level, a decrease in band 3 of red blood cells and fragmentation of the C-terminus of PRDX2 were observed, possibly due to oxidative stress-induced calpain activation[37]. In a study of 16 transplant patients, these changes were observed only in cases of severe GVHD with grade 3 or higher, and not in grade 1–2 GVHD[37]. This suggests that changes in the intensity of the total blood dielectric relaxation after HSCT reflect the severity of GVHD and oxidative stress. By comprehensively considering the results of this study and the principle of dielectric coagulation measurement, a conclusion can be reached that the dielectric relaxation strength sensitively reflects the distribution pattern of blood cells in the solvent and their shape change[14]. Based on clinical data and *in vitro* experiments, the stage from rouleux to aggregate formation may be an indicator of serious illness. From this perspective, the experimental results displayed in Figure 6 provide important information for the quantitative interpretation of the dielectric relaxation strength. Figure 8 displays a schematic illustration of the mechanism of circulatory and coagulopathy development in GVHD after HSCT, as proposed in this study, of changes in the dielectric relaxation strength and membrane protein changes in erythrocytes.

In this study, we could not compare various previously reported GVHD biomarkers with changes in the dielectric properties of whole blood. This report does not indicate that changes in the dielectric properties of blood are superior to those in previously reported GVHD biomarkers[46]. The changes in the dielectric properties of blood are not specific to GVHD. A modification in the dielectric properties of blood is believed to arise due to conditions that induce alterations in plasma composition, fostering the development of erythrocyte aggregations. One of these includes classically recognized acute inflammatory alterations, and as previously mentioned, the parameter known as ESR is believed to indirectly mirror similar phenomena. The pathway by which severe GVHD leads to irreversible organ failure is not necessarily limited to direct organ damage caused by the GVH reaction through the alloimmune response; secondary and latent circulatory disorders are also involved. From this perspective, we believe that the changes in the dielectric properties of

blood examined in this study provide a new perspective for understanding and managing GVHD.

CONCLUSION

The pathological significance of the dynamic changes in blood dielectric relaxation strength in acute GVHD identified in this study requires further investigation. In the future, we believe that more detailed quantitative analysis of dielectric relaxation strength and consideration of its relationship with other clinical parameters will be necessary. Furthermore, the clinical usefulness of dielectric relaxation strength as an interesting and unique biomarker as well as a target for therapeutic intervention should be duly considered.

ARTICLE HIGHLIGHTS

Research background

We previously presented the discovery of a principle and the development of a novel instrument for measuring whole blood coagulation. This was achieved by assessing the variations in the dielectric properties of whole blood.

Research motivation

This assay of dielectric properties of whole blood may be useful for evaluation of coagulation abnormalities observed in graft-versus-host disease (GVHD).

Research objectives

To investigate how GVHD affects the changes of dielectric properties of whole blood in patients with hematopoietic stem cell transplantation (HSCT) and pathological significance of dielectric properties of whole blood in GVHD.

Research methods

We examined the changes of dielectric properties of whole blood and erythrocyte proteins by sodium dodecyl sulfate-polyacrylamide electrophoresis sequentially in patients with HSCT and compared it with clinical symptoms and inflammatory parameters of GVHD.

Research results

During severe GVHD, the dielectric relaxation strength markedly increased and expression of band3 decreased. The dielectric relaxation strength normalized with the improvement of GVHD. *In vitro* analysis confirmed that the increase of relaxation strength was associated with severe erythrocyte aggregates, but not with decreased expression of band3.

Research conclusions

Severe erythrocyte aggregates observed in GVHD may cause coagulation abnormalities and circulatory failure, which, together with the irreversible erythrocyte dysfunction we recently reported, could lead to organ failure.

Research perspectives

The pathological significance of the dynamic changes in blood dielectric relaxation strength in acute GVHD identified in this study requires further investigation. Furthermore, the clinical usefulness of dielectric relaxation strength as an interesting and unique biomarker as well as a target for therapeutic intervention should be duly considered.

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FOOTNOTES

Author contributions: Nagasawa M conceptualized and designed the study, supervised the study, drafted and revised the manuscript.

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Informed consent statement: Written informed consent was obtained from the guardians of each SCT patient.

Conflict-of-interest statement: All the authors have no conflicts of interest to declare.

Data sharing statement: Data available on request from the authors.

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SCIENTOMETRICS

Unveiling transplantation research productivity of United States: A bibliometric analysis

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Abstract

BACKGROUND

The United States has witnessed significant advancements in the field of organ transplantation over the course of the last five decades, as demonstrated by a notable increase in the quantity of academic research. The presence of a highly dynamic research environment necessitates continuous evaluations to maintain the integrity and progress of the field.

AIM

To evaluate the total output and thematic emphasis of transplant research conducted in the United States.

METHODS

On January 10, 2023, we conducted a bibliometric search of United States research output in transplantation journals from the Web of Science database's Science Citation Index Expanded. We excluded editorials, meeting abstracts, and other non-article types. We analyzed annual trends, authors, institutions, articles, keywords, and countries collaborating with the United States, using VOSviewer 1.6.18 to create figures and tables.

RESULTS

The United States published 25956 papers (3078 reviews and 22878 articles) representing 37.7% of the world's scientific output. Canada emerged as the top collaborator with the United States, co-authoring 1263 articles. Leading institutions in United States transplantation research were the University of Pittsburgh (1749 articles), Mayo Clinic (1605 articles), Harvard Medical School (1549 articles), and Johns Hopkins University (1280 articles). The top three keywords with over 2000 occurrences were "recipients," "survival," and

"outcomes," indicating a focus on graft and recipient outcome markers by United States researchers.

CONCLUSION

Our findings demonstrate the United States leadership in organ transplantation research, contributing significantly to the global scientific output in this field. However, opportunities exist for fostering expansive partnerships, particularly with developing countries. This study provides valuable insights into the transplantation research landscape in the United States, emphasizing the importance of ongoing evaluations to maintain and propel advancements in this critical medical discipline. The results may facilitate future collaborations, knowledge exchange, and the pursuit of innovative solutions in the realm of organ transplantation.

Key Words: Scientometrics; Bibliometrics; Research output; Organ transplantation; United States

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Core Tip: This manuscript presents a compelling bibliometric analysis exploring the United States's pioneering productivity in the field of organ transplantation research. The study delves into 50 years of academic publications, providing valuable insights into annual trends, key authors, institutions, top keywords, and international collaborations. With 25956 papers published, representing 37.7% of the world's output, this research highlights the United States dominant position. The findings emphasize the significance of ongoing evaluations in sustaining advancements and fostering potential collaborations. Reviewers will appreciate the comprehensive approach and the potential to shape future research directions in transplantation.

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INTRODUCTION

Organ transplantation in the United States has a long and storied history[1-3]. Since the early twenty century, American researchers, along with others from around the world, have made incredible strides in understanding the fundamentals of transplantation[1,4]. However, the first successful organ transplant did not occur until the middle of the twentieth century, when the Murray team in Boston performed the first kidney transplantation in the globe[5]. The field of transplantation in the United States has advanced significantly in the last 50 years; this advancement in the field has resulted in a large number of publications.

The total number of scientific papers and citations is a marker in international scientific rankings and a measure of the academic productivity of the field for countries, organizations, and even researchers. Continuous evaluation of research publications is crucial to the growth and maintenance of the research enterprise. The SCImago Journal & Country Rank shows that in 2021, the United States published 726552 scientific papers, up from 603364 in 2010 and 371642 in 2000. According to the SCImago report, the number of medical publications published in 2021 was 296782, up from 190470 in 2010 and 134443 in 2000[6]. However, the progress in academic performance of organ transplantation research in the United States has rarely been studied.

Bibliometric analysis is frequently employed to study patterns in scholarly publications and the relative significance of articles on a particular subject[7-9]. Numerous medical specialties, including surgical oncology, anesthesia, cosmetic and reconstructive surgery, and others, have increasingly used bibliometric analysis to evaluate the output of national research in recent years[10-13]. However, to our knowledge, bibliometric studies of articles written in the United States about organ transplantation have not been done before.

In this study, we aimed to evaluate the research output of the United States in the field of organ transplantation and the contributions of United States transplant centers and researchers from 1998 to 2022. We also aimed to assess the development of the research status of organ transplantation in the United States by evaluating research interests and hot topics over time.

MATERIALS AND METHODS

Data collection and retrieval methods

On January 10, 2023, a bibliographic search was undertaken to identify the publications published in transplantation journals in the United States. The journals were collected from the transplantation category of the Science Citation Index Expanded provided by Clarivate in the Web of Science database. The Web of Science database has a vast collection of

academic journals, providing a comprehensive historical view of academic publications. The utilization of databases such as Scopus and PubMed provide valuable insights. However, because of its extensive breadth and historical coverage, Web of Science emerged as the most suitable option for our specific research investigation[14]. We chose the Science Citation Index Expanded over the Emerging Sources Citation Index explicitly. The selection was made of the well-established reputation of the Expanded Index in the field of bibliometric studies. Within the transplantation category, every material from the Emerging Sources Citation Index was represented in the Expanded section, Notably, the sole exception was the Journal of Transplantation, which was listed under Emerging Sources Citation Index only and comprised only eight articles. Given the limited content from this journal and the comprehensive coverage offered by Expanded section, we deemed the latter more appropriate for our study rendering it unnecessary to reference both categories concurrently.

We have queried the Web of Science database using the publication titles to search all documents published in transplantation journals in the field "publication titles", listed in the supplement file. Articles published after 1998 were available only on the Web of Science Data and were included. We only included articles or reviews; we did not include abstracts of meetings, letters, notes, editorials, or errata. All the included articles were in English, but one was in Russian. We did not include journals related to bone marrow transplant and artificial organs, which were: Bone Marrow transplantation, Stem Cells and Development, Biology of Blood and Marrow Transplantation, Artificial Organs, International Journal of Artificial Organs, Journal of Artificial Organs, and Asaio Journal. A supplement file with the exact algorithm is attached.

Data analysis

We have analyzed annual trends, authors, institutions, journals, articles, keywords, and countries that collaborated with the United States. Figures and tables were generated using VOSviewer version 1.6.18 and MS Excel from Office 365. We have used a flow chart to elaborate on our included and excluded results. The categorization of articles was conducted by utilizing the institutional affiliations provided within the articles. In particular, an article was designated as a "United States article with international affiliation" if at least one of its authors was affiliated with an institution located outside of the United States. The primary objective of this classification system was to offer a comprehensive perspective on global cooperation, with a foundation based on simplicity. It is worth noting that in cases when authors have dual affiliations, an item was classified under the category of "United States article with international affiliation" if any of the affiliations indicated were non-American. In the keyword analysis, we have manually removed words that implied the study design such as "clinical trial" or "retrospective study", and redundant words such as "human", "disease", "male", "female", "adult", *etc.* we also removed the words that are related to the search like "transplant" and "transplantation" and "US" or "United states".

VOSviewer network visualization interpretation

The terms in the network visualization are circles whose size depends on their weight. An item's color depends on its cluster. Linkages are shown by lines. The visualization's distance between circles roughly indicates the co-citation relationship between the terms represented by the circles. The closer two circles are, the more linked they are.

RESULTS

Included studies

The number of publications in transplant journals was 241864. After considering only the articles and review articles, we have included 69110 total publications. There was a total of 25956 papers published in the United States only, representing 37.7% of the world's research output, of which 3078 were reviews, and 22878 were articles (Figure 1). The United States research on transplantation got 776262 citations.

Annual trends

Figure 2 shows annual publications since 1998. United States published 434 articles in 1998. That number rose to 837 in 2003 and climbed to 1192 in 2013. In 2016, the number of publications declined to 1078, but they rose again to 1724 in 2021. However, the number of publications in 2022 displayed a significant decline, with just 1222 articles.

Institutions

In terms of the total number of publications, there were 111 United States institutions that published at least 100 articles, 55 that published at least 200 articles, and 41 that published at least 300 articles. 22 institutions published at least 500 articles. However, only six institutes published at least 1000 articles. The top contributing institutions were the University of Pittsburgh with 1749, Mayo Clinic with 1605; Harvard Medical School with 1549; and Johns Hopkins University with 1280 publications.

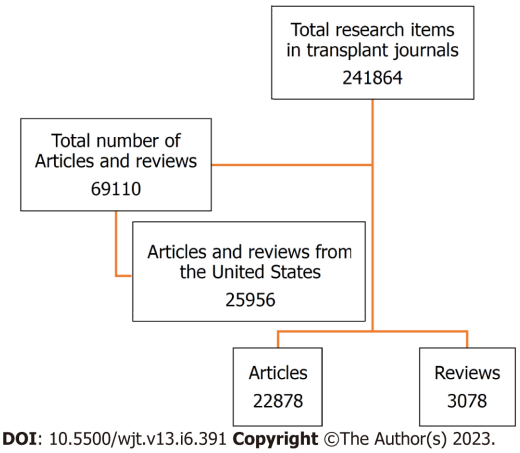
In terms of the number of citations, again, the University of Pittsburgh ranked first with 68810 citations, followed by Harvard Medical School with 54838 citations, the University of Michigan with 49111 citations, and the University of California, Los Angeles with 45440 citations (Table 1).

Authors

Seven hundred and thirty-seven authors published at least 20 documents, 81 authors published at least 50 articles, and

Table 1 Top-contributing institutions in United States transplantation research according to the number of citations

Organization	Citations	Total link strength
University of Pittsburgh	68810	23409
Harvard Medical School	54838	13446
University of Michigan	49111	17482
University of California Los Angeles	45440	16112
University of Minnesota	43839	16069
Mayo Clinic	42903	14975
University Calif San Francisco	41100	15648
University of Pennsylvania	31353	14566
Washington University	31142	12641
Stanford University	30728	12815
Johns Hopkins University	30682	14709
Columbia University	25437	11562
University Washington	24740	8223
Northwestern University	24273	12338
Massachusetts Gen Hosp	22332	9733
Emory University	21746	10037
Duke University	21557	10097
Cleveland Clinic	20612	10384
University of Miami	19751	5763
University of Alabama Birmingham	19735	10386



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Figure 1 Flow chart of the United States transplantation research output and exclusion criteria.

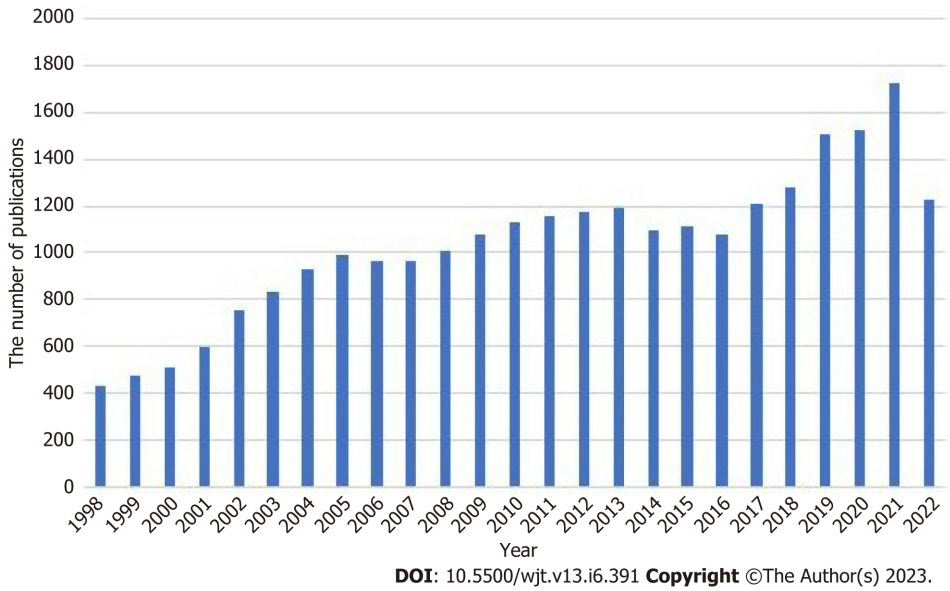
eight authors published at least 100 articles. In terms of citations, 138 authors got at least 2000 citations, 57 got at least 3000 citations, 36 got at least 4000 citations, and at least 23 authors got at least 5000 citations. The top 20 most cited authors are listed in Table 2. The top 5 authors, in order of citations on their transplant publications, were Dory Segev with 12490, James Kirklin with 10323, David Cooper with 10307, Merion, Robert M. with 9580, and Leah Edward with 9547.

Journals

The list under the category "transplantation" has 32 journals; after the exclusion, we searched 25 journals. Most publications were published in Transplantation (n = 4795) and the American Journal of Transplantation (n = 3954). Journal of

Table 2 Top 20 most cited authors in the transplantation research from the United States

Author	Research field	Citations	Documents
Segev Dorry L	Transplant epidemiology	12490	378
Kirklin James K	Heart transplantation	10323	145
Cooper David	Heart transplantation xenotransplantation	10307	228
Merion Robert M	Liver transplantation	9580	104
Edwards Leah B	Heart transplantation	9547	71
Stehlik Josef	Heart transplantation	9315	113
Naftel David C	Heart transplantation	8179	80
Kasiske Bertram I	Kidney transplantation	8144	179
Pagani Francis D	Heart transplantation	8039	52
Sachs David H	Transplant immunology	7942	207
Israni Ajay K	Kidney transplantation	7328	157
Kormos Robert I	Heart transplantation	7111	36
Snyder Jon J	Transplant epidemiology	6738	137
Kuchervavava Anna V	Research analyst/heart and lung	6248	35
Meier-Kriesche H-U	Kidney transplantation	5630	59
Yusen Roger D	Lung transplantation	5442	34
Wiesner Russel	Liver transplant	5338	40
Christie Jason D	Lung transplantation	5259	47
Skeans Melissa A	Kidney transplantation	5247	71
Smith Judi M	Kidney transplantation	4945	54



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Figure 2 Publication trends in the United States in the field of transplantation, as documented in transplantation journals from 1998 to 2022.

heart and lung transplantation (n = 2388). The American Journal of Transplantation has received the highest number of citations (n = 194905), followed by Transplantation (n = 185248) and the Journal of Heart and Lung Transplantation (n = 96827) on papers addressing transplantation. The Indian Journal of Transplantation, Transplant Research, Risk Management, and International Journal of Organ Transplantation Medicine have the least number of articles published in the United States, with 9, 7, and 7 documents, respectively. The lowest United States publications were found in the Russian Journal of Transplantology and Artificial Organs, with 1 document. Table 3 lists the transplant journals and the number of United States articles and citations found.

Countries collaborations

We found that American researchers were collaborating with individuals in 114 different nations. Fifty-five countries had at least ten articles in collaboration, 35 had at least 50, 22 had at least 100, 8 had at least 500, and 2 had at least 1000. The country with the highest number of articles collaborated with the United States with the highest number of articles was Canada, with 1263 articles, followed by Germany with 1012, England with 807, and Italy and France with 719 and 598, respectively. The collaboration also extends to Asia with Japan and China, which collaborated with 594 and 579 articles. Middle eastern countries also collaborated with Saudi Arabia with 75, United Arab Emirates and Jordan with 28 and 19, respectively. Table 4 and Figure 3 show the list of countries with the most publications on collaboration with the United States and a visualization of each country's collaboration and interconnections.

Keywords

The top 20 most frequently occurring keywords in this topic are shown in Table 5. There are 3 of them that have occurred more than 2000 times, including "recipients", "survival", and "outcomes". Figure 4 shows the most occurring keywords and their interconnection across the years.

DISCUSSION

This study provides a comprehensive review of scientific publications on organ transplantation in the United States during the past 25 years. The significant increase in publications demonstrates the growing commitment of the United States to advancing transplantation knowledge. This has been sparked by a number of factors, including increased organ donation and transplantation[15], the growth of transplant centers, innovations in machine perfusion and xenograft, and increased research funding[1,16].

Nevertheless, the decline in publications in the year 2022 necessitates a crucial reconsideration. Does the decrease in publication numbers suggest a diminished emphasis on transplantation-specific journals, or does it signify broader changes in research interests? The drop that has been seen highlights the importance of employing a diverse methodological approach in the assessment of research outputs. This may involve considering the inclusion of interdisciplinary journals in future evaluations.

The volume of research conducted on kidney transplantation corresponds with the frequency of kidney transplant surgeries in clinical practice[15]. However, this observation may also imply that there is an excessive focus on studies in specific areas, highlighting the necessity for a more diverse research strategy that encompasses less-explored organs or alternative transplantation approaches (Figure 5).

In 2022, American authors most frequently collaborated with authors from Canada, England, and Germany. In 2000, the United States collaborated most with Japan, Canada, and England. Canada, Germany, England, and Italy are the countries with the highest number of collaborative papers with the United States all over the years; nonetheless, it is noteworthy that Canada's collaboration with the United States increased steadily until its first peak in 2010 with 62 articles, after which it stabilized until a new spike in 2018 with 96 articles, double the number of articles published in 2014; this spike continued until its second peak in 2021 with 111 articles. On the other hand, cooperation with Germany has grown steadily since 2000, reaching a record high of 61 articles in 2011. However, the number of collaborative publications decreased from 2011 to 2015 before beginning to rise again, although not to the level of collaboration with Canada; the second peak was in 2021, with only 62 articles. With a peak of 81 articles in 2021, the number of articles written in collaboration with England has increased steadily and consistently since 2000.

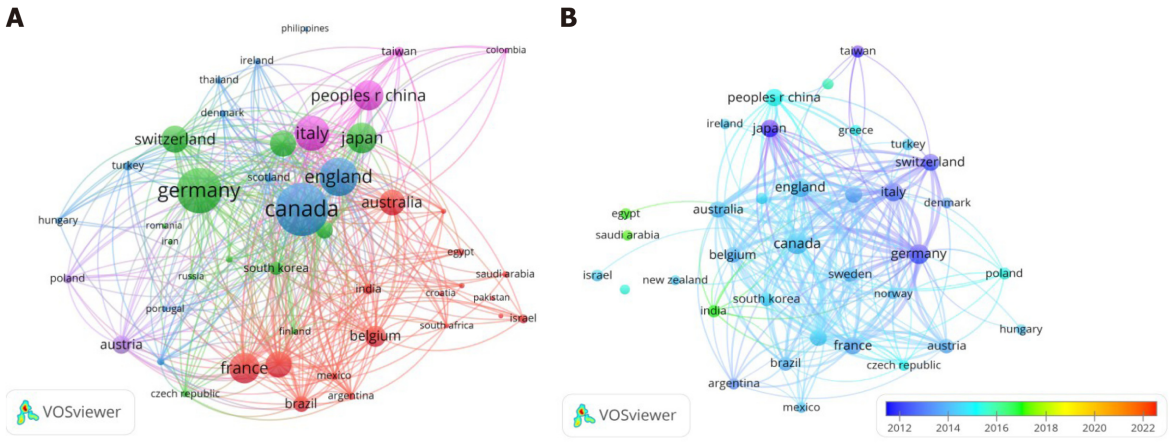
Until 2004, only one article was published by Chinese and American authors. Since then, it has progressively increased, peaking at 34 papers in 2012 and 59 articles in 2019, before declining significantly to 29 by 2022. African countries and institutes collaborated poorly. Egypt and South Africa collaborated the most, with 86 and 44 articles, respectively. Zambia, Nigeria, and Morocco collaborated in a few articles. South American collaboration is represented mainly by Brazil with 238 articles, Argentina with 91, Mexico with 78, and Peru with nine articles. Egypt, India, Saudi Arabia, and the Philippines were the countries that collaborated most recently, more so since 2016, compared to Germany, Italy, Switzerland, and Japan, which showed that the collaboration extends to 2010 and before, as shown in Figure 3B.

Since there is an imbalance between organ transplantation demand and availability in the United States, Global Paired Exchange could be an excellent option to improve the immunologic diversity of donors by including donor and recipient pairs from countries with low healthcare resources for end-stage renal disease. Alongside all precautions, We believe that collaborative research between the United States and other countries can enhance this global paired exchanges program [17-19].

Interestingly, the majority of the top 20 highly referenced authors were in the fields of heart and lung transplantation, with seven authors receiving citations for their papers on cardiac transplantations and three authors receiving the majority of citations for their papers on lung transplantations. Five authors on the list were cited for their research in the

Table 3 Number of publications and citations in transplant journals for transplantation-related research performed in the United States

Source	Citations	Documents	Total link strength
American Journal of Transplantation	194905	3954	41343
Transplantation	185248	4795	36949
Journal Of Heart and Lung Transplantation	96827	2388	11098
Liver Transplantation	74441	1815	11807
Nephrology Dialysis Transplantation	67526	1863	1779
Clinical Transplantation	32154	2082	15473
Cell Transplantation	25588	891	1668
Pediatric Transplantation	20700	1539	7404
Current Opinion in Organ Transplantation	13792	1029	10805
Transplant Infectious Disease	13246	932	3799
Transplantation Proceedings	12859	1166	4596
Transplant International	11987	624	5674
Xenotransplantation	11935	512	3930
Transplant Immunology	7017	342	2345
Progress In Transplantation	4622	550	2382
Transplantation Reviews	3010	153	2258
Experimental And Clinical Transplantation	1229	275	1272
Transplantation Direct	1183	341	2574
Annals of Transplantation	979	142	764
Transplantation And Cellular Therapy	902	375	166
Current Transplantation Reports	344	126	1366
International Journal of Organ Transplantation Medicine	35	7	35
Transplant Research and Risk Management	9	7	37
Indian Journal of Transplantation	0	9	52
Russian Journal of Transplantology and Artificial Organs	0	1	0

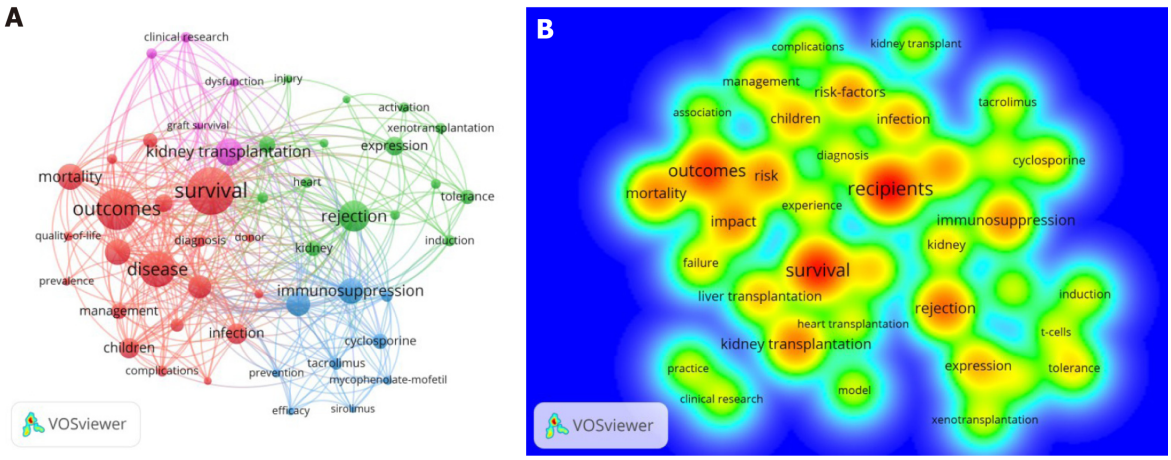


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Figure 3 Network visualization showing most cited countries contributed with the United States in the field of transplantation research. A and B: The size of the circles represents the weight of citations.

Table 4 Publications and citations of the top-collaborating countries with the United States

Country	Documents	Citations	Total link strength
Canada	1263	55702	28468
Germany	1012	44713	19065
England	807	36042	17916
Italy	719	33311	14855
France	598	32373	14968
Japan	594	21229	8395
China	579	13450	6755
Switzerland	506	25882	12413
Netherlands	479	18867	9232
Spain	478	24101	12506
Australia	473	24439	13353
Belgium	357	23002	9931
Austria	290	12571	7877
Sweden	266	11197	4958
Brazil	238	10420	6457
South Korea	197	6195	3019
India	138	4197	3039
Taiwan	129	4398	1949
Israel	116	2539	1121



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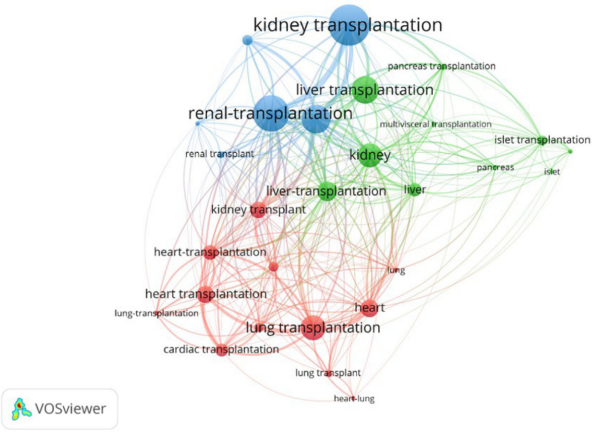
Figure 4 Cluster map of the most occurring keywords and their interconnection across the years. A: Each circle represents a keyword, and the size of the circles represents the frequency of occurrence. Larger circles indicate that the keyword appears more frequently. Keywords included in the same cluster are displayed in the same color. The distance between the 2 circles shows the degree of the relationship; B: Overlay map of keyword occurrence over time for papers published on the field of transplantation from the United States. The red color represents the key words that have been discussed more frequently.

field of kidney transplantation, while two were cited for their work in liver transplantation. One author is a research analyst, and the majority of citations received are for the work on registries, which may not provide any insight into the scientific work. Two authors published in the field of transplant epidemiology, including the most cited author, Dorry Segev, who published 378 documents that received 12490 citations in transplant journals.

There is no doubt that solid organ transplantation is the area of medicine in the United States that has paid the most attention to the process of evaluating recipient and graft outcomes. The results of this study confirmed this assertion, as "survival" and "outcome" were the most frequently used keywords in connection to graft and recipient outcome measurements. The United Network for Organ Sharing and Organ Procurement and Transplantation Network in the

Table 5 Most occurring keywords in the research on transplantation from the United States

Keyword	Occurrences	Total link strength
Recipients	3045	13158
Survival	2779	11573
Outcomes	2399	10308
Rejection	1792	7691
Kidney transplantation	1605	7823
Mortality	1501	6280
Risk	1497	6105
Impact	1490	6486
Immunosuppression	1484	7371
Renal-transplantation	1403	6297
Therapy	1347	4974
Risk-factors	1340	5482
Infection	1195	4580
Children	1154	4366
Expression	1083	3647
Kidney-transplantation	1080	4763
Liver transplantation	1020	3976
Lung transplantation	931	3809



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Figure 5 Network visualization of the most common keyword after restricting the search to organs transplanted name. Larger circles indicate that the keyword appears more frequently. Keywords included in the same cluster are displayed in the same color. The distance between the 2 circles shows the degree of the relationship.

United States are responsible for monitoring the outcomes of organ transplantation centers and patients[20,21]. Outcome management aims to ensure that transplant recipients receive the best possible care and that the transplant successfully improves the recipient's quality of life. This is achieved by using the data and information collected during the transplant process to make decisions about the recipient's care and treatment.

Although the United States has made significant advances in transplantation over the past few decades, readers should keep in mind that counts of publications and citations conceal unmeasured characteristics like the density of knowledge in each article and data sets that accompany articles when assessing the data presented in this report. Publication numbers are one indicator of a nation's research output, but not the only one.

Some of these articles' limitations should be addressed. First, the primary emphasis of our analysis was on academic journals categorized under the "transplant" category within the Web of Science database. This approach was taken to ensure that our study included fundamental research in the field of transplantation. Although this approach is thorough,

it might overlook journals that are not primarily categorized under the field of 'transplantation' but occasionally publish articles that are pertinent to the topic. Second, we removed journals specific for bone marrow transplant and artificial organs journals; however, specific articles published in the journals included in our analysis may not be directly connected to solid organ transplant. Furthermore, articles pertinent to transplant may have been published in other journals not included in our analysis. Consequently, our investigation may offer a cautious approximation of transplantation studies. However, despite the presence of consistent criteria, our findings continue to provide significant insights.

CONCLUSION

The number of scientific research articles authored by American authors on the subject of organ transplantation has been steadily increasing over the past 25 years, which has paralleled the progression of the field as a whole. However, there has been a significant reduction in research production in 2022, which may demand observation and monitoring in the coming few years. The top three most frequent words in this study were "outcome," "survival," and "recipients," indicating that graft and recipient outcome measurements were of considerable significance to American researchers. The United States has made substantial contributions to the global advancement of organ transplantation practice. Nevertheless, there is room for substantial partnerships with other countries, particularly developing ones.

ARTICLE HIGHLIGHTS

Research background

Over the years, significant advancements have been made in the field of organ transplantation, saving innumerable lives and improving the quality of life for patients worldwide. The United States plays a pivotal role in advancing these advancements, contributing a substantial volume of research and clinical innovations. Given this position of leadership, ongoing assessments are essential for navigating the swiftly evolving landscape of transplantation research. These evaluations aid in identifying emerging trends, identifying areas of interest, and highlighting opportunities for international collaborations. Therefore, periodic evaluations, especially using techniques such as bibliometric analysis, are essential for maintaining the United States' cutting-edge contributions to this vital medical field and for guiding future research endeavors.

Research motivation

Bibliometric analysis is a useful method for systematically evaluating research output in order to navigate this ever-expanding landscape. This form of analysis provides a comprehensive overview of current research trends, influential publications, and key areas of concentration. It establishes a data-driven foundation for future research directions, ensuring that efforts are focused on areas with the greatest impact and need. Consequently, periodic bibliometric assessments are essential for maintaining the field's ongoing progress and sustaining the vitality of research efforts in this essential medical discipline.

Research objectives

This study's primary objective is to conduct a thorough analysis of the current status of organ transplantation research in the United States. Specific objectives include identifying the primary contributing authors and institutions, assessing the predominant research topics through keyword analysis, and determining the scope of international collaborations.

Research methods

In this first-of-its-kind study, we utilized the Web of Science database to perform a comprehensive bibliometric analysis. This resource was selected due to its extensive collection of academic journals. The software VOSviewer was used to visualize data, enabling the identification of key trends, such as top-contributing institutions and international collaborations. This bibliometric approach provided unprecedented insight into the prevalent research trends, major contributors, and key focus areas in United States organ transplantation research output.

Research results

This comprehensive analysis provides important insights into the current status of organ transplantation research in the United States. The University of Pittsburgh emerges as an important institution, indicating a concentration of expertise and potentially functioning as a hub for future cooperation. The American Journal of Transplantation's high number of citations demonstrates its reputation as a prominent venue for disseminating influential research, thereby influencing the field's practices and policies. Moreover, Canada's position as the United States' top international collaborator demonstrates the efficacy of global partnerships in advancing research. Despite these contributions, obstacles remain, such as the need for expanded international collaborations, particularly with developing nations, and the exploration of under researched areas in organ transplantation. These findings highlight the significance of ongoing evaluations in maintaining and advancing the field of study.

Research conclusions

In this study, a bibliometric analysis method was introduced to quantitatively evaluate the landscape of organ transplantation research authored by American researchers. Over the past 25 years, the number of scientific research articles written by American authors on the topic of organ transplantation has increased consistently, paralleling the overall development of the field. Nevertheless, a significant decline in research output was observed in 2022, necessitating close observation and monitoring in the years to come. Our study revealed that the three most frequently occurring keywords were outcome, survival and recipients, indicating the importance of graft and recipient outcome measurements to American researchers. Although the United States has made significant contributions to the global advancement of organ transplantation practice, there is still plenty of opportunity for collaboration with other nations, particularly developing countries.

Research perspectives

The study sheds new light on collaboration in organ transplantation research. By utilizing bibliometric methods, we were able to identify crucial collaboration patterns. Within the United States, the interdependence of prominent institutions is evident. An important international collaborator stands out. These insights suggest that future research could benefit from targeted collaborations that capitalize on the assets of prominent United States and international centers and authors. Particularly, unrealized potential exists for partnerships with developing nations to expand the global scope of organ transplantation research.

FOOTNOTES

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