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Update on the management of gastrointestinal varices

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Abstract

Cirrhosis of liver is a major problem in the western world. Portal hypertension is a complication of cirrhosis and can lead to a myriad of pathology of which include the development of porto-systemic collaterals. Gastrointestinal varices are dilated submucosal veins, which often develop at sites near the formation of gastroesophageal collateral circulation. The incidence of varices is on the rise due to alcohol and obesity. The most significant complication of portal hypertension is life-threatening bleeding from gastrointestinal varices, which is associated with substantial morbidity and mortality. In addition, this can cause a significant burden on the health care facility. Gastrointestinal varices can happen in esophagus, stomach or ectopic varices. There has been considerable progress made in the understanding of the natural history, pathophysiology and etiology of portal hypertension. Despite the development of endoscopic and medical treatments, early mortality due to variceal bleeding remains high due to significant illness of the patient. Recurrent variceal bleed is common and in some cases, there is refractory variceal bleed. This article aims to provide a comprehensive review of the management of gastrointestinal varices with an emphasis on endoscopic interventions, strategies to handle refractory variceal bleed and newer endoscopic treatment modalities. Early treatment and improved endoscopic techniques can help in improving morbidity and mortality.

Key words: Portal hypertension; Esophageal varices; Gastric varices; Ectopic varices;

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Core tip: Cirrhosis of liver can lead to gastrointestinal varices. Gastrointestinal bleed from varices can be debilitating and can cause morbidity and mortality if not well controlled. This is a detailed review on the endoscopic management of variceal bleed and gives an insight into some of the new endoscopic techniques that can be helpful in treating variceal bleed.

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INTRODUCTION

Less than 1% of the United States population have cirrhosis of liver^[1]. In the western world, the most common etiology of portal hypertension is cirrhosis due to alcoholic liver disease, nonalcoholic steatohepatitis (NASH), and hepatitis C infection^[2]. According to a recent estimate 15 million people in the United States have alcohol abuse disorder, nearly 88000 people die annually due to alcohol, and 10%-15% of people with alcoholism develop cirrhosis^[3]. Another 3 million people have chronic hepatitis C infection^[4], and 25%-28% of these patients go on to develop cirrhosis^[5,6]. Nonalcoholic fatty liver disease (NAFLD) is a spectrum of chronic liver disease consisting of mild to an advanced form of fatty degeneration of the liver described as NASH. Prevalence of NASH is estimated to be around 3%-8% of the general population, and 10%-25% of these patients progress to cirrhosis^[7]. Moreover, the rate of NASH is rising due to the increasing prevalence of obesity, insulin resistance, and diabetes. NASH is the second most common cause among patients with cirrhosis who are currently waiting for liver transplant. Recent trends have indicated that NAFLD is expected to overtake hepatitis C and alcohol as the most common etiology of liver cirrhosis and indication for liver transplants in the western countries by year 2030^[8,9]. Therefore, in order to reduce morbidity and mortality, as well as the overall burden on healthcare, it is essential to develop cost-effective screening and management strategies for portal hypertension related to cirrhosis.

NATURAL HISTORY OF GASTROINTESTINAL VARICES

Gastrointestinal varices are abnormally dilated submucosal veins in the digestive tract due to portal hypertension and can potentially cause life-threatening bleeding. Prevalence of varices increases with the severity of liver disease (Child-Pugh class A 42.7%, class B 70.7% and class C 75.5%)^[2,10]. The Child-Pugh score is described in [Table 1](#). The incidence of esophageal varices in cirrhotic patients is around 5% at the end of one year and 28% at the end of three years. Small varices progress to large varices at a rate of 10% to 12% annually^[11]. Approximately 50% of all patients with a new diagnosis of cirrhosis have gastrointestinal varices^[2]. Annual risk of variceal bleeding among small and large varices is 5% and 15% respectively^[12]. The six-week mortality rate among patients with index variceal bleeding is approximately 20%^[13]. Risk of rebleeding without endoscopic intervention is almost 60% with an increased mortality rate (33%)^[14].

PATHOPHYSIOLOGY

The development of portal hypertension in cirrhosis is a multifactorial process with changes in both the portal and systemic circulation. This is shown in [Figure 1](#). The majority of patients in western countries with portal hypertension have underlying cirrhosis. Non-cirrhotic portal hypertension is typically less common and

Table 1 Child-Pugh scoring and classification

	Child-Pugh scoring		
	1 point	2 points	3 points
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)
Ascites	None	Mild	Moderate to severe
PT/INR	< 1.7	1.71-2.30	> 2.30
Serum albumin (g/L)	> 35	28-35	< 28
Total bilirubin (μmol/L)	< 34	34-50	> 50

Class A (score 5-6), class B (score 7-9), and class C (score 10-15). PT/INR: Prothrombin time/international standardized ratio.

encompasses a broad range of pathology, typically vascular in origin^[15]. Portal hypertension is defined as hepatic vein pressure gradient (HVPG) more than 5 mmHg. The HVPG is a surrogate means to measure pressure in the portal veins. Normal HVPG (= hepatic vein wedge pressure - free hepatic vein pressure) is around 3-5 mmHg. Varices usually develop when patients have HVPG >10 mmHg and presence of HVPG > 12 mmHg is a risk factor for variceal bleeding. Reduction in HVPG to less than 12 mmHg or by $\geq 20\%$ from baseline reduces the risk of initial bleeding, and other complications of portal hypertension (ascites, encephalopathy)^[14].

Porto-systemic shunting due to portal hypertension causes diversion of the portal blood into systemic circulation and results in variceal formation. Presence of ongoing liver injury due to alcohol, viral hepatitis (hepatitis B and C), or NASH can lead to increase in the size of the varices, whereas elimination of etiological factor can lead to decrease in the size or disappearance of varices in patients with alcoholic cirrhosis^[16,17].

Intrahepatic hemodynamics

Architectural distortion: Hepatocellular injury causes transformation of hepatic stellate cells into myofibroblasts. Increased expression of pro-inflammatory genes and fibrotic activity, as a result, promotes neoangiogenesis and interstitial collagen deposition resulting in distortion of the hepatic sinusoidal architecture^[18,19]. Architectural damage and regenerative nodules are responsible for nearly 2nd/3rd of the increase in intrahepatic resistance.

Increased vascular resistance: In addition to the known anatomical disruption in the sinusoidal architecture, it is now understood that there are changes in the neurohormonal regulation of vascular tone within the portal circulation. The hepatic injury causes increased production of vasoconstrictors (endothelin 1^[20,21] and thromboxane A2^[22,23]) and reduction in nitric oxide (NO) synthesis due to sinusoidal endothelial dysfunction^[24]. The imbalance in the production of vasoconstrictors and vasodilators causes impaired vasomotor control leading to further increase in resistance and is responsible for approximately 1st/3rd of the increase in intrahepatic resistance^[25,26].

Extrahepatic hemodynamics

Portal hypertension induces neurohormonal changes in the splanchnic circulation as well. Overproduction of NO from splanchnic endothelium leads to reduced splanchnic and systemic vascular resistance^[27-29]. Furthermore, a compensatory activation of the renin-angiotensin mechanism leads to increased cardiac output and hepatic blood flow. Increased portal pressure is also suspected to result in overproduction of angiogenic factors such as vascular endothelial growth factor, platelet-derived growth factor at the microcirculatory level, contributing to angiogenesis and collateral formation resulting in varices^[30,31].

ETIOLOGY

Gastrointestinal varices develop as a consequence of portal hypertension. Most common etiology of portal hypertension in the United States is cirrhosis due to alcohol, NASH, and hepatitis C. The exact prevalence of portal hypertension is not known. Causes of portal hypertension are classified as below.

Presinusoidal

Extrahepatic: Portal vein thrombosis, splenic vein thrombosis.

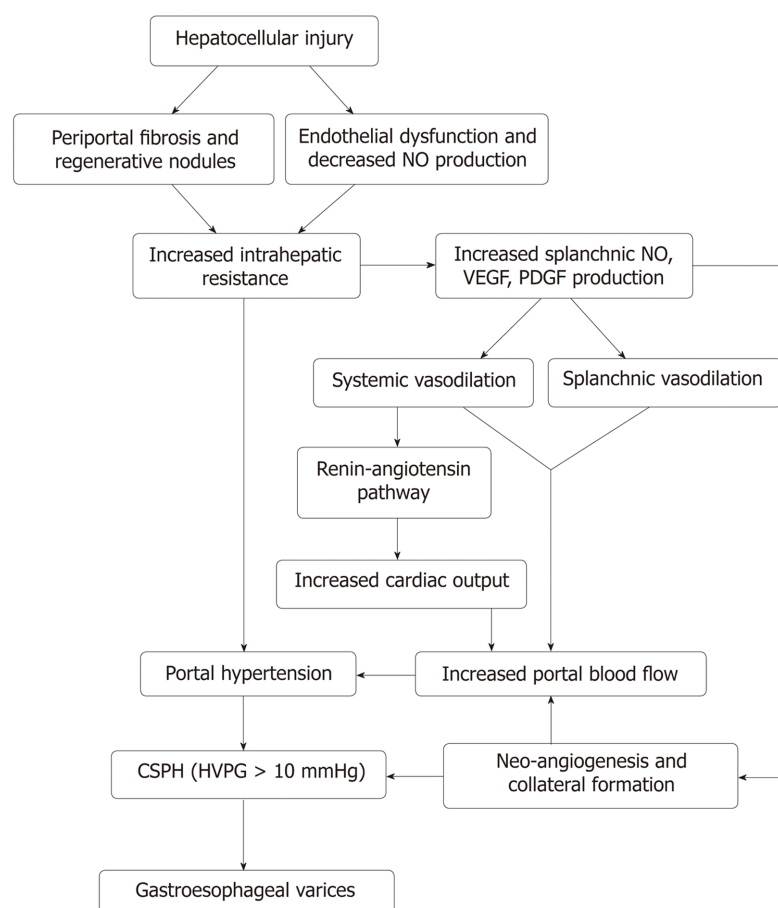


Figure 1 Mechanism of portal hypertension and the development of gastrointestinal varices. VEGF: Vascular endothelial growth factor; PDGF: Platelet-derived growth factor; NO: Nitric oxide; HVPG: Hepatic venous pressure gradient.

Intrahepatic: Schistosomiasis, congenital hepatic fibrosis, and sarcoidosis. (1) **Sinusoidal:** Cirrhosis due to viral hepatitis (hepatitis B and C), NASH, alcohol, primary biliary cirrhosis, primary sclerosing cholangitis, hemochromatosis, Wilson's disease, and cytotoxic drugs; and (2) **Postsinusoidal:** Budd-Chiari syndrome, caval web, constrictive pericarditis, and veno-occlusive disorders.

MECHANISM OF VARICEAL BLEEDING

Increased blood flow through the portosystemic collaterals due to portal hypertension causes dilation of the submucosal venous plexus resulting in elevated intravariceal pressure and wall tension. The mechanism of variceal rupture can be explained by Frank's modified Laplace's law^[32]. This is shown in [Figure 2](#).

Wall tension (T) = [Transmural pressure (P_{varices-Plumen}) × variceal radius (R)]/[Variceal wall thickness (WT)].

RISK STRATIFICATION FOR VARICEAL BLEEDING

HVPG > 12 mmHg

Rise in portal pressure causes increased flow through the varices and thus increased intravariceal pressure. In a randomized control trial (RCT) patients with HVPG < 12 mmHg did not develop variceal bleeding^[33], and presence of HVPG > 20 mmHg was associated with high risk of failed hemostasis and death^[34]. Whereas, a decrease in HVPG > 20% from the baseline reduces complications of portal hypertension including bleeding, ascites, encephalopathy, and death^[35-37].

Variceal size

Large varices (> 5 mm) have a higher tendency to bleed due to increased wall tension

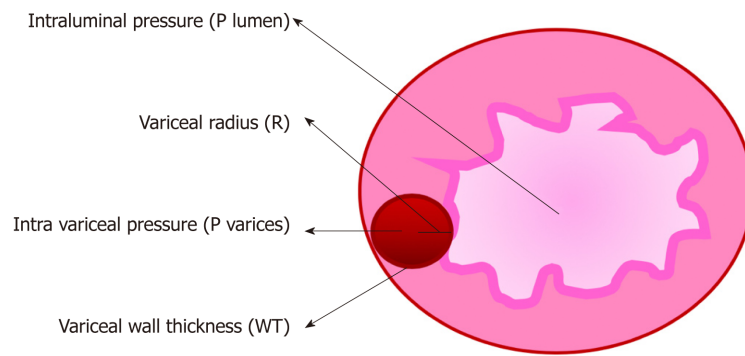


Figure 2 Mechanism of variceal bleeding. P: Pressure; R: Radius; WT: Wall thickness.

as explained above.

Wall tension

Increased wall tension and the presence of 'red wale sign' (dilated capillaries on the variceal wall) indicate a high risk for bleeding.

Other factors

Presence of coagulopathy, infection, and decompensated cirrhosis are other risk factors for variceal bleeding.

DIAGNOSTIC TESTS FOR GASTROINTESTINAL VARICES

Endoscopy

Esophago-gastro duodenoscopy (EGD) is the gold standard procedure used in the diagnosis of gastroesophageal varices (GOVs). Based on the endoscopic assessment, GOVs are classified into small (< 5 mm), and large varices(> 5 mm)^[38] for clinical management. Disadvantages of endoscopy include the risk of sedation, higher cost, bleeding and risk of aspiration.

Endoscopic ultrasound

Endoscopic ultrasound (EUS) has been evaluated as a diagnostic tool in assessing GOVs. EUS is better than EGD in detecting gastric varices (GVs), and its ability to evaluate the anatomy of collateral and perforating veins makes it an excellent choice in monitoring treatment response to endoscopic variceal ligation (EVL) and predicting recurrence^[39-41]. Currently, EUS is not considered as a primary diagnostic modality due to limited availability of local expertise.

Capsule endoscopy

A recent meta-analysis reviewed the use of capsule endoscopy for the diagnosis and grading of esophageal varices and noted a diagnostic accuracy of 90% with a pooled sensitivity and specificity of 83% and 85%, respectively^[42]. The inability of capsule endoscopy to detect GVVs is a significant drawback. Even though capsule endoscopy is relatively less invasive and does not require sedation, the diagnostic sensitivity is not adequate to advocate for index surveillance. It may be a consideration for a select subgroup of high-risk patients who are unwilling to undergo more invasive traditional endoscopic evaluation^[43,44]. One study showed that 97% of the patients preferred capsule endoscopy over endoscopy with or without sedation^[44].

Noninvasive testing

Various clinical findings, laboratory tests, and imaging studies have been considered as predictors of clinically significant portal hypertension (CSPH) (HVPG > 12 mmHg); however, they are not accurate enough to either reliably diagnose or exclude CSPH. Specifically, transient elastography, platelet count, spleen size, magnetic resonance elastography, and splenic stiffness are the most commonly used parameters to predict the presence of CSPH and varices in patients with cirrhosis. The presence of portosystemic collaterals on ultrasound, computed tomography, or magnetic resonance imaging is indicative of CSPH and necessitate screening endoscopy^[38]. Liver stiffness measured by transient elastography in combination with platelet count can rule out presence high-risk varices^[45]. A liver stiffness < 20 kPa and platelet count > 150000/ μ L indicate < 5% chance of having high-risk varices, and screening

endoscopy can be safely deferred as long as ongoing clinical monitoring can be assured^[46].

ESOPHAGEAL VARICES

Epidemiology

Esophageal varices are the most common type of gastrointestinal varices, and their prevalence in Child-Pugh class A is 42.7%, around 70.7% in class B, and 75.5% in class C^[2]. The bleeding risk for small varices and large varices is around 5% and 15% per year respectively. Early mortality rate (6 wk) is approximately 20%^[47] in esophageal varices after index bleeding.

Anatomy

Venous drainage from the sub-mucosal venous plexus of the esophagus drains into the collateral veins around the esophagus. The interconnected collateral venous plexus runs longitudinally along the esophagus and communicates with submucosal venous plexus through perforating veins in the palisading area. The cervical esophagus drains into inferior thyroid vein, the thoracic esophagus drains to azygous, hemizygous, intercostal, and bronchial veins, whereas the abdominal portion of the esophagus drains into the left gastric vein, which in turn empties into the portal vein. Portal hypertension leads to shunting of blood from the portal circulation into these low pressure, thin-walled submucosal systemic veins and manifest as varices.

Modified Paquet classification

Grade I: Varices extending just above the mucosal level.

Grade II: Varices projecting by one-third of the luminal diameter that cannot be compressed with air insufflation.

Grade III: Varices projecting up to 50% of the luminal diameter and in contact with each other.

Screening and surveillance EGD for esophageal VARICES

Shown in **Figure 3**. All patients who are newly diagnosed with cirrhosis should be screened for esophageal varices. Patients with compensated cirrhosis without varices in the absence of ongoing liver injury, endoscopy should be done every three years. Those who have compensated cirrhosis without varices, but have an ongoing liver injury (alcohol abuse, hepatitis C) and/or other cofactor diseases (alcohol/obesity) screening endoscopy should be repeated every two years.

Patients with small varices without ongoing liver injury or cofactor disease endoscopy is recommended every two years, and every year if either ongoing liver injury or cofactor disease is present. Patients with medium and large size varices should be started on nonselective beta-blockers or considered for EVL. If the patient is on nonselective beta blockers, no further surveillance endoscopy is needed.

On the other hand, if EVL is considered for primary prophylaxis endoscopy should be done every 1-2 wk until eradication and then repeated every 6-12 mo.

Management of patients with esophageal varices that have not bled

Either nonselective beta blockers or EVL (**Figure 4**) can be used as primary prophylaxis of variceal hemorrhage in patients with medium/large esophageal varices. Only approved nonselective beta-blockers are propranolol, nadolol, and carvedilol^[38,48-52]. The choice should be made based on the cost, contraindications, availability, and patient preference. Nonselective beta-blockers are preferred over EVL due to their low cost, easy availability, ability to reduce the HVPG. Nonselective beta-blockers reduce the risk of hemorrhage and other complications (ascites, encephalopathy, and death) of portal hypertension^[37]. Based on the currently available data, beta-blockers do not prevent the development of varices or their progression from small to large varices, although there is some reported benefit of reduction in risk of bleeding.

The effect of nadolol on the progression of variceal size was studied in a prospective randomized study. A total of 161 patients were randomized into nadolol ($n = 83$) and placebo ($n = 78$) groups. All patients had yearly screening endoscopy and with a mean follow up of 36 mo. The cumulative probability of bleeding and progression of small varices was lower in nadolol group (20%) when compared to placebo (51%) ($P < 0.001$) (absolute risk difference: 31%; 95% CI: 17%-45%)^[53]. However, this benefit has not been proven in other studies.

In a recent meta-analysis of 6 RCTs, the effect of nonselective beta-blockers in

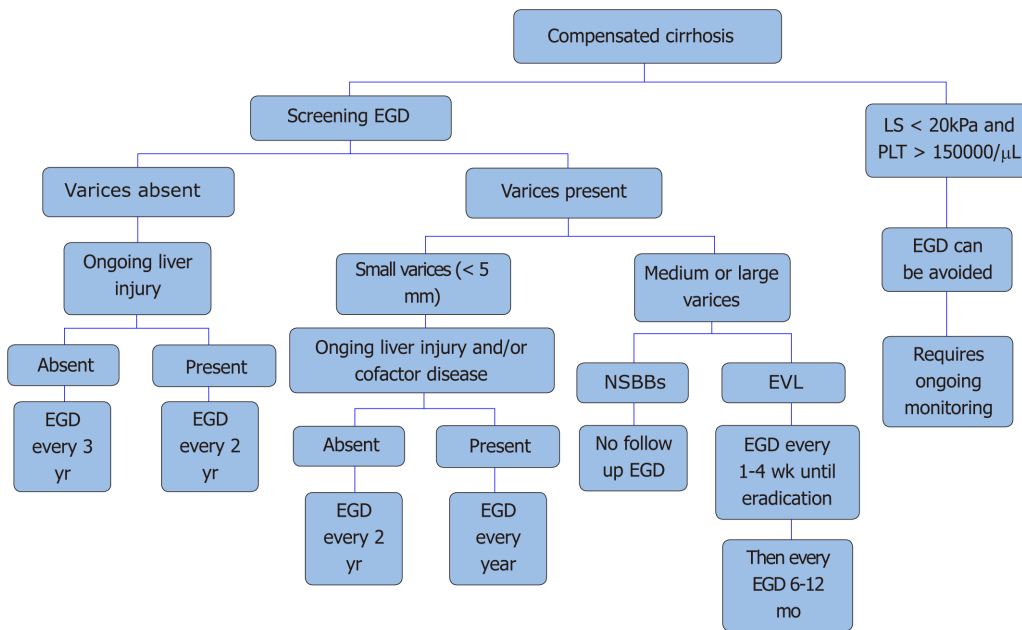


Figure 3 Screening endoscopy for esophageal varices per practice society guidelines^[38,48]. NSBBs: Nonselective beta-blockers; EVL: Endoscopic variceal ligation; EGD: Esophago-gastro duodenoscopy; LS: Liver stiffness; PLT: Platelet.

cirrhotic patients with no or small varices was analyzed. The incidence of large varices (OR = 1.05, 95% CI: 0.25-4.36; $P = 0.95$), first variceal bleeding (OR = 0.59, 95% CI: 0.24-1.47; $P = 0.26$) and death (OR = 0.70, 95% CI: 0.45-1.10; $P = 0.12$) were similar in both nonselective beta-blocker group and placebo group. However, the incidence of adverse events in the nonselective beta-blockers group was significantly higher than the placebo group. Notably, nonselective beta-blockers did not reduce the incidence of large varices or prevent the progression of small varices to large varices^[54].

On the other hand, when compared to nonselective beta blockers, EVL has a higher rate of recurrence of varices, lacks the benefit of HVPG reduction, and needs further endoscopic surveillance. EVL has lower but more severe side effects (bleeding, ulcers, and strictures) compared to nonselective beta-blockers (weakness, tiredness, shortness of breath). However, there is no significant difference in the mortality rate between the two^[46].

In a prospective randomized study, the combination of EVL and propranolol was compared to EVL alone among high-risk patients. One hundred forty-four patients in total were randomized into EVL + propranolol ($n = 72$) group and EVL alone ($n = 72$) group respectively. Addition of propranolol to EVL did not reduce the risk of first variceal bleed (7% vs 11%, $P = 0.72$) or death (8% vs 15%, $P = 0.37$). However, the combination group had significant adverse effects due to propranolol in 22% of the patients. Combination of nonselective beta-blockers and EVL is not recommended as primary prophylaxis due to a higher rate of side effects. However, the recurrence of varices was significantly lower when propranolol was added ($P = 0.03$)^[55]. Recent practice society guidelines suggest the use of nonselective beta-blockers as a recommended therapy for primary prophylaxis for small varices with high-risk features (presence of 'red wale' signs or decompensated cirrhosis)^[38,46].

Isosorbide mononitrate, sclerotherapy, glue injection, and transjugular intrahepatic portosystemic shunt (TIPS) shunt are not used as primary prophylaxis due to a higher rate of side effects without mortality benefit.

Use of nonselective beta-blockers among patients who have cirrhosis with refractory ascites is controversial. A prospective case study showed that the use of nonselective beta-blockers in this patient group was associated with increased mortality^[56]. Another study also showed the increased risk of renal injury, hospital stay and mortality with the use of nonselective beta-blockers with spontaneous bacterial peritonitis due to post-paracentesis circulatory dysfunction^[57]. However, a meta-analysis of 3 RCTs and 13 observational studies ($n = 8279$) showed no significant difference in mortality or incidence of hepatorenal syndrome and spontaneous bacterial peritonitis among cirrhosis patients with refractory ascites, when treated with nonselective beta blockers^[58]. Due to concern for possible deleterious effects in patients with advanced cirrhosis, many physicians now prefer EVL over nonselective beta blockers. Larger RCTs are required before nonselective beta-blockers are

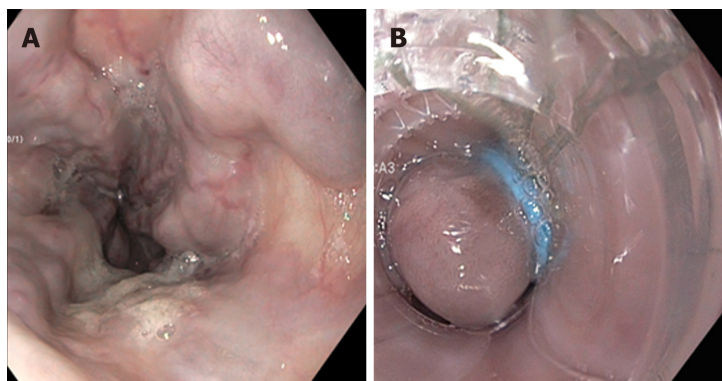


Figure 4 Endoscopic variceal ligation for primary prophylaxis. A: Esophageal varices before banding; B: Esophageal varix post banding.

considered as a contraindication in this subgroup.

Management of acute esophageal variceal bleeding

General measures: All patients with acute variceal bleeding should be resuscitated at an early stage to protect the airway and achieve hemodynamic stability, preferably in a medical intensive care unit. Prognostic indicators for early mortality due to acute variceal bleeding are HVPg, Child-Pugh score, and model for end-stage liver disease (MELD) score. A MELD score of > 19 showed 20% mortality due to index variceal bleeding^[34,47,59]. When measured within 24 h of acute bleeding, HVPg > 20 mmHg predicts a high risk of early rebleeding and death^[38,48,60]. The Child-Pugh score is also a significant predictor of early mortality and can help guide patient risk stratification^[61]. Medical management with vasoactive agents, antibiotics, blood transfusion, combined with EVL is the standard of care in treating acute variceal bleeding.

Restrictive transfusion strategy: All patients with Hb ≤ 7 g/dL should get packed red blood cells to maintain hemoglobin at 7-8 g/dL. Previous RCTs have shown a survival benefit, reduced need for blood transfusion, and a lower rate of adverse events with a restrictive strategy when compared to liberal transfusion^[62].

Most patients with acute variceal bleeding have elevated HVPg (> 12 mmHg). Further elevation of HVPg due to liberal transfusion can increase the risk of rebleeding. In a recent meta-analysis, the incidence of death (OR = 0.52, 95%CI: 0.31-0.87, $P = 0.01$), blood transfusion requirement (standard mean difference: -0.74, 95%CI: -1.15--0.32, $P = 0.0005$) and hospital stay (standard mean difference: -0.17, 95%CI: -0.30--0.04, $P = 0.009$) were significantly lower in the restrictive transfusion group compared to the liberal transfusion group^[63].

Therefore, a restrictive transfusion strategy should be employed in managing patients with acute variceal bleeding. The current practice society guidelines do not recommend routine use of plasma products and platelet transfusion in this setting due to inconsistent data on the use of plasma products and reliability of prothrombin time (PT)/international normalized ratio (INR) in patients with cirrhosis^[38,46]. However, platelet and plasma transfusion can be done in select patients who are hemodynamically unstable with active variceal bleeding (goal: platelet count $> 50000/\mu\text{L}$ and INR < 1.5)^[47].

Vasoactive agents: Vasoactive agents such as octreotide, terlipressin, somatostatin, and vasopressin cause splanchnic vasoconstriction and thus reduce portal pressure. All patients with confirmed or suspected variceal bleeding should be started on vasoactive agents as early as possible and should be continued for 2-5 d. They can be stopped early if the patient undergoes a TIPS procedure.

Terlipressin is a synthetic analog of vasopressin. The role of terlipressin in acute variceal bleeding was analyzed in a meta-analysis involving 1609 patients from 22 studies. Among those 22 studies, seven studies (443 patients) compared the effect of terlipressin to a placebo group. Terlipressin group was noted to have a statistically significant reduction in all-cause mortality (relative risk = 0.66, 95%CI: 0.49-0.88). Remaining studies compared terlipressin to somatostatin, octreotide, vasopressin or balloon tamponade. There was no significant difference in mortality or adverse events between the groups^[64,65].

Use of vasoactive agents has been shown to reduce acute bleeding, need for transfusion, and seven-day all-cause mortality^[66]. There was no significant difference in their efficacy or benefits noted between these agents^[67].

Antibiotics: Short-term antibiotics should be started in all patients with suspected or confirmed variceal bleeding to reduce bacterial infection, recurrent bleeding, and mortality^[38,48,68,69]. Bacterial infection is also considered to be an independent risk factor for variceal rupture. Choice of antibiotics should be based on local resistance pattern. However, third-generation cephalosporins with gram-negative coverage are commonly used. Intravenous ceftriaxone 1 g, every 24 h for a maximum of 7 d is preferred over oral fluroquinolones^[38,46].

Other considerations: Most patients with variceal bleeding have loss of intravascular volume, and it is paramount to prevent hypotension. Due to the risk of hypotension and hemodynamic deterioration, nonselective beta-blockers should not be started during acute variceal bleeding and should be discontinued if the patient is already taking. However, nonselective beta-blockers should be restarted after the acute event, once hemostasis is achieved and vasoactive agents are discontinued.

Endoscopic management

Endoscopic intervention should be performed as early as possible but should be within 12 h from the time of presentation as per practice society guidelines. The diagnosis of variceal bleeding as the etiology of acute upper gastrointestinal bleeding is made when any of the following is noted on upper endoscopy: (1) Actively bleeding varices (Figure 5); (2) Signs of recent bleeding noted on varices or high-risk stigmata; *e.g.*, telangiectasia, red color signs, platelet-fibrin plug (white nipple sign), red wale marking or varices on varices (Figure 6); (3) Presence of varices and blood is noted in the stomach, with no other source of bleeding noted.

EVL (Figure 7) was first proposed for the treatment of esophageal varices in 1988 by Van Stiegmann *et al*^[70]. Currently, EVL is considered to be the first line of endoscopic treatment for the management of bleeding esophageal varices. EVL has better hemostasis, a lower rate of side effects (ulcer, stricture), a reduced rate of early rebleeding, and a lower rate of early mortality compared to sclerotherapy. Higher rebleeding in sclerotherapy is thought to be due to sustained elevation of HVPG, whereas HVPG returned to baseline with EVL^[71-73]. The slightly higher rate of variceal recurrence after EVL, when compared to sclerotherapy is due to its inability to affect the blood flow through perforators and esophageal collateral veins.

Treatment failure

Sengstaken-Blakemore tube: Whenever variceal bleeding is not controlled by EVL, temporary hemostatic measures should be used as a bridge to more definitive treatment, such as TIPS or variceal shunt surgery. Sengstaken-Blakemore tube is inserted through the mouth or nose and then distended to achieve hemostasis during active variceal bleeding by tamponading varices. The rate of hemostasis with Sengstaken-Blakemore tube varies (47%-80%). It is associated with a high rate of serious adverse events including aspiration, esophageal ulceration, and rarely esophageal rupture. Sengstaken-Blakemore tubes cannot be left in place for more than 24 h due to an increased risk of adverse events and a high rate of rebleeding (50%)^[72,73].

Metal stents: Endoscopically placed self-expanding fully covered metal stents (Figure 8) can achieve hemostasis in most cases (80%-96%). The stents expand inside the esophagus and tamponade the varices to achieve hemostasis. They can be left in place for up to 2 wk and have a lower rate of serious adverse events and transfusion requirements when compared to balloon tamponade^[74,75]. Adverse events associated with this modality of treatment include stent migration (28%), rebleeding (16%) and ulcers. However, there was no significant difference in mortality compared to balloon tamponade^[76,77].

In a meta-analysis of 12 studies ($n = 155$) hemostasis was achieved in 96% (95%CI: 0.90-1.00) of the patients within 24 h with 97% technical success (95%CI: 0.91-1.00). Adverse events (rebleeding, ulceration and stent migration) were noted in 36% (95%CI: 0.23-0.50) of the patients. Pooled survival rate at 30 d and 60 d were 68% (95%CI: 0.56-0.80) and 64% (95%CI: 0.48-0.78) respectively^[78]. Similar results were noted in another meta analysis of 5 studies ($n = 80$) with technical success of 96.7% (95%CI: 91.6%-99.5%) and hemostasis of 93.9% (95%CI: 82.2%-99.6%). Rebleeding was observed in 13.2% (95%CI: 1.8%-32.8%) and the overall mortality was 34.5% (95%CI: 24.8%-44.8%)^[79].

Based on the above evidence, self-expanding metal stents are a better choice for bridge therapy in uncontrolled esophageal variceal bleeding and should be used whenever available.

TIPS

Patients with uncontrolled variceal hemorrhage despite the combination of medical

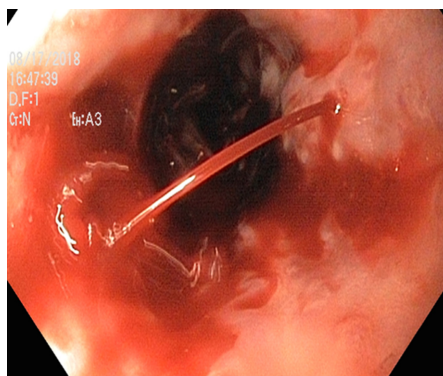


Figure 5 Bleeding esophageal varices.

and endoscopic treatment should be considered for early TIPS within (24 h) with covered PTFE (polytetrafluoroethylene) stents. TIPS is a shunt created by placing a stent between the portal vein and hepatic vein to reduce the portal pressure and thereby portal hypertension. Also, early rebleeding (within five days of initial bleeding) can be treated with repeat endoscopic intervention or covered TIPS stent^[38,46,48].

TIPS vs pharmacotherapy and endoscopic treatment

In a meta-analysis of six comparative studies, TIPS was compared with medical and endoscopic treatment for acute variceal bleeding. In this study, the survival rate (HR = 0.55; 95%CI: 0.38-0.812) was better in TIPS patients, and the incidence of bleeding-related death (OR = 0.19; 95%CI: 0.06-0.59) was lower compared to medical/endoscopic treatment. There was no significant increase in hepatic encephalopathy (OR = 1.37; 95%CI: 0.63-2.99) in TIPS patients. Although there was no significant difference in rebleeding rate between the two groups, it was evident that rebleeding in the high-risk patients was higher on subgroup analysis^[80].

Early TIPS vs pharmacotherapy and endoscopy in high-risk patients

Patients with Child-Pugh class B with active bleeding and class C are considered high-risk due to increased risk of treatment failure and rebleeding.

In a 2010 study, early TIPS was compared with pharmacotherapy (vasoactive agents) and EVL in Child-Pugh class C patients and class B patients with a high risk of treatment failure. Sixty-two patients were randomized into the treatment group (early TIPS, $n = 32$), and control group (pharmacotherapy and EVL, $n = 31$). Rescue TIPS was used in control group as needed for treatment failure. Rebleeding or failure to control bleeding occurred in one patient in the early TIPS group and 14 patients in the control group ($P = 0.001$). The one-year actuarial survival rate was 61% in the control group *vs* 86% in the early-TIPS group ($P < 0.001$)^[81].

In another international multicenter observational study (671 patients from 34 centers) patients who were admitted for acute variceal bleeding with Child-Pugh class C, and Child-Pugh class B with active bleeding were included in the study. Patients were treated with either pharmacotherapy and endoscopic interventions or preemptive TIPS. Preemptive TIPS was associated with significantly lower one-year mortality (22% *vs* 47%, $P = 0.002$), treatment failure and rebleeding (92% *vs* 74%, $P = 0.017$) when compared to patients treated with pharmacotherapy and endoscopic interventions. TIPS also prevented the development of new ascites or worsening of pre-existing ascites^[82]. Even though these results are encouraging, it was an observational study, and patients were not randomized. Each center chose to treat the patient with either preemptive TIPS or medications and endoscopy at its discretion. Therefore, the results may not be generalized. However, large RCTs can determine the use of preemptive TIPS in this high-risk population^[82].

Complications from TIPS include hepatic encephalopathy, heart failure, and stent stenosis. The incidence of hepatic encephalopathy is close to 50% without a significant difference in mortality^[83]. Absolute contraindications for TIPS include heart failure, severe pulmonary hypertension, severe tricuspid valve regurgitation, sepsis, and unrelieved biliary obstruction. Relative contraindications are portal vein thrombosis, hepatoma, uncorrected coagulopathy, and severe thrombocytopenia (platelet count $< 20000/\mu\text{L}$).

Direct ultrasound-guided direct intrahepatic porto-caval shunt

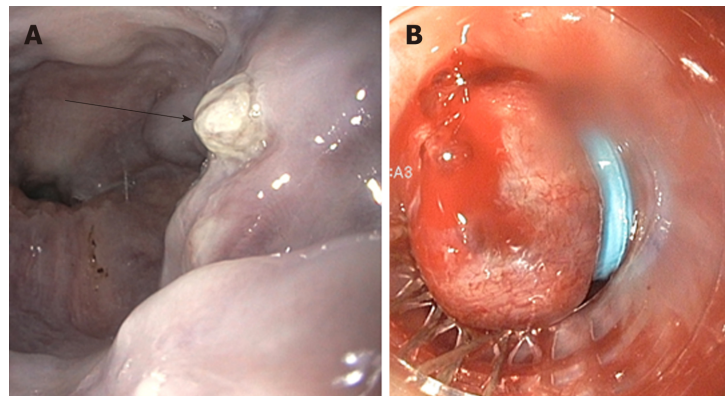


Figure 6 High-risk stigmata of bleeding from esophageal varices. A: Platelet-fibrin plug on esophageal varix (white nipple sign); B: Bleeding esophageal varix post banding.

Patients who failed TIPS, those who have altered anatomy due to previous surgery or congenital anomaly, or are otherwise not candidates for TIPS, can be treated with direct ultrasound-guided direct intrahepatic porto-caval shunt (DIPS)^[84]. The DIPS is a modified TIPS procedure, and it involves percutaneous ultrasound-guided puncture from the inferior vena cava to the portal vein through the caudate lobe of the liver.

Porto-caval shunt surgeries

Surgical shunts are considered when all other treatment modalities fail. Portocaval surgery has a very high rate of encephalopathy but does have good bleeding control. Most patients who undergo portocaval shunt surgery already have high morbidity and surgery adds to it further^[85]. In a recent RCT, emergency TIPS procedure was compared with emergency portocaval shunt surgery, and shunt surgery was noted to have superior bleeding control, long-term survival (10 years *vs* 1.99 years) and low rate of encephalopathy. However, this has not been replicated, and more evidence is required before using portocaval shunt surgery as a salvage procedure after failure of first-line treatment with medical therapy and EVL^[86].

Secondary prophylaxis

Patients who were treated with EVL and medical therapy without TIPS are at high risk for rebleeding. Approximately 60% of patients will experience rebleeding during the first year and have a high mortality rate (up to 33%) with no further intervention. Combination therapy with nonselective beta blockers (propranolol and nadolol) and EVL is the first line of treatment for secondary prophylaxis with a goal to eradicate varices and prevent recurrent bleeding^[87]. TIPS should be considered if patients do not tolerate or fail the combination of nonselective beta-blockers and EVL.

A multicenter RCT compared TIPS with the combination of EVL or glue injection and nonselective beta-blockers. Patients in the TIPS group had a significantly lower rebleeding rate (0%) compared to the EVL or glue injection and nonselective beta blockers group (29%) without a significant difference in survival benefit^[88].

GASTRIC VARICES

Epidemiology

GVs are less frequent compared to esophageal varices and are reported to be seen in 20% of the patients with portal hypertension^[38,89]. Bleeding from GV's account for 20% of all variceal bleeding^[48]. The annual bleeding rate in GV's, which have never bled before is reported to be as low as 16% per year. Sarin *et al*^[90] classified GV's based on their location.

Sarin classification

Shown in [Figure 9](#). Gastroesophageal varix type 1 (GOV1): Extension of esophageal varices along lesser curvature (most common 75% of GV's); GOV2: Extension of esophageal varices along the greater curvature; Isolated gastric varix type 1 (IGV1): Isolated varices seen in the fundus of the stomach; IGV2: Isolated varices in the stomach (body, pylorus, antrum).

Predictors of bleeding from GV's

Location (IGV1 > GOV2 > GOV1); The severity of liver disease; Stigmata of high-risk

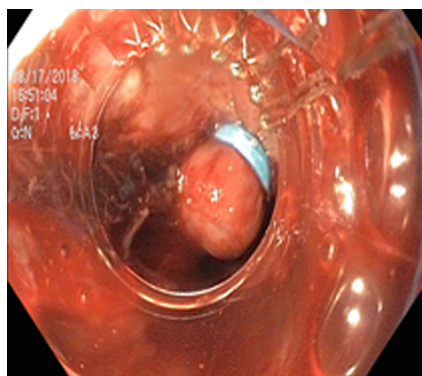


Figure 7 Endoscopic variceal band ligation.

bleeding such as 'red wale' sign.

GVs bleed less frequently but have high mortality due to the severity of bleeding. Bleeding from IGV is associated with the highest risk of death^[38,48,91].

Anatomy

GVs have complex anatomy and understanding the anatomy assists in the endoscopic management of GV. The most common type of GV is GOV1 and are usually associated with portal hypertension due to cirrhosis. They are a continuation of esophageal varices along the lesser curvature of the stomach. These are supplied by the esophageal collateral veins and are also treated similarly to esophageal varices.

On the other hand, GOV2 and IGV1 are supplied by the posterior and left gastric vein, which later drains into left renal vein due to porto-systemic shunting. Therefore GOV2 and IGV1 are together called cardiofundal varices^[91]. Isolated IGV1 can be associated with splenic vein thrombosis in the setting of pancreatitis or malignancy.

Diagnosis of GV

Diagnosis of GV (Figure 10) is commonly done with endoscopy. However, the recent use of EUS has increased the sensitivity of detecting GV. No guidelines are currently available regarding the use of endoscopy or EUS specifically to diagnose GV.

Management of patients with GV that have not bled

Primary prophylaxis for GV is not well established. Currently, nonselective beta-blockers are the first line of treatment as per practice society guidelines, in large part due to their ability to prevent other complications of cirrhosis. The role of endoscopic glue (N-butyl-2-cyanoacrylate) injection and EVL in primary prophylaxis are not clear. One study has shown glue injection was associated with lower bleeding and mortality due to GV when compared to nonselective beta blockers^[92]. Prophylactic EUS guided injection has also shown to be equally beneficial, and further studies are required to evaluate its role in primary prophylaxis for GV.

Management of acute gastric variceal bleeding

Medical management of suspected gastric variceal bleeding is similar to esophageal variceal bleeding as described above, including airway protection, admission to the intensive care unit, blood transfusion, vasoactive agents, and antibiotics (Figure 11).

Endoscopic interventions

Diagnosis of gastric variceal bleeding can be made based on endoscopic findings. Most practice guidelines recommend endoscopic glue injection as the first line of treatment in the management of acute gastric variceal bleeding. However, glue injection comes with the risk of several complications including venous and systemic thromboembolism (pulmonary embolism, stroke), ulcers, protracted bleeding, splenic and portal vein thrombosis^[93]. Portal vein thrombosis due to embolized glue can render a future plan for TIPS and liver transplantation ineffective. Embolized glue can also act as a nidus of infection and cause recurrent bacteremia^[94]. Successful glue injection requires experience due to gastric anatomy. Because of the drawbacks mentioned above, many centers use TIPS as the first line of treatment in managing acute gastric variceal bleeding.

A RCT compared efficacy and complication of TIPS and glue injection in treating GV. Rebleeding (11% *vs* 38%, $P = 0.014$; OR = 3.6, 95%CI: 1.2-11.1) and transfusion requirements were lower ($P < 0.01$) in TIPS compared to endoscopic glue injection with similar initial hemostasis, side effects, and mortality^[95].

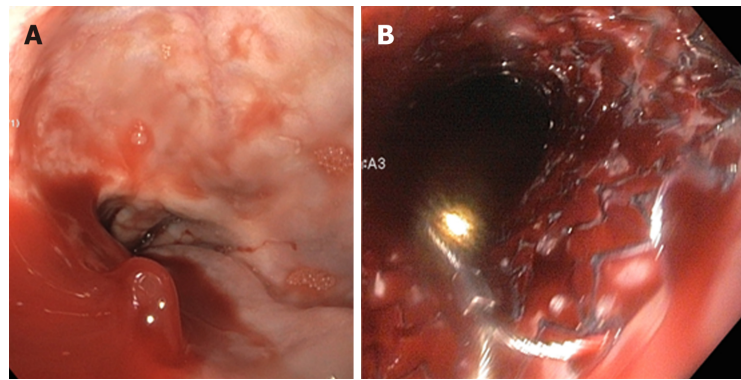


Figure 8 Metal stents for the treatment of bleeding esophageal varices. A: Bleeding esophageal varix before stenting; B: Esophageal varix after metal stent.

Even though initial hemostasis in both glue injection and EVL is similar for GOV1 GVs, rebleeding is high in EVL. So EVL should be avoided^[96-98]. Combination of sclerotherapy and EVL is currently not recommended due to a higher rate of complications, and adverse events without mortality benefit^[99]. In a recent RCT, scleroligation (variceal ligation + sclerotherapy) compared to EVL alone, in the management of GOVs, the scleroligation group required a lower number of endoscopic procedures, transfusion, and bands used, without a significant difference in recurrence rate, major side effects, and mortality^[100]. Further research is needed to prove the benefits of scleroligation.

The recent emergence of EUS guided glue and coil injection in treating GVs has shown a lower bleeding rate, transfusion requirements, and mortality when compared to glue injection. When EUS guided coil embolization alone was compared with EUS guided glue injection, both had similar hemostasis rates, but coil embolization had fewer adverse events and required a fewer number of endoscopies^[101]. When these two techniques were combined (glue + coil), the mean number of coils used, mean volume of glue used, and the recurrence rate was lower compared to either of them alone^[102].

Treatment failure

Patients with uncontrolled gastric variceal bleeding despite endoscopic intervention should be managed with balloon tamponade with Sengstaken-Blakemore tube or Linton-Nachlas tube as a bridge to definitive treatment. In a controlled trial Sengstaken-Blakemore tube failed to control gastric variceal bleeding in all the cases, and 50% hemostasis was achieved by Linton-Nachlas tube. Types of GVs and their frequency between the two groups was not available^[73]. This difference could be attributed to a larger gastric balloon (500 mL) when compared to smaller gastric balloon in the Sengstaken-Blakemore tube. Therefore, Linton-Nachlas tube should be used whenever possible.

Hemostatic powder

Hemostatic powder (TC 325 - hemospray) and similar products have been used as bridging therapy in controlling acute peptic ulcer bleeding in the past. The hemostatic powder when sprayed at the bleeding site, it absorbs water and creates a mechanical barrier to achieve hemostasis. Recently one study assessed its role in acute variceal bleeding. Hemostasis in the study group was better than the control group, with fewer study group patients requiring rescue endoscopy (12%). Rescue endoscopy was performed if initial hemostasis was not achieved within the first 12 h with hemospray. All patients were later treated with definitive endoscopic intervention after 24 h. Larger RCTs are required to evaluate the role of hemostasis powder, and currently not approved by Food and Drug Administration^[103,104].

Patients with GVs who fail to respond to the endoscopic treatment will require TIPS or shunt surgery to control acute variceal bleeding. Recurrent bleeding is noted in 11%-30% of the patients who undergo TIPS.

Balloon-occluded retrograde transvenous obliteration

Patients with GVs and gastro-renal collaterals can be treated with balloon-occluded retrograde transvenous obliteration (BRTO). This procedure involves retrograde cannulation of the outflow channels which drain the GVs through the femoral or jugular vein, and obliteration of the varices and collaterals assisted by balloon occlusion and followed by coil and sclerosant. Various studies have evaluated its

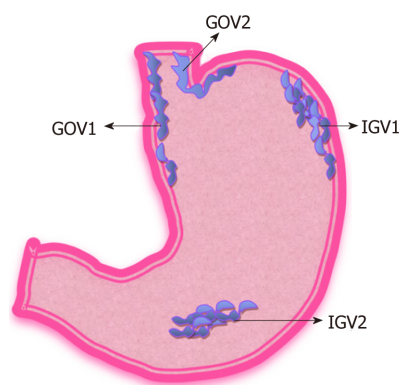


Figure 9 Sarin classification of gastric varices. GOV1: Gastroesophageal varix type 1; GOV2: Gastroesophageal varix type 2; IGV1: Isolated gastric varix type 1; IGV2: Isolated gastric varix type 2.

efficacy in treating GVs. A recent meta-analysis showed a success rate for obliteration was 97.3%, and 33.3% recurrence. BRTO can be considered as an alternative to TIPS in managing GVs. A retrospective review of 142 consecutive patients treated for acute gastric variceal bleeding comparing the efficacy of BRTO ($n = 95$) and TIPS ($n = 47$) showed significantly lower rebleeding rate in BRTO (8.6%) group compared to TIPS (19.8%)^[105] at the end of the first year. There was no significant difference in mortality. BRTO is mostly done in Asian countries, but recently it is gaining popularity in the United States^[38,48,106].

Secondary prophylaxis

Risk of rebleeding among patients who are treated with glue injection for gastric variceal bleeding was noted to vary from 15%-72%^[98,107,108]. TIPS is considered to be superior to endoscopic glue injection for secondary prophylaxis of GVs^[38]. However, there is no significant mortality benefit when compared to glue injection. The role of nonselective beta-blockers is not evident in secondary prophylaxis of GVs. Data on EUS guided glue injection and coiling for primary and secondary prophylaxis is lacking. Larger multicenter RCTs will help in understanding the role of EUS in the management of GVs.

ECTOPIC GASTROINTESTINAL VARICES

Gastrointestinal varices can develop in the duodenum, rectum, colon, small bowel, gallbladder and the retroperitoneal areas. The prevalence of ectopic gastrointestinal varices is unknown. According to one estimate, among patients with cirrhosis and portal hypertension who underwent angiography, 40% of patients had duodenal varices. Ectopic varices are responsible for up to 1%-5% of all variceal bleeding. Understanding the complex anatomy of ectopic varices, and their anastomosis with mesenteric veins is essential in managing ectopic varices^[91,109].

Duodenal varices

Duodenal varices are more commonly seen in noncirrhotic, extrahepatic portal hypertension (*e.g.*, portal vein thrombosis, splenic vein thrombosis) and their prevalence is around 0.4%^[109]. Duodenal varices form due to Porto-mesenteric and Porto-portal anastomosis. Duodenal varices are noted on endoscopy as submucosal dilated veins, usually arising from anastomosis between tributaries of the superior mesenteric vein and portal vein draining into inferior vena cava. EUS is notably superior in diagnosing duodenal varices compared to EGD^[110]. Acute duodenal variceal bleeding is usually treated with endoscopic glue injection. There have been no RCTs evaluating the treatment strategies for duodenal varices owing to their rarity. In the largest case series involving ten patients with duodenal variceal glue injection, 4 out of the five patients who presented with acute bleeding were treated with endoscopic glue injection and had 100% hemostasis rate without recurrence^[110]. Duodenal varices bleed at a lower hepatic venous pressure gradient, and therefore TIPS may not be sufficient to treat duodenal varices and need further definitive treatment with intravascular obliteration with glue injection, or embolization through BRTO. BRTO can also be used for patients who fail endoscopic therapy and are not candidates for TIPS^[111].

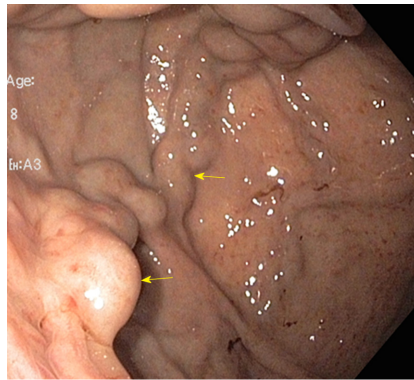


Figure 10 Gastric varices.

Rectal varices

Rectal varices usually arise from portosystemic anastomosis between superior hemorrhoidal veins (a tributary of the inferior mesenteric vein) and the middle or inferior hemorrhoidal veins (tributaries of iliac or pudendal veins). Prevalence of rectal varices patients with portal hypertension varies from 28%-56% in cirrhotic patients^[112], and are more common among patients with extrahepatic portal vein obstruction (up to 90%)^[113]. EUS has a higher sensitivity to detect rectal varices compared to endoscopy. Risk of bleeding from rectal varices is 8%-38%^[112]. Rectal varices bleed at the lower hepatic venous pressure gradient and may not disappear with TIPS. Endoscopic variceal band ligation is the preferred method of treatment for rectal varices compared to endoscopic sclerotherapy or glue injection, but the recurrence rate of rebleeding is high with Endoscopic variceal band ligation. Recurrent bleeding in endoscopic sclerotherapy (33%) was much lower compared to EVL (55.6%)^[114] but not commonly used due to the occurrence of severe ulcers. Endoscopic glue injection can be useful in managing rectal varices, but nearly 0.5%-4.3% of these patients develop embolization. EUS guided coil and glue embolization is also considered useful in large rectal varices that are not amenable to variceal ligation^[115]. Role of BRTO has been evaluated in small case series; no RCTs are available to compare its efficacy. Optimal management of rectal varices is not yet established.

Stomal varices

Stomal varices usually occur at the mucocutaneous junction of the stoma, due to portosystemic shunt between the portal circulation of the bowel and systemic circulation of the abdominal wall. Diagnosis of stomal varices is difficult, on physical exam, they appear as bluish discoloration of the skin. Visibly dilated veins and characteristic raspberry appearance of the stoma should prompt further evaluation for the cause of bleeding. Patients with stomal varices can be treated with a glue injection. Percutaneous sclerotherapy is not recommended due to increased risk of damaging the stoma. Gastrointestinal varices can also form in other parts of the gastrointestinal tract including jejunum, ileum, and colon as well. The actual prevalence of these varices is unknown but considered to be low.

CONCLUSION

In summary, development, and utilization of newer treatment modalities such as therapeutic EUS, BRTO, and hemospray in managing gastrointestinal varices will help to reduce further- the morbidity and mortality related to variceal bleeding. Further research in understanding the risk factors, mechanism of liver injury, and evaluation of antifibrotic agents to prevent architectural changes to the liver can revolutionize the management of portal hypertension and its complications.

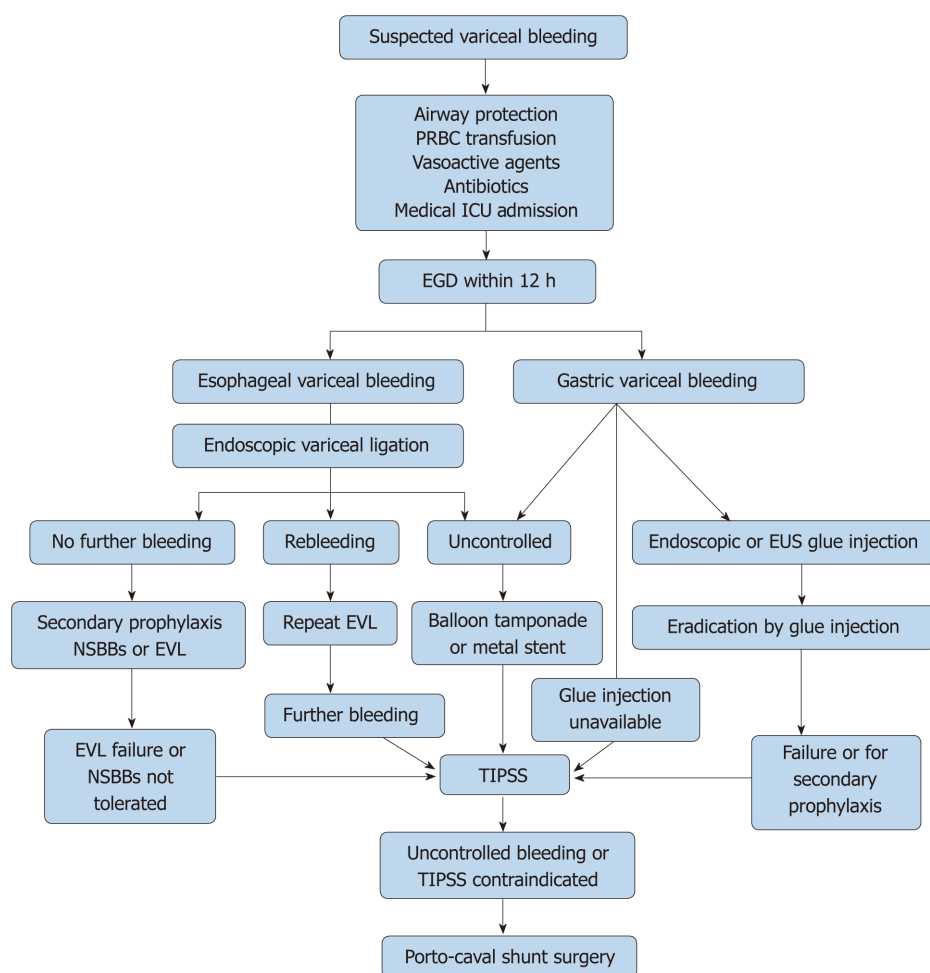


Figure 11 Algorithm for the management of acute variceal bleed. ICU: Intensive care unit; EGD: Esophago-gastro duodenoscopy; NSBB: Nonselective beta blockers; EVL: Endoscopic variceal ligation; TIPS: Transjugular intrahepatic portosystemic shunt.

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Retrospective Study

Opioid use and misuse in ulcerative colitis

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Institutional review board

statement: This study was reviewed and approved by the University of Virginia Institutional Review Board for Health Sciences Research (IRB-HSR).

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Patients were not required to give informed consent for this study as the analysis was conducted retrospectively and no identifying factors were used in the analysis.

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Abstract

BACKGROUND

Patients with ulcerative colitis (UC) may be exposed to opioids over their disease duration. The use of such medications carries significant risk, including intestinal dysmotility and potential for addiction. However, the rates of narcotic use and misuse in patients with UC have not been studied extensively. Functional gastrointestinal disorders (FGID) are prevalent in patients with UC, and have been shown to increase the risk of narcotic use and misuse in patients with Crohn's disease. We hypothesized that patients with UC and a concurrent diagnosis of FGID would have increased rates of both opioid use and misuse in our patient cohort.

AIM

To evaluate the prevalence of chronic opioid use and misuse in UC.

METHODS

A retrospective chart review of UC patients seen at the University of Virginia Digestive Health Center was performed on all patients evaluated between 2006 and 2011. Patient demographics, medical, surgical, and medication histories were obtained from the electronic medical record. Concomitant diagnosis of FGID was also noted at the time. The electronic prescription monitoring program was accessed to obtain prescription opioid filling histories. Prescription opioid misuse was defined as opioid prescriptions filled from four or more prescribers and four or more different pharmacies in a 12-mo period.

RESULTS

A total of 497 patients with UC were included. Patients with UC and FGID were

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more likely to be female, but no other demographic variables were associated with FGID. Of the UC patients who had FGID, a greater proportion were found to be using opioids chronically (36% with FGID *vs* 9% without FGID, $P < 0.0001$) and were misusing prescription opioids (12.8% *vs* 1.3%, $P < 0.001$). Multivariate logistic regression demonstrated a significant association with FGID and chronic opioid use (OR = 4.50; 95% CI: 1.91-10.59) and opioid misuse (OR = 5.19; 95% CI: 1.04-25.76). Tobacco use (OR 2.53; 95% CI: 1.06-6.08) and anxiety (OR 3.17; 95% CI: 1.08-9.26) were other variables associated with an increased risk of chronic narcotic use.

CONCLUSION

FGID was associated with a 4.5-fold increase in chronic opioid use and a 5-fold increased risk of opioid misuse in this patient cohort with UC.

Key words: Ulcerative colitis; Chronic opioid use; Opioid misuse; Narcotic; Functional gastrointestinal disorder

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Core tip: Rates of chronic opioid use and misuse among patients with ulcerative colitis (UC) have not been studied extensively, and it is unknown whether functional gastrointestinal disorder (FGID) affects these rates. The aims of this study were to evaluate rates of opioid use and misuse in UC and determine whether these rates were affected by concomitant FGID. Patients with FGID and UC were 4.5 times more likely to be using chronic opioids and 5 times more likely to be misusing opioids. This highlights the potential risks of opioid use in the management of UC, particularly in those patients with concomitant FGID.

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory gastrointestinal condition which can manifest with recurrent bouts of abdominal pain, rectal bleeding, and diarrhea. During disease flares, opioid medications may be prescribed in the acute setting for the treatment of pain, but carry significant negative consequences including worsening intestinal dysmotility and visceral hyperalgesia, along with the potential risk for medication dependency and addiction^[1,2].

Rates of opioid addiction, diversion, and overdose have risen dramatically in the United States over the past two decades^[3,4] and are currently at epidemic levels. State-run prescription monitoring programs (PMPs) have been established to combat this issue and make it possible to identify patients who have behaviors suggesting opioid misuse, such as “doctor shopping,” obtaining prescriptions from multiple prescribers, using multiple pharmacies, using multiple opioids simultaneously, and obtaining early refills of medications. While there is no standard definition for opioid misuse, Katz *et al*^[5] defined the use of greater than or equal to four pharmacies and greater than or equal to four prescribers of schedule II medications within a 12-mo period as “questionable activity” which is consistent with opioid misuse.

Functional gastrointestinal disorders (FGID) have been shown to be prevalent among patients with inflammatory bowel disease (IBD)^[6]. Simrén *et al*^[6] demonstrated that irritable bowel syndrome-like symptoms were two to three-fold more prevalent in patients with IBD in remission than in the general population, and patients with these symptoms also exhibited increased levels of depression and anxiety. FGID has been shown to be a significant risk factor for chronic opioid use and misuse among patients with Crohn’s disease^[7], representing a two-fold and three-fold increased risk of chronic opioid use and misuse, respectively. While the prevalence of opioid use has been previously reported in UC^[1,8], to our knowledge, the prevalence of opioid misuse has not been specifically studied in this population. The primary aim of this study

was to determine whether patients with UC and concurrent FGID had higher rates of chronic opioid use, and to determine the prevalence and risk factors for prescription opioid misuse in this patient population.

MATERIALS AND METHODS

Patients

A retrospective chart review was performed on patients with UC treated at the University of Virginia Digestive Health outpatient clinic from 2006 to 2011. Patient demographics were obtained from the electronic medical record (Epic Hyperspace, Verona, WI) including patient age, sex, race, insurance status, geographic area of residence, tobacco use, and alcohol use. Medical, surgical and psychiatric histories were recorded for each patient; including the diagnosis of any co-existing FGID. The Rome III criteria and diagnoses served as the basis for our inclusion of FGIDs in this study, and all patients with a FGID, regardless of whether their FGID related to upper or lower gastrointestinal symptoms, were marked as having FGID. Patients with symptoms of FGID without an existing diagnosis made by a clinician were not recorded as having FGID. Medication history was obtained from the electronic medical record including IBD-related therapy and non-IBD medications. Information on opioid use was also collected using electronic prescription monitoring program databases from Virginia and West Virginia (<https://virginia.pmpaware.net>). To access the PMP database, patient name, date of birth, and date of initial clinic visit were entered into the database, and information regarding the type and number of opioid prescriptions, as well as the number of different prescribers and pharmacies, were recorded. Prescription data was collected for a one-year period following the date of the initial office visit, and thus patients had an established diagnosis of UC at the time at which prescription data collection began.

Chronic opioid use was defined as having three consecutive prescriptions for opioids filled or having two or more opioid prescriptions filled within a six-month period. Opioid misuse was defined as a patient meeting the “4 + 4 criteria” of having opioid prescriptions given by four or more prescribing physicians and using four or more pharmacies in a 12-mo period^[5]. Post-operative pain medication prescriptions that were limited to one prescription were not counted toward the analysis.

Statistical analysis

Statistical analysis was performed by a biomedical statistician (Northup PG) using SAS 9.2 (SAS Institute Inc., Cary, NC). Comparisons of categorical variables were made using Chi-squared tests, odds ratios and 95%CI were used to assess the interaction between chronic opioid use and opioid misuse and the following variables: age, sex, alcohol use, cigarette smoking, Medicaid/disability insurance status, anxiety, depression, and FGID. Similar interactions were assessed between FGID and the following variables: age, sex, alcohol use, cigarette smoking, Medicaid/disability insurance status, anxiety, depression, chronic opioid use, and chronic opioid misuse. Univariate and multivariate logistic regression analyses were conducted to identify potential variables affecting rates of chronic opioid use and misuse. Approval for the study was obtained through the Institutional Review Board for Health Sciences Research at the University of Virginia.

RESULTS

A total of 497 patients with UC seen at the University of Virginia Digestive Health Clinic from 2006 to 2011 were included in the study cohort (Table 1). Of these, 39 (7.8%) patients were identified as having concurrent FGID. In addition, 103 (20.7%) patients had concomitant psychiatric disease including 68 patients with depression, 22 with anxiety, and 13 with an alternative psychiatric diagnosis. Forty-three (8.7%) patients were current tobacco users.

Patients with UC and FGID were no different in age than patients with UC without FGID (49.5 years *vs* 51.2 years, $P = 0.463$). Patients with FGID were more likely to be female (74% with FGID *vs* 48% without FGID, $P = 0.010$). There was a trend toward FGID and anxiety (23% with FGID *vs* 3% without FGID, $P = 0.055$). FGID was not significantly associated with depression, alcohol use, tobacco use, insurance or disability status in this patient cohort.

Of the 497 patients, 56 (11.3%) were identified as using chronic prescription opioids. The proportion of patients on chronic opioids was significantly greater among those with FGID than those without FGID (36% *vs* 9%, $P < 0.0001$, Figure 1).

Table 1 Patient characteristics n (%)

	FGID patients (n = 39)	Non-FGID patients (n = 458)	Total (n = 497)
Mean age (yr)	51.2	53.0	52.9
Sex (Female)	29 (74.4)	220 (48.0)	249 (50.1)
Disability/Medicaid status	4 (10.3)	14 (3.1)	18 (3.6)
Tobacco use	7 (17.9)	36 (7.9)	43 (8.7)
Alcohol use	12 (30.8)	185 (40.4)	197 (39.6)
History of depression	9 (23.1)	59 (12.9)	68 (13.7)
History of anxiety	9 (23.1)	13 (2.8)	22 (4.4)
Disease extent			
Proctitis	6 (15.4)	39 (8.5)	45 (9.1)
Left sided	12(30.8)	153 (33.4)	165 (33.2)
Extensive	20 (51.3)	227 (49.6)	247 (49.7)
Average disease duration (yr)	8.2	7.5	7.6

Among the patient characteristics analyzed, only female sex was associated with functional gastrointestinal disease (FGID) in comparison to the non-FGID cohort. FGID: Functional gastrointestinal disease.

Anxiety ($P = 0.035$) and tobacco use ($P = 0.038$) were associated with significantly higher rates of chronic opioid use. Using the PMP to review prescription data, there was evidence of opioid misuse in 11 (2.2%) patients using the 4 + 4 criteria. Of these, 5 of 39 patients (12.8%) with FGID were identified as misusing prescription opioids, compared with 6 of 458 patients (1.3%) without FGID ($P < 0.001$, [Figure 1](#)).

Multivariate logistic regression analysis demonstrated a significant association of chronic opioid use and FGID. Patients with UC and FGID had a 4.5-fold higher risk of chronic opioid use than those patients without FGID (OR = 4.50; 95%CI: 1.91-10.59). There was also an association of FGID and opioid misuse, with a five-fold increase in the risk of opioid misuse in FGID patients (OR = 5.19; 95%CI: 1.04-25.76). Tobacco use (OR = 2.53; 95%CI: 1.06-6.08) and anxiety (OR = 3.17; 95%CI: 1.08-9.26) were also associated with higher risk of chronic narcotic use, whereas patient gender, alcohol use, depression, and disability status were not ([Table 2](#)).

DISCUSSION

Within this UC patient cohort, chronic opioid use was identified in 11.3% of patients overall. UC patients with concomitant FGID were over four-fold more likely to be using chronic opioids than those UC patients without FGID. Prescription monitoring program data identified 2% of the total UC patient cohort to be misusing prescription opioids. Patients with UC and concurrent FGID had a 5-fold increased risk of opioid misuse, with 13% of patients in this group showing evidence of opioid misuse based on PMP data. The rates of chronic use and misuse of opioids are significant given the negative impacts that opioids have on disease outcomes in UC and FGID^[1,2], in addition to the potential risks of opioid dependency and addiction in this population.

Our study also found an increased risk of opioid misuse in patients with UC and FGID (OR = 5.19, 95%CI: 1.04-25.76); however the overall number of patients identified with opioid misuse was small, and larger numbers of patients would be needed to confirm this association. Tobacco use and anxiety were also associated with an increased risk of chronic narcotic use, associations which have been identified in prior studies^[9-11] and are also identified in our population to be risk factors for opioid misuse.

Given this was a retrospective study at a single tertiary care center, these results may not be generalizable to the UC population in the United States as a whole. The majority of our patient cohort resides in Virginia and West Virginia, and the opioid prescription information was limited to the PMPs from these two states. It is possible that some patients obtained opioid medications from other neighboring states and thus were not identified in the PMP data search, and this model does not account for patients using opioids that they have obtained outside of a provider's prescription. This model also assumes that all patients who filled opioid prescriptions took the medications themselves, and does not account for diversion of opioid medications. Another limitation of this study was that it was not possible in all instances to know the circumstances for which patients were using opioids (*e.g.*, flaring disease,

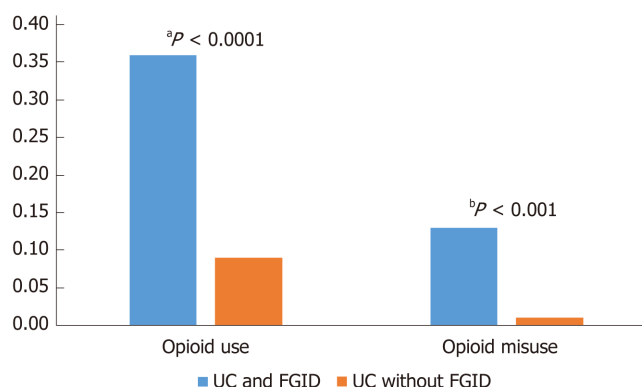


Figure 1 Rates of opioid use and misuse. Patients with ulcerative colitis and concomitant functional gastrointestinal disease had higher rates of prescription opioid use (36% vs 9%; $^aP < 0.0001$) and opioid misuse (13% vs 1%; $^bP < 0.001$). UC: Ulcerative colitis; FGID: Functional gastrointestinal disease.

abdominal pain in the absence of active UC). Thus it was not possible to stratify patients according to disease activity or severity, as patients often sought care in places other than our institution, such as from a local gastroenterologist, primary care provider, urgent care, or local emergency room.

Despite these limitations, this is the first study to our knowledge that assesses the risk of prescription opioid misuse in the UC population and identifies a subgroup of patients with concomitant FGID to be at particular risk for chronic opioid use and misuse. This has important implications in managing patients with UC and FGID as a particularly “at risk” group for opioid misuse and a population to be monitored for early intervention if this is occurring.

In conclusion, patients with UC and concomitant FGID have a 4.5-fold increased risk of chronic opioid use. Patients with UC and FGID are also at risk for opioid misuse, based on prescription monitoring program data. There is significant risk for development of opioid-related complications including opioid dependency and misuse in this population.

Table 2 Predictors of chronic narcotic use in patients with ulcerative colitis

Variables	Odds ratio estimates (Point estimates with 95% Wald confidence limits)	P value
FGID	4.50 (1.91-10.59)	< 0.001
Female sex	0.76 (0.41-1.42)	0.390
Tobacco use	2.53 (1.06-6.08)	0.038
Alcohol use	0.53 (0.27-1.04)	0.065
Anxiety	3.17 (1.08-9.26)	0.035
Depression	1.36 (0.59-3.11)	0.468
Disability/Medicaid insurance status	1.77 (0.49-6.38)	0.382

Among the risk factors included in the multivariate analysis, only functional gastrointestinal disease, tobacco use, and anxiety increased the risk for chronic narcotic use in ulcerative colitis. FGID: Functional gastrointestinal disease.

ARTICLE HIGHLIGHTS

Research background

Opioid use in the inflammatory bowel disease (IBD) population is common, given that symptoms of disease activity often include abdominal pain. While opioids may provide temporary relief, they carry long-term risks such as narcotic bowel syndrome and the potential for dependence and addiction. However, little is known about the specific rates of opioid use and misuse in the ulcerative colitis (UC) population. Functional gastrointestinal diseases often overlap with symptoms of IBD, and abdominal pain or functional symptoms in patients with UC with a concomitant diagnosis of functional gastrointestinal disorders (FGID) may be easily mistaken as a manifestation of active UC during periods of disease remission. In a previous study, we showed that rates of chronic opioid use and misuse among patients with Crohn's disease (CD) and concomitant FGID were two-fold and three-fold higher, respectively, than in patients with CD without a diagnosis of FGID.

Research motivation

Identification of risk factors for opioid abuse in the IBD population, specifically in UC patients, is key in prevention of complications of these medications. Patients at risk for chronic opioid use and misuse can be identified, and prescribers can be better informed, thereby preventing many of the adverse effects – physical, mental and psychosocial – associated with long-term opioid therapy in this vulnerable population.

Research objectives

The purpose of this study was to characterize rates of chronic opioid use and misuse in the UC population, as these have not been studied extensively. One of the objectives of this study was to investigate whether FGID was a risk factor for chronic opioid use and misuse in UC patients, as has been demonstrated in patients with CD and FGID.

Research methods

Following approval through the institutional review board, a retrospective chart review was conducted at the University of Virginia Digestive Health Center including all patients who had been evaluated for ulcerative colitis between 2006 and 2011. Patient demographics and selected variables (tobacco use, alcohol use, *etc.*), medical, surgical and psychiatric histories, and concomitant diagnoses of FGID (as outlined by Rome III criteria) were collected from the electronic medical record. Data on opioid use was collected from the electronic prescription monitoring program databases for the states of Virginia and West Virginia (<https://virginia.pmpaware.net>). Statistical analysis was conducted by a biomedical statistician and both univariate and multivariate regression analyses were performed.

Research results

This study cohort consisted of 497 patients with UC, who were seen at the University of Virginia from 2006 to 2011. Of these patients, 7.8% had a concurrent diagnosis of FGID as defined by Rome III criteria, 20.7% had concomitant psychiatric disease, and 8.7% were current tobacco users. Patients with UC and FGID were more likely to be female ($P = 0.010$), but no other risk factors were found to be associated with FGID in the UC cohort. A greater proportion of patients with FGID and UC were on chronic opioid therapy than patients with UC without FGID (36% *vs* 9%, $P < 0.0001$), and a greater proportion of patients with FGID and UC met criteria for opioid misuse (12.8% *vs* 1.3%, $P < 0.001$). In the multivariate logistic regression analysis, patients with FGID and UC had a 4.5-fold increased risk for chronic opioid use and 5-fold increased risk for opioid misuse in comparison to their UC counterparts without FGID. Tobacco use and anxiety also conferred higher risks for chronic narcotic use.

Research conclusions

To our knowledge, this is the first study which assesses the rates of and risk factors for both

chronic opioid use and misuse in the UC population. This study sheds light on the need for careful prescription practices among providers who have patients with UC, particularly those with concomitant diagnoses of FGID. As we hypothesized, FGID increased the risk for both chronic opioid use and misuse in our cohort of UC patients, which is a novel finding and may set the foundation for future studies. Tobacco use and anxiety also conferred an increased risk for chronic narcotic use in UC patients, as demonstrated in prior studies, but were not variables associated with FGID. While FGID did increase the risk for opioid misuse five-fold in our UC cohort, our numbers of patients meeting the definition of opioid misuse was small, and thus more associations may not have reached statistical significance.

Research perspectives

The insights gained from this study may provide the basis for practitioners to monitor opioid use in their UC cohorts, and potentially intervene when chronic opioid use and misuse are suspected. Furthermore, this study emphasizes that PMP databases are useful tools not only in the general population, but also in specific populations such as the IBD population. While this study was conducted at a tertiary referral center in the United States and a large number of patients were included, the results may not be generalizable to the US and worldwide, as this was a single-center study and the opioid epidemic has disproportionately affected some of the geographic areas (*e.g.*, Southwest Virginia) in which our patients reside. Future studies with a similar design and the inclusion of multiple sites may help to further define risk factors for chronic opioid use and misuse in the UC cohort. The data obtained from this study may, in the near future, also serve as a basis for quality improvement studies in which at-risk UC patients are identified and treated with alternatives for opioids in the appropriate situations.

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Ipilimumab and Nivolumab induced steroid-refractory colitis treated with infliximab: A case report

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Abstract

BACKGROUND

A variety of immune-modulating drugs are becoming increasingly used for various cancers. Despite increasing indications and improved efficacy, they are often associated with a wide variety of immune mediated adverse events including colitis that may be refractory to conventional therapy. Although these drugs are being more commonly used by Hematologists and Oncologists, there are still many gastroenterologists who are not familiar with the incidence and natural history of gastrointestinal immune-mediated side effects, as well as the role of infliximab in the management of this condition.

CASE SUMMARY

We report a case of a 63-year-old male with a history of metastatic renal cell carcinoma who presented to our hospital with severe diarrhea. The patient had received his third combination infusion of the anti-CTLA-4 monoclonal antibody Ipilimumab and the immune checkpoint inhibitor Nivolumab and developed severe watery non-bloody diarrhea the same day. He presented to the hospital where he was found to be severely dehydrated and in acute renal failure. An extensive workup was negative for infectious etiologies and he was initiated on high dose intravenous steroids. However, he continued to worsen. A colonoscopy was performed and revealed no endoscopic evidence of inflammation. Random biopsies for histology were obtained which showed mild colitis, and were negative for Cytomegalovirus and Herpes Simplex Virus. He was diagnosed with severe steroid-refractory colitis induced by Ipilimumab and

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Nivolumab and was initiated on Infliximab. He responded promptly to it and his diarrhea resolved the next day with progressive resolution of his renal impairment. On follow up his gastrointestinal side symptoms did not recur.

CONCLUSION

Given the increasing use of immune therapy in a variety of cancers, it is important for gastroenterologists to be familiar with their gastrointestinal side effects and comfortable with their management, including prescribing infliximab.

Key words: Colitis; Infliximab; Biologics; Immune mediated adverse events; Ipilimumab; Nivolumab; Case report

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Core tip: A variety of immune-modulating drugs are becoming increasingly used for various cancers. Despite increasing indications and improved efficacy, they are often associated with a wide variety of immune mediated adverse events. We report the first case of metastatic renal cell cancer treated with the anti-CTLA-4 monoclonal antibody Ipilimumab and the immune checkpoint inhibitor Nivolumab to develop severe steroid-refractory colitis, and describe its resolution after treatment with Infliximab.

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INTRODUCTION

A variety of immune-modulating drugs are becoming increasingly used for various cancers. Despite increasing indications and improved efficacy, they are often associated with a wide variety of immune mediated adverse events (IMAE), including gastrointestinal symptoms such as diarrhea, nausea and vomiting. We report a case of severe steroid-refractory colitis induced by the anti-CTLA-4 monoclonal antibody Ipilimumab and the immune checkpoint inhibitor Nivolumab in a patient with metastatic renal cell carcinoma, and its resolution after treatment with Infliximab.

CASE PRESENTATION

Chief complaints

A 63 year male diagnosed with metastatic renal cell carcinoma presents to the hospital with a several day history of diarrhea and fatigue.

History of present illness

The patient had received his third combination infusion of Ipilimumab and Nivolumab and developed severe watery non-bloody diarrhea the same day. He continued to have upwards of 10 watery bowel movements over the next week and ultimately presented to the hospital.

History of past illness

Past medical history included metastatic renal cell carcinoma, deep vein thrombosis of the lower extremity and hypertension.

Personal and family history

He had no significant family history of cancer or inflammatory bowel disease, and did not have a personal history of alcohol, tobacco, drug use or foreign travel.

Examinations

Physical examination revealed an ill-appearing man, with mild generalized

abdominal tenderness and tachycardia. He was found to be severely dehydrated, in acute renal failure (Creatinine 5.5 mg/dL) with a significant leukocytosis (WBC 20.4 $10^3/\mu\text{L}$) (Table 1). An extensive infectious workup for diarrhea was performed which was ultimately negative (Table 2). A computed tomography (CT) scan of the abdomen/pelvis was performed which revealed a moderate amount of liquid stool throughout the colon, greatest within the rectosigmoid colon.

A colonoscopy was obtained and revealed copious amounts of fluid and liquid stool, with over 2 liters of fluid suctioned out, but no endoscopic evidence of inflammation (Figure 1). Random biopsies for histology were obtained, as well as biopsies for cytomegalovirus and herpes simplex virus polymerase chain reaction (PCR) testing. His biopsies came back for mild colitis (Figure 2). His cytomegalovirus and herpes simplex virus PCR were also negative, as was testing for *C. difficile*, tuberculosis and hepatitis B.

FINAL DIAGNOSIS

The patient was diagnosed with immune-mediated colitis secondary to Ipilimumab and Nivolumab.

TREATMENT

On admission, the patient was started on broad spectrum antibiotics, intravenous (IV) fluids and electrolyte replenishment for his metabolic derangements. However given the temporal relationship between the onset of his symptoms and his immune treatment and the negative infectious workup, an immune-mediated colitis was suspected. His antibiotics were discontinued and the patient was started on high dose IV steroids. His renal function and leukocytosis improved but the diarrhea persisted. Ten days after receiving his treatment the gastroenterology service was consulted.

The patient had already been on high-dose steroids, diphenoxylate-atropine (Lomotil®), and loperamide without relief or resolution. He continued to have 5-10 large volume watery bowel movements a day, and was on continuous IV fluids, a bicarbonate drip as well as aggressive electrolyte replenishment. The patient was also initiated on a trial of mesalamine and subcutaneous octreotide injections with no improvement. After the colonoscopy was performed the patient was initiated on Infliximab 5 mg/kg.

OUTCOME AND FOLLOW-UP

After initiation of Infliximab, the patient noted improvement later the same day. The following day the patient had complete resolution of his diarrhea without any bowel movements. Over the next few days his renal function normalized and all medications were gradually discontinued. He was discharged with a steroid taper and instructed to follow up as an outpatient. On follow up in clinic his colitis had resolved, and he remained symptom free at 3 mo follow up.

DISCUSSION

Immune checkpoint inhibitors such as Ipilimumab, the CTLA-4 antibody, and Nivolumab, an anti-PD-1 antibody, have been increasingly used in cancers such as metastatic melanoma and renal cell carcinoma but have been associated with several IMAE, including a high incidence of diarrhea and colitis^[1]. Although more common in Ipilimumab than Nivolumab, the incidence of colitis is highest when these two drugs are used in combination^[2]. These side effects can be severe, and some patients may require the initiation of high dose intravenous steroids such as Methylprednisolone 2 mg/kg per day^[3]. However, up to 40% may not respond^[4], and many have used Infliximab for treatment of immune-mediated colitis in patients unresponsive to steroid therapy^[1-3,5-7]. Infliximab is thought to work in these cases by several mechanisms including opposing the activation of T cells by CTLA-4 antibodies by suppressing the pro-inflammatory cytokines IL-1 and IL-6^[8], enhancing FOXP3+ regulatory T cells^[9], as well as preventing tumor necrosis factor (TNF)-alpha from binding to its receptor, thereby preventing it from recruiting neutrophils to the site of inflammation in the colon^[10]. Abdominal CT imaging usually shows mesenteric vessel engorgement, bowel wall thickening, and fluid-filled colonic distention^[11]. In one

Table 1 Labs at admission

Items	Data
WBC	$20.39 \times 10^9/L$
Neutrophil	61%
Lymphocytes	6%
Monocytes	6%
Eosinophil	0%
Hemoglobin	9.9 mmol/L
Platelets	$335 \times 10^9/L$
RDW	20%
Sodium	132 mmol/L
Potassium	2.8 mmol/L
Chloride	92 mmol/L
CO ₂	7 mmol/L
Creatinine	486.2 μ mol/L
Calcium	2.3 mmol/L
Anion gap	33 mmol/L
Albumin	0.57 mmol/L
Phosphorous	3 mmol/L
AST	15 IU/L
ALT	26 IU/L
Total bilirubin	6.8 μ mol/L
Alkaline phosphatase	110 IU/L
Magnesium	1.1 mmol/L

AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CO₂: Serum carbon dioxide; RDW: Red blood cell distribution width; WBC: White blood cell count.

study, endoscopy of patients who ultimately required Infliximab revealed ulceration in 59%, inflammation in 36% and no endoscopic evidence in 5%. Histological findings included chronic inflammation in 68% and acute inflammation in 27%^[4]. The grade of diarrhea has not been found to be associated with endoscopic or histologic findings^[4,6], and on follow up over a third of patients develop recurrent diarrhea^[4]. The median time of response to Infliximab is 2 d, and some patients may need more than one treatment^[6]. Caucasians and patients with melanoma seem to have a higher incidence of diarrhea and colitis^[5]. Studies have suggested better overall outcomes and survival in patients who develop IMAE^[5,12], and in the case of colitis this is thought to be in part secondary to distinct baseline gut microbiota^[13]. Although the use of Infliximab has become part of the treatment algorithm for immune-mediated colitis, the influence of a TNF-alpha on the progression of metastatic cancer is unclear, and further studies evaluating long-term effects are needed. To our knowledge this is the first case of renal cell carcinoma treated with both Ipilimumab and Nivolumab with resultant steroid refractory colitis that resolved with Infliximab. Given the increasing use of immune therapy in a variety of cancers, it is important for gastroenterologists to be familiar with their gastrointestinal side effects and management.

CONCLUSION

The incidence of immune-mediated colitis is higher when Nivolumab is used with Ipilimumab, and many patients may require high dose intravenous steroids for therapy. However, up to 40% of patients will not respond and will need to be initiated on infliximab. Gastroenterologists should be able to recognize adverse events related to novel immune therapy agents and be comfortable managing them, including prescribing anti-TNF-alpha inhibitors for immune-mediated colitis. Future studies are needed to evaluate the response to alternate biological agents, long term management of recurrent immune mediated colitis, and the role of TNF-alpha administration on the progression of metastatic cancer.

Table 2 Infectious workup

Infectious workup
Clostridium difficile toxin B gene DNA PCR
Salmonella, shigella/enteroinvasive <i>E coli</i> , campylobacter, shiga toxin 1/2 NAAT
Cryptosporidium stool antigen, giardia stool antigen
Ova and parasite
Yersinia enterocolitica culture
Vibrio stool culture
Stool cultures
Influenza/respiratory syncytial virus / rhinovirus/adenovirus/metapneumovirus
Blood and urine cultures
Cytomegalovirus colon biopsy DNA PCR
Herpes simplex virus 1/2 colon biopsy DNA PCR

NAAT: Nucleic acid amplification test; PCR: Polymerase chain reaction.



Figure 1 Colonoscopy revealing copious amounts of fluids and liquid stools in colon without endoscopic evidence of disease after removal.

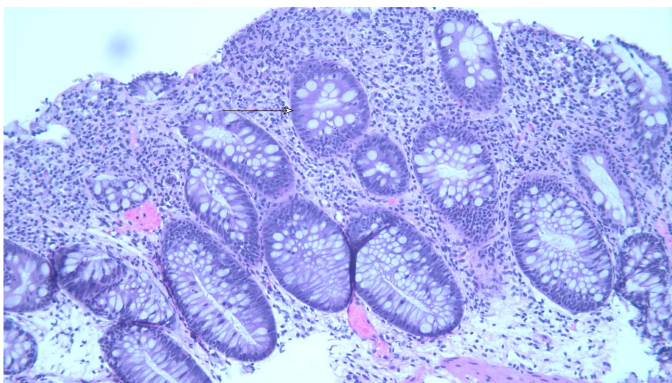


Figure 2 Mild active colitis with increased apoptotic bodies in crypts (arrowhead) and increased plasma cells in lamina propria (HE stain, × 100).

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Crohn's disease of esophagus, stomach and duodenum

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Abstract

Crohn's disease with involvement of the esophagus, stomach and duodenum has a prevalence of 0.5% to 4% in symptomatic adult patients, but some studies have shown that these results may be underestimated, since upper gastrointestinal endoscopy is not performed routinely in the initial evaluation of the disease in adult patients, as it is in the pediatric population. In general, involvement of the upper gastrointestinal tract in Crohn's disease occurs concomitantly with involvement of the lower gastrointestinal tract. The diagnosis depends on clinical, endoscopic, histological and radiological evaluation. The presence of aphthoid ulcers, longitudinal ulcers, bamboo-joint-like appearance, stenoses and fistulas are endoscopic findings suggestive of the disease, and it is important to exclude the presence of *Helicobacter pylori* infection. The primary histological findings, which facilitate the diagnosis, are the presence of a chronic inflammatory process with a predominance of lymphoplasmacytic cells and active focal gastritis. The presence of epithelioid granuloma, although less frequent, is highly suggestive of the disease in the absence of chronic granulomatous disease. Treatment should include the use of proton pump inhibitors associated with corticosteroids, immunomodulators and biological therapy according to the severity of the disease.

Key words: Crohn's disease; Upper gastrointestinal tract; Upper digestive endoscopy; Esophagus; Stomach; Duodenum; Chronic gastritis; Focal gastritis; Epithelioid granuloma

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Core tip: Crohn's disease is a chronic inflammatory disease, which involves any segment of the mouth to the anus, but the involvement of the upper tract is less known, especially in the adult population, in which routine upper endoscopy is not indicated, as in the pediatric population. It is important to know the aspects related to Crohn's disease with

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involvement of the esophagus, stomach and duodenum, in order to facilitate its diagnosis and treatment.

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INTRODUCTION

Crohn's disease (CD) is a heterogeneous disorder with a multifactorial etiology, including genetic factors, environmental insults and intestinal microbiota, characterized by chronic, segmental and transmural inflammation that affects the gastrointestinal tract and may involve any segment of the oral cavity up to the anus^[1,2]. This disease was first described in 1932 by Crohn, Ginzburg and Oppenheimer, initially as a disease involving only the terminal ileum, but two years after its initial publication, Crohn *et al*^[3] and Davis *et al*^[4] described that other segments of the gastrointestinal tract could also be affected. Changes in the upper gastrointestinal tract (UGT) were described by Gottlieb and Alpert in 1937, and since then, recognition of gastroduodenal CD has been increasing^[5]. With the evolution of the digestive endoscopy in recent decades, it has become possible to improve the detection of lesions involving the esophagus, stomach and duodenum. Previously, this evaluation was performed only through radiological studies or surgical specimens. Despite the great advances in the knowledge of CD, the experience with the involvement of the UGT remains limited, even though it is a predictor of recurrence and progression to complications^[6].

According to the Vienna classification, involvement of the UGT (L4) is characterized by the involvement of any segment proximal to the lower of the ileum^[7]. The Montreal classification^[8], which was created after the revision of the Vienna classification, the location in the UGT (L4) was considered a modifier of the disease and may or may not be associated with other locations (L1-L3). Patients with proximal CD (L4) often present with evidence of colonic disease or distal small intestine. The involvement of the upper tract in CD represents a risk for complications and surgery^[4,9-11]. It's worth pointing out that the contribution of esophagogastrroduodenal *vs* jejunal involvement among patients with proximal disease has not been evaluated^[9].

A cross-sectional study has demonstrated that proximal CD (L4) affects younger, nonsmoking patients, is less likely to involve the colon (L2), is more frequently present with concomitant ileal involvement and stenosing behavior, and has a higher probability of having one or more abdominal surgeries. When L4 (with jejunal involvement) and L4 esophagogastrroduodenoscopy (esophageal and gastroduodenal involvement) are compared, the former are twice as likely to present ileal disease, stenosing behavior and one or more abdominal surgeries. CD with involvement of the esophagus, stomach and duodenum is diagnosed at an earlier age and has a lower number of abdominal surgeries. In view of these differences, the authors suggest a review of the Montreal classification in order to reclassify the L4 location in L4a (upper tract proximal to the Treitz ligament) and L4b (below the Treitz ligament until proximal to the distal third of the ileum) in adult patients, as is done in the pediatric population^[9,12].

The prevalence of lesions in the UGT in symptomatic patients varies from 0.5% to 5%, but more recent observational studies show a higher frequency of endoscopic and histological alterations when upper digestive endoscopy (UDE) is performed routinely as part of the evaluation of the disease, regardless of the presence of gastrointestinal symptoms^[13-16]. Studies performed in the pediatric population demonstrate that the involvement of the UGT has a higher prevalence, since it is recommended to perform UDE with biopsies of the UGT routinely upon the initial presentation of inflammatory bowel disease (IBD) in this patient group^[17-21] (Table 1). In a prospective cohort of 1015 adult patients with CD, upper tract involvement occurred in 11.7%, and 60% of them also had concomitant involvement of the ileocolonic region^[22]. Despite the high prevalence of macroscopic and microscopic findings with the most frequent endoscopy of the UGT, many of them are not specific and present uncertain relevance in clinical practice^[23].

Table 1 Studies that evaluated the involvement of the upper gastrointestinal tract in patients with Crohn's disease

Authors	Study design	Sample	Objectives	Results
Cameron DJ, 1991 ^[19]	Observational, prospective	56 children and adolescents with CD	Evaluate the results of systematic upper and lower GI endoscopy in 56 patients with newly diagnosed CD	UGI symptoms 25% Macroscopic findings: 71% <i>H. pylori</i> infection: All the patients were negative Epithelioid granuloma: 27% Prevalence: 53.6%
Halme <i>et al</i> , 1996 ^[13]	Observational, cross sectional	62 adults with CD	Determine the prevalence of gastritis and <i>H. pylori</i> infection in patient with CD	Macroscopic findings : 53.2% <i>H. pylori</i> infection: 9.7% Microgranulomas: 6.4% Prevalence(<i>H. pylori</i> negative chronic gastritis): 34%
Abdullah <i>et al</i> , 2002 ^[17]	Observational, retrospective	111 children (81 CD and 34 UC)	Assess the role of esophagogastroduodenoscopy in the evaluation of children with suspected inflammatory bowel disease	Macroscopic findings(CD): 64%(52/81) Microscopic findings(CD): 81.6%(66/81) <i>H. pylori</i> infection: 1.2% Epithelioid granuloma: 28.4% Macroscopic finding(UC): 50% Microscopic finding(UC): 70.6% Granuloma: absent
Crocco <i>et al</i> , 2012 ^[18]	Observational, prospective	45 children and adolescents newly diagnosed with CD	Evaluate the prevalence and clinical implications of the upper gastrointestinal localization in pediatric patients affected by CD	UGI symptoms 54% Macroscopic findings: 38%(erosions and ulcers), 42.2%(edema and redness) <i>H. pylori</i> infection: 4.4% Epithelioid granuloma: 27%
Annunziata <i>et al</i> , 2012 ^[14]	Observational, prospective	119 adults with CD(45 newly diagnosed and 74 previous diagnosis)	Evaluate the prevalence of upper GI involvement in consecutive patients with known or suspected CD, irrespective of upper tract symptoms	UGI symptoms: 37% Macroscopic findings: 48.7% Microscopic findings: 59.7% <i>H. pylori</i> infection: 8.4% Epithelioid granuloma: 52.6% Prevalence (macroscopic + microscopic findings): 16%(19/119)
Sakuraba <i>et al</i> , 2014 ^[15]	Observational, retrospective	138 adults with CD	Define endoscopic UGI lesions and assess their prevalence in a cohort of CD patients	UGI symptoms: 25.4% <i>H. pylori</i> infection: 10.8%(4/37) Non caseating granuloma: 10.9% Prevalence (macroscopic specific findings): 51.3%
Horjus Talabur Horje <i>et al</i> , 2016 ^[16]	Observational, cross sectional	152 adults with CD newly diagnosed	Prospectively evaluate the prevalence of UGI involvement in a consecutive series of newly diagnosed, treatment-naïve adult patients with IBD irrespective of upper gastrointestinal tract symptoms	UGI symptoms 21% Macroscopic findings: 55% Microscopic findings: 71% <i>H. pylori</i> infection: 6% Epithelioid granuloma: 31% Prevalence: 41%
Park <i>et al</i> , 2017 ^[20]	Observational, retrospective	52 pediatrics patients with CD	Evaluate the prevalence of upper GI involvement and identify the clinical features of Korean children with CD symptoms	UGI symptoms: 30.8% Macroscopic findings: gastric ulcers (19.2%), duodenal ulcers (15.4%), gastric erosions (17.3%), duodenal erosions (5.8%) Microscopic findings: chronic inflammation (75%) <i>H. pylori</i> infection: 5.8%

CD: Crohn disease; UC: Ulcerative colitis; GI: gastrointestinal; UGI: upper gastrointestinal; IBD: Inflammatory bowel disease.

The European consensus on the diagnosis and management of CD [European Crohn's and Colitis Organization, (ECCO)] published in 2017 recommends that, irrespective of colonoscopy findings, additional research should be performed to define the location and extent of CD in the small intestine. However, performing routine EDA in adult patients with asymptomatic CD remains controversial^[11]. In patients with unclassified IBD (10% to 15%), HDE may contribute to the differentiation between CD and ulcerative colitis (UC)^[24].

Despite the inclusion of UGT as a disease modifier, there is no objective definition of the endoscopic and histological criteria needed to adequately characterize the involvement of these segments in CD^[16]. Nugent *et al*^[25], in their series of patients with duodenal CD, defined the following criteria for the diagnosis: the presence of noncaseous granuloma in the duodenum with or without involvement of the lower intestinal tract in the absence of any granulomatous disease or the presence of CD associated with duodenal inflammation consistent with CD. Although this definition does not consider other histological aspects, it can also be applied to the esophagus, stomach and jejunum^[26]. The ECCO guideline recommends that the diagnosis be confirmed by integrating clinical, endoscopic, histological, radiological and/or biochemical findings^[11].

ESOPHAGEAL CROHN'S DISEASE

Esophageal CD is rare and was described in 1950 by Frankly and Taylor^[27,28]. The prevalence of esophageal CD ranges from 3.3% to 6.8% in the adult population and from 7.6% to 17.6% in pediatric patients, but these data may be underestimated in adults due to the failure to perform HDE in asymptomatic patients^[29]. Decker *et al*^[30] reported 20 cases of esophageal involvement (0.2%) among 9900 CD patients, evaluated between 1976 and 1998, of whom 19 (95%) also had active bowel disease. The diagnosis was based on the endoscopic, histological, radiological and clinical impressions of the gastroenterologist. The mean age at diagnosis was 31 years, and the mean interval between the diagnosis of CD and involving the esophagus was 1 year^[30]. A retrospective observational study conducted at the Mayo Clinic between 1998 and 2012 identified 12367 patients with CD, and 57 of them were submitted to HDE to evaluate UGT symptoms, of which 24 presented esophageal involvement. The mean age at diagnosis was 16 years, and the mean time between diagnosis of CD and esophageal involvement was 3 years. The authors demonstrated that most of the patients were diagnosed with extraesophageal CD before the diagnosis of esophageal involvement. Only 3 cases were limited to the esophagus, and two of them developed extraesophageal CD in the follow-up^[29].

DIAGNOSIS

Clinical condition

Patients with esophageal involvement may present with symptoms such as heartburn, regurgitation and chest pain, similar to gastroesophageal reflux disease (GERD), and in more advanced cases, dysphagia, odynophagia, vomiting and weight loss. Less frequent symptoms such as hyperoxia and growth retardation may be present^[28-30]. In general, other segments of the gastrointestinal tract are affected, but some cases of isolated esophageal involvement are reported in the literature^[31-33]. The main complications associated with the disease are stenosis with or without obstruction, fistulas and perforation. Rarely, patients present fistulization to the bronchus, pleura, lungs, stomach and mediastinum, as well as abscess formation to adjacent organs^[34-37]. De Felice *et al*^[29] demonstrated that 86% of patients with esophageal CD showed symptoms, the main ones being dysphagia (54%), odynophagia (33%) and epigastric pain (33%). Oral ulcers were present concomitant to esophageal involvement in 33% and gastroduodenal involvement in 21%. Similar findings were reported by Decker *et al*^[30].

Radiology

The radiological study of the esophagus may show mucosal irregularities, ulcers, and polyps, but it is currently more commonly used to evaluate stenoses and fistulas. The most commonly described radiological findings are aphthous ulcers that appear as small particles of barium retained with a halo of translucent mucosal edema^[28]. Esophageal echoendoscopy may contribute to cases of difficult diagnosis, since it demonstrates the transmural character of the inflammatory process, characteristic of CD^[28].

Digestive endoscopy

The endoscopic findings are not specific, being described as friability, erosions, aphthoid ulcers, superficial or deep ulcerations (**Figure 1**), nodularity and stiffness of the mucosa, cobblestone appearance, inflammation and, less frequently, masses, stenoses and fistulas^[28,38,39]. Some reports and a series of cases demonstrate that ulcers may have a characteristic appearance called punched-out ulcers, which are larger and deeper than aphthoid ulcers and resemble ulcers caused by herpesviruses and cytomegalovirus^[40-42].

Aphthoid ulcers, followed by "punched-out" ulcers and linear erosions, were the main endoscopic findings identified by D'Haens *et al*^[41]. The most affected sites are the middle third and the distal third, and there may be, to a lesser degree, the diffuse involvement of the organ and the proximal third^[29,30]. Decker *et al*^[30] reported involvement of distal esophagus, middle and distal third and whole esophagus in 80%, 15% and 5% of the patients, respectively. The main findings were ulcers in 85% of patients, erythema or erosions in 40%, stenoses in 20%, fistulas in 5% and pseudopolyps in 5%^[30]. De Felice *et al*^[29] also demonstrated that the most common sites of involvement were the middle third (29%), distal (29%), medium and distal (17%), diffuse (21%) and proximal (4%). Surface ulcerations were present in 58%, erythema and/or erosions in 50%, deep ulcerations in 13%, pseudopolyps in 4%, stenoses in 17% and fistulas in 8%^[29].

Histology

Performing biopsies is critical to warding off other conditions, especially in the absence of involvement of other segments in the CD. It is important to ensure adequate fragments for the analysis, through larger and deeper biopsies, since superficial biopsies contribute little to the diagnosis because it is a transmural disease^[37]. The most frequent histological findings are chronic inflammatory infiltrate with a predominance of lymphocytes in the lamina propria and presence of ulcers^[30]. Noncaseous granulomas are rare and observed in fewer than 25% of cases^[28,30,38]. The granulomas are focal and are located in the deep submucosal and muscle, which could affect their identification^[43]. D'Haens *et al*^[41], in a series of cases, demonstrated esophageal granulomas in 57% of patients^[41]. However, this prevalence was different in the studies by Decker *et al*^[30] and De Felice *et al*^[29], who found 0% and 21.7%, respectively^[29,30].

Differential diagnosis

It is important to pay attention to other conditions that may involve the esophagus, such as viral esophagitis (cytomegalovirus, herpesvirus, human immunodeficiency virus), sarcoidosis, tuberculosis, reflux esophagitis, pill esophagitis, eosinophilic esophagitis, disseminated fungal disease, syphilis, Behçet's disease, carcinoma, lymphoma, metastasis of melanoma or lung cancer, and epidermolysis bullosa^[28,44,45].

TREATMENT

There are no guidelines for the treatment of esophageal CD due to the absence of randomized controlled trials conducted with this goal. Several options are reported in the literature. In general, they are based on experience with the treatment of ileocolonic disease, such as systemic corticosteroids, aminosalicylates, immunomodulators or biological therapy. The more intensive therapy is reserved for moderate to severe disease or refractory to corticosteroids^[28]. Progressive esophageal dilation with Savary-Gillard or balloon candles is indicated for cases with stenosis with persistent dysphagia^[42]. Placement of stents may represent an alternative treatment with good efficacy for benign stenoses. Esophagectomy is also an option considered in the disease complicated by fistulas, extensive stenoses, or abscesses and in refractory cases, for which medical therapy was not effective^[28].

D'Haens *et al*^[41] demonstrated that esophageal lesions in CD have, in most cases, a good response to clinical treatment but require courses of corticosteroids. They reported three patterns of disease behavior after initial treatment: those responding rapidly to corticosteroid therapy, achieving clinical and endoscopic response without

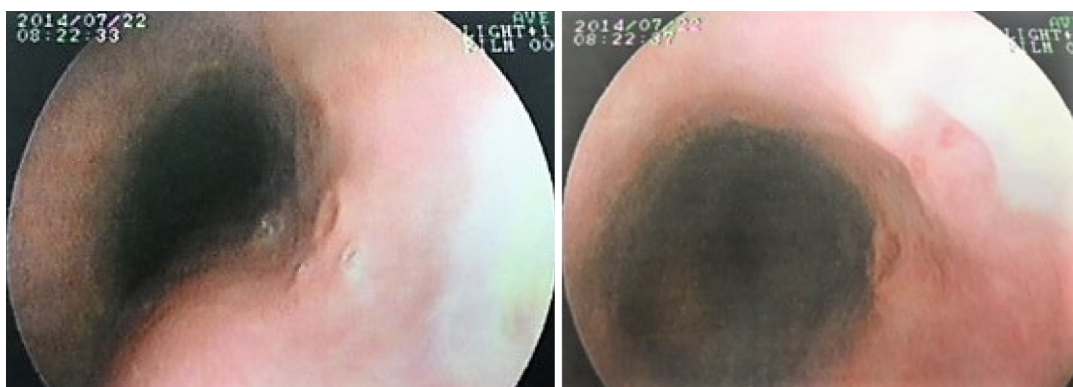


Figure 1 Esophageal ulcers in a patient with Crohn's disease.

relapse (57.2% of cases); those with persistent lesions despite the therapy (21.4%); and others with initial response and subsequent relapse (21.4%). They point out that “punched-out” ulcers recurred more frequently than aphthoid ulcers^[41]. Decker *et al*^[30] demonstrated that, among the 20 patients diagnosed with esophageal CD, 90% received corticosteroid therapy, 60% aminosalicylates, 25% H2 blockers and 25% proton pump inhibitors (PPIs). Esophageal dilation was required in six patients and surgery in three. The authors comment that the use of PPIs resulted in symptomatic improvement, but these drugs did not act in the control of the inflammatory response and should not be used as monotherapy, as is the case for aminosalicylates, since they are activated in the proximal intestine. They observed that half of the patients improved spontaneously or with the use of the first-line therapy, but one of the limitations was the non-accomplishment of HDE to evaluate the healing of the mucosa after the treatment. The remaining patients were treated with immunosuppressants, with a favorable response, and one of them with anti-tumor necrosis factor (anti-TNF) antibody. The authors suggest the use of acid suppressive therapy and corticosteroids in mild disease and immunomodulatory therapy in disease refractory or dependent on steroids^[30]. De Felice *et al*^[29] demonstrated that patients who presented inflammatory behavior responded to prednisone, topical budesonide and anti-TNF agents (infliximab and adalimumab). Stenting disease was treated successfully with immunomodulators and anti-TNF agents associated with dilation with or without steroid injection. Intensive treatment of fistulizing esophageal disease with immunomodulators, anti-TNF antibodies, or tacrolimus was not universally effective. Eight patients were treated with anti-TNF therapy, and all had a clinical response with dose adjustment, combination with immunosuppressive therapy or switching to another anti-TNF agent. Esophagectomy was not required^[29]. Some case reports reinforce the usefulness of biological therapy for the treatment of esophageal CD complicated or refractory to conventional therapy, both with infliximab and with adalimumab, avoiding esophagectomy^[46-48].

GASTRODUODENAL CROHN'S DISEASE

Gastroduodenal CD has a prevalence of 0.5% to 4%. The isolated involvement of the stomach and duodenum occurs in less than 0.07% of all cases of CD^[13,49-52]. A higher frequency of findings is reported in more recent studies, though with different diagnostic criteria. CD involving the duodenum is rare. A case series performed by Nugent *et al*^[25] demonstrated 36 cases of duodenal involvement, which represented 2% of the total population of new CD patients over a 20-year period. The proximal duodenal involvement was accompanied by distal involvement of the stomach in most cases, with a smaller number of patients with isolated involvement of the duodenum or in contiguity with the proximal jejunum^[25].

DIAGNOSIS

Clinical condition

In general, the patients are asymptomatic. Clinically symptomatic disease often arises at the same time or after the onset of bowel symptoms^[25]. The clinical picture includes abdominal pain, which can be localized in the epigastrium, nausea, vomiting,

postprandial fullness, anorexia, and fever. The presence of symptoms such as abdominal distension, postprandial vomiting, weight loss, and early satiety may indicate more severe disease, usually due to stenosis obstruction^[53]. Gastroduodenal involvement usually manifests itself through insidious, gastritis-like symptoms, but there are reports of atypical conditions, with rapid progression to obstructive forms^[52,54]. Less frequent presentations are upper gastrointestinal bleeding, delayed puberty, and chronic iron-deficiency anemia^[49,55]. Perforation, a frequent complication in peptic ulcer disease, is rare in gastroduodenal CD^[56]. Gastroduodenal fistulas are uncommon and usually result from inflammatory activity in adjacent organs such as the transverse colon and ileocolonic anastomosis^[26,57]. Duodenopancreatic fistula with refractory abdominal pain is rare^[58]. Duodenal CD may be a cause of acute or chronic pancreatitis due to the inflammatory process and fibrosis in the region of the vater ampulla, with duodenopancreatic reflux or fistulas between the duodenum and the pancreatic duct^[26,59,60].

Radiology

With the advancement of the digestive endoscopy, the radiological examinations have become less often used for the diagnostic evaluation of the UGT. The most frequent radiological findings are thickening of the folds, nodularity or cobblestone appearance, ulcerations, asymmetrical irregularities, pyloroduodenal deformity, stenoses, fissures and pseudodiverticula^[61,62]. The antrum and the duodenal bulb may be rigid and have a reduced peristalsis. The descending duodenum stenosis can be identified through the radiological finding called "string sign"^[26].

Gastroduodenal involvement with progressive pyloric stenosis can produce two radiological features: the "pseudo-Billroth I" characterized by the tubular appearance of the antrum, pylorus and duodenum, and the ram's horn sign, characterized by distensibility of the proximal stomach and rigid and stenotic aspect of the antrum and duodenum^[63]. The radiological study of the upper tract detects only one third of the gastrocolic fistulas, with barium enema being the examination of choice^[56,64]. Gastric fistulas often originate from the transverse colon and duodenal fistulae are derived from the colon or anastomosis colonic ileus. Primary gastroduodenal fistulas are rare and generally enterocutaneous^[56]. The three major radiological patterns of disease in the duodenum, in the case series described by Nugent *et al.*^[25], were the contiguous involvement of the proximal antrum and duodenum, followed by the isolated involvement of the descending duodenum and the distal duodenum^[25].

Endoscopic aspects

Endoscopic findings are similar to those described in other segments of the gastrointestinal tract, such as edema, enanthem, longitudinal or irregular erosions, ulcers that may be superficial or deep or aphthoid, linear or serpentine (Figure 2); nodularity of the mucosa and thickening or narrowing of the antrum, with reduction of distensibility; "cobblestone" appearance, duodenal stenosis, "notching" of the duodenal folds (Figure 3), protruding lesions in the bulb and second duodenal portion and a "bamboo-joint-like (BJL)" appearance^[4,38,49,65,66]. The protruding lesions may have a longitudinal arrangement described as "rosary-like protuberant lesions". Erosions may be circular or longitudinally aligned, usually located in the antrum and difficult to differentiate from other types of gastritis not associated with CD, so that the sensitivity of this finding is low^[38].

The places most frequently affected by gastroduodenal CD are the antrum, pylorus and proximal duodenum, while the proximal stomach is usually preserved^[64,66]. A retrospective cohort study of 138 CD patients submitted to HDE for investigation of high gastroduodenal symptoms or as part of the diagnostic investigation demonstrated that the ratio of specific CD lesions were higher in upper-middle (47.8%), lower (24.6%) and bulb (31.9%)^[15]. The BJL appearance was first described by Yokota *et al.*^[67] in 1997 and is characterized by linear fissures or grooves that cross the longitudinal folds of the small curvature of the cardia and upper gastric body. Although this finding can be identified by white light, it can be better observed through indigo carmine chromoscopy. A retrospective study by Kuriyama *et al.*^[66] in Japan suggests that the BJL appearance may be a specific finding of CD (sensitivity: 44% and specificity: 95%). The detection rate was 44% in patients with CD, whereas in patients with UC and GERD, it was 5% and 0%, respectively. Fujiya *et al.*^[68] demonstrated in a case-control study that included 81 CD patients, 81 non-IBD patients and 66 UC patients that in those with CD the incidence of BJL in the stomach was higher ($P < 0.001$), suggesting that this finding may be characteristic of gastroduodenal CD. The accuracy, sensitivity and specificity of this endoscopic finding were 67.9%, 38.3% and 97.5%, respectively [odds ratio (OR) 24.49; 95% confidence interval (CI) 5.61-106.85]. The authors described that the notch-like appearance and erosions and/or ulcerations had an incidence of 9.9% and 32.1%



Figure 2 Pre-pyloric gastric ulcer in a patient with Crohn's disease.

respectively^[68]. This endoscopic aspect is also described in patients with the disease in remission^[69].

Histology

The main histological findings described in CD of the stomach and duodenum are nonspecific acute and chronic inflammation, focal inflammatory changes, lymphoid aggregates, mucosal-muscular fibrosis, chronic *Helicobacter pylori* (*H. pylori*) negative gastritis, focal gastritis, epithelioid granulomas, and duodenitis with or without granulomas. The biopsies should be done in endoscopically normal areas and in altered areas, since the disease presents a focal distribution^[64]. Removal of several fragments is recommended.

Noncaseous granuloma, although a marker of the disease, has a very variable prevalence in the literature, occurring in 0% to 83% of the cases, since some studies only include histological analysis of biopsies and others of surgical specimens or both^[4,52,70]. Epithelioid granuloma is characterized by the capacity of secreting such cytokines as IL1, TNF-alpha and TGF-beta^[71]. Several studies have shown that the presence of epithelioid granuloma may be associated with a worse prognosis, however the results regarding the frequency and clinical significance are conflicting^[72-76]. In the UGT, granulomas are located more frequently in the stomach than in the duodenum and more frequently in the antrum than in the stomach body^[65] and can be detected in both normal-appearing and altered mucosa^[4,26].

The prevalence of granuloma detection may vary according to the type and location of the lesions, being identified in less than 25% of the esophageal lesions, 7%-87.7% of the gastric lesions, 14.3%-45.5% of the lesions with appearance in BJL and 0-49% of duodenal lesions^[38]. Similar results are reported in the pediatric population^[17]. One study showed that granulomas occur more in the stomach (9.4%), with a prevalence of 3.4% in the duodenum and 4.9% in both stomach and duodenum. The incidence of granulomas was higher in patients with enterocolonic disease and shorter duration of disease^[77]. A retrospective cohort study showed that noncaseous granulomas were detected in 10.9% of the patients, mainly in the lower stomach (25%) and duodenal bulb (11.4%). However, this study did not evaluate other histological changes, such as focal gastritis, and not all patients were evaluated for the presence of *H. pylori*^[15]. The variation between these results may be related to the biopsied site, the number of biopsies, the number of cuts performed, the use of serial sections and the pathologist's proficiency^[38,78].

A study by Yao *et al*^[79] evaluated noninflamed gastroduodenal mucosa through histological and immunohistochemical analysis and identified that microaggregates of macrophages and epithelioid granulomas were present only in CD patients and not patients with UC, so that this finding helped differentiate between the two diseases. Microaggregates of macrophages were more frequent than epithelioid granulomas in this population (54.5% × 18.2%, respectively).

Focal gastritis is characterized by infiltrating inflammatory cells in a foveolus or small groups of foveolae or gastric glands and has been described in several studies as a finding suggesting gastric CD (Figure 3). Magalhães-Costa *et al*^[80] demonstrated that focal active gastritis and the presence of macrophage microaggregates were associated with CD, once *H. pylori* infection was excluded. A prospective study evaluating the histology of gastric mucosa in 75 patients with CD of the small intestine or colon demonstrated that focal active gastritis was found in 76% of *H. pylori*-negative patients, with a positive predictive value of 97.5%. It was located more frequently in the antrum than in the body. The immunohistochemical study aided in the

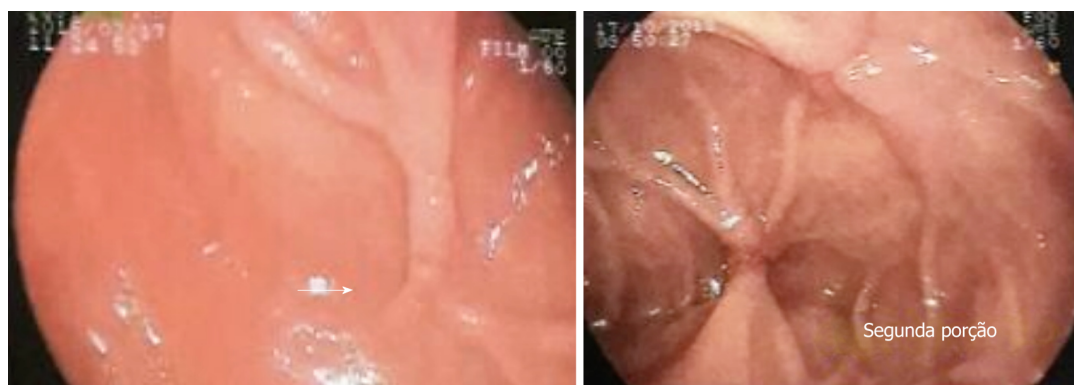


Figure 3 Duodenal involvement in a patient with Crohn's disease and *Helicobacter pylori* negative.

differentiation between the type of inflammatory infiltrate in active focal gastritis of CD compared to the control group. An important feature was the presence of accumulations of CD68⁺ and CD68R⁺ histiocytes and peripheral or periglandular CD3⁺ lymphocytes, findings not seen in the control group^[81]. A case-control study conducted by Parente *et al*^[82] showed that among 94 patients with CD who were *H. pylori* negative, 40 (43%) had focal gastritis, compared to 5 of the 52 patients with UA (12%) and 11 of the 57 control patients (19%). Among the patients with focal *H. pylori*-negative gastritis, only 4 presented granulomas. The main immunohistochemical finding of focal gastritis in CD patients was the accumulation of CD8⁺ and CD4⁺ lymphocytes and histiocytes, with a predominance of CD68⁺ cells, a similar finding in UC, whereas in controls without IBD, there was a predominance of T and B lymphocytes, histiocytes and CD8⁺ lymphocytes. Other authors have also demonstrated that, although active focal gastritis is more common in CD, it may also be present in UC^[16,83]. The main histological findings described in the BJL appearance are the presence of fissure-like erosions, edema, eosinophils and lymphoid follicles^[68]. Hirokawa *et al*^[84] demonstrated similar histological, including cleft-like erosions and/or mucosal clefts in 7 (50%) of the 14 CD patients and 1 (20%) of the 5 non-CD patients. Metaplasia, atrophy of fundic glands and abscesses of crypts were not identified.

Chronic *H. pylori*-negative gastritis is a common finding and has been reported at a high frequency in patients with CD^[13,85-87], mainly in young children and adults, while in the general population its prevalence is 2% according to Genta *et al*^[88]. Halme *et al*^[13] demonstrated an association between the finding of gastric involvement and greater severity of intestinal disease. A case-control study demonstrated that active chronic gastritis *H. pylori*-negative (OR 11.7, 95%CI 7.5-18), focal gastritis (OR 40.8, 95%CI 15.5-114.9), and duodenitis (OR 28, 2; 95%CI 17.1-46.5) were more frequent in CD than in patients with UC and healthy controls, especially in younger patients^[89]. Korean pilot study showed that active, chronic *H. pylori*-negative gastritis was present in 40% of patients, and *H. pylori* gastritis positive in 25%^[85].

The lower prevalence of *H. pylori* infection in CD patients is a controversial issue^[50,64,80]. This possible lower frequency may be justified by the prolonged use of medicines such as sulfasalazine, frequent use of antibiotics, socioeconomic distribution or unknown immune and infectious mechanisms^[13,87]. The interaction with the immune system of the host, acting on the dendritic cells, leading to an upregulation of the inflammatory T cells and, in turn, the reduction of the production of pro-inflammatory cytokines, downregulation of the Th1/Th17 cascade and increased levels of some cytokines are some of the mechanisms proposed to justify the protective role of *H. pylori* infection^[90,91].

A meta-analysis by Luther *et al*^[90] suggests a beneficial protective effect of *H. pylori* infection against the development of IBD. *H. pylori* infection was evidenced in 27.1% of patients with IBD and 40.9% of controls [Risk ratio (RR) 0.64, 95%CI 0.54-0.75]. In the subgroup analysis, a greater effect was observed in the group of subjects with CD (RR: 0.60, 95%CI 0.49-0.79) compared to UC (RR 0.75, 95%CI 0.62-0.90). However, significant heterogeneity of the included studies was observed ($I^2 = 5.8\%$), which limits the interpretation of this association. Another meta-analysis, performed in an Asian population that included 1299 patients with IBD and 1817 controls, showed that 24.9% and 48.3% had *H. pylori* infection, respectively. The RR of *H. pylori* infection in patients with IBD when compared to the control group was 0.47 (95%CI 0.43-0.54, $P < 0.001$), without significant heterogeneity ($I^2 = 21\%$). In the group of CD patients, 21.3% of patients with *H. pylori* infection were observed, compared to 47.7% in the control

group and (RR 0.43; 95%CI 0.37-0.50; $P < 0.001$), and there was nonsignificant heterogeneity ($I^2 = 43\%$)^[92]. Despite these results, high-quality controlled studies are needed to confirm these findings. Immunohistochemical study of the duodenum in CD patients demonstrates CD68-positive mononuclear cells that did not change after eradication of *H. pylori*^[93].

Isolated gastroduodenal CD represents a diagnostic challenge, since the histological analysis of biopsies may only demonstrate nonspecific inflammatory findings, and in some cases, only the study of the surgical specimens confirms the involvement of the UGT^[54]. The series of cases reported by Nugent *et al*^[25] did not demonstrate granulomas in biopsies taken by endoscopy. In contrast, they were found in the surgical specimen of some patients operated on later, reinforcing that the finding of nonspecific changes as well as normal mucosa does not rule out CD, since the findings are focal^[25]. It is important to emphasize that the presence of gastric lesions does not always reflect the activity of the disease^[38].

Differential diagnosis

The main differential diagnoses are peptic ulcer disease, Menetrier's disease, Zollinger-Ellison's syndrome, gastrinoma, tuberculosis, lymphoma, sarcoidosis, gastric syphilis, collagen diseases, plastic lymphoma, and amyloidosis^[49,52,64]. Intestinal tuberculosis should always be remembered in the differential diagnosis, especially in underdeveloped or developing countries where the incidence and prevalence of the disease are high. The main location in the intestinal tract is the ileocecal region, followed by the jejunum and colon. Gastric tuberculosis is rare (0.4%-2%) and is usually associated with pulmonary tuberculosis or immunodeficient states. Clinical symptoms are nonspecific and must be confirmed endoscopically. The main lesions described are ulcers located along the small curvature and pylorus, hypertrophic lesions and pyloric stenosis, with distortion of the anthropological region. Duodenal involvement is also rare, occurring in 2%-2.5% of all cases of gastrointestinal tuberculosis, the most common location being the third duodenal portion. The pattern of involvement may be intrinsic or extrinsic, ulcerative, hypertrophic or ulcero-hypertrophic, with formation of fistulas or stenoses^[45].

TREATMENT

The literature lacks controlled studies evaluating the effects of drugs available for the treatment of CD in the UGT, so treatment is based on the concomitant activity of the distal disease and clinical experience. PPIs relieve symptoms but have no effect on the chronic inflammatory process and therefore should not be used as an isolated therapy^[50]. Initial treatment of active gastroduodenal CD includes the use of systemic corticosteroids associated with PPIs. Immunomodulators such as 6-mercaptopurine and azathioprine are used to maintain corticoid remission in dependent or symptomatic patients who remain symptomatic despite corticosteroids^[51,94]. Aminosalicylates, even those with proximal release, have no benefit and can cause worsening of symptoms^[50,64].

The use of infliximab for gastroduodenal CD has been reported in the literature for the treatment of complicated disease, such as in cases of refractory duodenal ulcers, duodenal stenosis and pancreatic duodenum fistulas, with good results^[95-99]. The ACCENT I study included 43 subjects with gastroduodenal CD out of a total of 573 participants (8%), of whom 2 (56%) responded to therapy at week 2^[100]. Adalimumab is another treatment option with a satisfactory response, in the most severe cases and with complications, according to some case reports^[101,102]. Annunziata *et al*^[14] demonstrated in a prospective study that among 19 patients with gastroduodenal CD, 72.7% of infliximab- or adalimumab-treated patients achieved mucosal healing at endoscopy 12 wk after the start of treatment compared to 12.5% of patients treated with conventional therapy, although this study was not designed with the objective of evaluating treatment efficacy.

Short pyloric or duodenal stenoses are treated through balloon dilatation, with a low risk of complications such as perforations (1%-2%). In general, there is a high rate of recurrence of obstructive symptoms, and repeated dilatations are required to treat them properly and avoid surgery^[50,103]. A retrospective study by Guo *et al*^[104] evaluated the safety and efficacy of endoscopic balloon dilations for the treatment of stenoses in 24 patients with gastroduodenal DC associated with obstructive symptoms, less than 4 cm, not associated with fistulas or abscesses. They demonstrated that the procedure was safe but had unfavorable long-term effectiveness. The main predictor of long-term response was the absence of a new intervention in the first month after initial dilatation. Systematic review by Hassan *et al*^[105] evaluated the efficacy and safety of

endoscopic dilations. A total of 353 stenoses were dilated in 347 patients, the majority (66%) in anastomoses of the colonic ileum and only 3% in the UGT. Endoscopic dilation avoided future surgical interventions and was a safe method with a low complication rate (2%). Stenoplasty can be used as an option in the treatment of gastroduodenal obstruction, but few studies have compared their results with bypass surgery^[94]. This procedure may have serious complications such as ruptured anastomosis, persistent obstructive symptoms and restenosis at the site of previous stenoplasty^[57].

The first reports of upper limb involvement cases in the prebiological therapy era and before the introduction of digestive endoscopy as a diagnostic method demonstrated that surgical treatment was the main option in the management of more advanced disease and with complications^[106]. The main surgical indications are fistulas, stenosis refractory to dilation, ulcers not responsive to medical therapy and persistent high digestive hemorrhage, with excellent results. The most commonly used techniques are bypass with gastrojejunostomy, gastroduodenostomy and duodenojejunostomy. Gastrojejunostomy with highly selective vagotomy is the surgery of choice for reducing the number of complications^[64].

Vagotomy may reduce the incidence of anastomotic ulcers, but it increases the chance of diarrhea in these patients and has a controversial indication. Laparoscopic gastrojejunostomy is an option for the treatment of obstructive gastroduodenal disease, with lower morbidity, shorter recovery time and shorter hospitalization^[107]. In a retrospective study of 54 patients with gastroduodenal CD treated between 1958 and 1997, Yamamoto *et al*^[57] demonstrated that surgical treatment was performed in 33 patients (61%), with gastroduodenal obstruction (30 patients) being the most frequent indication, followed by duodenocutaneous fistula in 2 patients and massive bleeding in 1 patient. Bypass surgery was the procedure of choice, but it had a high incidence of postoperative complications, such as anastomotic leakage (13%), enterocutaneous fistula (6%), intraabdominal abscess (13%), anastomotic obstruction (25%), stoma (13%), small bowel obstruction (6%), and persistent obstructive symptoms (19%), and of the need for reinterventions.

CONCLUSION

The prevalence, complications, therapeutic and prognostic implications of involvement of the esophagus, stomach and duodenum in CD has not been thoroughly elucidated to date. UDE and histological study are useful diagnostic methods for the adequate identification and characterization of the lesions that can affect these segments, but these results should be interpreted with caution, staying aware of other conditions that can mimic this disease. Despite the inclusion of upper tract involvement as a disease modifier in the Montreal classification, routine upper gastrointestinal endoscopy is not indicated for assessing the extent of the disease in adult patients without UGT symptoms, as the clinical impact of this conduct is uncertain. Prospective studies may help to define the real contribution of upper gastrointestinal endoscopy in CD patients and to define the endoscopic and histological criteria necessary to better characterize the involvement of the UGT in these patients.

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Nutritional status as a predictor of hospitalization in inflammatory bowel disease: A review

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Abstract

BACKGROUND

Inflammatory bowel disease (IBD) presents an inflammatory picture that in the long run can lead to complications and consequently more hospitalizations compared to other diseases.

AIM

To evaluate the influence of nutritional status on the occurrence of IBD-related hospitalization.

METHODS

This integrative review was conducted in the online databases PubMed and MEDLINE, using the terms "obesity" and "malnutrition" accompanied by "hospitalization", each combined with "Crohn's disease" or "ulcerative colitis". Only studies conducted with humans, adults, and published in English or Spanish were selected, and those that were not directly associated with nutritional status and hospitalization were excluded from this review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guide was used as the basis for selection of studies.

RESULTS

Of the 80 studies identified, only five met the proposal of this review. None evaluated the association of good nutritional status with the risk of hospitalization. Malnutrition had a strong correlation with the risk of hospitalization related to IBD, and there was disagreement among three studies regarding the association of obesity and hospitalization rates.

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CONCLUSION

Few studies have evaluated nutritional status as a predictor of IBD-related hospitalization. The presence of malnutrition appears to be associated with hospitalization in these patients, but further studies are needed to elucidate the issue.

Key words: Nutritional status; Inflammatory bowel disease; Hospitalization; Obesity; Malnutrition

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Core tip: Hospitalization in patients with inflammatory bowel disease (IBD) is common. Identifying involved factors, especially controllable ones, may help the development of strategies that can decrease the number of hospitalizations. Among these potential factors is nutritional status, as it is associated with the clinical evolution of patients with IBD. However, few studies have evaluated the association between nutritional status and hospitalization, the consequent complications of the disease, and surgical procedures. Few studies have described the association of malnutrition with hospitalization in IBD, and we cannot say whether adequate nutritional status alters this risk, and the results with obesity are conflicting. Thus, further studies are needed to answer this question.

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INTRODUCTION

Inflammatory bowel disease (IBD) affects different portions of the gastrointestinal tract and can be classified as Crohn's disease (CD) and ulcerative colitis (UC). IBD is an inflammatory condition, and long term it can lead to complications and consequently a greater number of hospitalizations compared to patients with other diseases. In addition to the greater number of hospitalizations, these patients require longer hospital stays, resulting in significant expenditures for the health system^[1,2].

The hospitalizations of patients with IBD are associated with complications of the disease, which involve the absence of specialized outpatient follow-up, surgical procedures, and non-use of medication for treatment. Thus, keeping the disease in the remission phase, in this case, is an important protective factor to prevent the occurrence of complications and consequent hospitalizations^[1,3].

It is known that enteral nutritional support for patients with IBD helps to increase body mass index (BMI) as well as improve disease activity, clinical signs, and symptoms, and it also allows adequate food consumption of energy, proteins, fats, carbohydrates, and fibers^[2]. However, few studies have evaluated the association between nutritional status and hospitalization of patients with IBD and the consequent complications in the disease and surgical procedures^[4-8]. Thus, the objective of this study was to evaluate the influence of nutritional status on the occurrence of hospitalization related to IBD.

MATERIALS AND METHODS

The research was conducted in the PubMed and MEDLINE online databases in May 2018, using the terms "obesity" and "malnutrition" accompanied by "hospitalization", each combined with "Crohn's disease" or "ulcerative colitis". Only articles published in English or Spanish until May 2018, with patients diagnosed with IBD, were included.

The studies were selected by three independent authors and include information on a large number of individuals and adults, with a diagnosis of CD or UC. Initially, 80 studies were found, and 61 were selected after reading the title. After reading the abstract, 25 were excluded because they were articles of revision, case reports, or

abstracts of symposium. For the analysis of the full text, 36 articles were elected, and 29 were excluded because they did not directly associate nutritional status and hospitalization for IBD. The flow chart for the selection of the studies of this review was constructed from the structure of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^[9] (Figure 1).

RESULTS

Of the 36 articles selected, only five evaluated the association between nutritional status and hospitalization for IBD^[4-8]. One study included a small number of children, and the information on the sample size was confusing^[4]. Four studies had a cohort study design^[4-7], three of which were retrospective^[4,5,7] and one was a cross-sectional study (Table 1).

Adequate nutritional status and hospitalization

The articles evaluated did not describe an association between good nutritional status and the risk of hospitalization for IBD.

Malnutrition versus hospitalization

We accept the definition of malnutrition that each author used in the studies. Of the five studies, two evaluated nutritional deficits using different databases in the United States^[7,8]. In both cases, Ananthakrishnan *et al*^[7] and Gajendran *et al*^[8], malnutrition was diagnosed by the ICD-9-CM (International Classification of Diseases), which used serum levels of albumin (< 3.4) as indicators; involuntary weight loss of 5% in 3-6 mo and 10% in 6-12 mo; BMI < 18.5 kg/m² associated with comorbidity, poor diet, and loss of muscle mass^[7,8]. In the cross-sectional study, the presence of malnutrition was associated with hospitalization in patients with IBD^[8]. Similarly, in the retrospective study, severe hospitalization (classified as the need for any intestinal surgery or hospitalization time for more than 7 d) was also associated with malnutrition in patients with CD^[7].

Obesity and hospitalization

Three studies evaluated obesity as a risk factor for IBD-related hospitalization, and the results were contradictory^[4-6]. In Blain *et al*^[4], it was observed that obese patients with CD had a greater chance of hospitalization related to the disease than those who were non-obese. However, in Flores *et al*^[5], obese and overweight patients with CD and UC were less likely to experience a hospital stay related to IBD than those with eutrophic/thinness, thus suggesting that excess weight is an indicator of lower severity of disease. In a prospective study, Seminerio *et al*^[6] observed that high a BMI (obesity classes I, II and III) is not associated with rates of hospitalization for IBD.

DISCUSSION

The main difficulty in nutritional assessment studies is exactly how to define nutritional status or to choose the indicator to be used. This is due to some limitations of the indicators and the consequent need to use several anthropometric parameters, biochemical tests, physical examinations, and food surveys and the interpretation of the data collected to arrive at an individualized diagnosis^[10]. BMI is the most used nutritional indicator in clinical practice and in studies because it is simple, low cost, noninvasive, and practical^[11]. Of the five studies evaluated, the majority used only BMI as an indicator of nutritional status, and only two studies defined nutritional status using other indicators^[7,8].

Malnutrition is the most commonly found nutritional status in patients with hospitalized IBD, and in about 50% of those with severe malnutrition, the loss of body mass occurs 6 mo before hospital admission^[2,12]. Quality of life in these patients is generally lower^[13], and malnutrition has been associated with increased in-hospital mortality and length of stay and increased risk of hospitalization for IBD^[8,14]. However, only two of the five studies selected evaluated malnutrition as a risk variable for hospitalization for IBD^[7,8].

The use of nutritional therapy in patients with undernourished IBD has efficacy in improving nutritional status in some studies, especially in cases of disease-related surgery^[15,16]. In one study, improvement in the malnutrition status after use of exclusive preoperative enteral nutrition in patients with CD was characterized by increased serum albumin levels and body weight gain in a 45 d period^[15]. On the other hand, in patients with hospitalized undernourished CD, the need for nutritional

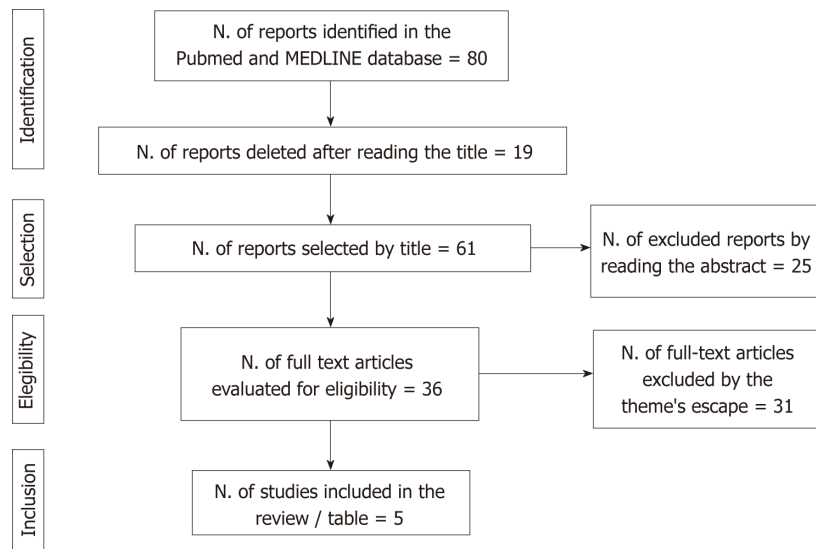


Figure 1 Flowchart adapted from PRISMA.

therapy was identified as a predictor of disease severity^[7]. Nutritional therapy and the risk of hospitalization IBD was not an objective of this study, but it is a relevant topic for future revisions.

Serum albumin, although commonly used to identify the nutritional status of patients with IBD, is not a good indicator, especially in the active phase of the disease due to the negative effect of inflammatory cytokines on this plasma protein^[15,17,18]. However, it may influence the prognosis and consequent hospitalization related to IBD. In patients with UC, higher albumin values at admission were a protective factor for early hospital readmission^[19]. In a sample evaluating mortality predictors in IBD patients admitted to the intensive care unit, hypoalbuminemia was associated with increased mortality in this population^[20].

Poor or insufficient serum vitamin D levels increased the need for surgeries and hospitalizations in IBD patients when compared to patients who had normal serum vitamin D^[21,22]. Considering that vitamin D is also referred to by some authors as a hormone and that diet is one of the factors that has little influence on the serum concentrations of 25(OH)D^[23], some studies^[21,24] were not chosen in our sample since the authors did not evaluate dietary intake or use of vitamin D supplements.

The prevalence of obesity has increased in patients with IBD, and in some places it is highly prevalent. This higher prevalence is accompanied by an increase in obese individuals in the general population^[4,5,25], which may contribute to the early initiation of drug therapy, a greater number of surgeries, and more complications due to the disease^[26]. Visceral obesity and IBD have in common the increased production of proinflammatory cytokines in the body; however, few studies have evaluated the relationship between obesity and the evolution and severity of IBD^[11,27].

Different studies indicate that obesity in patients with IBD is not related to complications of the disease or need for surgeries, and it represents a less severe course of the disease in obese individuals^[28,29]. The meta-analysis that assessed the impact of obesity on the clinical course of patients with IBD found that obese patients had less hospitalization experiences than non-obese patients (RR = 0.84 (95% CI: 0.74-0.94); Heterogeneity $I^2 = 0\%$, $P = 0.32$)^[29]. These authors based their conclusions with a moderate degree of evidence from two studies, both included in this review: Flores *et al*^[5], a retrospective, follow-up study of 518 patients with IBD in which obese and overweight patients were less likely to have hospitalization experience than the group with low/adequate BMI (42% vs 44% vs 66%, $P < 0.001$) and Seminerio *et al*^[6], a prospective study of 1494 patients with IBD. There was no association between increased BMI and hospitalization in patients with IBD, in both those with CD and UC ($P = 0.396$).

The controversial results can be explained by the inclusion of retrospective studies in two of them and the nutritional indicator used to define obesity, BMI. BMI as the only measure of obesity has limitations because it does not differentiate between subcutaneous and visceral adipose tissue, resulting in an inadequate association with IBD^[11,30,31]. Visceral obesity is more related to an increase in inflammatory cytokines, and assessing abdominal obesity requires other indicators, such as waist circumference^[11,32].

Table 1 Five studies on nutritional status as a predictor of hospitalization in patients with inflammatory bowel disease

Author	Study design/study population	Main results
Blain <i>et al</i> ^[4] , 2002	Retrospective study, follow-up 2065 patients of any age with CD: 62 obese <i>vs</i> 124 non-obese, matched by age, sex, disease location and date of diagnosis of CD	3% (62) were obese Patients with obese CD had a higher chance of hospitalization than non-obese patients (OR = 2.35, 95%CI: 1.56-3.52)
Flores <i>et al</i> ^[5] , 2015	Retrospective study, follow-up 518 patients with IBD divided into obese (BMI ≥ 30 kg/m ²), overweight (25-29.9 kg/m ²), eutrophic (18.5-24.9 kg/m ²) and low weight (< 18.5 kg/m ²)	Obese and overweight patients are less likely to experience hospitalization than the group with low / adequate BMI (42% <i>vs</i> 44% <i>vs</i> 66%, <i>P</i> < 0.001)
Seminario <i>et al</i> ^[6] , 2015	Prospective study 1494 patients with IBD	There was no association between increased BMI and hospitalization in patients with IBD, in both those with CD and UC (<i>P</i> = 0.396)
Ananthakrishnan <i>et al</i> ^[7] , 2010	Retrospective study cohort 6169 patients with CD	Severe hospitalizations were more associated with anemia (20.8% <i>vs</i> 15.1%, <i>P</i> < 0.001) and malnutrition (8.7% <i>vs</i> 2.3%, <i>P</i> < 0.001)
Gajendran <i>et al</i> ^[8] , 2016	Cross-sectional study (2 yr) Patients diagnosed with IBD Estimated number of 109392 annual visits with a primary diagnosis of IBD	There is an association between malnutrition and hospitalization of patients diagnosed with IBD (OR = 6.29, 95%CI: 5.84-6.78)

CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; BMI: Body mass index.

Some studies have identified bariatric surgery as important in the treatment of obese patients with IBD, showing benefits such as the interruption or significant reduction in drug use and/or improvement of IBD-related symptoms^[33,34]. New studies with more detailed investigation are needed to elucidate the role of obesity in IBD.

Nutritional status may influence hospitalizations for IBD. Among the few studies analyzed, the relationship with adequate nutritional status was not described, but malnutrition was related to hospitalization for the disease. Due to the contradictory results among studies on obesity, it was not possible to conclude the correlation with protective or risk factors for hospitalization for IBD. Since there were few studies identified for this review, further investigations are needed to evaluate the association between nutritional status and hospitalizations for IBD.

ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel disease (IBD) presents an inflammatory picture that in the long run can lead to complications and consequently more hospitalizations when compared to other diseases.

Research motivation

Few studies have evaluated the association between nutritional status and hospitalization of patients with IBD and the consequent complications in the disease and surgical procedures.

Research objectives

The objective of our study was to evaluate the influence of nutritional status on the occurrence of IBD-related hospitalization.

Research methods

The research was conducted in the PUBMED and MEDLINE online databases in May 2018.

Research results

Of the 80 studies initially identified, five met the inclusion criteria of this review. None evaluated the association between good nutritional status and the risk of hospitalization. Malnutrition had a strong correlation with the risk of hospitalization related to IBD, and there was disagreement among the three studies regarding the association of obesity and hospitalization rates.

Research conclusions

Few studies have evaluated nutritional status as a predictor of IBD-related hospitalization, and the presence of malnutrition appears to be associated with hospitalization in these patients. Additional studies are needed to elucidate the issue.

Research perspectives

The few studies found in this review reveal the need for further investigations to evaluate the association between nutritional status and hospitalizations for IBD.

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Prospective Study

Novel device for monitoring respiratory rate during endoscopy-A thermodynamic sensor

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Abstract

BACKGROUND

Monitoring ventilation accurately is an indispensable aspect of patient care in procedural settings. The current gold standard method of monitoring ventilation is by measuring exhaled carbon dioxide concentration, known as capnography. A new device utilizing thermodynamic measurement, the Linshom Respiratory Monitoring Device (LRMD), has been designed to measure respiratory rate (RR) by using the temperature of exhaled breath. We hypothesized that the temperature sensor is at least equivalent in accuracy to capnography in monitoring ventilation.

AIM

To determine if the temperature sensor is equivalent to capnography in monitoring procedural ventilation.

METHODS

In this prospective study, participants were individually fitted with a face mask monitored by both LRMD and capnography. The following data were collected: gender, age, body mass index, type of procedure, and doses of medication. For each patient, we report the mean RR for each device as well as the mean

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difference. All analyses were performed using SAS, and a $P < 0.05$ was considered statistically significant.

RESULTS

Twelve consecutive patients undergoing endoscopic procedures at our institution were enrolled. Four patients were excluded due to incomplete data, inadequate data, patient cooperation, and capnography failure. Overall, we found that LRMD RR highly correlated to capnography RR ($P < 0.001$); the average capnography RR increases by 0.66 breaths for every one additional breath measured by the LRMD. In addition, apnea rates were 7.4% for the capnography and 6.4% for the LRMD (95% confidence interval: 0.92-1.10).

CONCLUSION

The LRMD correlated with the gold standard capnography with respect to respiratory rate detection and apnea events. The LRMD could be used as an alternative to capnography for measuring respiration in endoscopy.

Key words: Sedation; Capnography; Linshom; Thermodynamic sensor; Endoscopy

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Core tip: The current gold standard method of monitoring ventilation during procedures is capnography. A new device utilizing a thermodynamic measurement, Linshom Respiratory Monitoring Device (LRMD) has been designed to measure respiratory rate by using the temperature of exhaled breath. This study showed that the LRMD correlated with the gold standard capnography with respect to respiratory rate detection and apnea events. The LRMD could be used as an alternative to capnography for measuring respiration in endoscopy.

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INTRODUCTION

As endoscopic procedures continue to increase in complexity, adequate monitoring of vital signs, specifically respiratory status and ventilation, is of utmost importance^[1]. Accurate monitoring of oxygenation and ventilation status is critical during the intra-operative and post-operative period^[2]. Monitoring ventilation appropriately is a crucial yet challenging aspect of patient management. The importance of monitoring respiratory rate as a key vital sign has been well defined in medicine^[3]. An abrupt alteration in respiratory rate can help detect changes in the status of a patient during a crucial period where modifications in management might be needed^[3]. Respiratory monitoring is important for both patients receiving general anesthesia as well as for those who require moderate sedation. Patients who do not require anesthesia but are at high risk of respiratory compromise given a multitude of co-morbidities, including underlying respiratory or cardiovascular disease, also need to be closely monitored. A recent study revealed that at least 5%-10% of patients undergoing surgery experienced some type of pulmonary complications^[4]. That risk more than doubles to as high as 22% in high risk patient populations^[4].

Respiratory problems, including but not limited to hypercarbia, hypoxemia, apnea, and respiratory arrest, are among the most common adverse events seen in the perioperative period, especially as a complication of anesthesia used during gastrointestinal endoscopy^[5]. Significant respiratory complications include pneumonia, respiratory failure, atelectasis, sepsis, and even cardiac arrest^[6,7]. In addition, poor monitoring of ventilation can result in exacerbation of chronic conditions and other pulmonary diseases. Therefore, given the high risk of any endoscopic or surgical procedure for possible post-operative pulmonary sequelae, close monitoring of respiratory parameters provides clinical information that may

help reduce morbidity and mortality^[5,8,9]. Standards have been developed by the American Society of Anesthesiologists (ASA) that state that during the use of all anesthetics, a patient's oxygenation, ventilation, circulation, and temperature should be continuously evaluated^[10]. Continual monitoring for the presence of expired carbon dioxide with the use of capnography has been advocated as the standard of care and recommended by ASA to be utilized in any gastrointestinal endoscopic procedure utilizing moderate or deep sedation. It is important to note that, although capnography has been used as the standard of care in critical care settings and operating rooms, the hardware is expensive, cumbersome to transfer, and results are influenced by secretions and moisture. In addition, when carbon dioxide insufflation is utilized, particularly of upper endoscopic procedures, the use of the CO₂ gas confounds the capnography monitoring by elevating the end tidal CO₂ level, leading clinicians to assume falsely that profound hypoventilation is occurring.

The Linshom Respiratory Monitor Device (LRMD) is a thermodynamic respiratory device that is novel, non-invasive, and portable and can potentially modernize the way physicians monitor respiratory activity both within critical care and ambulatory settings. The LRMD consists of two rapid-responding medical-grade thermistors (1.5 mm diameter) with a unique control-loop algorithm executed by a microcontroller (United States Patents: 8579829 and 8911380). The technology utilizes a highly sensitive thermistor-based sensor that compares the instantaneous temperature of the breath inside the mask with the ambient temperature. The sensor is comprised of an actively controlled thermistor inside the mask along with a Thermo-Electric Cooler (TEC) outside the mask. The device maintains the thermistor in thermal balance with the TEC utilizing the Peltier effect. During power-up initialization, the sensor measures the ambient temperature and uses this as a set point for the control loop. As the expired breath heats the thermistor, the thermal balance is disrupted, and this generates a feedback signal *via* the control loop. The generated signal is an accurate signature representation of the breath, capturing the subtle detail of the breathing cycle. After each breath, the control-loop returns the sensor to thermal balance with the ambient temperature and ready for the next breath. The aim of this study was to compare the effectiveness of apnea detection by these two devices.

MATERIALS AND METHODS

Patients and methods

In this prospective study, 12 participants were consecutively enrolled. Institutional Review Board approval was obtained prior to study initiation and consent was obtained from all participants. The study participants were collected at random to ensure there was no underlying bias and were patients already scheduled to undergo routine procedures at our endoscopy unit. The study was conducted at Cleveland Clinic Main Campus from June to July 2016. All participants were individually fitted with a standard face mask fitted with both capnography and the LRMD. The following data were collected from the medical record: Gender, age, type of procedure, type of sedation, and dose of medication administered. Vital signs, including respiratory rate, heart rate, blood pressure, temperature, and body mass index, were recorded. Patients were screened for medical issues, including cardiac and pulmonary disease, with responses noted in the data collection. Standard monitoring and sedation procedures were employed. The choice of sedation was also performed at random considering physician preference and endoscopy unit location where the patients were scheduled to undergo the procedure. Most of the procedures were performed with moderate sedation. All procedures took place in either of our two designated endoscopy suites, with most procedures occurring with nursing personnel and anesthesia if needed. Testing and data collection occurred in the same conditions with trained personnel (JJV, VW, and RF). The ambient temperature was 71°-72° F and ambient pressure 1 atmosphere.

Two different sensors were attached to the mask: A temperature sensor and CO₂ detection tubing. The LRMD was connected *via* a cable to the main computer control station. The facemask utilized allows for passage of an upper endoscope and is the standard mask used in our practice. Throughout the entire study, particular attention was paid to ensure tubing and sensors were not in contact with devices or objects that could affect data results. After the subjects were informed about the procedure and the planned protocol, oxygen was delivered at a flow rate of 6 L/min. Subjects were permitted to breathe through either their nasal or oral passages spontaneously without regulating tidal volumes. Participants were also instructed to avoid excessive movements that would affect data gathering.

The LRMD and capnography data were collected simultaneously *via* the Linshom

information gathering software for later comparison. For each patient, we recorded the mean respiratory rate for each device separately. We also reported the mean differences between the two devices with corresponding 95% confidence interval (CI). Each patient's distinct characteristics were noted and plotted against one another in order to determine the mean, standard deviation, and *P* values of the study group. In addition, Pearson's correlation was calculated to describe the correlation between the respiratory rate as calculated by the capnography and the LRMD. Bland-Altman Graphs were plotted to illustrate how differences in respiratory rate vary based on the rate of respiration.

Statistical analysis

For each patient, we reported the mean respiratory rate for each device as well as the mean difference between the two devices with corresponding 95% CI. In addition, we calculated Pearson's correlation coefficient to describe the correlation between capnography and thermodynamic respiratory rate. We did not use a concordance correlation coefficient because of the known differences on how the devices measure respiratory rate. Bland-Altman graphs were plotted to illustrate how the difference in respiratory rate varies based on the magnitude of the respiratory rate. In addition, generalized estimating equations (GEE) were used to compute the difference in percentage of reports showing apnea between the two devices while accounting for the paired nature of the data. Linear mixed models were used to evaluate overall association between capnography respiratory rate and Linshom respiratory rate while accounting for within subject correction due to multiple measurements per patient. Lastly, GEE analysis was used to assess the overall difference between Linshom and capnography apnea rates taking into consideration the correlation between measures done in the same subject. All analysis were performed using SAS (version 9.4, The SAS Institute, Cary, NC, United States) and a *P* value of less than 0.05 was considered statistically significant.

RESULTS

Twelve consecutive patients scheduled to undergo endoscopic procedures at our facility in Cleveland Clinic, Ohio, were enrolled. Eight patients underwent colonoscopy, and four underwent an upper endoscopy. One patient underwent both upper and lower endoscopy. Patients' age ranged between 41 and 90 years. There were seven males and five females in the conducted study. Both conscious sedation and monitored anesthesia care was used during the study (Tables 1 and 2).

After data review, 4 patients had to be excluded. Patients were subjected to exclusion for various reasons, including technical difficulties with capnography machine operations leading to incomplete data gathering due to constant calibration of capnography and respiratory mask falling off during procedure due to patient cooperation. When the mask fell, neither Linshom nor capnography data could be captured. There were no issues with the Linshom monitor capturing data. Out of the 12 patients who were selected, data was gathered over a total time period of 190 min. Approximately 3000 breaths were collected over the 190 min period given that each patient averaged 16 breaths per minute. Based on the data collection and review, we found that the LRMD was able to capture a statistically significant number of respirations compared to the conventional capnography monitor.

The LRMD respiratory rate highly correlated with capnography respiratory rate with a *P* value of < 0.001 . In addition to being statistically comparable to the capnography device in measuring respiratory rate, the LRMD was also able to detect increases in respiratory rate similar to that of the capnography device. The average capnography respiratory rate increased by 0.66 breaths for every additional one breath measured by the LRMD.

Breaths per minute comparison per patient

Figure 1 depicts respiratory rate (breaths per minute) *vs* time for each patient measured by both capnography and LRMD. Table 3 presents the mean respiratory rate for each patient as well as the average difference between the two. Note that the differences between the two devices are very small, with distinct significance seen as there is a large number of observations captured per patient to power further and detect such small differences. Figure 2 shows Bland-Altman plots. This scatterplot of measurement averages on the horizontal axis and differences in measurements plotted on the vertical axis shows the amount of disagreement between the two measurements by analyzing *via* means of the difference. The plots can also highlight certain types of anomalies in the measurements. Based on review of the data, it seems that there are inconsistencies between the two devices in the lower respiratory rate

Table 1 Patient characteristics

Patient	Age	Sex	Weight in kg	Height in cm	BMI in kg/m ²	ASA class	Sleep apnea	Included
1	70	Male	96.6	168	34.4	III	Yes	Yes
2	51	Female	79.4	165	29.1	II	No	No
3	61	Female	99.8	168	35.5	II	Yes	No
4	90	Male	72.6	163	27.5	II	No	Yes
5	51	Male	95.3	170	32.9	III	No	Yes
6	71	Male	145.2	191	40	IV	Yes	Yes
7	65	Male	108.0	180	33.2	III	No	Yes
8	51	Female	96.2	152	41.4	III	Yes	No
9	65	Male	115.7	175	37.7	II	No	Yes
10	47	Male	79.4	175	25.8	I	No	Yes
11	41	Female	64.0	157	25.8	III	No	Yes
12	77	Female	65.8	157	26.5	III	No	No

BMI: Body mass index; ASA class: American Society of Anesthesiologists classification.

values as seen on the plot, especially when the respiratory rate is less than 10.

Apnea

Apnea was also investigated during this study. When evaluating for apnea events, it is apparent that the two devices have similar rates of detection (< 2%). Subject 6 was the only exception to this as there were 7% more events detected by capnography compared to LRMD (Table 4).

DISCUSSION

In this prospective study, we measured the ability of LRMD to accurately and precisely detect respiration rate and variations thereof relative to commonly used capnography. Overall, the LRMD breaths per minute highly correlated to the capnography respiratory rate ($P < 0.001$). In addition to monitoring respirations per minute, fluctuations in respiratory rate also proved to be similar when comparing both these devices. We also found that the average capnography respiratory rate increased by 0.66 breaths for every one additional breath measured by LRMD, further demonstrating the ability of the LRMD to detect respiration just as accurately as standard capnography. When monitoring for adverse events in respiration, the LRMD was able to detect apnea rates 6.4% of the time compared to 7.4% with capnography, corresponding to an average 1% difference in reporting apnea events between the two devices.

This study demonstrated that the LRMD can be used in both critical care and ambulatory settings in place of conventional capnography for respiratory status monitoring, as has been shown previously^[11]. The advent of the LRMD allows us to measure ventilation in a new, easier to use, efficient, and more affordable manner. With the results of this study, this device can potentially prove to be an effective and safe alternative to monitoring ventilation in various settings. Interestingly, the greatest inconsistencies between capnography and LRMD were noticed in respiratory rates less than 10 (Figure 2). This is clinically relevant as hypoventilation state may be a preceding factor for apnea and respiratory failure. This observation may be explained by the fact that the algorithm used by the capnography takes time to analyze the data while the LRMD is instantaneous. In this scenario, we could argue that the LRMD is a superior monitor than capnography.

Although this research was able to reach our primary endpoint, there were some unavoidable shortcomings. First, because it was unclear just how many participants would be needed to collect a substantial amount of data, the sample size was small, totaling eight participants after four were excluded. Therefore, to generalize the results for larger groups, the study should have recruited more applicants in both groups. Secondly, this study does not apply to mechanically ventilated individuals, as none of the participants in this study were monitored *via* mechanical ventilation. The study may also not be generalizable to patients of all ages, as no children were studied. Moreover, the study was non-randomized and open label, further leading to limitations. Researchers were aware of the aim of the study, which introduces

Table 2 Procedure data

Patient	Procedure	Date	RR	O ₂ Sat%	HR	BP inmmHg	Sedationused	Included
1	EGD	6/13/16	20	97	87	145/78	Conscious	Yes
2	Colonoscopy	6/13/16	18	100	68	159/93	Conscious	No
3	Colonoscopy	6/13/16	19	97	87	139/73	Conscious	No
4	Colonoscopy	6/13/16	18	97	79	142/74	Conscious	Yes
5	EGD	6/14/16	18	98	76	133/80	Conscious	Yes
6	Colonoscopy	6/16/16	16	92	64	151/92	MAC	Yes
7	EGD	6/16/16	16	98	70	155/81	MAC	Yes
8	EUS	6/16/16	16	98	59	120/61	MAC	No
9	Colonoscopy	7/25/16	20	97	55	133/74	Conscious	Yes
10	Colonoscopy	7/25/16	16	99	64	117/67	Conscious	Yes
11	Colonoscopy	7/26/16	18	99	55	111/62	MAC	Yes
12	EGD/ Colonoscopy	7/26/16	16	98	77	177/107	MAC	No

RR: Respiratory rate; O₂ sat.: Oxygen saturation; BP: Blood pressure; EGD: Esophagogastroduodenoscopy; MAC: Monitored anesthesia care.

unintentional confounders that could influence the study results.

Although there were some limitations to our study, the development of this novel apparatus has the potential to improve upon the current standards of how we monitor vital signs, specifically respiration and ventilation. The ASA aims to ensure adequate oxygen concentration in inspired gas and blood as well as adequate ventilation during all procedures^[3,6,10]. The LRMD provides a minimally invasive, inexpensive, and portable means to measure respiration^[11]. This device has the potential to allow medical personnel to recognize properly any deterioration in respiratory status, noted either with a decline in tidal volume or change in respiratory rate, therefore providing an increased measure for patient safety and the need to intervene more promptly if need be^[3,11]. Not only is this device extremely accurate and reliable based on our data, but this easy to use respiratory monitor is independent of motion artifact and electrical interference making it user friendly^[11].

Further studies are needed to demonstrate the entire magnitude of LRMD capabilities, including the ability to monitor tidal volume. One of the most profound weaknesses of capnography is the inability to measure tidal volume. The LRMD is able to measure accurately tidal volume in addition to respiration rate, as has been reported previously^[11]. Unfortunately, our study was not designed to evaluate tidal volume monitoring; and hence, further studies are needed that would incorporate this while comparing with capnography.

In summary, our results demonstrate that the LRMD has the potential to be utilized as an alternative to capnography for measuring respiratory rate, specifically in the endoscopy setting, and may also be potentially useful in post-anesthesia care, critical care, ambulatory environments, and during in-hospital monitoring where similar sedation practices are applied^[3,11]. The LRMD and capnography were at least equivalent in measuring respiration rate and apnea events. The implication of our results will need further studies that will include a larger sample size, both pediatric and geriatric patients, and a multitude of settings, including in-patient as well as ambulatory settings, to determine its ability to be used in these areas of care.

Table 3 Comparison of measured respiratory rate between capnography and LRMD

Subject	Capnostream, mean $\pm$ SD	Linshom, mean $\pm$ SD	Capnostream–Linshom (95%CI)	Pearson's Correlation ¹ (95%CI)
1	14.9 $\pm$ 1.9	15.3 $\pm$ 2.1	-0.46 (-0.50, -0.42)	0.41 (0.40, 0.43)
4	15.6 $\pm$ 2.6	15.8 $\pm$ 3.3	-0.21 (-0.25, -0.17)	0.62 (0.61, 0.63)
5	25.1 $\pm$ 4.2	26.6 $\pm$ 2.9	-1.4 (-1.5, -1.3)	0.61 (0.60, 0.62)
6	7.9 $\pm$ 5.8	8.4 $\pm$ 5.2	-0.52 (-0.56, -0.48)	0.72 (0.72, 0.73)
7	23.1 $\pm$ 2.7	23.3 $\pm$ 4.4	-0.21 (-0.28, -0.14)	0.27 (0.25, 0.28)
9	13.2 $\pm$ 3.3	12.9 $\pm$ 3.4	0.37 (0.35, 0.39)	0.84 (0.84, 0.84)
10	15.7 $\pm$ 3.0	15.0 $\pm$ 3.6	0.76 (0.74, 0.78)	0.76 (0.75, 0.76)
11	15.8 $\pm$ 1.5	15.5 $\pm$ 1.7	0.26 (0.24, 0.27)	0.65 (0.64, 0.65)

¹We did not use a concordance correlation coefficient because of the known differences on how the devices measure respiratory rate. CI: Confidence interval.

Table 4 Comparison of apnea events reported by Capnostream and Linshom devices

Subject	Capnostream	Linshom	Capnostream–Linshom (95%CI)
1	0	0	--
4	0	1.4 (1.4, 1.4)	-1.4 (-1.4, -1.4)
5	0	0	--
6	30.3 (29.9, 30.8)	23.3 (23.0, 23.7)	7.0 (6.7, 7.3)
7	0	0.81 (0.81, 0.81)	-0.81 (-0.81, -0.81)
9	4.8 (4.6, 5.0)	5.1 (4.9, 5.3)	-0.30 (-0.40, -0.20)
10	0.83 (0.76, 0.91)	1.8 (1.7, 1.9)	-0.93 (-1.03, -0.84)
11	0	0	--

CI: Confidence interval.

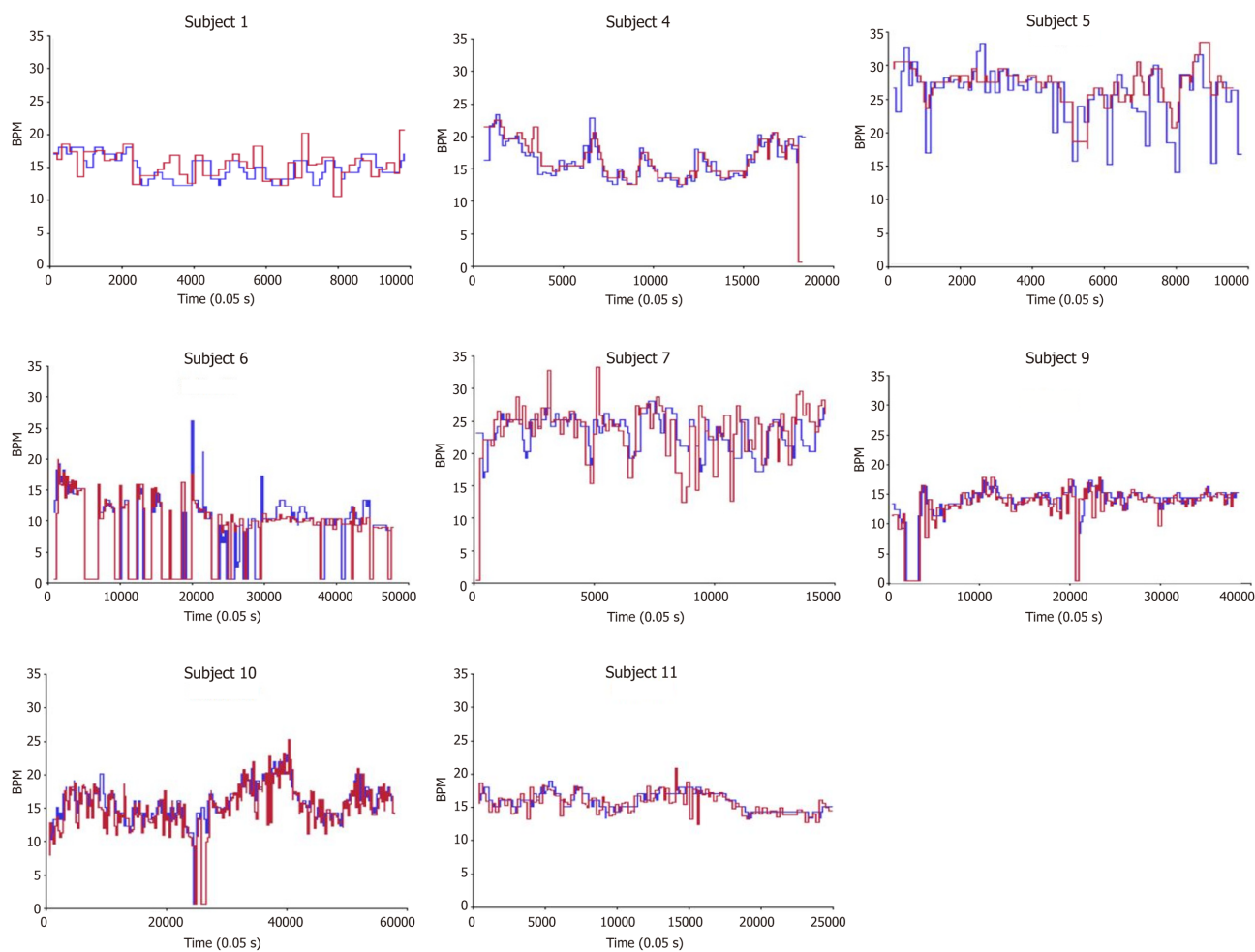


Figure 1 A comparison of the respiratory rates in breaths per minute (y-axis) plotted against time measured by capnography (red) and Linshom Respiratory Monitoring device (blue). BPM: Breaths per minute, signifying the respiratory rate.

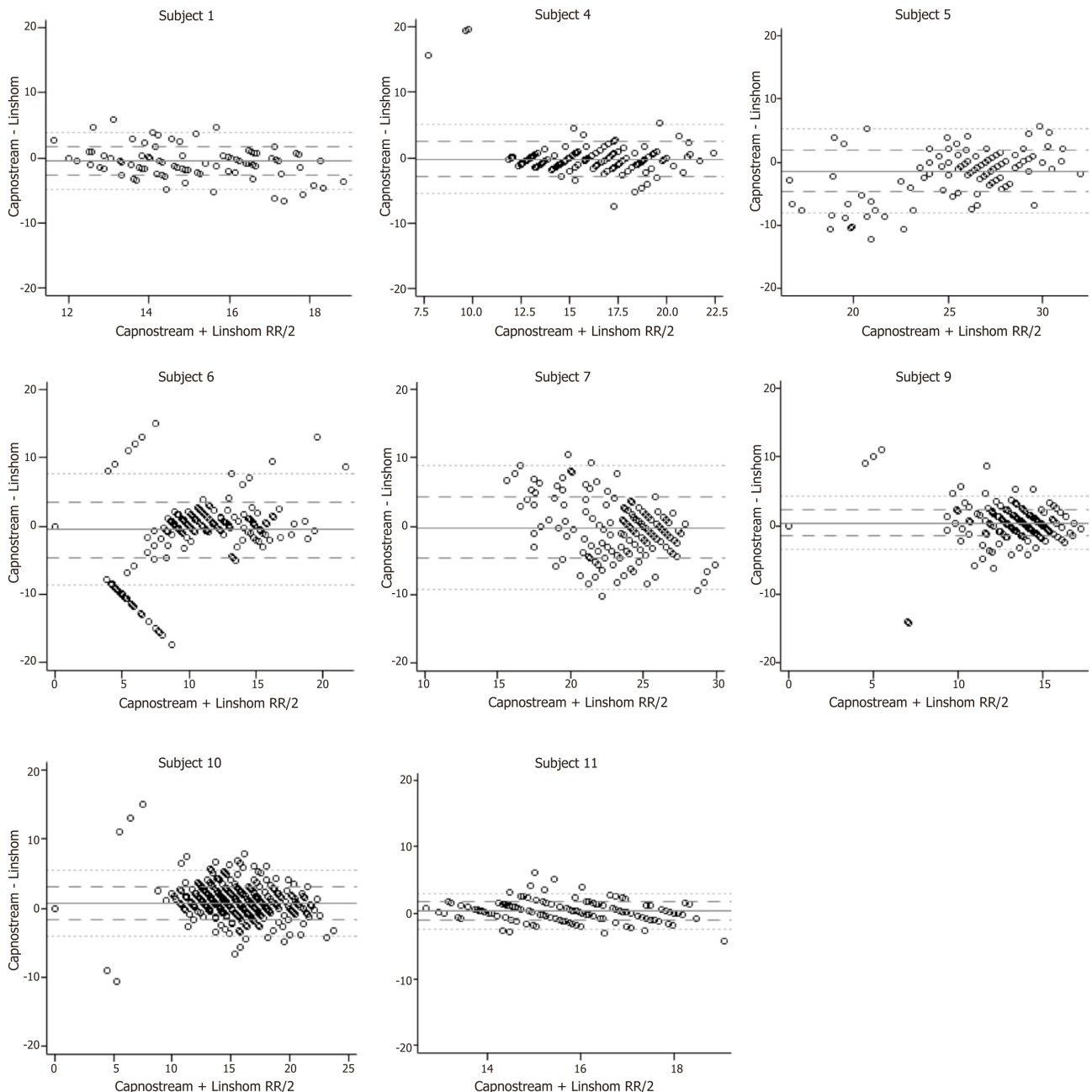


Figure 2 Bland-Altman Plots. The difference in results (y-axis) is plotted against the average magnitude of the result (x-axis). A difference of 0 indicates equivalent results. The dark horizontal reference line is the mean difference in results. The dashed and dotted lines are the first and second standard deviation of the difference. RR: Respiratory rate.

ARTICLE HIGHLIGHTS

Research background

Monitoring ventilation appropriately during endoscopic procedures is a crucial yet challenging aspect of patient management and safety. Capnography is currently the standard of care for monitoring respiratory rate during endoscopy, but it is expensive and cumbersome to transfer. Furthermore, secretions, moisture, and carbon dioxide gas influence its results. The Linshom Respiratory Monitoring Device (LRMD) is a novel, non-invasive, and portable method for physicians to monitor respiratory activity during endoscopic procedures.

Research motivation

There is very limited data on how this novel and convenient method of monitoring respiratory rate, the LRMD, compares to the standard of care, capnography.

Research objectives

The main objective was to compare the effectiveness of apnea detection of the LRMD and

capnography.

Research methods

A prospective study was performed. Twelve participants scheduled to undergo routine endoscopic procedures at Cleveland Clinic Main Campus were consecutively enrolled. All participants were individually fitted with a standard facemask fitted with both capnography and the LRMD. Data were collected from the medical record (gender, age, type of procedure, type of sedation, and dose of medication) and during the procedure (vital signs and body mass index). The data for the LRMD and capnography were collected simultaneously. A biomedical statistician conducted statistical analysis. The mean difference between the two devices was calculated. Pearson's correlation was calculated to describe the correlation between the respiratory rate as calculated by the capnography and the LRMD.

Research results

Twelve patients were enrolled. Four were excluded due to technical difficulties. Data were gathered for approximately 3000 breaths over a total period of 190 min. The LRMD respiratory rate highly correlated with the capnography respiratory rate with a *P* value of < 0.001. LRMD and capnography had similar rates of detecting apnea.

Research conclusions

Our prospective study found that the respiratory rate measured by the LRMD highly correlates with the respiratory rate measured by capnography. The LRMD and capnography were also similar in detecting increases in respiratory rates and apnea episodes. This study demonstrates that the LRMD can be used in place of conventional capnography for monitoring respiratory status. This gives physicians an alternative to capnography that is new, efficient, easier to use, and more affordable. This reliable device can be an effective and safe alternative to monitoring ventilation in various settings.

Research perspectives

Our results show that the LRMD may be used as an alternative to capnography for measuring respiratory rate in the endoscopy setting and potentially in the post-anesthesia care, critical care, and other ambulatory settings. Further studies are needed to demonstrate the entire magnitude of LRMD capabilities, including the ability to monitor tidal volume. These studies should include the use of the LRMD in other settings.

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Case Control Study

- 67 Risk factors for recurrence after bowel resection for Crohn's disease
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Case Control Study

Risk factors for recurrence after bowel resection for Crohn's disease

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Abstract

BACKGROUND

Complications of Crohn's disease such as intestinal obstruction, fistula or perforation often need surgical treatment. Nearly 70%-80% patients with Crohn's disease would receive surgical treatment during the lifetime. However, surgical treatment is incurable for Crohn's disease. The challenge of recurrence postoperatively troubles both doctors and patients. Over 50% patients would suffer recurrence postoperatively. Some certain risk factors are associated with recurrence of Crohn's disease.

AIM

To evaluate the risk factors for endoscopic recurrence and clinical recurrence after bowel resection in Crohn's disease.

METHODS

Patients diagnosed Crohn's disease and received intestinal resection between April 2007 and December 2013 were included in this study. Data on the general demographic information, preoperative clinical characteristics, surgical information, postoperative clinical characteristics were collected. Continuous data are expressed as median (inter quartile range), and categorical data as frequencies and percentages. Kaplan-Meier method was applied to estimate the impact of the clinical variables above on the cumulative rate of postoperative endoscopic recurrence and clinical recurrence, then log-rank test was applied to test the homogeneity of those clinical variables. Multivariate Cox proportional hazard regression analysis was performed to identify the risk factors of postoperative endoscopic recurrence and clinical recurrence.

and revised according to the STROBE Statement.

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RESULTS

A total of 64 patients were included in this study. The median follow-up time for the patients was 17 (9.25-25.75) mo. In this period, 41 patients (64.1%) had endoscopic recurrence or clinical recurrence. Endoscopic recurrence occurred in 34 (59.6%) patients while clinical recurrence occurred in 28 (43.8%) patients, with the interval between the operation and recurrence of 13.0 (8.0-24.5) months and 17.0 (8.0-27.8) mo, respectively. In univariate analysis, diagnosis at younger age ($P < 0.001$), disease behavior of penetrating ($P = 0.044$) and preoperative use of anti-tumor necrosis factor (TNF) ($P = 0.020$) were significantly correlated with endoscopic recurrence, while complication with perianal lesions ($P = 0.032$) and preoperative use of immunomodulatory ($P = 0.031$) were significantly correlated with clinical recurrence. As to multivariate analysis, diagnostic age ($P = 0.004$), disease behavior ($P = 0.041$) and preoperative use of anti-TNF ($P = 0.010$) were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions ($P = 0.023$) was an independent prognostic factor for clinical recurrence.

CONCLUSION

Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were independent risk factors for postoperative recurrence in Crohn's disease.

Key words: Risk factor; Endoscopic recurrence; Clinical recurrence; Bowel resection; Crohn's disease

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Core tip: Our study aimed at evaluating the risk factors for recurrence after bowel resection in Crohn's disease. This study included 64 patients diagnosed Crohn's disease and received intestinal resection. The result showed that diagnosis at younger age, disease behavior of penetrating and preoperative use of anti-tumor necrosis factor were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions was an independent prognostic factor for clinical recurrence.

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INTRODUCTION

Crohn's disease, one kind of inflammatory bowel disease, is a chronic inflammatory disorder in the digestive tract, with an incidence and prevalence of 6-15 and 50-200 per 100000 persons, respectively^[1]. Although there has been significant improvement in the diagnosis and conservative medical treatment, the risk of surgical resection for Crohn's disease could be as high as 70% to 80% during the lifetime^[2,3]. Unlike the curability of operation for ulcerative colitis, surgical treatment can only help to resolve the complications of Crohn's disease, such as intestinal obstruction, fistula or perforation. In other words, surgical treatment is incurable for Crohn's disease. The challenge of recurrence postoperatively troubles both doctors and patients.

Buisson *et al*^[4] reviewed the rates and risk factors for clinical and endoscopic recurrence in population-based studies, and found that approximately half of patients experienced clinical recurrence at 10 years. And Watanabe *et al*^[5] found that overall 5-year and 10-year cumulative reoperation rates were 31.4% and 61.2% in Japan, respectively. Many factors were found related with postoperative recurrence, such as disease behavior, use of medicine and technique of surgery^[6-8]. Most these studies were about population from Caucasians and Southeast Asia such as Japan and South Korea. Our study aims to evaluate the risk factors for recurrence after bowel resection in patients with Crohn's disease, from a tertiary care center in China.

MATERIALS AND METHODS

Patients selection

Patients diagnosed Crohn's disease and received intestinal resection between April 2007 and December 2013 at the Sixth Affiliated Hospital, Sun Yat-Sen University were enrolled in this study. Data on the general demographic information, preoperative clinical characteristics, surgical information, postoperative clinical characteristics were obtained by careful chart review, including sex, diagnostic age, disease-behavior, anatomical site of disease, perianal lesions, preoperative body mass index, preoperative laboratory examinations, preoperative medication [corticosteroid, immunosuppressant, anti-tumor necrosis factor (TNF)], preoperative duration of disease, indication of operation, postoperative laboratory examinations, postoperative colonoscopy, time of endoscopic recurrence and clinical recurrence. Endoscopic recurrence was defined as the presence of aphthous ulcer, deep and large ulcer, nodular hyperplasia and stenosis at the anastomotic site and in the intestinal wall of the anastomotic site confirmed by postoperative colonoscopy. Clinical recurrence was defined as symptom recurrence including obvious abdominal pain, diarrhea, abdominal mass and extraintestinal manifestations, accompanied with imaging and endoscopic lesions; or complications such as abdominal abscess, fistula formation and intestinal obstruction which may require a second operation.

Statistical analysis

Data analyses were performed with the Statistical Package for Social Science software, version 21.0 (SPSS Inc., Chicago, IL, United States). Continuous data are expressed as median (inter quartile range), and categorical data as frequencies and percentages. Kaplan-Meier method was applied to estimate the impact of the clinical variables above on the cumulative rate of postoperative endoscopic recurrence and clinical recurrence, then log-rank test was applied to test the homogeneity of those clinical variables. Multivariate Cox proportional hazard regression analysis was performed to identify the risk factors of postoperative endoscopic recurrence and clinical recurrence. The differences were considered statistically significant when the two-sided *P* values were < 0.05.

RESULTS

Patient characteristics and surgical variables

A total of 64 patients were included in our study. The average age at diagnosis was 29.23 years old, while the gender ratio was 2.76:1 (male:female 47/17). The distribution of diagnostic age was single-peak curve, with the peak age of 22-36 years old. As to the Montreal classification, 49 (76.6%) patients were A2 subtype; L3 subtype account for 73.4% (47 patients); and most patients manifested B2 subtype (25/39.1%) or B3 subtype (37/57.8%) of disease behavior. 22(34.4%) patients complicated with perianal lesions. Preoperative use of medication was found in 29 patients (45.3%), including 23 cases of steroid, 24 cases of immunomodulator and 4 cases of anti-TNF. The clinicopathological characteristics of the patients are summarized in [Table 1](#).

As to the indications of operation, most patients had to receive operation because of intestinal obstruction (27 cases, 42.3%) and intestinal fistula (34cases, 53.1%). 47 patients who exhibited disease in the ileocolon (L3) mentioned above received ileocolonic resection and 15 patients received intestinal resection. Detail about the surgery was showed in [Table 2](#).

Recurrence

The median follow-up time for the patients was 17 (9.25-25.75) mo. In this period, 41 patients (64.1%) had endoscopic recurrence or clinical recurrence. Endoscopic recurrence occurred in 34 (59.6%) patients while clinical recurrence occurred in 28 (43.8%) patients, with the interval between the operation and recurrence of 13.0 (8.0-24.5) mo and 17.0 (8.0-27.8) mo, respectively. 6 (9.4%) patients needed reoperation because of recurrence. The cumulative rate of endoscopic recurrence was 37.0%, 60.0% and 90.0% at 12, 24 and 36 mo, respectively, after intestinal resection. And the cumulative rate of clinical recurrence was 18.0%, 44.0% and 67.0% at 12, 24 and 36 mo, respectively. The cumulative incidence curve was showed in [Figure 1](#).

The endoscopic recurrence rate for patients with age ≤ 16, between 17-40 and > 40 was 100.0%, 63.0% and 12.5%, respectively; and diagnosis at younger age was significantly correlated with endoscopic recurrence (*P* < 0.001). The endoscopic recurrence rate for patients with B1, B2 and B3 subtype of disease behavior was 0.0%, 50.9%, 73.2%, respectively; and disease behavior of penetrating was significantly

Table 1 Demographic and clinical characteristics of the patients, *n* (%)

Variables	Number of patients
Gender	
Male	47 (73.4)
Female	17 (26.6)
Age at diagnosis	27.5 (8, 78)
Disease period before operation	9.5 (2.0, 48.0)
Montreal classification	
Age, yr	
A1 (≤ 16)	6 (9.4)
A2 (17-40)	49 (76.6)
A3 (> 40)	9 (14.1)
Behavior	
B1 (Inflammatory)	2 (3.1)
B2 (Stricturing)	25 (39.1)
B3 (Penetrating)	37 (57.8)
Location	
L1 (Terminal ileum)	9 (14.1)
L2 (Colon)	1 (1.6)
L3 (Ileocolon)	47 (73.4)
L4 (Upper disease)	7 (10.9)
Perianal disease	22 (34.4)
Preoperative use of medication	29 (45.3)
Steroid	23 (35.9)
Immunomodulator	24 (37.5)
Anti-TNF	4 (6.2)

TNF: Tumor necrosis factor.

correlated with endoscopic recurrence ($P = 0.044$). Moreover, preoperative use of anti-TNF ($P = 0.020$) were significantly correlated with endoscopic recurrence, while complication with perianal lesions ($P = 0.032$) and preoperative use of immunomodulatory ($P = 0.031$) were significantly correlated with clinical recurrence. As to multivariate analysis, diagnostic age [Hazard ratio (HR) 0.323, 95% confidence interval (CI): 0.148-0.703, $P = 0.004$], disease behavior (HR 1.969, 95%CI: 1.028-3.775, $P = 0.041$) and preoperative use of anti-TNF (HR 4.414, 95%CI: 1.424-13.682, $P = 0.010$) were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions (HR 2.956, 95%CI: 1.163-7.513, $P = 0.023$) was an independent prognostic factor for clinical recurrence. Results of univariate and multivariate analyses were showed in [Table 3](#).

DISCUSSION

Crohn's disease is characterized by relapsing episodes of active inflammation alternating with remission of disease^[9]. Recurrence is a common but intractable problem for the patients with Crohn's disease even if they received surgical therapy. It is well known that anastomotic recurrence occurs endoscopically as early as several months after bowel resection and anastomosis, followed by symptomatic recurrence^[10]. The rate of postoperative recurrence varied in different studies. Endoscopic studies have shown that up to 70% patients developed endoscopic recurrence within 1 year and nearly all the patients would have new lesions in the neoterminal ileum at 3 years after resection^[11,12]. Rutgeerts reported that about 20%-30% patients would have a clinical recurrence within the first year after curative resection of the ileum or ileocolon with ileocolonic anastomosis, with a 10% increase after each subsequent year^[13]. In our study, the cumulative rate of endoscopic recurrence was 37.0%, 60.0% and 90.0% at 12, 24 and 36 mo after intestinal resection and the cumulative rate of clinical recurrence was 18.0%, 44.0% and 67.0% respectively. The recurrence rate in our study was similar to the previous reported

Table 2 Surgical details, *n* (%)

Variables	Number of patients
Indication of surgery	
Intestinal obstruction	27 (42.3)
Intestinal fistula	34 (53.1)
Abscess	2 (3.2)
Bleeding	1 (1.6)
Site of resection	
Ileocolon	47 (73.4)
Intestine	15 (23.4)
Colon	1 (1.6)

results.

Many prognostic factors have been investigated to predict postoperative recurrence. The presence of perianal disease has been proved one of the predictors of postoperative recurrence by many previous studies. Bernell *et al*^[14] found perianal fistulas increased the relative risk (RR) of recurrence after resection in Crohn's disease (RR 1.4, 95%CI, 1.2-1.7). Beaugerie *et al*^[15] found the presence of perianal disease significantly associated with subsequent 5-year disease disabling course (overall risk 1.8, 95%CI, 1.2-2.8), which meant more patients with perianal disease required early intensive therapy and suffered from disabling chronic symptoms. Another study from Korea showed patients with perianal Crohn's disease had a higher risk of reoperation^[16]. In our study, we also found preoperative complication with perianal lesions was an independent prognostic factor for clinical recurrence.

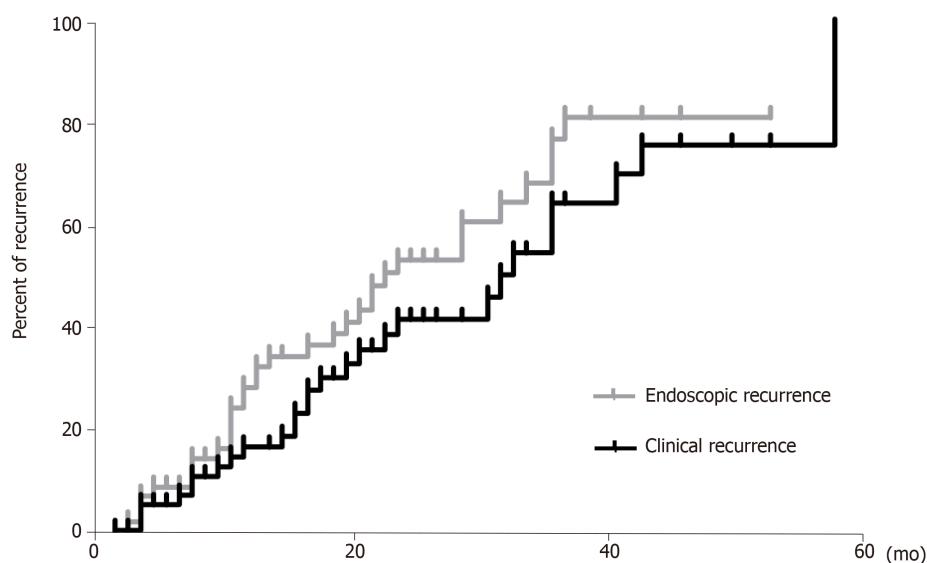
Medication is also an important predictor for recurrence of Crohn's disease. Many studies focused on postoperative medication. Yoshida *et al*^[17] conducted a 3-year prospective randomized open trial about the effect of postoperative scheduled infliximab monotherapy on recurrence of Crohn's disease, and the result showed that an early intervention with infliximab monotherapy should prevent clinical, serological, and endoscopic Crohn's disease recurrence following ileocolic resection. Yang *et al*^[8] found postoperative use of anti-TNF agents could reduce the risk of reoperation. Immunomodulators such as 6-MP or azathioprine are also widely used postoperatively and were found independently associated with reduction in surgical rate^[18,19]. In our study, we focused on the preoperative medication and found preoperative use of anti-TNF was significantly associated with endoscopic recurrence and preoperative use of immunomodulatory seemed correlated with clinical recurrence. The opposite effects of postoperative and preoperative medication on postoperative recurrence of Crohn's disease might be due to different severity of disease as in our hospital, preoperative medication especially anti-TNF tended to be used in patients with more aggravated disease.

Other risk factors for postoperative recurrence which have been found in published studies included younger diagnostic age, perforating type of disease, sex, smoking and so on^[7,20]. In our study, we also found diagnosis at younger age and disease behavior of penetrating were associated with an increased risk for endoscopic recurrence.

In conclusion, this retrospective study of Crohn's disease in China revealed that diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were independent risk factors for postoperative recurrence.

Table 3 Univariate and multivariate analysis of factors associated with endoscopic recurrence and clinical recurrence

Variable	Endoscopic recurrence		Clinical recurrence	
	Univariate	Multivariate	Univariate	Multivariate
Gender	0.683		0.939	
Diagnostic age	0.000 ^b	0.004 ^b	0.422	
Disease behavior	0.044 ^a	0.041 ^a	0.686	
Disease location	0.146		0.315	
Perianal disease	0.357		0.032 ^a	0.023 ^a
Preoperative use of steroid	0.739		0.700	
Preoperative use of immunomodulator	0.085		0.031 ^a	0.092
Preoperative use of anti-TNF	0.020 ^a	0.010 ^a	0.438	
Preoperative body mass index level	0.230		0.705	
Preoperative leukocytosis	0.760		0.627	
Preoperative C-reactive protein level	0.290		0.917	
Preoperative erythrocyte sedimentation rate level	0.078		0.247	
Preoperative albumin level	0.368		0.271	

^a $P < 0.05$,^b $P < 0.01$. TNF: Tumor necrosis factor.**Figure 1** Kaplan-Meier curves for endoscopic recurrence and clinical recurrence.

ARTICLE HIGHLIGHTS

Research background

Nearly 70%-80% patients with Crohn's disease would receive surgical treatment during the lifetime. However, surgical treatment is incurable for Crohn's disease. The challenge of recurrence postoperatively troubles both doctors and patients. Over 50% patients would suffer recurrence postoperatively.

Research motivation

A great amount of patients with Crohn's disease would receive surgical treatment but over one half patients would suffer recurrence postoperatively. It is important to recognize the risk factor for postoperative recurrence. Further clinical research base on certain risk factor would favor the prognosis.

Research objectives

This study aims to evaluate the risk factor of endoscopic recurrence and clinical recurrence after bowel resection for Crohn's disease. Further relative clinical research could focus on the risk factor found in this study and help to improve the prognosis for certain patients.

Research methods

Patients diagnosed Crohn's disease and received intestinal resection were included in this study. Data on the general demographic information, preoperative clinical characteristics, surgical information, postoperative clinical characteristics were collected. Continuous data are expressed as median (inter quartile range), and categorical data as frequencies and percentages. Kaplan-Meier method was applied to estimate the impact of the clinical variables above on the cumulative rate of postoperative endoscopic recurrence and clinical recurrence, then log-rank test was applied to test the homogeneity of those clinical variables. Multivariate Cox proportional hazard regression analysis was performed to identify the risk factors of postoperative endoscopic recurrence and clinical recurrence.

Research results

Diagnosis at younger age, disease behavior of penetrating and preoperative use of anti-tumor necrosis factor (TNF) were significantly correlated with endoscopic recurrence, while complication with perianal lesions and preoperative use of immunomodulatory were significantly correlated with clinical recurrence. As to multivariate analysis, diagnostic age, disease behavior and preoperative use of anti-TNF were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions was an independent prognostic factor for clinical recurrence. The result of this study discovered some risk factors for recurrence in patients with Crohn's disease after bowel resection. Prospective clinical study with more patients remains to be performed to confirm the result.

Research conclusions

Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were independent risk factors for postoperative recurrence in Crohn's disease. Patients with younger diagnostic age, disease behavior of penetrating and preoperative use of anti-TNF tended to have endoscopic recurrence, while patients with perianal lesions tended to suffer from clinical recurrence. Some certain factors are associated with postoperative recurrence of Crohn's disease. In this study, diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were proved as independent prognostic factors. The recurrence rate of Crohn's disease after bowel resection is high and some certain clinical factors have been proved associated with postoperative recurrence. In this study, we found diagnostic age, disease behavior and preoperative use of anti-TNF were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions was an independent prognostic factor for clinical recurrence. Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were related with postoperative recurrence in Crohn's disease. This study adopts the classical methods. Endoscopic recurrence occurred in 34 (59.6%) patients while clinical recurrence occurred in 28 (43.8%) patients, with the interval between the operation and recurrence of 13.0 (8.0-24.5) mo and 17.0 (8.0-27.8) mo, respectively. Diagnostic age, disease behavior and preoperative use of anti-TNF were independent prognostic factors for endoscopic recurrence, while complication with perianal lesions was an independent prognostic factor for clinical recurrence. Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were related with postoperative recurrence in Crohn's disease. Patients with such risk factors should be strictly followed up and receive appropriate medical therapy if necessary.

Research perspectives

Diagnostic age, disease behavior, preoperative use of anti-TNF and complication with perianal lesions were independent risk factors for postoperative recurrence in Crohn's disease. Prospective clinical study with more patients remains to be performed to confirm the results. Prospective clinical trial with multi centers and more patients would be the best method for future research.

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