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Big data and variceal rebleeding prediction in cirrhosis patients

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Abstract

Big data has convincing merits in developing risk stratification strategies for diseases. The 6 "V"s of big data, namely, volume, velocity, variety, veracity, value, and variability, have shown promise for real-world scenarios. Big data can be applied to analyze health data and advance research in preclinical biology, medicine, and especially disease initiation, development, and control. A study design comprises data selection, inclusion and exclusion criteria, standard confirmation and cohort establishment, follow-up strategy, and events of interest. The development and efficiency verification of a prognosis model consists of deciding the data source, taking previous models as references while selecting candidate predictors, assessing model performance, choosing appropriate statistical methods, and model optimization. The model should be able to inform disease development and outcomes, such as predicting variceal rebleeding in patients with cirrhosis. Our work has merits beyond those of other colleagues with respect to cirrhosis patient screening and data source regarding variceal bleeding.

Key Words: Big data; Disease onset; Prognosis; Modeling; Cirrhosis; Gastrointestinal rebleeding

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Core Tip: Big data have been applied in many fields including finance, traffic control, logistics, healthcare, and environmental protection. Modeling is an efficient method for completing various tasks, and verification of its validity is vital for ensuring high-quality operation and yielding satisfactory results. Predictor screening guarantees the establishment of a practical, convenient, and favorable model for prognosis prediction. Utilizing a regression model trained with numerous data mined from big data acquired from real-world hospitals is helpful for informing disease or status onset and its prognosis such as in variceal rebleeding, which is one of the leading causes of death in cirrhosis patients.

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INTRODUCTION

Many risk stratification strategies for diseases mainly depend on single-/medium-sized cohort studies or their meta-analysis[1,2], with lead-time bias taken into consideration[3,4]. This type of study method is, by design, well scheduled and well phenotyped but selective for the population sampled, which may not reflect the real-world, pan-subject profile. Real-world patients may have comorbidities, be taking concomitant medications, may be excluded from short-term follow-up, or have poor patient compliance. Direct data acquisition from basic healthcare institutions and cohorts is more representative than limited sampling.

HISTORY OF BIG DATA

Although the use of piles of data in the medical field has a relatively long history[5-7], the term “big data” appeared only in the 1990s and quickly became popular[8-10]. “Big” is a relative term, especially when it relates to data. Big data usually refers to datasets that exceed the capabilities of commonly used software tools to store, manage, and process that amount of data within a suitable period of time[11]. The term is described by 315 characteristics[12] and fundamentally by the 6 “V”s: volume, velocity, variety, veracity, value, and variability[13-17] (Figure 1).

During the recent decade, methods for collecting, storing, and managing big data have evolved[18-20]. We are now entering an era of monitoring health changes using clinical indicators, such as vital signs, serum sugar, lipids, sweating, and bladder fullness, with wearable devices[11]. These changes can reflect physiological change. Constant variation and altered levels may result in different pathological states. Here, we review the applications of big data in predicting disease onset and prognosis, especially variceal rebleeding prediction in cirrhosis patients.

APPLICATIONS OF BIG DATA

Applications of big data include its use as a tool to monitor the onset of conditions and diseases. Big data have been used for this purpose in relation to hypertension[21], pediatric oncology[22], oral care [23], general practice[24], rheumatic diseases[25], renal diseases[26], mechanical ventilation management in the intensive care unit[27], and cirrhosis and hepatocellular carcinoma morbidity in the nonalcoholic fatty liver disease/nonalcoholic steatohepatitis population[28]. Situations such as the commencement, development, and control of diseases can be studied and visualized using big data techniques, which is a promising and beneficial approach. With the help of big data, the creation of large, collaborative data can lay a more solid foundation for robust data sharing and scientific discovery in predicting the onset of pediatric oncology. Registry-based research, however, is one of the conventional research methods regarding pediatric cancers. In these studies, a multisite registry for the study of pediatric patients was utilized, including fields of descriptive epidemiology, survivors, genomics, new registry description, data harmonization, palliative and supportive care, radiology, consensus guidelines, hereditary pediatric cancer, electronic health records, and prospective clinical trials. Limitations of registry-based research include the latest publication time range only, a restricted single publication database, and a limited amount of research and registries only if they have yielded publicly-published peer-reviewed papers[22]. With this study strategy, data cannot be automatically mined, cleaned, and integrated to perfect the already existing study. When it comes to new subjects, we need to redo the statistical analysis, while modeling and machine study in the big data scenario can perform the

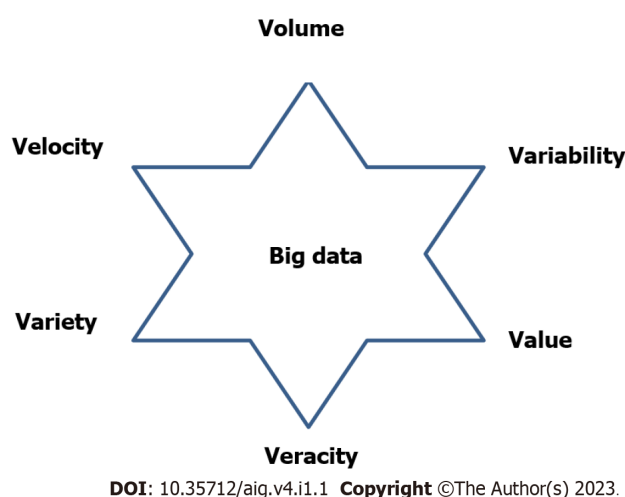


Figure 1 Six “V”s of big data.

whole analysis process.

Healthcare data in some regions are complete and accessible for analysis. Real-world data from primary healthcare facilities in communities in European countries are a good resource, as the primary healthcare service is state-covered and there are few or no co-payments. Therefore, healthcare information and data are collected and stored by state-run big data centers. Most residents are registered at birth and have their complete healthcare information in electronic form, which can be accessed by regional practitioners and analyzed for real-world application scenarios[29]. However, numerous parameters, especially administrative data, mined from patients' inpatient and outpatient Hospital Information System/Electronic Medical Record system *via* various algorithms are at risk of information and privacy leaking. Therefore, preliminary selection of data, especially low-dimensional administrative data, is preferable to decrease information leakage and privacy invasion.

Big data boosts the depth and breadth of research in fundamental biology and clinical medicine. There is already impressive progress due to this, including in exome sequencing[30], genomics, and proteomics. Taking the coronavirus disease 2019 pandemic as an example, primary research, clinical practices regarding treatment, and even trends in media campaigns of whether or not executing lockdown and a positive policy of nucleic acid testing can be swiftly analyzed with big data tools to assist epidemic control[31].

STUDY DESIGN

Study design comprises data source selection, inclusion and exclusion criteria, standard confirmation and cohort establishment, follow-up strategy, and events of interest. A multicountry European real-world study acquired patient data within a set research period mined from central transcription, laboratories, pharmacy offices, medical insurance departments, administrative departments, and other departmental databases *via* an electronic health record data repository along with molecular typing from molecular biology laboratories for preventing outbreaks of hospital infections[32]. Chart presentations can be used to analyze and interpret descriptive data. The Fib-4 score (age, aspartate aminotransferase, alanine aminotransferase, and platelets), which is composed of entirely non-invasive parameters, has been used to detect early liver fibrosis[28].

MODEL DEVELOPMENT AND EFFICACY VERIFICATION

With respect to development and efficiency verification of disease onset and prognosis models, researchers have performed extensive work. Model development is the process of collecting vital parameters (risk factors) of consequence and weighted with varied weight coefficients to form a weighted function. This requires the identification of predominant predictors from a large amount of preselected candidate predictors, assigning proper weights to each predictor to obtain a combined risk score, and assessing the model's predictive performance with statistical methods such as a calibration plot. The latter includes calibration, discrimination, and (re)classification properties, assessing its potential for generalization using internal validation techniques and if necessary optimizing the model to avoid overfitting. Data sources should preferably be prospective cohort(s) with a randomized controlled trial design or real-world medical record data. Preferred outcome choices are those that are

related to patients or individuals such as remission time and follow-up period. Methods for outcome verification should be included, and the blind method is preferred.

Regarding the selection of candidate predictors, a surplus should be defined and analyzed before finally including a subset in the final model. Incorporation bias should be avoided by blinding. Data quality control, missing data processing, continuous predictor modeling, final model development, relative weight assignment for each predictor, and internal validation are essential in the process of creating a final prediction model[33].

Choosing appropriate statistical methods during model establishment is vital to guarantee reliability and validity. Regression analysis, including univariate and multivariate regression, is the most commonly used statistical method, especially Cox regression[34] and LASSO[35]. The hazard ratio is used to differentiate cohorts across different conditions and coefficients. Featured with net benefit and threshold probability for more convenient yet trusty clinical decision making, decision curve analysis has been used to evaluate whether or not to use a certain prediction model[36]. In this approach, the theoretical relationship between the threshold probabilities of a disease (that a disease will take place) and the relative frequency of false positives and false negatives are examined to ensure the validity of a prediction model.

The benefits of applying decision curve analysis can be quantified as whether a model can be easily and effectively applied in clinical situations. Its ability to help compare several different models regarding one issue is another advantage[37]. The parameter indicating risk threshold “T value” has been used to study treatment decisions in risk models. The harm-to-benefit ratio is related to the T value, which is in line with the former. Balancing all benefits and harms in different scenarios is key to determining which T value is reasonable[38]. The net benefit (NB) value, which is a combined “net” effect of the true positives and false positives, was introduced to evaluate the potential clinical application of an estimating tool or a risk-predicting model. Setting the decisive threshold range in modeling is important, which is the boundary to determine whether a patient is judged as positive for a disease or not[39]. However, NB does not directly make up the harms and costs in acquiring the predictors for the chosen model. The focus of NB is to derive the best tradeoff between sufficient indicators and convenience in clinical application[40].

Model optimization should be conducted in order to reduce the number of predictors and avoid an unmanageable dataset or workload. AMSGrad (“far from the minimum”), a putative optimal method for optimizing models, is commonly used for low-cost cause. By switching to the direct linear method near the end of the optimization, AMSGrad can do its magic as it has long convergence tails[41]. As for multiobjective racing algorithms with fixed confidence, SPRINT-Race is the first algorithm developed and uses a nonparametric, ternary-decision, dual-sequential probability ratio test to infer a pairwise dominance or nondominance relationship. In order to minimize the computational effort, the probability of mistakenly erasing any Pareto-optimal models or returning any clearly dominating models is restricted, which can achieve a pre-estimated confidence level to ensure the quality of the models generated[42], by sequentially applying a Holm’s step-down family-wise error rate control method. The quantification of model-to-data correspondence is pivotal to measure a model’s performance and future application for the problem at hand. The *Drosophila melanogaster* gap gene system model demonstrated the importance of error quantification, and it is applicable to a wide array of developmental modeling studies[43]. The support vector machine, GLM-Net, generalized linear model, partial least squares, neural network, k-nearest neighbors, random forest, and boosted tree are useful tools for establishing the model to predict prognosis in patients with breast cancer[44]. Comparing their differences in performance and necessary model optimization can lead to better and more efficient application in practice.

PREDICTOR SCREENING FOR PROGNOSIS

Researchers have proposed methods for predictor screening with regard to disease prognosis, such as the Model for End-stage Liver Disease (MELD) for cirrhosis-related mortality prediction and the APACHE model for critically ill patients. The clinical data of cirrhosis patients who had early admission, including clinical and socioeconomic factors, were mined from electronic medical records and classified for risk stratification in order to predict readmission within 30 d[45]. The European Organization for Research and Treatment of Cancer (EORTC) risk tables[46], which include six clinical and pathological factors (number of tumors, tumor size, prior recurrence rate, T category, carcinoma *in situ*, and grade), were recommended by the European Association of Urology and used to separately predict the short-term and long-term risks of progression and recurrence in an individual patient with a non-muscular invasive bladder tumor. It divided patients into four groups with individual recurrent and progression scores. However, as EORTC risk tables overestimated recurrence in all risk groups and progression in the high-risk group, the Club Urológico Español de Tratamiento Oncológico scoring model[47] was developed. The well-known new EORTC model[48], or European Association of Urology risk groups, was popular in recurrence and progression prediction, in which tumor diameter and extent were key predictors for progression prediction in multistate analyses. The health belief model has been

used for risk factors identifying aged Jordanian adults for prostate cancer screening[49]. Development and validation of a prediction model, including internal and external, temporal and geographical, domain validation, and their revision, are all crucial to identify predictors of prognosis[50].

RISK INDICATORS OF VARICEAL REBLEEDING IN CIRRHOSIS

Studies have reported several prediction models that predict variceal rebleeding in patients with cirrhosis. Risk indicators are components of prediction models. Invariably, studies in spotting possible risk indicators of variceal rebleeding among cirrhosis patients require a long study period. Child-Pugh score and hepatic-venous pressure gradient are the most significant prognostic factors in stratifying the probability of variceal rebleeding[51]. Antiviral treatment significantly reduced rebleeding in patients with hepatitis B virus (HBV)-related cirrhosis. In-time prophylactic endoscopic treatment of upper gastrointestinal varices after first-time bleeding, including endoscopic varix ligation (EVL) and gastric fundus varix gluing, is important in postponing variceal rebleeding[52]. Tachycardia, high creatinine level, and low albumin level are independent factors associated with rebleeding, suggesting a potential predictive role. The transverse of these variables into predictive scores may provide improved prognosis for patients with variceal bleeding[53]. Pre-emptive transjugular intrahepatic portosystemic shunt was independently related to a lower rebleeding rate[54]. Albumin transfusion in patients with low albumin levels was positively associated with a decreased rebleeding rate[55]. Five studies showed a lower rebleeding rate after EVL or drug therapy (non-selective β -blockers $\pm$ isosorbide mononitrate), and four trials found decreased variceal rebleeding with combined therapy (EVL+ non-selective β -blockers+ isosorbide mononitrate)[56].

However, some indicators have a negative function in preventing rebleeding. A multicenter, double-blind, parallel study of 158 patients indicated that taking simvastatin besides standard prophylaxis (rest, fluid restriction, preventing infection, regular endoscopic examination, anti-HBV therapy, non-selective β -blocker, *etc.*) did not decrease the rebleeding rate[57]. The rate of variceal rebleeding was not reduced after anticoagulation according to a single-center, prospective cohort study[58]. Worsened liver function or insensitive hemodynamic response to non-selective β -blockers indicated an elevated rebleeding rate [51]. A Chinese study of 3289 hospitalized patients who underwent EVL indicated that male sex, Child-Pugh score > 7.2 , and volume of blood vomited before EVL were independent risk indicators of early rebleeding, while albumin concentration > 31.5 g/L was a protective indicator[59]. Bacterial infection in patients with variceal bleeding was strongly positively related to early rebleeding[60]. Acute-on-chronic liver failure is an independent risk factor of variceal rebleeding[54]. The presence of ascites or hepatic encephalopathy, MELD score > 12 , or hepatic-venous pressure gradient > 20 mmHg indicated an elevated early (less than 6 wk) rebleeding rate[61].

The above indicators were then filtered and optimized by statistical methods, such as Cox regression or LASSO, and systemically integrated into a function with the help of programming or statistical software such as R, Python, SPSS, or SAS. This function was actually a preliminary prediction model.

SIGNIFICANCE OF PREDICTION MODELS

Models predicting disease onset and prognosis play an essential and sometimes surprising role as convenient assistants in planning prophylactic, therapeutic, and follow-up strategies. Traditionally, medical data such as medical history, results of physical examination, laboratory tests, imaging and endoscopic information, *etc.* were integrated by doctors' clinical comprehension or into patients' timelines drafted on a paper to identify how disease progressed and predicted the possible prognosis according to the trend in medical indicators. Prediction models free doctors from numerous medical data of patients with different diseases, complications, physical, psychological, and socioeconomic situations. All they need to do is to type prescribed parameters into the model and click! The results of the onset and prognosis of a given disease are then provided.

Prediction models are currently extensively applied in the medical field to inform individuals and healthcare providers on the risks of developing a particular disease, its outcome, and to guide doctors to make better decisions in mitigating these risks. A recent Chinese study indicated that the MELD score and MELD-Na score, including the R score, were useful in predicting variceal rebleeding[62]. Another study indicated that the MELD-Na score model, which indicates liver function, was more efficient than the MELD model and Child-Pugh score model in predicting rebleeding among cirrhosis patients who underwent EVL.

SAFETY AND PRIVACY CONCERNS

Last but not least, it is worth noting that models using low-dimensional administrative data outper-

formed in big data analysis with respect to decreasing information safety and privacy invasion. According to several studies, the models did not improve when high-resolution, privacy-invasive behavioral data were included[63]. De-ID software (De-ID Data) has been used to assign a study identification number to every enrolled patient. Therefore, criteria, included in the informed consent established by the research review board, for exemption from enrollment were met[32]. The *Drosophila melanogaster* gap gene system gives a good example of demonstrating the significance of error quantification, in which model parameters were optimized against *in situ* immunofluorescence intensities. It can be applied to other studies in various fields with regard to model development.

DISCUSSION

Gastrointestinal (GI) rebleeding is a leading cause of mortality in patients with cirrhosis, as massive GI bleeding can induce hemorrhagic shock, disseminated intravascular coagulation, and opportunistic infections, especially pulmonary infection and spontaneous bacterial peritonitis. Thus, reducing or postponing GI rebleeding is significant. A handy tool for clinicians that can be operated on smart phones or other mobile intelligent devices within seconds to evaluate the GI rebleeding rate is interesting and useful for risk grading. Just type in several common laboratory test indicators, click on “go,” and the rebleeding rate and prognosis of a specific patient are provided.

Our work has merits beyond those of other colleagues. According to our literature retrieval on PubMed, there are no other studies on the prediction and prognosis analysis of GI rebleeding except for one article published last year indicating that the degree of liver stiffness is consistent with GI rebleeding rate in cirrhosis patients[64]. However, the above mentioned exclusive study has limitations. First, it was a prospective cohort study with only 289 patients enrolled in the final analysis, although PASS 15 was applied to calculate the statistically minimum sample size. In our ongoing study applying big data platform to evaluation the rebleeding rate of cirrhosis patients, we obtained real-world data from a big data platform collecting many more indicators from six hospitals, which were automatically collected. Second, our study included patients with esophageal and gastric fundus varices rebleeding, which were the most common varices presented in cirrhosis patients, and the other study only included esophageal varix rebleeding. Finally, the previous study only included patients with HBV-related decompensated cirrhosis, while our data were collected from cirrhosis patients with alcohol-related cirrhosis, autoimmune-related cirrhosis, primary biliary cirrhosis, and lipogenic cirrhosis in addition to HBV-related cirrhosis. Following parameter filtering and modeling, our study used a visual nomogram to demonstrate correlations among risk indicators, occurrence, and prognosis of GI rebleeding, which provides clinicians with a more explicit demonstration of all indicators and their effects on one page to easily and rapidly evaluate a patient to establish a strategy for further management and follow-up.

CONCLUSION

Modeling is popular using regression analysis and has vast applications in predicting disease occurrence and prognosis. However, modeling and its validation are not the ultimate objective in terms of healthcare provider’s clinical participation and patients’ health outcomes. They need to be applied and provide convenience for clinical practice. Studies on the application and optimization of these models should be designed and conducted, focusing on the utilization of existing and updated models and their impact on behavior and (self-) management of physicians, healthcare providers, and general individuals[65,66], especially in patients with decompensated cirrhosis at high risk of variceal rebleeding and mortality. For diagnostic and prognostic modeling with higher consistency and efficiency in predicting, treating, and following up decompensated cirrhosis, more comprehensive data and a clearer display mode are needed.

FOOTNOTES

Author contributions: Yuan Q selected the topic and performed the majority of conception, writing, and revision of the manuscript; Zhao WL provided think tank, platform with regard to big data, site for academic discussion, and revision suggestions for the manuscript; Qin B provided administrative help and was the instigator and coordinator of the study; All authors have read and approved the final manuscript.

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Retrospective Study

Risk factor profiles for gastric cancer prediction with respect to *Helicobacter pylori*: A study of a tertiary care hospital in Pakistan

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Abstract

BACKGROUND

Gastric cancer (GC) is the fourth leading cause of cancer-related deaths worldwide. Diagnosis relies on histopathology and the number of endoscopies is increasing. *Helicobacter pylori* (*H. pylori*) infection is a major risk factor.

AIM

To develop an *in-silico* GC prediction model to reduce the number of diagnostic surgical procedures. The meta-data of patients with gastroduodenal symptoms, risk factors associated with GC, and *H. pylori* infection status from Holy Family

Hospital Rawalpindi, Pakistan, were used with machine learning.

METHODS

A cohort of 341 patients was divided into three groups [normal gastric mucosa (NGM), gastroduodenal diseases (GDD), and GC]. Information associated with socioeconomic and demographic conditions and GC risk factors was collected using a questionnaire. *H. pylori* infection status was determined based on urea breath test. The association of these factors and histopathological grades was assessed statistically. K-Nearest Neighbors and Random Forest (RF) machine learning models were tested.

RESULTS

This study reported an overall frequency of 64.2% (219/341) of *H. pylori* infection among enrolled subjects. It was higher in GC (74.2%, 23/31) as compared to NGM and GDD and higher in males (54.3%, 119/219) as compared to females. More abdominal pain (72.4%, 247/341) was observed than other clinical symptoms including vomiting, bloating, acid reflux and heartburn. The majority of the GC patients experienced symptoms of vomiting (91%, 20/22) with abdominal pain (100%, 22/22). The multinomial logistic regression model was statistically significant and correctly classified 80% of the GDD/GC cases. Age, income level, vomiting, bloating and medication had significant association with GDD and GC. A dynamic RF GC-predictive model was developed, which achieved > 80% test accuracy.

CONCLUSION

GC risk factors were incorporated into a computer model to predict the likelihood of developing GC with high sensitivity and specificity. The model is dynamic and will be further improved and validated by including new data in future research studies. Its use may reduce unnecessary endoscopic procedures. It is freely available.

Key Words: Gastric cancer; Gastritis; Machine learning; Prediction model; *Helicobacter pylori*

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Core Tip: This is a retrospective study to report the prevalence of *Helicobacter pylori* (*H. pylori*) infection in Pakistan along with its association with various risk factors having direct or indirect relationships with different gastroduodenal diseases (GDD) such as gastritis, ulcers, and gastric cancer (GC). GC risk factors were incorporated into a highly sensitive and specific dynamic computer tool for the prediction of GC with an impressive > 80% confidence. This GC prediction model is freely available and may be used to reduce unnecessary invasive procedures such as endoscopies. The research study assists the healthcare authorities in their understanding of the burden of GDD and GC, which is intertwined with *H. pylori* infection.

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INTRODUCTION

Gastric cancer (GC) is the fourth most common cancer in the world and the second-most common cause of cancer-related deaths[1] with the highest incidence observed in Eastern Asia and the lowest in Western Europe and North America[2]. The main environmental factor causing GC is *Helicobacter pylori* (*H. pylori*) infection[1], and it has been classified as a class I carcinogen by the International Agency for Research on Cancer[3]. It is, however, an insufficient cause, and other hereditary[4], environmental and lifestyle factors are of importance in GC development as well[1,5-8]. GC risk factors and epidemiology in Pakistan were reviewed in 2015[9] and 2018[10] stressing the importance of sanitary conditions, purified drinking water and healthy nutrition in a developing country with 24.3% poverty rate[11]. The latter meta-analysis remarked on the population heterogeneity in different parts of the country, where various ethnic groups follow their own lifestyle traditions so that cancer statistics vary considerably [10]. A National Cancer Registry is presently not available but is in the process of being set up by the Pakistan Health Research Council.

GC risk factors include age[11], gender[12] and all factors which are commonly named as general health risks such as smoking[13,14], alcohol and junk food consumption as well as reduced physical exercise[5,6,15,16]. Diet and, in particular, controlled sugar and salt consumption play a specific role in GC prevention[17-19]. Proton pump inhibitors (PPI), which are routinely prescribed in the management of gastric-acid-related disorders, may also pose a risk, when improperly used[20,21]. Harvard University adds in its “10 commandments of cancer prevention”[22] factors such as exposure to radiation and industrial and environmental toxins, little sleep and lack of vitamin D to the list. Furthermore, local habits in different countries or ethnicities may influence the risk of GC development. In Asia, for instance, Miswak (toothbrush tree, *Salvadora persica* L.) is commonly used for oral hygiene counteracting *H. pylori* infection[23]. High chili consumption in some regions of South America, on the other hand, sensitizes the mucosa and poses a cancer risk[24].

Histological examination of gastric biopsies is currently the gold standard for GC diagnosis[15]. However, the demand for endoscopy is increasing along with the financial burden for the health care system so that the number and appropriateness of referrals is more and more discussed[25]. Guidelines were published in what instances endoscopic biopsies should be performed[26], not only for economic reasons, but also to avoid stressing patients with false-positive results in cases of abnormal appearance of gastric mucosa in endoscopy but normal histopathology[27]. Moreover, health care-allied infections are significantly associated with contaminated endoscopes. The most commonly used flexible multi-channel endoscopes need utmost care in high-level disinfection and proper cleaning before endoscopic procedures, as they cannot be heat-sterilized. Otherwise, bacteria may form biofilms on the inner surfaces and pose a serious risk to patients[28].

In the Center for Liver and Digestive Diseases of the tertiary care Holy Family Hospital in Rawalpindi we have also seen an overload in referrals to endoscopic procedures. In order to find a measure for improved patient referral we collected clinical data of 341 patients having symptoms of gastroduodenal disorders and asked them to fill in a questionnaire concerning their living conditions as well as diet and daily habits. It included the risk factors discussed above and factors important with respect to *H. pylori* infection like overcrowding and source of drinking water, because sanitary conditions contribute significantly to the spread of microorganisms[29-31]. The aim of this study was to set up an *in silico*-model, which could be continuously trained with new patients of our clinic, and which would allow us to limit the referrals to endoscopy to the most serious cases based on risk factor assessment. Such machine-learning models are increasingly being used in gastroenterology[32-34], most recently for the prediction of GC risk after *H. pylori* eradication[34]. All these efforts were, however, retrospective studies, while we try to build up a prognostic tool, which is closely associated with the clinic and integrated in everyday use, and which is constantly being improved with new data. Despite the low number of starting data - in comparison to these other models, which are in part based on ten thousands of patients -, we can present a model, which already predicts the GC risk with an impressive > 80% confidence.

Artificial intelligence (AI) is playing an increasing role in the healthcare industry including gastroenterology and gastrointestinal oncology. AI can assist physicians in invasive procedures such as endoscopy, capsule endoscopy, and colonoscopy for disease diagnosing[32], radiology[35], and the detection of the cancerous and precancerous lesions in the intestine[36].

MATERIALS AND METHODS

Ethical approval and study population

Ethical approvals were granted from the Ethical Technical Committee, Pakistan Institute of Nuclear Science and Technology (PINSTECH), Islamabad (Ref.-No. PINST/DC-26/2017), the Bioethics Committee, Quaid-i-Azam University, Islamabad, Pakistan (Ref.-No. BBC-FBS-QAU2019-159), and the Institutional Research Forum, Holy Family Hospital, Rawalpindi Medical University, Rawalpindi (Ref.-No. R-40/RMU).

Inclusion and exclusion criteria

Primary data of 341 patients having persistent dyspeptic symptoms of gastroduodenal disorders including acid reflux, abdominal pain, heartburn, vomiting, and bloating, or alarm symptoms who were thus attending the Centre for Liver and Digestive Diseases, Holy Family Hospital, Rawalpindi for upper gastroduodenal endoscopy of age group above 18 years was collected in this study from 2018 to 2021. They also signed the informed written consent.

However, patients having a history of confounders of gastric cancer such as gastric surgery, corrosive intake, varicel bleed with chronic liver disease, or use of antibacterial and gastric acid inhibitors during the past 30 d which may effects on diagnosis of *H. pylori* infection and anticancer drugs were excluded from this study, so were pregnant women.

After diagnostic endoscopic evaluation, the enrolled patients were divided into three groups: Normal gastric mucosa (NGM), GC and gastroduodenal diseases (GDD). The GDD group included patients who had gastritis (mild, moderate, marked and PAN gastritis (chronic form of gastritis, which affects the

entire gastric mucosa). The patients with gastritis were subcategorized into mild (mild erythema or scanty erosions), moderate (neither mild nor marked), and marked (diffuse erythema, nodularity, hypertrophy of gastric folds and friability of gastric mucosa) according to Kyoto classification system [37]. Moreover, ulcers (gastric, duodenal, and peptic ulcer diseases) were also included in this group.

Questionnaire for exploring demographics and socioeconomic status

Patients were interviewed using a Likert-scale questionnaire developed earlier for the investigation of *H. pylori* infection in Pakistan [29]. Information associated with socioeconomic and demographic conditions such as gender, age, education, income, and living conditions was collected in addition to GC risk factors including specific dietary habits. There have been studies, which associated dairy products with GC [38] and those who did not [39] as well as studies, which evaluated the influence of red and processed meat [40], high salt consumption due to salted fish and meat [19], and black and green tea [7]. An unhealthy diet very high in carbohydrates (rice, potato) and low in fresh vegetables and fruit is also critical [1,4,7,8] and questions to that effect were included in the questionnaire. Moreover, the history concerning the intake of antibacterial drugs, PPI, non-steroidal anti-inflammatory drugs and other medicines was recorded. Categories of responses were defined as listed in Table 1 [41].

Diagnosis of *H. pylori* infection

Standard non-invasive and invasive diagnostic tests were performed for the determination of *H. pylori* infection. All the modalities including nuclear stable isotope ^{13}C urea breath test (UBT), histopathological examinations (HPE) and rapid urease test (RUT) were used to diagnose *H. pylori* infection with the exception that biopsy specimens were not available for all the patients. The ^{13}C UBT was, however, used for all enrolled subjects.

Nuclear stable isotope ^{13}C UBT: Active *H. pylori* infection was determined using non-invasive nuclear stable isotope ^{13}C UBT as described previously [29]. Briefly, after all-night fasting, a pre-dose breath sample was collected from the patient. A dose containing 75 mg ^{13}C enriched urea (Cambridge Isotope Laboratories, United States) was given to the patient and post-dose breath sampling was performed after 30 min. Breath samples were analyzed for $^{13}\text{CO}_2/^{12}\text{CO}_2$ ratio using BreathMAT^{plus} mass spectrometer (Thermo Finnigan, Germany) and Delta V Plus mass spectrometer (Thermo Scientific, United States). A change in the $\delta^{13}\text{C}$ value over baseline of more than 3‰ was considered positive.

Gastric biopsy collection: Specimens were collected from those patients who had symptoms suggestive of a need for upper gastroduodenal endoscopy. Multiple biopsy specimens were collected from antrum and corpus within 3 cm of the pylorus of each patient undergoing this surgery. Biopsy specimens were placed in 10% formalin for HPE. One biopsy was collected for RUT.

RUT: The rapid urease kit to assess the active growth of *H. pylori* was indigenously prepared in Patients Diagnostic Lab, PINSTECH. Briefly, fresh gastric biopsy specimen were immediately placed in urea agar base with 40% urea solution for 1 h of incubation at 37°C. A change of color from pale yellow to pink red was interpreted as a positive result.

HPE: Gastric (antrum and corpus) biopsy specimens were processed for histopathological examination according to the Operative Link for Gastritis Assessment (OLGA/OLGIM) scoring [42] alongside with Lauren and World Health Organization (WHO) classification systems [43] for the determination of NGM, gastritis, gastric ulcer, duodenal ulcer and GC differentiation and invasions.

Statistical analysis

Chi-squared (χ^2) test was used to assess the association of socioeconomic demographics, different risk factors, and histopathological grades among the three groups (NGM, GDD, GC). Spearman correlation coefficient test was employed to find the relationship between *H. pylori* infection and histopathological variables among gastric biopsies of antrum and corpus. The association between the predictor variables in the three groups was evaluated using multinomial logistic regression analysis. Nine variables having a *P* value < 0.1 were selected for multinomial logistic regression analysis. Risk factors included in the multivariable model were age, education level, income level, symptoms (abdominal pain, acid reflux, vomiting, bloating), chili consumption, excessive intake of salt and medication usage. Frequency categories were combined to achieve sufficient statistical power. Multinomial logistic regression analysis was used to determine factors associated with the three groups. To evaluate the interaction of different risk factors among the three groups, likelihood ratio tests were used to calculate *P* values comparing models with main effects to models with main effects plus relevant interaction terms. Principal components analysis (PCA) was carried out for risk factors, symptoms and *H. pylori* tests restricting the number of factors to three. For initial data classification with respect to endoscopic data and a focus on GC, decision tree analysis was performed with risk factors. All *P* values were reported as two-sided test with an alpha level of 0.05. Statistical analysis was carried out with SPSS 21.0 statistical software (SPSS Inc, Chicago, United States).

Table 1 Score response categories of Likert scale questionnaire

Study variables/risk factors	Category	Consumption/behavior frequency in d/wk
Tooth brushing and miswak usage	Always	7
	Often	4-6
	Seldom	1-3
	Never	0
Consumption of chili, dairy products, rice, potatoes, red and processed meat, sweets, junk food	No	0
	Rarely	1-2
	Moderately	2-4
	Frequently	5-6
Servings per day		
Drinking black and green tea	Normal	1-2
	Moderate	3-4
	High	5-7
Habits per day		
Washing hands with soap before meal and after use of toilet	Always	7
	Often	4-6
	Seldom	1-3
	Never	0
Addiction and passive smoking	No	< 10 (In Pakistan smoking is common practice.)
	Yes	> 10
Consumption of cooked food		
Salt/sodium chloride consumption; Normal: 2300 mg/d; Low: 140 mg/serving; High: > 3400 mg/d[38]	No	Without salt (Patients with high blood pressure did not use salt in their food)
	Normal	Without adding salt
	Low	With additional pinch of salt/serving; 1 Pinch = 0.36 g or 360 mg
	High	After addition of several pinches of salt/serving

RESULTS

General characteristics of study participants

Participants (341) with the mean age of 41.9 ± 15.9 years and an age range from 18 to 87 years were included in this study. All data are supplied in the Supplementary Excel file of Supplementary material. The overall frequency of *H. pylori* infection was 64.2% (219/341). The enrolled patients were separated in the following groups: NGM 15% (50/341), GC 9.1% (31/341), and GDD 76.2% (260/341). The frequency of *H. pylori* infection among NGM participants was 72% (36/50), 62% (160/260) in GDD, and 74.2% (23/31) in GC. About half of the participants were male (177/341, 51.9%); 48.1% (164/341) were females. The frequency of *H. pylori* infection was higher in males (54.3%, 119/219) as compared to females (45.7%, 100/219). Clinical symptoms observed among enrolled patients were abdominal pain (72.4%, 247/341), vomiting (57.8%, 197/341), bloating (54.5%, 186/341), acid reflux (52.8%, 180/341) and heartburn (52.8%, 180/341). The majority of the GC patients were older than 45 years (71%, 22/31) and experienced symptoms of vomiting (91%, 20/22) with abdominal pain (100%, 22/22).

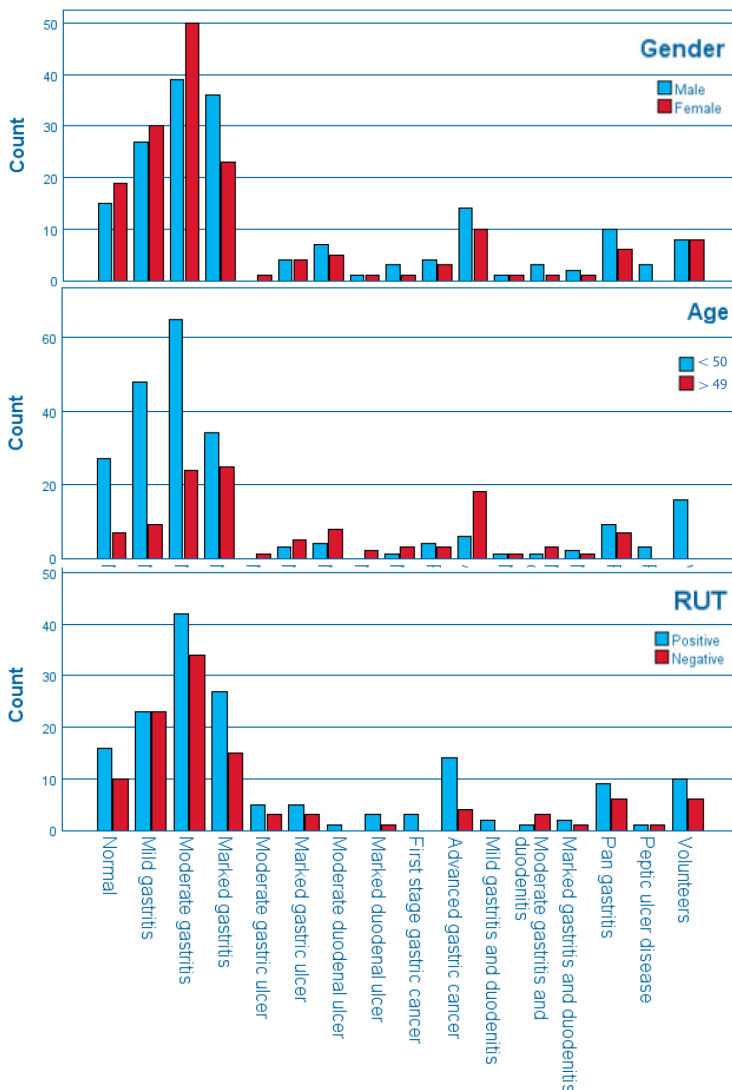
Descriptive characteristics of the cohort and results of the Chi-squared (χ^2) test to assess the association of socioeconomic demographics, risk factors, and histopathological grades among the three groups (NGM, GDD, GC) are presented in **Table 2**. Significant factors were age, education (one-third of the participants were illiterate) and, conclusively, income level, and the clinical symptoms (except heartburn). Cross-correlation was computed for visualization of the data set as is exemplary shown for age, gender and RUT results in **Figure 1**.

Table 2 Descriptive characteristics of the proband cohort groups and results of χ^2 /Fisher's exact test (*P* value)

Factor	Categories	NGM	GDD	GC	P value	Significant
		% (number of patients/total number of patients)				
Infection status	Negative	28 (14/50)	39 (100/260)	26 (8/31)	0.176	> 0.05
	Positive	72 (36/50)	62 (160/260)	74 (23/31)		
Gender	Male	46 (23/50)	52 (136/260)	58 (18/31)	0.553	> 0.05
	Female	54 (27/50)	48 (124/260)	42 (13/31)		
BMI	Normal, underweight	58 (29/50)	63 (163/260)	78 (24/31)	0.191	> 0.05
	Overweight, obese	42 (21/50)	37 (97/260)	23 (7/31)		
Marital status	Married	78 (39/50)	80 (208/260)	87 (27/31)	0.580	> 0.05
	Single	22 (11/50)	20 (52/260)	13 (4/31)		
Age	< 46	82 (41/50)	65 (170/260)	29 (9/31)	0.000	< 0.01
	> 45	18 (9/50)	35 (90/260)	71 (22/31)		
Ethnic background	Federal	6 (3/50)	6 (16/260)	3 (1/31)	0.291 ^f	> 0.05
	Lower punjab	16 (8/50)	15 (40/260)	13 (4/31)		
	Kashmir	12 (6/50)	5 (14/260)	3 (1/31)		
	Upper punjab	60 (30/50)	62 (161/260)	81 (25/31)		
	Khyber pakhtunkhwa	6 (3/50)	11 (29/260)	0 (0/31)		
Education level	Illiterate	18 (9/50)	35 (90/260)	48 (15/31)	0.013	< 0.05
	Literate	82 (41/50)	65 (170/260)	52 (16/31)		
Medication	Antibiotics	44 (22/50)	33 (86/260)	32 (10/31)	0.132 ^f	> 0.05
	PPI	22 (11/50)	36 (93/260)	45 (14/31)		
	NSAID	12 (6/50)	4 (9/260)	3 (1/31)		
	Others	8 (4/50)	10 (27/260)	3 (1/31)		
	NIL	14 (7/50)	17 (45/260)	16 (5/31)		
Income level	10.000	6 (3/50)	7 (19/260)	3 (1/31)	0.007 ^f	< 0.05
	11.000-30.000	48 (24/50)	69 (178/260)	84 (26/31)		
	> 30.000	46 (23/50)	24 (63/260)	13 (4/31)		
Acid reflux	No	66 (33/50)	45 (116/260)	39 (12/31)	0.013	< 0.05
	Yes	34 (17/50)	55 (144/260)	61 (19/31)		
Abdominal pain	No	54 (27/50)	25 (64/260)	10 (3/31)	0.000	< 0.01
	Yes	46 (23/50)	75 (196/260)	90 (28/31)		
Heartburn	No	56 (28/50)	46 (119/260)	45 (14/31)	0.403	> 0.05
	Yes	44 (22/50)	54 (141/260)	55 (17/31)		
Vomiting	No	64 (32/50)	41 (107/260)	16 (5/31)	0.000	< 0.01
	Yes	36 (18/50)	59 (153/260)	84 (26/31)		
Bloating	No	74 (37/50)	41 (106/260)	39 (12/31)	0.000	< 0.01
	Yes	26 (13/50)	59 (154/260)	61 (19/31)		
Black tea	Low	80 (40/50)	69 (178/260)	71 (22/31)	0.261	> 0.05
	High	20 (10/50)	32 (82/260)	29 (9/31)		
Green tea	Low	70 (35/50)	70 (181/260)	65 (20/31)	0.837	> 0.05
	High	30 (15/50)	30 (79/260)	36 (11/31)		
Chili consumption	Low	30 (15/50)	39 (102/260)	48 (15/31)	0.240	> 0.05

	High	70 (35/50)	61 (158/260)	52 (16/31)		
Dairy product consumption	Low	36 (18/50)	32 (83/260)	32 (10/31)	0.853	> 0.05
	High	64 (32/50)	68 (177/260)	68 (21/31)		
Fresh fruit & vegetable consumption	Low	28 (14/50)	18 (46/260)	23 (7/31)	0.222	> 0.05
	High	72 (36/50)	82 (214/260)	77 (24/31)		
Rice consumption	Low	26 (13/50)	37 (94/260)	23 (7/31)	0.154	> 0.05
	High	74 (37/50)	64 (166/260)	77 (24/31)		
Potato consumption	Low	32 (16/50)	40 (104/260)	32 (10/31)	0.422	> 0.05
	High	68 (34/50)	60 (156/260)	68 (21/31)		
Red meat consumption	Low	54 (27/50)	47 (123/260)	55 (17/31)	0.543	> 0.05
	High	46 (23/50)	53 (137/260)	45 (14/31)		
Processed meat consumption	Low	70 (35/50)	77 (199/260)	77 (24/31)	0.597	> 0.05
	High	30 (15/50)	24 (61/260)	23 (7/31)		
Junk food consumption	Low	78 (39/50)	84 (218/260)	84 (26/31)	0.596	> 0.05
	High	22 (11/50)	16 (42/260)	16 (5/31)		
Sweets consumption	Low	62 (31/50)	69 (178/260)	68 (21/31)	0.671	> 0.05
	High	38 (19/50)	32 (82/260)	32 (10/31)		
High salt intake	No	16 (8/50)	31 (80/260)	23 (7/31)	0.081	> 0.05
	Yes	84 (42/50)	69 (180/260)	77 (24/31)		
Overcrowding	Yes	54 (27/50)	42 (108/260)	55 (17/31)	0.129	> 0.05
	No	46 (23/50)	59 (152/260)	45 (14/31)		
Oral hygiene	Yes	84 (42/50)	87 (226/260)	77 (24/31)	0.340	> 0.05
	No	16 (8/50)	13 (34/260)	23 (7/31)		
Hand hygiene	Yes	98 (49/50)	99 (256/260)	97 (30/31)	0.437 ^f	> 0.05
	No	2 (1/50)	2 (4/260)	3 (1/31)		
House insects	No	0 (0/50)	2 (4/260)	0 (0/31)	1.00 ^f	> 0.05
	Yes	100 (50/50)	99 (256/260)	100 (31/31)		
Household animals	No	62 (31/50)	69 (180/260)	22/31 (71)	0.570	> 0.05
	Yes	38 (19/50)	31 (80/260)	29 (9/31)		
Potable water source	In	4 (2/50)	14 (37/260)	13 (4/31)	0.136	> 0.05
	Out	96 (48/50)	86 (223/260)	87 (27/31)		
Sewage system	Proper	0 (0/50)	3 (7/260)	7 (2/31)	0.196 ^f	> 0.05
	Damaged	100 (50/50)	97 (253/260)	94 (29/31)		
Addiction	No	66 (33/50)	68 (176/260)	71 (22/31)	0.897	> 0.05
	Yes	34 (17/50)	32 (84/260)	29 (9/31)		
Passive smoking	No	58 (29/50)	62 (162/260)	65 (20/31)	0.806	> 0.05
	Yes	42 (21/50)	38 (98/260)	36 (11/31)		
Physical activity	Low	80 (40/50)	80 (208/260)	77 (24/31)	0.944	> 0.05
	High	20 (10/50)	20 (52/260)	23 (7/31)		
Family history of stomach disease	No	74 (37/50)	72 (187/260)	84 (26/31)	0.361	> 0.05
	Yes	26 (13/50)	28 (73/260)	16 (5/31)		
Type 2 diabetes	No	94 (47/50)	92 (238/260)	97 (30/31)	0.680 ^f	> 0.05
	Yes	6 (3/50)	9 (22/260)	3 (1/31)		

^fFor the expected counts less than 5, *P* values were obtained from Fisher's exact test. Significant discriminators are marked in bold. BMI: Body mass index; NGM: Normal gastric mucosa, GC: Gastric cancer; GDD: Gastroduodenal diseases; NSAIDS: Non-steroidal anti-inflammatory drugs; PPI: Proton pump inhibitors.



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Figure 1 Cross-correlation bar charts for the study cohort with respect to gender, age and *Helicobacter pylori* infection status based on rapid urease test. RUT: Rapid urease test.

Multinomial logistic regression analysis

The associations of risk factors with GDD and GC among the three groups are presented in Table 3. Chi squared analysis showed a significant association at $P < 0.05$ between 7 independent variables among 3 groups. Out of 38 indicators, 9 variables added to the multinomial logistic regression analysis with $P < 0.1$. Multinomial logistic regression was performed to ascertain the effects of predictor variables on the likelihood that participants had GDD or GC. Model fitting information described the relationship between the dependent and independent variables and revealed that the probability of the model Chi-square 97.028 was 0.01, less than the level of significance of 0.05 (*i.e.*, $P < 0.05$). The model explained 32.0% (Nagelkerke R^2) of the variance in groups and correctly classified 80% of the cases; 10% of the cases from GC, 98% from GDD and 30% of the NGM participants.

According to Wald statistics, age, income level, vomiting, bloating and medication were the significant factors associated with GDD and GC. People younger than 45 years were less likely to have GC as compared to GDD (OR 0.19, 95%CI: 0.08-0.46, $P < 0.05$) and as compared to normal (OR 0.08, 95%CI: 0.02-0.29, $P < 0.05$). People belonging to the middle class were more likely to have GDD (OR 2.32, 95%CI: 1.09-4.91, $P < 0.05$) and GC (OR 4.86, 95%CI: 1.25-18.84, $P < 0.05$) as compared to NGM. Similarly, patients without the symptoms of vomiting (OR 0.16, 95%CI: 0.05-0.53, $P < 0.05$) and

Table 3 Factors associated with gastroduodenal diseases and gastric cancer vs normal gastric mucosa

Variable	Category	GDD/NGM		GC/GDD		GC/NGM	
		Significant	Odds ratio (95%CI)	Significant	Odds ratio (95%CI)	Significant	Odds ratio (95%CI)
Age	< 46	0.078	0.45 (0.18-1.09)	0.00	0.19 (0.08-0.46)	0.000	0.08 (0.02-0.29)
	> 45		Reference		Reference		Reference
Education level	Illiterate	0.404	1.44 (0.61-3.43)	0.609	1.25 (0.53-2.95)	0.325	1.81 (0.56-5.86)
	Literate		Reference		Reference		Reference
Income level	Low	0.767	1.25 (0.29-5.44)	0.847	0.79 (0.07-8.61)	0.992	0.99 (0.06-15.29)
	Middle	0.028	2.32 (1.09-4.91)	0.218	2.1 (0.65-6.8)	0.022	4.86 (1.25-18.84)
	Upper		Reference		Reference		Reference
Vomiting	No	0.088	0.54 (0.27-1.09)	0.599	1.26 (0.53-3.01)	0.003	0.16 (0.05-0.53)
	Yes		Reference		Reference		Reference
Bloating	No	0.012	0.37 (0.17-0.8)	0.019	0.29 (0.1-0.81)	0.184	0.47 (0.15-1.44)
	Yes		Reference		Reference		Reference
Abdominal pain	No	0.075	0.52 (0.25-1.07)	0.092	0.32 (0.09-1.2)	0.016	0.17 (0.04-0.72)
	Yes		Reference		Reference		Reference
Acid reflux	No	0.220	0.63 (0.3-1.32)	0.944	0.97 (0.41-2.3)	0.379	0.61 (0.2-1.83)
	Yes		Reference		Reference		Reference
Medication	Antibiotics	0.686	0.81 (0.29-2.25)	0.519	1.51 (0.43-5.24)	0.803	1.22 (0.25-5.85)
	PPI	0.520	1.45 (0.47-4.44)	0.139	2.48 (0.74-8.26)	0.118	3.58 (0.72-17.76)
	NSAIDS	0.020	0.16 (0.03-0.75)	0.936	1.1(0.1-11.93)	0.212	0.18 (0.01-2.68)
	Others	0.512	1.64 (0.38-7.12)	0.598	0.54 (0.06-5.3)	0.928	0.88 (0.06-12.75)
	Nil		Reference		Reference		Reference
High salt intake	No	0.215	1.77 (0.72-4.37)	0.215	0.55 (0.21-1.42)	0.965	0.97 (0.27-3.49)
	Yes		Reference		Reference		Reference

Nine variables were added to the multinomial logistic regression analysis with $P < 0.05$ (marked in bold). GDD: Gastroduodenal diseases; NGM: Normal gastric mucosa; NSAIDS: Non-steroidal anti-inflammatory drugs; PPI: Proton pump inhibitors; Sign.: Significant.

abdominal pain (OR 0.17, 95% CI: 0.04-0.72, $P < 0.05$) were less likely to have GC than NGM. Patients without the symptoms of bloating are also less likely to have GDD as compared to NGM (OR 0.37, 95% CI: 0.17-0.8, $P < 0.05$) and GC as compared to GDD (OR 0.29, 95% CI: 0.1-0.8, $P < 0.05$).

Upper gastroduodenal endoscopic evaluation

The total of 341 patients underwent upper gastroduodenal endoscopy. Among these patients, 15% (50/341) had NGM, 67% (230/341) patients had gastritis, 9% (30/341) had gastroduodenal ulcers including gastric ulcers (70.0%, 21/30), duodenal ulcers (20%, 6/30), and peptic ulcer disease (10%, 3/30). Those patients with gastric ulcers, duodenal ulcers and peptic ulcer disease had a frequency of *H. pylori* infection 62% (13/21), 83% (5/6) and 67% (2/3), respectively. Moreover, all ulcers were categorized as clean-based ulcers and classified as Forrest III (lesions without active bleeding). Additionally, 9.1% (31/341) patients were suspected (based on lesion, polyp, and large growth) for GC and their gastric biopsy specimens were taken for histopathological examination (HPE) to rule out the malignancies.

GC evaluation and differentiation

HPEs showed that 51% (117/230) of the patients had mild gastritis, 40% (93/230) moderate gastritis, and 2% (4/230) marked gastritis. The frequency of *H. pylori* infection in patients with mild gastritis was 62% (72/117), with moderate gastritis 59% (55/93), and with marked gastritis 0.5% (2/4). A total of 31 patients were histopathologically confirmed for GC. Among those patients, 23% (7/31) had first and 77% (24/31) had advanced stage GC. The frequency of *H. pylori* infection in first and advanced stage GC was 86% (6/7) and 71% (17/24), respectively. Additionally, those patients were also evaluated and

differentiated into various cancer types including adenocarcinoma (48%, 15/31), signet ring cell carcinoma (45%, 14/31) and undifferentiated carcinomas (6.4%, 2/31) with 93% (13/14), 60% (9/15) and 50% (1/2) frequency of *H. pylori* infection, respectively. Moreover, gastric biopsies were also examined and graded according to Lauren and WHO classifications into intestinal (19%, 6/31), diffuse (81%, 21/31), tubular (48%, 15/31) and poorly cohesive (52%, 16/31) carcinomas. The frequency of *H. pylori* infection among these patients was: 33% (2/6), 68% (21/31), 60% (9/15), 88% (14/16), respectively.

Correlation of histopathological variables of antrum and corpus biopsies

The Spearman coefficient correlation test for histopathological assessment of multiple gastric biopsies from antrum and corpus revealed a highly significant correlation ($P < 0.05$) between *H. pylori* infection and histopathological grades including *H. pylori* load, neutrophil infiltration, mononuclear cell infiltration, inflammation, atrophy, atypia, metaplasia, dysplasia, atrophy score (OLGA), metaplasia score (OLGIM), gastritis and ulceration (Table 4).

PCA and decision trees

When testing for the factors with the most influence in the dataset using PCA, not unexpectedly, factors related to *H. pylori* infection (^{13}C UBT, RUT) were dominant followed by characteristic symptoms for gastroduodenal diseases (heartburn, vomiting, reflux; Supplementary Table 1). Decision tree analysis with a focus on GC (Supplementary Figure 1A) revealed age as the main separator with people younger than 50 years showing only 1/3 of all GC cases. When age was excluded from the analysis (Supplementary Figure 1B), the factor abdominal pain collected 28 of 31 GC patients in the node, which were further split for 26 suffering from vomiting. Bloating was not a useful selection criterion for GC, because only 1/3 of all GC cases reported it.

Machine-learning algorithm

Resulting from extensive literature review and the findings of this study, 23 factors associated with GC were selected and used to train a GC prediction model using python language (Table 5). The diagnostic approach using machine learning was carried out in two steps, firstly model trained itself by recognizing patterns in the data of all classes of gastric diseases and secondly, the pre-learned model classified new patients after identification of similar pattern of newly provided data. The probabilities of specific disease were predicted due to closer pattern after input of patient's data.

The primary dataset (parameters in textual and structural format, Supplementary Excel file Training_Testing_Data of Supplementary material) contained upper-gastroduodenal symptoms, potential GC risk factors, *H. pylori* infection status, and clinical endoscopic and histopathological findings. Factor categories were reduced to yes and no in some cases to provide sufficient numbers of samples, respectively, analysis power. The primary data was imbalanced containing a higher number of gastritis patients as compared to ulcer and GC patients. Therefore, 70% samples of each class were used to train the model and the remaining 30% for testing (Table 6). The algorithm randomly performed this 70-30 distribution of the dataset. During testing, the pre-learned machine learning model truly classified 72% cases of each class with greater accuracy.

Two machine learning models based on K-Nearest Neighbors (KNN) and Random Forest (RF) supervised learning algorithms were separately trained to calculate the risk of a specific gastroduodenal disease. In the KNN model, a simple elucidation distance of the test samples with all training samples was calculated. Top 'K' training samples, i.e. patient feature vectors with a minimum distance with the test samples, decided the highest risk of a certain disease by voting for the most frequent class. In general, for samples in n-dimensional Euclidean space, the distance is, with p and q being two points in Euclidean n-space.

RF is an ensemble of, in our case 10, decision trees. It eradicated the over-fitting that is a major issue of decision tree. Each tree made decisions based on importance of each risk factor, i.e., starting from features that are more distinct to the less important features. Importance is defined as the distinguishability of a feature and it was measured by Gini Gain or Importance Gain (for more details see Explanation S1 in the Supplementary material). We have used the Gini Index to train our model. With KNN we achieved 74% and with RF 82% test accuracy. We thus incorporated the latter algorithm in the published software tool. RF is a decision tree based stacking classifier which is freely available with a few tunable hyper parameters. It is not constructed from scratch but trained by using patient's data and also optimized by fine tuning of the important parameters.

The user interface of the GC Prediction System is shown in Figure 2. The input is limited to the most critical factors with respect to risk modelling. The software was written for Windows 10 and is distributed as archive containing an executable program file (www.medizin.uni-muenster.de/cu-proteomics/projekte.html). Running the tool simply requires to unzip and join the three archives and then run the executable file on any Windows-based computer. Results are reported online and are saved in pdf-format in the program directory. Via the input page, data can be added to the model to train it further, but this needs to be done in the original python-based environment and is thus not available to the standard user. The source code is shared in collaborations.

Table 4 Correlation of histopathological variables, antral vs corpus biopsies ($P < 0.01$)

Variable	Spearman correlation coefficient
<i>Helicobacter pylori</i> load	0.991
Neutrophil infiltration	1.000
Mononuclear cell infiltration	0.942
Atrophy	0.969
Atypia	0.881
Metaplasia	1.000
Dysplasia	0.786
Atrophic score (OLGA)	0.951
Metaplasia score (OLGIM)	1.000
Inflammation	0.930
Gastritis	0.921
Ulceration	1.000
Eosinophilia	1.000

OLGA: Operative link for gastritis assessment; OLGIM: Operative link on gastric intestinal metaplasia.

Table 5 Gastric cancer associated risk factors chosen for prediction model building

Risk factors	Ref.
<i>H. pylori</i> infection	[1]
Family history	[4]
PPI	[8,20,21]
Addiction (smoking)	[13]
Passive smoking	[44,64]
Sewage system (cockroaches/ <i>H. pylori</i>)	[31]
Potable water source (<i>H. pylori</i>)	[30]
Exercise/fruits and vegetables	[7,8]
BMI	[16]
Gender (male)	[12]
Age	[11]
High salt intake/green and black tea	[7,58]
Chili consumption	[24]
Processed food (meat) consumption	[19,40]
Sugar intake	[17]
Excess of rice and potatoes	[18]
Miswak usage	[23]

BMI: Body mass index; PPI: Proton pump inhibitors; *H. pylori*: *Helicobacter pylori*.

DISCUSSION

H. pylori infection is a serious public health problem with a high frequency among the population of developing countries[44]. Globally, 4.4 billion individuals have been identified to harbor *H. pylori*. The frequency of *H. pylori* infection in developing and developed countries has been reported as 70%-90%

Table 6 Dataset used to train the gastric cancer prediction model

Clinical findings	Total samples	Training dataset	Test dataset
NGM	50	35	15
Gastritis	232	162	70
Ulcer	30	21	9
GC	29	20	8
Total	341	239	102

GC: Gastric cancer; NGM: Normal gastric mucosa.

and 10%-30%, respectively[45]. Our previous study showed more than 70% frequency of *H. pylori* infection in the northern region of Pakistan[46]. Six years later[47], active *H. pylori* infection was detected in 50% of the symptomatic patients in Pakistan of whom 76% had clinical symptoms like abdominal pain. In the present investigation, we found 64% infection in symptomatic patients indicating a considerable increase over time. As the consistent presence of *H. pylori* infection in a large part of the population provides the basis for several gastroduodenal clinicopathological conditions including gastritis, ulcers and most importantly GC[1,3], this is an alarming situation. In earlier studies conducted on symptomatic patients from Pakistan, GC frequency was reported as 6.0% and 6.4%, respectively[10, 48], while, here, 9.1% were calculated. In agreement with our previous findings[47], the infection rate in males (54%) was marginally higher compared to females (46%) possibly due to their higher social interaction in Pakistan. Likely for the same reason, people younger than 46 years were more often infected by *H. pylori* (64%). Infection takes place in childhood and adolescence and reaches its peak in adulthood at an age of 35-44 years[45,49].

The increased risk of *H. pylori* positivity in developing countries has been associated with several environmental factors including lower socioeconomic conditions such as crowded households and poor hygiene[50]. Already in our previous study[29], these risk factors, further including pets and other household animals, have been significantly associated with *H. pylori* infection. Here, we also showed the influence of education and income level. Educated people can take advantage of the available knowledgebase and better care for their health. Moreover, with education comes job advancement and improved financial means to provide for optimal living conditions. The frequency of *H. pylori* infection (64%) was expectedly higher in patients with comparatively low family income (51-139 USD; 11000-30000 PKR, 1 USD=215 PKR) where living conditions are difficult. About 256465 PKR (1194 USD) are required for appropriate living conditions and fulfillment of basic needs[51].

Personal hygiene of the oral cavity is another risk factor as the mouth is the first pool of *H. pylori* infection and has a positive correlation with gastroduodenal pathologies[52]. Miswak has been traditionally used in Pakistan for oral hygiene due its antibacterial properties against both Gram positive and negative bacteria[23]. As is demonstrated in this study, a higher risk of *H. pylori* infection was found in patients who did not use it or other forms of oral hygiene.

Dietary habits such as meat consumption and the use of outdoor potable water were described as significant independent variables for both *H. pylori* infection and GC risk before[53]. A study conducted in Korea indicated that high salt intake was associated with a higher risk of atrophic gastritis and intestinal metaplasia[54] and other authors showed that it can lead to the onset of pre-malignant lesions [55]. In addition, the carcinogenic effects of major *H. pylori* virulence factor cytotoxin associated gene A (*cagA*)-positive strains were increased[56,57]. We confirmed the higher risk of *H. pylori* infection (73%) in patients with a higher salt intake than 5 g/d as recommended by the WHO[58].

A diet rich in carbohydrates and sweets is generally not healthy and the positive correlation with *H. pylori* infection was established in a study conducted in Japan in 2016[59] as well as here. It was also reported that for people who engage in regular exercise in the presence of *H. pylori* infection, the GC risk was reduced by approximately 50% in both males and females[60]. We saw more *H. pylori* infections in patients who did not have a habit of physical activity in their routine life but there was no correlation with GC incidence.

It has been suggested that a *Lactobacillus rhamnosus*-providing dairy-rich diet may counteract *H. pylori* infection[38]. In general, dairy products are a source of many nutrients and are highly recommended in dietary guidelines. Nevertheless, some studies found adverse effects of dairy consumption with GC[39] that is why we included this factor in our questionnaire. No clear conclusion can however be drawn from the available reports as some studies appear to have been flawed in their design[39]. Given the clear advantages of diet containing milk and dairy products, we do not wish to over-interpret our data, which positively correlate *H. pylori* infection and use of dairy products. It may rather be advisable for patients sensitive to gastroduodenal symptoms to test their response to milk and other dairy products (allergies) and adjust their diet accordingly.

Gastric Cancer Prediction System Artificial Intelligence Model

Please enter the following data of patient (Fill all fields),

Personal Details

Name: Gender: ☒ Male ☐ Female

Age: Weight (kg):

Height : cm

Symptoms

Acid Reflux: ☒ Yes ☐ No Abdominal Pain: ☒ Yes ☐ No

Heartburn: ☒ Yes ☐ No Vomiting: ☒ Yes ☐ No

Bloating: ☒ Yes ☐ No

¹³C Urea Breath Test

Helicobacter pylori Infection Status: ☒ Yes ☐ No

Risk Factors

Miswak: ☒ Yes ☐ No Physical Activity: ☒ Yes ☐ No

Chilli Consumption: ☐ Yes ☒ No Addiction: ☒ Yes ☐ No

Excessive use of Dairy Products: ☒ Yes ☐ No Passive Smoker: ☐ Yes ☒ No

Black Tea: ☒ Yes ☐ No Family History: ☐ Yes ☒ No

Excessive use of Rice: ☒ Yes ☐ No Sewage System: ☒ Proper ☐ Damaged

Eating Processed Meat: ☒ Yes ☐ No Portable Water Source: ☒ Indoor Tap Water ☐ Outdoor Tap Water
(Cured, Salted, Smoked, Dried or Canned Meat)

Excessive use of Sweets: ☒ Yes ☐ No Salt Intake:

Excessive use of Junk Food: ☒ Yes ☐ No Medication Used:

Clinical Findings	Probabilities
Normal Gastric Mucosa	0.00
Gastritis	0.20
Gastric Ulcer	0.20
Gastric Cancer	0.60

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Figure 2 Exemplary input to gastric cancer prediction tool interface to record patient data, symptoms, ¹³C urea breath test results and risk factors. Following input, a click on the “Result” button shows the probability of developing gastric cancer. A report can be generated in pdf-format. The “Update Data” button is used only when including new patient data into the model.

Black and green tea have been named as GC risk factors[7], because, in particular, green tea contains antioxidant compounds, which showed remarkable antibacterial activity especially against *H. pylori* and were beneficial against associated gastric diseases during *in vitro* and *in vivo* experiments[61]. As did other authors[62], we observed more *H. pylori* infection in patients who did not drink green tea in their routine life (68%).

Clinical symptoms such as vomiting were significant independent variables, which matched the results of others[50]. The coefficient correlation for *H. pylori* loads (0.542), neutrophil (0.644) and mononuclear cell infiltration (0.173) for antrum and corpus was assessed with a significance level of $P = 0.000$ before[49]. In our study, there was also a significant positive correlation ($P < 0.01$) among

histopathological grades including *H. pylori* load (0.991), neutrophil (1.000) and mononuclear cell infiltration (0.942) for antrum and corpus biopsies. The significant correlation among all histopathological grades in gastric biopsies suggests that a minimum number of biopsies can be sufficient to rule out malignancies. Other authors have reported the need for 6-8 gastric biopsies to ensure confident diagnosis[63]. A high number of gastric biopsy specimens may, however, create problems apart from procedure prolongation including active bleeding[63].

We have incorporated the pre-endoscopic patient's data from this study and the literature for risk factors and *H. pylori* infection status into a machine-learning algorithm and generated a GC model, which the practitioner can use for a quick check of the GC risk. Other efforts with respect to computer models in gastroenterology were retrospective studies[32-34], while we aim for a prognostic tool, which is constantly being improved with new data. Our model reached > 80% confidence in GC prediction and it may be helpful in making a decision pro and con gastroduodenal endoscopy in some cases. However, it is only based on 341 patients of which 31 had GC, so it clearly cannot be used as sole decisive factor; the experience of the physician is not to be underestimated. We plan to continuously improve the tool by the addition of new patient data from our clinic. We will release an updated version to the scientific community from time to time, because we do believe that this screening tool can be helpful.

CONCLUSION

We report a high and increasing level of *H. pylori* infection in Pakistan and its association with different risk factors, which, in turn, have direct or indirect relationships with gastroduodenal diseases including gastritis, ulcers, and GC. Our study identified GC risk factors such as age, sanitary conditions and clinical symptoms and incorporated them into a dynamic computer tool for GC prediction.

GC is a huge burden in developing countries. Awareness should be raised at an individual level through social media, schools, medical camps, and other means of public education to reduce the risk of gastric malignancies especially in the presence of *H. pylori* infection. Individual habits regarding diet or hygiene can be targeted in that way. Other risk factors require political intervention or governmental decisions. *H. pylori* infection monitoring and eradication strategies, for instance, are means of GC prevention[53]. The general improvement of living conditions and infrastructure will advance sanitary conditions and, conclusively, support the battle against GC. The investigation assists the healthcare authorities in their understanding of the burden of GDD and GC, which is intertwined with *H. pylori* infection.

ARTICLE HIGHLIGHTS

Research background

Gastric cancer is the 4th main reason for cancer-associated deaths around the globe. Diagnosis mainly depends on histopathological examinations and the number of endoscopic procedures is increasing. *Helicobacter pylori* (*H. pylori*) infection is a main risk factor for this cancer.

Research motivation

The increasing prevalence of gastric cancer due to late diagnosis or at an advanced stage was the main cause to conduct this research study to diagnose gastric cancer at an early stage.

Research objectives

The main research objectives of this study were: (1) Diagnosis of *H. pylori* infection; and (2) Development of gastric cancer prediction model using non-invasive characteristics of enrolled subjects.

Research methods

The 341 dyspeptic patients were enrolled after endoscopic evaluation and metadata was collected using a Likert scale questionnaire. The infection status was determined with the help of three modalities including 13C urea breath test, rapid urease test, and histopathological examinations. A Random Forest (RF) -gastric cancer (GC) prediction model was developed using non-invasive characteristics of patients.

Research results

This study reported a higher frequency of *H. pylori* infections among enrolled subjects. It was greater in gastric cancer as compared to other groups and also higher in males in comparison with females. Abdominal pain was observed more than other clinical symptoms. The majority of gastric cancer patients experienced symptoms of vomiting with abdominal pain. The multinomial logistic regression model correctly classified 80% of gastric cancer cases. The RF GC predictive model achieved > 80% test accuracy.

Research conclusions

The gastric cancer risk factors were incorporated into a computer model to predict the likelihood of developing gastric cancer with high sensitivity and specificity. The model is dynamic and will be further improved and validated by including new data in future research studies. Its use may reduce unnecessary endoscopic procedures.

Research perspectives

The computer model will predict the likelihood of developing gastric cancer with high sensitivity and specificity. Moreover, it will be helpful in diagnosing other gastric diseases such as gastritis and ulcer and assist gastroenterologists to start palliative therapy to reduce unnecessary endoscopic procedures.

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FOOTNOTES

Author contributions: Rasheed F and Aziz S contributed to conceptualization; Aziz S contributed to methodology; Umer M contributed to software; Aziz S contributed to validation; Aziz S, König S and Ibrar M contributed to formal analysis; Rasheed F contributed to resources; Akhter ST and Iqbal S contributed to endoscopic procedures; Aziz S and König S contributed to writing – original draft preparation; Aziz S, König S, Ahmad T, Rasheed F, Hanafia A, and Rehman UT contributed to writing – review & editing; König S contributed to visualization; Zahra R and Rasheed F contributed to supervision; Aziz S and Rasheed F contributed to project administration; Aziz S and Rasheed F contributed to funding acquisition.

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Informed consent statement: The investigators explain the study to each patient and informed written consent was obtained to participate in this research and their clinical data was collected during interview using a questionnaire after endoscopic evaluation. Moreover, patients were also required to give informed consent to the study for analysis and publication of their anonymous clinical data.

Conflict-of-interest statement: All the authors declare no conflict of interest.

Data sharing statement: All the data has been shared in supplementary files.

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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Gastroenterology* (AIG, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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Role of artificial intelligence in Barrett's esophagus

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Abstract

The application of artificial intelligence (AI) in gastrointestinal endoscopy has gained significant traction over the last decade. One of the more recent applications of AI in this field includes the detection of dysplasia and cancer in Barrett's esophagus (BE). AI using deep learning methods has shown promise as an adjunct to the endoscopist in detecting dysplasia and cancer. Apart from visual detection and diagnosis, AI may also aid in reducing the considerable interobserver variability in identifying and distinguishing dysplasia on whole slide images from digitized BE histology slides. This review aims to provide a comprehensive summary of the key studies thus far as well as providing an insight into the future role of AI in Barrett's esophagus.

Key Words: Artificial intelligence; Barrett's esophagus; Dysplasia; Cancer

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Core Tip: Barrett's esophagus is a significant precursor to esophageal adenocarcinoma. Detection of dysplasia or neoplastic changes in Barrett's esophagus can often be difficult as endoscopic changes can be subtle. Artificial intelligence has the potential to aid endoscopist in detecting such lesions endoscopically and also reduce the interobserver variability in detecting dysplasia in Barrett's esophagus histologically.

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INTRODUCTION

"Artificial Intelligence" (AI) is a generic term used to denote the ability of a computer program to learn and solve problems autonomously[1]. AI uses input data to learn with the intention of refining the ability to process new data samples that are not part of the original set of training data. This process of "machine learning" (ML) uses mathematical algorithms to capture structure and patterns in large data sets, often in a way that allows the learned function to be applied to new data. Machine learning can be supervised or unsupervised depending on whether the algorithms were trained with known patterns or unknown patterns respectively[2]. Deep learning is a subtype of machine learning in which a convolutional neural network (CNN) receives input (*e.g.*, endoscopic images), learns specific patterns (*e.g.*, mucosal surface/vascular pattern) and processes this information through the multi-layered network to produce an output (*e.g.*, presence or absence of neoplasia). This form of deep learning algorithm is the main driver for the rapidly advancing role of computer-aided diagnosis (CAD) in detection and characterization of lesions during endoscopy[3].

The greatest impact of AI in gastrointestinal (GI) endoscopy has been made in the area of colonic polyp and adenoma detection[4]. Several clinical studies and meta-analyses have shown the potential and at times, the superiority of AI in colonic adenoma detection rate compared to the endoscopist[5-8]. The crux of AI research in GI endoscopy has focused primarily on three domains which include detection, classification and delineation of lesions or disease entities[9]. There is an increasing amount of research in all three domains with regards to the application of AI in BE.

BARRETT'S ESOPHAGUS

Barrett's esophagus (BE) is defined as a change in the squamous lining of the distal esophagus to metaplastic columnar epithelium with goblet cells[10]. This is typically associated with chronic gastroesophageal reflux disease (GERD) with as much as 12% of patients with GERD symptoms harboring BE[11]. While there are variances in how BE is defined between different guidelines[12-14], there is definitive data that it is a precursor that increases the risk of esophageal adenocarcinoma (EAC)[15]. Hence early detection of dysplasia within BE is crucial to institute definitive treatment where possible and prevent further progression into neoplasia. However, this remains a challenge as endoscopic changes indicating dysplasia or early neoplasia can be subtle and be easily missed[16]. Even when there is no visible dysplasia and biopsies are done as per the Seattle protocol, sampling error can lead to areas of concern being missed[17]. The endoscopic diagnosis of BE dysplasia is generally a two-step process of primary detection in overview, followed by detailed inspection of these visible abnormalities for characterization[18]. This process relies on the individual experience of the endoscopist, which might further introduce variations and bias, leading to misjudgment and potentially delay in diagnosis and treatment.

Initially there was great interest in image enhancement technologies to overcome these challenges but to date only virtual and dye based chromoendoscopy have met the parameters outlined in American Society for Gastrointestinal Endoscopy's (ASGE) Preservation and Incorporation of Valuable Endoscopic Innovations (PIVI). Specific to BE imaging [19], PIVI recommends that imaging technology with targeted biopsies should have a per-patient sensitivity of 90% or greater and a specificity of 80% or higher to allow reduction in the number of biopsies.

AI has since emerged as a promising adjunct on this front. AI uses various ML algorithms including CNN to identify and process real time endoscopic data to overcome the inherent limitations of an endoscopist.

AIM OF REVIEW

This review will provide a comprehensive summary of the present evidence, recent research advances and future perspectives regarding the utility of AI in BE endoscopy. AI may overcome the human limitations related to poor intra- and inter-observer agreement, a burden that affects many aspects of medical imaging and endoscopy. If a CAD system was to be trained to distinguish between neoplastic and non-neoplastic BE macroscopically on endoscopy and microscopically on histology with almost-perfection, it seems logical these limitations can be overcome and better tailored medical management can be rendered.

METHODS AND LITERATURE SEARCH

A comprehensive electronic literature search was performed in the PubMed, MEDLINE and EMBASE databases from inception to the 1st September 2022 using the following key search terms "artificial intelligence" OR "AI" OR "convolutional neural network" OR "deep learning" OR "computer-aided detection" OR "computer-aided diagnosis" AND "Barrett's esophagus." The search was limited to human studies.

Titles and abstracts were screened to exclude studies that did not address the purpose of this review article. The titles of all the identified studies were screened by two reviewers (TNCH and RR) to exclude studies not related to the study topic. The full texts of the screened studies were then assessed for inclusion. Review articles and letters to the editor were excluded. Studies that used other endoscopic techniques such as volumetric laser endomicroscopy were also excluded. Any disagreements were resolved through discussion with senior author LJW until consensus was achieved.

Eligible studies including 12 meta-analyses which reported the use of AI in Barrett's endoscopy and histopathology were included in the review. The analysis flow chart of the included studies is shown in [Figure 1](#).

EXISTING DATA ON THE UTILITY OF AI IN BARRETT'S ESOPHAGUS

Identification and classification of Barrett's esophagus

Pan *et al*[20] developed a DL algorithm using 443 endoscopic images from 187 patients to automatically identify and segment the gastroesophageal junction and squamous-columnar junction of BE. The performance of this automated segmentation algorithm demonstrated satisfactory agreement with expert annotations as measured by intersection over union. This study demonstrates the potential of DL in automating the identification and the classification of BE according to the Prague C&M classification[21] while reducing the inter-observer variability.

DETECTION OF DYSPLASIA AND ADENOCARCINOMA

Following successful identification and classification of BE, the subsequent detection of dysplasia or EAC can be clinically challenging, particularly for non-experts[22]. Further differentiation between non-dysplasia, low-grade dysplasia, high-grade dysplasia and EAC can be subjective and difficult when a focal lesion has been detected. Ebigo *et al*[23] managed to demonstrate that a CAD system using deep learning of still images [248 high-definition white light images and 74 narrow band images (NBI)] from two databases, was able to diagnose EAC with sensitivity of 97% and 92% as well as specificity of 88% and 100% for white light images (WLI) in both databases respectively. Additionally, the CAD system was able to achieve sensitivity of 94% and specificity of 80% for NBI images. This study demonstrated that a CNN algorithm was able to accurately identify EAC in still endoscopic images, all validated by expert pathologists, at a sufficiently high sensitivity and specificity to meet the PIVI standards mentioned previously.

Due to the limitations of using still endoscopic images, further steps were taken to validate the AI system in real-time by assessing captured endoscopic images taken by an expert BE endoscopist to differentiate between EAC and normal BE with a sensitivity and specificity of 83.7% and 100% respectively with an overall accuracy of 89.9%[24].

Concurrently, de Groof *et al*[25] conducted a pilot study to develop a CAD system using white light endoscopic images from 60 patients to delineate between BE neoplasm and non-dysplastic BE. One endoscopic image from each patient was included in the CAD system with per-image analysis demonstrating sensitivity of 95%, specificity of 85% and diagnostic accuracy of 91.7%. The CAD system was not only able to delineate a BE neoplastic lesion but also able to indicate the most abnormal area within that delineation to obtain a targeted biopsy. Additionally, it took an average of 1.051 s for the algorithm to analyze an endoscopic image and subsequently produce its lesion delineation, signaling the potential to be used in a real-time, automated setting.

The same group of investigators went on further to develop a deep-learning CAD system for primary detection of neoplasia in patients with BE using a CNN model. The system was initially pretrained with a large dataset of 494364 Labeled endoscopic images from multiple locations of the GI tract using a supervised learning approach. The system was then subsequently trained with BE-specific endoscopic images containing a total of 1544 images of BE neoplasia and non-dysplastic BE before being validated using two separate external datasets. The CAD system managed to classify images as containing neoplasms or non-dysplastic BE with 89% accuracy, 90% sensitivity and 88% specificity. Performance was also benchmarked against 53 general endoscopists with a wide range of experience. When compared to the endoscopists, the CAD system managed to achieve higher diagnostic accuracy of 88% *vs* 73%, sensitivity of 93% *vs* 72% and specificity of 83% *vs* 74%[26]. Apart from the large databases used to develop and validate the CNN based algorithm, the computational speed per image analysis was 0.24 s which was a significant improvement from their previous CAD system, paving the way for the incorporation of the CAD system during live endoscopic procedures to help delineate BE neoplastic lesions.

For further validation, the CAD system was tested during live endoscopic procedures in 10 patients with non-dysplastic BE and 10 patients with confirmed BE neoplasia. White light endoscopic images were obtained at every 2 cm level of the Barrett's segment and analyzed by the CAD system. The per-level analysis was 90% accurate with a 91% sensitivity and 89% specificity[27], highlighting the comparable diagnostic performance of the CAD system in both real-time and "offline" settings.

Another study also utilized image databases to develop an AI algorithm using 132 high-definition white light endoscopic images from 46 lesions of histologically confirmed Barrett's neoplasia and 119 images on non-dysplastic Barrett's from 20 patients. The images were used for training, validation and testing of a CNN algorithm to detect Barrett's neoplasia with a sensitivity of 93%, specificity of 78% and accuracy of 83%[28].

The utility of AI in CAD of BE neoplasia was further highlighted in another pilot study, in which Hashimoto *et al*[29] developed a CNN algorithm using 916 images of histology-proven early BE neoplasia containing high-grade dysplasia or T1 stage adenocarcinoma and 919 control images of BE without high-grade dysplasia. The trained CNN algorithm managed to correctly detect early neoplasia in a total of 458 test images with sensitivity of 96.4%, specificity of 94.2% and accuracy of 95.4%.

With the widespread use of image enhanced endoscopy like NBI in routine endoscopic practice for further lesion characterization, it is only natural that a deep learning algorithm would be developed to interpret NBI images and to aid in the diagnosis of BE neoplasia. A study was conducted using a trained CAD system to interpret 183 NBI zoom images

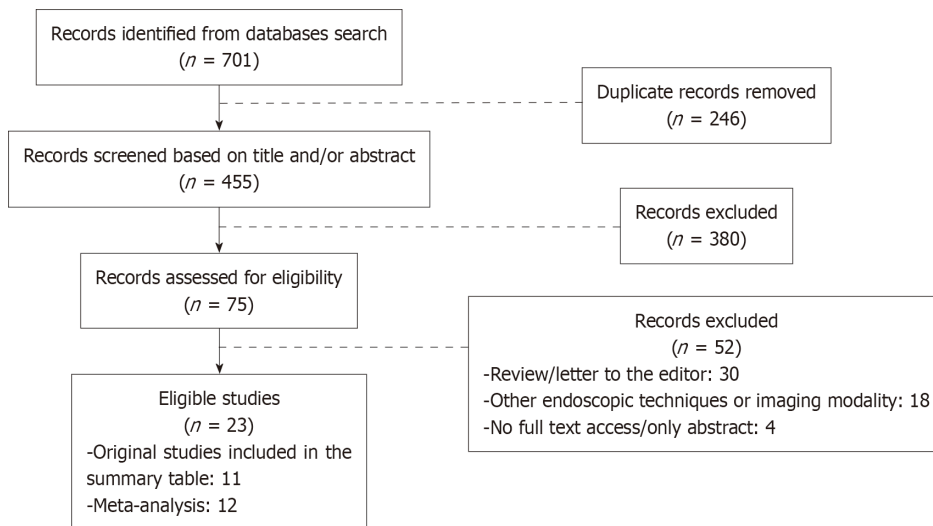


Figure 1 Identification of studies *via* databases – analyses flow chart of included studies.

and 157 NBI zoom videos with similar diagnostic accuracy of 84%-85%[30].

As most AI studies were largely image database studies and relatively small in number, a meta-analysis of the studies on the performance of AI in detection and characterization of upper GI neoplasia was performed by Arribas *et al*[34], which included nine studies[22-26,28,31-33] on BE neoplasia detection (total of 12909 images from 1506 patients used for training and a total of 2340 images from 445 patients used for testing). The pooled sensitivity and specificity of BE neoplasia detection was 89% and 88% respectively.

A more recent meta-analysis of twelve studies[22,24-28,30,35-38] was conducted to evaluate the diagnostic performance of AI in detecting BE neoplasia comprising 1361 patients and utilizing 532328 images for training. Pooled sensitivity was 90.3% while pooled specificity was 84.4%. Further subgroup analysis demonstrated that pooled sensitivity and specificity were also similar in six studies that used WLI as the main mode of modality[39]. An interesting observation from the meta-analysis was that there was significant heterogeneity amongst the included studies with I^2 of > 50% but the area under the summary of receiver operating characteristics curve was 0.94 (95%CI: 0.92-0.96). Upon further assessment of these studies, multiple factors such as the definitions of dysplastic Barrett's, the different types of AI algorithm and imaging modality used are very likely to contribute to the heterogeneity of the study outcome. This highlights the importance for further standardization of future study protocols with regards to the definition of BE neoplastic lesions and imaging modality used.

PREDICTION OF SUBMUCOSAL INVASION IN BARRETT'S ESOPHAGUS

Apart from detection and classification of neoplasia in BE, the application of AI has shown promise in predicting submucosal invasion in Barrett's cancer. The identification of submucosal invasion (T1b) in Barrett's cancer is important as it has implications for the choice of treatment. Lesions with suspected submucosal invasion should be treated with endoscopic submucosal dissection (ESD) instead of the conventional endoscopic mucosal resection (EMR). ESD is a viable alternative to surgery and considered curative if the resected specimen fulfills the necessary criteria including submucosal invasion depth < 500 μ m, good to moderate differentiation and no lympho-vascular invasion[13,40]. A retrospective, multicenter study was conducted to evaluate the diagnostic performance of a CNN based algorithm using a total of 230 white-light endoscopic still images to discriminate between mucosal (T1a) and submucosal (T1b) Barrett's cancer. The trained AI algorithm was able to predict submucosal invasion and differentiate between T1a and T1b carcinoma with a sensitivity of 77%, specificity of 64% and an accuracy of 71%. The AI algorithm demonstrated comparable performance to five international Barrett's expert endoscopists who evaluated the same set of images[41]. This study brings to light the potential for AI to support the clinical decision-making process with regards to the endoscopic *vs* surgical resection of precancerous lesions by predicting the submucosal invasion in Barrett's cancer.

ARTIFICIAL INTELLIGENCE IN BARRETT'S HISTOPATHOLOGY

Interobserver agreement between pathologists can be variable with regards to interpretation of BE histology, a recognized issue particularly for low grade dysplasia (LGD) and indefinite dysplasia (IND)[42]. A study showed that concordance between pathologists progressively decreased from non-dysplastic BE (79%), high grade dysplasia (71%), LGD (42%) to IND (23%)[43]. Given that a diagnosis of dysplasia has significant implications on surveillance schedule and BE therapy, American College of Gastroenterology recommends confirmation by a second GI pathologist for dysplasia of any grade

detected on biopsy[12].

Attempts have been made to use AI to complement the pathologist and improve interpretation of BE histology. It has been made possible with the rapid advancement in the field of digital pathology and the subsequent incorporation of image analysis using AI. Since the introduction of commercial digital slide scanners, it was possible to digitize glass histology slides into whole-slide images (WSI), to facilitate slide-sharing and clinical discussion, archiving of digitized slides and extraction of histopathological features using deep learning methods for image analysis[44].

A study utilized an attention-based CNN algorithm to analyze BE and esophageal adenocarcinoma using high-resolution WSI and achieved a mean classification accuracy of 83%[45]. Similarly, another study trained and validated a deep learning model using WSI from 542 patients that managed to demonstrate sensitivity and specificity > 90% at the various grades of dysplasia (non-dysplastic BE, LGD and HGD)[46]. In time, we expect more studies and advances in this field that can improve interpretation of BE histology with reproducible reliability.

FUTURE PERSPECTIVES OF ARTIFICIAL INTELLIGENCE IN BARRETT'S ESOPHAGUS

GI endoscopy has seen remarkable progress throughout the last few decades with incremental step-wise progress through incorporation of breakthrough technology and medical device innovation. AI has the potential to push the innovation boundary of GI endoscopy by leveraging on existing and new information as well as vast databases to formulate algorithms, and to support the clinician in identifying and characterizing suspicious lesions. In practice, live upper endoscopic images can be sent locally or remotely to the AI system and be analyzed in real time. Based on the available data and capability, the system will be able to detect suspicious lesions for neoplasia and alert the endoscopists to those lesions either with a screen alert or location box. The endoscopist can then decide on the management of the highlighted lesion based on the characterization provided by the system.

AI can lead to earlier detection of neoplasia in BE, improvement in prognosis and reduction of mortality due to EAC. AI in BE is still in its infancy and there is no long-term data to determine the impact of AI on reduction of EAC incidence and EAC-related mortality[47]. But it is not difficult to envision that early and correct staging of neoplasia will spare the patient from the grueling experience of esophageal surgery and will enable the possibility of minimally invasive endoscopic treatments. Additionally, as described above, the invasion of depth of detected lesions could be characterized with a higher level of confidence, in particular among less experienced endoscopists, in the differentiation between mucosal and submucosal invasion. This has therapeutic consequences in the endoscopic resection approach; EMR *vs* ESD. The studies described were summarized in Table 1.

Table 1 Summary of the original research studies included in the review

Ref.	Study objective	Diagnostic modality	Study type	Real time	Dysplasia inclusion	Test images, n	Diagnostic performance
Pan <i>et al</i> [20], 2021	BE segment identification	WLI, NBI	Retrospective	No	NA	443	IOU: GEJ 0.56, SCJ 0.82, GEJ+SCJ 0.66
Ebigbo <i>et al</i> [23], 2019	BE neoplasia detection	WLI, NBI	Retrospective	No	EAC	MICCAI: 100; Ausburg: 148	Sen 92%, Spec 100%; WLI: Sen 97%, Spec 88%; NBI: Sen 94%, Spec 80%
Ebigbo <i>et al</i> [24], 2020	BE neoplasia detection	WLI	Prospective	Yes	EAC	191	Sen 83.7%, Spec 100%
de Groof <i>et al</i> [25], 2019	BE neoplasia detection	WLI	Retrospective	No	HGD, EAC	60	Sen 95%, Spec 85%
de Groof <i>et al</i> [26], 2020	BE neoplasia detection	WLI	Retrospective	No	HGD, EAC	297; 80; 80	Sen 87.6%, Spec 88.6%; Sen 90%, Spec 87.5%; Sen 92.5%, Spec 82.5%
de Groof <i>et al</i> [27], 2020	BE neoplasia detection	WLI	Prospective	Yes	HGD, EAC	144	Sen 91%, Spec 89%
Abdelrahim <i>et al</i> [28], 2020	BE neoplasia detection	WLI	Retrospective	No	NA	251	Sen 93%, Spec 78%
Hashimoto <i>et al</i> [29], 2020	BE neoplasia detection	WLI, NBI	Retrospective	No	HGD, EAC	458	Sen 96.4%, Spec 94.2%
Struyvenberg <i>et al</i> [30], 2021	BE neoplasia detection	NBI	Retrospective	No	HGD, EAC	183 zoom images; 157 zoom videos	Sen 88%, Spec 78%; Sen 85%, Spec 83%
Ebigbo <i>et al</i> [41], 2021	BE cancer invasion	WLI	Retrospective	No	EAC (T1a, T2a)	230	Sen 77%, Spec 64%
Tomita <i>et al</i> [45],	BE neoplasia	NA	Retrospective	No	LGD, HGD,	123 WSI	Mean accuracy 83%

2019	histology detection	EAC
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BE: Barrett's esophagus; WLI: White-light images; NBI: Narrow-band images; LGD: Low grade dysplasia; HGD: High grade dysplasia; EAC: Esophageal adenocarcinoma; IOU: Intersection over union; GEJ: Gastro-esophageal junction; SCJ: Squamo-columnar junction; Sen: Sensitivity; Spec: Specificity; MICCAI: Medical Image Computing and Computer-Assisted Intervention; WSI: Whole-slide images; NA: Not available.

AI has also the potential to reduce inter-observer variability in interpretation of not only endoscopic images but also of high-resolution, digitized histology slides to ascertain presence of dysplasia or EAC, thereby alleviating the burden of having a second pathologist for confirmation. As AI systems develop and assimilate into clinical practice, it becomes imperative that they are tested and validated in real-world settings, in diverse patient populations, with physicians of varying expertise, with different endoscope types and in different practice settings. There has been a proposal by ASGE AI task force to develop a large open-source image library as a resource to validate AI systems and to moderate data variability[48].

It is also conceivable that a trained AI system will also be able to generate an endoscopy report at the end of a session, including automated Prague C&M measurements, measurements of hiatal hernia and so on to be reviewed by the endoscopist for verification. Extending beyond that, AI has the potential, *via* a subtype of deep learning called natural language processing[49,50], to automatically extract and analyze keywords from free-text endoscopic and pathology reports, potentially aiding the physician to diagnose, plan and to recommend the appropriate endoscopic surveillance intervals for patients with BE.

CONCLUSION

AI has made significant progress in diagnostic endoscopy and in the identification of BE pathology using a digital workflow. AI driven systems are likely to become an important tool to detect and to characterize Barrett's esophagus related dysplasia and early adenocarcinoma as they can present as very subtle lesions on endoscopy. Further development and validation are required before AI can be adopted mainstream in the clinical management of BE.

FOOTNOTES

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Observational Study

Drug-induced liver injury and COVID-19: Use of artificial intelligence and the updated Roussel Uclaf Causality Assessment Method in clinical practice

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Abstract

BACKGROUND

Liver injury is a relevant condition in coronavirus disease 2019 (COVID-19) inpatients. Pathophysiology varies from direct infection by virus, systemic inflammation or drug-induced adverse reaction (DILI). DILI detection and monitoring is clinically relevant, as it may contribute to poor prognosis, prolonged hospitalization and increase indirect healthcare costs. Artificial Intelligence (AI) applied in data mining of electronic medical records combining abnormal liver tests, keyword searching tools, and risk factors analysis is a relevant opportunity for early DILI detection by automated algorithms.

AIM

To describe DILI cases in COVID-19 inpatients detected from data mining in electronic medical records (EMR) using AI and the updated Roussel Uclaf Causality Assessment Method (RUCAM).

METHODS

The study was conducted in March 2021 in a hospital in southern Brazil. The NoHarm® system uses AI to support decision making in clinical pharmacy. Hospital admissions were 100523 during this period, of which 478 met the inclusion criteria. From these, 290 inpatients were excluded due to alternative causes of liver injury and/or due to not having COVID-19. We manually reviewed the EMR of 188 patients for DILI investigation. Absence of clinical information excluded most eligible patients. The DILI assessment causality was possible *via* the updated RUCAM in 17 patients.

RESULTS

Mean patient age was 53 years (SD $\pm$ 18.37; range 22-83), most were male (70%), and admitted to the non-intensive care unit sector (65%). Liver injury pattern was mainly mixed, mean time to normalization of liver markers was 10 d, and mean length of hospitalization was 20.5 d (SD $\pm$ 16; range 7-70). Almost all patients recovered from DILI and one patient died of multiple organ failure. There were 31 suspected drugs with the following RUCAM score: Possible (n = 24), probable (n = 5), and unlikely (n = 2). DILI agents in our study were ivermectin, bicalutamide, linezolid, azithromycin, ceftriaxone, amoxicillin-clavulanate, tocilizumab, piperacillin-tazobactam, and albendazole. Lack of essential clinical information excluded most patients. Although rare, DILI is a relevant clinical condition in COVID-19 patients and may contribute to poor prognostics.

CONCLUSION

The incidence of DILI in COVID-19 inpatients is rare and the absence of relevant clinical information on EMR may underestimate DILI rates. Prospects involve creation and validation of alerts for risk factors in all DILI patients based on RUCAM assessment causality, alterations of liver biomarkers and AI and machine learning.

Key Words: Chemical and drug induced liver injury; RUCAM; Artificial intelligence; COVID-19; Liver injury

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Core Tip: This is a real-life study that correlated hospital clinical pharmacy data with artificial intelligence (AI) and pharmacovigilance in coronavirus disease 2019 (COVID-19) inpatients. Inpatient screening for liver injury was made with AI and drug-induced liver injury was evaluated with the Roussel Uclaf Causality Assessment Method (RUCAM) algorithm. A total of 17 COVID-19 inpatients were evaluated, there were 31 suspected drugs, RUCAM score: possible (n = 24), probable (n = 5), and unlikely (n = 2). This study contributed to the patient safety and pharmacovigilance database. These results are included in a project of clinical pharmacy using AI tools.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic put global health systems at risk of collapse worldwide, with more than 510270667 globally confirmed cases and 6233526 deaths in the past two years[1]. COVID-19 patients may be asymptomatic or develop severe acute respiratory syndrome (SARS) with mild to severe manifestations. As a multiple organ disease, extrapulmonary clinical features range from gastrointestinal to hematological effects. Critically ill patients or those with comorbidities commonly present venous and arterial thromboembolic events, liver injury, secondary bacterial infections including sepsis or cytokine storm, contributing to a poor prognosis and higher mortality rates[2-4]. Current treatment options can be supportive clinical management to drug use such as oxygen, dexamethasone for systemic inflammation, heparin/enoxaparin in prophylaxis of venous thromboembolism, and antiviral or monoclonal antibody such as remdesivir, baricitinib, tofacitinib, and tocilizumab[1,5].

Liver injury is a relevant condition in COVID-19 inpatients. In 2020, liver enzyme abnormalities were estimated to occur in 14% to 53% of patients[6,7]. The liver injury pattern is mild to moderate hepatocellular injury, considering aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $<5\times$ the upper limit of normal (ULN) and cholestatic for Delta/Omicron variants[8,9]. High levels of AST and ALT, gamma-glutamyl transferase, and total bilirubin have been associated with severe COVID-19, intensive care unit (ICU) admission, and prolonged hospital stay[10-12]. Pathophysiology possibilities of liver injury in COVID-19 vary from direct infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), hypoxic changes, systemic inflammation, exacerbation of underlying disease and adverse drug reactions. Drug-induced liver injury (DILI) may be present in COVID-19 patients due to wide exposure to multiple treatments with antipyretic, antibiotics, corticosteroids, immunomodulators, and antiviral drugs[13,14].

DILI is a rare adverse drug reaction (ADR) that can cause acute liver failure and even the need for liver transplantation in the worst cases[15]. The disease is classified as hepatocellular, cholestatic, or mixed[16]. The diagnosis is made by exclusion of other liver pathologies such as cirrhosis, viral hepatitis, auto-immune hepatitis or other chronic liver diseases. In clinical practice, relevant DILI occurs when patients present ALT>5×ULN with jaundice, hepatomegaly, hyperbilirubinemia, or right-upper-quadrant pain. In most DILI cases, withdrawal of suspected drug(s) and supportive therapy are the standard treatment practices[13,15,17]. DILI detection and monitoring is clinically relevant, as it may contribute to poor prognosis, prolonged hospitalization and increase indirect healthcare costs[12,14,15].

The updated Roussel Uclaf Causality Assessment Method (RUCAM) is a causality assessment tool strongly recommended by specialists worldwide to evaluate and correlate liver damage to drug/herb use due to its hepatic specificity[18]. The updated RUCAM was complemented by additional criteria to establish DILI with a high degree of certainty, such as clarification of ambiguous questions related to alcohol use, exclusion of non-drug causes as a checklist of differential diagnosis[16].

DILI causality is scored in RUCAM by seven domains: time to symptoms onset, ALT course, patient's risk factors such as alcoholism and age, concomitant drug use, non-drug causes of liver injury, previous knowledge on the hepatotoxicity of the drug, and response to rechallenge. The individual points range from -3 to +3 and the total possible score ranges from -9 to +14. The interpretation of the final score is as follows: 0 or less indicates that the drug is "excluded" as a cause; 1 to 2 that it is "unlikely"; 3 to 5, "possible"; 6 to 8, "probable"; and greater than 8, "highly probable". Although RUCAM provides an objective scoring system, its use still shows limitations regarding expert interpretation and comorbidities such as COVID-19 itself[13,19]. Lack of good quality evidence-based DILI is a reality in Brazil and its early detection by healthcare professionals is an important challenge[20]. DILI sub notification may be attributed to lack of knowledge on how to properly assess DILI and apply RUCAM.

Recent literature has shown the use of technologies to actively search and assess ADR. Artificial intelligence (AI) algorithm-based applications simulate human decision making based on large datasets and health information patterns [21,22]. In the field of *in vitro* studies, AI that uses prediction models based on the chemical structure of compounds and the exploration of 2D and 3D *in vitro* imaging data have demonstrated interesting results in predicting DILI for novel drugs[23]. In clinical practice, a systematic review demonstrated that AI has been used in COVID-19 for diagnosis, clinical decision making, drug discovery, vaccine development and surveillance and chest images classification[21].

Literature has shown interesting AI tools to detect and analyze COVID-19 patients such as rapid classification of medical images (X-ray) through convolutional neural networks using datasets with positive and negative images of COVID-19 inpatients[24]. Specifically for DILI, AI applied in data mining of EMR combining abnormal liver tests, keyword searching tools, and risk factors analysis is a relevant opportunity for automated algorithms to detect possible DILI cases early[25].

Despite global large-scale vaccination slowing the advance of the COVID-19 pandemic, the disease remains a serious concern, demanding clinical investigation and elucidation. Polypharmacy and off label drugs use in COVID-19 are an alert for DILI screening since they can contribute to poor clinical outcomes. This observational study aims to describe DILI cases in COVID-19 inpatients retrospectively detected using AI from data mining in EMR. We intend to discuss the hepatotoxicity profile of drugs used in COVID-19 detected cases assessed by RUCAM, as well as the current prospects and challenges of applying AI and the updated RUCAM in inpatient evaluation that may contribute to patient safety and pharmacovigilance practices.

MATERIALS AND METHODS

We conducted a descriptive retrospective study investigating alterations in liver markers in patients diagnosed with COVID-19 who were admitted to a reference COVID-19 hospital complex in southern Brazil during March 2021. The hospital complex comprises 7 hospitals with different specialties such as cardiology, pulmonology, neurology, pediatrics, and general care, with emergencies, ICU, and a surgical center. In March, 100523 patients were admitted.

We included all patients aged 18 years or more who had COVID-19 diagnosed by real-time polymerase chain reaction assays, with at least one complete set of ALT, AST, and alkaline phosphatase (ALP) results during their inpatient stay and with at least one normal and one abnormal ALT value. We excluded patients with liver injuries defined by other etiologies such as viral hepatitis, alcoholic hepatitis, hepatocellular carcinoma, autoimmune hepatitis, cytomegalovirus, leptospirosis, Epstein Barr, hemolytic diseases, among other hepatobiliary disorders.

The hospital is associated with the NoHarm®[26], a system that uses AI to support decision making in clinical pharmacy. It currently develops two algorithms to optimize pharmacist validation for prioritizing non-standard prescriptions and identifying critical patients. The system is linked to hospital data and indicates potential prescription errors, increasing quality of care and hospital efficiency. We used this AI platform to automatically screen EMR of inpatients with ALT>3×ULN who were suspected of having DILI. We accessed each patient in this platform to check inclusion/exclusion criteria. Afterwards, a chart with ALT course during hospitalization was presented to guide investigators in which days relevant clinical information should be collected. The ALT>3×ULN was chosen to be a cut off to pre-analyze patients for DILI.

We applied the updated RUCAM to all suspected cases of DILI[27]. Then, two independent reviewers (GL and GXO) separately assessed the likelihood of altered liver tests being related to drug use during hospital stay. In the case of disagreement, a third pharmacist reviewed the suspected DILI case. If there was still no consensus, the case was discussed with a fourth hepatology specialist. The domains evaluated were liver injury pattern, timing of events, rechallenge, risk factors, comedications, alternative causes, hepatotoxicity previously established in the scientific

literature, and response to unintentional rechallenge.

The RUCAM classifies DILI as highly probable (≥ 9), probable (6-8), possible (3-5), unlikely (1-2), or excluded (≤ 0) [16]. Cases scored as highly probable, probable, and possible were considered as DILI. Since this is a retrospective study, not all patients would have the same profile of laboratory tests to rule out other causes of abnormal liver chemistries. The RUCAM is used for DILI diagnosis in individual cases, case series, registries, or epidemiological studies involving any types of drugs, herbal medicines, or dietary supplements. Thus, assessments were only based on information available in EMR. Missed information in EMR may compromise RUCAM scores, decreasing punctuation as well as the likelihood of DILI. Drugs with a well-established pattern of absence of liver toxicity in which they were used at usual doses and treatment times were not included in the RUCAM analysis, unless they were the only drug used and the timeframe of events were highly compatible with DILI. Liver injury pattern is defined by the R (the ratio of ALT and ALP expressed as multiples of the ULN) and corresponds to: (1) Hepatocellular if $R \geq 5$, (2) mixed if $2 < R < 5$, and (3) cholestatic if $R \leq 2$.

Data were constituted by the patient's profile, symptoms, drugs, laboratory tests, image and biopsy exams, if available, hospitalization time, and outcomes. Due to the small sample, statistical analysis of independent variables (risk factors) of DILI was not performed. However, it did not compromise the purpose of the study which is to describe possible DILI cases and suspected COVID-19 medications. The analysis evaluated DILI causality.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations checklist was applied to this study to facilitate critical appraisal and interpretation of cross-sectional study results [28]. This study was approved by the Ethics Committee (number 4763390 CAEE 46652521.9.0000.5530).

RESULTS

In total, 100523 patients were admitted into the hospital in March 2021, with 478 inpatients showing at least one ALT result $>3 \times \text{ULN}$ detected by AI. Of these, we excluded 290 inpatients with alternative causes of liver enzyme elevation, and who were not positive for COVID-19. We reviewed 188 EMR. From these, absence of essential clinical information excluded most patients. **Figure 1** summarizes patients' inclusion and exclusion criteria. The main missing information was serum transaminases follow-up in 91 patients as the patient was released for outpatient follow-up at the slightest improvement. A total of 34 patients had COVID-19 but the ALT peaks were due to other causes such as sepsis, cardiopulmonary arrest, or hypovolemic shock; 16 patients did not use any suspected drug; and 10 patients used medications before hospital admission with no posology information. Lack of virology tests excluded 20 patients who could possibly have had DILI. Drugs used in those patients were chlorpromazine, azithromycin, ceftriaxone, bicalutamide, and ivermectin (off-label use). All of them are well established common DILI agents. We assessed DILI causality with the updated RUCAM in 17 patients and **Table 1** shows the complete RUCAM score.

The mean age of patients was 53 years ($\text{SD} \pm 18.37$; range 22-83). Most were male (70%), and admitted to the non-ICU sector (65%). The liver injury pattern was mainly mixed with mean normalization of liver injury within 10 d and mean length of hospitalization was 20.5 days ($\text{SD} \pm 16$; range 7-70). Almost all patients recovered from DILI and one patient died of multiple organ failure. There were 31 suspected drugs with 2 medications suspected per inpatient. The RUCAM score distribution was as follows: 24 possible cases, 5 probable, and 2 unlikely. The DILI agents in our study were ivermectin, bicalutamide, linezolid, azithromycin, ceftriaxone, amoxicillin-clavulanate, tocilizumab, piperacillin-tazobactam, and albendazole. Antimicrobials were 77% of the suspected agents, followed by antiparasitic 16%, and antineoplastic and immunomodulating agents 7%.

DISCUSSION

The DILI prevalence was 1.6 to every 10000 inpatients in this study differing from the 9.8% in China [29]. The first review of Brazilian DILI case reports was published in 2019 showing DILI as a rare ADR; however, this is controversial since DILI underreporting is a major concern leading to alarmingly low rates of its suspicion and identification [30]. The DILI prevalence in hospitalized patients tends to be higher than in our study. A prospective study from France reported a DILI prevalence of 6.6 per 1000 per week among hospitalized patients. DILI incidence in Switzerland on hospitalization admission was 0.7% and in Turkey prevalence among inpatients was 3.1% [31]. In Iceland, the crude annual incidence rate of DILI was 19.1 cases per 100000 patients [32]. The discrepancy may be related to the calculation of prevalence since we only entered patients whose causality could be assessed with RUCAM unlike other studies that consider DILI if the patient had all other liver diseases excluded.

Most (77%) of our patients with ALT above 5 times the UNL were mainly men and had mild to moderate DILI. Regarding clinical features, COVID-19 Chinese DILI patients' median age was 61 years, they were mainly men, the mean (SD) hospital stay was 21.49 (11.89) d, and the mean (SD) days for the first acute liver injury was 9.57 (9.38) after admission [29]. These findings corroborate with our study, demonstrating a set of specific clinical features for patients with DILI and COVID-19.

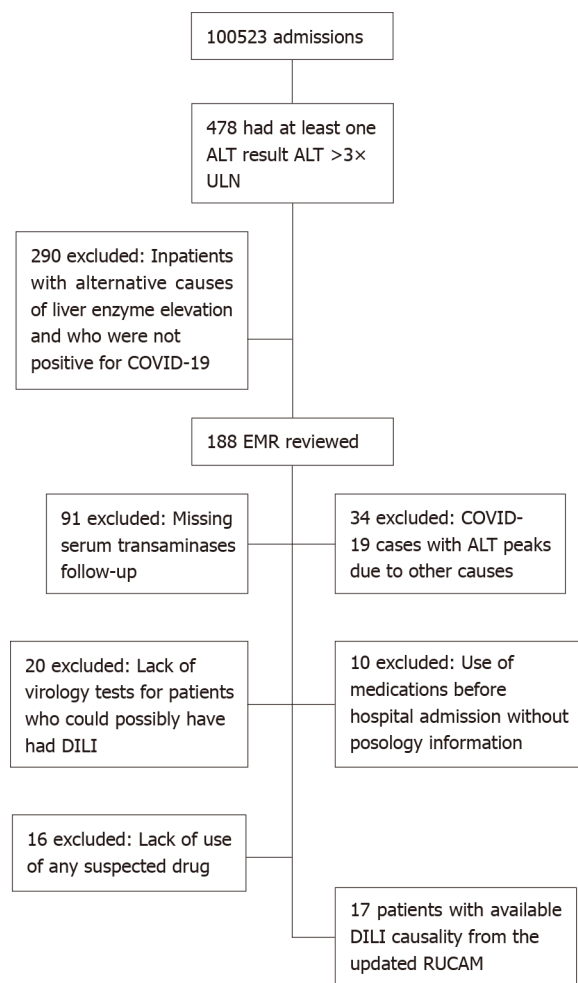
Almost all patients' normalized liver markers showed a time frame from drug suspension to recovery ranging from 2 to 25 d. Our findings were consistent with the scientific literature of DILI for COVID-19 and non-COVID-19, suggesting a moderate severity of liver injury, rarely progressing to severe and spontaneously recovering. Even so, clinically monitoring DILI is recommended since it can contribute to a reserved prognosis and prolong length of hospital stay (LOS) [15,33]. Prolonged LOS is associated with negative patient experience and inpatient complications such as infections and falls [34]. None of the patients received drug treatment specifically for DILI besides clinical monitoring and suspected

Table 1 Characteristics of the coronavirus disease 2019 inpatients with drug-induced liver injury detected by artificial intelligence in March, 2021

Patient ID	Age/sex	ALT peak (U/L)	Hospital sector	Type of liver injury	Suspected drug	Posology/time treatment	RUCAM score	Causality	DILI diagnosis in EMR	Outcomes (timeframe)	Hospital length of stay (d)
1	83/M	388	ICU	Unclassified	Ivermectin	48 mg daily/6 d	3	Possible	No	Recovered (10 d)	18
					Bicalutamide	150 mg daily/8 d	2	Unlikely			
					Linezolid	600 mg 12/12 h/5 d	4	Possible			
					Azithromycin	500 mg daily/5 d	4	Possible			
					Ceftriaxone	2 g 12/12 h/3 d	4	Possible			
2	61/M	269	ICU	Mix	Amoxicillin + Clavulanate	625 mg 8/8 h/3 d	7	Probable	No	Recovered (7 d)	40
					Azithromycin	500 mg daily/7 d	7	Probable			
					Ceftriaxone	1 g 12/12 h/5 d	7	Probable			
3	62/M	307	ICU	Mix	Tocilizumab	800 mg/1 d	1	Unlikely	No	Recovered (12 d)	31
4	67/M	222	Non-ICU	Cholestatic	Azithromycin	500 mg daily/3 d	3	Possible	No	Recovered (25 d)	28
					Ceftriaxone	1 g 12/12 h/4 d	3	Possible			
5	69/F	588	ICU	Cholestatic	Azithromycin	500 mg daily/5 d	4	Possible	No	Death	25
					Ceftriaxone	2 g daily/7 d	4	Possible			
6	78/M	163	Non-ICU	Unclassified	Ceftriaxone	2 g daily/7 d	3	Possible	No	Recovered (23 d)	70
7	55/M	682	Non-ICU	Hepatocellular	Azithromycin	500 mg daily/5 d	3	Possible	No	Recovered (6 d)	8
					Ivermectin	18 mg daily/4 d	4	Possible			
8	50/F	157	Non-ICU	Unclassified	Ivermectin	18 mg daily/5 d	3	Possible	No	Recovered	7
9	49/F	127	ICU	Cholestatic	Azithromycin	500 mg daily/6 d	3	Possible	No	Recovered (2 d)	17
					Ceftriaxone	2 g daily/9 d	3	Possible			
10	57/M	274	Non-ICU	Mix	Azithromycin	500 mg daily/5 d	6	Probable	No	Recovered (4 d)	10
11	22/M	312	Non-ICU	Hepatocellular	Azithromycin	500 mg daily/4 d	4	Possible	No	Recovered	5
					Ceftriaxone	1 g 12/12 h/3 d	4	Possible			
12	33/M	551	Non-ICU	Hepatocellular	Ceftriaxone	1 g 12/12 h/53 d	3	Possible	No	Recovered	8
13	61/F	168	Non-ICU	Mix	Piperacillin + tazobactam	4.5 g 8/8 h/9 d	6	Probable	No	Recovered	21
14	32/M	489	Non-ICU	Cholestatic	Ceftriaxone	2 g daily/5 d	5	Possible	No	Recovered (10 d)	10
15	73/M	160	Non-ICU	Mix	Ceftriaxone	1 g daily/8 d	6	Possible	No	Recovered	15
16	29/F	369	Non-ICU	Mix	Amoxicillin + clavulanate	625 mg 8/8 h/3 d	4	Possible	Yes	Recovered	15
17	33/M	213	ICU	Mix	Azithromycin	500 mg daily/5 d	5	Possible	No	Recovered (10 d)	22

Piperacillin + tazobactam	4.5 g 8/8 h/10 d	4	Possible
Ivermectin	18 mg daily/1 d	5	Possible
Albendazole	400 mg daily/2 d	5	Possible

Outcomes (timeframe): Timeframe between drug suspension and recovery of liver injury. Patients 8, 11, 12, 13, and 15 were discharged for ambulatory care without alanine aminotransferase follow-up. Patient 16: Drug-induced liver injury diagnosis was presented in electronic medical record by physicians; however, the suspected drug was ivermectin used by self-medication prior to hospital stay. DILI: Drug-induced liver injury; EMR: Electronic medical records; RUCAM: Roussel Uclaf causality assessment method; ICU: Intensive care unit.



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Figure 1 Patient selection flowchart for drug-induced liver injury assessment. ALT: Alanine aminotransferase; COVID-19: Coronavirus disease 2019; DILI: Drug-induced liver injury; EMR: Electronic medical records; RUCAM: Roussel Uclaf causality assessment method; ULN: Upper limit of normal.

drug suspension.

Serum transaminase elevation presented no determined cause for 171 of our patients and DILI could neither be confirmed nor excluded. This finding suggests that DILI diagnosis remains a challenge due to its multifactorial characteristics and many confounders. Proper diagnosis will depend on the healthcare professional's familiarity with DILI[30]. The fifth RUCAM domain decreases DILI causality if there is no information for any of the following viruses: hepatitis C virus (HCV), hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis E virus (HEV). In our cases, if virology results were available and negative, drugs scored as "Unlikely" would change to "Possible", suggesting underestimation of DILI prevalence. Medication reconciliation was incomplete for 10 patients, making it infeasible to apply RUCAM. Drugs used before hospital admissions were ivermectin, azithromycin, cefuroxime, hydroxychloroquine, dexamethasone, and prednisone, but posology and duration of treatment were not available in EMR.

Another study evaluating the association between drug treatments and incidence of liver injury and DILI in inpatients with COVID-19 presented the same limitation, since 10% of the suspected cases were excluded due to incomplete EMR [29]. The more incomplete the relevant clinical information, such as the presence of serologies to exclude other possible

causes of liver injury, the less likely it is to assign adequate scores to drugs that may be associated with DILI. Considering this scenario and our findings, quality data on DILI cases assessed by RUCAM in COVID-19 patients are scarce[33].

Literature demonstrates that suspected DILI agents in COVID-19 are mostly antiviral, antibacterial, antifungal drugs, hydroxychloroquine/chloroquine, corticosteroids, and immunotherapy[29]. In a systematic review of 996 DILI cases published in 2020/2021 based on RUCAM as a causality assessment method, antiviral drugs given empirically were mainly responsible for DILI. Liver injury pattern was mainly hepatocellular, differently from our prevalence of mixed pattern. This may be associated with different types of drugs used, as they have diverse DILI pathology mechanisms. Most patients had a positive outcome most likely due to quick cessation of drug treatment, even though DILI was fatal in 19 cases. The ALT and AST peak values were 1.541 U/L and 1.076 U/L, respectively[33]. In contrast, our study showed a maximum ALT of 682 U/L and AST of 556 U/L.

In active search for DILI cases in COVID-19 patients, using lower cutoff points such as ALT one to three times the ULN instead of five times the ULN is preferable, so that no case is missed, since many medicines are used off label and DILI data could demonstrate different hepatotoxicity profiles. Comparison of different liver test thresholds for DILI in hospital patients demonstrate that higher cut-offs, such as ALT levels greater than $5 \times$ the ULN on two consecutive occasions and/or ALP levels greater than $2 \times$ the ULN on two consecutive occasions, as proposed by the DILI Network, are more effective in detecting relevant cases; however, it misses positive cases that were found when the National Medical Products Administration of China, using ALT levels greater than $1 \times$ the ULN on two consecutive occasions or ALT levels greater than $2 \times$ the ULN. In other words, much more labor is required to detect DILI at lower thresholds, despite higher negative predictive values[35]. Automated algorithms to detect DILI using AI may overcome the time-consuming limitation of lower cut-offs, such as when it uses $ALT > 3 \times ULN$, as it performs better in sensitivity, a desirable characteristic to detect rare events and avoid missing cases[36]. ALT values $5 \times ULN$ are considered clinically significant, as they will be the best signal allied to symptoms for physicians to consider stop suspected drug treatment[13].

The DILI agents in our study were ivermectin, bicalutamide, linezolid, azithromycin, ceftriaxone, amoxicillin-clavulanate, tocilizumab, piperacillin-tazobactam, and albendazole. The updated Brazilian report of clinical guidelines for inpatient treatment of COVID-19[37] indicates: (1) Anticoagulants: Unfractionated heparin, enoxaparin, or fondaparinux; (2) corticosteroids: Dexamethasone, methylprednisolone, or hydrocortisone; and (3) antimicrobials according to institutional protocols only in the suspected presence of associated bacterial infection. The report demonstrates the lack of evidence for clinical benefit in the hospitalized patient regarding the use of: Azithromycin, chloroquine, colchicine, hydroxychloroquine, ivermectin, and lopinavir/ritonavir. Attention is needed to the irrational use of azithromycin and ivermectin since those drugs have no evidence of clinical benefits in patients with COVID-19 and, as our findings suggest, may even worsen liver injury[38-40].

Antibiotics were the most common agents both in this study and the international literature[17,41]. Ceftriaxone was the main DILI suspected causative agent (10 cases) followed by azithromycin (9 cases). Ceftriaxone is very likely causative of cholestatic injury with minimal symptoms due to crystallization of ceftriaxone in bile present in the gallbladder[42]. Azithromycin is a well-known but rare cause of clinically apparent self-limited cholestatic hepatitis with rapid resolution of symptoms whether the drug is stopped or not[43]. Amoxicillin-clavulanate is the main one of the top-ranking drugs implicated in RUCAM-based DILI cases retrieved from large international medical centers[41]. It causes mostly self-limited cholestatic or mixed idiosyncratic DILI. The onset of injury is a few days to 8 wk after therapy initiation[44,45]. It appeared in only one case probably related to prescription pattern rather than prevalence ratio. Piperacillin-tazobactam rarely causes self-limited cholestatic idiosyncratic DILI[46].

Ivermectin and albendazole are antiparasitic agents used off-label for COVID-19 treatment. Ivermectin presented *in vitro* antiviral effects and a few studies suggested clinical benefits against COVID-19 in the early stages of the pandemic [47]. However, medical centers and governmental organizations such as the Food and Drug Administration and the World Health Organization (WHO) rapidly identified the poor quality data of the publications and ivermectin use was not recommended[48]. The DILI caused by ivermectin and albendazole is extremely rare, with one case report[49]. Ivermectin ADR with COVID-19 reported in the WHO's pharmacovigilance database evidenced a considerable increase ($> 50\%$) in ivermectin related reports since May 2020. Among 53 serious cases, eight cases presented gastrointestinal ADR including one death[50]. Ivermectin is not a potential hepatotoxicity agent; however, in our study, dosages were considerably higher than recommendations leading to causality assessment of "possible" DILI agent.

The COVID-19 patients with DILI presented polypharmacy with acetaminophen, azithromycin, ceftriaxone, dextropropofen, doxycycline, enoxaparin, hydroxychloroquine, interferon, levofloxacin, lopinavir, metamazole, omeprazole, pantoprazole, piperacillin-tazobactam, remdesivir, ritonavir, and tocilizumab[51]. Domain four of the updated RUCAM [16] regarding concomitant use of drugs lowers scores of a specific drug assessed if the patient is also using another hepatotoxic drug. In the COVID-19 polypharmacy scenario, this is a controversial concern since suspected cases previously scored as "possible" or "probable" would change to high causality association if hepatotoxicity synergism was considered.

It is controversial that the combination of hepatotoxic drugs may increase the risk of DILI. Evidence exists that rifampicin increases the risk of hepatotoxicity when combined with isoniazid for tuberculosis treatment due to a synergistic effect. Anti-tuberculosis treatment combined with non-nucleoside reverse transcriptase inhibitors and protease inhibitors is more likely to cause DILI than both treatments alone[52]. Concomitant administration of drugs metabolized by the liver (*via* CYP450) modulates active metabolites *via* induction, inhibition, or substrate competition and may increase DILI risk[53]. On the other hand, RUCAM decreases an individual medication's score when concomitant hepatotoxic drugs are co-administered, since sufficient evidence regarding synergistic hepatotoxicity of drugs beyond antiretroviral and anti-tuberculostatic is still lacking[16]. We found only one article summarizing possible ADR worsening by drug-drug interactions in COVID-19, which specifically mentioned remdesivir *vs* rifampicin and ribavirin and human immunodeficiency virus antiviral treatment contraindication due to hepatotoxicity[54]. As a result, especially

for COVID-19, cases of DILI could be missed or sub classified after a RUCAM score considering the fourth domain.

Intrinsic DILI is drug dose-dependent, thus the risk of developing liver injury may increase accordingly when the potential safety range of the drug dose is exceeded. In addition, lipophilicity molecules may enter hepatocytes and hepatic metabolism, which hypothetically could increase DILI risk[31]. Alcohol consumption is included in the RUCAM causality assessment scale as a risk factor due to liver metabolization, especially regarding acetaminophen, isoniazid, methotrexate, and halothane[55]. In our study, none of the patients were heavy alcohol consumers excluding this risk factor and probable confounder. The role of pre-existing liver disease on DILI is yet to be completely understood.

There is no consensus if chronic hepatic diseases, such as non-alcoholic fatty liver disease, hepatocellular carcinoma, or viral hepatitis, could worsen DILI severity outcomes[31]. Currently, RUCAM decreases DILI causality if the patient has HAV (type A viral hepatitis), HBV (type B viral hepatitis), HCV (type C viral hepatitis), HEV (type E viral hepatitis), ultrasound alterations of the hepatobiliary tract, acute hypotension (especially cardiac arrest), sepsis, malignant metastatic disease, autoimmune hepatitis, chronic hepatitis, primary biliary cholangitis, sclerosing cholangitis, genetic liver diseases, Cytomegalovirus infection, Epstein-Barr Virus infection, Herpes Simplex Virus infection, and Varicella Zoster Virus infection[16].

Idiosyncratic DILI occurs independently of drug dose, route, duration of treatment, or administration. The RUCAM score increases if patients are 65 years or older, and older age is considered a risk factor. The underlying mechanisms include declination in liver capacity, underlying diseases and alterations in pharmacokinetics features[56]. Data from the WHO Safety Report Database revealed that elderly patients were much more likely to develop cholestatic DILI[32]. Even though gender is not independently associated with DILI, cases are preponderantly in females, especially severe and immune-mediated DILI. Nowadays, literature demonstrates that polymorphisms of genes involved in drug metabolism and transport and human leukocyte antigen are risk factors for DILI.

COVID-19 itself has been associated with transaminase elevation either caused by viral direct damage, hypoxemia, or multisystem inflammatory syndrome. Thus, we suggest reviewing the updated RUCAM's domain number five and adding COVID-19 as an alternative cause of increased ALT/AST. The systematic review of 966 DILI cases in COVID-19 patients also evidenced barriers to properly determine the quantitative contribution of DILI and COVID-19 in abnormal liver tests, suggesting COVID-19 as a DILI confounder[31]. Although we have identified these possible weaknesses in applying the RUCAM to assess DILI in COVID-19 patients, the algorithm remains the best choice to assist health care professionals in the diagnosis and causality assessment of liver injury when alternative causes are excluded[57]. We strongly recommend the prospective use of RUCAM in healthcare services to overcome poor DILI clinical assistance.

The main challenges in the DILI field refer to early detection and diagnosis by healthcare professionals. Using AI and machine learning may be the key to overcoming this scenario. Literature has focused on AI on quantitative structure activity relationship analysis to predict hepatotoxicity substances in drug development with interesting contributions[58, 59]. However, relevant clinical application of AI would consist of machine learning algorithms automatically and prospectively tracing DILI in EMR and patients' hospitals datasets by crosslinking DILI threshold criteria, risk factors, liver injury International Classification of Diseases (ICD-10) codes, liver tests, and data mining[60,61]. In the next step, an alert would be triggered in electronic systems to physicians and clinical pharmacists informing of potential DILI cases for clinical follow-up[62].

Research that used EMR algorithms for DILI screening found low positive predictive values (PPV)[13]. A recent meta-analysis showed that PPV was only 14.6% for machine learning and AI in EMR. Divergences in liver tests reference values and DILI threshold criteria among different studies decrease comparisons and evaluations of sensitivity and specificity [25]. In this study, we used AI to automatically detect COVID-19 patients with abnormal liver markers and compiled data with dashboards to identify key days patients should be investigated. However, the updated RUCAM application was still manually performed. Prospects in our work involves creating and validating signals for pharmacists generated from automated scores for all DILI patients based on RUCAM assessment causality, AI, and machine learning.

This study has the limitations of a retrospective study design. Incomplete case datasets in EMR that could impact different RUCAM scores may underestimate the prevalence of DILI as well as the hepatotoxicity profile of the suspected drug. No statistical analysis was performed due to the small and non-homogenous sample. Therefore, these findings may only suggest associations, propose insight into DILI, and guide further investigations since the results lack external validation. The assessment of DILI and vaccines was not performed as it was out of the study scope.

CONCLUSION

Our study shows that DILI has a rare incidence in COVID-19 inpatients and the absence of relevant clinical information on EMR may underestimate DILI rates. Abnormal liver tests such as ALT and AST are important triggers to detect DILI, but since they lack specificity a complete evaluation of the patient is necessary for a proper diagnosis. The DILI features in COVID-19 inpatients are provided by age, gender, patients, suspected drugs, type of injury, laboratory data, and clinical outcomes and these findings are consistent with DILI literature of non-COVID-19 cases.

The DILI diagnosis is still a challenge due to its multifactorial character and many confounding factors, including COVID-19, and its early detection by health professionals is an important challenge. The updated RUCAM is the standard tool to assess hepatotoxicity and future research must focus on its prospective applicability to improve DILI quality data. The use of AI in clinical pharmacy decision support in conjunction with RUCAM can contribute to patient safety and pharmacovigilance practices, improving clinical outcomes.

ARTICLE HIGHLIGHTS

Research background

Liver injury is a relevant condition in coronavirus disease 2019 (COVID-19) inpatients. Drug-induced liver injury (DILI) may be present in COVID-19 patients due to wide exposure to multiple treatments. Artificial intelligence (AI) applications are interesting tools for early detection of DILI cases in hospitals using electronic medical records.

Research motivation

DILI detection and monitoring is clinically relevant, as DILI may contribute to poor prognosis, prolonged hospitalization and increase indirect healthcare costs.

Research objectives

To demonstrate the use of AI and the updated Roussel Uclaf Causality Assessment Method (RUCAM) to detect DILI cases from data mining in electronic medical records (EMR) of COVID-19 inpatients.

Research methods

The study was conducted in March 2021 in a hospital in southern Brazil. Hospital admissions were 100523 during this period. The NoHarm® system uses AI to support decision making in clinical pharmacy. 478 cases met the inclusion criteria and from these, 290 inpatients were excluded due to alternative causes of liver injury and/or due to not having COVID-19. We manually reviewed the EMR of 188 patients for DILI investigation. Absence of clinical information excluded most eligible patients. The updated RUCAM was applied to all suspected cases of DILI.

Research results

In total, 17 COVID-19 inpatients were evaluated and there were 31 suspected drugs with the following RUCAM score: possible ($n = 24$), probable ($n = 5$), and unlikely ($n = 2$). DILI agents were ivermectin, bicalutamide, linezolid, azithromycin, ceftriaxone, amoxicillin-clavulanate, tocilizumab, piperacillin-tazobactam, and albendazole. Lack of essential clinical information excluded most patients.

Research conclusions

These results are included in a project of clinical pharmacy using AI tools. Future research must focus on the prospective applicability of the updated RUCAM to improve DILI quality data. The use of AI in clinical pharmacy decision support in conjunction with RUCAM can contribute to patient safety and pharmacovigilance practices, improving clinical outcomes.

Research perspectives

These results are included in a project of clinical pharmacy using AI tools. Future research must focus on the prospective applicability of the updated RUCAM to improve DILI quality data. The use of AI in clinical pharmacy decision support in conjunction with RUCAM can contribute to patient safety and pharmacovigilance practices, improving clinical outcomes.

FOOTNOTES

Author contributions: Ortiz GX conceptualization, data curation, formal analysis, and writing the original draft; Ulbrich AHDPS and dos Santos HDP resources, software and reviewing; Becker MW, Lenhart G, and Schwambach KH writing, reviewing, and editing; Blatt CR project administration and reviewing; All authors contributed to the article and approved the submitted version.

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Artificial Intelligence in Gastroenterology

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ABOUT COVER

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The primary aim of *Artificial Intelligence in Gastroenterology* (AIG, *Artif Intell Gastroenterol*) is to provide scholars and readers from various fields of artificial intelligence in gastroenterology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIG mainly publishes articles reporting research results obtained in the field of artificial intelligence in gastroenterology and covering a wide range of topics, including artificial intelligence in gastrointestinal cancer, liver cancer, pancreatic cancer, hepatitis B, hepatitis C, nonalcoholic fatty liver disease, inflammatory bowel disease, irritable bowel syndrome, and *Helicobacter pylori* infection.

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Role of artificial intelligence in the characterization of indeterminate pancreatic head mass and its usefulness in preoperative diagnosis

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Abstract

Artificial intelligence (AI) has been used in various fields of day-to-day life and its role in medicine is immense. Understanding of oncology has been improved with the introduction of AI which helps in diagnosis, treatment planning, management, prognosis, and follow-up. It also helps to identify high-risk groups who can be subjected to timely screening for early detection of malignant conditions. It is more important in pancreatic cancer as it is one of the major causes of cancer-related deaths worldwide and there are no specific early features (clinical and radiological) for diagnosis. With improvement in imaging modalities (computed tomography, magnetic resonance imaging, endoscopic ultrasound), most often clinicians were being challenged with lesions that were difficult to diagnose with human competence. AI has been used in various other branches of medicine to differentiate such indeterminate lesions including the thyroid gland, breast, lungs, liver, adrenal gland, kidney, etc. In the case of pancreatic cancer, the role of AI has been explored and is still ongoing. This review article will focus on how AI can be used to diagnose pancreatic cancer early or differentiate it from benign pancreatic lesions, therefore, management can be planned at an earlier stage.

Key Words: Artificial intelligence; Indeterminate pancreatic lesion; Imaging; Biomarkers; Diagnosis

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Core Tip: Surgical management of a pancreatic head lesion usually requires pancreaticoduodenectomy, which is associated with significant morbidity and mortality. For a benign lesion it is unacceptable. The investigation modalities *i.e.* computed tomography, magnetic resonance imaging, endoscopic ultrasound, positron emission tomography, and biochemical markers are available today to distinguish benign from malignant lesions and have their limitations (human judgmental errors). The application of artificial intelligence (AI) algorithms can minimize human errors and improve the sensitivity and specificity of diagnostic yield. The AI can help with great precision in differentiating benign from malignant lesions, affecting the management strategy and minimizing post-operative complications.

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INTRODUCTION

The concept of a machine that can think like a human being was proposed by Mr. Alan Turing in the year 1950 in his book entitled "Computing Machinery and Intelligence" and later, the term "artificial intelligence (AI)" was coined by John McCarthy[1,2]. The applicability of AI ranges from simple tasks to more complex tasks mimicking a human brain. There are six major sub-fields of AI: machine learning (ML), neural network, deep learning (DL), natural language processing (NLP), cognitive computing, and computer vision. ML can learn from data, recognize typical patterns, and make decisions with little or no human interference. A neural network is the field of AI that is inspired by the human brain, where a set of algorithms is used to derive a correlation. Most of the AI models in the medical field use ML and neural networks. NLP is a method where textual data has been used to search, analyze, and comprehend complex information. Computer vision understands visual inputs (radiological or pathological images, surgical videos) and derives desired information. There are many modifications of conventional sub-fields of AI which have been in use. The twentieth century has seen that AI has become an essential part of day-to-day life, including health tracking devices[3], automobiles[4], banking and finances (robo-traders)[5], surveillance, social media, entertainment, education, space exploration, and disaster management, *etc*[6,7].

AI has been used in various fields of medicine including online appointments and hospital check-ins, medical records digitalization, follow-up, drug dosage reminders, adverse effect warnings, *etc*. Moreover, its application in the field of oncology is paramount. AI can be useful in cancer detection, screening, diagnosis, classification, prognostication, new drug discovery, *etc*[8-11]. It has played its role in differentiating various indeterminate lesions in the thyroid gland[12, 13], breast[14], lungs[15,16], liver[17], adrenal[18,19], kidneys[20], and indeterminate biliary strictures[21] (Table 1). Various authors have studied the role of AI algorithms to identify pancreatic lesions from imaging modalities computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), positron emission tomography (PET) scan, *etc* and thus can differentiate malignant indeterminate pancreatic lesions (IPLs) from benign ones for better management at an early stage.

IPLs are those detected by imaging techniques performed for non-specific abdominal complaints or detected incidentally, otherwise known as pancreatic incidentaloma. With the increase in imaging modalities, the detection of such IPLs has increased[22]. These incidentalomas are mostly detected in other organs, *i.e.* the thyroid gland, pituitary gland, kidney, lungs, adrenal gland, *etc*. Though, the incidence of indeterminate lesions is less in the pancreas, however, most of them are malignant compared to other sites[23]. Identification of such lesions creates confusion in clinicians and anxiety among the patients. Moreover, early diagnosis of malignancy can provide reasonably early management and better overall outcomes. Therefore, it is necessary to diagnose such lesions for better patient management.

The overall prevalence of such lesions was reported to be 0.01%–0.6% in 2009, which may be less compared to its true incidence[24]. A review of a series of pancreatic resections shows an asymptomatic neoplastic lesion to be 6%–23% (24% to 50% of them are malignant, and 24% to 47% are considered potentially malignant or pre-malignant)[25,26]. A recently published Leopard-2 trial comparing laparoscopic and open pancreaticoduodenectomy has shown the incidence of benign or pre-malignant lesions to be 12%[27]. Frequently, cystic lesions of the pancreas are detected on MRI and their incidence is up to 20%[28] and recent series shows the incidence to be 49% in the general population[29]. The majority of cystic lesions are benign, however, approximately, 3% are malignant or potentially malignant[30].

The etiology of such lesions is diverse, benign adenoma to adenocarcinoma, borderline malignant tumors, mesenchymal tumors, neuroendocrine tumors, cysts, congenital changes, metastatic lesions, inflammatory masses *etc*[23]. These lesions may be broadly divided into benign, pre-malignant, or malignant lesions[24]. Figure 1 shows different pathologies of IPLs[31].

There is a considerable overlap of imaging features of different benign and malignant pancreatic lesions. Cystic degeneration of solid tumors may masquerade as cystic lesions. Various modalities (ultrasonography, contrast-enhanced CT, MRI, EUS, PET, cytopathology, histopathology, and tumor markers) have been used to differentiate the possible etiology, however, there are limitations of each modality intrinsic to the investigation itself or on the operator. Recently, AI has been used to distinguish various indeterminate lesions in the breast, lungs, adrenal gland, kidney, *etc*. Thus, the use of AI in association with conventional imaging or diagnostic modalities can improve their overall diagnostic yield

Table 1 Studies on differentiation of indeterminate lesions using artificial intelligence

No.	Ref.	Number of patients	Organ of interest	Sub-type of AI	Outcome
1	Ippolito <i>et al</i> [12], 2004	453	Thyroid nodule (benign <i>vs</i> malignant)	ANN	Refinement of risk stratification of FNAB and clinical data
2	Daniels <i>et al</i> [13], 2020	121	Indeterminant thyroid nodule	ML	ML and ultrasonography can identify genetically high risk lesions
3	Becker <i>et al</i> [14], 2018	632	Breast lesion (benign <i>vs</i> malignant)	Generic DLS	Aids diagnosing cancer on breast ultrasound images with an accuracy comparable to radiologists
4	Scott <i>et al</i> [15], 2019	125	Lung GGO (benign <i>vs</i> malignant)	ANN	Improve diagnostic ability using CT scan, PET, and clinical data
5	Guo <i>et al</i> [16], 2022	20	Indeterminant small lung lesions	DNN	DNN based method may detect small lesions < 10 mm at an effective radiation dose < 0.1 mSv.
6	Yasaka <i>et al</i> [17], 2018	460	Liver mass (HCC <i>vs</i> others)	CNN	High diagnostic performance in differentiation of liver masses using dynamic CT
7	Moawad <i>et al</i> [18], 2021	40	Adrenal incidentaloma (benign <i>vs</i> malignant)	ML	Machine learning and CT texture analysis can differentiate between benign and malignant indeterminate adrenal tumors
8	Stanzione <i>et al</i> [19], 2021	55	Indeterminant solid adrenal lesions	ML	MRI handcrafted radiomics and ML can be used to different adrenal incidentalomas
9	Massa'a <i>et al</i> [20], 2022	160	Indeterminant solid renal mass (benign <i>vs</i> malignant)	ML	MRI-based radiomics and ML can be useful in differentiation
10	Saraiva <i>et al</i> [21], 2022	85	Indeterminant biliary strictures	CNN	CNN can accurately differentiate benign strictures from malignant ones

AI: Artificial intelligence; ANN: Artificial neural network; CNN: Convolutional neural network; CT: Computed tomography; DNN: Deep neural network; DLS: Deep learning software; FNAB: Fine needle aspiration biopsy; GGO: Ground glass opacities; HCC: Hepatocellular carcinoma; ML: Machine learning; MRI: Magnetic resonance imaging.

and therefore, more precise diagnosis and patient care.

This paper reviews the current status of AI in the differentiation of various IPLs and its future implications.

METHODS AND LITERATURE SEARCH

All the relevant articles were searched from PubMed and Google Scholar using the keywords, *i.e.* “artificial intelligence” AND “pancreatic lesions” OR “cystic lesions”, OR “CT”, OR “MRI”, OR “EUS”, OR “PET” OR “pathology”, OR “biomarkers” between 2005 and 2023, and only full articles were studied. Articles discussing the differentiation of different types of pancreatic lesions were included and screened by all authors. Abstracts and conference presentations were excluded. Studies discussing the differentiation of any pancreatic lesion (benign *vs.* malignant) were included in relevant sections for discussion. The study flow chart is shown in Figure 2.

Role of clinical parameters and AI on the identification of IPLs

Pancreatic cancer is one of the leading causes of cancer-related death worldwide, thus early diagnosis is crucial for better management. Often, patients are asymptomatic to start with, so presentation is delayed leading to advanced disease at diagnosis. This delay in diagnosis can be minimized by the identification of high-risk groups and the introduction of targeted screening of high-risk populations. Any lesion identified in these patient groups can be subjected to further evaluation using an AI augmented imaging system (CT, MRI, PET, EUS), which will be discussed later. The proposed schema of patient evaluation and management is presented in Figure 3.

Several clinical parameters can be used to predict the future incidence of pancreatic cancer including, symptoms, hereditary factors (BRCA1, BRCA2, PALB2, Hereditary pancreatitis, and Peutz-Jeghers Syndrome), pre-existing clinical conditions (new-onset diabetes mellitus), lifestyle (smoking, alcohol, obesity, nutrient-poor diet), and demographic factors. Elevation of CA 19-9, CEA, and recently developed CEMIP (cell migration-inducing hyaluronan binding protein) can be considered as an early indicator of pancreatic cancer[32-34]. None of these parameters can confirm pancreatic cancer, however, a combined assessment can suggest a possible pancreatic cancer leading to screening of high-risk populations. In a retrospective study from Kaiser Permanente Southern California, an algorithm for risk stratification for pancreatic cancer was generated using imaging (CT/magnetic resonance) and clinical factors[35]. In this study, imaging features used were pancreatic duct dilatation as a predictor of malignancy and other features such as atrophy, calcification, pancreatic cyst, and irregular pancreatic duct. Multi-state prediction model showed a discriminatory index (c-index: 0.825–0.833) between normal individuals and individuals with pancreatic cancer. A study at the Biomedical

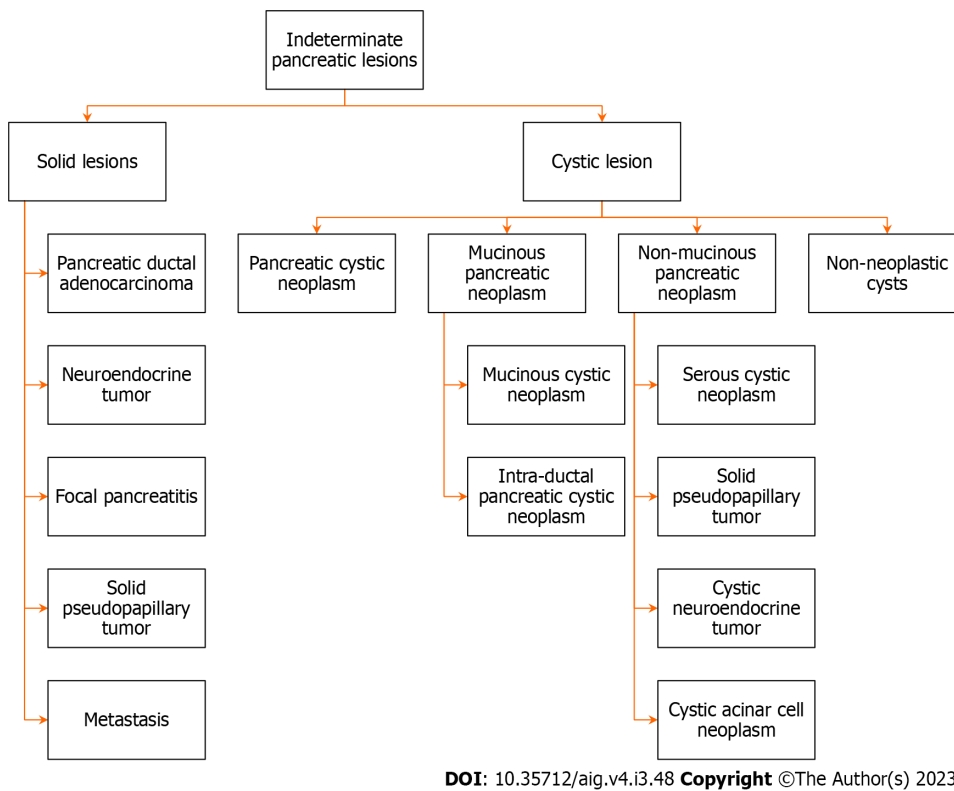


Figure 1 Pathology of different indeterminate pancreatic lesions.

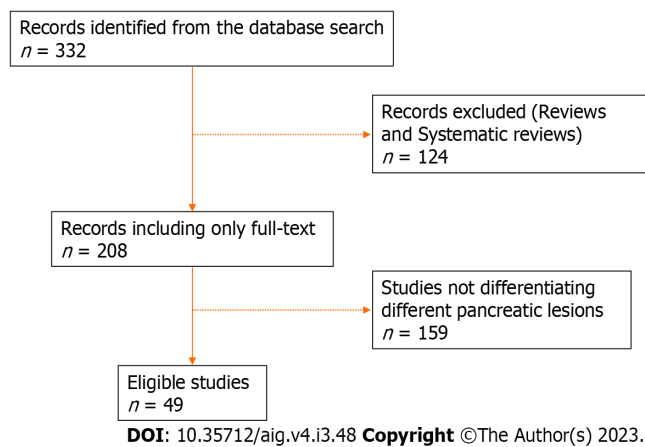


Figure 2 Study flow chart.

Imaging Research Institute of Cedars Sinai Medical Center, Los Angeles used ML and CT-based radiomic features as an indicator of pancreatic ductal adenocarcinoma (PDAC)[36]. The scans were obtained in non-pancreatic cancer patients for different purposes, who later developed pancreatic cancer after 6 mo to 3 years. The AI model had an accuracy of 86% in the prediction of PDAC. As CT scans were performed frequently for different purposes, such AI models can identify patients having potential risk for future pancreatic malignancy.

Muhammad *et al*[37], Placido *et al*[38], and Chen *et al*[39] used demographic and clinical parameters with artificial neural networks (ANNs) algorithms to predict pancreatic cancer. In the validation arm, the area under the curve (AUC) was 0.85, and the sensitivity and specificity of diagnosis were 80.7%. Malhotra *et al*[40] used ML principles to identify symptoms to predict pancreatic cancer. Their algorithm could detect 41.3% of patients with pancreatic cancer < 60 years of age, 20 mo earlier than diagnosis (AUC: 0.66), and 43.2% of patients with pancreatic cancer > 60 years of age, 17 mo earlier than diagnosis (AUC: 0.61). Appelbaum *et al*[41] used neural network algorithms to identify high-risk groups 1 year in advance. Thus, these AI techniques not only help to detect pancreatic cancer but also, earlier than conventional imaging.

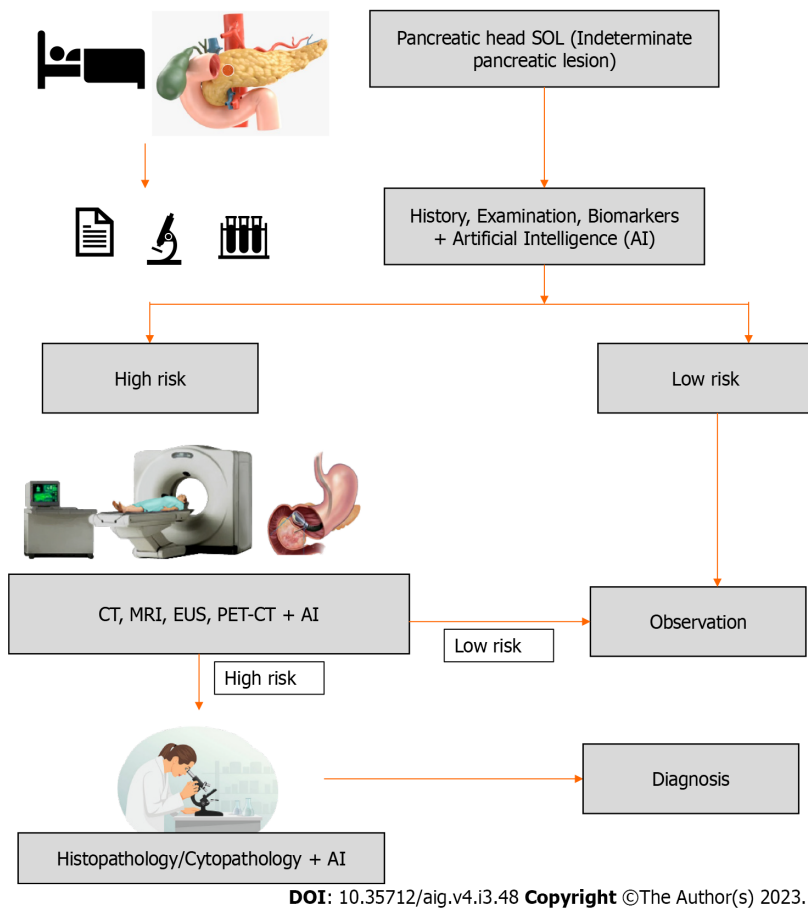


Figure 3 Schematic presentation of diagnosis of indeterminate pancreatic lesion using artificial intelligence. AI: Artificial intelligence; CT: Computed tomography; EUS: Endoscopic ultrasonography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; SOL: Space occupying lesion.

Role of AI on CT scan imaging on detection of pancreatic lesions

If a mass lesion is detected in the pancreas, the possibility of neoplasm is kept as a differential diagnosis. The most common (85%–95%) among the lesions is pancreatic ductal adenocarcinoma (PDAC) and it has a poor prognosis[42,43]. Ill-defined hypovascular mass is the characteristic of PDAC in contrast-enhanced imaging[44]. Atypical imaging of a solid mass may harbor a malignancy, however, its mimic, an inflammatory mass, can have a better prognosis than PDAC, and management of both these conditions is different.

Among all the imaging modalities, CT is most commonly favored for the investigation of a pancreatic lesion, as it is widely available, quick to acquire, has a high spatial resolution, assesses relationship to vascular structures, and determines surgical planning. Recent advances in CT imaging in the form of multiplanar reformatted images, and three-dimensional (3D) techniques have improved sensitivity by up to 96% in tumor identification[45,46]. However, small tumors or tumors with atypical features may not be visible on CT scans or subtle changes may not be appreciable to the human eye and prone to errors. These limitations of conventional CT imaging can be overcome by the use of AI algorithms.

Differentiation of PDAC

Among all malignancies, PDAC has the worst overall survival[47]. It is because patients present late at an advanced stage due to late detection of asymptomatic subtle pancreatic lesions on imaging[40]. Zhu *et al*[48] and Liu *et al*[49] have used DL to detect pancreatic cancer and in the study by Liu *et al*[49], malignancy could be detected in just 3 s with an AUC of 0.96. Chu *et al*[50] could diagnose PDAC with an AUC of 99.9% using ML algorithms.

Differentiation of cystic lesions

With the increase in the frequency of cross-sectional imaging, the detection of cystic lesions of the pancreas has increased and it is aptly called “technopathies”. Management of these cystic lesions requires classification of the type of lesion and the risk of malignancy which is sub-optimal with present imaging modalities[51,52]. AI has been used to differentiate the types of cystic lesions into, intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystic neoplasia (SCN), solid pseudopapillary neoplasia, *etc*[53,54]. Dmitriev *et al*[53] used the convolutional neural network (CNN) model (contrast-enhanced CT and clinical data) to differentiate the types of cystic lesions with an accuracy of 84% which is better than radiologists which has an accuracy of less than 70%[53,55]. However, Li *et al*[54] used only CT images and AI (DL) to differentiate the cystic lesions with an accuracy of 73% compared to radiologists in

their study which had an accuracy of only 48%. Differentiation of SCN from other cystic lesions is important as they have a rare chance of being malignant, thus, Wei *et al*[56] used an ML-based algorithm to distinguish SCN from others based on CT images. Yang *et al*[57] and Chen *et al*[58] have used AI algorithms to distinguish SCN from MCN. Chakraborty *et al*[59] and Polk *et al*[60] used the RF model to differentiate low-grade IPMN from high-grade IPMN which has management implications. Table 2 summarizes studies on the uses of AI along with CT images in the differentiation of pancreatic lesions.

Role of AI on MRI on the detection of pancreatic lesions

MRI is favored over CT scan due to superior soft tissue delineation and it also helps to detect small lesions, assessment of the vascular relationship, and relationship to the pancreatic duct, lymph node, or distant metastasis[43,61]. Detection of iso-attenuating pancreatic lesions on CT scan is challenging which is observed in approximately 10% of patients. In these situations, indirect evidence of malignancy is used for diagnosis, *i.e.* convex pancreatic contour, double duct sign, vascular involvement, mass effect, *etc*[42]. However, MRI can be helpful to diagnose such lesions. Recently, the use of AI algorithms has improved the diagnostic ability of MRI. Li *et al*[62] and Chen *et al*[63] used AI algorithms for the identification of PDAC on different phases of MRI (Table 3).

Management of cystic lesions depends upon the precise characterization, which indicates its clinical behavior[64]. However, overlapping imaging features make differentiation challenging[64]. The role of imaging is to differentiate benign from malignant cystic neoplasms. MRI uses T2 images to identify ductal communication and post-contrast images to characterize the lesion. It is limited in the detection of calcifications which is better appreciated on a CT image. MRI can differentiate benign from malignant lesions with an accuracy of 73% to 81% compared to a CT scan which has an accuracy of 75% to 78%[52,65,66].

The use of AI has enabled MRI to detect high-grade dysplasia or malignancy in IPMN with a sensitivity and specificity of 75% and 78%, respectively[67]. Corral *et al*[67] used 3D CNN to classify IPMN into different types with an accuracy of 58%. Interestingly, Cheng *et al*[68] compared radiomics features of CT and MRI using AL algorithms [LASSO, LR, support vector machine (SVM)] and found out that, the MRI-based model(AUC: 0.940) had better diagnostic ability than the CT based model(AUC: 0.864). Studies on the use of AI with MRI to detect the type of cystic or solid pancreatic lesions are presented in Table 3.

Role of AI on EUS in the detection of pancreatic lesions

EUS uses a high-frequency transducer at the tip of an endoscope. It helps to obtain high-resolution images of the pancreas through the esophagus, stomach, or duodenum. Various modalities of EUS including contrast-enhanced EUS, EUS-guided fine needle aspiration (FNA), and EUS elastography have been used for the evaluation of pancreatic cancer, detection of small lesions, differentiation of solid from cystic tumors, and assessment of resectability[69]. Most importantly, it helps to obtain tissue for cytopathology or histopathology[70,71]. The main drawback is operator dependency, which may reduce the diagnostic yield[72,73]. AI algorithms have been used in association with EUS to detect pancreatic cancers and to differentiate from other lesions (Table 4). Mass-forming chronic pancreatitis may masquerade as pancreatic malignancy, EUS based AI algorithms can be used to distinguish pancreatic cancer from chronic pancreatitis.

Authors have used ML algorithms to differentiate normal pancreatic tissue from PDAC with more than 93% accuracy [74-76]. Two studies have used AI to distinguish chronic pancreatitis from PDAC on EUS images with an accuracy of more than 80%[77,78]. Săftoiu *et al*[79] demonstrated better diagnostic ability of contrast-enhanced EUS (94.6% and a specificity of 94.4%) compared to EUS-FNA (87.5% and 92.7%) in differentiating CP from PDAC using AI.

Recently, EUS elastography has been used to diagnose focal pancreatic lesions. Using ANN, it can differentiate benign from malignant lesions with an accuracy of 95%[80]. In another multicenter prospective study using ANN, they demonstrated that EUS elastography (sensitivity (87.6%) and specificity (82.9%)) had better diagnostic ability than two experienced endoscopists combined (sensitivity 80.0%, specificity 50.0%)[81]. Udristoiu *et al*[82] used ML principles to distinguish focal pancreatitis from pancreatic mass (neuroendocrine tumor or PDAC) with an accuracy of 98.26%. Differentiation of benign IPMN from malignant IPMN has management implications, Kuwahara *et al*[83] studied to detect malignant IPMN using CNN (ResNet-50).

Role of AI on PET imaging on the detection of pancreatic lesions

PET is a functional imaging technique used for staging malignant lesions and is based on the physiological characteristics of tumor cells[84,85]. However, inflammation may mimic a malignant lesion due to high metabolic activity giving rise to false positive results, conversely, in patients with hyperglycemia, it can give a false negative result[86,87]. PET CT is also useful in the assessment of tumor response to therapy[43]. Li *et al*[88] used a hybrid feedback-SVM-random forest model to detect pancreatic cancer from a normal pancreas with an accuracy of 96.47%. Liu *et al*[89] studied the role of dual time PET/CT and SVM model to differentiate PDAC from AIP with an AUC of 0.96 similarly, Xing *et al*[90] showed a diagnostic performance of 0.93 of AUC.

Role of AI in pathological examination on detection of pancreatic lesions

Often, imaging cannot achieve an accurate diagnosis, requiring a tissue diagnosis-cytology or histology[91,92]. AI can be applied to hematoxylin-eosin-stained slides for the detection of pancreatic cancer[93]. Song *et al*[94] used AI algorithms to segment epithelial cell nuclei on slide images and extract morphological features and could differentiate SCN from MCN and grading of PDAC[95]. The CNN was used by Kriegsmann *et al*[96] to localize pancreatic intra-epithelial neoplasm or PDAC in a slide. Niazi *et al*[97] used DL to detect neuroendocrine tumors from normal tissues on Ki-67 stained biopsy

Table 2 Studies on differentiation of indeterminate lesions using artificial intelligence algorithms on computed tomography images

No.	Ref.	Number of patients	Primary objective	Sub-type of AI used	Outcome
1	Qureshi <i>et al</i> [36], 2022	108	Identification of PDAC	ML	Accuracy: 86%
2	Ebrahimian <i>et al</i> [121], 2022	103	Differentiation of benign <i>vs</i> malignant pancreatic lesions	RF	AUC: 0.94
3	Chakraborty <i>et al</i> [59], 2018	103	High risk <i>vs</i> low risk IPMN	RF, SVM	AUC: 0.81
4	Polk <i>et al</i> [60], 2020	29	High risk <i>vs</i> low risk IPMN	LR	AUC: 0.90
5	Ikeda <i>et al</i> [122], 1997	71	PDAC <i>vs</i> pancreatitis	NN	AUC: 0.916
6	Chen <i>et al</i> [58], 2021	100	SCN <i>vs</i> MCN	LASSO and RFE_Linear SVC	AUC: 0.932
7	Yang <i>et al</i> [57], 2019	53	SCN <i>vs</i> MCN	LASSO	AUC: 0.66
8	Yang <i>et al</i> [123], 2022	63	SCN <i>vs</i> MCN	MMRF-ResNet	AUC: 0.98
9	Ren <i>et al</i> [124], 2020	112	PDAC <i>vs</i> pancreatic adenosquamous carcinoma	RF	AUC: 0.98
10	Xie <i>et al</i> [125], 2021	226	MCN <i>vs</i> ASCN	RF	AUC: 0.734
11	Ziegelmayr <i>et al</i> [126], 2020	86	AIP <i>vs</i> PDAC	CNN, ML	AUC: 0.90
12	Li <i>et al</i> [62], 2022	97	Focal-type AIP <i>vs</i> PDAC	LASSO regression	AUC: 0.97
13	Gao <i>et al</i> [127], 2021	170	MCN <i>vs</i> SCN	mRMR + LASSO	AUC: 0.91
14	Dmitriev <i>et al</i> [53], 2017	134	Classification of pancreatic cyst	RF, CNN	Accuracy: 83.6%
15	Li <i>et al</i> [54], 2019	206	Classification of pancreatic cysts	DNN (Dense-Net)	Accuracy: 72.8%
16	Wei <i>et al</i> [56], 2019	260	SCN <i>vs</i> other cystic neoplasms	ML	AUC: 0.767

AI: Artificial intelligence; AIP: Autoimmune pancreatitis; ASCN: Atypical serous cystic neoplasm; AUC: Area under the curve; CNN: Convolutional neural network; DNN: Deep neural network; IPMN: Intraductal papillary mucinous neoplasm; LASSO: Least absolute shrinkage and selection operator; LR: Logistic regression; MCN: Mucinous cystic neoplasm; ML: Machine learning; PDAC: Pancreatic ductal adenocarcinoma; RFE: Recursive feature elimination; RF: Random forest; SCN: Serous cystic neoplasm; SVM: Support vector machine; NN: Neural network; mRMR: Minimum redundancy maximum relevance; SVC: Support vector classifier; MMRF: Multi-channel-multiclassifier-random forest.

Table 3 Studies on differentiation of indeterminate lesions using artificial intelligence algorithms on magnetic resonance images

No.	Ref.	Number of patients	Primary objective	Sub-type of AI used	Outcome
1	Li <i>et al</i> [62], 2022	267	PDAC detection	UDA + meta learning + GCN	DSC (62.08%, T1), (61.35%, T2), (61.88%, DWI), (60.43%, AP)
2	Chen <i>et al</i> [63], 2022	73	PDAC detection	Spiral-ResUNet	DSC: 65.60%, Jaccard index: 49.64%
3	Liang Y <i>et al</i> [128], 2020	56	PDAC detection	CNN	DSC: 71%
5	Cui <i>et al</i> [129], 2021	202	Grading-BD IPMN	LASSO	AUC: 0.903
6	Corral <i>et al</i> [67], 2019	139	Classification of IPMN	CNN	AUC: 0.783
7	Cheng <i>et al</i> [68], 2022	60	Malignant IPMN	LR, SVM	MRI + SVM: AUC: 0.940, CT + SVM: AUC: 0.864
8	Hussein <i>et al</i> [130], 2019	171	Classification of IPMN	SVM, RF, 3D, CNN	Accuracy 84.22%

AI: Artificial intelligence; AP: Arterial phase; AUC: Area under the curve; CT: Computed tomography; CNN: Convolutional neural network; DSC: Dice similarity coefficient; DWI: Diffusion weighted image; GCN: Graph convolutional network; IPMN: Intraductal papillary mucinous neoplasm; LASSO: Least absolute shrinkage and selection operator; LR: Logistic regression; MRI: Magnetic resonance and imaging; PDAC: Pancreatic ductal adenocarcinoma; RF: Random forest; SVM: Support vector machine; UDA: Unsupervised data augmentation.

Table 4 Studies on differentiation of indeterminate lesions using artificial intelligence algorithms on endoscopic ultrasonography images

No.	Ref.	Number of patients	Primary outcome	Sub type of AI used	Outcome
1	Zhu <i>et al</i> [78], 2013	262	PDAC <i>vs</i> CP	SVM	Accuracy: 94.2%
2	Zhu <i>et al</i> [131], 2015	100	AIP <i>vs</i> CP	SVM	Accuracy: 89.3%
3	Zhang <i>et al</i> [74], 2010	216	Normal pancreas <i>vs</i> PDAC	SVM	Accuracy: 97.98%
4	Ozkan <i>et al</i> [76], 2016	332	Recognition of pancreatic cancer amongst various age group	ANN	Accuracy: Average: 87.5% (all ages), Min: 88.46% (40-60 yr), Max: 92% (< 40 yr)
5	Kuwahara <i>et al</i> [83], 2019	50	Benign <i>vs</i> malignant IPMN	CNN	Accuracy: 94%
6	Das <i>et al</i> [75], 2008	56	PDAC <i>vs</i> normal pancreas <i>vs</i> CP	ANN	AUC: 0.93
7	Săftoiu <i>et al</i> [80], 2008	68	Benign <i>vs</i> malignant pancreatic lesion	ANN	Accuracy: 89.7%
8	Tonozuka <i>et al</i> [132], 2021	139	PDAC <i>vs</i> CP	CNN	AUC: 0.94
9	Marya <i>et al</i> [133], 2021	583	PDAC <i>vs</i> benign causes of pancreatic SOL	CNN	AUC: 0.976
10.	Xu <i>et al</i> [134], 2013	Systemic Analysis of 6 studies	Benign <i>vs</i> malignant pancreatic lesion	-	AUC: 0.962

AI: Artificial intelligence; AIP: Autoimmune pancreatitis; ANN: Artificial neural network; CNN: Convolved neural network; CP: Chronic pancreatitis; IPMN: Intraductal papillary mucinous neoplasm; PDAC: Pancreatic ductal adenocarcinoma; SOL: Space occupying lesion; SVM: Support vector machine.

images with a 97.8% sensitivity and 88.8% specificity. Momeni-Boroujeni *et al*[98] could differentiate benign from malignant pathology using a K-means clustering algorithm from FNA-based slides with an accuracy of 100%. Naito *et al* [99] used CNN in FNB-based slides to assess PDAC with an AUC of 0.984. Cyst fluid analysis is an essential part of the diagnosis of pancreatic cystic lesions. Kurita *et al*[100] used a neural network to differentiate benign from malignant cysts taking into consideration biomarkers in cyst fluid, cytology and clinical parameters.

Role of AI in biomarkers on detection of pancreatic lesions

Biomarkers act as an adjunct in diagnosis, prognosis, and screening for recurrence and they can be used for early diagnosis of tumors. However, in the case of pancreatic cancer, it lacks sensitivity and specificity for routine clinical practice[91,101,102]. Liquid biopsy is one of the recent developments in oncology, developed with the intent of detecting tumor cells from blood when biopsy cannot be obtained, or to assess tumor response to therapy (surgery or chemoradiotherapy) and assess genetic mutation. It includes three types of sampling of biological materials; which are circulating tumor cells (CTCs), circulating tumor DNA, and exosomes. CTCs have faced difficulties for years because of very low concentrations in many studies, which is 1–10 cells per 10-mL of blood (much lower than billions of hematopoietic cells) and short half-life (approximately from 1 to 2.4 h) in blood which poses difficulty in further study. AI can be used in the detection of disease from these biomarkers and various studies have explored AI algorithms for biomarkers for diagnosis [91,103]. Studies used exosomes[104–106], cell-free DNA[107], extracellular vesicles long RNA[108], proteins[109–112], and circulating microRNA[113] in association with AI for diagnosis of pancreatic cancer. Table 5 shows studies on the role of biomarkers and AI in the differentiation of pancreatic lesions.

This review has shown that AI can be used in routine investigation modalities (CT, MRI, EUS, PET, biomarkers) to improve diagnostic and differentiating potential; however, it is still in progress. In the beginning, studies have trained and validated AI algorithms, in the future it is a challenge to implement such studies at different geographical locations, ethnicity, genetic makeup, *etc.* The majority of studies have explored the potential to differentiate, chronic pancreatitis from pancreatic ductal adenocarcinoma, SCN from MCN, and high-risk *vs.* low-risk IPMN, however, there can be other differential diagnoses in a clinical scenario.

DISCUSSION

Surgery for malignant pancreatic head lesions was standardized by Whipple *et al*[114] which is acceptable worldwide. It includes a complex single-stage procedure of pancreaticoduodenectomy, which is associated with morbidity (25%) and mortality (0%–9.3%) even in high-volume centers[115–117]. Professor Whipple[118] reported a mortality of 29.2% in his series of patients who underwent pancreaticoduodenectomy. Though, recent series have reported reduced mortality following pancreaticoduodenectomy, morbidity of the procedure continues to be high. Recently, many modifications have been made to reduce morbidity, however, none of the measures appeared to be successful. Are *et al*[119] reported a

Table 5 Studies on differentiation of indeterminate lesions using artificial intelligence algorithms on different biomarkers

No.	Ref.	Number of samples	Type of biomarker used	Sub-type of AI used	Conclusion
1	Chen <i>et al</i> [104], 2019	28	Exosomes	LDA	Accuracy: 100%
2	Zheng <i>et al</i> [105], 2022	220	Exosomes	ANN	AUC: 0.86
3	Ko <i>et al</i> [106], 2017	28	Exosomes	LDA	Accuracy: 100%
4	Cristiano <i>et al</i> [107], 2019	34	Cell-free DNA	GBM	AUC: 0.86
5	Yu <i>et al</i> [108], 2020	501	extracellular vesicles long RNA	SVM	AUC: 0.96
6	Gao <i>et al</i> [109], 2012	199	Proteomes	SVM, KNN, ANN	AUC: 0.971
7	Yu <i>et al</i> [110], 2005	100	Proteomes	DT	Sensitivity: 88.9%, specificity: 74.1%
8	Qiao <i>et al</i> [112], 2022	136	Proteomes	CNN	Accuracy: 87.63%
9	Alizadeh <i>et al</i> [113], 2020	671	Circulating micro RNA	ANN	Accuracy: 0.86

AI: Artificial intelligence; ANN: Artificial neural network; CNN: Convolved neural network; DT: Digital transformation; KNN: K-nearest neighbor; GBM: Gradient boosting machine; LDA: Linear discriminant analysis; SVM: Support vector machine.

historical perspective where 7 out of 37 pancreaticoduodenectomies performed by Prof Whipple AO turned out to be chronic pancreatitis (18.9%), where such a morbid procedure could have been avoided. Recent series have also supported these findings of incidence of benign pathology following pancreaticoduodenectomy in the range of 5%-10% [117,120]. Hence, there is an unmet need to differentiate benign pancreatic lesions from malignant ones. Multiple imaging modalities have been used to distinguish benign from malignant lesions, however, each investigation modality has its limitations which are compounded by human errors. The application of AI has minimized those errors and can make diagnoses earlier. Table 6 shows how AI increases the yield of different imaging modalities for predicting a malignant pancreatic head lesion. We have proposed an algorithm for the diagnosis of such entities. Whenever a patient presents to a clinician, history and clinical examination precede imaging. Hence, AI can be used to develop algorithms to predict malignancy [32-34]. In a patient with a high risk of pancreatic malignancy, a pancreatic indeterminate lesion should be investigated further with imaging or biopsy to rule out malignancy. Studies have reported the usefulness of biomarkers in the diagnosis of pancreatic cancer [107-110]. Hence, all non-invasive markers (clinical, biochemical) can be used to develop an algorithm that can predict pancreatic cancer before imaging has been performed and it can differentiate malignant pancreatic lesions. As shown in Table 6, AI has an added advantage over conventional imaging in differentiating pancreatic cancer from benign conditions. So, those high-risk patients marked on non-invasive pancreatic cancer detection models can be subjected to AI-enhanced imaging for better diagnosis. Further in line, to clarify the final tissue diagnosis, AI can help to detect subtle markers that can be ignored by human error. Therefore, AI can be used in every step of the diagnosis of an indeterminate pancreatic head mass, to detect malignant lesions early thus, availing proper oncological management.

Pancreatic incidentalomas or indeterminate lesions are on the rise due to the plethora of cross-sectional imaging performed to diagnose non-specific abdominal complaints. Though plenty of studies have been made in the fields of breast cancer, lung cancer, hepatocellular carcinoma, renal cell carcinoma, and adrenal tumors, there is a dearth of literature discussing how to differentiate benign pancreatic lesions from benign ones. The current literature included studies comparing individual pancreatic lesions, *i.e.* serous cystadenoma *vs.* mucinous cystadenoma, autoimmune pancreatitis *vs.* pancreatic adenocarcinoma, low-grade *vs.* high-grade IPMN, *etc.* However, a comprehensive review discussing how to differentiate various malignant pancreatic lesions (both cystic and solid) from benign lesions with the help of AI is lacking. Hence, in this review, we have discussed how to differentiate different pancreatic lesions encountered in day-to-day clinical practice using different algorithms of AI. We have discussed individually about different diagnostic modalities and different types of pancreatic lesions. There are more studies available in the field of radiological investigations and fewer studies available for the histopathological diagnosis or intra-operative differentiation of malignant from benign lesions. As the understanding of the usefulness of AI is increasing, these limitations can be curtailed in the near future.

FUTURE PERSPECTIVES

There is a surge in the number of medical imaging for different indications leading to the identification of many indeterminate pancreatic lesions (IPLs), which help to diagnose a disease earlier or can lead to a plethora of other investigations, psychological stress, clinical dilemmas, *etc.* Human judgment is prone to errors as subtle differences in these small or atypical lesions are challenging to discern leading to inter-observer and intra-observer variations which can be

Table 6 Studies demonstrating impact of artificial intelligence on increasing efficacy of diagnostic modalities

No.	Ref.	Objective	Modality	Sensitivity	Specificity	Accuracy
1	Corral <i>et al</i> [67], 2019	Differentiate cystic SOL of pancreas	Fukuoka guideline	62%	77	77.5%
			Deep learning	75%	78%	78.3%
2	Kuwahara <i>et al</i> [83], 2019	Detection of malignant IPMN	Human pre-operative diagnosis (Clinical + lab + imaging)	95.7%	22.2%	56%
			Artificial intelligence	95.7%	92.66	94%
3	Gao <i>et al</i> [135], 2020	Ability to differentiate pancreatic disease	CE-MR	NA	NA	83.93%
			GAN	NA	NA	76.79%
4	Rigioli <i>et al</i> [136], 2021	Detection of pancreatic cancer and SMA involvement	CT scan	NA	NA	71%
			Artificial intelligence	62%	77%	54%
5	Chen <i>et al</i> [137], 2023	Detection of pancreatic cancer	CT scan	89.9%	95.9%	AUC: 0.96
			CNN	90%	93%	NA
6	Tang <i>et al</i> [138], 2023	Pancreatic mass diagnosis	EUS FNA	81.6%	100%	87.9%
			CE EUS Master-guided FNA	90.9%	100%	93.8%

CE-MR: Contrast enhanced-magnetic resonance; CT: Computed tomography; CNN: Convolved neural network; EUS: Endoscopic ultrasound; FNA: Fine needle aspiration; GAN: Generative adversarial network; IPMN: Intraductal papillary mucinous neoplasm; NA: Not available; SMA: Superior mesenteric artery; SOL: Space occupying lesion.

minimized with the use of AI.

CONCLUSION

AI is an evolving technical advancement in the field of medicine and can play a significant role in differentiating IPLs into benign or malignant, by enhancing the diagnostic yield of conventional imaging (CT, MRI, PET), EUS, tissue diagnosis (cytopathology, histopathology), and biomarkers (liquid biopsy). An early and accurate diagnosis may lead to timely intervention, thereby improving the patient outcome. The current literature on this is still limited and sparse, therefore, more studies are required to reach a standard approach for the application of AI in IPLs.

FOOTNOTES

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Use of artificial intelligence in total mesorectal excision in rectal cancer surgery: State of the art and perspectives

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Abstract

BACKGROUND

Colorectal cancer is a major public health problem, with 1.9 million new cases and 953000 deaths worldwide in 2020. Total mesorectal excision (TME) is the standard of care for the treatment of rectal cancer and is crucial to prevent local recurrence, but it is a technically challenging surgery. The use of artificial intelligence (AI) could help improve the performance and safety of TME surgery.

AIM

To review the literature on the use of AI and machine learning in rectal surgery and potential future developments.

METHODS

Online scientific databases were searched for articles on the use of AI in rectal cancer surgery between 2020 and 2023.

RESULTS

The literature search yielded 876 results, and only 13 studies were selected for review. The use of AI in rectal cancer surgery and specifically in TME is a rapidly

evolving field. There are a number of different AI algorithms that have been developed for use in TME, including algorithms for instrument detection, anatomical structure identification, and image-guided navigation systems.

CONCLUSION

AI has the potential to revolutionize TME surgery by providing real-time surgical guidance, preventing complications, and improving training. However, further research is needed to fully understand the benefits and risks of AI in TME surgery.

Key Words: Artificial intelligence; Machine learning; Rectal cancer; Total mesorectal excision; Colorectal surgery

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Core Tip: This review provided an overview of the current use of artificial intelligence methods in surgery and the latest findings on their use during total mesorectal excision dissection in rectal cancer procedures. It also discussed the main limitations of artificial intelligence in surgery and that it is still not used in clinical settings.

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INTRODUCTION

Colorectal cancer is a significant public health concern, with 1.9 million new cases and 953000 deaths worldwide in 2020. It is the third most common cancer and the second leading cause of cancer-related deaths globally, according to GLOBOCAN data[1]. Despite advances in non-surgical treatment of colorectal cancer, oncological radical surgical excision of the primary tumor and locoregional lymph nodes represents the predominant aspect of curative treatment. Total mesorectal excision (TME) is a surgical technique that has become the standard of care for the treatment of rectal cancer and involves the complete removal of the rectum and surrounding tissues, including the mesorectum, the fatty tissue that surrounds the rectum. The technique was first introduced in the 1980s and has since been shown to improve local control of the disease and reduce the risk of recurrence, leading to better long-term outcomes for patients[2]. This surgery requires skill and expertise to achieve both oncological radicality and preservation of the presacral nerves responsible for continence and sexual function.

Incomplete TME is directly linked to local tumor recurrence and decreased overall survival. Curtis *et al*[3] demonstrated that surgeons in the top skill quartile consistently achieved superior-quality histopathological TME specimens, resulting in improved patient outcomes. Many countries are considering centralizing rectal cancer treatment for this reason. The application of adjunctive measures such as artificial intelligence (AI) could aid surgeons in performing an adequate TME. The effect is likely to be more pronounced in surgeons who are still at the beginning of their learning curve but may also be useful to orientate more experienced surgeons in challenging cases, such as cases of recurrent rectal cancer and patients who have previously received neoadjuvant treatment.

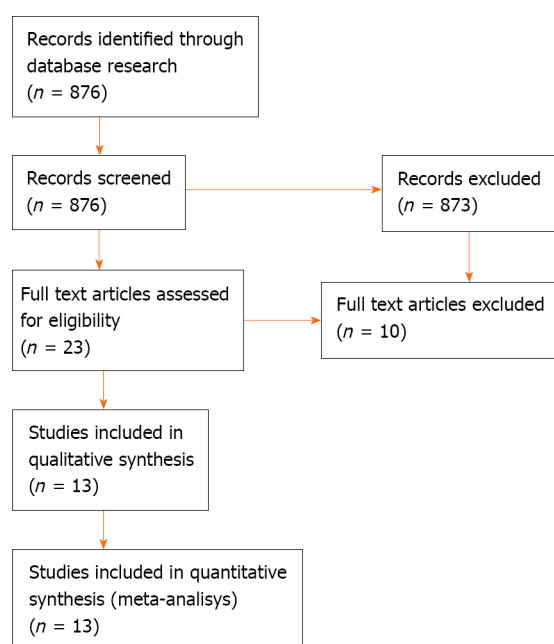
This review provided an overview of the current state of knowledge on the use of AI, specifically in the performance of a TME dissection, focusing on the scientific evidence that supports its use in the management of rectal cancer.

MATERIALS AND METHODS

A comprehensive literature search was conducted to identify relevant studies for this review. The search was performed using the PubMed electronic database, using the following search terms: "TME" OR "Total Mesorectal Excision" OR "Rectal Cancer Surgery" AND "Artificial Intelligence" OR "Machine Learning" OR "Deep Learning." The search was limited to studies published between 2020 and 2023. Only articles published in English were included. Only studies addressing the use of AI in rectal cancer surgery and specifically in TME were selected.

RESULTS

The literature search yielded 876 results. Thirteen studies met our inclusion criteria. The selection flowchart is illustrated in Figure 1. In an initial screening, only the title and abstract of the papers were analyzed until we obtained 26 results. After reading the full text, only 13 studies were selected for review.



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Figure 1 Study selection flowchart.

Overview of AI in medicine

AI is a technology that today encompasses several approaches, such as machine learning (ML), a complex set of mathematical algorithms that allow computers to learn through experience[4], deep learning (DL), or computer vision (CV). The concept of ML is to identify patterns and optimize their parameters to better solve a specific problem by analyzing large-scale datasets[5]. ML has shown encouraging results in the analysis of data such as texts, images, and videos. DL is a subfield of ML that uses multilayer artificial neural networks to draw pattern-based conclusions from input data[6]. In medicine, a large amount of data is visualized in the form of images, and CV is another subfield of ML, which trains machines to extract valuable information from images (e.g., radiological and histopathological) and videos (e.g., endoscopic and surgical videos)[7].

Several groups have developed radiological image processing algorithms to enable faster diagnoses, improve the visualization of pathologies, and recognize emergency situations[8-12]. Recent examples include DL-based algorithms to achieve accurate carotid artery stenosis detection and plaque classification using computed tomography angiography [11], 3D convolutional neural networks to automate tumor volumes using positron emission tomography computed tomography and magnetic resonance images[12], automatic detection of lymph node metastases in colon and head-and-neck cancer[13,14], and DL models for automatic classification of thyroid biopsies based on microscope images taken with a smartphone[15].

AI in surgery

Surgical data science describes an emerging field of research concerned with the collection and analysis of surgical data [16]. The application of AI technology in surgery was first studied by Gunn[17] in 1976, when he explored the possibility of diagnosing acute abdominal pain using computer analysis. Over the last two decades, interest in the application of AI in general and in colorectal surgery has increased. AI methods have been applied in multiple areas of colorectal surgery, preoperatively, intraoperatively, and postoperatively[18]. Preoperatively, AI can help diagnose and clinically classify patients as accurately as possible and offer a personalized treatment plan. Postoperatively, it can integrate the pathway to better recovery after surgery, automate pathology assessment, and support research. All these elements contribute to improved patient outcomes and provide promising results.

Intraoperatively, it could help improve the surgeon's skills during laparoscopic and robotic procedures. The development of AI-based systems could support anatomy detection and trigger alerts, providing surgical guidance on dangerous actions at crucial stages and improving surgeons' decision-making. ML algorithms have been used to identify surgical instruments as they enter the surgical field and the identification of anatomical landmarks such as vascular and nervous structures and organs[19]. This is achieved using methods that first assess the presence and second analyze the movement pattern of surgical instruments and/or by automatic assessment of surgical phases[20]. In 2022, the work of Mascagni *et al*[21] developed a DL model that automatically segments the hepatocystic triangle and automatically determines compliance with the critical view of safety criteria during laparoscopic cholecystectomy, with the aim of reducing bile duct injuries.

Although this is an evolving field, it is important to point out that AI-based assistance during surgery is still at an embryonic stage, and its developments, such as video segmentation and automatic detection of instruments, have so far shown little benefit, as no AI algorithm has yet been approved for clinical use.

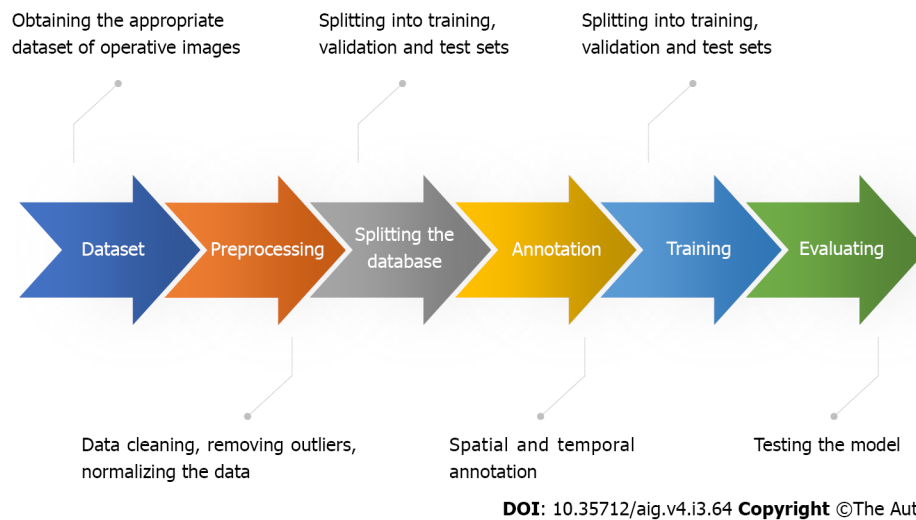


Figure 2 Machine learning pipeline.

AI in surgery focuses on training neural networks. This process starts with splitting the data into two main parts: the training data and the test data. The training data is a predetermined part of the overall data from which the network learns most of its information. The test data is used to see how well the network can apply what it has learned to new, unseen data. The neural network is then fine-tuned through a validation dataset, evaluating various hyperparameters so that the network can estimate the spectrum of data that it may receive.

The DL task can be divided into three categories depending on the type of output expected from the network: (1) Classification. The task of categorizing a given input into two or more possible classes. For example, a classification model could be used to identify the type of tissue in a medical image; (2) Detection. The task of identifying and localizing an object of interest in an image. For example, a detection model could be used to identify and track the surgical tools in a video; and (3) Segmentation. The task of assigning a label to each pixel in an image. For example, a segmentation model could be used to identify the different organs in a medical image. Surgical phase and tool detection models are two early examples of DL for surgical applications[20]. These models have been used to improve the accuracy and efficiency of surgical procedures.

The ML process used in surgical applications can be generally outlined with the following steps (Figure 2): (1) Obtaining an appropriate dataset. The dataset should contain surgical images linked to clinical outcomes. In some cases, a simple and effective way to verify that the data is sufficiently informative is to ask an expert to look at the data and perform the same task proposed for the model. People without medical education could correctly annotate the presence or absence of tools in images. However, the same cannot be said for annotating surgical phases, as this requires surgical understanding and a common definition of what exactly defines and delineates phases; (2) Pre-processing of data. This may include cleaning the data, removing outliers, and normalizing the data; (3) Splitting the dataset. The database is split into training, testing, and validation sets. It is good scientific practice to keep these sets as independent from each other as possible, as the network may develop biases; (4) Annotation. Data labeling is a crucial step in the ML pipeline, as it enables supervised training for ML models. Annotations can be temporal or spatial. Temporal annotations are useful when we need to determine surgical phases during an operation. Spatial annotations are used to identify surgical instruments in the surgical scene or anatomical structures (e.g., tool detection); (5) Training the model. This involves feeding the data into the model and allowing it to learn the patterns in the data. The training process can be computationally expensive, depending on the size of the dataset and the complexity of the model; (6) Evaluation of the model. This involves testing the model on a verified dataset and evaluating its performance. This ensures that the model is not overfitted to the training data; and (7) Deployment of the model. This means making the model available for use in real-world applications.

As mentioned in the annotation description, phase recognition is the process of classifying frames in a video or image sequence according to a predetermined surgical phase. It is a CV task in which visual data is analyzed to identify and understand different phases or actions. The goal is to recognize the sequence of frames in a video or image sequence to identify specific actions or events that occur at different points in time. This can be done by observing characteristic visual cues, such as motion, changes in shape, or object interactions, to differentiate between different phases.

In semantic segmentation, an image is divided into meaningful regions or segments, and each segment is assigned a semantic label. The goal is to understand what the different parts of an image represent. To accomplish this task, an algorithm analyzes the image at the pixel level and assigns each pixel a label indicating which object or category it belongs to. By observing patterns and features in the training data, the algorithm can generalize its understanding to detect and classify new images.

In the context of surgical applications, semantic segmentation can be used to identify different anatomical structures, such as organs, tissues, and blood vessels. This information can be used to guide surgeons during surgery and to improve the accuracy and safety of the procedure. Examples of semantic segmentation in surgical applications include identification of the tumor and surrounding tissue in cancer surgery, localization of the surgical target in minimally invasive

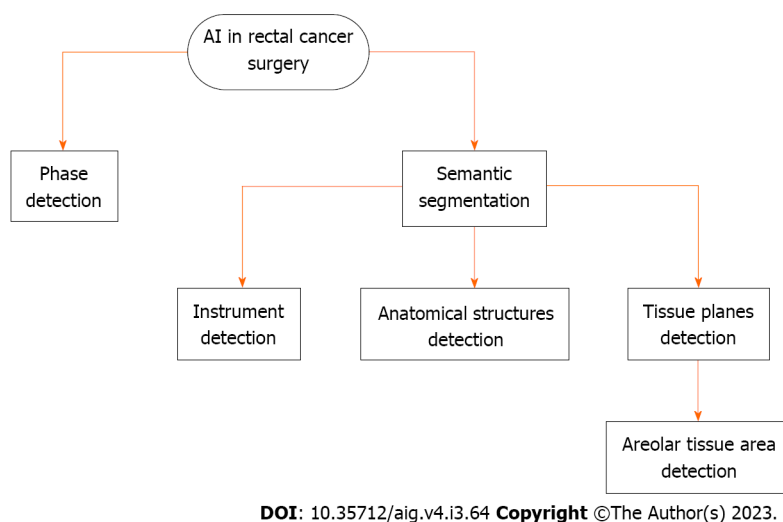


Figure 3 Role of artificial intelligence in rectal cancer surgery. AI: Artificial intelligence.

surgery, tracking the movement of organs and tissues during surgery, detecting and removing blood clots, and preventing accidental injury to surrounding tissue.

One of the challenges in semantic segmentation for surgical applications is the complexity of the images. Surgical images are often cluttered with noise and artifacts, which can make it difficult for the algorithm to accurately segment the different objects. Another challenge is the variability of surgical procedures. Each procedure is unique, and the objects and tissues involved can differ from patient to patient. This makes it difficult to train a single algorithm that can be used for all surgical procedures. Recent advances in DL have made it possible to develop more accurate and robust semantic segmentation algorithms for surgical applications. These algorithms can learn the complex patterns in surgical images and generalize their understanding to new datasets[22].

The role of AI in TME surgery

In anterior rectal resection and TME, studies to date have focused on the development of DL-based phase, act, and tool recognition[22] as well as DL-based image-guided navigation systems for areolar tissue at the level of TME[23].

As mentioned earlier, TME is a complex surgical procedure in rectal cancer surgery consisting of the complete resection of the mesorectal envelope, which requires that the resection is performed in the correct plane and preserves vulnerable anatomical structures, such as the autonomic nerve plexus. An injury of this type could cause major issues such as postoperative incontinence and sexual dysfunction. Robotic-assisted surgery is particularly useful in TME surgery, although the authors acknowledge that no substantial clinical benefit over laparoscopic surgery has been demonstrated[24]. It does, however, offer advantages in terms of acquiring high-quality image data due to the benefits of 3D vision and a more stable camera platform. An additional advantage is that the system recognizes when a new instrument has been connected to the console, making it easy to compare instrument recognition algorithms.

In this context, AI could provide surgical guidance by identifying anatomical structures and helping to improve surgical quality, reduce differences between surgeons, and provide better clinical results. To date, efforts have been made to develop image recognition algorithms using minimally invasive video data, with a particular focus on automated instrument detection, which has only indirect surgical benefits[20,25]. Significant results have also been achieved in the recognition of relevant anatomical structures during less complex surgical procedures such as cholecystectomy[21,26].

The 2022 work by Kolbinger *et al*[22] (republished in 2023) was based on 57 robot-assisted rectal resections and focused on developing an algorithm for automatic detection of surgical phases and identification of determined anatomical structures. In particular, the algorithm achieved the best results in detecting the mesocolon, mesorectum, Gerota's fascia, abdominal wall, and dissection planes during mesorectal excision.

In 2022, Igaki *et al*[23] relied on the idea of the "holy plane," first proposed by Heald[27] in the 1980s when describing TME dissection. The holy plane lies between the mesorectal fascia and the parietal pelvic fascia through fibroareolar tissue and is an important landmark to follow an avascular pathway, ensuring that TME can be performed safely and effectively. Igaki *et al*[23] developed a DL algorithm to automatically detect areolar tissue using the open-source DeepLabv3plus software (Figure 3).

One limitation of the studies was the uncertainty of detection. According to the experience of Kolbinger *et al*[22], automatic recognition of thin and small structures is more difficult, *e.g.*, the recognition of the exact position of the dissection line in mesorectal excision. Furthermore, in TME, patient-related aspects such as individual anatomical variations and the history of neoadjuvant (radio) therapy can lead to the dissection lines being very different throughout the dataset and therefore difficult to detect automatically. These limitations could be overcome by technical improvements, *e.g.*, by displaying the detection uncertainty of the target structures using Bayesian calculation methods, which would increase acceptance among surgeons. Another improvement could be real-time display by minimizing the computational delay, which is currently 4 s[22].

The essential points for the integration of the above improvements and in general for the development of better algorithms for automatic recognition are the availability of data, the creation of publicly available datasets for complex surgical procedures, and the creation of multicenter studies for these applications.

DISCUSSION

In TME, identification of embryonic tissue planes and the closely associated line of dissection at the mesorectal fascia can be challenging because of significant variation due to neoadjuvant (radio) therapy and individual factors such as body composition. AI algorithms can improve intraoperative identification and highlight important parts of the anatomy involved in TME, such as the fibroareolar tissue plane and vascular and neural structures.

In robotic surgery, the use of visual aids could be considered more important than in laparoscopic surgery due to the lack of haptic feedback, *i.e.*, the sense of touch and force feedback that surgeons rely on in traditional open or laparoscopic surgery. To compensate for the lack of haptic feedback, visual augmentation plays a crucial role. In addition, advanced technologies such as fluorescence and near-infrared imaging are frequently used in robotic surgery. These techniques allow visualization of blood flow, tissue perfusion, and identification of vital structures that are not readily visible under normal lighting conditions. Combined with AI-assisted visual enhancements, the surgeon's ability to make critical decisions and perform delicate maneuvers such as TME with the required precision is improved.

Studies on AI-powered surgical guidance, which uses context-aware ML algorithms to automatically identify anatomical structures, surgical instruments, and surgical phases in complex abdominal surgery, require the creation of publicly available datasets and multicenter studies. This is because the datasets need to be large and diverse enough to train AI algorithms that can be generalized to new patients. Additionally, multicenter studies are necessary to ensure that the results are valid and reproducible.

CONCLUSION

The use of AI in TME is still in its infancy, but it has the potential to revolutionize the procedure. For example, AI algorithms can be used to identify and highlight key anatomical structures such as the mesorectal fascia, the vascular bundle, and the autonomic nervous structure. This could provide real-time identification of surgical structures and allow surgeons to perform complex procedures more accurately and safely, even in cases where the anatomy is challenging.

AI algorithms can also be used to track the movement of instruments, tissues, and organs during surgery. This can help prevent complications, such as accidental injury to surrounding tissue. For example, AI algorithms can track the movement of the rectum during dissection to prevent accidental perforation. AI algorithms can also be used to improve surgeons' training and help them become familiar with the complex anatomy of the pelvis and the techniques of TME.

While studies have shown that DL-based algorithms in TME are able to identify fibroareolar tissue and several other anatomical structures, these models have not related the results to postoperative outcomes. This may be due to experienced surgeons evaluating the algorithms, and the true effect is most apparent in those surgeons who are still in the learning phase.

The use of AI in TME is a promising area of research that has the potential to improve the safety and effectiveness of this important surgical procedure. However, more research is needed to fully understand the benefits and risks of this technology, including issues of safety, privacy, and ownership of sensitive data.

ARTICLE HIGHLIGHTS

Research background

Colorectal cancer is a major public health problem, with 1.9 million new cases and 953000 deaths worldwide in 2020. Total mesorectal excision (TME) is the standard of care for the treatment of rectal cancer, but it is a technically challenging surgery. Artificial intelligence (AI) has the potential to improve the performance of TME surgery, especially for surgeons who are still at the beginning of their learning curve.

Research motivation

AI in surgery is a rapidly evolving field with applications in the preoperative, intraoperative, and postoperative settings. In colorectal surgery, AI has been used to automate tasks such as instrument detection and anatomical structure identification. AI has also been used to develop image-guided navigation systems for TME surgery. One of the challenges of AI in surgery is the complexity of the images. Another challenge is the variability of surgical procedures. Recent advances in deep learning have made it possible to develop more accurate and robust AI algorithms for surgical applications.

Research objectives

To investigate the potential of AI in surgery, particularly in colorectal surgery, and the current state of the art. To describe AI algorithms for surgical applications, such as instrument detection, anatomical structure identification, and image-guided navigation systems. To describe their limitations and future developments, such as AI algorithms that can be used

in real time. To propose the evaluation of the safety and efficacy of AI in surgery through clinical trials.

Research methods

A literature search was conducted to identify relevant studies on the use of AI in rectal cancer surgery and specifically in TME. The search was performed using the PubMed electronic database and was limited to studies published between 2020 and 2023. Only articles published in English were included.

Research results

The use of AI in rectal cancer surgery and specifically in TME is a rapidly evolving field. There are a number of different AI algorithms that have been developed for use in TME, including algorithms for instrument detection, anatomical structure identification, and image-guided navigation systems.

Research conclusions

The results of these studies are promising, but more research is needed to fully evaluate the safety and efficacy of AI in TME. Challenges that need to be overcome before AI can be widely adopted in TME include the need for large datasets of labeled images to train AI algorithms, the need to develop AI algorithms that can be used in real-time, and the need to address the ethical concerns raised by the use of AI in surgery.

Research perspectives

AI has the potential to revolutionize TME by providing real-time surgical guidance, preventing complications, and improving training. However, more research is needed to fully understand the benefits and risks of AI in TME.

FOOTNOTES

Author contributions: Mosca V and Pellino G conceived and presented the idea; Mosca V and Fuschillo G wrote the manuscript with the support of Sahnun K and Pellino G; Sciaudone G, Sahnun K, and Selvaggi F supervised the results of this work; Pellino G oversaw the process and was responsible for the overall planning and management; All authors discussed the results and contributed to the final manuscript.

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