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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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MINIREVIEWS

The role of computed tomography for the prediction of esophageal variceal bleeding: Current status and future perspectives

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Abstract

Esophageal variceal bleeding (EVB) is one of the most common and severe complications related to portal hypertension (PH). Despite marked advances in its management during the last three decades, EVB is still associated with significant morbidity and mortality. The risk of first EVB is related to the severity of both PH and liver disease, and to the size and endoscopic appearance of esophageal varices. Indeed, hepatic venous pressure gradient (HVPG) and esophago-gastroduodenoscopy (EGD) are currently recognized as the "gold standard" and the diagnostic reference standard for the prediction of EVB, respectively. However, HVPG is an invasive, expensive, and technically complex procedure, not widely available in clinical practice, whereas EGD is mainly limited by its invasive nature. In this scenario, computed tomography (CT) has been recently proposed as a promising modality for the non-invasive prediction of EVB. Although CT is only a diagnostic modality, thus being not capable of supplanting EGD or HVPG in providing therapeutic and physiological data, it could potentially assist liver disease scores, HVPG, and EGD in a more effective prediction of EVB. However, to date, evidence concerning the role of CT in this setting is still lacking. Our review aimed to summarize and discuss the current evidence concerning the role of CT in predicting the risk of EVB.

Key Words: Esophageal variceal bleeding; Variceal upper gastrointestinal bleeding; Portal hypertension; Computed tomography; Computed tomography angiography

Core Tip: Esophagogastroduodenoscopy is currently considered the diagnostic reference standard for the prediction of esophageal variceal bleeding (EVB) among cirrhotic patients. Recently, computed tomography (CT) has emerged as a promising tool for the non-invasive prediction of EVB. Nevertheless, to date, evidence concerning the role of CT in this setting is still lacking. Thus, our study aimed to review the current evidence regarding the role of CT in the prediction of EVB.

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INTRODUCTION

Variceal upper gastrointestinal bleeding (VUGIB) is one of the most severe and common complications related to portal hypertension (PH) occurring in patients affected by liver cirrhosis. The annual incidence of esophageal varices (EV) among cirrhotic patients is 7%-8%, with a five-year cumulative incidence rate reaching approximately 20%. Furthermore, once EV develop, their risk of first bleeding is 5%-15% per year, being related to the severity of both PH and liver disease, and to the size and endoscopic appearance of EV[1-3].

Despite marked advances in its management during the last three decades, VUGIB is still a potentially life-threating event with a high morbidity and a 6-week mortality as high as 10%-20%[4,5]. Moreover, esophageal variceal bleeding (EVB) is a negative prognostic factor. Indeed, the mortality of patients sustaining a EVB is as high as 35% at 3 mo and 70% at 2 years[6,7]. Thus, it is of paramount importance to carefully identify cirrhotic patients with a high-risk of EVB requiring prompt primary prophylaxis, in order to reduce first EVB incidence and improve the overall survival[8].

Nowadays, screening for EV by means of esophagogastroduodenoscopy (EGD) is suggested in decompensated cirrhotic patients, whereas primary prophylaxis is recommended in patients with cirrhosis and medium-large size varices and in those with small size varices as long as they are classified as Child-Pugh C or have variceal red signs[9-13]. Currently recommended strategies for the EVB primary prophylaxis include the use of traditional non-selective beta-blockers (NSBB), carvedilol or endoscopic variceal ligation (EVL)[9-13]. However, the superiority of one prophylactic alternative over the others is controversial. Indeed, while EVL might be superior to pharmacological therapy regarding the prevention of the first bleeding episode, either traditional NSBB or carvedilol seem to play a more crucial role in the mortality reduction. Furthermore, although not routinely recommended as a first-line option, combined pharmacological and endoscopic primary prophylaxis has been reported to be capable to achieve a greater reduction in the risk of the first EVB episode[14]. EGD is currently regarded as the diagnostic reference standard for detecting the presence of EV and predicting their bleeding risk[9-13]. The North Italian Endoscopy Club index and its variations, composed of scores for Child-Pugh class, EV size, and red wale markings, are validated as significant predictors of first EVB[3,15,16].

However, EGD is invasive and capable to identify EV within only the superficial portions of intrinsic veins, ignoring the remaining esophageal venous plexuses[17]. Furthermore, only about a third of EVB patients have risk factors predictive of hemorrhage, such as large EV size, endoscopic red color signs, and severe liver dysfunction[3]. Finally, of note, inter-observer EV size agreement has been reported to be higher by the use of CT as compared to endoscopy[18,19].

In addition to EGD, hepatic venous pressure gradient (HVPG) is recognized as the "gold standard" for the measurement of portal pressure, the prediction of the occurrence of EVB and other PH-related complications, and for the assessment of the response to pharmacological treatment[9,10,20]. Clinically significant PH, which is an at-risk condition for decompensation and EV development, is defined by HVPG ≥ 10 mmHg, whereas a gradient > 12 mmHg defines severe PH, which is associated with a higher risk of EVB and mortality[11,21]. Indeed, an HVPG threshold value > 12 mmHg was shown to be necessary for the occurrence of EVB[22,23]. Furthermore, a decrease of baseline HVPG to ≤ 12 mmHg or by ≥ 20% by beta-blockers has been shown to be associated with a significant reduction in the risk of EVB and mortality[24].

However, HVPG is an invasive and expensive procedure, requiring high expertise. Thus, it is not readily and widely available in clinical practice, and its cost-effectiveness has been also questioned[25]. Moreover, the clinical utility of repeated monitoring HVPG after pharmacological therapy has not been established[26].

In this scenario, a promising role of computed tomography (CT) in the non-invasive prediction of EVB has been suggested. CT is commonly performed in cirrhotic patients, as in the case of hepatocellular carcinoma screening/follow-up or first decompensation episode investigation. To date, CT angiography has shown good accuracy in the detection and grading of EV[27]. However, only a few studies have explored the utility of information provided by CT imaging to predict EVB, and evidence is still limited. Although CT is only a diagnostic modality, thus being not capable of supplanting EGD or HVPG in providing therapeutic and physiological data, it could potentially assist liver disease scores, HVPG, and EGD in a more effective prediction of EVB.

The aim of our study was to extensively review the current evidence with regard to the role of CT in the prediction of EVB among cirrhotic patients.

LITERATURE SEARCH

We performed a comprehensive literature search of the PubMed (MEDLINE) and EMBASE electronic databases up to June 2023, in order to identify relevant studies evaluating the role of CT in the prediction of EVB among cirrhotic patients. Studies evaluating the VE presence only or comparing CT findings with endoscopic grade of EV were not included in our review. The medical search strategy used the terms "computed tomography", "CT", "computed tomography angiography", "CTA", "multidetector computed tomography", "MDCT", "variceal upper gastrointestinal bleeding", "variceal upper gastrointestinal haemorrhage", "esophageal variceal haemorrhage" and "esophageal variceal bleeding" in various combinations, using the Boolean operators AND, OR, and NOT. Search strategy was limited to non-animal studies conducted in adult population, and to articles written in English. Meeting abstracts, case reports/series (< 10 cases), review articles, position papers, editorials, commentaries, and book chapters were excluded from our study.

The reference lists of pertinent identified studies and related review articles were carefully hand-searched in order to retrieve any additional eligible studies.

ROLE OF CT IN THE PREDICTION OF EVB

Evidence

A total of 9 studies were included in our final analysis[28-36]. All of them were retrospective, single-center studies[28-36]. All but two European and one American studies, were from Asian countries. Intravenous contrast-enhanced CT, with at least one portal venous phase, was performed in all of the included studies. With the exception of one study[28], no contrast medium was orally administered in any of the included studies. Multidetector CT (MDCT) technology was adopted in most of the included studies[28,30-32,35,36]. Main characteristics of the included studies are summarized in Tables 1-3.

In 2014, Somsouk *et al*[28] first retrospectively evaluated the role of MDCT angiography in predicting the occurrence of EVB among cirrhotic patients. A large maximal EV diameter was shown to be significantly associated with EVB. Furthermore, an MDCT threshold of < 3 mm and ≥ 5 mm appeared to discriminate between low- and high-risk individuals, respectively. Other CT findings, including the size of the paraumbilical vein (PUV), the coronary vein, and the presence of ascites reached statistical significance, but less powerfully discriminated for EVB. Conversely, neither portal vein diameter nor spleen size showed significant association with EVB. Of note, the model for end-stage liver disease (MELD) score measured at the time of the CT execution was not significantly different between the bleeding and the control groups. However, among the included patients who experienced EVL, the average time between CT and EVB was 7 mo. Moreover, another limitation of the study is the inclusion of patients undergoing EVB pharmacological prophylaxis in both the bleeding and the control groups[28].

Later on, Ge *et al*[29] showed not only EV diameter but also diameter of inferior mesenteric vein (IMV), posterior gastric vein, and short gastric vein were significantly correlated with EVB among HBV cirrhotic patients. For IMV and short gastric vein, the smaller the diameters, the higher hemorrhage rates were, whereas for EV and posterior gastric vein, the EVB rate was proportional to the diameter. Of note, the authors did not measure the EV diameter only, but a previously reported radiological score was adopted, providing the following 3 grades: (1) One varix less than 5 mm in diameter detected on the inner surface of the esophagus; (2) several varices less than 5 mm in diameter detected on the inner surface of the esophagus; and (3) one varix 5 mm or greater in diameter, or varices occupying more than half the circumference of the esophagus[37]. Conversely, no significant correlation was found with portal vein, superior mesenteric vein, splenic vein, PUV, coronary vein, spleno-renal shunt, short gastric vein, and azygos vein. Notably, a significant difference in term of Child-Pugh was observed between the bleeding and the control group[29].

In 2017, Calame *et al*[30] retrospectively evaluated the association between the presence/size of PUV on CT and a first EVB in 172 cirrhotic patients. The authors showed that a small/absent PUV was significantly associated with a first EVB. Moreover, the authors observed no case of first EVB in any patients with a PUV > 10 mm, assuming that a large patent PUV may act in a transjugular intrahepatic portosystemic shunt-like manner, lowering portal venous pressure. The presence of an enlarged left gastric vein (LGV), *i.e.* when tortuous and > 3 mm, was also significantly more frequent in patients with a first EVB. Conversely, LGV diameter and presence or diameter of spleno-renal shunt were not associated with first EVB. The study findings were in contrast with those from Somsouk *et al*[28], who reported a significant positive association of PUV diameter with EVB, as well with those from other groups who did not report any significant association between PUV and EVB[29,32]. To be noted, the most common etiology of cirrhosis in both the bleeding and the control groups was alcoholic, in which the PUV prevalence is probably higher as compared with other cirrhosis etiology, likely affecting the study outcomes. Moreover, Child-Pugh score was significantly different between the two groups[30].

Later on, a well-designed retrospective study from South Korea evaluated the utility of CT-measured liver volume for the prediction of EVB during primary prophylaxis with propranolol. Of interest, liver volume index, an estimated-to-actual liver volume index corrected for patients' body build, was shown to be significantly higher in the prophylaxis failure group, indicating that corrected liver volume was significantly smaller in patients without prophylaxis failure. Conversely, hepatic and spleen volumes were not significantly different between the case and control groups. Notably, neither Child-Pugh nor MELD scores were predictive of prophylaxis failure[31].

Subsequently, a single center retrospective study from Iran investigated the role of abdominal MDCT angiography in the prediction of EVB, comprehensively evaluating the value of different collateral veins. Intriguingly, the presence of EV on MDCT together with the presence and/or the size of various collaterals, including coronary, short gastric, paraeso-

Table 1 Characteristics of the included studies

Ref.	Study design	Country	Study type	Enrollment period
Somsouk *et al*[28], 2014	R	United States	Unicentric	2002-2007
Ge *et al*[29], 2015	R	China	Unicentric	2008-2014
Calame *et al*[30], 2017	R	France	Unicentric	2010-2012
Kim *et al*[31], 2019	R	South Korea	Unicentric	2003-2015
Salahshour *et al*[32], 2020	R	Iran	Unicentric	2013-2019
Xie *et al*[33], 2020	R	China	Unicentric	2015-2018
Peisen *et al*[34], 2021	R	Germany	Unicentric	2010-2019
Wan *et al*[35], 2021	R	China	Unicentric	2014-2019
Wan *et al*[36], 2022	R	China	Unicentric	2017-2020

Table 2 Demographics and clinicopathological features of the included studies

Ref.	Patients, *n*	Mean age (range), years	Sex male, %	Cirrhosis etiology, %	Child-Pugh class, %	MELD score
Somsouk *et al*[28], 2014	80 (cases: 27; controls: 53)	Cases: 58 (-); Controls: 55 (-)	Cases: 96; Controls: 96	HCV: 71 (cases); 77 (controls); HBV: 0 (cases); 9 (controls); Alcoholic: 83 (cases); 64 (controls)	-	-[1]
Ge *et al*[29], 2015	98 (cases: 57; controls: 41)	Cases: 49.9 (-); Controls: 53.9 (-)	56	HBV: 100	A: 15 (cases); 28 (controls); B: 21 (cases); 12 (controls); C: 5 (cases); 4 (controls)	-
Calame *et al*[30], 2017	172 (cases: 43; controls: 129)	Cases: 59.6 (12-85); Controls: 60.2 (33-86)	Cases: 77; Controls: 62	Alcoholic: 77 (cases); 70 (controls); NASH: 9 (cases); 13(controls) HCV: 9 (cases); 9 (controls); HBV: 7 (cases); 4 (controls); Other: 5 (cases); 13 (controls)	A: 16 (cases); 43 (controls); B: 46 (cases); 27 (controls); C: 37 (cases); 29 (controls)	-
Kim *et al*[31], 2019	309 (cases: 37; controls: 272)	Cases: 58 (-); Controls: 58 (-)	Cases: 81; Controls: 72	HBV: 46 (cases); 61 (controls); HCV: 16 (cases); 7 (controls); Non-B/C: 38 (cases); 32 (controls)	A: 57 (cases); 48 (controls); B: 40 (cases); 44 (controls); C: 3 (cases); 8 (controls)	-
Salahshour *et al*[32], 2020	124 (cases: 50; controls: 74)	Cases: 49.2 (-); Controls: 52.14 (-)	Cases: 46; Controls: 54	HBV: 24.2; HCV: 5.6; BCS: 8.1; Alcoholic: 9.7; NASH: 14.5; ASH: 4.0; PSC: 9.7; Wilson disease: 2.4; PBC: 1.6; Cryptogenic: 10.5; Other: 9.7	-[2]	-[2]
Xie *et al*[33], 2020	264 (cases: 132; controls: 132)	Cases: 54 (30-76); Controls: 54 (25-79)	Cases: 85%; Controls: 88%	HBV: 87 (cases); 95 (controls); Alcoholic: 11 (cases); 1 (controls); HCV: 2 (cases); 4 (controls)	-	-
Peisen *et al*[34], 2021	66 (cases: 8; controls: 58)	68	89	HCV: 32; Alcoholic: 48; Cryptogenic: 14; HBV: 6	A: 53%; B: 38%; C: 9%	-
Wan *et al*[35], 2021	217 (cases: 17; controls: 27)	Cases: 52.8; Controls: 52.4	Cases: 53; Controls: 56	Post-hepatic: 53 (cases); 41 (controls); Alcoholic: 18 (cases); 15 (controls); PBC: 29 (cases); 19 (controls); Mixed: 0 (cases); 7 (controls) Other: 0 (cases); 19 (controls)	A: 47 (cases); 33 (controls); B: 35 (cases); 33 (controls); C: 18 (cases); 33 (controls)	-
Wan *et al*[36], 2022	136 (cases: 89; controls: 47)	-	63	Post-hepatic: 60; Alcoholic: 25; PBC: 9; Mixed: 4; AIH: 1	A: 28; B: 46; C: 26	-

[1]No significant difference between case and control groups.
[2]Significant difference between case and control groups.
MELD: Model for end-stage liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NASH: Nonalcoholic steatohepatitis; BCS: Budd-Chiari syndrome; AIH: Autoimmune hepatitis; PSC: Primary sclerosing cholangitis; PBC: Primary biliary cirrhosis.

phageal, and paraesophageal draining, showed a significant relationship with EVB. The presence of EV on MDCT was defined as enhancing dots and linear structures within esophageal wall or protruded into the esophageal lumen[38]. In addition, size of main coronary vein, gastric fundus varices and IMV, and ascites also had significant correlation with EVB. Conversely, omental, perisplenic and spleno-renal collaterals, spleen size, PUV size/presence, size of portal vein, inferior vena cava, superior mesenteric vein and left renal vein did not show any significant association with EVB. However, of note, all of the above-mentioned CT features were also associated with EV presence, thus limiting their

Table 3 Summary of the included studies reporting on the role of computed tomography in the prediction of esophageal variceal bleeding

Ref.	Inclusion criteria	Exclusion criteria	Study aim	Results
Somsouk *et al*[28], 2014	Cirrhotic patients with EVB who underwent CT prior to EVB (case group); cirrhotic patients without EVB who underwent CT and EGD within 45 d (control group)	Previous EVB, EVL, or OLT	To identify CT features associated with EVB	Features associated with EVB: EV diameter: 5.8 mm case group *vs.* 2.7 mm control group (P < 0.001); Maximal EV diameter ≥ 5 mm: 63% case group *vs.* 7.5% control group (P < 0.001); Maximal EV diameter < 3 mm: 7.4% case group *vs.* 54.7% control group (P = 0.001); LGV diameter: 2.3 mm case group *vs.* 1.6 mm control group (P = 0.001); PUV diameter: 1.9 mm case group *vs.* 1.1 mm control group (P < 0.001); Ascites: 74% case group *vs.* 25% control group (P < 0.001)
Ge *et al*[29], 2015	HBV-related cirrhotic patients who underwent CT	HCC, PVT, and non HBV-related cirrhosis	To identify CT features associated with EVB	Features associated with EVB: IMV diameter (P = 0.0528); PGV diameter (P = 0.0283); EV score (P = 0.0221)
Calame *et al* [30], 2017	Cirrhotic patients who underwent CT and EGD within 6 mo	BB, TIPS, EVL, PVT, liver resection/loco-regional treatment, and esophageal cancer	To evaluate the association between the presence/size of PUV on CT and first EVB	Features associated with first EVB: Small/absent PUV (P < 0.001); Spleen size >135 mm (P < 0.001); Ascites (P = 0.001)
Kim *et al* [31], 2019	Cirrhotic patients receiving propranolol for the primary prophylaxis of EVB who underwent CT	Duration of propranolol prophylaxis < 6 mo, previous EVB and/or EVL before propranolol therapy, and lack of contrast-enhanced liver CT data within 6 mo before or after first propranolol dosage	To evaluate liver volume for the prediction of EVB during primary prophylaxis	Association of liver volume index with EVB (P = 0.044)
Salahshour *et al*[32], 2020	Cirrhotic patients who underwent EGD and CT within 6 mo	Liver resection/loco-regional treatment, and esophageal cancer	To identify CT features associated with EVB	Features associated with EVB: EV presence (P = 0.002); Short gastric collateral presence/size (P < 0.001/P < 0.001); Coronary collateral presence (P = 0.02); Paraesophageal collateral presence/size (P = 0.01/P = 0.03); Paraesophageal draining collateral presence/size (P = 0.02/P = 0.02); LGV size (P = 0.03); Gastric fundus varices size (P = 0.001); IMV size (P = 0.04); Ascites (P = 0.04)
Xie *et al* [33], 2020	Cirrhotic patients with EV who underwent EGD and CT, and were followed-up for 6 mo	Cardiovascular disease, hematologic disease, renal insufficiency, or malignancy; previous shunt, devascularization,EIS, or EVL; use of vasopressin, somatostatin or propranolol within 1 wk before hospitalization; NVUGIB	To evaluate sensitivity and specificity of EV diameter, EV cross-sectional number, and EV total area in the prediction of first EVB	EV diameter: Sensitivity 0.8; specificity 0.52; AUC 0.72; critical point 5.55 mm; EV cross-sectional number: sensitivity 0.73; specificity 0.6; AUC 0.68; critical point 4; EV total cross-sectional area: sensitivity 0.75; specificity 0.73; AUC 0.82; critical point 1.03 cm^2
Peisen *et al* [34], 2021	Cirrhotic patients who underwent PCT and EGD within 3 mo	Diffusely infiltrating HCC, TIPS, and PVT	To evaluate the correlation between PCT-derived variables (HPI, PVP and SBF) and EVB	Weak correlation of HPI, PVP, and SBF with EBV (Eta correlation coefficient 0.126, 0.031, and 0.119, respectively)
Wan *et al* [35], 2021	Cirrhotic patients with EV who underwent EGD and CT within 4 wk	Prior EV treatment (*e.g.* BB, EVL); PVT; HCC; splenectomy, hepatectomy or portal-azygous disconnection	To identify CT-derived quantitative parameters of liver lobe associated with first EVB	Features associated with first EVB: CV (P = 0.012); CFV (P = 0.03); CV/TV (P < 0.001); CFV/TFV (P < 0.001)
Wan *et al* [36], 2022	Cirrhotic patients with EV who underwent contrast-enhanced CT within 4 wk of EGD	Prior EV treatment (*e.g.*, BB, EVL); PVT; HCC; splenectomy, hepatectomy or portal-azygous disconnection	To identify CT quantitative parameters associated with EVB	No significant difference in EV grade, EV diameter, CSA, EV volume, SNV, LGV diameter, PV, SV, and the opening type of LGV between bleeding and non-bleeding groups

EVB: Esophageal variceal bleeding; CT: Computed tomography; EGD: Esophagogastroduodenoscopy; EVL: Endoscopic variceal ligation; OLT: Orthotopic liver transplantation; EV: Esophageal varices; PUV: Paraumbilical vein; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; PVT: Portal vein thrombosis; IMV: Inferior mesenteric vein; PGV: Posterior gastric vein; BB: Beta-blockers; TIPS: Transjugular intrahepatic portosystemic shunt; EIS: Endoscopic injection sclerotherapy; NVUGIB: Nonvariceal upper gastrointestinal bleeding; AUC: Area under the curve; PCT: Perfusion computed tomography; HPI: Hepatic perfusion index; PVP: Portal venous perfusion; SBF: Splenic blood flow; CV: Caudate lobe volume; CFV: Caudate lobe functional volume; TV: Total volume; TFV: Total functional volume; CSA: Cross-sectional surface area; SNV: Splenic vein; LGV: Left gastric vein; PV: Portal vein; SV: Spleen volume.

clinical usefulness in the prediction of EVB. Furthermore, the bleeding and non-bleeding groups significantly differed with regard to MELD score and Child-Pugh class[32].

In 2020, the largest included study from China retrospectively evaluated the accuracy of the diameter of EV, the number of cross-sectional EV, and the total cross-sectional area of EV in the prediction of first EVB among 264 cirrhotic patients. All of these 3 EV indicators were shown to be significantly associated with first EVB. Of interest, the EV total cross-sectional area showed a higher accuracy, with a sensitivity of 0.75, a specificity of 0.73, and a critical point of 1.03 cm^2. The main limitation of this study was the absence of data regarding the liver function and the cirrhosis stage of the included patients[33].

Later on, Peisen *et al*[34] failed to identify any significant correlation between hepatic perfusion index, portal venous perfusion, and splenic blood flow, measured by means of perfusion CT, and EVB. However, of note, the study was limited by a very small sample size, including only a very few cases of EVB (8/66) and Child-Pugh class C patients (6/66). Indeed, the authors concluded that their results should be limited to patients in Child-Pugh class A and B.

In 2021, Wan and colleagues conducted a well-designed retrospective study in order to evaluate the role of CT-derived quantitative parameters of liver lobe volume in the prediction of first EVB. Caudate volume, caudate functional volume, caudate volume/total volume, and caudate functional volume/total functional volume were all shown to be significantly associated with first EVB. However, all these features were also associated with the EV severity. Moreover, given the rigorous inclusion criteria and the follow-up strategy, another study limitation was the small sample sizes of both the first-EVB and non-first EVB groups[35].

Finally, the same group investigated the potential of various quantitative CT-derived parameters, including EV grade, EV diameter, cross-sectional surface area, EV volume, spleen volume, splenic vein, portal vein, diameter of LGV, and the opening type of LGV, in predicting the risk of EVB. The EV grading system on CT images was made in accordance with the criteria proposed by Kim *et al*[39], classifying EV as I–IV mainly according to the EV diameter and their distribution around the inner wall. Although some of these CT parameters proved to be significantly associated with EV severity, none of them showed a significant association with EVB. However, as stated by the same authors, the enrolled study population was mainly composed of patients with severe EV, bringing a potential bias of the study cohort, and large samples with more patients with mild to moderate EV would have been warranted to reach high-quality evidence for further validation[36].

CONCLUSION

As expected, EV diameter/grade was the CT feature significantly associated with EVB most frequently reported among the included studies[28,29,32,33]. Conversely, with regard to major collateral vessels, LGV size/enlargement was shown to be significantly associated with EVB in only two of the included studies[28,30]. PUV showed conflicting results in the prediction of EVB in two studies[28,30]. As previously mentioned, this may be explained by an enrollment bias in the study from Calame *et al*[30], in which the alcoholic etiology of cirrhosis was prevalent. Moreover, IMV size was shown to be a significant predictor of EVB in two studies[29,32], while the size of posterior gastric vein and short gastric vein was demonstrated as such only in one study, respectively[29,32]. Finally, none of the included studies found a significant association of spleno-renal vein with EVB occurrence.

Worth mentioning, portal-systemic collaterals development varies from patient to patient, being likely influenced by the etiology of cirrhosis, and with each subject showing his own pattern, either single or a combination of multiple collaterals[40,41]. Moreover, with the exception of LGV, the value of these collaterals in the prediction of EVB has not been clearly established[41,42].

EGD is currently regarded as the diagnostic reference standard for the prediction of EVB, being capable to identify high-risk EV, such as medium or large-sized, and small-sized with red wale markings EV[9]. Furthermore, primary prophylaxis against EVB is recommended in cirrhotic patients with high-risk EV and in those with small size EV who are classified as Child-Pugh C class[9-13]. Nevertheless, the occurrence of EVB during primary prophylaxis with propranolol has been reported in up to 30% of cases[11]. HVPG is considered the "gold standard" for the assessment of the response to pharmacological prophylaxis and may be adopted in order to reduce the rate of primary prophylaxis failure[9,10,24]. However, HVPG is invasive and expensive. Moreover, it is not readily and widely available in routine clinical practice, and its cost-effectiveness and clinical usefulness have also been questioned[25,26].

EGD is invasive, costly, and potentially associated with the risk of iatrogenic bleeding. With regard to high-risk EV identification, a lower inter-observer agreement of EGD has also been reported as compared with CT imaging[18,19]. Moreover, frequent endoscopic screening may result in poor patients' compliance and loss of patients to follow-up[22,43]. Despite these limitations, in our opinion, CT should not be intended to replace EGD in the prediction of EVB. Nevertheless, CT may be useful in the identification of patients with a very-high risk of EVB. Given that CT is increasingly performed with various indications among cirrhotic patients, it could potentially assist liver disease scores, HVPG, and EGD in a more effective prediction of EVB. Moreover, CT may be able to support clinicians in their daily practice in accurately identifying very high-risk patients for EVB, in whom a combined pharmacological and endoscopic primary prophylaxis may be systematically considered and/or a more aggressive therapeutic monitoring strategy may be adopted.

Of note, all of the included studies in our review demonstrated severe limitations, likely affecting the study outcomes. First of all, bleeding and control groups significantly differed in terms of Child-Pugh class and/or MELD score in three out of 9 studies[29,30,32], whereas liver disease scores were not reported in another study[33]. Second, their retrospective nature[28-36]. Lastly, their small sample size[28-36].

The role of CT in the prediction of EVB, especially by the measurement of various EV indicators and some collateral veins, appears to be promising and intriguing. However, to date, evidence is still lacking. In our opinion, large, multicenter prospective controlled trials with adequate follow-up, should be conducted in order to evaluate if the EVB prediction rate may be further improved by adding MDCT to currently validated modalities (*i.e.* liver disease scores combined with endoscopy and/or HVPG). Moreover, the capability of selected and standardizable MDCT parameters to predict EVB should be prospectively evaluated, adopting EGD with or without HVPG as the reference standards. MDCT should be performed at the same time as the other validated modalities, without significant delay, and results should be stratified according to liver disease scores, endoscopic scores, and cirrhotic etiology. Of note, no significant differences in terms of liver disease severity, etiology, ongoing liver injury, or prophylactic therapy should be encountered between the enrolled groups. High morbidity and mortality rates still associated with EVB justify active research in this field.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Study

Improved visibility of colorectal tumor by texture and color enhancement imaging with indigo carmine

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Abstract

BACKGROUND

Accurate diagnosis and early resection of colorectal polyps are important to prevent the occurrence of colorectal cancer. However, technical factors and morphological factors of polyps itself can lead to missed diagnoses. Image-enhanced endoscopy and chromoendoscopy (CE) have been developed to facilitate an accurate diagnosis. There have been no reports on visibility using a combination of texture and color enhancement imaging (TXI) and CE for colorectal tumors.

AIM

To investigate the visibility of margins and surfaces with the combination of TXI and CE for colorectal lesions.

METHODS

This retrospective study included patients who underwent lower gastrointestinal endoscopy at the Toyoshima Endoscopy Clinic. We extracted polyps that were resected and diagnosed as adenomas or serrated polyps (hyperplastic polyps and sessile serrated lesions) from our endoscopic database. An expert endoscopist performed the lower gastrointestinal endoscopies and observed the lesion using white light imaging (WLI), TXI, CE, and TXI + CE modalities. Indigo carmine dye was used for CE. Three expert endoscopists rated the visibility of the margin and surface patterns in four ranks, from 1 to 4. The primary outcomes were the aver-

age visibility scores for the margin and surface patterns based on the WLI, TXI, CE, and TXI + CE observations. Visibility scores between the four modalities were compared by the Kruskal-Wallis and Dunn tests.

RESULTS

A total of 48 patients with 81 polyps were assessed. The histological subtypes included 50 tubular adenomas, 16 hyperplastic polyps, and 15 sessile serrated lesions. The visibility scores for the margins based on WLI, TXI, CE, and TXI + CE were 2.44 ± 0.93, 2.90 ± 0.93, 3.37 ± 0.74, and 3.75 ± 0.49, respectively. The visibility scores for the surface based on WLI, TXI, CE, and TXI + CE were 2.25 ± 0.80, 2.84 ± 0.84, 3.12 ± 0.72, and 3.51 ± 0.60, respectively. The visibility scores for the detection and surface on TXI were significantly lower than that on CE but higher than that on WLI ($P < 0.001$). The visibility scores for the margin and surface on TXI + CE were significantly higher than those on CE ($P < 0.001$). In the sub-analysis of adenomas, the visibility for the margin and surface on TXI + CE was significantly better than that on WLI, TXI, and CE ($P < 0.001$). In the sub-analysis of serrated polyps, the visibility for the margin and surface on TXI + CE was also significantly better than that on WLI, TXI, and CE ($P < 0.001$).

CONCLUSION

TXI + CE enhanced the visibility of the margin and surface compared to WLI, TXI, and CE for colorectal lesions.

Key Words: Texture and color enhancement imaging; Indigo carmine; Adenoma; Colonoscopy; Sessile serrated lesion

Core Tip: The visibility of colorectal tumors was investigated using texture and color enhancement imaging (TXI) and chromoendoscopy (CE). The combination of TXI and CE showed higher visibility than white-light imaging, TXI, or CE alone for the margins and surfaces of colorectal adenomas and serrated polyps.

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INTRODUCTION

Colorectal cancer is the third most common malignancy. Accurate diagnosis and early resection of colorectal adenomas are important for preventing the development of colorectal cancer[1,2]. Endoscopic resection of colorectal polyps contributes to over 50% reduction in colorectal cancer mortality, which is the basis for the importance of endoscopic resection[3]. However, 28% of polyps are missed on white light imaging (WLI)[4]. The causes of missed polyps include technical factors and morphological factors of polyps itself, such as superficial types, which are often overlooked[5].

Chromoendoscopy (CE) and image-enhanced endoscopy (IEE) have been developed[6]. Dye-based CE enhances the appearance of the mucosal surface and color patterns, which improves lesion recognition. Indigo carmine highlights the demarcation line of neoplastic lesions, and improves the detection. Pancolonic CE significantly increased the detection rates of adenomas and serrated lesions[7].

IEE includes narrowband imaging, linked color imaging (LCI), and texture and color enhancement imaging (TXI). The TXI mode is characterized by the adjustment of texture and brightness and the enhancement of color[8] and was installed in a new EVIS X1 endoscopy system (Olympus Corporation, Tokyo, Japan). Regarding the TXI principle, the image captured from WLI was separated into a base and a detailed image. The texture and brightness of the two images were adjusted. These were then recombined and called TXI mode 2. Furthermore, color enhancement was applied, and it was called TXI mode 1. We previously reported that TXI showed better visibility than WLI for colorectal adenoma[9] and serrated polyps, including sessile serrated lesions[10].

Recently, Okimoto *et al*[11] reported that magnified endoscopy with TXI and CE improved the visibility of duodenal tumor. There has also been a case report showing the usefulness of TXI and CE in early gastric cancer[12]. However, there have been no reports on the visibility of colorectal tumors using a combination of TXI and CE. Therefore, we examined the efficacy of TXI + CE in colorectal adenomas and serrated polyps. TXI + CE was compared with CE, TXI, and WLI for visibility of the margin and surface pattern.

MATERIALS AND METHODS

Patients

This retrospective study included patients who underwent lower gastrointestinal endoscopy at the Toyoshima Endoscopy Clinic between May and June 2022. We removed polyps suspected to be cancerous, adenomatous, or clinically significant serrated polyps[2,13]. All resected lesions were pathologically diagnosed using hematoxylin and eosin staining. Patients diagnosed with adenomas or serrated polyps (sessile serrated lesions or hyperplastic polyps) were enrolled in this study. Polyps diagnosed as normal or other, were excluded. We excluded patients with poor bowel preparation or ulcerative colitis. Indications for lower gastrointestinal were investigation of symptoms, such as hematochezia or abdominal pain, investigation of a positive fecal occult blood test, and screening.

Ethics

This study complied with the Ethical Guidelines for Medical Studies in Japan and the Declaration of Helsinki. The study was approved by the certified ethics committee of the Yoyogi Mental Clinic (certificate number: RKK227). We published this study's protocol on the website of the Toyoshima Endoscopy Clinic, allowing patients to opt out of the study if desired.

Endoscopy

The Toyoshima Endoscopy Clinic has introduced the EVIS X1 video system center, a 4 K resolution ultra-high-definition display monitor, and utilized colonoscopes PCF-H290ZI and CF-HQ290ZI (Olympus, Japan). We used the TXI Mode 1. The TXI Mode 2 is same as TXI mode 1 without color enhancement[14]. CE was performed by spraying 0.05% indigo carmine[15]. The endoscopic pictures and the endoscopic reports were stored with the T-File System (STS-Medic Inc., Tokyo, Japan)[16].

A board certified fellow/trainer of the Japan Gastroenterological Endoscopy Society (Toyoshima O) performed the lower gastrointestinal endoscopy and observed the lesions with the WLI, TXI, CE, and TXI + CE. Firstly, the lesions were cleaned with water. Images of the WLI and TXI were captured. Then, indigo carmine was sprinkled, and CE and TXI + CE images were captured.

Visibility scoring

The visibility of the margins and surface patterns was surveyed. The definition of margin was the detectability of the lesion border without magnification[9]. The definition of surface patterns was the mucosal structures, including granular, villous, lobular, pit, and superficial microvessel patterns. According to the previous treatises, the visibility score was as follows: A score of 1 was not detectable without repeated careful observation. A score of 2 was considered fair (barely detectable without careful observation). A score of 3 was considered acceptable (detectable without careful observation). A score of 4 was considered excellent (easily detectable)[10,17]. Three expert endoscopists rated the visibility the visibility in four ranks. An expert endoscopist was defined as one who has conducted > 5000 colonoscopies[9,18]. This study did not include magnified observations.

Outcomes

The primary outcomes were the average visibility scores for the margin and surface patterns based on WLI, TXI, CE, and TXI + CE. We compiled information on histological subtype, polyp location, size, and morphology based on the Paris endoscopic classification[19].

Statistical analysis

Visibility scores between the four modalities were compared by the Kruskal-Wallis and Dunn tests[10]. Stat Mate IV software (version 4.01, ATOMS, Japan) was used for the statistical analysis. The definition of statistical significance was P value < 0.05.

RESULTS

Patients

Table 1 shows the clinicopathological characteristics of the 81 polyps enrolled in our study. Histologically, 50 (61.7%) of the 81 polyps were tubular adenomas, 15 (18.5%) were sessile serrated lesions, and 16 (19.8%) were hyperplastic. Regarding tumor location, 7 polyps (8.6%) were in the cecum, 18 (22.2%) in the ascending colon, 39 (48.1%) in the transverse colon, 6 (7.4%) in the descending colon, 9 (11.1%) in the sigmoid colon, and 2 (2.5%) in the rectum. The average tumor size was 5.8 ± 3.7 mm. Macroscopic findings were as follows: 1 (1.2%) 0-Is, 76 (93.8%) 0-IIa, and 4 (4.9%) 0-IIb in the Paris endoscopic classification. Figure 1 shows a design flowchart for this study.

Visibility scores of margins and surface for all lesions (adenoma and serrated polyps)

The visibility scores for the margin and surface on TXI were significantly lower than that on CE but higher than that on WLI. The visibility scores for the margins and surface on TXI + CE were significantly higher than those on CE (P < 0.001) (Table 2).

Table 1 Clinicopathological characteristics of polyps

Polyps, *n*	81
Histological subtype, *n*	
Tubular adenoma	50
Sessile serrated lesion	15
Hyperplastic polyp	16
Location; *n*, cecum, ascending, transverse, descending, sigmoid, rectum	7, 18, 39, 6, 9, 2
Size, average (standard deviation, range); mm	5.8 (3.67, 1-20)
Morphology; *n*, 0-Is, 0-IIa, 0-IIb	1, 76, 4

Table 2 Visibility scores of margin and surface for white light imaging, texture and color enhancement imaging, chromoendoscopy and texture and color enhancement imaging + chromoendoscopy

	WLI	TXI	CE	TXI + CE	WLI *vs* TXI, *P* value	TXI *vs* CE, *P* value	CE *vs* TXI + CE, *P* value
Margin, mean (SD)	2.44 (0.93)	2.90 (0.93)	3.37 (0.74)	3.75 (0.49)	< 0.001	< 0.001	< 0.001
Surface, mean (SD)	2.25 (0.80)	2.84 (0.84)	3.12 (0.72)	3.51 (0.60)	< 0.001	< 0.01	< 0.001

The visibility score was defined as follows: Score 4, excellent (easily detectable); score 3, good (detectable without careful observation); score 2, fair (hardly detectable without careful examination); score 1, (not detectable without repeated careful examination). WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy; TXI + CE: Texture and color enhancement imaging + chromoendoscopy.

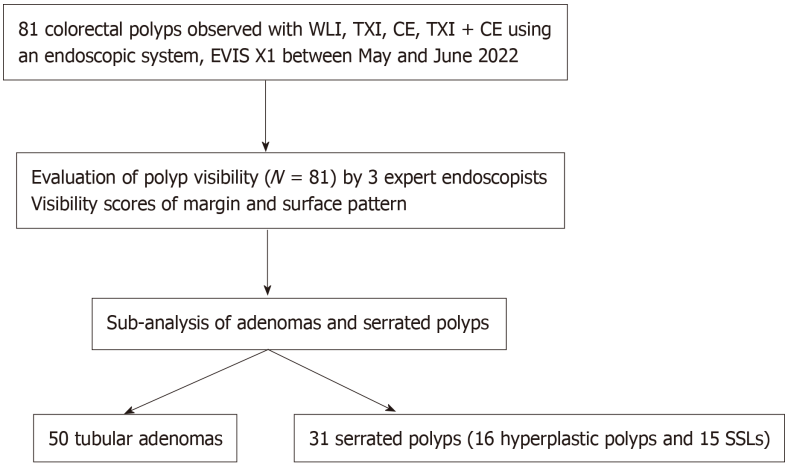

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Figure 1 Flowchart for the study design. WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy; SSL: Sessile serrated lesion.

Visibility scores of margins and surface of adenoma

In the sub-analysis of adenomas, the visibility score for the margin of TXI was significantly lower than that of CE but higher than that of WLI. The visibility for the margin on TXI + CE was significantly better than that on CE ($P < 0.001$) (Table 3). In the sub-analysis of adenomas, the visibility for the surface on TXI was significantly better than that of WLI. No statistically significant differences were observed between the TXI and CE. The visibility for the surface on TXI + CE was significantly better than that on CE (Table 3). Figure 2 shows representative images of adenoma.

Visibility score of detection and surface of serrated polyps

In the sub-analysis of serrated polyps, the visibility score for the margin on TXI was significantly lower than that on CE but higher than that on WLI. The visibility for the margin on TXI + CE was significantly better than that on CE ($P < 0.01$) (Table 4). In the sub-analysis of serrated polyps, the visibility for the surface on TXI was significantly better than that on WLI. No statistically significant differences were observed between the TXI and CE. The visibility for the surface on TXI +

Table 3 Visibility scores of margin and surface of adenomas for white light imaging, texture and color enhancement imaging, chromoendoscopy and texture and color enhancement imaging + chromoendoscopy

	WLI	TXI	CE	TXI + CE	WLI *vs* TXI, *P* value	TXI *vs* CE, *P* value	CE *vs* TXI + CE, *P* value
Margin, mean (SD)	2.54 (0.84)	3.00 (0.85)	3.46 (0.72)	3.81 (0.42)	< 0.001	< 0.001	< 0.001
Surface, mean (SD)	2.34 (0.75)	2.93 (0.79)	3.19 (0.70)	3.58 (0.56)	< 0.001	NS	< 0.001

The visibility score was defined as follows: Score 4, excellent (easily detectable); score 3, good (detectable without careful observation); score 2, fair (hardly detectable without careful examination); score 1, (not detectable without repeated careful examination). NS: Not significant; WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy; TXI + CE: Texture and color enhancement imaging + chromoendoscopy.

Table 4 Visibility scores of margin and surface of serrated polyps for white light imaging, texture and color enhancement imaging, chromoendoscopy and texture and color enhancement imaging + chromoendoscopy

	WLI	TXI	CE	TXI + CE	WLI *vs* TXI, *P* value	TXI *vs* CE, *P* value	CE *vs* TXI + CE, *P* value
Margine, mean (SD)	2.29 (1.05)	2.73 (1.03)	3.23 (0.75)	3.63 (0.56)	< 0.05	< 0.05	< 0.01
Surface, mean (SD)	2.11 (0.86)	2.69 (0.89)	3.01 (0.75)	3.41 (0.66)	< 0.001	NS	< 0.01

The visibility score was defined as follows: Score 4, excellent (easily detectable); score 3, good (detectable without careful observation); score 2, fair (hardly detectable without careful examination); score 1, (not detectable without repeated careful examination). NS: Not significant; WLI: White light imaging; TXI: Texture and color enhancement imaging; CE: Chromoendoscopy; TXI + CE: Texture and color enhancement imaging + chromoendoscopy.

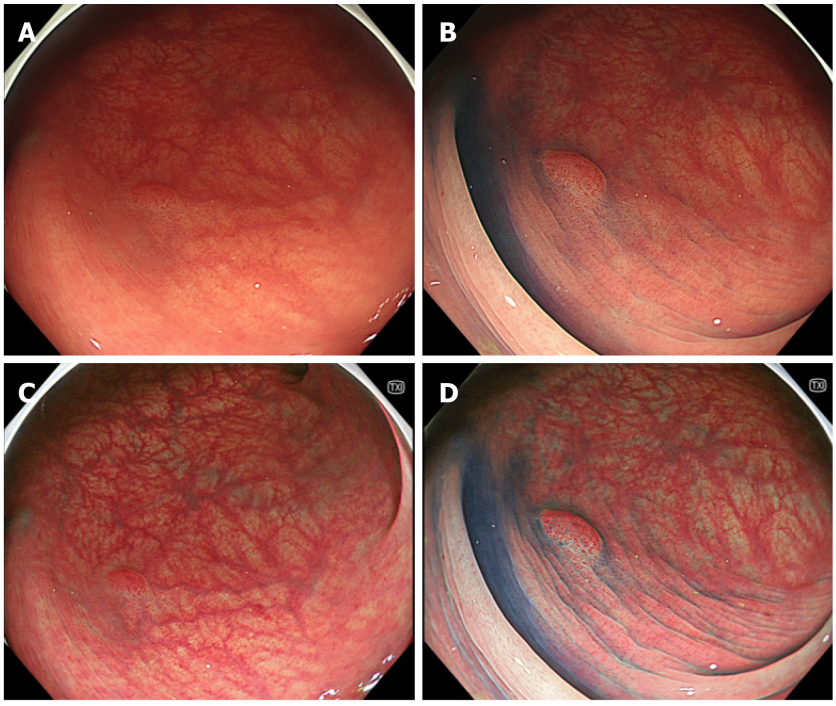

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Figure 2 Representative images of adenoma. A: White light imaging; B: Chromoendoscopy; C: Texture and color enhancement imaging; D: Chromoendoscopy and texture and color enhancement imaging.

CE was significantly better than that on CE (Table 4). Figure 3 shows representative images of serrated polyp (sessile serrated lesion).

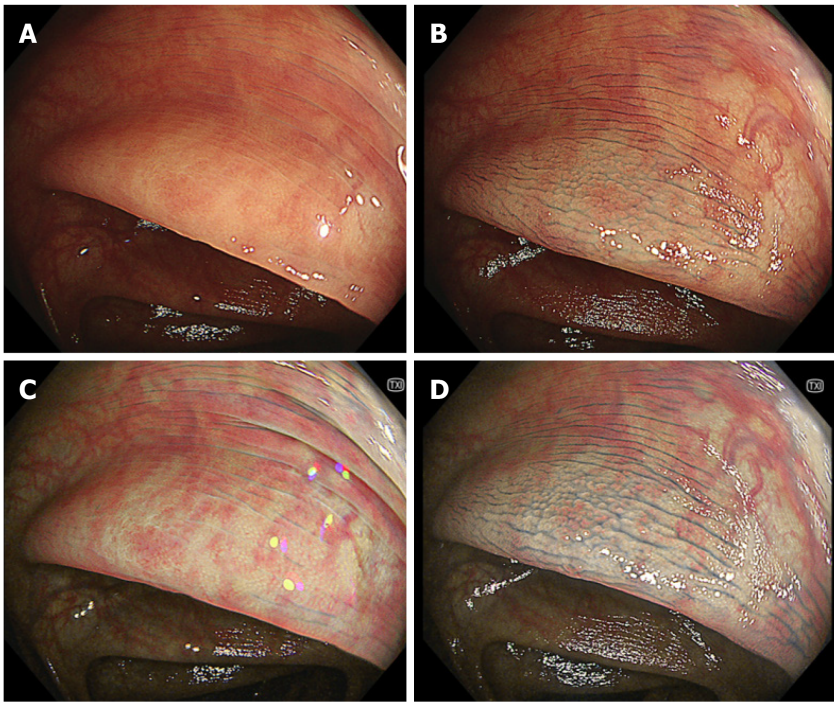

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Figure 3 Representative images of serrated polyp (sessile serrated lesion). A: White light imaging; B: Chromoendoscopy; C: Texture and color enhancement imaging; D: Chromoendoscopy and texture and color enhancement imaging.

DISCUSSION

The present study showed that the visibility of the margins and surfaces of colorectal lesions was in the order of TXI + CE, CE, TXI, and WLI, with TXI + CE being the best. In the sub-analysis of adenomas and serrated polyps, TXI + CE provided better visibility than WLI, TXI, or CE. This is the first report on the superiority of TXI + CE in colorectum.

Fujifilm corporation developed an LCI, which is considered a virtual CE. Yoshida *et al*[20] demonstrated that LCI improved the visibility scores of polyps compared with WLI. Suzuki *et al*[21] conducted an international randomized control trial that showed that LCI increased the adenoma detection rate compared to WLI (58.7% *vs* 45.7%; $P < 0.01$). LCI-based observations are becoming routine in clinical practice and could decrease interval cancer rate[22].

Recently, Olympus developed the TXI as a mode corresponding to LCI. Although TXI is similar to LCI in terms of this concept, the TXI algorithm differs from that of LCI. LCI uses narrowband light, the images are converted to those similar to WLI, and the color is enhanced from red to vivid red, and white to clear white. On the other hand, TXI uses white light without narrowband light, enriches texture and color, and selectively enhances brightness in dark areas[14,23]. TXI enhances slight changes in the structure and color of images that are difficult to observe using WLI.

We previously reported that TXI had better visibility than WLI for colorectal adenomas, regardless of the endoscopist's experiences[9]. Furthermore, TXI showed better visibility than WLI for colorectal serrated polyps[10]. In this study, the visibility on TXI was better than that on WLI for adenomas and serrated polyps, consistent with previous reports.

Both TXI and CE improve the visibility of colorectal lesions. CE has been reported to increase adenoma detection rate significantly[24,25]. Pohl *et al*[7] showed that pancolonic CE significantly improved the detection rate for adenomas (0.95 *vs* 0.66 per patient) and serrated lesions (1.19 *vs* 0.49 per patient) ($P < 0.001$). Our study also showed that the visibility on CE was better than that on WLI for adenomas and serrated polyps, consistent with previous reports.

For CE it takes time to sprinkle indigo carmine and suck out the excess. Pohl *et al*[7] reported that the extubation time in the pancolonic CE group was significantly longer than that in the control group (11.6 min *vs* 10.1 min; $P < 0.001$), but the difference was relatively small. They concluded that pancolonic CE was acceptable for routine clinical practice. The cost of indigo carmine is also an issue in pancolonic CE [1.75 $ (245 yen) for one ampule (20 mg/5 mL) of indigo carmine; Daiichi Sankyo Company, Limited, Japan]. Indigo carmine in ampule can also be used for intravenous injection; using it for endoscopic spray is expensive. We used the guaranteed reagent of indigo carmine [50.7 $ (7100 yen), 25 g powder; Fujifilm Wako Pure Chemical Corporation, Japan] in our study and diluted the solution to 0.05%[26]. This method required some time but reduced the cost of indigo carmine by 2.3%.

Magnified endoscopy with TXI and CE has been reported to provide higher visibility of duodenal tumors. Our study confirmed that the combination of TXI and CE was effective in visualizing colorectal lesions. Furthermore, our study used non-magnified endoscopy. TXI + CE is also suitable for observing the colon from a distant view. Although indigo carmine spray decreased the brightness of the entire endoscopic field, TXI adjusted the brightness. Taken together, these results suggest that TXI + CE can replace WLI in routine colonoscopy.

There are several limitations in our study. Although significant differences were statistically confirmed, this was a pilot study conducted at a single center with a sample size of 81 participants. This study was retrospective and included a potential selection bias. Therefore, prospective randomized control trials are desired to verify these findings.

CONCLUSION

TXI + CE enhanced the visibility of the margins and surface of colorectal lesions compared to WLI, TXI, and CE.

ARTICLE HIGHLIGHTS

Research background

Texture and color enhancement imaging (TXI) was developed to provide higher visibility of colorectal lesions. Chromoendoscopy (CE) also improved the recognition of colorectal lesions.

Research motivation

There is no literature regarding visibility on the combination of TXI and CE for colorectal tumors.

Research objectives

This study assessed the effectiveness of TXI + CE for the treatment of colorectal adenomas and serrated polyps.

Research methods

Endoscopic images of adenomas or serrated polyps were obtained with white light imaging (WLI), TXI, CE, and TXI + CE modalities. Expert endoscopists evaluated the visibility scores of the margins and surface patterns. The visibility scores were given in four ranks.

Research results

The visibility of margins and surfaces of the colorectal lesions was in the order of TXI + CE, CE, TXI, and WLI, with TXI + CE being the best. In the sub-analysis of adenomas and serrated polyps, the visibility for the margins and surface on TXI + CE was significantly better than that on WLI, TXI, and CE alone ($P < 0.001$).

Research conclusions

Regarding the visibility of margins and surface of colorectal lesions, the combination of TXI + CE was better than that of WLI, TXI, and CE alone.

Research perspectives

A prospective randomised controlled trial is desired to confirm these findings.

FOOTNOTES

Author contributions: Hiramatsu T and Nishizawa T drafted the article; Hiramatsu T and Toyoshima O reviewed endoscopic images; Hiramatsu T edited endoscopic images; Nishizawa T contributed to the review of endoscopic and statistical analysis; Kataoka Y, Yoshida S, Matsuno T, Mizutani H, Nakagawa H, Ebinuma H, and Fujishiro M participated in the critical review and final manuscript approval; Toyoshima O involved in the conception of article, taking endoscopic images, review of endoscopic images, and final manuscript approval.

Institutional review board statement: Our study was approved by the ethics committee of the Certified Institutional Review Board of the Yoyogi Mental Clinic (certificate number. RKK227).

Informed consent statement: We published the study protocol on our clinic's website (www.ichou.com), allowing patients to opt out of the study if desired. Written consent to participate in the study was obtained before endoscopy.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Retrospective Study

Evaluation of appendiceal mucinous neoplasms by curved linear-array echoendoscope: A preliminary study

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Abstract

BACKGROUND

Preoperative diagnosis of appendiceal mucinous neoplasms is challenging, and there are few reports regarding the endosonographic characteristics of these neoplasms.

AIM

To provide a retrospective assessment of the imaging features of appendiceal mucinous neoplasms using endoscopic ultrasound (EUS) by curved linear-array echoendoscope.

METHODS

A database of all patients with appendiceal mucinous neoplasms who had received EUS examination at our hospital between January 2018 and July 2023 was retrospectively analyzed. The EUS characteristics and patients' clinical data were reviewed.

RESULTS

Twenty-two patients were included in the study. The linear-array echoendoscope successfully reached the ileocecal region in every patient. In the endoscopic view,

we could observe the protrusion in the appendiceal orifice in all patients. A volcano sign was observed in two patients, and an atypical volcano sign was seen in two patients. EUS showed that all 22 lesions were submucosal cystic hypoechoic lesions with clear boundaries. No wall nodules were observed, but an onion-peeling sign was observed in 17 cases.

CONCLUSION
Linear-array echoendoscope is safe to reach the ileocecal region under the guidance of EUS. Image features on endoscopic and echoendosonograhic views could be used to diagnose appendiceal mucinous neoplasms.

Key Words: Appendiceal mucinous neoplasm; Endoscopic ultrasound; Appendix; Endoscopy; Colonoscopy

Core Tip: Appendiceal mucocele is a relatively rare disease. The preoperatively accurate diagnosis is crucial to the treatment strategy. Endoscopy has played an important role in the diagnosis of appendiceal mucocele. Image features on endoscopic and echoendosonograhic views could be used to diagnose appendiceal mucinous neoplasms.

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INTRODUCTION

Appendiceal mucocele is a relatively rare disease. Based on the pathological type, appendiceal mucocele can be classified as mucosal hyperplasia, mucinous cystadenoma, or mucinous cystadenocarcinoma. Even though appendiceal mucocele, expect mucinous cystadenocarcinoma, does not typically show definitive malignant features, it can rupture and lead to the development of pseudomyxoma peritonei, a life-threatening complication with a 10-year survival rate of 45%[1]. Therefore, an accurate diagnosis is crucial to the treatment strategy. However, patients with appendiceal mucocele do not have specific clinical manifestations, delaying diagnosis[2,3]. The patient may have no symptoms or show acute appendicitis-like presentation in the early stages of the disease with right lower quadrant pain secondary to distention of the appendix by mucin[4]. Since the development of endoscopic ultrasound (EUS)[5], endoscopy has played an important role in the diagnosis of appendiceal mucocele. To date, only a few studies have demonstrated the EUS characteristics of appendiceal mucocele using miniprobe catheter EUS. Moreover, miniprobe EUS exhibited limited depth of penetration. In this work, we evaluated the EUS characteristics of appendiceal mucocele by curved linear-array echoendoscope to assess the accurate diagnosis.

MATERIALS AND METHODS

Patients with a pathological diagnosis of appendiceal mucocele who had received EUS examination by linear echoendoscope from January 2018 to July 2023 were reviewed. The patients' general characteristics, EUS results, and surgery method were recorded. This study was approved by the institutional review board of Hebei Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine.

Intubation of the linear echoendoscope

All cases were performed after a standard bowel preparation, using either a linear echoendoscope (3870UTK, Pentax company, Japan) or linear echoendoscope (EG-580UT, Fujifilm company, Japan). We inserted the linear echoendoscope with the guidance of endoscopic and ultrasound views. During the insertion of the endoscope, if the angle of the colon was too large to display the endoscopic view, we used ultrasound to scan the direction of the proximal colon to assist in inserting the endoscope (Figure 1). Closed intestinal cavities are often difficult to distinguish on ultrasound images. The direction of the intestinal cavity can be easier to identify by injecting water into the cavity.

RESULTS

This study included 22 patients that were diagnosed with appendiceal mucocele and received EUS examination. Among them, there were 9 male and 13 female patients, aged 26-80 years. The average age was 60.9 ± 12.6 years. Clinical symptoms included discomfort in the right lower abdomen in 6 cases, appendicitis in 10 cases, and physical examination

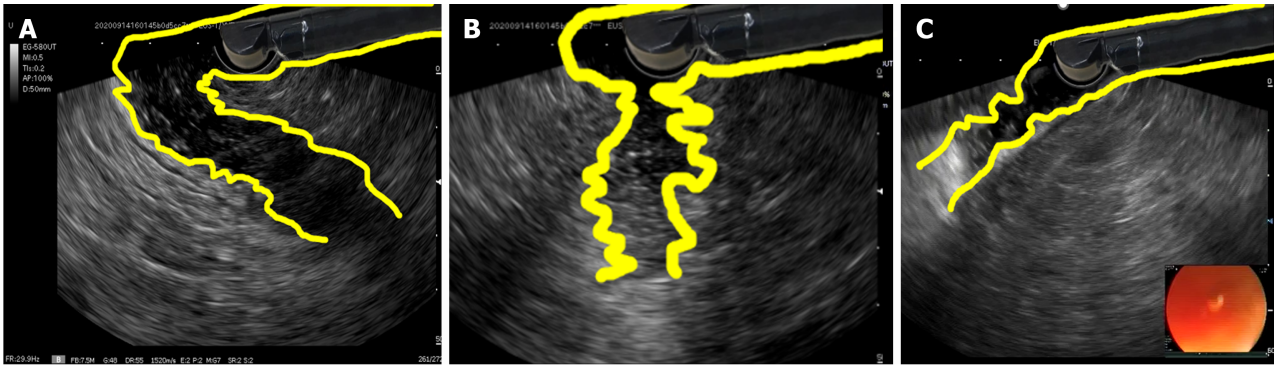

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Figure 1 Using ultrasound to scan the direction of the proximal colon to assist in inserting the endoscope. A: The direction of the proximal colon is at an acute angle; B: The direction of the proximal colon is almost at a right angle; C: The direction of the proximal colon is almost at an obtuse angle.

in 6 cases.

The echoendoscope successfully reached the ileocecal region in all 22 patients. In the endoscopic view, we could observe the protrusion in the appendiceal orifice. The surface of the protrusion was smooth, and no secretion was observed in 20 cases, of which the appendiceal orifice was compressed to one side of the lesion in 18 cases and the appendiceal orifice was located on the surface of the lesion in 2 cases (volcano sign). The appendiceal orifice was located on the surface of the lesion with white secretion in 2 cases (atypical volcano sign) (Figure 2). EUS showed that all 22 lesions were submucosal cystic hypoechoic lesions with clear boundaries and no wall nodules were observed. The size of the lesions ranged from 1.1 cm to 5.7 cm, with the average size being 3.1 ± 1.1 cm. Onion-peeling sign, which was defined as intermittent hyperechoic lines in the hypoechoic lesion, could be observed in 17 cases (Figure 3). Overall, 16 cases underwent appendectomy, 4 cases received ileocecal resection, and 2 cases underwent right hemicolectomy. The surgical process was smooth and there were no complications. Postoperative pathology confirmed 20 cases of appendiceal mucinous adenoma and 2 cases of mucinous adenocarcinoma.

DISCUSSION

Appendiceal mucocele, caused by dilation of the lumen because of an accumulation of mucus, is a relatively uncommon disease. Appendiceal mucinous cystadenoma can secrete mucin and present in a malignant fashion, resulting in the development of life-threatening pseudomyxoma peritonei. However, it is difficult to make the diagnosis of appendiceal mucocele. The presentation of appendiceal mucocele is quite variable, and the clinical symptoms are vague and non-specific. For asymptomatic patients, appendiceal mucocele may be incidentally detected on imaging examination or during a colonoscopy. For symptomatic patients, appendiceal mucocele has an overlap of symptoms with acute appendicitis, frequently leading to a preoperative misdiagnosis. Therefore, sufficient preoperative examinations are necessary to make an accurate diagnosis. For multiphase computed tomography images, appendiceal mucocele should be considered when a focal well-defined cystic mass with slightly higher water attenuation, thickened cystic wall with ring mural enhancement, and a characteristic progressive contrast enhancement in imaging, especially in older females with non-specific symptoms that are similar to appendicitis[6].

During colonoscopy, the classical appearance of appendiceal mucocele is a ''volcano sign'', with the appendiceal orifice seen at the center of the mound[7,8]. Colonoscopic biopsy is not recommended because the overlying mucosa is not involved, and biopsy carries the potential risk of rupturing the appendiceal mucocele. The author described an atypical "volcano sign" with mucus spewing out of the appendicular orifice and the final diagnosis was appendiceal mucinous adenocarcinoma[9]. Our study also found two mucinous adenocarcinomas that presented as an atypical "volcano sign", which may be caused when the tumor ruptured into the lumen of the colon, releasing mucus. Overall, an atypical "volcano sign" might be the sign of mucinous adenocarcinoma.

EUS can be useful in confirming the nature of the lesion, thereby ruling out solid lesions such as carcinoid, lipoma, or gastrointestinal stromal tumor[10,11]. Due to the maneuverability of the linear array echoendoscope, it was widely used to evaluate lesions in left colon and rectum[12,13]. Using a linear array echoendoscope to evaluate the proximal colon has been reported in only a few studies. For more proximal areas of the colon, forward-viewing echocolonoscopes and through-the-scope miniprobe catheter ultrasound were typically used, but these methods have limitations. In this study, we used a linear array echoendoscope to evaluate the appendiceal lesions. Advancement of a conventional curved linear echoendoscope beyond the sigmoid colon usually requires previous placement of an overtube or a guidewire[14]. In this study, we inserted the linear echoendoscope just with the guidance of endoscopic and ultrasound views. If the intestinal lumen could not be seen under endoscopic view, we injected water into the intestinal lumen to help identify the direction of the intestinal lumen using ultrasound view. We passed through the sigmoid and descending colon without loop and maintained a good freedom of scope. If the scope is difficult to pass, we could use a guidewire method. Appendiceal mucocele is a hypoechoic lesion with clear boundaries and is without mural nodes. In addition, we found that the "onion-peeling sign" could be seen in most cases, which may be due to the different timing of mucus secretion. The "onion-

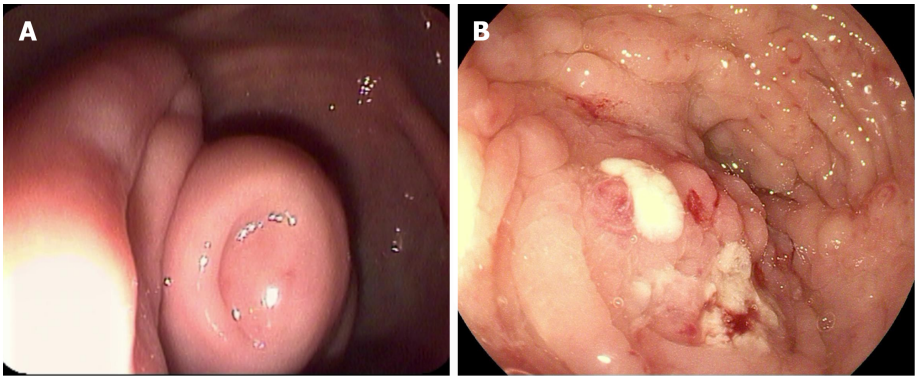

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Figure 2 Endoscopic view of appendiceal mucinous neoplasms. A: A volcano sign that the appendiceal orifice was located on the surface of the protrusion is shown; B: An atypical volcano sign that the appendiceal orifice was located on the surface of the protrusion with white secretion is shown.

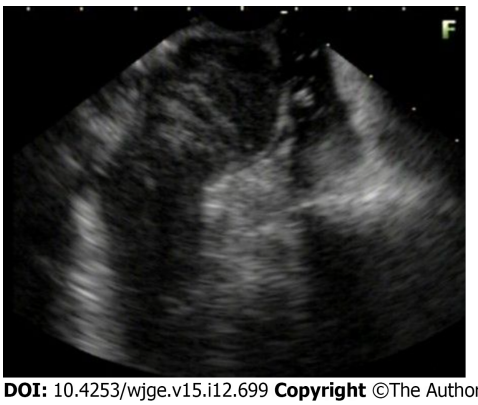

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Figure 3 An onion-peeling sign with intermittent hyperechoic lines was seen in the hypoechoic lesion.

peeling sign" could help us to make a differential diagnosis. For unclear lesions, EUS-fine-needle aspiration (FNA) could be performed to confirm the diagnosis[15-17]. However, if appendiceal mucocele is suspected, EUS-FNA is forbidden to avoid the formation of pseudomyxoma peritonei.

Surgery is a standard method for the treatment of appendiceal mucocele. A simple appendectomy could be performed for mucosal hyperplasia and mucinous cystadenoma. In addition, a right hemicolectomy with lymph node dissection is indicated for cystadenocarcinoma. After surgery, patients should be offered follow-up to exclude the subsequent development of pseudomyxoma peritonei[18]. The risk of pseudomyxoma peritonei is related to the pathological finding and is higher if acellular mucin is found beyond the appendiceal serosa[19].

There are limitations in our study. The study was a retrospective study and only a small cohort of patients were included. All the procedures were performed by experienced doctor. For difficult colonoscopy, the safety of intubation of linear echoendoscope into cecum should be further studied.

CONCLUSION

Endoscopy plays an important role in the diagnosis of appendiceal mucocele. We can safely evaluate the lesion in the ileocecal region by using a linear-array echoendoscope. A volcano sign on endoscopic view and EUS features could be used to diagnose appendiceal mucinous neoplasms.

ARTICLE HIGHLIGHTS

Research background

Appendiceal mucinous neoplasms can present in a malignant fashion, but preoperative diagnosis of appendiceal mucinous neoplasms is difficult. Endoscopy plays an important role in the diagnosis of appendiceal mucinous neoplasms. There are limited reports regarding the endosonographic characteristics of these neoplasms.

Research motivation
We evaluated the imaging features of appendiceal mucinous neoplasms using endoscopic ultrasound (EUS) by curved linear-array echoendoscope.

Research objectives
To describe image features on endoscopic and echoendosonograhic views of appendiceal mucinous neoplasms.

Research methods
The EUS characteristics and patients' clinical data were reviewed.

Research results
The appendiceal orifice located on the surface of the lesion in 2 cases (volcano sign) and the appendiceal orifice located on the surface of the lesion with white secretion in 2 cases (atypical volcano sign) were seen. EUS showed that the lesions were submucosal cystic hypoechoic lesions with clear boundaries and no wall nodules were observed. Onion-peeling sign, which was defined as intermittent hyperechoic lines in the hypoechoic lesion, could be observed in part of cases.

Research conclusions
This study demonstrated that we can safely evaluate the lesion in the ileocecal region by using a linear-array echoendoscope. A volcano sign on endoscopic view and EUS features could be used to diagnose appendiceal mucinous neoplasms.

Research perspectives
In the future, for difficult colonoscopy, the safety of intubation of linear echoendoscope into cecum should be studied.

FOOTNOTES

Author contributions: Hu JL, Zhang JC, Ma YY, and Lan YZ designed and performed the research study; Hu JL, Li SB, and Wang X analyzed the data and wrote the manuscript; and all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Effect of a disposable endoscope precleaning kit in the cleaning procedure of gastrointestinal endoscope: A multi-center observational study

Yi-Fan Wang, Yu Wu, Xiao-Wei Liu, Jian-Guo Li, Yan-Qiong Zhan, Bin Liu, Wen-Ling Fan, Zi-Heng Peng, Jin-Tao Xiao, Bing-Bing Li, Jian He, Jun Yi, Zhao-Xia Lu

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Abstract

BACKGROUND

Precleaning is a key step in endoscopic reprocessing.

AIM

To develop an effective and economic endoscope cleaning method by using a disposable endoscope bedside precleaning kit.

METHODS

Altogether, 228 used gastrointestinal endoscopes were selected from five high-volume endoscopy units and precleaned by a traditional precleaning bucket (group T) or a disposable endoscope bedside precleaning kit (group D). Each group was further subdivided based on the replacement frequency of the cleaning solution, which was replaced every time in subgroups T1 and D1 and every several times in subgroups Ts and Ds. The adenosine triphosphate (ATP) level and residual proteins were measured three times: Before and after precleaning and after manual cleaning.

RESULTS

After precleaning, the precleaning kit significantly reduced the ATP levels (P = 0.034) and has a more stable ATP clearance rate than the traditional precleaning bucket. The precleaning kit also saved a quarter of the cost of enzymatic detergent used during the precleaning process. After manual cleaning, the ATP levels were also significantly lower in the precleaning kit group than in the traditional precleaning bucket group (P < 0.05). Meanwhile, the number of uses of the cleaning solution (up to four times) has no significant impact on the cleaning effect (P > 0.05).

CONCLUSION

Considering its economic cost and cleaning effect, the use of a disposable endoscope bedside precleaning kit can be an optimal option in the precleaning stage with the cleaning solution being replaced several times in the manual cleaning stage.

Key Words: Cleaning effect; Economic cost; Endoscope; Multi-center study; Precleaning

Core Tip: Precleaning is a key step in endoscopic reprocessing, but related studies on the matter are few. In the present study, we evaluated the role of a self-developed disposable endoscope bedside precleaning kit for endoscopic cleaning. We compared the cleaning effects between the disposable precleaning kit and traditional precleaning buckets in five endoscopy units and found that the precleaning kit has advantages in the precleaning stage. Its better precleaning effect can improve the effectiveness of the subsequent reprocessing procedures. Meanwhile, the cleaning solution used in the precleaning and manual cleaning stages was reduced, suggesting a significant cost advantage in the clinical practice.

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INTRODUCTION

With the development of gastrointestinal endoscopic techniques, endoscopy has become an essential part in the diagnosis and management of gastrointestinal diseases[1,2]. Endoscopes are reusable devices that require reprocessing (cleaning, high-level disinfection or sterilization, and drying) to be safely used in other patients[3]. As complex reusable instruments with narrowed lumens, gastrointestinal endoscopes are easily contaminated by blood, secretions, and microorganisms during its use[4]. Besides, heat-sensitive materials are used in these devices; hence, gastrointestinal endoscopes must be sterilized by low-temperature chemical methods, such as liquid chemical germicide, rather than by steam sterilization, thus necessitating higher requirements for more standard cleaning and disinfection procedures[5]. There may be a high risk of iatrogenic cross infection if the endoscope is not thoroughly cleaned and disinfected. In 1993, Spach *et al*[6] summarized the most common infectious agents transmitted by endoscopy. Many studies have reported a gradual increase in the outbreaks of endoscopy-related infections. Epstein *et al*[7] reported a carbapenem-resistant *Escherichia coli* infection in a hospital in the United States caused by exposure to duodenoscopes with bacterial contamination. Naas *et al*[8] also described a multihospital outbreak of carbapenemase-producing *Klebsiella pneumoniae* associated with a contaminated duodenoscope. Moreover, Bajolet *et al*[9] studied a gastroscope-associated outbreak in four patients with an extended spectrum β-lactamase-producing *Pseudomonas aeruginosa* (*P. aeruginosa*). Additionally, Birnie *et al*[10] documented a case of hepatitis B virus transmission *via* gastrointestinal endoscopy. Although there is currently no evidence of transmission of the variant Creutzfeldt - Jakob disease infectivity by endoscopy (or any other medical or surgical device), laboratory tests have indicated that the standard disinfection and sterilization procedures may be insufficient to completely remove infectious proteins from contaminated instruments[11]. In view of the aforementioned cases, improper or incorrect reprocessing may be responsible for the outbreak of these endoscopy-related infections. Concurrently, in recent years, concerns have been raised that many of these infectious risks to patients may be underestimated due to under-reporting or nonrecognition. Therefore, an improvement in endoscope cleaning and disinfection

procedures is critical to prevent infection outbreaks in the future.

After an endoscopic procedure, transferring the contaminated endoscopes to the cleaning and disinfection center is time consuming. The remaining body fluids, blood, or debris on the outer surface and lumen of the contaminated endoscopes are prone to dry and solidify, which make it easier for bacteria to form biofilms in the endoscopic channel. Biofilms comprise multiple layers of bacterial or fungal cell clusters, embedded in an amorphous extracellular material composed of exopolysaccharide-derived bacteria[12]. In clinical practice, biofilm formation may be associated with incomplete manual cleaning and drying[13]. Biofilm formation protects microorganisms from biocides and disinfectants, which may result in the failure of cleaning and disinfection procedures[10]. Precleaning is the first step in preventing the development of biofilms within endoscopes, highlighting the importance of diligent and consistent precleaning, first, in reprocessing[14]. Proper precleaning (wiping and rinsing with air and water) immediately after use is necessary to prevent drying and curing of residual organic matters in the endoscope[3]. The current precleaning procedure worldwide is conducted in accordance with the national endoscope cleaning and disinfection guidelines. The multi-society guideline for reprocessing flexible gastrointestinal (GI) endoscopes and accessories (2020) stipulated that endoscopes should be precleaned at the bedside by aspirating the detergent solution through all channels (including the air/water and biopsy channels) after use[14], but they have not specified the replacement frequency and holding device of the detergent solution. The manufacturer's instructions for detergent solution only include requirements for the concentration, temperature, and effective time. Moreover, studies that explored the precleaning methods are few, suggesting the necessity for investigating the current situation of the precleaning practice and conducting relevant clinical research. According to the summarized data of the 2020 China Digestive Endoscopy Census in Hunan Province by our hospital, most hospitals only use a precleaning bucket with an effective concentration of detergent solution to save clinical costs, which is continuously used for the precleaning of all endoscopes in a clinic. In an endoscopy center in the United States, a *P. aeruginosa* infection after endoscopic retrograde cholangiopancreatography occurred due to the contamination of storage tanks of enzymatic solutions used in precleaning, and the outbreak was terminated after removing the refillable enzymatic bottles and replacing them with single-case enzymatic packs[15]. All these cases suggest that this phenomenon is common worldwide and may lead to the development an infection. Therefore, there is a reason to believe that the traditional precleaning buckets may increase the risk of cross contamination and microbial residues. Accordingly, our research group previously designed a disposable endoscope bedside precleaning kit and attained the practical new patent (patent No.: ZL201920911448.7). In our previous small-scale single-center clinical study, this patented kit can improve the precleaning and manual cleaning effects[16]. To further explore the role of this precleaning kit in improving endoscopic cleaning, we designed a multi-center study to further confirm its clinical effectiveness, safety and economic benefits.

MATERIALS AND METHODS

Study design and ethics

Altogether, 228 used gastroscopes and colonoscopes (Olympus, GIF-HQ290|GIF-XQ260, CF-HQ290I|CF-H260AI, Fukushima, Japan) were selected from five high-volume endoscopy units in Hunan Province, including Xiangya Hospital, the First Hospital of Changsha, the Fourth Hospital of Changsha, Xiangtan Central Hospital, and Zhuzhou Central Hospital. All units have > 200 daily patient volumes. The present investigation was an open study, with pseudo-randomization. In the pseudo-randomization procedure, the endoscopes were grouped according to the collection order. The first half of endoscopes tested at each unit comprised the group T, whereas the second half formed group D, with 114 pieces in each group. Repeated testing in an endoscope might result in an inaccurate representation, as the previous test could potentially remove or wipe away any bioburden. Therefore, 54 samples in each group were only tested by adenosine triphosphate (ATP) bioluminescence assay, and the remaining 60 samples were only subject to residual protein testing. In the precleaning stage, traditional precleaning buckets were used in group T, and the disposable endoscope bedside precleaning kit was used in group D. Altogether, three tests were performed on each endoscope. After the endoscopy procedure, the ATP assay or residual protein test was performed, first, before the precleaning procedure. The second test was performed after completing the precleaning process. Then, the endoscopes were subject to manual cleaning. In this stage, each group was randomly divided into two subgroups based on the replacement frequency of the cleaning solution, namely groups Ts, T1, Ds, and D1. Among them, the cleaning solution in groups Ts and Ds were replaced several times, including every two times, every three times, and every four times, specifically named T2, T3, and T4, respectively, and D2, D3, and D4, respectively, whereas groups T1 and D1 were replaced every time. The third test was conducted after manual cleaning. The specific flow chart is shown in Figure 1. The present study was reviewed and approved by the Medical Ethics Committee of Xiangya Hospital of Central South University and the committee considered that this research did not require ethical approval related to the use of a human body.

Precleaning and manual cleaning

All technical staff working in the five endoscopy units had undergone cleaning and reprocessing competency technical training of endoscopes in the Gastrointestinal Endoscopy Center of Xiangya Hospital, a unit of Hunan Provincial Gastrointestinal Endoscopy Medical Quality Control Center, and obtained the qualification certificate. The detergent solution used for precleaning and manual cleaning were high-concentration enzyme cleaning agents (CL-MA, 210611, Sakura, Tokyo, Japan) with a dilution concentration of 1:1000. After using the endoscope, the exterior of the endoscopes was immediately wiped with a detergent solution. In group T, the detergent was aspirated from the traditional precleaning bucket through biopsy channels until the aspirant became clear, whereas, in group D, the clean water was aspirated until the aspirant became clear; then, 100 mL of the detergent was aspirated from the disposable endoscope

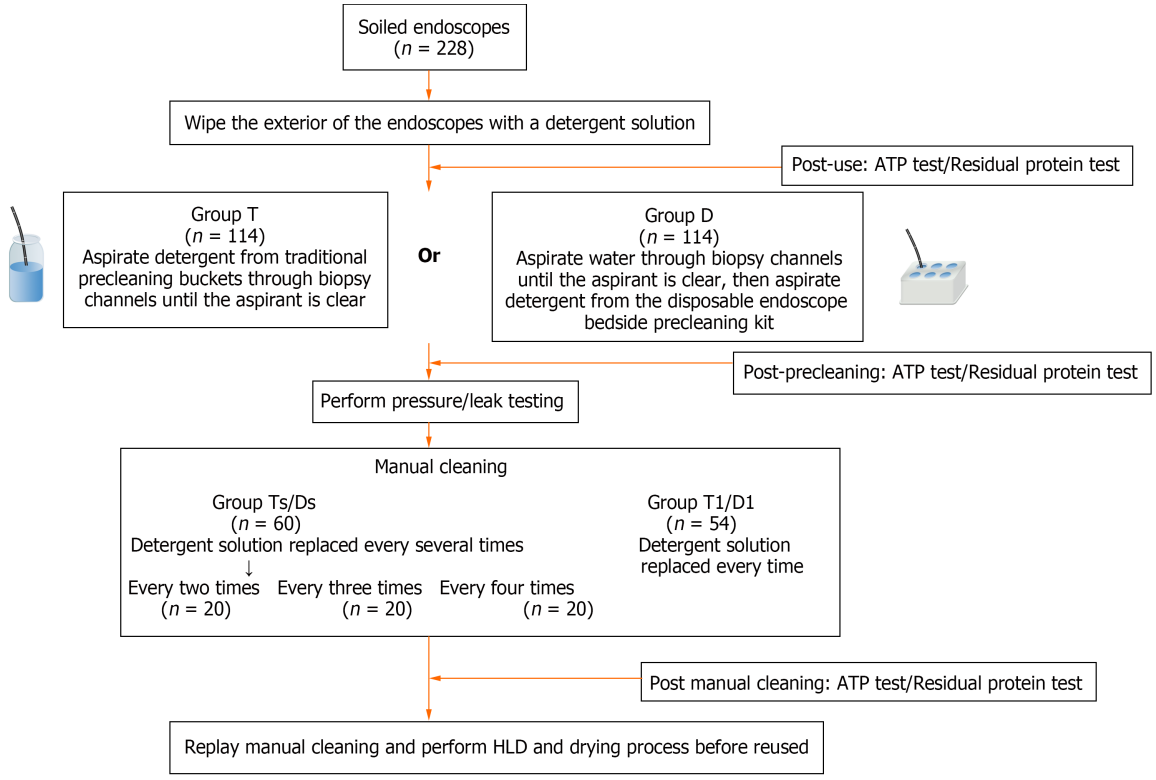

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Figure 1 Experimental flow chart. ATP: Adenosine triphosphate; HLD: High-level disinfection.

bedside precleaning kit. The precleaning process of the five units was performed by the same staff, and the equipment used was also consistent. The manual cleaning process was in strict conformity with the Regulation for Cleaning and Disinfection Technique of Flexible Endoscope (WS507-2016)[17].

ATP test

Following an endoscopic procedure, 40 mL of sterile phosphate buffered saline (BL302A, Biosharp, Beijing, China) was flushed through the endoscopic working channel and collected at the endoscope's distal end in a sterile specimen container. The Hygiena AquaSnap™ Total ATP water test swab (AQ-100X, 16022, Hygiena, Camarillo, United States) was dipped into the sample for sampling and then placed into the ATP luminometer (BT-112D, Beijing Chuang Xin Shi Ji Biochemical Science & Technology Development Co., Ltd., Beijing, China) for measurement. The ATP levels are expressed in relative light units (RLU). The manufacturer specifies a cleaning failure at the threshold of the RLU of ≥ 20000.

Residual protein test

The residual protein test kit (NICE CHECK, Clean Chemical Co., Ltd., Osaka, Japan) contains the following three components: Staining, cleaning, and extraction solutions. By infusing 5 mL of staining solution into the endoscopic working channel, the dye was allowed to bind to any residual proteins in the channel. Next, the unbound excess dye was washed off with 5 mL of washing solution. Then, the sample of the dye bound to the residual protein was collected by infusion of 5 mL of the extraction solution. The residual protein was quantitated with bovine serum albumin as a standard.

Statistical analysis

All data are presented as mean ± SD, unless otherwise indicated. The Student's *t*-test was used to assess the statistical significance of the differences between the two groups. One-way analysis of variance (ANOVA) was employed to analyze the significant differences among groups. Tukey's test was used for pairwise comparison. A P value < 0.05 was considered statistically significant. Data were plotted and analyzed using Microsoft Excel and GraphPad Prism version 7.0.

RESULTS

Test results at all stages for all endoscopes

Both precleaning and manual cleaning can significantly reduce the ATP levels and residual proteins in the endoscopic

channels. Before precleaning, the ATP level of the gastroscopes after use was significantly higher than that of the colonoscopes ($P < 0.001$). However, there was no significant difference in the residual protein ($P > 0.05$) between the gastroscopes and colonoscopes, despite the discovery of a relatively higher level in the colonoscopes. Nevertheless, the difference between the gastroscopes and colonoscopes disappeared after manual cleaning ($P > 0.05$). See the details in Table 1. To avoid any result error caused by this difference before manual cleaning, two subgroups of T and D groups were established separately for both the gastroscopes and colonoscopes.

Less amount of enzymatic detergent used with the precleaning kit in the precleaning stage

In addition to the normal experimental procedure, we did a small experiment to measure the amount of enzymatic detergent when using the traditional pretreatment bucket. Eighty endoscopes were divided into eight groups, with each group precleaned in the same traditional pretreatment bucket. Finally, the total amount of enzymatic detergent used in each group was measured, as shown in Supplementary Table 1. The average amount of enzymatic detergent used for one endoscope was approximately 136 mL, although the disposable precleaning kit limited the amount of detergent used each time to 100 mL, which greatly reduced the amount of enzymatic detergent used in precleaning stage.

Better precleaning effect of the precleaning kit based on the ATP result

In the post-use stage, the mean levels of ATP and residual proteins were not significantly different between groups T and D (both $P > 0.05$). After precleaning, the mean ATP level was lower in group D than in group T ($P = 0.034$). However, no significant difference was observed in the mean residual protein between the two groups ($P > 0.05$). See the details in Table 2. Moreover, by comparing the relationship between the precleaning sequence and ATP clearance rate, which was defined as the ATP difference value before and after precleaning/ATP value before precleaning × 100%, it was found that with the increase in the frequency of use, especially from the ninth use, the ATP clearance rate of the traditional bucket gradually decreased, whereas that of the disposable endoscope bedside precleaning kit was relatively stable (Figure 2).

Influence of different precleaning methods and cleaning solution replacement frequency on the manual cleaning effect

The ATP levels after manual cleaning were analyzed by pairwise comparison. Significant differences in the ATP levels were observed between groups Ts and Ds ($q = 4.585$, $P = 0.0085$), groups Ts and D1 ($q = 5.104$, $P = 0.0026$), groups T1 and Ds ($q = 4.232$, $P = 0.0179$), and groups T1 and D1 ($q = 4.756$, $P = 0.0059$) (Figure 3A). In other words, the mean ATP level after treatment using the traditional precleaning bucket was higher than that of the disposable endoscope bedside precleaning kit, although the difference between Ts and T1 or between Ds and D1 was not statistically significant (both $P > 0.05$). Additionally, in groups Ts and Ds, there was no significant difference in the ATP levels when the cleaning solution was replaced every two times, every three times, and every four times (all $P > 0.05$; Figure 3B).

Regarding the residual proteins after manual cleaning, there were no significant differences between any two groups ($P > 0.05$; Figure 3C). Moreover, in groups Ts and Ds, no significant difference in residual proteins among the groups with cleaning solution replaced every two times, every three times, and every four times (all $P > 0.05$; Figure 3D). See the details in Table 3.

DISCUSSION

Strict and appropriate endoscopic cleaning procedures are crucial for preventing future infection outbreaks. The present study demonstrated that our patented disposable endoscope bedside precleaning kit has obvious advantages over traditional precleaning buckets, in terms of better cleaning effect and cost advantage during precleaning procedure, and can enhance the effectiveness of subsequent reprocessing procedure.

In our study, the ATP levels were significantly lower after precleaning with the precleaning kit, and the precleaning effect of traditional precleaning buckets decreased due to the increase of pollutants and reduction of active ingredients with the increase in the frequency of use, whereas that of the disposable endoscope bedside precleaning kit was relatively stable. The ATP test is an effective method for detecting the cleaning effect of endoscopes. ATP is present in microorganisms and human cells, and the RLU value of ATP *via* bioluminescence assay in endoscopic working channels can reflect the residual situation of ATP-containing microorganisms or patients' secretions[18,19]. In a previous systematic review investigating the correlation between ATP test and bacterial culture based on the summary of the data reported in published studies, researchers have pointed out that the ATP test can be a useful tool for evaluating the adequacy of manual cleaning, although current studies did not support it as a substitute for bacterial culture[20]. Another study found that gram-negative bacteria could be reliably eliminated by endoscopic cleaning under monitoring by using the ATP test [21]. Our study found that, before precleaning, the ATP level of the gastroscopes after use was significantly higher than that of colonoscopes, consistent with other studies[22,23], which was possibly related to the presence of other nonmicrobial sources of ATP in the upper gastrointestinal tract, such as oral secretions, gastric acid, and bile.

The residues of patient tissue proteins in the endoscopic working channel may be associated with bacterial, viral, or prion infection[24]. Residual proteins provide favorable conditions for microbial colonization and biofilm formation[12]. Therefore, monitoring the residual proteins after cleaning is greatly important. Although no significant effect on residual proteins was observed when using the two methods, a significant decrease was noted after precleaning than that before precleaning (107.58 ± 61.40 *vs* 40.07 ± 19.31, $P < 0.0001$), which may be attributed to the components of the multi-enzyme cleaning solution, including protease, enzyme stabilizer, and surfactant that have a strong cleaning effect on the residual protein. Besides, the amount of residual proteins in the used endoscopes was not high, with an unqualified rate of only 17.5% according to the manufacturer's instructions. Therefore, the two precleaning methods revealed no significant

Table 1 The test results at all stages for all endoscopes (mean ± SD)

Test method	Endoscopes	Postuse	Postprecleaning	Postmanual cleaning
ATP test (RLU)	Gastroscopes (n = 60)	5313645 ± 3919731	120035 ± 214287[a]	1567 ± 1152[b]
	Colonoscopes (n = 48)	1235303 ± 1182027	31293 ± 78392[a]	1450 ± 1945[c]
Residual protein test (μg)	Gastroscopes (n = 88)	102.39 ± 58.09	39.08 ± 19.60[a]	32.04 ± 15.63[c]
	Colonoscopes (n = 32)	121.87 ± 68.66	42.80 ± 18.53[a]	30.34 ± 10.42[c]

[a]P < 0.0001 postuse *vs* postprecleaning.
[b]P < 0.0001 postprecleaning *vs* postmanual cleaning.
[c]P < 0.01 postprecleaning *vs* postmanual cleaning.
ATP: Adenosine triphosphate; RLU: Relative light unit.

Table 2 Comparison of the postuse and postprecleaning adenosine triphosphate and residual protein results (mean ± SD)

Test method	Postuse		Postprecleaning	
	Group T (n = 60)[1]	Group D (n = 54)[2]	Group T (n = 60)[1]	Group D (n = 54)[2]
ATP test (RLU)	3536861 ± 3665062	3465218 ± 3643658	116120 ± 236664	45068 ± 44132[a]
Residual protein test (μg)	109.01 ± 60.30	106.16 ± 62.95	39.36 ± 17.70	40.78 ± 20.93

[a]P < 0.05 group T *vs* D.
[1]Of 30 samples for the adenosine triphosphate test and 30 samples for the residual protein test.
[2]Of 24 samples for the adenosine triphosphate test and 30 samples for the residual protein test.
ATP: Adenosine triphosphate; RLU: Relative light unit.

Table 3 The adenosine triphosphate and residual protein results after manual cleaning in the different groups (mean ± SD)

Groups		Samples	ATP test (RLU)	Samples	Residual protein test (μg)
T1		24	2141 ± 1913	30	31.27 ± 12.81
Ts	T2	10	2362 ± 1981	10	31.44 ± 14.19
	T3	10	2340 ± 2017	10	29.28 ± 8.46
	T4	10	1795 ± 1406	10	33.67 ± 19.75
	Total	30	2166 ± 1779	30	31.46 ± 14.46
D1		24	756 ± 834	30	30.51 ± 17.95
Ds	D2	10	1083 ± 854	10	28.80 ± 10.64
	D3	10	913 ± 730	10	34.33 ± 12.96
	D4	10	918 ± 956	10	36.18 ± 13.28
	Total	30	971 ± 826	30	34.66 ± 15.50

ATP: Adenosine triphosphate; RLU: Relative light unit.

difference in the removal of residual proteins. It is interesting to note that another study also reached a similar conclusion; this study used a Coomassie protein assay reagent to measure the residual proteins of the used endoscopes and observed no significant change before and after cleaning[25].

Simultaneously, further comparison after manual cleaning revealed that the RLU values were higher when using traditional precleaning buckets than when using the patented precleaning kits. This result indicates that, in addition to its better precleaning effect, our patented precleaning kit also has a beneficial effect on the subsequent cleaning process, that is, a more effective precleaning will improve the effectiveness of the entire cleaning process.

Moreover, the precleaning kit has better economic benefits in terms of medical safety. When using the traditional precleaning bucket, the amount of enzymatic detergent was determined by whether the aspirant is clarified, which varied from 100 mL to 200 mL according to different operators, with an average of approximately 136 mL. The disposable precleaning kit limited the amount of detergent used each time to 100 mL, which reduced the amount of enzymatic

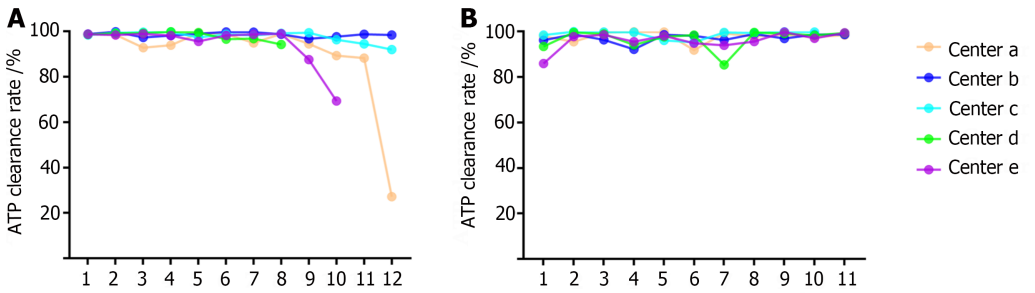

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Figure 2 The relationship between the precleaning sequence and adenosine triphosphate clearance rate at different centers (a-e). A: The relationship between the precleaning sequence and adenosine triphosphate (ATP) clearance rate when using the traditional precleaning bucket; B: The relationship between the precleaning sequence and ATP clearance rate when using disposable endoscope bedside precleaning kit. ATP: Adenosine triphosphate.

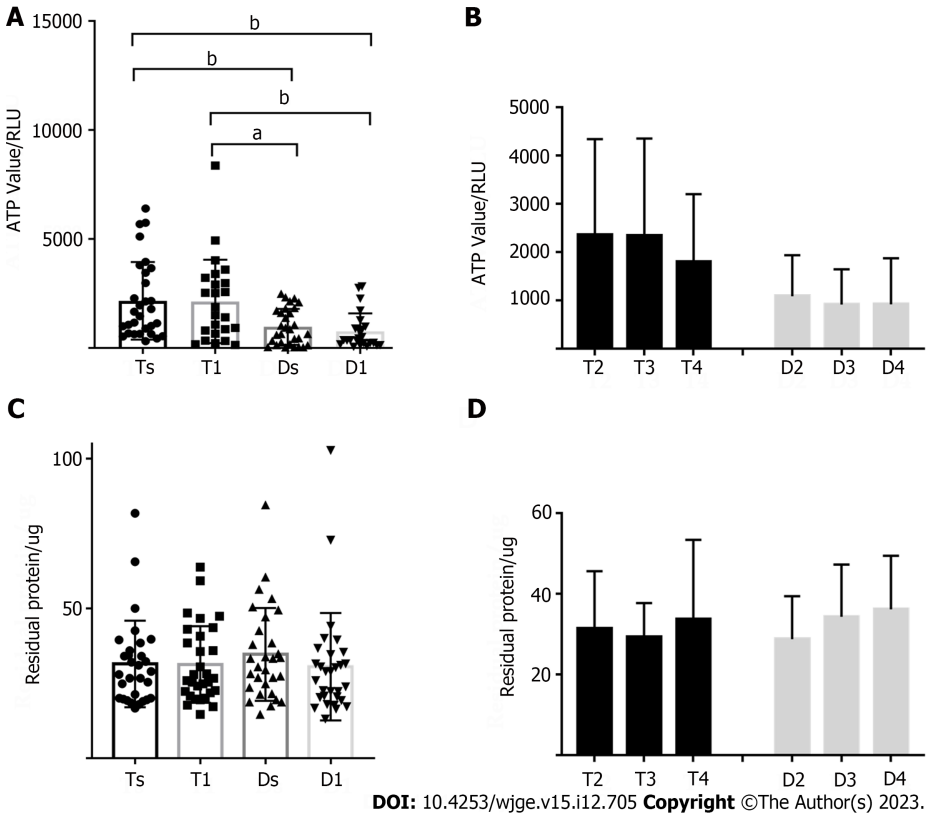

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Figure 3 Comparison of the adenosine triphosphate and residual protein results after manual cleaning. A: The adenosine triphosphate (ATP) results after manual cleaning by using different precleaning methods; B: The ATP results after manual cleaning at different cleaning solution replacement frequencies; C: The residual protein results after manual cleaning by using different precleaning methods; D: The residual protein results after manual cleaning at different cleaning solution replacement frequency. ATP: Adenosine triphosphate; RLU: Relative light unit. $^{a}P < 0.05$, $^{b}P < 0.01$.

detergent used for each endoscope in the precleaning process by approximately a quarter. Additionally, during manual cleaning in our research, no statistical difference was found among groups at different cleaning solution replacement frequencies of several times or every time, and the cleaning solution could still achieve a similar cleaning effect as the first time even after its fourth use. The multi-society guideline for reprocessing flexible GI endoscopes and accessories (2020) requires that the detergent solution should be replaced after each use and when the solution exceeds the specified dilution concentration or temperature range[14]. However, it shows a low level of evidence, and there are no large-scale clinical trials to prove its necessity. Moreover, clinically, there is no additional charge for endoscope reprocessing in most areas in China. Due to the high cost and increased usage of enzymatic detergents, the cost of enzymatic detergents accounts 20% of the total cost of the reprocessing procedures (take our hospital as an example). Therefore, it will be of great significance if the cleaning solution can be used more than one time while ensuring the cleaning effect, which may greatly reduce the clinical cost. According to our results, the cleaning solution can be used up to four or more times in the manual cleaning stage, thereby greatly reducing the usage of the enzymatic detergents and saving costs. Considering medical safety, our study did not further evaluate the cleaning effect when the cleaning solution was used for more than four times, although the test results indicated that it may still qualify after five times of use in the pre experiment; our

data may be supplemented in our future research. Overall, the disposable precleaning kit can save a quarter of the cost of the enzymatic detergent during the precleaning process, whereas, in manual cleaning, it can save three-quarters of the cost of the cleaning solution, as it allows the cleaning solution to be used four times before being replaced.

The present study has still some shortcomings. The enzymatic detergents work within a certain temperature range, whereas warm water is used in the manual cleaning stage. The cleaning effect of the enzymatic detergent will be weakened since there is no constant temperature device during precleaning. Additionally, a recent study found that cough evoked during endoscopy is a major source of elevated aerosol levels. Therefore, endoscopy should be regarded as a procedure with a high risk of producing respiratory aerosols, especially in patients with the coronavirus disease 2019 or infected by other respiratory pathogens[26-29]. Our future research direction is to continue optimizing the design of the disposable endoscope bedside precleaning kit, with the primary plan of equipping the device with a thermostat to maintain the temperature of the enzyme detergent, and adding a lid to prevent aerosol pollution. In the future, we will conduct experiments to detect viruses and prions to perfect our research. Moreover, we will continue to promote the application of precleaning kits nationwide to obtain more clinical data.

CONCLUSION

The disposable endoscope bedside precleaning kit has advantages in the precleaning stage and can save cost in terms of the amount of detergent used in the precleaning stage. Moreover, its better and more stable precleaning effect can improve the effectiveness of the subsequent reprocessing procedures. Meanwhile, with this precleaning kit, the cleaning solution can be used up to four times without reducing the cleaning effect in the manual cleaning stage, suggesting a significant cost advantage in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Precleaning is a key step in endoscopic reprocessing. There are some non-standard operations in the endoscopic precleaning stage in clinical practice, which increases the risk of endoscopic related infections. Therefore, it is important to improve the endoscopic precleaning method.

Research motivation

The research aims to develop an effective and economic endoscope cleaning method to reduce endoscopic related infections and reduce clinical costs.

Research objectives

The research aims to verify the clinical effectiveness, safety and economic benefits of our designed disposable endoscope bedside precleaning kit and it is expected to improve and supplement the endoscopic cleaning methods.

Research methods

Exploring the effectiveness of a disposable endoscope bedside precleaning kit through multi-center and observational research, and the precleaning kit is a patented product.

Research results

The disposable endoscope bedside precleaning kit can save cost in terms of the amount of detergent used in the precleaning stage and has better and more stable precleaning effect, which can improve the effectiveness of the subsequent reprocessing procedures. Meanwhile, the cleaning solution can be used up to four times without reducing the cleaning effect in the manual cleaning stage. The results provide a reference for the improvement of endoscopic precleaning methods. However, a larger sample size and more detection methods are still needed to verify this result.

Research conclusions

This study proposes a new endoscopic reprocessing method that uses a disposable endoscope bedside precleaning kit for precleaning and reuses the cleaning solution during the manual cleaning, which can improve cleaning effectiveness and reduce clinical costs.

Research perspectives

The future research direction is to continue optimizing the design of the disposable endoscope bedside precleaning kit and conduct experiments to detect viruses and prions to perfect the research. Moreover, it is particularly important to promote the application of precleaning kits nationwide to obtain more clinical data.

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FOOTNOTES

Author contributions: Wang YF, Wu Y, and Liu XW designed the study; Wang YF, Wu Y, Li JG, Zhan YQ, Liu B, Fan WL, Peng ZH, Xiao JT, Li BB, and He J performed the study and collected the data; Wang YF analyzed data and wrote the manuscript; Yi J, and Lu ZX revised the manuscript; Wu Y and Liu XW modified the manuscript critically; and all authors have read and approve the final manuscript.

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ORIGINAL ARTICLE

Observational Study

Disparities in esophageal cancer incidence and esophageal adenocarcinoma mortality in the United States over the last 25-40 years

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Abstract

BACKGROUND

Esophageal carcinoma presents as 2 types, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) with the frequency of both changing in the United States (US).

AIM

To investigate EAC/ESCC incidence time trends among the 3 main US racial groups and investigate trends in US EAC survival by ethnicity.

METHODS

Twenty-five years (1992-2016) of data from SEER 13 program was analyzed to compare incidence trends in EAC and ESCC between non-Hispanic whites (nHW), non-Hispanic Blacks (nHB) and Hispanics (Hisp) using SEERStat®. In addition, SEER 18 data, from 1975-2015, on EAC in the US was analyzed to evaluate racial disparities in incidence and survival using SEERStat® and Ederer II method.

RESULTS
In the 3 major US ethnic groups, age-adjusted incidence of ESCC has declined while EAC has continued to rise from 1992-2016. Of note, in Hisp, the EAC incidence rate increased while ESCC decreased from 1992 to 2016, resulting in EAC as the predominant esophageal cancer subtype in this group since 2011, joining nHW. Furthermore, although ESCC remains the predominant tumor in nHB, the difference between ESCC and EAC has narrowed dramatically over 25 years. EAC survival probabilities were worse in all minority groups compared to nHw.

CONCLUSION
Hisp have joined nHW as US ethnic groups more likely to have EAC than ESCC. Of note, EAC incidence in nHB is increasing at the highest rate nationally. Despite lower EAC incidence in all minority groups compared to nHW, these populations have decreased survival compared to nHW.

Key Words: Esophageal carcinoma; Ethnicity; Incidence; Survival; Disparity; Race

Core Tip: There is a higher incidence of esophageal adenocarcinoma (EAC) in non-Hispanic whites (nHw). Esophageal squamous cell carcinoma (ESCC) is more common than EAC in non-Hispanic Blacks. Previous research reported higher incidence of ESCC compared to EAC in Hispanics (Hisp) as well. This study reveals that Hisp have joined nHw as US ethnic groups with EAC as the predominant esophageal cancer. Despite lower EAC incidence in all minority groups compared to nHw, these populations have lower survival compared to nHw.

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INTRODUCTION

Esophageal carcinoma (EC) is the eight most common malignancy and the sixth leading cause of cancer related mortality globally[1,2]. The 5 year survival rate of esophageal carcinoma is 15%-30%, making it one of the most lethal malignancies [3-5]. There are 2 main histological subtypes of esophageal carcinoma, esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC). Depending on the histological subtype, incidence of esophageal carcinoma is 3-10 times higher in males compared to females[6].

Ethnic disparities in esophageal carcinoma incidence and prevalence have been evaluated in the past. Higher incidence of EAC in non-Hispanic White (nHW) males is well known and it has been reported to be the most rapidly increasing solid organ malignancy in this ethnic and gender group[7]. In contrast, ESCC is more common than EAC in non-Hispanic Blacks (nHB)[8]. In addition to environmental factors, genetic factors are also thought to play an important role in EC ethnic disparities[9].

Hispanics (Hisp) comprise 18.5% of the total US population, making them the largest minority ethnic group in the United States (US) per the US Census Bureau[10]. Very limited data is available evaluating esophageal cancer in Hisp. Ricardo *et al*[11] reported higher number of metastatic and untreated EC cases in Hisp despite lower prevalence compared to nHW. Previous research also reported higher incidence of ESCC in Hisp[12]. In addition, incidence trends of EAC in other minority ethnic groups like Hisp, non-Hispanic American Indians/Alaska native (nHAI/AN), non-Hispanic Asians/Pacific islanders (nHA/PI) have not been well assessed. Furthermore, EAC-related survival in US minority groups has not been studied. Thus, the primary study aim was to examine EC incidence time trends (both EAC & ESCC) between the 3 main US racial groups, with a focus on Hisp, assessing 25 years of data and the second aim of our study was to investigate temporal trends in incidence of EAC over the last 40 years in the US and highlight ethnic disparities in survival.

MATERIALS AND METHODS

Phase 1

Using data from the Surveillance, Epidemiology, and End Results 13 (SEER) program of cancer registries, we collected 25 years (1992-2016) data on EAC and ESCC in the US. This data was adjusted for age to the US 2000 standard population using SEERStat®. After age adjustment, this data was plotted using Microsoft Excel® to visually compare incidence trends

in EAC and ESCC over 25 years in nHW, nHB and Hisp. Annual percent change (APC) was calculated using weighted least squares method and p values were calculated using SEERStat® and *t*-test.

Phase 2

Using data from the Surveillance, Epidemiology, and End Results 18 (SEER) program of cancer registries, we collected 40 years (1975-2015) data on esophageal adenocarcinoma in the US. After adjusting for age using SEERStat®, this data was plotted to visually compare trends over the last 40 years in different ethnic groups. Ten years of (2006-2016) data was used to calculate relative survival rates at 1, 2, 3, 4, and 5 years for different ethnic groups using Ederer II method and compared between these groups.

RESULTS

In phase 1 of this study, 25 years of data from SEER 13 cancer registry was analyzed. For the 3 largest ethnic groups in the US (nHw, nHB, Hisp), EAC age adjusted incidence increased during the study period while the ESCC rate declined. In Hisp, the incidence rate of EAC increased from 0.8 to 1.5/100000 (APC = 1.5, $P < 0.001$) compared to ESCC decreasing from 2.2 to 0.8/100000 over the study period (APC = -3.1, $P < 0.001$, Figure 1, Table 1). This change over time has resulted in EAC becoming the predominant esophageal cancer since 2011 in Hisp. Among nHw, the EAC incidence rate increased from 1.7 to 3/100000 (APC = 2.2, $P < 0.001$) while ESCC incidence decreased from 1.8 to 0.9/100000 (APC = -2.5, $P < 0.001$, Figure 1, Table 1). This has lead to EAC as the predominant esophageal cancer since 1993 within this group. For nHB, EAC incidence increased from 0.4 to 0.8/100000 (APC = 2.6, $P < 0.001$) while ESCC dramatically decreased from 8.8 to 2.7/100000 (APC = -5.2, $P < 0.001$, Figure 1, Table 1) over the study interval. Despite these EC changes in nHB, ESCC remains the predominant esophageal cancer in this group.

Table 1 Age adjusted incidence rates per 100000 (1992-2016) and annual percent change in esophageal squamous cell and adenocarcinoma for different racial groups in the United States

	nHW		nHB		Hisp	
	EAC	ESCC	EAC	ESCC	EAC	ESCC
1992-2016 APC	2.2	-2.5	2.6	-5.2	1.5	-3.1
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Year	**Rate**	**Rate**	**Rate**	**Rate**	**Rate**	**Rate**
1992	1.7	1.8	0.4	8.8	0.8	2.2
1993	1.8	1.8	0.5	8.4	1	1.9
1994	1.8	1.7	0.3	7.6	1.1	1.6
1995	1.9	1.8	0.3	7.3	0.9	1.8
1996	2.3	1.6	0.6	7.9	1.1	1.4
1997	2.2	1.6	0.5	6.4	1.4	1.4
1998	2.3	1.6	0.3	5.7	1.1	1.1
1999	2.6	1.5	0.6	5.4	1.5	1.7
2000	2.6	1.4	0.6	5.2	1.2	1.4
2001	2.5	1.6	0.6	4.9	1.4	1.3
2002	2.6	1.3	0.6	4.9	1.2	1.1
2003	2.7	1.3	0.4	5.3	0.9	1.1
2004	3	1.5	0.5	4.7	1.5	1.4
2005	2.7	1.3	0.7	3.9	1.3	1.1
2006	2.9	1.2	0.5	4.1	0.8	1
2007	3	1.2	0.7	3.7	1.1	1.2
2008	3.2	1.1	0.9	3.5	1.2	0.9
2009	3	1.3	0.9	3.6	1.4	1
2010	2.9	1.1	0.6	3.4	1.2	1.3

2011	3.2	1.2	0.6	2.7	1.6	0.9
2012	3	1.1	0.8	2.6	1.8	0.9
2013	3.1	1.1	0.8	2.9	1.3	0.9
2014	3	1	0.8	2.7	1.3	0.9
2015	3.1	1.1	0.6	2.4	1.6	0.9
2016	3	0.9	0.8	2.7	1.5	0.8

ESCC: Esophageal squamous cell; EAC: Adenocarcinoma; nHB: Non-Hispanic Blacks; nHW: Non-Hispanic Blacks; Hisp: Hispanics.

In phase 2, 40 years of EAC data was analyzed (1975 to 2015). The overall age adjusted incidence rate of EAC progressively increased from 1975 to 2007 in the US (0.4/100000 to 2.8/100000). Following, a plateau in the age adjusted incidence rate was observed (Age adjusted incidence rate of EAC for all races in 2007 = 3/100000, age adjusted incidence rate of EAC for all races in 2016 = 3/100000) (Table 2, Figure 2). A similar trend was observed in nHw and nHB. In nHw, age adjusted incidence rate of EAC was 3/000000 in 2007 and 3.1/100000 in 2016. In nHB, age adjusted incidence rate of EAC was 0.6/100000 in 2007 and 0.5/100000 in 2016 (Table 2, Figure 2). However, in the other minority group (a combination of nHAI/AN and nHA/PI), EAC incidence continues to rise after 2007. The age adjusted incidence rate was 0.5/100000 in 2007 and 0.8/100000 in 2016 in the combined other minority group.

Table 2 Age adjusted esophageal adenocarcinoma incidence rates per 100000, United States ethnic groups (1975-2015)

Year	All races	nHW	nHB	Others (American Indian/AK Native, Asian/PI)
1975	0.4	0.4	0.2	0
1976	0.4	0.4	0.1	0
1977	0.4	0.4	0	0
1978	0.4	0.4	0.2	0
1979	0.7	0.7	0.1	0.1
1980	0.5	0.6	0.1	0
1981	0.5	0.6	0.2	0.1
1982	0.6	0.6	0.1	0
1983	0.8	0.9	0.1	0.2
1984	0.7	0.8	0.2	0.3
1985	0.8	0.9	0.4	0.1
1986	0.9	1	0.2	0.5
1987	1.1	1.2	0.1	0
1988	1.1	1.3	0.2	0.1
1989	1.1	1.3	0.1	0.3
1990	1.3	1.5	0.5	0.4
1991	1.3	1.5	0.2	0.4
1992	1.5	1.7	0.3	0.4
1993	1.6	1.8	0.4	0.5
1994	1.6	1.8	0.3	0.6
1995	1.6	1.8	0.3	0.5
1996	2	2.3	0.5	0.7
1997	1.9	2.2	0.5	0.3
1998	2	2.4	0.3	0.2
1999	2.2	2.6	0.5	0.3

2000	2.2	2.6	0.6	0.7
2001	2.2	2.5	0.4	0.5
2002	2.2	2.6	0.5	0.4
2003	2.2	2.6	0.4	0.4
2004	2.7	3.1	0.6	0.8
2005	2.4	2.8	0.7	0.9
2006	2.4	2.9	0.5	0.6
2007	2.5	3	0.6	0.5
2008	2.7	3.2	0.8	0.8
2009	2.5	3	0.6	0.6
2010	2.4	2.8	0.6	0.7
2011	2.6	3.1	0.5	0.5
2012	2.6	3.1	0.7	0.5
2013	2.6	3.1	0.7	0.4
2014	2.5	3	0.7	0.7
2015	2.7	3.2	0.6	0.8
2016	2.6	3.1	0.5	0.8

nHB: Non-Hispanic Blacks; nHW: Non-Hispanic Blacks; PI: Pacific islanders.

The comparison of relative survival in EAC yields noteworthy results. Minority groups had much worse EAC survival probabilities compared to nHw despite lower incidence rates. Relative survival was 44% in nHB, 46% in Hisp and 48% in nHW after 1 year of diagnosis with the worst 1 year EAC survival probability noted in non-Hispanic American Indians/Alaska Natives (nHAI/AN) at 33%. Five year survival rate was 14% for Hisp and nHB while 18% for nHw with worst 5 year survival probability seen for nHA/PI with relative survival rate of 12% only (Figure 3, Table 3).

Table 3 Relative survival rates of different ethnic and racial groups for esophageal adenocarcinoma (2007-2016)

Mo	Non-Hispanic White (%)	Non-Hispanic Black (%)	Non-Hispanic American Indian/Alaska Native (%)	Non-Hispanic Asian or Pacific Islander (%)	Hispanic (%)
12	48.80	44.10	33.10	46.00	46.20
24	30.60	26.90	23.10	27.30	29.40
36	23.50	18.20	19.30	21.30	22.30
48	20.20	14.60	17.50	15.00	17.70
60	18.20	14.20	17.50	12.30	14.30

DISCUSSION

EC is a malignancy with dismal survival probabilities. It shows significant racial disparities in incidence and survival rates. Thus, it became important to obtain and assess updated data on EC for analysis to study ongoing EC trends in minority groups.

In phase 1 of our study, we gathered 25 years of (1992-2016) data using the SEER 13 cancer registry and studied trends in both EAC and ESCC in 3 main racial groups in the US. The most prevalent esophageal cancer subtype among Hisp initially was ESCC. Revel *et al*[12] showed ESCC comprised 59.8% cases compared to 40.8% of EAC among Hisp diagnosed with EC from 2003 to 2008. The significant finding of the current investigation is the shift in incidence of histologic subtypes of esophageal cancer among Hisp. In this group, EAC incidence increased over 25 years from 0.8 to 1.5/100000 while ESCC incidence fell during this interval from 2.2 to 0.8/100000, resulting in EAC as the predominant esophageal cancer in Hisp. Our study is the first to report this change. Recent studies have also reported changing trends of EC subtypes in nHB. Ashktorab *et al*[13] reported decreased frequency of ESCC as part of overall EC cases from 97% in 1960s to 68% in 2000s while noting an increase in EAC from 2.7% to 31% over the same period. The current study showed age adjusted incidence rate of EAC increased from 0.4 to 0.8/100000 and incidence of ESCC declined from 8.8 to 2.7/

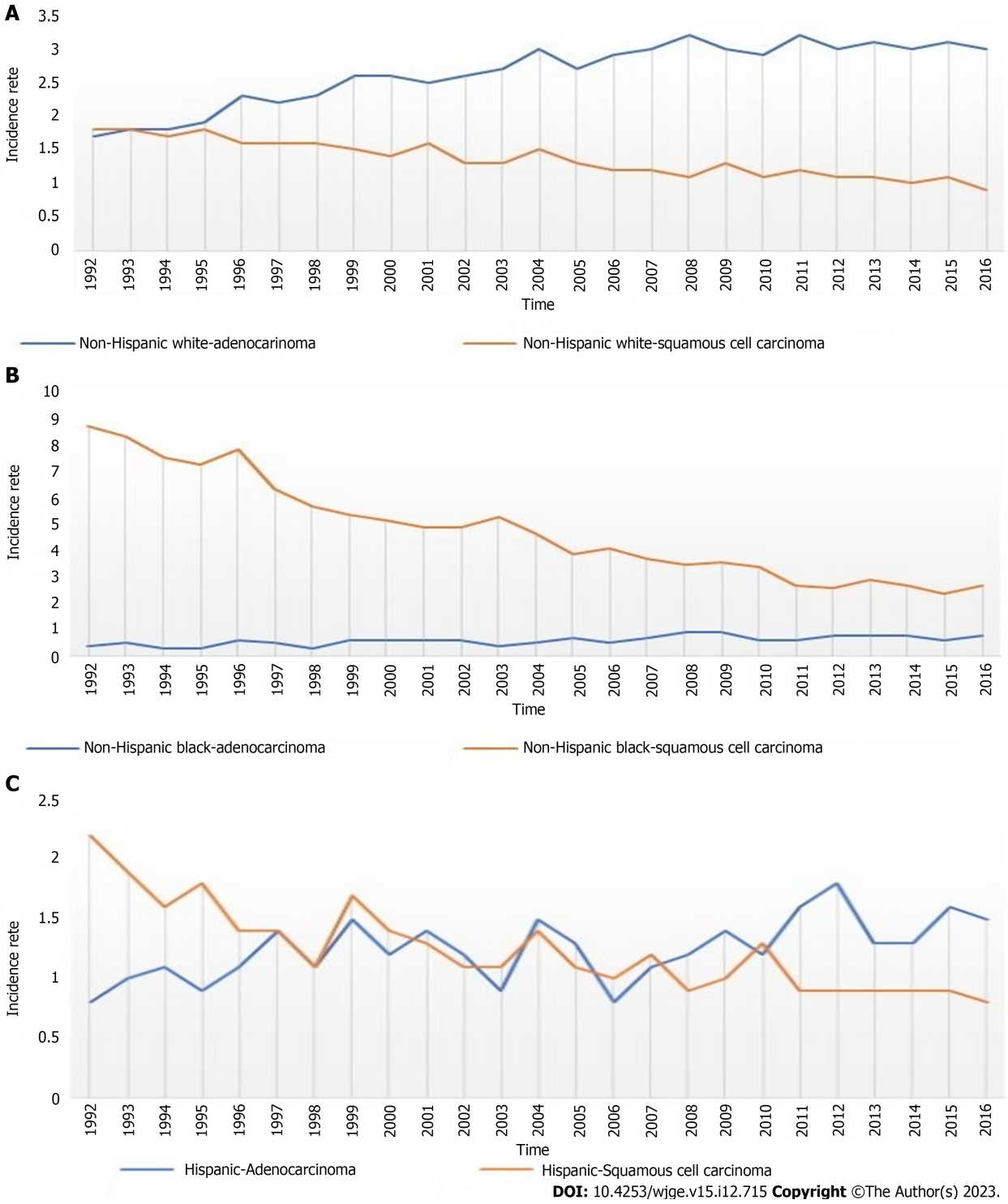

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Figure 1 Age adjusted incidence rates (1992-2016) of esophageal adenocarcinoma and squamous cell carcinoma in non-Hispanic White, non-Hispanic Black, and Hispanics. A: Non-Hispanic White; B: Non-Hispanic Black; C: Hispanics.

100000 in nHB. If current trends continue over the next two decades, it is likely that nHB will join nHW and Hisp in terms of higher EAC incidence compared to ESCC.

In phase 2 of our study, using 40 years (1975-2015) of data from SEER 18 cancer registries, we focused on EAC and investigated ethnic disparities in incidence and survival probabilities. The overall age-adjusted incidence rate of EAC increased progressively between 1975 to 2007. Similar trends were reported by Heitmiller *et al*[14] using the data from Johns Hopkins tumor registry and by Daly *et al*[15] using the National Cancer Database. The etiology of the changing trend remains to be elucidated, but it is noteworthy that it is accompanied by a parallel rise in the incidence of cancer of gastroesophageal junction, the precursor of which is Barrett's esophagus and metaplastic changes induced by reflux disease[16,17]. After 2007, the incidence rate of EAC seems to plateau in nHw and while increasing slowly in all minority groups. There is limited literature for EAC incidence and ethnic disparities after 2007. In a study using the United States Cancer Statistics database, Patel *et al*[18] showed recent trends in EAC which were similar to our findings. Similar to

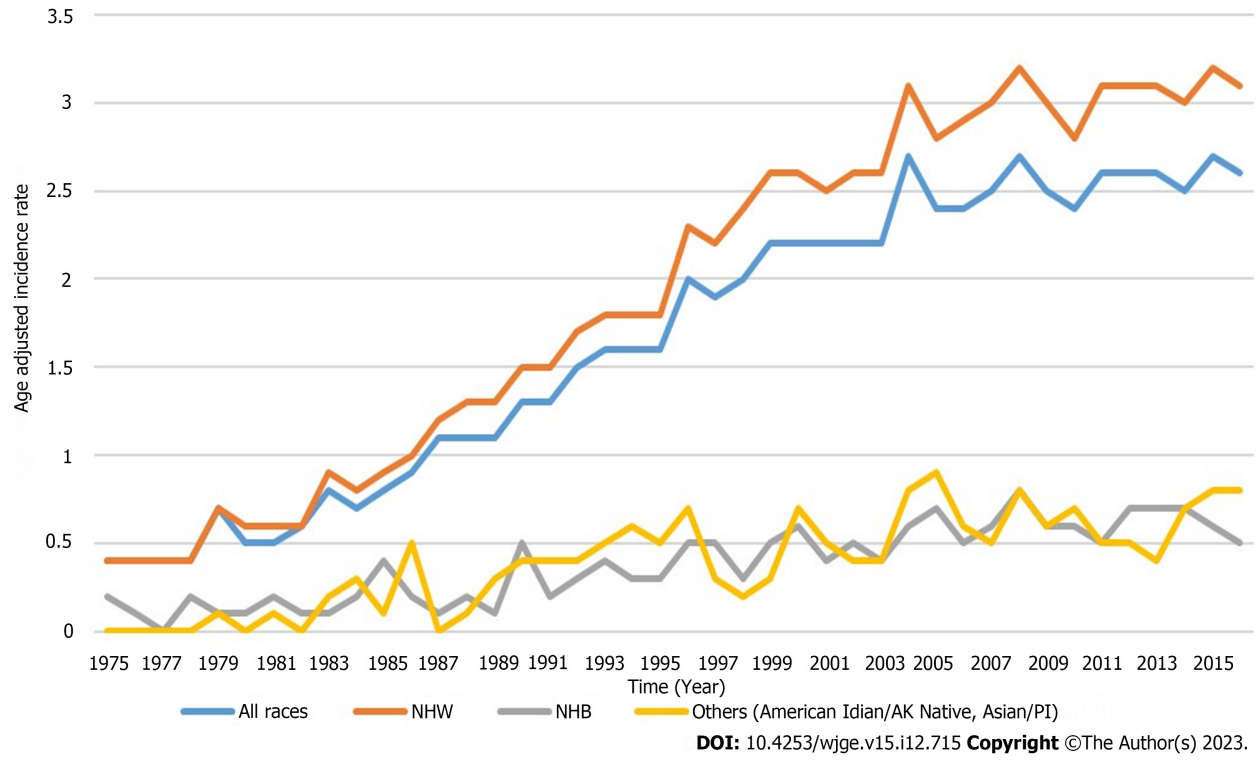

Figure 2 Age adjusted incident rates of esophageal adenocarcinoma for all ethnicities (1975-2015).

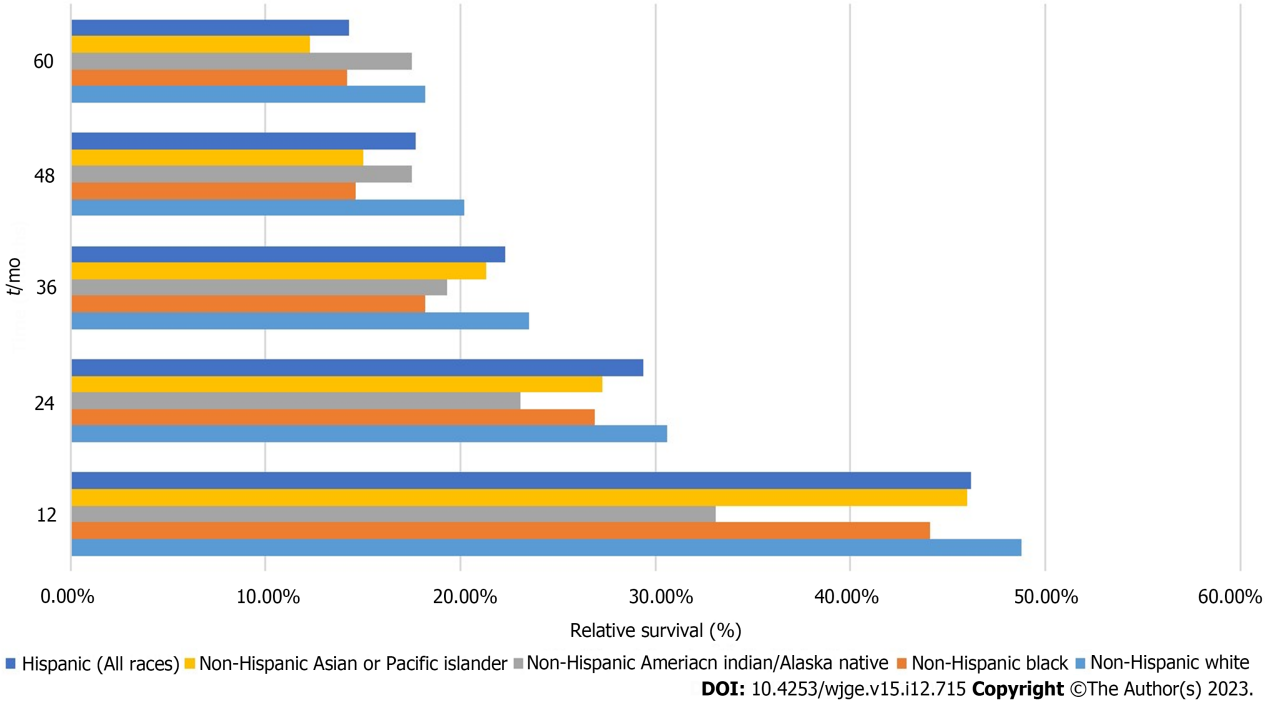

Figure 3 Racial disparities in relative survival after diagnosis of esophageal adenocarcinoma (2007-2016).

multiple prior studies, our study again showed that EAC incidence remains higher in nHW compared to other minority ethnic groups (2016; nHW = 2.6/100000, nHB = 0.5/100000, others = 0.8/100000)[8,19-22].

Gastroesophageal reflux disease (GERD) and obesity are major risk factors for EAC, amongst others[4,23]. A recent systematic review by El-Serag showed increasing prevalence of GERD worldwide, and the same is true for the trends of obesity[24,25]. GERD poses a directly proportional risk for EAC which explains increasing incidence trend of EAC in our study[26]. Bersentes and colleagues showed comparable trends of prevalence of Barrett's esophagus between nHw and Hisp which may explain increasing incidence of EAC in Hisp observed in the current investigation[27]. Genetic factors can also potentially explain the change in incidence trends observed in our study. Genome-wide association studies have

identified various susceptibility loci for EAC that demonstrate familial clustering, leading to a shift in ethnic trends in incidence and prevalence of EAC[4,28,29].

Although ethnic disparities in survival have been reported previously for EC, only one study has been performed previously to evaluate disparities specifically for EAC. In addition, very limited research has been performed to evaluate survival probabilities for minority ethnic groups like Hisp, nHAI/AN, nHA/PI. Greenstein *et al*[30] showed higher mortality rates among nHB when compared to nHw after EC diagnosis. Multiple investigators also showed similar trends and confirmed that nHB, Hisp and other minority groups show greater mortality and poor survival than nHw[12,31,32]. Adams *et al*[19] showed ethnicity is not an independent risk factor for EC in their population-based analysis of EC cases. In contrast, Laszkowska *et al*[33] suggested mortality was higher in EAC in nHW than nHB, Hisp and nHA/PI. However, this study used incidence-based mortality assessment for statistical analysis which lacks information about disease onset. In the present study, the latest data over a decade was evaluated to investigate survival probabilities in different racial groups at 1, 2, 3, 4, and 5 years after diagnosis. The results showed nHw with decreased mortality rates compared to all minority groups at 1 and 5 years. Prior studies investigating poor EC survival have pointed out that advanced stage malignancy at presentation and underutilized cancer-directed surgical therapy in potentially resectable tumors results in poor survival in minority groups[12,31,34]. Socioeconomic factors, cultural beliefs, and language barriers in minority groups may also be other potential contributory factors to survival disparities. Moreover, the rapidly accumulating amount of genetic and transcriptomic date will hopefully allow for improved stratification resulting in optimal therapy and prognosis based on molecular subtype[35].

This investigation has limitations that require comment. First, the presence or absence of Barrett's esophagus was not reported. Second, other known clinical risk factors such as smoking, alcohol use, obesity or ongoing reflux disease was not assessed because information on these items is not available in the SEER database. Furthermore, errors may be present in the database due to misclassification of patient race/ethnicity information.

Conversely, there are strengths to the current study. The sample size allows for improved understanding of trends in incidence and survival of EC subtypes in different races. In addition, demonstration of opposing ethnic trends in different histologic types of esophageal cancer in the same population confers internal validity to the study results.

CONCLUSION

In summary, Hisp have joined nHw as US ethnic groups with EAC as the predominant esophageal cancer. Furthermore, nHB have the highest APC in EAC incidence among the 3 main US racial groups. Regrettably, all US minority groups with EAC have lower survival than nHw despite a decreased incidence of this cancer compared to nHw. Understanding EAC in Hisp may provide insight regarding changes in EAC incidence among US minority groups. In addition, evaluation of potential factors contributing to worse short and long-term survival for US minority EAC patients is warranted.

ARTICLE HIGHLIGHTS

Research background

Esophageal adenocarcinoma (EAC) and esophageal squamous cell carcinoma (ESCC) frequency have changed and are continuing to change in the United States (US).

Research motivation

To determine EAC/ESCC incidence among the 3 main US racial groups and investigate US EAC survival by ethnicity.

Research objectives

To investigate time trends in EAC/ESCC incidence among the 3 main US racial groups and investigate trends in US EAC survival by ethnicity.

Research methods

Analysis of 25 years (1992-2016) SEER 13 data to compare incidence trends in EAC and ESCC between non-Hispanic whites (nHW), non-Hispanic Blacks (nHB) and Hispanics (Hisp). In addition, SEER 18 data, from 1975-2015, on EAC in the US was analyzed to evaluate racial disparities in incidence and survival among nHW, nHB and Hisp.

Research results

In Hisp, the EAC incidence rate increased while ESCC decreased from 1992 to 2016, resulting in EAC as the predominant esophageal cancer subtype in this group since 2011, joining nHW. Furthermore, although ESCC remains the predominant tumor in nHB, the difference between ESCC and EAC has narrowed dramatically over 25 years. EAC survival probabilities were worse in all minority groups compared to nHw.

Research conclusions

Hisp are the 2nd US ethnic group to have EAC as their predominant EC cancer type. Of note, EAC incidence in nHB is

increasing at the highest rate nationally. Despite lower EAC incidence in all minority groups compared to nHW, these populations have decreased survival compared to nHW.

Research perspectives

Understanding EAC in Hisp may provide insight regarding changes in EAC incidence among US minority groups. In addition, evaluation of potential factors contributing to worse short and long-term survival for US minority EAC patients is warranted.

FOOTNOTES

Author contributions: Arshad HMS and Vega KJ designed the research study; All authors performed the research; Arshad HMS and Vega KJ analyzed the data and wrote the manuscript; All authors have read, edited and approve the final manuscript version.

Institutional review board statement: Studies using SEER database are considered exempt by the Institutional Review Board of Augusta University-Medical College of Georgia.

Informed consent statement: This study utilized SEER cancer incidence and mortality data from population-based cancer registries covering approximately 47.9 percent of the U.S. population which did not require a specific informed consent.

Conflict-of-interest statement: All the authors have no relevant financial or non-financial interests to disclose.

Data sharing statement: No additional data are available.

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ORIGINAL ARTICLE

Prospective Study

New hope for esophageal stricture prevention: A prospective single-center trial on acellular dermal matrix

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Abstract

BACKGROUND

Given the high incidence of esophageal cancer in China, an increasing number of patients there are undergoing endoscopic mucosal dissection (ESD). Although the 5-year survival rate after ESD can exceed 95%, esophageal stricture, the most common and serious postoperative complication, affects the long-term prognosis of patients and the quality of life. Autologous mucosal grafts have proven to be successful in preventing stricture after ESD for early esophageal cancer.

AIM

To examine the viability of acellular dermal matrix (ADM) as an alternative to

autologous mucosa for the prevention of stricture after ESD.

METHODS

This is a prospective, single-center, controlled study. Consecutive patients who underwent ESD surgery and were willing to undergo autologous mucosal transplantation were recruited between January 1 and December 31, 2017. Consecutive patients who underwent ESD surgery and were willing to undergo ADM transplantation were recruited between January 1 to December 31, 2019. A final three-year follow-up of patients who received transplants was conducted.

RESULTS

Based on the current incidence of esophageal stricture, the sample size required for both the autologous mucosal graft group and the ADM group was calculated to be 160 cases. Due to various factors, a total of 20 patients with autologous mucosal grafts and 25 with ADM grafts were recruited. Based on the inclusion exclusion and withdrawal criteria, 9 patients ultimately received autologous mucosal grafts and completed the follow-up, while 11 patients received ADM grafts and completed the follow-up. Finally, there were 2 cases of stenosis in the autologous mucosal transplantation group with a stenosis rate of 22.22% and 2 cases of stenosis in the ADM transplantation group with a stenosis rate of 18.18%, with no significant difference noted between the groups (P = 0.94).

CONCLUSION

In this prospective, single-center, controlled trial, we compared the effectiveness of autologous mucosa transplantation and ADM for the prevention of esophageal stricture. Due to certain condition limitations, we were unable to recruit sufficient subjects meeting our target requirements. However, we implemented strict inclusion, exclusion, and withdrawal criteria and successfully completed three years of follow-up, resulting in valuable clinical insights. Based on our findings, we hypothesize that ADM may be similarly effective to autologous mucosal transplantation in the prevention of esophageal stricture, offering a comparable and alternative approach. This study provides a new therapeutic idea and direction for the prevention of esophageal stricture.

Key Words: Over-the-scope clip; Duodenal subepithelial lesion; Endoscopic resection; Perforation

Core Tip: Preventing esophageal stricture after endoscopic submucosal dissection (ESD) is a critical challenge in the successful treatment of early esophageal cancer. Acellular dermal matrix (ADM) has recently emerged as a potential solution. This study showed that the preventive effect of ADM on esophageal stricture was comparable to that of autologous mucosa. Despite the study's limited sample size, it includes improved postoperative follow-up and holds clinical significance. The results validate ADM as a viable alternative for preventing esophageal stricture. These findings will potentially revolutionize ESD treatment for early esophageal cancer and provide safer and more accessible options for such patients.

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INTRODUCTION

With the maturity of endoscopic technology, endoscopic submucosal dissection (ESD) can now be used to remove large lesions and ensure a negative margin to the greatest extent[1], making it the preferred treatment for early esophageal cancer. Esophageal stricture is one of the most common and serious complications after ESD, with an incidence of approximately 37%-92%[2]. Its incidence is affected by many factors, mainly including mucosal resection > 3/4 of the esophagus circumference[3], resection length > 30 mm, muscular propria injury, and deep resection depth[4].

Among these factors, the one most closely related to the incidence of stenosis was found to be the scope of resection. According to reports, the incidence of stenosis in mucosal resection > 3/4 cases is 60%-100%, while the stenosis rate in near-total resection can reach 88%-100%[5]. Patients with esophageal stenosis may have varying degrees of dysphagia in more stenotic cases. In severe cases, nausea and vomiting may occur after eating, resulting in long-term insufficiency in the nutritional intake, water and electrolyte imbalance, cachexia, and even fatal inhalation[6,7], seriously affecting the long-term quality of life of patients. Furthermore, in severe cases, repeated endoscopic esophageal dilation or even surgical intervention may be required[8]. This increases the financial, physical, and psychological burden on patients.

How to prevent esophageal stricture safely and effectively is thus a key issue influencing the ESD-based treatment of early esophageal cancer.

At present, the commonly used measures to prevent stenosis are mainly local or systemic applications of glucocorticoids[9]. After the application of hormones, the overall incidence of esophageal stricture was 13.5%, thus effectively reducing the incidence of esophageal stricture[6,10]. However, there is a risk of local esophageal perforation or secondary fatal infection, and some patients are contraindicated for hormone application due to their condition, so hormone therapy cannot be used to prevent stricture in all cases.

With the advent of autologous mucosal transplantation technology, relevant studies have explored the effectiveness of mucosal transplantation in preventing esophageal stricture through animal and human experiments[11,12]. However, while the utility of autologous mucosa for preventing esophageal stricture is well-established, autologous mucosal grafts are still subject to many limitations, as the acquisition of autologous mucosa is dependent on the patient and the required slice of mucosal cells, depending on the extent of the lesion. For example, for large lesions, it is necessary to obtain and prepare the appropriate mucosal slices, which can cause secondary damage to the patient. In addition, not all patients are in a condition to accommodate the acquisition and preparation of autologous mucosa. Therefore, such patients may not be able to undergo transplantation and thereby reduce their risk of stenosis.

Several trials have confirmed that cell sheets prepared by culturing oral mucosal cells have the same characteristics as mucosa and can be applied to prevent stenosis. However, the preparation process is time-consuming, which may delay the patient's treatment window and affect the prognosis. Acellular dermal matrix (ADM) is a kind of dermal substitute obtained from the allogeneic dermis after special treatment to remove its cellular components[13]. It is usually made of pig or human skin inactivated by a virus and cobalt-60[14]. It is prepared by sterilization, decellularization, and other processes[14]. The allogeneic dermis that has cellular components removed and retains elastin, keratan sulfate, laminin, and collagen has very low immune activity and will not induce any rejection[15,16]. In addition, studies have shown that ADM can be beneficial for inducing tissue regeneration and promoting cell growth[17]. During this process, ADM is degraded and utilized by local tissues, which is accompanied by the degradation of ADM itself[18]. It is expected to replace autologous mucosa as a graft after ESD for esophageal cancer and thereby prevent the occurrence of esophageal stricture.

Overall, as a novel material, ADM has the potential to replace autologous mucosal grafts for the prevention of esophageal stenosis. This prospective, single-center controlled study investigated the role of ADM as a substitute for autologous mucosa in the prevention of post-cancer surgery stenosis, with an aim to provide a new perspective and approach for the treatment of esophageal stenosis.

MATERIALS AND METHODS

Study design

This prospective, single-center, controlled study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Taizhou Hospital, Zhejiang Province, under the Institutional Review Board of Wenzhou Medical University (autologous mucosa transplantation approval number: K20190123; ADM transplantation approval number: X20190603). It was registered with the Center for Clinical Trials under registration number ChiCTR200040119.

Inclusion criteria: A preoperative chromoendoscopy assessment meeting the surgical indications; lesion circumference > 1/2; endoscopic treatment under general anesthesia able to be tolerated; agreed to accept inclusion in the clinical trial and sign the informed consent form for the operation.

Exclusion criteria: Eating disorders and absorption disorders with other causes; complication with diabetes and autoimmune diseases or a recent history of taking hormones and immunosuppressants; a history of serious cardiovascular and cerebrovascular diseases, serious liver and kidney insufficiency, or serious chronic lung diseases; acute or chronic infection.

Exit criteria: Postoperative pathological results indicating the need for further surgery, radiotherapy, chemotherapy, or other treatments; severe postoperative stenosis with a poor effect of repeated endoscopic catheter dilation, necessitating radial esophagotomy and surgery; withdrawing from the trial or being lost to follow-up for any reason; patient death.

At the follow-up evaluation, cases with difficulty swallowing and endoscopy showing that the gastroscope could not pass smoothly through the narrowest part, requiring intervention such as endoscopic dilation therapy, were defined as having postoperative stenosis.

Operation details

The surgery was performed using an Olympus GIF-Q260J gastroscope (Olympus Corporation, Japan), high-frequency electric generator, needle-type incision knife, terminal insulated scalpel (IT knife), triangular terminal scalpel (TT knife), trap, and thermal biopsy forceps.

Eligible patients underwent routine ESD and postoperative stenting. At the same time, autologous mucosal transplantation and ADM transplantation were performed for patients in need. Figure 1 illustrates the surgical procedure in brief. Postoperative fasting was performed for 1 to 2 d, and proton pump inhibitor injections were performed for 3 d. Cases with no gastrointestinal bleeding or esophageal perforation were discharged for follow-up. The stent was removed 1 wk after the operation, and gastroscopy was rechecked at 2 wk and 1 and 6 mo to judge whether or not the ESD wound

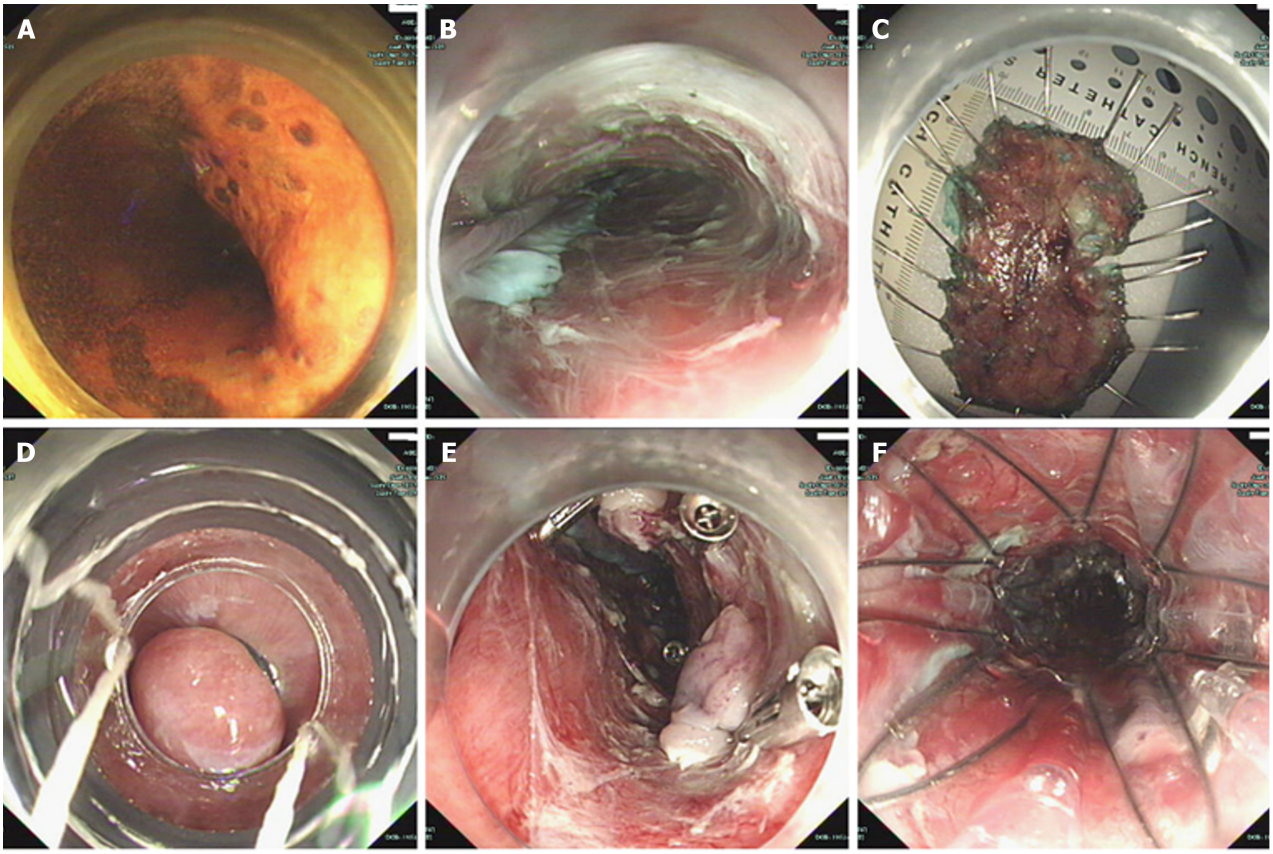

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Figure 1 Operation process of 5/6 periesophageal endoscopic mucosal dissection resection combined with autologous esophageal mucosal transplantation and esophageal covered stent implantation. A: Lugol fluid was sprayed on the whole esophageal mucosa; B: Endoscopic mucosal dissection was performed, and the wound after resection showed an annular mucosal defect; C: The cancerous tissue was removed; D: At the selected normal esophageal mucosa, the mucosa to be transplanted was removed by endoscopic mucosal resection using a polycyclic mucosal resection device; E: A titanium clip was used to secure the excised normal mucosa to the endoscopically peeled mucosal wound; F: The esophageal covered stent was implanted into the compressed transplanted mucosa.

was stenotic using a standard gastroscope entering the gastric cavity to check the survival of the grafted mucosa. Esophageal stenosis was defined as the inability of an Olympus GIF-Q260J gastroscope (with a diameter of 9.9 mm) to pass through the narrow area.

RESULTS

Based on the current incidence of esophageal stricture, a sample of 160 cases was calculated to be required for both the autologous mucosal graft group and the ADM group. A total of 20 patients were recruited in the autologous mucosal transplantation group during the recruitment period from January 1 to December 31, 2017, and a total of 13 patients met the inclusion criteria (excluding 1 with a lesion circumference < 1/2, 1 who refused to sign the informed consent form, 2 with reflux esophagitis, 2 with chronic hepatitis, and 1 with coronary artery disease); of these, 2 patients requested to withdraw from the trial after surgery, 2 were lost to follow-up, and 9 were ultimately included and completed the follow-up.

During the patient recruitment period for the ADM group from January 1 to December 31, 2019, 25 patients were recruited, of whom 14 met the inclusion criteria (excluding 2 with a lesion circumference < 1/2, 3 with reflux esophagitis, 1 with chronic hepatitis, 1 with coronary artery disease, 1 with reflux esophagitis, and 3 with recent aspirin or hormone use), and 3 were lost to follow-up; thus, a total of 11 patients were included and completed the follow-up.

The flow chart is shown in Figure 2. A total of 20 patients in the two groups included in the analysis had completed ESD surgery and follow-up, including 14 males and 6 females, with a mean age of 63.85 ± 7.66 years old and a median age of 64 years old. Four of the patients had hypertension, with the rest showing no other remarkable medical history, and 10 cases had a lesion circumference ≥ 3/4, while another 10 had a circumference of 1/2 to 3/4. There were 3 cases with a lesion length of 1 to 3 cm and 17 with a lesion length of > 3 cm. Six cases of stage IIa, three stage IIb, four stage IIc, and six stage IIa + IIc were analyzed endoscopically; seven cases showed an infiltration depth to the mucosal layer, three to the lamina propria, five to the myxomucosa, and four to the submucosa. Four patients had stenosis after surgery, with a stenosis rate of 20.00%, including 2 patients in the autologous mucosa group with a stenosis rate of 22.22% and a mean

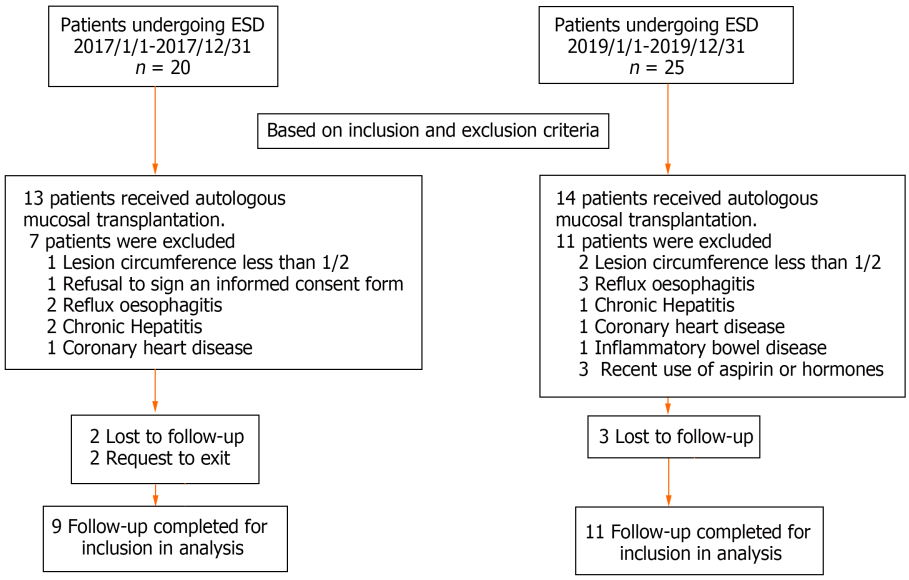

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Figure 2 Flow chart of patient inclusion.

follow-up period of 39.67 ± 2.79 d and 2 patients in the ADM group with a stenosis rate of 18.18% and a mean follow-up period of 43.16 ± 1.77 d (P = 0.94).

Specific details concerning the enrolled patients are shown in Table 1. The comparison between the autologous mucosa group and the ADM group is shown in Table 2.

DISCUSSION

The main components of ADM are collagen and other extracellular matrices, and after modification, it has suitable pore size, porosity, and mechanical strength[19]. It is a scaffold-like repair material with a three-dimensional spatial structure [20]. A large number of studies have confirmed that ADM can induce vascularization and promote cell growth and proliferation when used in the repair of tissues and organs and has good histocompatibility and a low inflammatory response [17,21-23]. Because ADM retains its complete matrix structure and has a unique three-dimensional spatial structure[24], when transplanted into wound repair, it can achieve clinical effects equivalent to autologous full-thickness skin grafting, mainly because ADM plays the role of the dermis when repairing wounds[25]. As a template, ADM can function as a scaffold for cell growth. When ADM is used as an implant, a physical barrier layer can be formed locally to prevent tissue adhesion and pathological proliferation in the local wound so that different tissues can independently complete their healing processes[25].

Some studies have reported the use of ADM as an implant barrier to prevent Frey's syndrome after parotidectomy[26,27], with none of the implants showing rejection reactions. The iodine G-starch test was used one year after surgery, and only two cases were positive, showing a significant difference from the control group[26]. ADM also covers wounds and fills tissue defects. The suitable structure, performance, and function of ADM are a strong guarantee of its utility as a bioremediation material.

ADM has received much attention and been widely used in clinical practice, such as in the repair of burn wounds[28], breast reconstruction[29], and oral mucosa repair[30]. In addition, as a new medical material, it can be degraded and absorbed by the human body. The process of degradation and absorption promotes the regeneration of the patient's own tissues and reduces the occurrence of inflammation. In theory, it can also completely replace autogenous mucosa[18,31].

Compared to ADM, autologous mucosa requires a longer preparation time, which can delay treatment and result in a poor prognosis. In addition, the mucosa can be obtained and prepared in such a way that it can cause secondary damage to the patient, which can be aggravated if the lesion is large; at the same time, since the autologous mucosa is taken from the patient, the quality of the mucosa can be affected if the patient has more underlying diseases, thus affecting the outcome. In addition, if the patient is unable to donate mucosa for the preparation of a mucosal sheet for grafting, the mucosa cannot be grafted postoperatively to prevent stenosis. It has been reported that the same effect can be achieved by preparing mucosal slices from autologous oral mucosa culture. Although this approach reduces the damage and impact caused by the patient's own factors, it also requires a relatively long preparation time.

For early-stage esophageal cancer, early surgery is necessary to obtain a better prognosis. The use of ADM overcomes these issues. The preparation of ADM is not dependent on the patient, so it is not affected by the patient's own condition and does not delay treatment. Furthermore, since the components of the cells that cause the body's immune response are removed, there is basically no immune response.

Table 1 Basic information of 20 patients

Participant	Age (yr)	Gender	Endoscopic morphology	Trauma length (cm)	Circumference of the wound	Infiltration depth	Postoperative stenosis	Occurrence of stenosis time (d)	Number of ADM used (slices)	Follow-up time (mo)	Graft mucosa survival
1	63	Male	IIa + IIc	6	2/3	Mucosal muscle layer	No	No	0	44.13	Yes
2	63	Male	IIb	5	3/4	Submucosa	No	No	0	42.73	Yes
3	58	Male	IIb	2	1/2	Mucosal muscle layer	No	No	0	40.87	Yes
4	67	Male	IIa	4	1/2	Mucosa layer	No	No	0	39.93	Yes
5	73	Female	IIb	4	4/5	Mucosal muscle layer	No	No	0	39.70	Yes
6	58	Male	IIa + IIc	5	1	Superficial submucosa	No	No	0	38.77	Yes
7	69	Female	IIa	6	4/5	Mucosal layer	No	No	0	38.53	Yes
8	69	Female	IIa	5	3/4	Mucosal layer	Yes	98	0	37.83	Yes
9	56	Male	IIa + IIc	8	1	Submucosa	Yes	44	0	34.57	Yes
10	56	Male	IIa	2	2/3	Mucosal layer	No	No	1	44.90	Yes
11	65	Male	IIa + IIc	3	2/3	Mucosal muscle superficial layer	No	No	1	44.90	Yes
12	60	Male	IIc	3	2/3	Mucosal lamina propria	No	No	1	44.43	Yes
13	73	Male	IIc	5	3/5	Mucosal lamina propria	No	No	1	43.97	Yes
14	49	Male	IIc	3	1/2	Mucosal layer	No	No	1	43.97	Yes
15	73	Female	IIa	5	3/5	Mucosal muscle layer	Yes	41	4	43.50	Yes
16	66	Male	IIc	2	4/5	Mucosal layer	No	No	1	43.03	Yes
17	78	Male	IIa + IIc	5	3/4	Mucosal layer	No	No	3	42.57	Yes
18	61	Female	IIa	3	1/2	Mucosal layer	No	No	1	42.57	Yes
19	52	Female	IIa	10	1	Submucosa	Yes	62	4	42.33	Yes
20	68	Male	IIa + IIc	6	1	Mucosal lamina propria	No	No	1	38.60	Yes

ADM: Acellular dermal matrix.

Table 2 Analysis of lesions in the autologous mucosal transplantation group and acellular dermal matrix transplantation group

	Group 1 (*n* = 9)	Group 2 (*n* = 11)	*P* value
Gender			0.77
Male	6	8	
Female	3	3	
Age			0.94
≥ 60 yr	3	4	
< 60 yr	6	7	
Wound circumference			0.23
1/2-3/4 circumference	3	7	
3/4-full circumference	6	4	
Wound length			0.22
< 10 mm	0	0	
10-30 mm	1	2	
> 30 mm	8	9	
Endoscopic morphology			0.81
IIa	3	3	
IIb	3	0	
IIc	0	4	
IIa + IIc	3	3	
Invasion depth			0.19
Mucosal layer	3	4	
Lamina propria	0	3	
Muscularis mucosa	3	2	
Submucosa	3	1	
Follow-up time (mo)	39.67 (34.57-44.13)	43.16 (38.60-44.90)	0.52

Group 1: Autologous mucous membrane transplantation group; Group 2: Acellular dermal matrix transplantation group.

Given the above, ADM seems to have the same potential as autologous mucosa to prevent esophageal stricture, but no reports or studies on the use of ADM to prevent stricture after human esophageal ESD have yet been published. The present study was conducted to verify the utility of ADM to prevent esophageal stricture in a prospective manner. A total of 9 patients with autologous mucosal grafts and 11 with ADM grafts were enrolled in the study and followed for approximately 3 years with a mean follow-up time of 41.59 mo. There were 2 cases of stenosis in the autologous mucosa, with a stenosis rate of 22.22%, and 2 cases of stenosis in the ADM graft group, with a stenosis rate of 18.18%, with no marked difference noted between the groups (P = 0.94). In this prospective study, strict inclusion and exclusion criteria were established during the experimental design phase, and by estimating the sample size, a sample of 160 cases per group was deemed to be required if the effects of autologous mucosal transplantation and ADM transplantation were to be compared. A total of 20 patients willing to receive autologous mucosal transplantation were recruited from January 1 to December 31, 2017, and 9 patients received autologous mucosal transplantation; a total of 25 patients willing to receive ADM transplantation were recruited from January 1 to December 31, 2019, and 11 patients received ADM transplantation. All of these patients completed a three-year follow-up.

During recruitment, the study failed to enroll sufficient patients who completed the three-year follow-up as required by the trial. Only 9 patients in the autologous mucosa group and 11 patients in the ADM group completed the 3-year follow-up, which is insufficient to draw definitive conclusions. While the stenosis rate did not differ significantly between the groups, it is less than the 37% stenosis rate noted in the relevant study[2]. While it has been shown to have some effect in preventing esophageal stricture, the effect of ADM remains unknown[12,32]. Based on the above results, we can speculate that ADM may exert some preventive effects against esophageal stricture, and its effects may be comparable to those of autologous mucosa. However, due to the many limitations of this trial, including the recruitment of an insufficient number of subjects, the results should be interpreted with caution.

CONCLUSION

Future studies using our established strict inclusion and exclusion criteria and improved follow-up may provide new insight into the prevention of esophageal stricture.

ARTICLE HIGHLIGHTS

Research background

Mucosal autograft transplantation has been reported to be effective in preventing esophageal stricture after endoscopic submucosal dissection (ESD) for esophageal cancer.

Research motivation

The preparation of autologous mucosa is an intricate process that demands a significant amount of time, potentially delaying the treatment of diseases. It is imperative to explore potential substitutes for autologous mucosa.

Research objectives

The efficacy of acellular dermal matrix (ADM) in preventing esophageal stricture is equivalent to that of autologous mucosal transplantation and has a substitutive effect.

Research methods

This is a prospective, single-center controlled study. Patients who underwent ESD surgery and were willing to undergo autologous mucosal transplantation and ADM transplantation were consecutively recruited for the study. A three-year follow-up was conducted for the transplanted patients.

Research results

Autologous mucosal grafts and ADM grafts demonstrated no significant differences in preventing esophageal stenosis, exhibiting similar preventive effects against esophageal narrowing.

Research conclusions

ADM possesses the potential to prevent esophageal stricture, exhibiting comparable preventative efficacy to autologous mucosal grafts while providing substitutive benefits.

Research perspectives

We shall persist in our research endeavors, enlisting additional participants to further validate the efficacy of ADM in preventing esophageal stricture. This shall furnish a multitude of options and avenues towards the treatment of esophageal stenosis.

FOOTNOTES

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Co-corresponding authors: Shao-Wei Li and Xin-Li Mao.

Author contributions: Fu XY, Zhang CY, Lin JY, Yan XD, Li XK, Wang Y, and Mao XL participated in the design of the study and performed the statistical analysis; Fu XY, Jiang ZY, Zhang CY, Lin JY, and Li SW drafted the manuscript. All authors read and approved the final manuscript.

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META-ANALYSIS

Clinical usefulness of linked color imaging in identifying *Helicobacter pylori* infection: A systematic review and meta-analysis

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Abstract

BACKGROUND

Accurate diagnosis of *Helicobacter pylori* (*H. pylori*) infection status is a crucial premise for eradication therapy, as well as evaluation of risk for gastric cancer. Recent progress on imaging enhancement endoscopy (IEE) made it possible to not only detect precancerous lesions and early gastrointestinal cancers but also to predict *H. pylori* infection in real time. As a novel IEE modality, linked color imaging (LCI) has exhibited its value on diagnosis of lesions of gastric mucosa through emphasizing minor differences of color tone.

AIM

To compare the efficacy of LCI for *H. pylori* active infection *vs* conventional white light imaging (WLI).

METHODS

PubMed, Embase, Embase and Cochrane Library were searched up to the end of April 11, 2022. The random-effects model was adopted to calculate the diagnostic efficacy of LCI and WLI. The calculation of sensitivity, specificity, and likelihood ratios were performed; symmetric receiver operator characteristic (SROC) curves and the areas under the SROC curves were computed. Quality of the included studies was chosen to assess using the quality assessment of diagnostic accuracy studies-2 tool.

RESULTS
Seven original studies were included in this study. The pooled sensitivity, specificity, positive likelihood rate, and negative likelihood rate of LCI for the diagnosis of *H. pylori* infection of gastric mucosa were 0.85 [95% confidence interval (CI): 0.76-0.92], 0.82 (95%CI: 0.78-0.85), 4.71 (95%CI: 3.7-5.9), and 0.18 (95%CI: 0.10-0.31) respectively, with diagnostic odds ratio = 26 (95%CI: 13-52), SROC = 0.87 (95%CI: 0.84-0.90), which showed superiority of diagnostic efficacy compared to WLI.

CONCLUSION
Our results showed LCI can improve efficacy of diagnosis on *H. pylori* infection, which represents a useful endoscopic evaluation modality for clinical practice.

Key Words: *Helicobacter pylori* infection; Endoscopic diagnosis; Linked color imaging; Gastric cancer; Meta-analysis

Core Tip: As a novel imaging enhancement endoscopy modality, linked color imaging (LCI) has exhibited its value on diagnosis of lesions of gastric mucosa through emphasizing minor differences of color tone. In this meta-analysis enrolled seven clinical trials, we showed LCI can improve efficacy of diagnosis on *Helicobacter pylori* infection compared with white light endoscopy, which represents a useful endoscopic evaluation modality for clinical practice.

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INTRODUCTION

Growing evidences has supported the predominant role of *Helicobacter pylori* (*H. pylori*) infection in development of gastric cancer, since World Health Organization designated *H. pylori* a type 1 carcinogen in 1993. It has been widely accepted that *H. pylori* infection leads to the progressive way from chronic atrophic gastritis, intestinal metaplasia, to dysplasia[1]. Moreover, prolonged infection with *H. pylori* cause inflammation, abnormal cell proliferation, release of bacterial virulence factors, and nitrate reduction, all of which contribute to the development of gastric cancer[1]. Recent random controlled trials and meta-analysis have verified that *H. pylori* eradication therapy appears to reduce new-onset gastric cancer[2-5]. Therefore, from the perspective of clinical practice, it is important to make diagnosis accurately of active *H. pylori* infection by endoscopic observation with the prevalence of gastroscopy screening in population.

The Kyoto classification of gastritis was advocated in 2013 to evaluate the gastric background mucosa by endoscopic features, eventually to assess the risk of developing gastric cancer[6,7]. Some typical endoscopic findings of gastric mucosa have been literally associated to active *H. pylori* infection, including diffuse redness, gooseflesh-like nodularity in antrum, and enlarged folds, while regular arrangement of collecting venules presents a sign of non-infection status of *H. pylori*[8-10]. With the advances of endoscopic techniques, it is feasible to make diagnosis of presence or absence of active *H. pylori* infection of stomach by using conventional white light imaging (WLI) and imaging enhancement endoscopy (IEE).

Linked color imaging (LCI) is a novel mode of IEE recently launched by FUJIFILM Corporation (Tokyo, Japan), which uses a color tone like WLI by emphasizing minute differences in mucosal colors[11]. In common, mucosal lesions seen in red or white by WLI get redder or whiter under LCI endoscopy, thereby making the lesions more visible during screening. Growing studies have demonstrated that LCI endoscopy can obviously improve the visibility of diffuse redness, map-like redness as well as atrophy and intestinal metaplasia, thus showing the reliability of LCI in recognition of gastritis and early gastric cancer[12-14]. Meanwhile, studies have also conducted to evaluate the diagnostic effect of LCI endoscopy on *H. pylori* infection status. *H. pylori* infected mucosa is redder than other uninfected areas due to post-inflammatory congestion and oedema[15]. Compared to WLI, this difference in coloration was amplified by LCI, which may lead to easier identification of lesions suspected of *H. pylori* infection by the endoscopist, increasing the accuracy of the diagnosis for *H. pylori* infection. However, the difference between WLI and LCI for *H. pylori* diagnostic rates remains unknown. Hence in current study, we aim to assess the diagnostic value of LCI for *H. pylori* active compared to WLI by performing a meta-analysis, to provide evidences for extending the clinical application of LCI endoscopy.

MATERIALS AND METHODS

Literature search strategy

Online English literatures were searched using electronic literature databases including PubMed, Embase, Cochrane and Web of Science. The cut-off time of the articles published was set on April 15, 2022. The keywords used in literature search were "linked color imaging" and "*Helicobacter pylori* infection" as well as their corresponding abbreviations.

Study inclusion and exclusion

Literature reviews, letters, meeting abstracts, case reports were not included. In addition, duplicated data records were also excluded. In all included studies, the diagnosis of *H. pylori* active infection under LCI endoscopy was eventually determined by rapid urease test which is the most common test for diagnosis of *H. pylori* infection. There were no restrictions in terms of the age or sex of study participants.

Data extraction and quality assessment

Data extracted from each study mainly included the following information: First author, year of publication, country, study design, object of research, number of cases, endoscopic system, and test parameters (true positive, false positive, false negative, and true negative). The first and second authors screened the enrolled studies and extracted relevant data. When critical data was not clearly stated, it would be resolved through discussion with the corresponding author.

Risk of bias assessment

The quality assessment tool of diagnostic tests, the quality assessment of diagnostic accuracy studies-2 was used to evaluate the risk of bias[16]. The scale comprises assessment of risk of bias and applicability. The risk-of-bias assessment is composed of patient selection, evaluated tests, the criterion and patient flow and progress. The applicability assessment included 3 aspects: Patient selection, evaluated tests and the golden criterion. In each aspect, the of bias was defined as "high", "low", or "unclear".

Statistical analysis

The "midas" command of Stata 15.0 (StataCorp LLC, College Station, TX) was used to fit the two-variable mixed-effect model, and the point estimates of the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic ratio and their corresponding 95% confidence interval (CI) in each group were combined to draw the comprehensive subject working characteristics [symmetric receiver operator characteristic (SROC)], area under the curve (AUC) and its 95%CI were calculated. The Deek's funnel plot was used to determine publication bias, and Q statistics and I^2 statistics were used to determine whether there was heterogeneity between studies. Levels of 0%-25%, 26%-50%, 51%-75% and more than 75% indicate insignificant, low, moderate, and high heterogeneity respectively. $P < 0.05$ was considered statistically significant.

RESULTS

Searched literatures and bias risk

We initially searched 94 articles including 25 in PubMed, 16 in Embase, 19 in Cochrane, and 34 in Web of Science. Careful review of the title and abstract and full-text reading were performed independently by two reviewers and the Kappa value was calculated as 0.849. Finally, 7 research articles were selected[17-23] (Table 1). Of them, two studies evaluated the diagnostic effect of LCI by computer-aided diagnosis system (CAD) and artificial intelligence (AI) but not by endoscopist. The specific literature screening process for the included studies is shown in Figure 1. The assessment of bias risk is shown in Figure 2. Of the seven included studies, two were case-free, so there was some bias on patient selection. In addition, in the study performed by Sun *et al*[21], both measures were tested interchangeably in the same group, and the outcome data were not completely distinguished.

WLI has moderate effect on detecting active H. pylori infection of gastric mucosa

For the overall detection effect on active *H. pylori* infection in the enrolled studies, WLI endoscopy had a moderate effect of diagnosis with a heterogeneity (I^2 = 97) by pooled sensitivity = 0.63 (95%CI: 0.46-0.77) (Figure 3A), pooled specificity = 0.73 (95%CI: 0.66-0.78) (Figure 3B), positive likelihood rate (PLR) = 2.32 (95%CI: 1.8-3.0) (Figure 3C, Supplementary Figure 1C), and negative likelihood rate (NLR) = 0.51 (95%CI: 0.34-0.76) (Figure 3C, Supplementary Figure 1C). The posterior probability was calculated by plotting Fagan diagram assuming the anterior probability was 50%. When *H. pylori* infection was diagnosed based on WLI, the probability of confirming *H. pylori* infection was 70%. In the case of negative results, the probability of *H. pylori* infection was 34% (Figure 3C). In addition, the diagnostic odds ratio (DOR) was 5 (95%CI: 2-9), and SROC was 0.75 (95%CI: 0.71-0.78) (Figure 3D). The Deeks' funnel plot was used to evaluate publication bias. The P value was calculated as 0.12 which indicates the risk of publication bias is not significant (Supplementary Figure 1A). The high heterogeneity existed among the studies with I^2 = 97 (95%CI: 94-99). The further bivariate box-type diagram showed that two of the seven included studies (10 groups) fell outside the box-type diagram suggesting the two studies might be the main source of heterogeneity, The high heterogeneity of the enrolled publications may be caused by the small sample size, study type and study population (Supplementary Figure 1B).

Table 1 Characteristics of the enrolled studies

Ref.	Country	Trial design	Participants (M/F)	Mean age (yr)	Definitive test for *H. pylori*	Cases of *H. pylori* infection
Lee *et al*[19], 2020	United Kingdom	Single center, prospective	100 (58/42)	51.2	RUT	37
Ono *et al*[20], 2020	Japan	Multiple centers, prospective	127 (66/61)	62.4	UBT, serum antibody test	64
Wang *et al*[23], 2019	China	Single center, retrospective	103 (42/61)	48.0	RUT, histological staining	27
Dohi *et al*[22], 2016	Japan	Single center, retrospective	60 (37/23)	67.4	RUT, UBT, serum antibody test	30
Nakashima *et al*[17], 2020	Japan	Single center, prospective	120 (-)	57.2	UBT, serum antibody test	40
Nakashima *et al*[18], 2018	Japan	Single center, prospective	120 (-)	-	Serum *H. pylori*, IgG test	60
Sun *et al*[21], 2019	China	RCT	Group A: 127 (66/61)	47.2	RUT, histological staining	64
			Group B: 126 (68/58)	49.7		57

H. pylori: *Helicobacter pylori*; RUT: Rapid urease test; UBT: Urea breath test; IgG: Immunoglobulin G; RCT: Randomised controlled trial; M/F: Male/female.

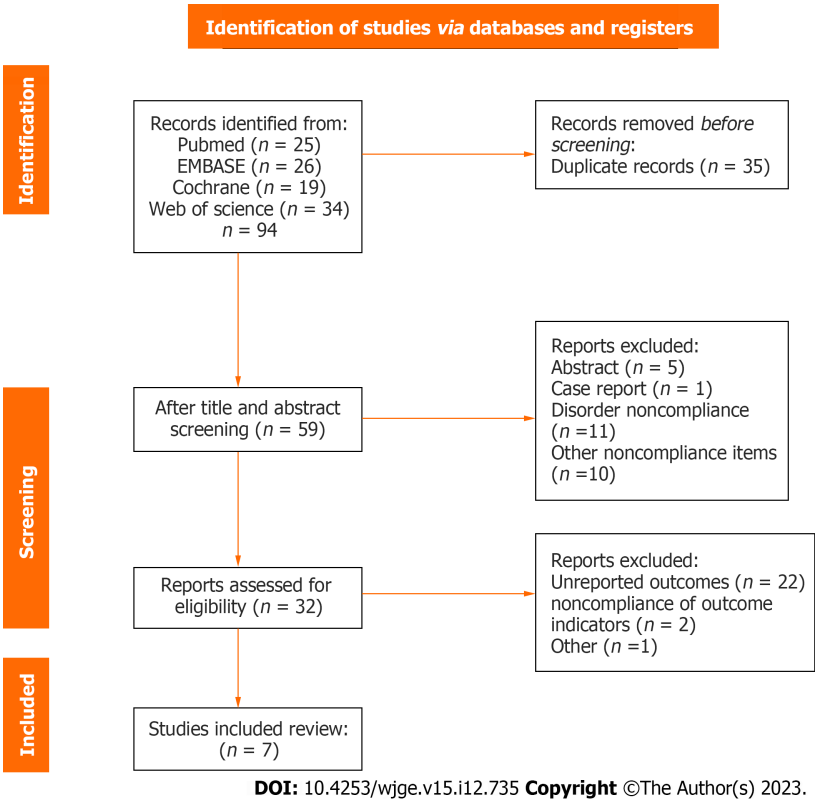

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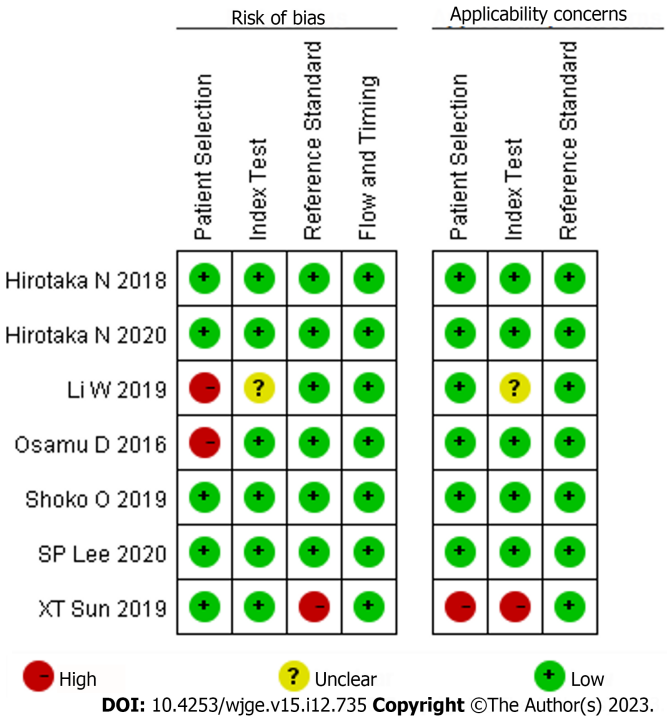
Figure 1 Flow diagram of specific literature searching process.

LCI exhibits better diagnostic value of H. pylori infection compared to WLI

The sensitivity, specificity, PLR, and NLR of LCI endoscopy for the diagnosis of *H. pylori* infection of gastric mucosa were 0.85 (95%CI: 0.76-0.92) (Figure 4A), 0.82 (95%CI: 0.78-0.85) (Figure 4B), 4.71 (95%CI: 3.7-5.9) (Figure 4C, Supplementary Figure 2C), and 0.18 (95%CI: 0.10-0.31) (Figure 4C, Supplementary Figure 2C) respectively. The posterior probability was calculated by plotting the Fagan diagram assuming the anterior probability to be 50%. When *H. pylori* infection was diagnosed based on LCI, the probability of diagnosis of *H. pylori* infection was 82%. In the negative case, the probability of *H. pylori* infection was 15% (Figure 4C). Moreover, the DOR was 26 (95%CI: 13-52), and SROC was 0.87 (95%CI: 0.84-



DOI: 10.4253/wjge.v15.i12.735

Figure 2 The assessment of bias risk.

0.90) (Figure 4D). The high heterogeneity of this analysis was 90 (95%CI: 80-100). We calculated the *P* value as 0.72 indicating an insignificant risk of publication bias. The higher heterogeneity existed among the studies with I^2 = 90 (95%CI: 80-100). The bivariate box-type diagram showed that one study of the seven included studies (10 groups) fell outside the box-type diagram (Supplementary Figure 2A), suggesting that this one study might be the main source of heterogeneity (Supplementary Figure 2B). The results indicate LCI has significant superiority over WLI when they are used in diagnosis of *H. pylori* infection.

DISCUSSION

Diagnosis of the status of *H. pylori* infection represents a crucial step in prior to assess the risk of atrophy, intestinal metaplasia and *H. pylori* associated gastric cancer, according to current consensual strategy on prevention and treatment of gastric cancer. However, the endoscopic diagnosis of *H. pylori* associated gastritis does not often correspond with the histological findings in clinical practice[24]. Previous studies have disclosed that the accuracy of endoscopic diagnosis of *H. pylori* infection ranged from 64% to 71% based on the endoscopic appearance alone[19,25]. This moderate accuracy of diagnosis suggests that endoscopy may not be definitive method, but can be important part of comprehensive diagnosis with other invasive or noninvasive tests such as biopsy based rapid urease test or urea breath test.

In the past decades, image enhancement technique upgraded the conventional endoscopy to an indispensable test for diagnosis of gastrointestinal diseases including early malignancies. Emerged researches have demonstrated that various types of IEEs such as blue laser imaging, narrow band imaging and LCI can improve accuracy of diagnosis on *H. pylori* infection status[20,26-28]. As the latest IEE technique, LCI endoscopy can theoretically highlight the color tone of mucosa thus facilitating the visuality of endoscopic features for active infection of *H. pylori*, such as diffuse redness, mucosal edema, hemorrhagic spots, enlarged folds, and gooseflesh-like nodularity[29]. Correspondingly, growing evidences have emerged that LCI endoscopy significantly improves recognition of *H. pylori* associated changes of mucosa to help making diagnosis of *H. pylori* infection more accurately than conventional WLI endoscopy[18-23].

The combined accuracy of LCI endoscopy on diagnosis of *H. pylori* active infection concluded by our meta-analysis, is obviously higher than that of conventional WLI endoscopy, which is demonstrated by 0.85 (95%CI: 0.76-0.92) of sensitivity, 0.82 (95%CI: 0.78-0.85) of specificity, 4.71 (95%CI: 3.7-5.9) of PLR, and 0.18 (95%CI: 0.10-0.31) of NLR, with the AUC being 0.87. Although this accuracy is not high enough, it apparently indicates the advantage of LCI endoscopy before patients with suspected *H. pylori* infection are subjected to invasive tests. Moreover, it has been elucidated that LCI endoscopy not only have good efficacy on diagnosis of current *H. pylori* infection, but also superior in diagnosis of other abnormalities of *H. pylori* associated gastritis, such as gastric intestinal metaplasia and atrophy[14,30,31]. Some most recent studies have further demonstrated better effects of LCI endoscopy, in comparison with WLI endoscopy or indigo carmine chromoendoscopy, on identifying featured mucosal appearances after successful *H. pylori* eradication, thus facilitating to recognize early gastric cancer[32-35]. Therefore, LCI endoscopy is exhibiting the potential as an important alternative modality of endoscopy for gastrointestinal disease screening in future, or at least, as a feasible supplementary method of WLI endoscopy-based screening strategy.

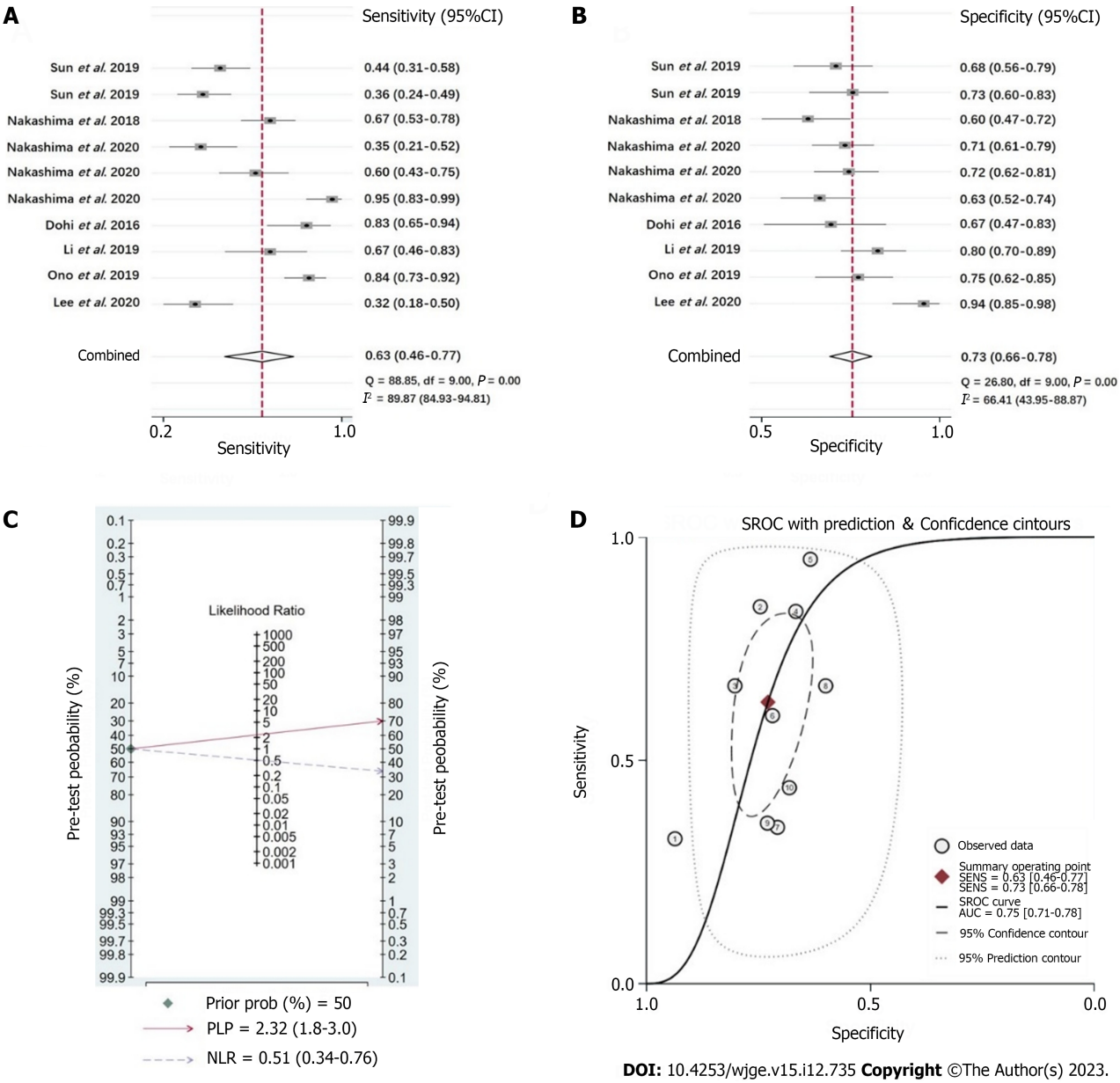


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Figure 3 Pooled results of efficacy of white light imaging on *Helicobacter pylori* infection diagnosis. A-D: Pooled sensitivity (A), specificity (B), positive likelihood ratio and negative likelihood ratio (C). Symmetric receiver operator characteristic curve and area under the curve (D). 95%CI: 95% confidence interval; SROC: Symmetric receiver operator characteristic; PLR: Positive likelihood rate; NLR: Negative likelihood rate.

Our analysis had several limitations that may have influence on the results. Firstly, there haven't been insufficient original studies related to the diagnosis efficacy of LCI on *H. pylori* infection. The selected studies in our analysis were almost performed in single center, and enrolled relatively small size of patient samples, which restrict further subgroups analysis based on variables. Secondly, these enrolled studies performed different tests to make definite diagnosis of *H. pylori* infection after LCI endoscopy, such as biopsy based histological staining or rapid urease test, urea breath test, and serological test. Thirdly, two studies of Nakashima *et al*[17,18] proposed inconsistent diagnosis accuracy of LCI on *H. pylori* infection, when using AI or CAD instead of endoscopists, that was 96.7% of sensitivity, 83.3% of specificity, 0.95 of AUC for AI, and 62.5% of sensitivity, 92.5% of specificity, 0.82 of AUC for CAD. These problems mentioned above may bring heterogeneity of the analysis and further lead to instability of the results.

CONCLUSION

Summarily, as a novel technique of image enhancement endoscopy, growing evidences have proved that LCI can significantly improve accuracy of diagnosis on *H. pylori* infection, as well as *H. pylori* associated changes of gastric mucosa, including atrophy and gastric intestinal metaplasia. Moreover, by emphasizing the difference of color tone between lesion and surrounding normal mucosa, LCI also shows promising usefulness in detecting early gastric cancer. Combined with current knowledge, it is anticipated to use LCI endoscopy alone for detection of gastric diseases instead

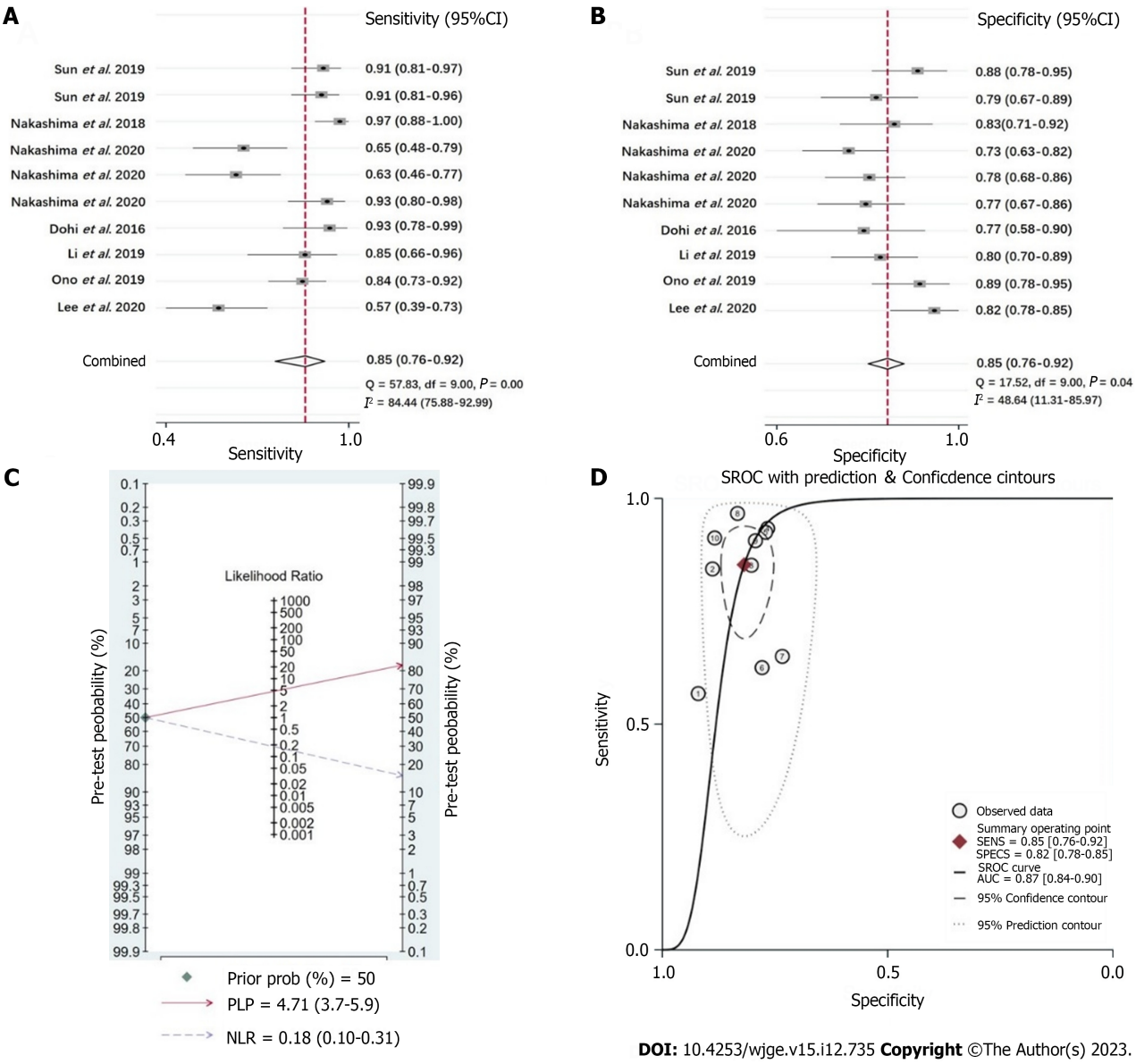

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Figure 4 Pooled results of efficacy of linked color imaging on *Helicobacter pylori* infection diagnosis. A-D: Pooled sensitivity (A), specificity (B), positive likelihood ratio and negative likelihood ratio (C). Symmetric receiver operator characteristic curve and area under the curve (D). 95%CI: 95% confidence interval; SROC: Symmetric receiver operator characteristic; PLR: Positive likelihood rate; NLR: Negative likelihood rate.

of WLI endoscopy in future, while a screening strategy of LCI followed by magnifying IEEs may theoretically have better clinical prospects for early cancer detection.

ARTICLE HIGHLIGHTS

Research background

Diagnosis of *Helicobacter pylori* (*H. pylori*) infection is a critical step in assessing the risk of chronic atrophic gastritis, intestinal metaplasia, and *H. pylori* related gastric cancer. Eradication therapy of *H. pylori* appears to reduce the incidence of new gastric cancers. Therefore, accurate diagnosis of active *H. pylori* infection by using endoscopy is essential for the diagnosis and treatment of gastric cancer.

Research motivation

Linked color imaging (LCI) is a novel endoscopic modality recently introduced. Compared to the common white light imaging (WLI), the mucosal lesions in red or white color seen on LCI endoscopy are more visible, which makes it easier to identify early gastric cancer. However, the detection rate of *H. pylori* with LCI compared to WLI remains to be evaluated.

Research objectives

The diagnostic value of LCI compared with WLI for *H. pylori* activity was assessed by meta-analysis, to provide evidence for expanding the clinical application of LCI endoscopy.

Research methods

PubMed, Embase, Embase, and Cochrane Library databases were searched for literature related to LCI and WLI diagnosis of *H. pylori*. The "midas" command of Stata 15.0 was used to fit the two-variable mixed-effect model. The point estimates of the sensitivity, specificity, likelihood ratio, and diagnostic ratio were combined to draw the comprehensive subject working characteristics [symmetric receiver operator characteristic (SROC)], and area under the curve (AUC) and its 95% confidence interval (CI) were calculated. The Deek's funnel plot was used to determine publication bias, and *Q* statistics. I^2 statistics were used to determine whether there was heterogeneity between studies.

Research results

In this study, 94 articles were initially searched, including 25 in PubMed, 16 in Embase, 19 in Cochrane, and 34 in Web of Science, and 7 research articles were ultimately screened. In WLI diagnosis, the probability of confirming *H. pylori* infection was 70%. In the case of negative results, the probability of *H. pylori* infection was 34%. The diagnostic odds ratio (DOR) was 5 (95%CI: 2-9), and SROC was 0.75 (95%CI: 0.71-0.78). In LCI diagnosis, the probability of diagnosis of *H. pylori* infection was 82%. In the negative case, the probability of *H. pylori* infection was 15%. The DOR was 26 (95%CI: 13-52) and SROC was 0.87 (95%CI: 0.84-0.90).

Research conclusions

LCI improves the diagnostic accuracy of *H. pylori* infection as well as *H. pylori*-associated gastric mucosal lesions, which anticipates that LCI alone, rather than WLI, may be applied in the future to screen for gastric disease.

Research perspectives

The screening strategy of LCI followed by magnifying image-enhanced endoscopy may theoretically have better clinical perspectives in early cancer diagnosis.

FOOTNOTES

Author contributions: Guo Q brought the idea of this study; Wang JZ, Bai X, and Zhang PL worked together for literature searching and data analysis; Zhang Y wrote the manuscript.

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CASE REPORT

Magnetic compression anastomosis for sigmoid stenosis treatment: A case report

Miao-Miao Zhang, Yi Gao, Xiao-Yang Ren, Huan-Chen Sha, Yi Lyu, Fang-Fang Dong, Xiao-Peng Yan

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Provenance and peer review: Unsolicited article; Externally peer reviewed.

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Peer-review report's scientific quality classification

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Grade B (Very good): B, B
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Abstract

BACKGROUND

Endoscopic balloon dilation is a minimally invasive treatment for colorectal stenosis. Magnetic compression anastomosis can be applied against gastrointestinal anastomosis. When combined with endoscopy, it offers a unique approach to the recanalization of colorectal stenosis.

CASE SUMMARY

We have reported here the case of a 53-year-old female patient who underwent a descending colostomy due to sigmoid obstruction. Postoperative fistula restoration was not possible in her due to sigmoid stenosis. Accordingly, endoscopic-assisted magnetic compression anastomosis for sigmoid stenosis was performed, and the sigmoid stenosis was recanalized 15 d after the surgery. Subsequently, a reduction colostomy was successfully performed after 10 d.

CONCLUSION

This case report proposes a novel minimally invasive treatment approach for colorectal stenosis.

Key Words: Colorectal stenosis; Endoscopy; Magnetic compression anastomosis; Magnamosis; Magnetosurgery; Case report

Core Tip: Colorectal stenosis is common in clinical practice, for which endoscopic treatment is the preferred choice; however, most patients require multiple balloon dilation or even stent placement. Clinicians should consider the novel approach of endoscopic magnetic compression anastomosis in applicable cases of colorectal stenosis.

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INTRODUCTION

Colorectal anastomotic stenosis usually occurs after colorectal cancer surgery or even after radiation therapy for abdominal and pelvic tumors. Endoscopic balloon dilation or stent placement is the main clinical approach in such cases. However, some patients with severe stenosis often require multiple endoscopic treatments, albeit show poor outcomes. Re-surgery may incur a very high rate of restenosis and refrain patients from an opportunity to restore the stoma, which may seriously affect their quality of life. The combination of magnetic compression anastomosis with endoscopic technique provides a new minimally invasive treatment modality for rectal stenosis.

CASE PRESENTATION

Chief complaints

A 53-year-old female patient was admitted to our hospital on July 26, 2022, for sigmoid stenosis. The patient had undergone a descending colostomy in a local hospital for sigmoid obstruction 11 mo ago and had recovered well after surgery. One month ago, she was treated in the same hospital for a reduction colostomy. A colonoscopy revealed that her sigmoid was narrow (Figure 1), hence the reduction operation could not be performed. For further treatment, the patient was admitted to the Magnetic Surgery Clinic of the First Affiliated Hospital of Xi'an Jiaotong University.

History of present illness

At 11 mo ago, the patient underwent a descending colostomy in a local hospital for sigmoid obstruction and a colonoscopy 1 mo before the indication of sigmoid stenosis.

History of past illness

The patient was diagnosed with cervical cancer at a local hospital 9 years ago and has been clinically cured after multiple radiotherapy treatments. She has a history of hypertension for 1 year and diabetes for 2 years. Through oral drug treatment, her blood pressure and blood glucose levels were well-controlled.

Personal and family history

The patient did not have any relevant family medical history.

Physical examination

The patient's vital signs were stable, with no obvious abnormalities in the physical examination of both her lungs and heart; her abdomen was flat and soft, with no abdominal tenderness; Shifting dullness in the abdomen was negative, and bowel sounds were normal, and the descending colostomy stoma was visible in the left lower abdomen.

Laboratory examinations

The patient's hematology results were normal.

Imaging examinations

A small amount of contrast agent could enter the proximal intestinal tube through the stenosis, and the intestinal tube could be fully developed through the catheterization of the colostomy, indicating sigmoid stenosis (Figure 2).

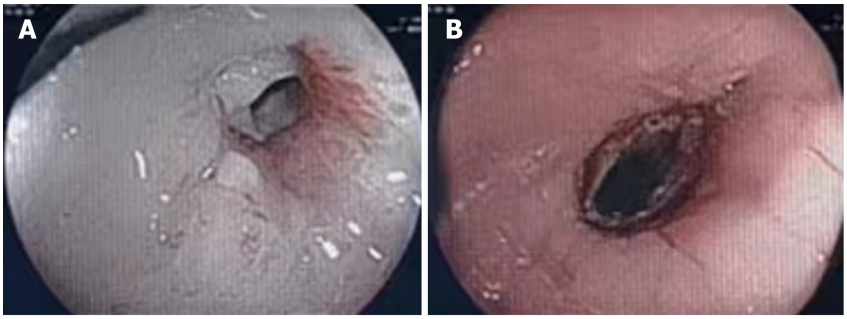

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Figure 1 Colonoscopy. A: Distal stenosis; B: Proximal stenosis.

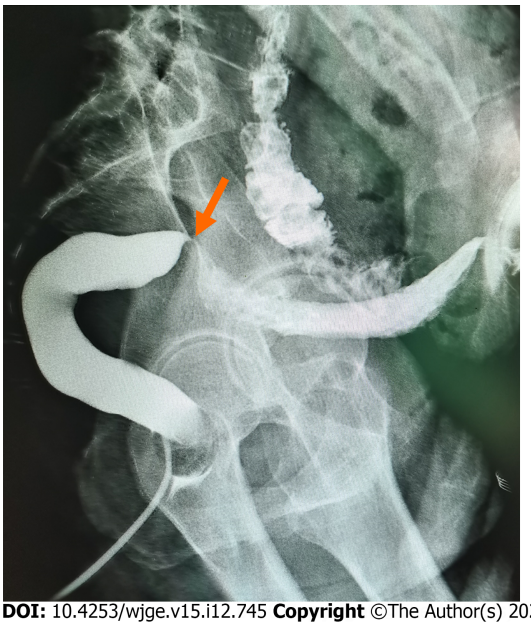

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Figure 2 Colonography: Arrow points to the stenosis.

FINAL DIAGNOSIS

According to the medical history of the patient, imaging examination, and colonoscopy, sigmoid stenosis was clearly diagnosed.

TREATMENT

The patient underwent endoscopy-assisted magnetic compression anastomosis of sigmoid stenosis under intravenous anesthesia on July 27, 2022. After the patient was administered intravenous anesthesia, a colonoscopy was conducted in the right lateral position through the descending colostomy. A stenosis could be visible at a distance of 15 centimeters from the colostomy during colonoscopy. A zebra guide wire was next sent through the biopsy hole, and the lead end of the guide wire was passed through the narrow segment of the sigmoid colon into the distal intestinal. The daughter magnet and the parent magnet were inserted through the zebra guide wire at the end of the colostomy and the anal end, respectively, and the push tube was pushed close to the narrow section along the zebra guide wire, as such the parent and daughter magnets were automatically attracted (Figure 3A and B). After the X-ray images confirmed that the magnets were attracted (Figure 3C), the zebra guide wire was removed. After the operation, the patient was returned to the ward safely.

X-ray examination was performed weekly after the operation to monitor the positions of the magnets (Figure 4A and B). On the 15th day of the operation, the parent and daughter magnets were removed *via* colonoscopy (Figure 4C). The magnetic compression anastomosis was established under colonoscopy (Figure 4D). Finally, the patient underwent colostomy reduction 10 d later.

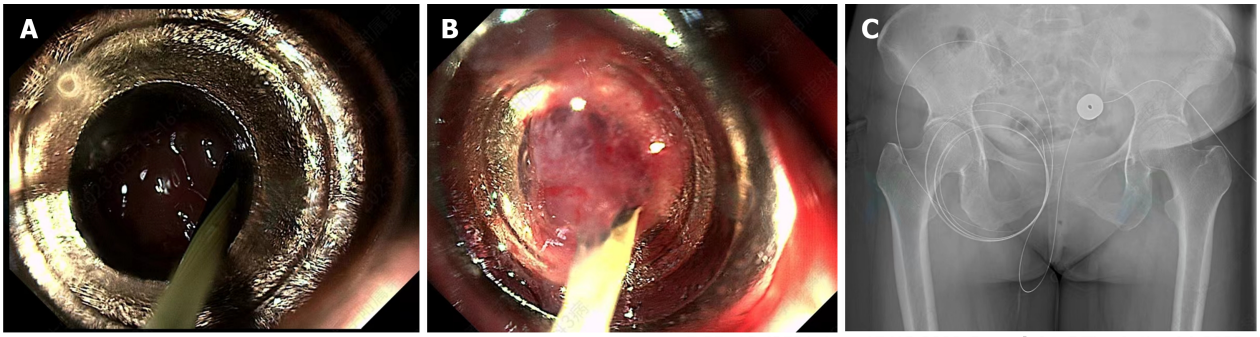

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Figure 3 Magnet placement process. A: The daughter magnet was inserted through the colostomy; B: The parent magnet was inserted through the anus; C: Intraoperative X-ray examination confirmed that the daughter and parent magnets were attracted.

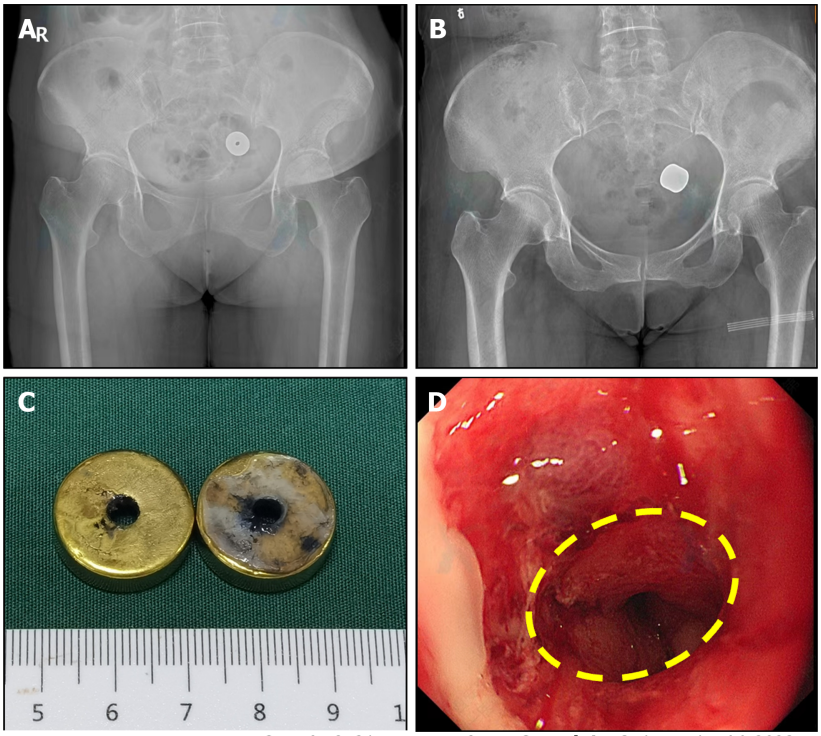

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Figure 4 Postoperative X-ray and colonoscopic observations. A: X-ray examination 1 wk after the surgery; B: X-ray examination 2 wk after the surgery; C: The magnet was removed by colonoscopy 15 d after the surgery; D: The anastomosis was detected on colonoscopy.

OUTCOME AND FOLLOW-UP

The 13-mo follow-up of the patient showed a generally good condition with normal bowel movements.

DISCUSSION

Colorectal stenosis is a common clinical disease, whose clinical treatment is mainly based on endoscopic balloon dilation or stent placement[1], it has the advantages of less trauma and not affected by enterostomy. However, some patients often require multiple endoscopic treatments. Patients who do not respond well to endoscopic therapy may face re-surgery or permanent indwelling. In 1978, Obora *et al*[2] was the first to report the use of magnets for vascular anastomosis research [2], and after more than 40 years of its development, magnetic compression anastomosis is being applied for digestive tract anastomosis[3,4], vascular anastomosis[5,6], and magnetic compression cystostomy[7]. The combination of magnetic compression anastomosis and endoscopic technique can transform some surgical operations into endoscopic ones, which offers unique advantages for the treatment of gastrointestinal stenosis[8].

This present case presented the following two characteristics: (1) The surgical procedure was simple, mainly because the zebra guide wire could pass through the narrow section of the intestinal tube and the length of the narrow section was small, because of which the magnetic force of conventional magnets met the requirements; (2) The parent and daughter magnets remained discharged for 2 wk. The shedding time of magnets during digestive tract magnetic compression anastomosis is closely related to the anastomosis site, magnetic force, inflammatory scar formation of the digestive tract, and other related factors. Owing to the limited clinical reports on such cases, it remains impossible to determine the reasonable time range of magnets excreted during the digestive tract magnetic compression anastomosis. In our previous large animal experiments, we found that gastrointestinal magnetic compression anastomosis could be established in 10–14 d after the surgery. Therefore, in the present case, we removed the magnets under the endoscope 15 d after the surgery, and the results indicated that the anastomosis was well-formed by this time; and (3) Based on the patient's history, we believe that the cause of the patient's sigmoid stenosis may be related to pelvic radiation therapy. Radiation enteritis is usually treated with medication or endoscopy, but this patient developed severe sigmoid stenosis and caused intestinal obstruction, and did not respond to medication or endoscopy. Presently, only a few cases have been reported in the literature using magnetic compression anastomosis to treat colorectal stenosis, and the relevant clinical application experience is limited. The successful implementation of this case thus enriches the clinical application experience of magnetic surgery and can provide valuable learning and reference significance for future applications.

CONCLUSION

This case report proposes a new approach for clinicians to treat colorectal stenosis. A combination of magnetic compression anastomosis with endoscopic technique can be potentially applied for the treatment of colorectal stenosis, considering the advantages of simple operation, non-trauma, and exact effect achieved through this procedure.

FOOTNOTES

Co-first authors: Miao-Miao Zhang and Yi Gao.

Co-corresponding authors: Xiao-Peng Yan and Yi Lyu.

Author contributions: Zhang MM and Gao Y contributed equally to this work and are the co-first author; Lyu Y and Yan XP designed the operational plan; Ren XY and Yan XP performed the endoscopic magnetic compression anastomosis; Dong FF assisted in patient care; Zhang MM and Gao Y wrote the manuscript; Zhang MM, Gao Y and Sha HC assisted in data collection and manuscript revision; all authors have read and approved the final manuscript.

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