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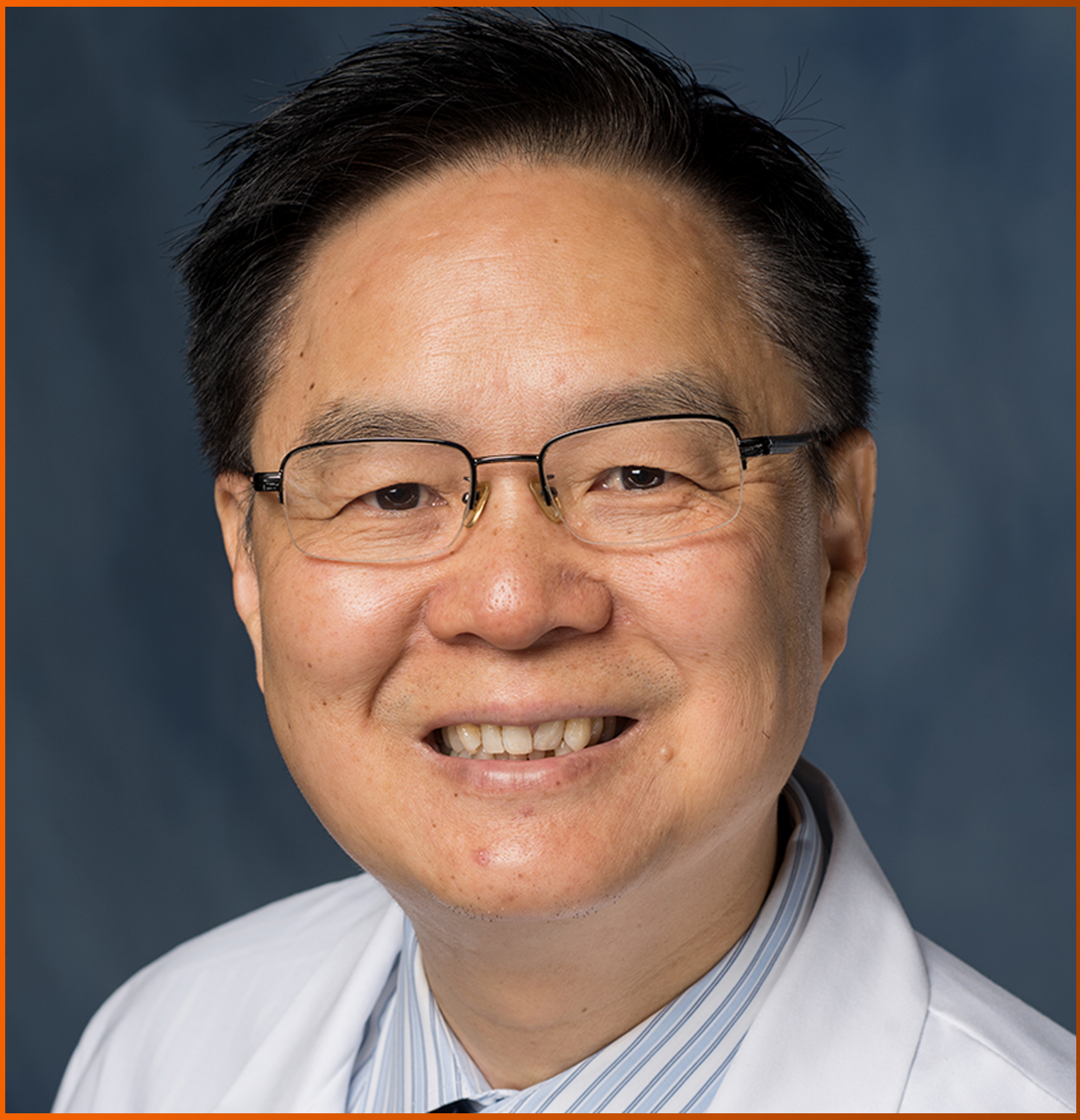

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ORIGINAL ARTICLE

Retrospective Study

Human immunodeficiency virus patients with low CD4 counts are more likely to have precancerous polyps identified during index colonoscopy

Michelle Likhtshteyn, Evan Marzouk, Fray M Arroyo-Mercado, Gurasees Chawla, Sabrina Rosengarten, Renata Lerer, Hector Ojeda-Martinez, Savanna Thor

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Abstract

BACKGROUND

Antiretroviral treatment (ART) has improved the life expectancy of patients living with human immunodeficiency virus (HIV). As these patients age, they are at increased risk for developing non-acquired immunodeficiency syndrome defining malignancies (NADMs) such as colon cancers.

AIM

To determine which factors are associated with the development of precancerous polyps on screening colonoscopy in patients with HIV and to investigate whether HIV disease status, measured by viral load and CD4 count, might influence precancerous polyp development.

METHODS
A retrospective review of records at two urban academic medical centers was performed for HIV patients who had a screening colonoscopy between 2005-2015. Patients with a history of colorectal cancer or polyps, poor bowel preparation, or inflammatory bowel disease were excluded. Demographic data such as sex, age, race, and body mass index (BMI) as well as information regarding the HIV disease status such as CD4 count, viral load, and medication regimen were collected. Well-controlled patients were defined as those that had viral load < 50 copies, and poorly-controlled patients were those with viral load ≥ 50. Patients were also stratified based on their CD4 count, comparing those with a low CD4 count to those with a high CD4 count. Using colonoscopy reports in the medical record, the size, histology, and number of polyps were recorded for each patient. Precancerous polyps included adenomas and proximal serrated polyps. Data was analyzed using Fisher's exact tests and logistic regression through SAS 3.8 software.

RESULTS
Two hundred and seven patients met our inclusion criteria. The mean age was 56.13 years, and 58% were males. There were no significant differences in terms of age, race or ethnicity, insurance, and smoking status between patients with CD4 counts above or below 500. BMI was lower in patients with CD4 count < 500 as compared to those with count > 500 (P = 0.0276). In patients with CD4 > 500, 53.85% of patients were female, and 70.87% of patients with CD4 < 500 were male (P = 0.0004). Only 1.92% of patients with CD4 ≥ 500 had precancerous polyps *vs* 10.68% of patients with CD4 < 500 (P = 0.0102). When controlled for sex, BMI, and ART use, patients with CD4 < 500 were 9.01 times more likely to have precancerous polyps [95% confidence interval (CI): 1.69-47.97; P = 0.0100]. Patients taking non-nucleoside reverse transcriptase inhibitors were also found to be 10.23 times more likely to have precancerous polyps (95%CI: 1.08-97.15; P = 0.0428). There was not a significant difference noted in precancerous polyps between those that had viral loads greater or less than 50 copies.

CONCLUSION
Patients with low CD4 counts were more likely to have precancerous polyps on their screening colonoscopy although the etiology for this association is unclear. We also found an increased risk of precancerous polyps in patients taking non-nucleoside reverse transcriptase inhibitors, which is contradictory to prior literature showing ART has decreased the risk of development of NADMs. However, there have not been studies looking at colorectal cancer and ART by drug class, to our knowledge. Further prospective studies are needed to determine the effect of HIV control and therapies on polyp development.

Key Words: Colonoscopy; Non-acquired immunodeficiency syndromes defining malignancies; Human immunodeficiency virus; Adenoma detection rate; Antiretroviral treatment; Advanced adenoma

Core Tip: Aging human immunodeficiency virus (HIV) patients are at a higher risk for developing non-acquired immunodeficiency syndrome defining malignancies. We investigated the factors associated with the development of precancerous polyps on index colonoscopy and whether HIV disease state might influence precancerous polyps. We divided patients into two groups based on their viral load and CD4 count. We retrieved colonoscopy results, patient demographics, and relevant HIV data from the electronic medical record. We determined that patients with low CD4 counts were more likely to have precancerous polyps on their index colonoscopy. We found an increased risk of precancerous polyps in patients taking non-nucleoside reverse transcriptase inhibitors.

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INTRODUCTION

Antiretroviral therapy has dramatically changed and improved the life expectancy of patients coping with human immunodeficiency virus (HIV). With the introduction of antiretroviral treatment (ART) in 1996, the worldwide life expectancy of HIV-infected people has improved significantly. As the HIV disease state is being better controlled with ART, this patient population is at lower risk for developing acquired immunodeficiency syndrome (AIDS) defining illnesses. However, as these patients live longer, they become vulnerable to developing non-AIDS defining malignancies (NADMs) such as colon cancers[1]. In 1994, Klugman and Schaffner[2] published a case report of a 25-year-old African

American man with HIV who was found to have an advanced right sided colonic adenocarcinoma postmortem. At that time, ART therapy had not yet been introduced or widely accepted, and it was thought that the most significant manifestation of HIV in the gastrointestinal tract was Kaposi's sarcoma[2]. However, even Krugman postulated that HIV might play a role in the development of colon cancer.

While some studies have shown that highly active antiretroviral therapy (HAART) decreases the risk of developing colorectal cancer[3], other studies propose that HIV patients are at higher risk and develop colorectal cancer at younger ages[4,5]. Conversely, other studies have shown that the rates of colorectal cancer are similar between people with and without HIV[6]. According to current guidelines, HIV infection does not change the age at which screening colonoscopies are performed. A consensus regarding HIV infection and colonic neoplasms has not been reached, possibly due to a paucity of data regarding these two diseases. We aimed to identify which factors are associated with the development of precancerous polyps on index (first) screening colonoscopy in patients with HIV and to investigate whether HIV disease status, measured by viral load and CD4 count, may influence precancerous polyp growth.

MATERIALS AND METHODS

A retrospective review of medical records at Kings County Hospital and SUNY Downstate Health Sciences University for patients with HIV who had received a screening colonoscopy between 2005 and 2015 was performed. Patient demographics were collected, HIV disease status was documented, and information regarding the colonoscopy was collected. Important factors from the colonoscopy data included the types of polyps, if a polypectomy were performed, if a diagnosis of advanced adenoma was made, or if a diagnosis of adenocarcinoma was made.

Patients with a known history of malignancy, history of colon polyps, inflammatory bowel disease, active gastrointestinal infection, and poor bowel preparation were excluded, as were patients undergoing colonoscopy for surveillance or diagnostic purposes. Data collected for each patient included age, biological sex, ethnicity, age at colonoscopy, body mass index (BMI) at time of colonoscopy, alcohol history use, tobacco use, diabetes history, year of HIV diagnosis, duration in years of HIV diagnosis at time of colonoscopy, CD4 count nadir, CD4 count value closest to colonoscopy date, viral load value closest to colonoscopy date, and ART therapy regimen. Colonoscopy data was collected including the date of colonoscopy, colonoscopy type (screening/diagnostic), proceduralist, family history of polyps, history of polyps or colon cancer, biopsy information (if any), polyp type, polyp size, determination of adenoma, designation of advanced adenoma, diagnosis of adenocarcinoma or anal cancer, quality of preparation, withdrawal time greater than 6 min, and type of anesthesia. Advanced adenomas were categorized as adenomatous polyps being > 1 cm, having greater than 3 adenomas, and/or having a sessile serrated adenoma.

The baseline characteristics and prevalence of polyps in HIV disease groups (based on the viral load and/or CD4 count definitions) were compared using Wilcoxon signed-rank tests and Fisher's exact tests. For the two groups based on CD4 count, a logistic regression controlling for BMI, sex, and medications while looking at the odds of precancerous polyps was run. All statistics were performed using SAS Studio 3.8 software.

Patients were categorized into two groups based on their HIV disease state. They were determined to be either well-controlled HIV or poorly-controlled HIV patients (using viral load as a designation) and using CD4 count where patients were determined to be controlled or uncontrolled using a CD4 cutoff of 500. HIV patients determined to be well-controlled/controlled were likened to the general population and served as a control group (Figure 1).

RESULTS

HIV viral load for designation of well-controlled vs poorly-controlled HIV

A total of 370 records were reviewed. Of these patients, 163 were excluded due to having either a diagnostic colonoscopy, surveillance colonoscopy, or poor preparation. In total, 207 patients were found to have screening colonoscopies with good or excellent prep (Boston Bowel Prep Score > 7) and met our inclusion criteria. The mean age of our patient population was 56.13 years; 58% of our patients were male. Patients were divided into two separate groups based on their HIV disease state using viral load. Patients were denoted to be well-controlled based on a viral load < 50 copies/mL and poorly-controlled if their viral load was > 50 copies/mL. Based on these criteria, we had a total of 133 well-controlled patients and 74 poorly-controlled HIV patients. Using these two defined groups, baseline characteristics between them were compared.

Baseline characteristics between these two groups including age, sex, race, ethnicity, history of diabetes, smoking status, and insurance were not found to be statistically significant. However, the average BMI in well-controlled patients was found to be higher (27.8 kg/m^2) than the average (25.9 kg/m^2) in poorly-controlled HIV patients (P = 0.0207). See Table 1 for baseline characteristics.

At an alpha level of 0.05, the prevalence of polyps in both groups was not significantly different. Among the patients with well-controlled HIV, 13% had polyps, while 8% of patients in the poorly-controlled group had polyps. In the well-controlled group, 7.52% of patients had precancerous polyps, and 4.05% of poorly-controlled patients had precancerous polyps. Advanced and right colon adenomas were also found more often in the well-controlled group (5% and 4% *vs* 1% and 0%, respectively). However, this was not a significant difference.

Table 1 Baseline characteristics for CD4 count < 500 and CD4 count > 500 groups

Clinical features	Parameter, *n* = 207 total	Controlled, *n* = 104	Uncontrolled, *n* = 103	*P* value
Age	Yr	55.9 (47-71)	56.3 (39-76)	0.6369
Sex	Male	46.15	70.87	0.0004
Race	Black	93.27	90.29	0.8201
	Hispanic	3.85	5.83	
	White	2.88	2.91	
Ethnicity	African American	26.32	39.29	0.6478
	Afro-Caribbean	31.58	25.00	
	Hispanic	21.05	25.00	
	Other	21.05	10.71	
BMI in kg/m^2		28.0	26.2	0.0276
Diabetes mellitus	Diabetic	14.42	11.76	0.6807
Smoking	Current	18.27	27.18	0.2451
Insurance	HIV specific	8.65	14.56	0.4638
	Medicare	10.58	14.56	
	Medicaid	60.58	53.40	
	Private	16.35	16.50	
	Self-Pay	1.92	0.97	

Data are presented as mean (range) or %, except BMI which is presented as mean. BMI: Body mass index; HIV: Human immunodeficiency virus.

CD4 count for designation of controlled vs uncontrolled HIV

There is some debate as to whether HIV viral load or CD4 count is the best stratifier to use for HIV disease progression[7-9]. Thus, we also analyzed the effect of CD4 count on polyp prevalence. To designate controlled and uncontrolled HIV, we used a CD4 count cutoff value of 500 cells/μL. Patients with a CD4 count > 500 cells/μL were considered to have controlled HIV while those with a CD4 count equal to or less than 500 cells/μL were considered to have uncontrolled HIV. Using these cutoff values, 104 patients met the criteria for controlled HIV and 103 met the criteria for uncontrolled HIV. With this definition, there were significant differences in the baseline characteristics of sex as well as BMI. As above, BMI was significantly higher in the controlled group (28 kg/m^2 *vs* 26.2 kg/m^2). Additionally, there was a significantly greater proportion of males in the uncontrolled group (71%) as opposed to the controlled group (46%).

The uncontrolled group had significantly more polyps and precancerous polyps than the controlled group. Among the patients with uncontrolled HIV, 17% had any polyp on colonoscopy, while only 5% of patients with controlled HIV had any polyp. Precancerous polyps were also more likely to be found in the uncontrolled group (11%) *vs* the controlled group (2%). There were no significant differences in the prevalence of adenomas or other polyp types between the two groups.

Finally, a logistic regression demonstrated that the odds of precancerous polyps was 9.01 times greater [95% confidence interval (CI): 1.69-47.97] in the uncontrolled group than in the controlled group after adjusting for BMI, sex, and medication types. Of note, non-nucleoside reverse transcriptase inhibitors (NNRTIs) were also associated with increased odds of precancerous polyps (odds ratio: 10.23; 95%CI: 1.08-97.15) (Figure 2).

DISCUSSION

Using CD4 count > 500 cells/μL as controlled HIV and CD4 count < 500 cells/μL as uncontrolled HIV, there was a significant association between HIV control and precancerous polyp presence. However, when using viral load < 50 copies for the definition of well-controlled *vs* poorly-controlled, there was not a significant difference in precancerous polyps noted. It was important to investigate these relationships using both viral load and CD4 count as disease status markers because there is debate as to which criteria is superior to demonstrate HIV disease status[9]. Using CD4 count, BMI was again found to be significantly different between the controlled (n = 104) and uncontrolled (n = 103) HIV groups (P = 0.0276).

Interestingly, using CD4 counts to compare groups, 53.85% of controlled patients were females, and 70.87% of uncontrolled patients were males (P = 0.0004). In the controlled group, 1.92% of patients were found to have precancerous polyps, while 10.68% of uncontrolled patients had precancerous polyps, (P = 0.0102) (Table 2). In a logistic regression that

Table 2 Fisher's exact two-sided tests for the incidence of polyps in the CD4 count > 500 and CD4 count < 500 groups

Variable	Controlled, *n* = 104	Uncontrolled, *n* = 103	*P* value
Any polyp	5 (4.81)	18 (17.48)	0.0040
Polyp type			0.0736
Adenoma	1 (0.96)	6 (5.83)	
Hyperplastic	3 (2.88)	4 (3.88)	
Serrated	1 (0.96)	5 (4.85)	
Precancerous	2 (1.92)	11 (10.68)	0.0102
Advanced adenoma	1 (0.96)	6 (5.83)	0.0651
Right colon adenoma	1 (0.96)	4 (3.88)	0.2119

Data are presented as *n* (%).

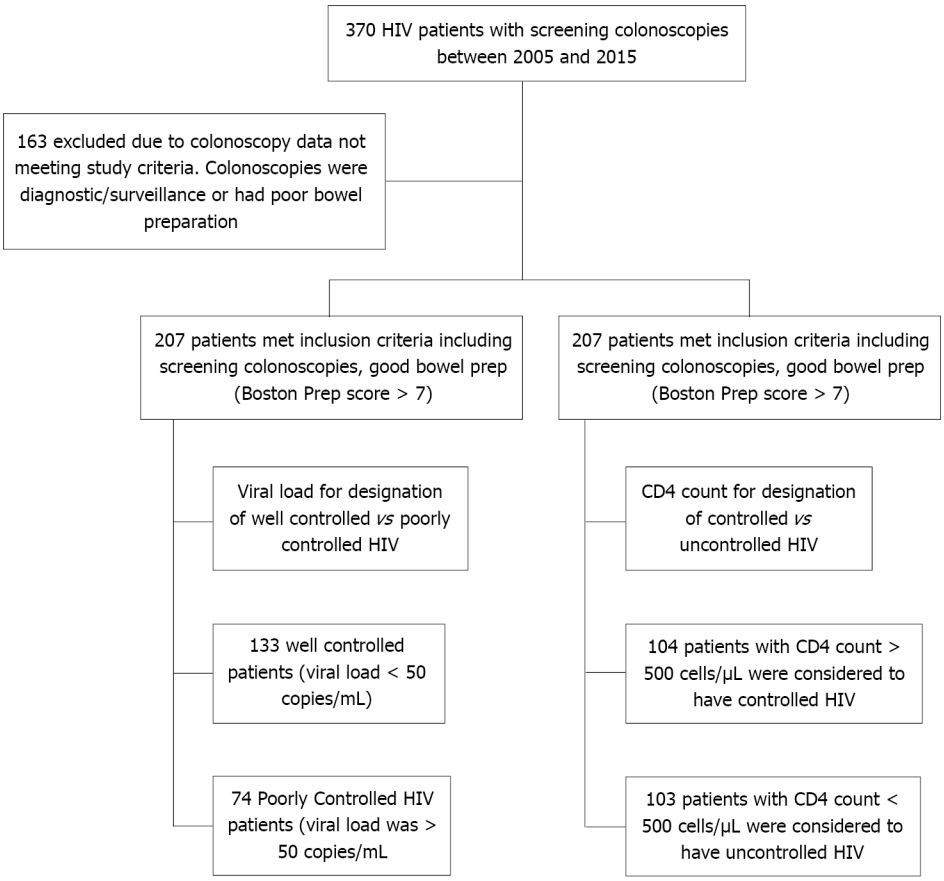

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Figure 1 Patient inclusion flow chart showing number of patients reviewed and division of human immunodeficiency virus groups based on viral load and CD4 count.

was performed to control for and assess the effects of sex, BMI, and antiretroviral use, uncontrolled patients were 9.01 times more likely to have precancerous polyps identified on their colonoscopy (95%CI: 1.69-47.97) (P = 0.0100). Patients taking NNRTIs were also found to be 10.23 times more likely to have precancerous polyps (95%CI: 1.08-97.15) (P = 0.0428) (Table 3). No significant differences were found with other types of HAART medicines. However, it is important to consider that HAART therapy combines multiple medicines.

The adenoma detection rate (ADR) for our HIV population was found to be 3.3%, which is seemingly low. However, in similar studies of HIV patients performed in urban academic centers, ADRs ranged between 6.6%-7.8%, and these studies included screening, diagnostic, and surveillance colonoscopies[3,5,6]. It is likely that if other types of colonoscopies such as diagnostic and surveillance were included in our study, our ADR would have been higher. Ultimately, institutions with large HIV patient populations or specialized HIV care may consider further investigating these complex relations, as

Table 3 Logistic regression of HIV control and precancerous polyps controlling for other variables

Variable	Odds ratio (95%CI)	*P* value
CD4 < 500 *vs* CD4 > 500	9.01 (1.69-47.97)	0.0100
Female *vs* male	2.58 (0.64-10.34)	0.1839
BMI	0.99 (0.89-1.11)	0.8956
NRTIs	1.50 (0.27-8.36)	0.6425
NNRTIs	10.23 (1.08-97.15)	0.0428
PIs	3.23 (0.35-29.98)	0.3032
FIs	0.44 (0.01-23.08)	0.6832
INSTIs	4.01 (0.23-69.67)	0.3403
CCR5 antagonists	15.39 (0.22-999.99)	0.2073

BMI: Body mass index; CI: Confidence interval; CCR5: C-C chemokine receptor 5; FIs: Fusion inhibitors; INSTI: Integrase strand transfer inhibitors; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NRTIs: Nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors.

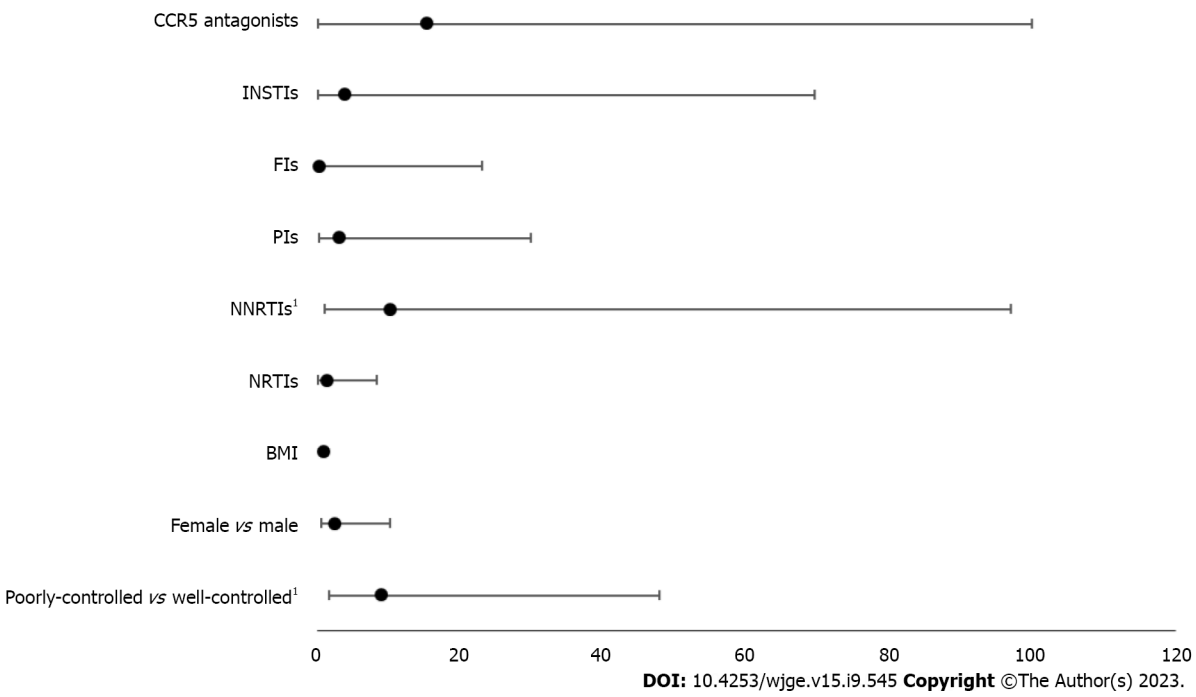

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Figure 2 Odds ratio for precancerous polyps stratified by variables. [1]Statistical significance. BMI: Body mass index; CCR5: C-C chemokine receptor 5; FIs: Fusion inhibitors; INSTIs: Integrase strand transfer inhibitors; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; NRTIs: Nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors.

this would help to increase the study ADR.

Using viral load to determine our two HIV groups, we found no differences in precancerous polyp detection. However, using CD4 count to determine the two groups, we found a significant difference, with uncontrolled patients having more precancerous polyps. Prospective studies involving HIV patients undergoing screening colonoscopy should be performed where CD4 count and HIV viral load are recorded on the day of procedure in order to better classify patients in terms of their disease status as it may relate to their findings on colonoscopy.

Our analysis also suggested an increased risk of precancerous polyps in patients who were taking NNRTIs. Most literature supports the concept that HAART has decreased the risk of HIV patients ever developing NADMs[2,6]; however, there have not been studies analyzing colorectal cancer development and HAART by drug class or drug combination. It is unclear what the mechanism of action may be regarding the use of NNRTIs and polyp growth. A study conducted by Chao *et al*[10] at Kaiser Permanente suggested that for patients with long-term use of protease inhibitors, there was an associated higher risk of anal cancer[10]. That same study did not show any association between NRRTI use and anal cancer. Similarly, a study by Piketty *et al*[11] also reported an increased anal cancer risk in HAART users, suggesting that ART therapy does not appear to prevent anal cancer. While anal cancer, advanced polyps, and colon

cancer all have different pathogeneses, we highlighted that there is still work to be done to understand the mechanism behind neoplasm development in HIV patients.

Future studies need to be performed to determine if any specific HAART regimen might impact colorectal cancer development. Conversely, some studies have shown that the occurrence of NADMs has increased since the introduction of HAART in 1996. Prior studies show an association between NNRTI use and NADMs[12]. While HAART does not have a direct effect on host DNA, there is substantial evidence that HAART alters gut microbiota[13], which may serve as a theoretical mechanism for the increased ADR in patients on NNRTIs. In addition, it is possible that the use of NNRTIs may increase NADMs by increasing lifespan of HIV patients and the rate of obesity, both of which may contribute to adenomatous polyp development.

CONCLUSION

In our study, we found there was an increased rate of precancerous polyps in patients who had lower CD4 counts and those taking NNRTIs. While the overall precancerous polyp and ADR was low in this population, further studies are needed to elucidate the possible mechanism of these differences.

ARTICLE HIGHLIGHTS

Research background

Antiretroviral therapies have improved the life expectancy of patients living with human immunodeficiency virus (HIV). As these patients live longer, they can develop non-acquired immunodeficiency syndrome defining malignancies such as colon cancers.

Research motivation

Some studies have shown that highly active anti-retroviral therapy (HAART) decreases the risk of developing colorectal cancer, while other studies propose that HIV patients are at higher risk and develop colorectal cancer at younger ages. There is no recommendation in gastrointestinal guidelines regarding special screening ages for HIV patients.

Research objectives

Our objective was to identify which factors are associated with the development of precancerous polyps on index screening colonoscopy in patients with HIV and to investigate whether HIV disease severity, measured by viral load and CD4 count, might impact adenoma growth.

Research methods

A retrospective review of electronic medical charts at Kings County Hospital and SUNY Downstate Health Sciences University for patients with HIV who had received a screening colonoscopy between 2005 and 2015 was performed.

Research results

We determined there was an increased rate of precancerous polyps in patients who had lower CD4 counts and those taking non-nucleoside reverse transcriptase inhibitors.

Research conclusions

We determined there was a relationship between HIV disease status and precancerous polys found on colonoscopy. Further studies need to be done to further explore this relationship in patients with HIV.

Research perspectives

Further studies and work need to be done to determine if any specific HAART regimen might impact colorectal cancer development.

FOOTNOTES

Author contributions: Likhtshteyn M, Marzouk E, Arroyo-Mercado FM, Chawla G, and Lerer R contributed equally to this work; Thor S was the research mentor specializing in gastroenterology; Ojeda-Martinez H was the research mentor specializing in Infectious Diseases and HIV; Rosengarten S performed statistical analysis; Likhtshteyn M, Marzouk M, Rosengarten S, and Thor S wrote the manuscript; Likhtshteyn M and Thor S were responsible for revising the manuscript; All authors read and approved the final version.

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ORIGINAL ARTICLE

Observational Study

Graft dilatation and Barrett's esophagus in adults after gastric pull-up and jejunal interposition for long-gap esophageal atresia

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Abstract

BACKGROUND

Esophageal replacement (ER) with gastric pull-up (GPU) or jejunal interposition (JI) used to be the standard treatment for long-gap esophageal atresia (LGEA). Changes of the ER grafts on a macro- and microscopic level however, are unknown.

AIM
To evaluate long-term clinical symptoms and anatomical and mucosal changes in adolescents and adults after ER for LGEA.

METHODS
A cohort study was conducted including all LGEA patients ≥ 16 years who had undergone GPU or JI between 1985-2003 at two tertiary referral centers in the Netherlands. Patients underwent clinical assessment, contrast study and endoscopy with biopsy. Data was collected prospectively. Group differences between JI and GPU patients, and associations between different outcome measures were assessed using the Fisher's exact test for bivariate variables and the Mann-Whitney *U*-test for continuous variables. Differences with a *P*-value < 0.05 were considered statistically significant.

RESULTS
Nine GPU patients and eleven JI patients were included. Median age at follow-up was 21.5 years and 24.4 years, respectively. Reflux was reported in six GPU patients (67%) *vs* four JI patients (36%) (P = 0.37). Dysphagia symptoms were reported in 64% of JI patients, compared to 22% of GPU patients (P = 0.09). Contrast studies showed dilatation of the jejunal graft in six patients (55%) and graft lengthening in four of these six patients. Endoscopy revealed columnar-lined esophagus in three GPU patients (33%) and intestinal metaplasia was histologically confirmed in two patients (22%). No association was found between reflux symptoms and macroscopic anomalies or intestinal metaplasia. Three GPU patients (33%) experienced severe feeding problems *vs* none in the JI group. The median body mass index of JI patients was 20.9 kg/m^2 *vs* 19.5 kg/m^2 in GPU patients (P = 0.08).

CONCLUSION
The majority of GPU patients had reflux and intestinal metaplasia in 22%. The majority of JI patients had dysphagia and a dilated graft. Follow-up after ER for LGEA is essential.

Key Words: Long-gap esophageal atresia; Jejunal interposition; Gastric pull-up; Barrett's esophagus; Intestinal metaplasia; Esophageal replacement

Core Tip: Long-gap esophageal atresia (LGEA) remains a surgical challenge. Preservation of the native esophagus in LGEA is the treatment of choice. Previously however, almost all LGEA patients underwent esophageal replacement (ER). This study evaluated long-term clinical symptoms and anatomical and mucosal changes in adolescents and adults after ER for LGEA. We found that long-term symptoms and graft alterations were common. The majority of gastric pull-up patients had reflux symptoms with intestinal metaplasia in 22%. The majority of jejunal interposition (JI) patients had dysphagia symptoms and more than half of the JI grafts were dilated.

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INTRODUCTION

Long-gap esophageal atresia (LGEA) is present in approximately 10% of all EA[1] and remains a surgical challenge[2,3]. Preservation of the native esophagus in LGEA is the treatment of choice, which can be accomplished by delayed primary anastomosis[4,5] or elongation techniques[6-10] in experienced centers. Previously however, almost all LGEA patients underwent esophageal replacement (ER) with gastric[11], jejunal[12] or colonic[13] conduit.

Since survival rates have improved up to 90% in EA[14], focus has shifted to the investigation and treatment of long-term morbidities and quality of life. Gastrointestinal symptoms, including gastroesophageal reflux (GER) and dysphagia, are frequent in EA[15]. The incidence of (severe) reflux is expected to be even higher in patients after a gastric pull-up (GPU)[16]. This may be explained by mobilization of the stomach into the mediastinum. This results in alteration of the shape of the gastroesophageal junction and consequently the loss of the angle of His, which is one of the anti-reflux barriers. Moreover, the negative intrathoracic pressure and the positive intraluminal pressure in the transposed stomach may increase GER[17]. Micro-aspiration due to GER may contribute to chronic cough and asthma-like symptoms[18,19]. Chronic GER may lead to esophageal mucosal alterations with a four times higher incidence of Barrett's esophagus compared to healthy controls[20]. Literature on the long-term outcome of ER is scarce[16,21-23]. Studies on long-term

endoscopic findings in LGEA patients are lacking. Therefore, this study aims to evaluate the long-term outcome of jejunal interposition (JI) and GPU on clinical symptoms and anatomical and mucosal changes in adolescents and adults after LGEA.

MATERIALS AND METHODS

Study design and participants

A cohort study was conducted including all LGEA patients ≥ 16 years old who had undergone JI or GPU at the University Medical Center Utrecht (UMCU) and the University Medical Center Groningen between 1985 and 2003. As of 2018, all 17-year-old EA patients are routinely referred to the gastroenterologist for clinical assessment and endoscopic and histologic screening for esophageal mucosal lesions. All adult LGEA patients (> 17 years), that were not yet included in the routine follow-up, were invited for screening. Patients that had ER for LGEA underwent an one-time barium contrast study, to evaluate the anatomy of the graft. Data was collected prospectively. Gastroscopies that were performed after the age of 17 years and within the last four years, were reviewed retrospectively.

Surgical procedures

All ERs had been performed by experienced pediatric surgeons. The GPU was performed as previously described by Spitz *et al*[11,24]. In short, after mobilization of the stomach and a pyloromyotomy transhiatal posterior mediastinal tunnel is created and the stomach is transposed into the thorax through the esophageal hiatus. Thereafter, the proximal esophagus and the apex of the stomach are anastomosed in the neck. JI was performed as described in these studies[12,25,26]. The pedicle graft is created: The jejunum is transected close to Treitz ligament and at the level of the third mesenteric artery branch. The uppermost part of the graft is tunneled into the right chest, behind the stomach and through the posterior part of the hiatus. Thereafter, two anastomosis are performed, one between the proximal esophagus and the jejunal graft and another between the distal esophagus and the jejunal graft.

Clinical assessment

Baseline characteristics, including gender, age, type of EA and associated anomalies were obtained from the electronic medical records.

Gastro-intestinal symptoms: Gastrointestinal symptom assessment (*e.g.*, reflux, dysphagia) was derived from the routine outpatient follow-up at the Gastroenterology Department.

Contrast study: Upper gastrointestinal barium contrast studies were analyzed by an experienced radiologist and pediatric surgeon for the following parameters: Anastomotic stenosis, stasis of contrast, reflux, graft-dilatation and graft-lengthening (resulting in a siphon shaped graft) of the JI and the position of the stomach in GPU patients.

Upper endoscopy and histology: Upper endoscopy was performed by a gastroenterologist to assess the esophagus, the anastomotic site(s), the grafts, the gastroesophageal junction and the stomach. Reflux esophagitis and intestinal metaplasia were scored according to the Los Angeles (LA) classification[27] and Prague criteria[28]. Barrett's esophagus was defined as columnar lined esophagus on endoscopy in combination with intestinal metaplasia on histology. In patients with JI, biopsies were taken from both the distal and proximal esophagus. Jejunal grafts were evaluated on proximal or distal stenosis, (distal) dilatation of the graft and on macroscopic lesions. Biopsies of the jejunal graft were taken if mucosal abnormalities were present. The GPU was evaluated on anastomotic stenosis, macroscopic lesions and altered anatomy. In patients with GPU, biopsies were taken just proximal to the anastomosis. In case of macroscopic abnormalities of the GPU, biopsies were taken. Endoscopies were reviewed by an experienced gastroenterologist and a pediatric surgeon. Biopsies were evaluated for inflammation, eosinophilia and metaplasia by the Pathology Department by an expert gastrointestinal pathologist.

Ethical approval

This study was part of a larger cohort study on the long-term outcome in LGEA patients. The study protocol was submitted to the UMCU Ethics Committee (METC 18-458/C). According to the Medical Research Involving Human Subject Act, no ethical approval was required.

Statistical analysis

Continuous skewed variables were presented as median and range, categorical data were presented as frequencies and percentage. Group differences between JI and GPU patients, and associations between different outcome measures were assessed using the Fisher's exact test for bivariate variables and the Mann-Whitney *U*-test for continuous variables. Differences with a P value < 0.05 were considered statistically significant. The analyses were performed using SPSS for Windows, version 25.0 (IBM Corp., Armonk, NY).

RESULTS

Between 1985 and 2003, a total of 24 patients underwent ER for LGEA (Figure 1). One JI patient was deceased at the age of 10 years due to massive aspiration. After following the exclusion criteria, twenty patients were included in this study. Nine patients underwent GPU and eleven underwent JI. Median age at follow-up was 21.5 years (range 20.2-34.1) for GPU patients and 24.4 years (range 16.1-31.2) for JI patients. Five JI patients (46%) and all GPU patients were male (P = 0.01). Associated anomalies (*e.g.*, cardiac, renal, musculoskeletal anomalies) were more present in GPU patients than in JI patients (100% *vs* 55%, P = 0.04). In both groups severe mental retardation and Down syndrome were present in one patient. Patient characteristics are shown in Table 1. Preoperative gastrostomy was present in all JI patients and in eight (89%) GPU patients. Anastomotic strictures requiring dilatation had developed in eight JI patients (73%) and five GPU patients (55%). Fundoplication was required in one JI patient at the age of 2 years (Table 2).

Clinical assessment

Reflux complaints were reported in six of the nine GPU patients (67%) and in four out of 11 JI patients (36%) (P = 0.37). Dysphagia symptoms were scored in seven JI patients (64%) *vs* two GPU patients (22%) (P = 0.09). Three GPU patients (33%) experienced severe feeding problems. Due to swallowing disabilities, one patient was still fully dependent on jejunostomy feeding, with minimal attempts of liquid oral feeds. Another patient required additional jejunostomy feeding until the age of 21 years, but has recently reached a full oral diet. One patient required additional drink nutrition to achieve a full oral diet. In the JI group, no severe feeding problems were observed.

The median body mass index (BMI) of JI patients was 20.9 kg/m^2 (range 17.9-27.6) *vs* 19.5 kg/m^2 (range 17.5-21.6) in GPU patients (P = 0.08). Two JI patients (18%) were underweight (BMI < 18.5 kg/m^2) and one patient was overweight (BMI > 25 kg/m^2) (Table 3). Three GPU patients (33%) were underweight, none of the patients were overweight.

Contrast study

GPU: Barium contrast studies were performed in five of the nine GPU patients (56%). In one patient, the stomach was completely transposed into the thorax. This patient showed some lengthening of the distal esophagus and stasis of liquids in the distal esophagus. Another patient, with Down syndrome, also showed stasis of contrast in the esophagus. No reflux was observed in these patients.

Four out of nine GPU patients did not undergo a contrast study; three patients did not consent because they did not experience major gastro-intestinal complaints. One patient with mental retardation was unable to perform a contrast study due to severe swallowing difficulties.

JI: Barium contrast studies were performed in all 11 JI patients. Ten patients (91%) showed stasis of contrast in the ER graft. None of the patients had a proximal or distal stenosis. The jejunal graft was dilated in six (55%) patients. In two of these patients, graft dilatation was severe. In four of these six patients, mild to moderate lengthening of the distal part of the jejunal graft was observed (Figure 2).

Endoscopic results

GPU: All GPU patients (n = 9) had undergone gastroscopy. The median distance from the incisors to the anastomosis was 19 cm (range 17-24). Macroscopic anomalies of the native esophagus were seen in five patients (56%); three patients showed columnar lined esophagus (33%) (C0M2, C0M2, C1M2) (Figure 3). One patient had an erosion at the distal part of the esophagus and another patient, who was jejunostomy dependent due to severe swallowing difficulties, had a pinpoint stenosis of the anastomosis (Table 4).

JI: All JI patients (n = 11) had undergone upper endoscopy. The median distance from the incisors to the proximal anastomosis was 21 cm (range 18-25), the median length of the jejunal graft was 15 cm (range 12-22) and the median length of the distal esophagus was 4.5 cm (range 0-8). In none of the patients a proximal or distal anastomotic stenosis was present. Macroscopic anomalies were seen in five patients (45%): Two patients showed macroscopic esophagitis of the distal esophagus according to the LA classification (grade A, n = 1; grade B, n = 1), one patient had fields of squamous epithelium in the proximal part of the jejunal graft, one patient showed elevation of normal mucosa in the distal esophagus and a neurological impaired patient had stasis of food and an ulcer at the distal part of the jejunal graft. None of the JI patients showed columnar-lined esophagus (Table 4).

Histologic results

GPU: In three patients with macroscopic columnar-lined esophagus, biopsies of the native distal esophagus showed intestinal metaplasia in two patients (22%), both with Prague classification C0M2 (2 men; median age 21.6 years). In two patients, biopsies of the distal esophagus showed chronic inflammation. Biopsies in another two patients showed hyperplastic squamous epithelium without dysplasia. In one patient, histopathology revealed that biopsies of cardia and corpus were obtained. Histopathology showed no signs of dysplasia in any of the patients. In one patient without macroscopic anomalies, no biopsies specimens were taken (Table 4).

JI: In three patients, histology of the native distal esophagus showed normal esophageal mucosa. In one patient, biopsy of the native distal esophagus showed a single glandular tube with signs of intestinal metaplasia. A target biopsy of a small mucosal elevation of the distal esophagus in another patient showed mild reactive changes of the mucosa. In two patients, biopsies of the stomach were obtained. Biopsies in one patient showed no abnormalities. In the other patient without macroscopic anomalies, biopsy of the stomach showed lymphoid infiltration, further investigation excluded

Table 1 Patient characteristics gastric pull-up & jejunal interposition

Value	GPU (*n* = 9)	JI (*n* = 11)	*P* value
Male	9 (100%)	5 (46%)	0.01[a]
Gestational age (wk)	33.9 (29-39)	34.7 (32.3-41.3)	0.15
Premature	7 (78%)	8 (73%)	1.0
Birthweight (grams)	1680 (1030-3040)	2010 (1115-3755)	0.49
Gross type EA			0.63
A	5 (56%)	4 (36%)	
B	3 (33%)	6 (55%)	
C	1 (11%)	1 (9%)	
Associated anomalies[1]	9 (100%)	6 (55%)	0.04[a]
Down syndrome	1 (11%)	1 (9%)	
Anorectal malformations	1 (11%)	1 (9%)	
Duodenal atresia	1 (11%)	1 (9%)	
Musculoskeletal	4 (44%)	3 (27%)	
Cardiac	1 (11%)	2 (18%)	
Renal anomaly	4 (44%)	1 (9%)	
Palatoschisis	2 (22%)	0	

[1]Some patients have multiple anomalies.
[a]Indicating statistical significance.
All data are presented as median (range) or *n* (%). GPU: Gastric pull-up; JI: Jejunal interposition; EA: Esophageal atresia.

Table 2 Gastrointestinal outcome in gastric pull-up & jejunal interposition

Variable	GPU (*n* = 9)	JI (*n* = 11)	*P* value
Age at surgery (d)	128 (1-323)	67 (41-149)	0.21
Gastrostomy	8 (89%)	11 (100%)	0.45
Fundoplication	0	1 (9.1%)	1.0
Stenosis[1]	5 (56%)	8 (73%)	0.64
Dilatations total (*n*)	3 (1-4)	3 (1-15)	0.76
Dilatations within 1st yr (*n*)	1 (1-3)	2.5 (0-15)	0.26

[1]Stenosis requiring intervention
Data are presented as median (range) or *n* (%). GPU: Gastric pull-up; JI: Jejunal interposition.

lymphoma. None of the biopsies showed signs of esophageal dysplasia. In four patients without suspected macroscopic anomalies (36%), no biopsies specimens were taken (Table 4).

Symptom and graft analysis

Columnar-lined esophagus of the native esophagus occurred more often in the GPU group compared to the JI-group (3 *vs* 0 patients, $P = 0.07$). No associations were found in GPU patients between reflux symptoms and macroscopic mucosal abnormalities during upper endoscopy or with intestinal metaplasia. Both patients that had confirmed intestinal metaplasia, reported reflux symptoms and were treated with proton-pump inhibitors (PPIs). No association was found between intestinal metaplasia and GER symptoms. No association was found between BMI and reflux.

Of the six patients with a dilated JI-graft, five (83%) reported dysphagia complaints. Of the four patients with lengthening of the JI-graft, three (75%) reported dysphagia symptoms. However, there was no statistically significant association between dilatation or lengthening and dysphagia.

Table 3 Clinical data

Variable	GPU (*n* = 9)	JI (*n* = 11)	*P* value
Age at follow-up (median, yr)	21.5 (20.2-34.1)	24.4 (16.1-31.2)	0.85
GER complaints	6 (67%)	4 (36%)	0.37
Dysphagia	2 (22%)	7 (64%)	0.09
FOIS			
Total oral diet with no restrictions	5	5	
Specific food limitations	1	2	
Multiple consistencies, requiring special preparation	1	0	
Tube-dependent	1	0	
Missing	1	4	
PPI use	4 (44%)	3 (27%)	0.38
BMI (kg/m^2)	19.5 (17.5-21.6)	20.9 (17.9-27.6)	0.08

Data are presented as median (range) or *n* (%). GPU: Gastric pull-up; JI: Jejunal interposition; GER: Gastroesophageal reflux; FOIS: Functional Oral Intake Scale; PPI: Protein-protein interaction; BMI: Body mass index.

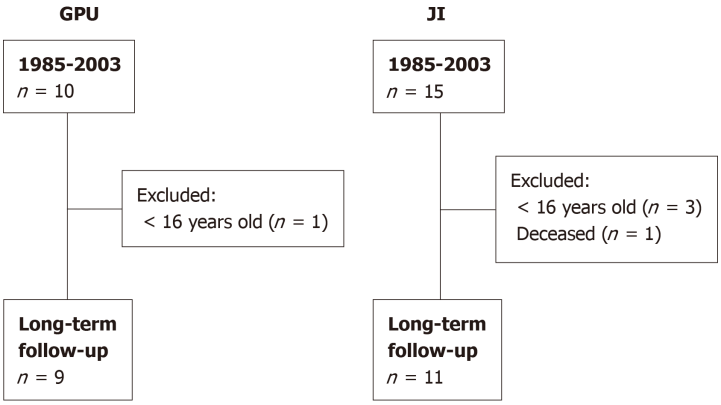

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Figure 1 Flowchart of patients included in the study. GPU: Gastric pull-up; JI: Jejunal interposition.

DISCUSSION

This is the first study to evaluate very long-term changes in ER grafts for LGEA by contrast study and endoscopy, showing intestinal metaplasia in 22% of GPU patients and graft dilatation in JI patients. Furthermore, this study evaluates gastrointestinal symptoms during a long-term follow-up.

We found that the majority of GPU patients had reflux symptoms, which is in line with the outcome of the study of Hannon *et al*[21]. In our study, reflux symptoms were assessed at the outpatient clinic by a gastroenterologist. EA patients might consider reflux symptoms as normal after prolonged periods of reflux. Symptom-related questions asked by a specialist may identify patients with reflux symptoms who would otherwise consider themselves free of symptoms[29]. This can explain the high incidence of reflux found in this study.

This study showed that reflux symptoms occurred less in JI patients compared to GPU patients. This difference may be explained by the fact that several physiological anti-reflux mechanisms are altered in GPU patients, such as the intrathoracic position of the stomach with a negative intrathoracic pressure and loss of the His angle[17]. In the JI patient group, the distal esophagus remained intact with an intra-abdominal position in all but one patient. Although peristalsis of the graft is not as efficient as a native esophagus, the other antireflux barriers are preserved.

Postoperative dysphagia was present in the majority of JI patients. Their nutritional status, however, was good on the long term and all JI patients had a full oral intake. This is in contrast to previous studies[30,31], with only 33%-57% of JI patients tolerating a complete oral intake. This difference may be explained by the occurrence of severe postoperative complications in both studies, including graft loss.

In our study, GPU patients reported less dysphagia symptoms compared to JI patients. Our GPU group also reported less dysphagia symptoms than the GPU group of Hannon *et al*[21], although this difference is relatively small. Lower BMI has been described in GPU patients compared to primary repair EA patients[21]. This is in line with our findings, in

Table 4 Radiologic, endoscopic and histologic data

Variable	GPU (*n* = 9)	JI (*n* = 11)	*P* value
Barium contrast results	*n* = 5	*n* = 11	
Stasis	3 (60%)	10 (91%)	0.14
Stricture	0	0	-
Dilated JI graft	N/A		N/A
Mild		4 (36%)	
Severe		2 (18%)	
Lengthening of JI graft	N/A	4 (36%)	N/A
Endoscopy results	*n* = 9	*n* = 11	
Length proximal esophagus (cm)	20 (17-24)	21 (18-25)	-
Length jejunal graft (cm)	N/A	15 (12-22)	-
Length distal esophagus (cm)	N/A	4.5 (0-8)	-
Macroscopic anomalies	5 (56%)	5 (45%)	1.0
Macroscopic esophagitis[1]			
Grade A	0	1 (9%)	-
Grade B	0	1 (9%)	-
Columnar-lined esophagus	3 (33%)	0	0.07
Histology results	*n* = 8	*n* = 7	
Normal mucosa	1 (13%)	3 (43%)	0.58
Inflammation	2 (25%)	1 (14%)	1
Intestinal metaplasia	2 (25%)	0	0.47
Other	3 (38%)	3 (43%)	1.0

[1]According to the Los Angeles classification.

Data are presented as median (range) or *n* (%). GPU: Gastric pull-up; JI: Jejunal interposition; N/A: Not applicable.

which one third of the GPU patients were underweight and needed nutritional supplements. One might speculate that reflux negatively influences the achievement of an adequate caloric intake and consequent lower BMI[32,33]. However, in our study, an association between reflux and BMI could not be found.

Our study showed that the majority of patients had a dilated JI graft. Although almost all of these patients reported dysphagia complaints, an association between the dilatation and dysphagia was not statistically significant. The dilatation of the jejunal graft may be explained by the slower motility of the jejunal graft compared to the faster motility of the esophagus. Stasis of food due to dysmotility of the jejunal graft and the distal esophageal remnant may result in dilatation of the graft and may cause dysphagia symptoms in these patients. Lengthening of the JI graft may also contribute to dysmotility and therefore dysphagia due to the siphon shape. Previously, JI graft dilatation has only been described by Saeki *et al*[22]. In his study on JI for LGEA (mean age 10 years) dilatation of a graft was observed in one patient. This was due to a stenosis of the distal anastomosis. In our study, lengthening of the jejunal graft was seen in 36% of JI patients, which is in line with previous studies[22,23].

Upper endoscopy showed columnar-lined esophagus in one third of the GPU patients and in none of the JI patients in our study. Histology reported intestinal metaplasia in 22% of GPU patients and in none of the JI patient. These findings are in contrast to the only other published study using endoscopy in adults after LGEA by Vergouwe *et al*[20]. The latter showed no signs of Barrett's esophagus in LGEA patients with ER. However, they showed an incidence of 6.6% Barrett's esophagus in their total cohort of 151 adult EA patients. Vergouwe *et al*[20] also showed two patients with esophageal cancer. Esophageal cancer after primary repair of EA at the site of the anastomosis in a patient with severe reflux has also been described[34]. In our study, no patients were found with esophageal cancer.

Our findings reveal that the macroscopic and microscopic tissue changes seen in the GPU grafts were not significantly associated with reflux symptoms. This may be explained by the fact that many patients were treated with PPIs. Also, metaplasia of the esophageal mucosa can protect against acid reflux and therefore prevent symptoms of discomfort. Furthermore, one can expect that EA patients may get used to reflux symptoms, although this is not evidence based. Reflux symptoms can thus not be used as a reliable detector for the presence of intestinal metaplasia. Since GPU is the most frequently performed ER procedure for LGEA and intestinal metaplasia or Barrett's esophagus may occur more frequently in this subset of patients, further follow-up of GPU in the long-term may clarify this concern. Barrett's

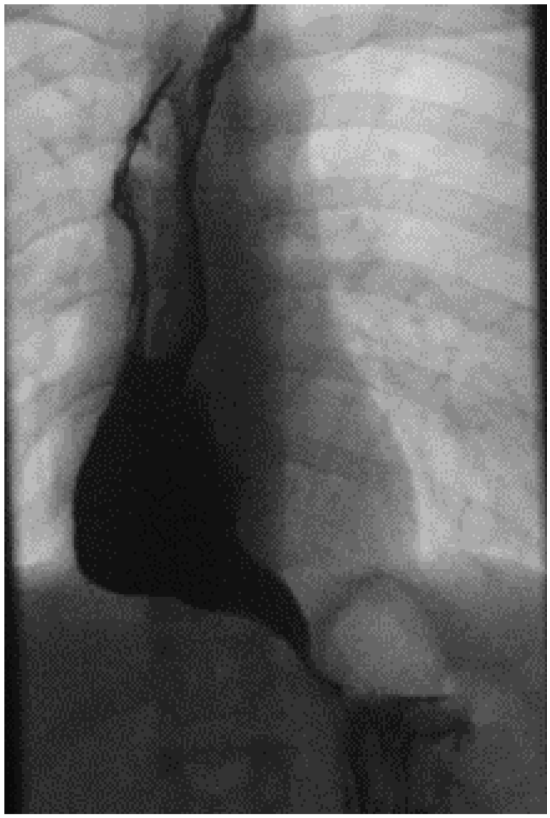

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Figure 2 Lengthening and dilatation of the distal jejunal graft.

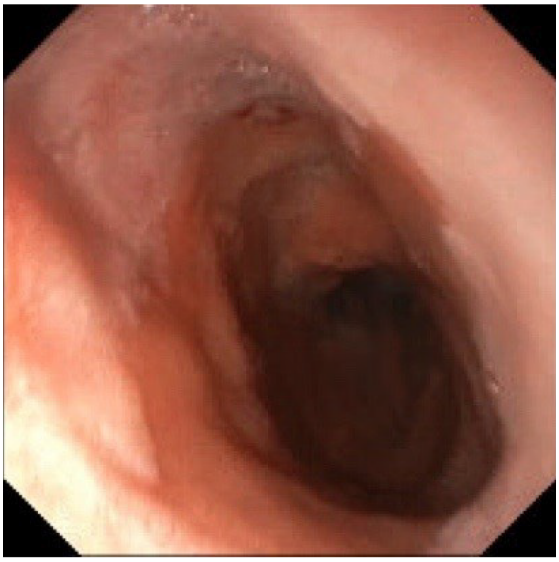

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Figure 3 Barrett's esophagus (C0M2) in a gastric pull-up patient.

esophagus in the normal population increases steeply from young adulthood until the 6th decade of life. Since our cohort consists of young patients, the prevalence of Barrett's esophagus will become more clear after long term follow-up.

Due to the rarity of LGEA, data are scarce. This inevitably limits our study and therefore, interpretations must be made with caution. Furthermore, treatment for LGEA is being corrected by using the thoracoscopic traction technique in our center. In our opinion, this is now the treatment of choice for LGEA, but only in experienced centers. Alternatively, if experience in this challenging procedure is not available, a GPU can be performed.

Other limitations in this study include the retrospective design of the study and the missing histology in five JI patients and one GPU patient. Although the macroscopic aspects during endoscopy seemed normal in these patients, histological evidence would be preferred. Also, contrast studies were missing in four GPU patients. Furthermore, review of contrast

studies is not standardized and therefore subjective. However, all contrast studies were analyzed by an experienced radiologist and pediatric surgeon to minimize bias.

CONCLUSION

This study shows that ER grafts show significant macroscopic and microscopic abnormalities after long-term follow-up. Dilatation of the graft and dysphagia symptoms were present in the majority of JI patients. GPU patients may have an increased risk of intestinal metaplasia. Therefore, increased awareness and endoscopic follow-up during adulthood is suggested for LGEA patients after ER. Especially since GPU has been and still is the most frequently used treatment for LGEA.

ARTICLE HIGHLIGHTS

Research background

Previously, esophageal replacement (ER) with gastric pull-up (GPU) or jejunal interposition (JI) used to be the standard treatment for long-gap esophageal atresia (LGEA). Gastrointestinal symptoms are common in EA patients and may occur even more frequently after ER, due to a change of the anatomy.

Research motivation

Long-term macroscopic and microscopic graft changes are currently unknown and may be clinically relevant in patients with LGEA.

Research objectives

This study aims to evaluate clinical symptoms and macroscopic and microscopic graft changes in adolescence and adulthood.

Research methods

A cohort study including all LGEA patients ≥ 16 years who had undergone ER between 1985-2003 at two tertiary centers in the Netherlands was conducted. Clinical symptoms, contrast studies and endoscopies were collected prospectively.

Research results

Nine GPU patients and eleven JI patients were included in this study, with a median age of 21.5 years and 24.4 years respectively. Six of nine GPU patients (67%) reported reflux complaints and 64% of JI patients reported dysphagia symptoms. Dilatation of the jejunal graft was observed in 55%. Three GPU patients had columnar-lined epithelium and in two of these patients intestinal metaplasia was histologically confirmed.

Research conclusions

Long-term follow-up revealed significant macroscopic and microscopic graft changes after ER. Furthermore, this study revealed long-term clinical symptoms after both GPU and JI. GPU patients may have an increased risk on intestinal metaplasia. Dilatation of the graft and dysphagia symptoms were present in the majority of JI patients. Follow-up during adulthood after ER for LGEA is therefore suggested.

Research perspectives

This study highlights the importance of implementing an endoscopic follow-up program after ER for LGEA, particularly after GPU. Further investigations with larger patient cohorts are necessary to validate these findings.

FOOTNOTES

Author contributions: van Tuyll van Serooskerken ES, Gallo G, Hulscher JB, Tytgat SH, and Lindeboom MY conceptualized and designed the study; van Tuyll van Serooskerken ES and Gallo G collected the data, carried out the initial analysis, drafted the initial manuscript; van Tuyll van Serooskerken ES, Gallo G, Weusten BL, Westerhof J, Brosens LA, Zwaveling S, Ruiterkamp J, Hulscher JB, Arets HG, Bittermann AJ, van der Zee DC, Tytgat SH, and Lindeboom MY reviewed and revised the manuscript; Hulscher JB, Tytgat SH, and Lindeboom MY contributed to the writing; Weusten BL, Westerhof J, Brosens LA, Hulscher JB, Tytgat SH, and Lindeboom MY supervised the data collection and the progress the manuscript; Weusten BL, Westerhof J, and Brosens LA provided input to the study; Zwaveling S, Ruiterkamp J, Arets HG, Bittermann AJ, and van der Zee DC reviewed the study design, supervised the process and contributed to the interpretation of data; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Institutional review board statement: This study was part of a larger cohort study on the long-term outcome in LGEA patients. The study protocol was submitted to the UMCU Ethics Committee (METC 18-458/C). According to the Medical Research Involving Human Subject

Act, no ethical approval was required.

Informed consent statement: This study was part of a larger cohort study on the long-term outcome in LGEA patients. The study protocol was submitted to the UMCU Ethics Committee (METC 18-458/C). According to the Medical Research Involving Human Subject Act, no informed consent was required.

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ORIGINAL ARTICLE

Prospective Study

Endoscopic Ruler for varix size measurement: A multicenter pilot study

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Abstract

BACKGROUND
We invented Endoscopic Ruler, a new endoscopic device to measure the size of varices in patients with cirrhosis and portal hypertension.

AIM
To assess the feasibility and safety of Endoscopic Ruler, and evaluate the agreement on identifying large oesophageal varices (OV) between Endoscopic Ruler and the endoscopists, as well as the interobserver agreement on diagnosing large OV using Endoscopic Ruler.

METHODS
We prospectively and consecutively enrolled patients with cirrhosis from 11 hospitals, all of whom got esophagogastroduodenoscopy (EGD) with Endoscopic Ruler. The primary study outcome was a successful measurement of the size of varices using Endoscopic Ruler. The secondary outcomes included adverse events, operation time, the agreement of identifying large OV between the objective measurement of Endoscopic Ruler and the empirical reading of endoscopists, together with the interobserver agreement on diagnosing large OV by Endoscopic Ruler.

RESULTS
From November 2020 to April 2022, a total of 120 eligible patients with cirrhosis were recruited and all of them underwent EGD examinations with Endoscopic Ruler successfully without any adverse event. The median operation time of Endoscopic Ruler was 3.00 min [interquartile range (IQR): 3.00 min]. The kappa value between Endoscopic Ruler and the endoscopists while detecting large OV was 0.52, demonstrating a moderate agreement. The kappa value for diagnosing large OV using Endoscopic Ruler among the six independent observers was 0.77, demonstrating a substantial agreement.

CONCLUSION
The data demonstrates that Endoscopic Ruler is feasible and safe for measuring the size of varices in patients with cirrhosis and portal hypertension. Endoscopic Ruler is potential to promote the clinical practice of the two-grade classification system of OV.

Key Words: Oesophageal varices; Cirrhosis; Portal hypertension; Esophagogastroduodenoscopy; Endoscopic ruler

Core Tip: We invented Endoscopic Ruler, a new endoscopic device to measure the size of varices in patients with cirrhosis and portal hypertension. This study demonstrates that Endoscopic Ruler is feasible and safe for measuring the size of varices in patients with cirrhosis and portal hypertension. Endoscopic Ruler is potential to promote the clinical practice of the two-grade classification system of oesophageal varices.

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INTRODUCTION

Oesophageal varices (OV) is a common complication among patients with cirrhosis and portal hypertension[1]. The prevalence of OV is approximately 30%-40% and 85% in compensated and decompensated cirrhosis respectively[2]. Variceal haemorrhage is a potential lethal complication of OV with a six-week morality of 15%-25%[3]. Given the mortality and morbidity associated with variceal haemorrhage, esophagogastroduodenoscopy (EGD) is recommended as a golden standard for the early detection and screening of high-risk OV in the current guidelines[1-4]. EGD screening is generally performed by endoscopists with different levels of experience. In the procedure, operators assess the locations and sizes of OV according to subjectivity. Therefore, accuracy and consistency in the classification of OV performed by endoscopists will have direct effect on subsequent management.

The recent Baveno VII consensus emphasizes a 2-grade classification system of OV followed from the management perspective[1] in which the varix size is quantitatively classified into either small (< 5 mm) or large (≥ 5 mm). This system was initially created by the North Italian Endoscopy Club, which found the high-risk features of variceal bleeding and was endorsed in the Baveno I consensus meeting in 1992[5,6]. However, this quantitative system is not widely used in clinical practice probably due to the following limitations: A doubtful accuracy due to varix size assessment demanding high-level experience in specialized centers; a lack of data on the interobserver agreement and reproducibility. To overcome these limitations, we invented Endoscopic Ruler, a novel endoscopic device to measure the size of varices in patients with cirrhosis and portal hypertension. The primary aim of this pilot study was to evaluate the feasibility and safety of Endoscopic Ruler. The secondary aim was to assess the agreement on detecting large OV between the objective measurement of Endoscopic Ruler and the empirical reading of endoscopists, as well as the interobserver reliability on identifying large OV using Endoscopic Ruler.

MATERIALS AND METHODS

Study patients and design

This study was a multicenter pilot study (CHESS2005, ClinicalTrials.gov identifier: NCT04639323), in which we prospectively and consecutively recruited cirrhotic patients from 11 hospitals in China from November 2020 to April 2022. Inclusion criteria were: (1) Confirmed cirrhosis based on clinical, biochemical and radiology findings; (2) A schedule to undergo EGD screening; (3) Age between 18 and 75 years; and (4) A written informed consent. Patients were excluded for the following: Active upper gastrointestinal bleeding and without OV diagnosed *via* EGD (including isolated gastric varices).

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, and was approved by the Institutional Review Board of principle research institutions. A written informed consent was obtained from all enrolled participant. All authors had an access to the study data and reviewed the final manuscript.

Endoscopic Ruler device and procedure

EGD examinations were performed using GIF-HQ290 (Olympus, Japan), GIF-H260Z (Olympus, Japan), or EG-601WR (FUJINON, Japan), with Endoscopic Ruler. Endoscopic Ruler consists of three parts: A tip, a sheath and an operating handle. The measurement range of Endoscopic Ruler is 1-10 mm. There are ten black alternating with white grids and the width of each grid is 1 mm (Figure 1). The procedures were carried out by one specific experienced endoscopist (have performed EGD examinations for more than 10 years and regularly performed endoscopic variceal ligation for at least 3 years) at individual centers. Ten to fifteen minutes before EGD, topical pharyngeal anaesthesia was applied to the posterior pharynx (dyclonine hydrochloride mucilage, 8-10 mL oral, 10 mL/dose; China).

An empirical interpretation of OV performed by endoscopists was prior to the measurement of Endoscopic Ruler and the results would be recorded by a specific recorder at individual centers. Endoscopic Ruler was inserted through the biopsy channel of EGD and with its tip kept in the sheath until the sheath was sent into the region of interest. Endoscopists controlled the direction of the tip according to the angle of EGD and the location of lesions to make Endoscopic Ruler parallel with the target OV (the largest one), and then the varix size was measured. After measurement, Endoscopic Ruler could be drawn out slowly with the tip shut (Figure 2). All major findings with and without Endoscopic Ruler were recorded on digital pictures.

Study outcomes

The primary outcome was the successful measurement of varix size using Endoscopic Ruler: From Endoscopic Ruler being sent into the region of interest, the largest OV being measured, to Endoscopic Rule being drawn out. Secondary outcomes were the safety, operation time of Endoscopic Ruler, agreement on diagnosing large OV between the empirical reading of endoscopists and the objective measurement using Endoscopic Ruler as well as interobserver reliability on diagnosing large OV using Endoscopic Ruler.

Safety was assessed according to adverse events associated with the procedures. Operation time was calculated from the time when Endoscopic Ruler was inserted through the biopsy channel of EGD to that when it was drawn out, which was recorded by recorders. Large OV was defined as those with the largest varix size ≥ 5mm[1]. A total of 120 sets of pictures of the 120 patients enrolled with and without Endoscopic Ruler were digitally stored., ten of whom were randomly selected to explore the interobserver agreement. Six independent blinded observers excluding the endoscopists who recorded the procedures evaluated the selected records, including three experienced endoscopists who had performed EGDs more than ten years and regularly performed dedicated lists for variceal screening as well as endoscopic

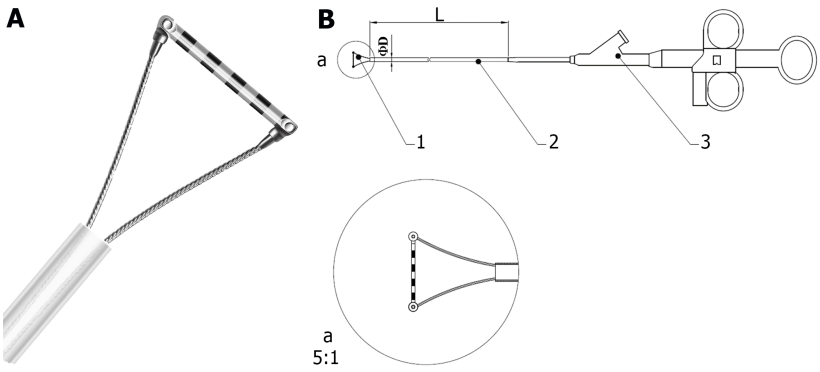

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Figure 1 Diagram of Endoscopic Ruler. A: The tip of Endoscopic Ruler; B: The structure of Endoscopic Ruler. 1: Tip; 2: Sheath; 3: Operating handle.

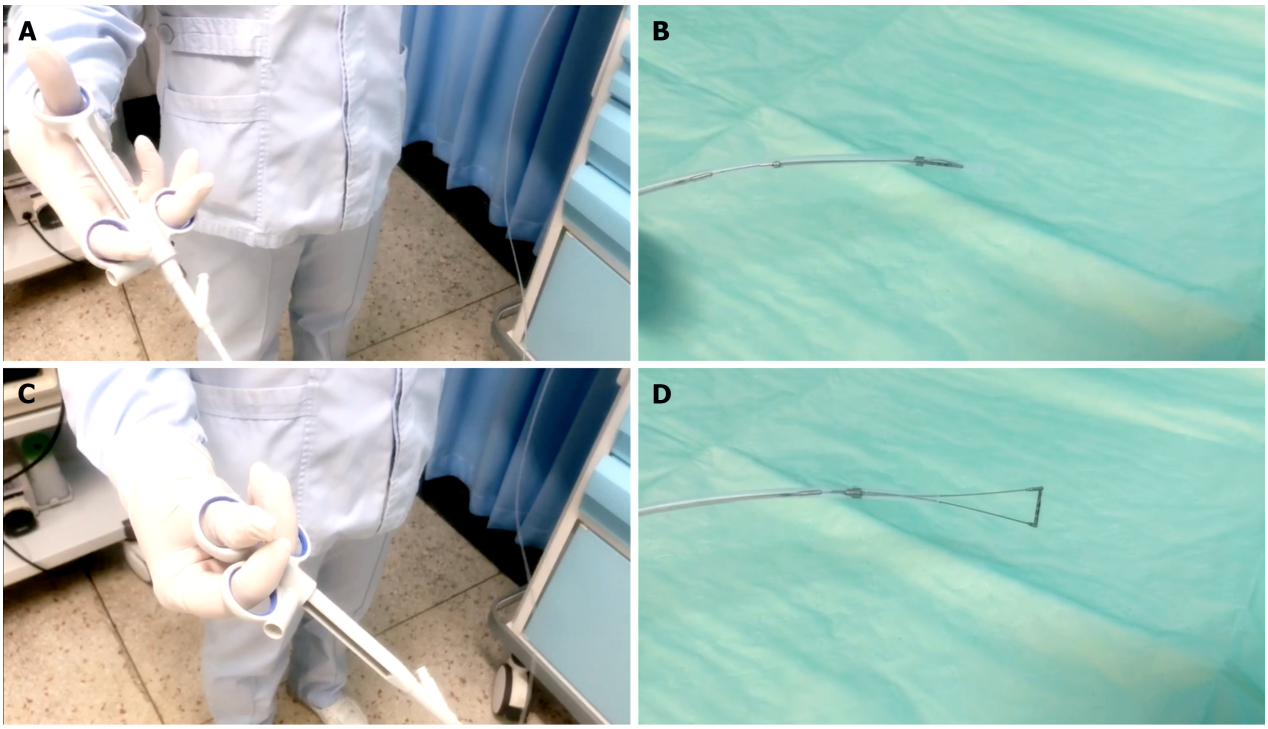

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Figure 2 Measurement procedure of Endoscopic Ruler. A and B: The operating handle of Endoscopic Ruler (A) when the tip is shut (B); C and D: The operating handle of Endoscopic Ruler (C) when the tip is open (D).

variceal ligation and three inexperienced endoscopists who performed EGD for five to ten years but hadn't performed regular variceal screening or endoscopic variceal ligation.

Statistical analysis

Categorical data was expressed as numbers (percentages), and continuous variables were expressed as mean (standard deviation) or median (IQR). The agreement on diagnosing large OV between the empirical reading of endoscopists and the objective measurement using Endoscopic Ruler as well as the interobserver reliability on diagnosing large OV using Endoscopic Ruler were assessed according to the kappa value. Cohen's kappa was used in case of two observations (*i.e.* agreement between endoscopists and Endoscopic Ruler) and Fleiss kappa in case of more than two observations (*i.e.* interobserver reliability). Kappa values were considered as a slight agreement between 0 and 0.20, a fair agreement between 0.21 and 0.40, a moderate agreement between 0.41 and 0.60, a substantial agreement between 0.61 and 0.80 as well as an almost-perfect agreement between 0.81 and 1.00[7]. A P value of < 0.05 was considered significant. All statistical calculations were performed with R language (version 4.1.3, R Core Team, 2022).

RESULTS

Study population

From November 2020 to April 2022, 122 patients with cirrhosis from 11 hospitals in China were recruited, two of whom with isolated gastric varices were excluded. There were 120 patients involved in the final analysis (mean age of 54.02 years; male 59.17%). Of them, the main etiology of cirrhosis was Hepatitis B virus infection (n = 82, 68.33%). The number of patients with Child-Pugh A, B, and C were 43 (35.83%), 59 (49.17%) and 18 (15.00%) respectively. Baseline characteristics of the enrolled patients were summarized in Table 1.

Feasibility, safety and operation time of Endoscopic Ruler

All the 120 patients underwent EGD examinations with Endoscopic Ruler successfully, without any adverse event (n = 0, 0%) related to EGD or Endoscopic Ruler. The median operation time of Endoscopic Ruler was 3.00 min (IQR: 3.00 min) (Table 2).

Agreement on detecting large OV between Endoscopic Ruler and endoscopists

Endoscopic Ruler detected large OV in 101 (84.17%) patients and endoscopists identified 94 large OV among them. In seven cases, the diagnosis of large OV by Endoscopic Ruler was not found by endoscopists. Endoscopic Ruler detected small OV in 19 (15.83%) patients and endoscopists identified small OV in 11 of them. In eight cases, the diagnosis of small OV by Endoscopic Ruler was not confirmed by endoscopists (Figure 3). The agreement between Endoscopic Ruler and endoscopists on diagnosing large OV was moderate, with a kappa value of 0.52 [95% confidence interval (95%CI): 0.31-0.73].

Interobserver reliability on detecting large OV

The agreement among the six independent observers on detecting large OV was substantial, with a kappa value of 0.77 (95%CI: 0.61-0.93). The kappa scores on detecting OV using Endoscopic Ruler were 0.71 (95%CI: 0.36-1.00) with a substantial agreement among the three experienced endoscopists, and the same [0.71 (95%CI: 0.36-1.00), P = 1.00] among the three inexperienced endoscopists, respectively (Table 3). The kappa score of the overall agreement on detecting OV through the empirical reading of endoscopists among six observers was 0.52 (95%CI: 0.36-0.68), demonstrating a moderate agreement, and it was significantly smaller than that using Endoscopic Ruler (P < 0.05). The kappa score on detecting OV by empirical reading of endoscopists was 0.57 (95%CI: 0.21-0.93) among the three experienced endoscopists, greater than that [0.40 (95%CI: 0.04-0.76)] among the three inexperienced ones (P < 0.05).

DISCUSSION

A careful endoscopic evaluation is one of the cornerstones for the full-course management of cirrhosis and portal hypertension as well as care of OV[8]. The application of the 2-grade classification system is recommended in the Baveno VII consensus, which has previously been validated as a predictor of variceal haemorrhage[1,2,5]. It is crucial to ensure that OV needing treatment is acted on if the present and accurate classification of small and large OV is the key. At present, the measurement of the varix size is mainly performed visually by endoscopists with subjectivity. Besides, biopsy forceps and other physical standards are applied in some trials but not clinical practice and the aforementioned methods are of a limited credibility and repeatability[9-11]. Shimoda *et al*[12] reported a virtual scale endoscope (VSE) to help estimate the size of colorectal lesions in real time during colonoscopy. However, its usefulness of VSE was evaluated in a virtual environment instead of actual clinical settings, nor was it applied to measure the size of varices[12]. Li *et al*[13] demonstrated a self-made virtual endoscopic measuring scale with a moderate accuracy but didn't conduct a clinical evaluation on its efficacy.

To our knowledge, the present study is the first to demonstrate a special-designed endoscopic device, Endoscopic Ruler, for varix size measurement in clinical trials. Endoscopic Ruler succeeds in measuring the varix size of all enrolled patients without any adverse event associated to the procedures. Endoscopic Ruler is feasible and safe for measuring varix size, meanwhile, its median operation time is only 3.00 minutes, which avoids significant increase of procedural time and complication risk[14].

The agreement analysis demonstrated a moderate agreement between the objective measurement of Endoscopic Ruler and the empirical reading of endoscopists on the diagnosis of large OV. However, there were seven (5.83%) large OV according to Endoscopic Ruler that was misdiagnosed as small OV by endoscopists and eight (6.67%) small OV according to Endoscopic Ruler that was wrongly diagnosed as large OV by endoscopists. That is, without any consideration for other high-risk factors of OV (red signs or Child-Pugh C), there might be 5.83% of patients misdiagnosed with non-high-risk OV, who would miss the primary prophylaxis of variceal bleeding; there might be 6.67% of patients wrongly diagnosed with high-risk OV, who might receive an overtreatment. Moreover, the overall kappa value on detecting OV among the six observers using Endoscopic Ruler was greater than that through the empirical reading of endoscopists (0.77 *vs*. 0.52, P < 0.05). The subjective nature of differentiating small OV from large OV remains a challenge for the 2-grade classification varix system.

The interobserver reliability results suggested that Endoscopic Ruler decreased such discrepancies. Besides, our study revealed that the kappa values on detecting large OV using Endoscopic Ruler were similar with that performed by experienced endoscopists and inexperienced endoscopists (0.71 *vs*. 0.71, P = 1.00), while the kappa value on detecting OV through the empirical reading of endoscopists among experienced endoscopists was greater than that among inexper-

Table 1 Baseline characteristics of patients

Parameters	Patients (*n* = 120)
Age (yr), mean (SD)	54.02 (11.90)
Sex *n* (%)	
Male	71 (59.16%)
Female	49 (40.83%)
Complication, *n* (%)	
Ascites	36 (30.00%)
Hepatocellular carcinoma	5 (4.17%)
Etiology, *n* (%)	
Hepatitis B infection	82 (68.33%)
Alcoholic liver disease	11 (9.17%)
Autoimmune	6 (5.00%)
Primary biliary cirrhosis	4 (3.33%)
Hepatitis C infection	2 (1.67%)
Others	15 (12.50%)
Child-Pugh Class, *n* (%)	
Class A	43 (35.83%)
Class B	59 (49.17%)
Class C	18 (15.00%)
Laboratory tests, median (IQR)	
Platelet count (10^9/L)	70.00 (59.75)
Alanine aminotransferase (U/L)	26.50 (21.10)
Aspartate aminotransferase (U/L)	32.00 (22.00)
Albumin (g/L)	34.04 (9.45)
Total bilirubin (μmol/L)	26.27 (23.90)
Prothrombin time (s)	14.25 (3.40)
Creatinine (μmol/L)	61.10 (21.35)

SD: Standard deviation; IQR: Interquartile range.

Table 2 The feasibility, safety, operation time of Endoscopic Ruler, and the agreement on diagnosing large oesophageal varices between endoscopists and Endoscopic Ruler

Outcome	Patients (*n* = 120)
Primary outcome	
Technical success of Endoscopic Ruler, *n* (%)	120 (100.00%)
Secondary outcomes	
Adverse events, *n* (%)	0 (0.00%)
Operation time (min), median (IQR)	3.00 (3.00)
Kappa value	0.52 (95%CI: 0.31- 0.73)

95%CI: 95% confidence interval; OV: Oesophageal varices; IQR: Interquartile range.

Table 3 The interobserver reliability on detecting large oesophageal varices

Assessment	Raters	Kappa value (95%CI)
Objective measurement of Endoscopic Ruler		
All observes	6	0.77 (0.61-0.93)
Experienced endoscopists	3	0.71 (0.36-1.00)
Inexperienced endoscopists	3	0.71 (0.36-1.00)
Empirical reading of endoscopists		
All observes	6	0.52 (0.36-0.68)
Experienced endoscopists	3	0.57 (0.21-0.93)
Inexperienced endoscopists	3	0.40 (0.04-0.76)

95%CI: 95% confidence interval.

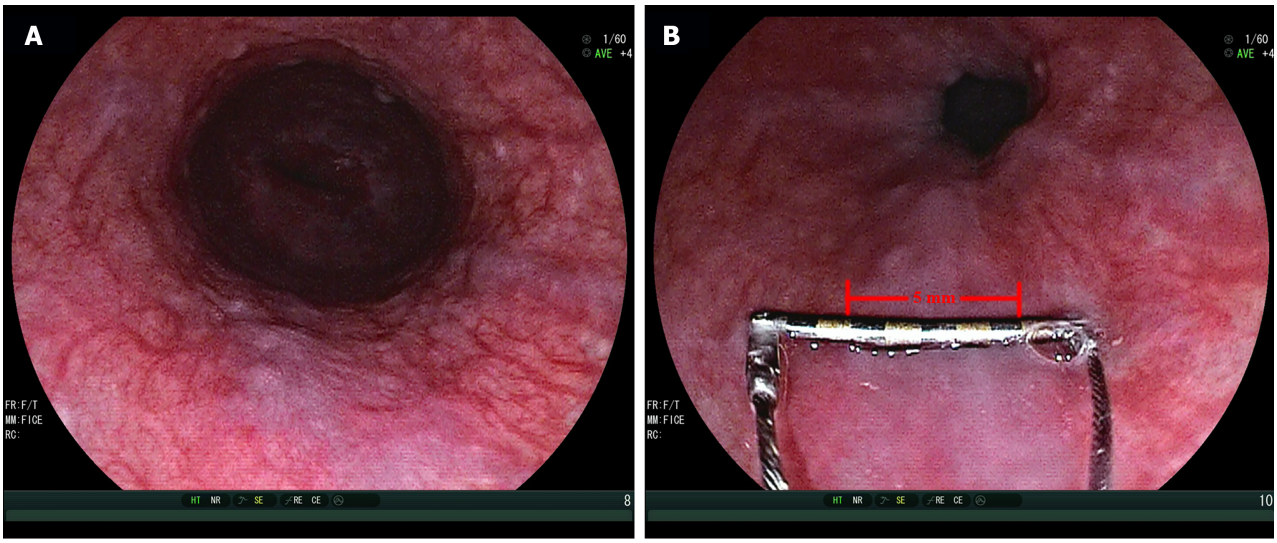

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Figure 3 Representative examples of measurement of varix size by Endoscopic Ruler. A: Small varices by endoscopists (varix size = 3-4 mm); B: Large varices by Endoscopic Ruler (varix size = 5 mm).

ienced endoscopists (0.57 *vs*. 0.40, $P < 0.05$). That is, with the application of Endoscopic Ruler, the value of an experienced operator was weakened, and it might improve the management of patients with cirrhosis and portal hypertension in non-tertiary hospitals without experienced endoscopists. Overall, Endoscopic Ruler might help to optimize the accuracy of the 2-grade classification system for OV followed from a management perspective.

Recently, non-invasive tools, such as Baveno VI criteria[1,15], the liver stiffness- spleen diameter to platelet ratio score [16], capsule endoscopy[17], and other emerging methods have been identified as complementary parameters of EGD to detect and screen high-risk OV[18-20]. However, the use of EGD interpretation by endoscopists as reference standard might bring bias due to the subjectivity and a lack of substantial agreement. Endoscopic Ruler might be used to normalize and promote the development of novel non-invasive methods for OV screening.

There were still some limitations. The sample size was limited. A well-designed real-world study of Endoscopic Ruler augmenting the sample size and introducing the follow-up and clinical data would be needed for its further popularization in clinical practice. In addition, although adverse events occurred in no procedures of the present study, Endoscopic Ruler had the potential risk to injure patients, such as mucosal damage during operation. Therefore, we improved Endoscopic Ruler according to endoscopists' experience as follows: (1) Enhancing the contrast of the scale at the tip for easy reading; (2) Shortening the scale range and shrinking the tip for retaining the function of detecting large OV as well as reducing the risk of adverse damage; (3) Adding a feature of synchronous rotation for more convenient practice; and (4) Optimizing the design of more smooth edge for reducing the risk of damage. Figure 4 shows the improved version of the structure.

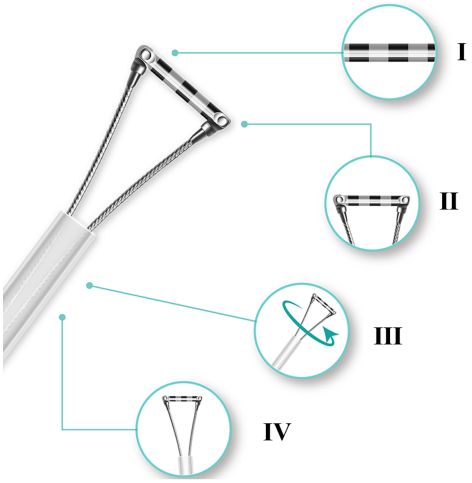

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Figure 4 Diagram of improved Endoscopic Ruler. I: Clear scale; II: Shorter tip; III: Synchronous rotation; IV: More smooth edge.

CONCLUSION

In conclusion, our study demonstrates that Endoscopic Ruler is feasible and safe for measuring the size of varices in patients with cirrhosis and portal hypertension. Endoscopic Ruler is potential to promote the clinical practice of the two-grade classification system of OV.

ARTICLE HIGHLIGHTS

Research background

Esophagogastroduodenoscopy (EGD) screening is usually performed by endoscopists with different levels of experience, and the they assess the locations and size of oesophageal varices (OV) according to the subjectivity. The recent Baveno VII consensus emphasized 2-grade classification system of Ovs followed from a management perspective, and the 2-grade classification system quantitatively classifies varix size into either small (< 5 mm) or large (≥ 5 mm).

Research motivation

The quantitative system is not widely used in clinical practice probably due to following limitations: Doubtful accuracy due to varix size assessment demanding high level of experience in specialized centers; lack of data on the interobserver agreement and reproducibility. We invented Endoscopic Ruler, a new endoscopic device to measure the size of varices in patients with cirrhosis and portal hypertension.

Research objectives

This study aims to assess the feasibility and safety of Endoscopic Ruler, and evaluate the agreement on identifying large OV between Endoscopic Ruler and the endoscopists, as well as the interobserver agreement on diagnosing large OV using Endoscopic Ruler.

Research methods

We prospectively and consecutively enrolled patients with cirrhosis from 11 hospitals, all of whom got EGD with Endoscopic Ruler. The primary study outcome was a successful measurement of the size of varices using Endoscopic Ruler. The secondary outcomes included adverse events, operation time, the agreement of identifying large OV between the objective measurement of Endoscopic Ruler and the empirical reading of endoscopists, together with the interobserver agreement on diagnosing large OV by Endoscopic Ruler.

Research results

From November 2020 to April 2022, a total of 120 eligible patients with cirrhosis were recruited and all of them underwent EGD examinations with Endoscopic Ruler successfully without any adverse event. The median operation time of Endoscopic Ruler was 3.00 min (IQR: 3.00 min). The kappa value between Endoscopic Ruler and the endoscopists while detecting large OV was 0.52, demonstrating a moderate agreement. The kappa value for diagnosing large OV using Endoscopic Ruler among the six independent observers was 0.77, demonstrating a substantial agreement.

Research conclusions

Endoscopic Ruler is feasible and safe for measuring the size of varices in patients with cirrhosis and portal hypertension.

Research perspectives

Endoscopic Ruler weakened the value of an experienced operator and it might improve the management of patients with cirrhosis and portal hypertension in the non-tertiary hospitals without experienced endoscopist. Endoscopic Ruler might help to optimize the accuracy of the 2-grade classification system of OV followed from a management perspective. Endoscopic Ruler might normalize and promote development of novel non-invasive methods for OV screening.

FOOTNOTES

Author contributions: Qi XL designed the research; Huang YF, Hu SJ, Bu Y, Li YL, Deng YH, Hu JP, Yang SQ, Shi RC, Li XQ, Song TY, Qi HL, Shen Q, Jiao TW, Liu MY, He F, Zhu J, Ma B, Yu XB, Guo JY, Yu YH, Yong HJ, Yao WT, Ye T, Wang H, Dong WF, Liu JG, Wei Q, Tian J and Li XG collected the data; Huang YF analyzed the data; Huang YF Wrote the first draft; Qi XL, Dray X and McAlindon M revised the paper; Huang YF, Hu SJ, Bu Y, Li YL, Deng YH, Hu JP, Yang SQ, and Shen Q contributed equally to this work.

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Clinical trial registration statement: This study is registered at https://www.clinicaltrials.gov/. The registration identification number is NCT04639323.

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META-ANALYSIS

Comparison of trans-gastric *vs* trans-enteric (trans-duodenal or trans-jejunal) endoscopic ultrasound guided gallbladder drainage using lumen apposing metal stents

Dheera Grover, Ifrah Fatima, Murali Dharan

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Peer-review model: Single blind

Peer-review report's scientific quality classification
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Grade C (Good): C, C
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Abstract

BACKGROUND

Endoscopic ultrasound guided gallbladder drainage (EUS-GBD) is being increasingly used in practice (either as a bridge to cholecystectomy in high-risk patients or as destination therapy in non-surgical patients). Stents are used to create a conduit between the lumen of the gallbladder (GB) and the intestinal lumen through the gastric or enteric routes. Among the various types of stents used, cautery-enhanced lumen apposing metallic stents (LAMS) may be associated with fewer adverse events (AEs).

AIM

To compare the clinical success, technical success, and rate of AEs between transgastric (TG) and trans-enteric [transduodenal (TD)/transjejunal (TJ)] approach to GB drainage. Further, we analyzed whether using cautery enhanced stents during EUS-GBD impacts the above parameters.

METHODS

Study was registered in PROSPERO (CRD42022319019) and comprehensive literature review was conducted. Manuscripts were reviewed for the data collection: Rate of AEs, clinical success, and technical success. Random effects model was utilized for the analysis.

RESULTS

No statistically significant difference in clinical and technical success between the

TD/TJ and TG approaches ($P > 0.05$) were noted. There was no statistically significant difference in the rate of AEs when comparing two-arm studies only. However, when all studies were included in the analysis difference was almost significant favoring the TD/TJ approach. When comparing cautery-enhanced LAMS with non-cautery enhanced LAMS, a statistically significant difference in the rate of AEs was observed when all the studies were included, with the rate being higher in non-cautery enhanced stents (14.0% *vs* 37.8%; $P < 0.01$).

CONCLUSION

As per our study results, TD/TJ approach appears to be associated with lower rate of adverse events and comparable efficacy when compared to the TG approach for the EUS-GBD. Additionally, use of cautery-enhanced LAMS for EUS-GBD is associated with a more favorable adverse event profile compared to cold LAMS. Though the approach chosen depends on several patient and physician factors, the above findings could help in deciding the ideal drainage route when both TG and TD/TJ approaches are feasible.

Key Words: Transduodenal; Transgastric; Cautery; Endoscopic ultrasound guided gallbladder drainage; AXIOS

Core Tip: Endoscopic ultrasound guided gallbladder drainage (EUS-GBD) is increasingly used in management of gallbladder disease. EUS-GBD can be achieved using trans-gastric or trans-enteric (trans-duodenal or trans-jejunal) approach There are currently no randomized controlled trials comparing these two approaches. We performed a meta-analysis of the existing literature on EUS guided gallbladder drainage. Trans-enteric approach was observed to have a more favorable safety profile compared to trans-gastric approach. Further use of cautery enhanced lumen apposing metallic stents (LAMS) to achieve EUS-guided GBD was associated with lesser adverse effects when compared to use of non-cautery enhanced (cold) LAMS.

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INTRODUCTION

Acute cholecystitis is an acute inflammation of the gall bladder (GB) characterized by the clinical syndrome of right upper quadrant pain, fever, and leukocytosis. The primary underlying etiology is gallstones, but 5%-10% of cases may be due to acalculous cholecystitis[1]. Open or laparoscopic cholecystectomy is the definitive treatment; however, many patients with acute cholecystitis are not good surgical candidates due to comorbidities. Percutaneous gallbladder drainage (PT-GBD) has emerged as an alternative but is limited by complications such as recurrent cholecystitis, bile peritonitis, puncture-induced hemorrhage, drain site pain, and infection[2]. PT-GBD is a temporizing treatment modality that can be a bridge to surgery until patient's clinical status to improves. Often patients are unable to undergo surgery and are left with a permanent percutaneous drain[3,4].

Endoscopic ultrasound guided gallbladder drainage (EUS-GBD) is a minimally invasive alternative to PT-GBD. It is preferred due to its comparable clinical and technical success and minimal adverse events (AEs)[5]. Even though EUS-GBD initially was an alternative to surgery, the current indications have expanded to include: Destination therapy in poor surgical candidates, bridging to cholecystectomy, conversion of PT-GBD to EUS-GBD, alternative to failed PT-GBD or failed ET-GBD (endoscopic trans-papillary GBD) or alterative to failed EUS-guided biliary drainage (EUS-BD)[3]. Drainage of the GB is done by either transduodenal (TD)/transjuojenal (TJ) or transgastric (TG) approach. This allows for decompression of the GB by bypassing the obstruction. The best transluminal access to achieve gallbladder drainage has not been well established. In addition, there is limited literature comparing trans-gastric and trans-enteric (TD/TJ) approaches for EUS-GBD[6-8]. With the increasing use of EUS-GBD, it becomes important to ascertain the best trans-luminal approach to gallbladder drainage. Hence, we undertook a study to analyze the available evidence on this topic.

EUS-GBD can be achieved using plastic stents, self-expandable metal stents (SEMS) and lumen apposing metallic stents (LAMS). LAMS maintains a strong seal, reducing the risk of bile leakage and stent migration. Hence, LAMS is ideal for EUS-GBD[9-11]. The novel cautery-enhanced LAMS (hot) is being increasingly used and has the advantage of completing the procedure in one step without additional exchanges and reducing the need for fluoroscopic assistance compared to non-cautery enhanced (cold) LAMS[12,13]. The design of the stent with flares at both ends may mitigate risk of stent migration[14]. Our study aimed to compare the clinical success, technical success, and rate of AEs between the approaches used for the site of puncture and the type of LAMS used for EUS-GBD.

MATERIALS AND METHODS

The study was registered in The International Prospective Register of Systematic Reviews (PROSPERO), and a comprehensive literature search was done on PubMed, Embase, Scopus, CENTRAL, CINAHL, and Web of Science. The literature search was done using words: "Ultrasonography", "Endosonography", "Endosonograph", "Endoscopic ultrasound", "lumen apposing metal stent", "LAMS", "transgastric", "transduodenal", hot" or "cold" AND "Gallbladder diseases", Gallbladder", "biliary", "cholecyst", AND "drainage", "drain". The references of the included studies were thoroughly reviewed. In total, 3707 studies were screened. For the comparison of TG and TD/TJ approach, twenty-four met the inclusion criteria (Figure 1). The inclusion criteria included randomized or nonrandomized controlled clinical trials and prospective and retrospective studies. Due to a lack of data, abstracts presented at conferences and case series (with four or more patients) were also included in the study. Reviews, meta-analyses, animal studies, letters from the editor, case reports, opinion articles, and editorials were not included. The other exclusion criteria included animal studies and studies in languages other than English. No age and gender restrictions were applied. A post-hoc analysis was done to compare the cautery-enhanced (hot) *vs* non-cautery enhanced approach and only twelve studies met the above-mentioned inclusion criteria (Figure 2). Manuscripts were reviewed for the data collection: Rate of AEs, clinical success, and technical success. The search was conducted again couple of days prior to the submission of this manuscript for the emerging data. Random effects models were estimated using Comprehensive Meta-Analysis (Biostat Inc.) software. A *P* value of less than 0.05 was considered significant.

RESULTS

The analysis was done using two methods. Method 1 included analysis of studies with patients in both arms only and method 2 included analyses of ALL studies. Due to limited data, we could not analyze the baseline characteristics and specific AEs. In the majority of the studies, technical success was defined as adequate access and drainage of the GB with the placement of the LAMS stent. Clinical success was described as a decline in serum bilirubin levels in patients with obstructive jaundice to 10% of the initial levels and improvement of cholestatic parameters in those without jaundice.

TG vs TD/TJ

Analyses were done by two methods. Pooled odds ratios for AE, clinical success and technical success were calculated (Table 1, Figure 3).

Method 1: Analysis of studies with patients in both arms only. TG *vs* TD/TJ: Pooled odds ratio (95% confidence interval), *P* value: AEs (6 studies): 1.58 (0.46-5.45), *P* = 0.47; clinical success (3 studies): 0.30 (0.06-1.48), *P* = 0.14; and technical success (3 studies): 0.30 (0.05-1.89), *P* = 0.20.

Method 2: Analysis of all studies (in total 15 using TD/TJ approach and 9 using TG approach). TG *vs* TD/TJ: AEs (Studies: 9 *vs* 15): 27.5% (17.1%-41.1%) *vs* 15.2% (9.5%-23.6%), *P* = 0.07; clinical success (Studies: 6 *vs* 13): 83.3% (71.0%-91.0%) *vs* 91.7% (82.4%-96.3%), *P* = 0.16; and technical success (Studies: 9 *vs* 15): 91.3% (83.6%-95.6%) *vs* 95.3% (90.7%-97.7%), *P* = 0.22.

Cautery enhanced vs non-cautery enhanced LAMS

Analyses were done by two methods. Pooled odds ratios for AE, clinical success and technical success were calculated (Table 2, Figure 4).

Method 1: Analysis of studies with patients in both arms only. Cautery-enhanced *vs* non-cautery enhanced-pooled odds ratio (95% confidence interval); *P* value: AEs (2 studies): 0.55 (0.19-1.64), *P* = 0.28; clinical success (2 studies): 1.81 (0.50 to 6.61; *P* = 0.37). There was only one study that compared the technical success of both the arms.

Method 2: Including all the studies (in total 9 using cautery-enhanced LAMS and 3 using non-cautery enhanced LAMS). Cautery-enhanced *vs* non-cautery-enhanced-pooled percentage (IQR), *P* value: AEs (Studies: 9 *vs* 3): 14% (9.1%-21.0%) *vs* 37.8% (26.5%-50.6%), *P* ≤ 0.001; Clinical success (Studies: 11 *vs* 3): 89.9% (86.1%-92.7%) *vs* 93.4% (72.8%-90.3%), *P* = 0.12, and technical success (Studies: 11 *vs* 3): 94.4% (91.3%- 96.4%) *vs* 93.8% (86.3% *vs* 97.3%), *P* = 0.82.

DISCUSSION

Traditionally, early laparoscopic cholecystectomy is the gold standard treatment for cholecystitis[1,13]. In patients who are poor surgical candidates due to comorbidities, conservative management or percutaneous drainage of the GB is recommended. In the CHOCOLATE trial, for patients with a high APACHE II score, urgent laparoscopic cholecystectomy was associated with a reduced hospital length of stay, complications, and reinterventions compared to percutaneous drainage[15]. Hence, patients with cholecystitis should undergo cholecystectomy even in emergent conditions if well tolerated. Cholecystectomy has the additional advantage of obviating the future risk of recurrent cholecystitis.

Recent studies have reported EUS-GBD as a minimally invasive alternative to percutaneous drainage for cholecystitis in patients who are poor surgical candidates[16]. EUS-GBD has been studied for technical success, clinical success, and

Table 1 Comparison of rate of adverse events, clinical success and technical success between the approaches according to puncture site (transduodenal/transjejunal *vs* transgastric)

	n of studies	Pooled odds ratio (TG *vs* TD/TJ) or AE (%)	95%CI	*P* value
Method 1: Including studies with patients in both arms only				
Adverse events	6	1.58	0.46-5.45	0.47
Clinical success	3	0.30	0.06-1.48	0.14
Technical success	3	0.30	0.05-1.89	0.20
Method 2: Including all studies				
Adverse events	9 *vs* 15	27.5% *vs* 15.2%	(17.1%-41.1%) *vs* (9.5%-23.6%)	0.07
Clinical success	6 *vs* 13	83.3% *vs* 91.7%	(71.0%-91.0%) *vs* (82.4%-96.3%)	0.16
Technical success	9 *vs* 15	91.3% *vs* 95.6%	(83.6%-95.6%) *vs* 90.7%-97.7%)	0.22

TG *vs* TD/TJ: Transduodenal/transjejunal *vs* transgastric; AE: Adverse event; 95%CI: 95% confidence interval.

Table 2 Comparison of the parameters between cautery-enhanced and non-cautery enhanced approaches for endoscopic ultrasound guided gallbladder drainage

	n of studies (cautery-enhanced *vs* non-cautery enhanced)	Pooled odds ratio (cautery-enhanced *vs* non-cautery enhanced) or AEs (%)	95%CI	*P* value
Method 1: Including studies with patients in both arms only				
Adverse events	2	0.55	0.19-1.64	0.28
Clinical success	2	1.81	0.50-6.61	0.37
Method 2: Including all studies				
Adverse events	9 *vs* 3	14.0% *vs* 37.8%	(9.1%-21.0%) *vs* (26.5%- 50.6%)	0
Clinical success	11 *vs* 3	89.9% *vs* 93.4%	(86.1%-92.7%) *vs* (72.8%-90.3%)	0.12
Technical success	11 *vs* 3	94.4% *vs* 93.8%	26.5%-50.6%	0.82

AE: Adverse event; 95%CI: 95% confidence interval.

rate of AEs comparable to standard percutaneous techniques with decreased tube-related complications, including tube dislodgement, migration, obstruction and peri-tubal leakage[2,16,17]. In a meta-analysis by Luk *et al*[17], EUS-GBD was reported to have comparable technical and clinical success; however, EUS-GBD was associated with lower post-procedure adverse events, shorter hospital stays, and fewer reinterventions and readmissions compared to PT-GBD.

The efficacy and feasibility of EUS-GBD using different stents, including plastic stents, SEMS, and LAMS has been well documented[7,18-20]. Stent placement can result in complications such as stent migration, occlusion, bleeding, bile leak and pneumoperitoneum and associated morbidity. Plastic double pigtail stents are commonly associated with bile leaks, bile peritonitis and stent migration. SEMS provides the advantage of longer stent patency and prevents bile leakage but risk of stent migration remains. Both plastic stents and SEMS do not maintain apposition to seal the gap and reliably form a fistula. LAMS is considered an ideal stent due to its ability to make a firm seal with decreased complications[7,9,14].

The drainage of the GB is done by creating a cholecysto-enteric communication, *via* either TD/TJ or TG approach under the endoscopic/endosonographic guidance. In the TD approach, the retro-peritoneal duodenum is relatively immobile and thus provides a stable access site to the neck of GB which is the puncture site in this approach[6]. In addition, the inflamed GB wall may become adherent to the wall of the duodenum/jejunum lending further stability for access. Compared to stomach, the wall of duodenum/jejunum has less peristaltic activity which may decrease the risk of stent migration and stent occlusion due to tissue overgrowth[6,7]. Potential for reflux of food contest into the gallbladder may be lesser with TD approach resulting in reduced risk of stent occlusion or infection related to reflux[6,7]. The flow of food into the biliary system during EUS-GBD can lead to cholangitis or obstructive jaundice by occluding the stent. Due to the above reasons, TD/TJ is thought to be a safer option, but it has several limitations[6,7]. One of the limitations is the technical difficulty in accessing the neck of the GB, the puncture site in the TD/TJ approach. With TG approach the access

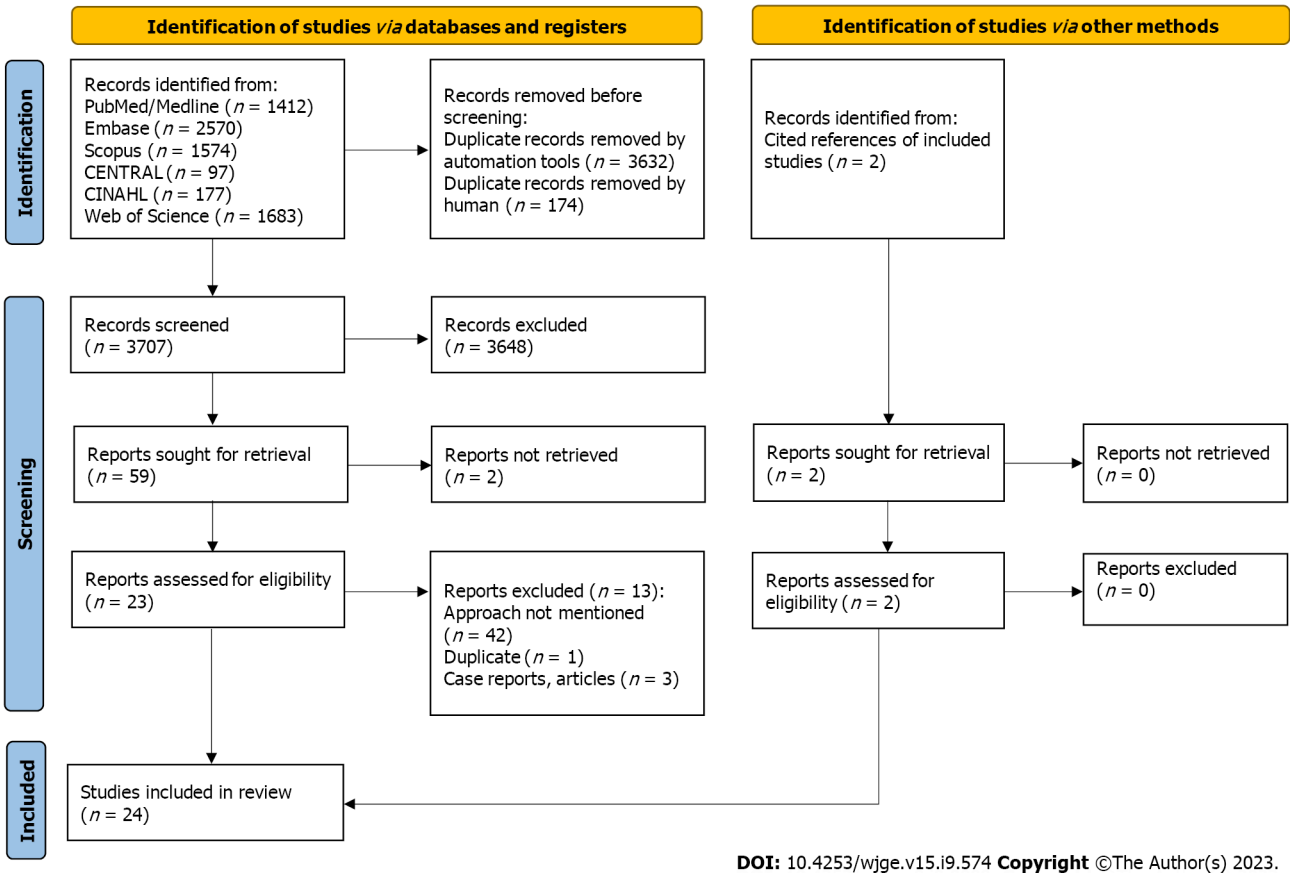

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Figure 1 PRISMA flow diagram. PRISMA flow diagram elucidating screening and selection studies for comparison of transduodenal/transjejunal *vs* transgastric approaches.

point is usually the gallbladder body which provides a larger landing zone for deployment of the inner flange of the lumen apposing metal stent[6].

The thicker wall of the stomach may have larger perforating blood vessels (as compared to the duodenum) which can increase the risk of bleeding during transluminal access of the gallbladder. Management of delayed AEs may be easier with TG approach as the stomach is more accessible at laparoscopy compared to the duodenal bulb and thicker gastric wall permits more reliable wound closure[6]. Our study aimed to compare the clinical success, technical success, and rate of AEs between the approaches used for the site of puncture, *i.e.*, TD/TJ *vs* TG.

Our meta-analysis showed no statistically significant difference in the clinical and technical success between the TD/TJ and TG approaches. In addition, we did not observe any statistically significant difference in the rate of AEs when comparing the two-arm studies only; however, the difference was almost significant (TG *vs* TD/TJ: 27.5% *vs* 15.2%, P = 0.07) when all the studies were analyzed with higher rates of AE noted with the TG approach. The commonly noted AEs with EUS-GBD include stent migration, stent occlusion, biliary peritonitis, pneumoperitoneum and recurrence of cholecystitis due to food impaction[18].

We also analyzed the above outcomes when deploying the cautery-enhanced (hot) *vs* non-cautery enhanced (cold) LAMS for EUS-GBD. The cautery-enhanced LAMS is a novel, fully covered, self-expanding stent with an electrocautery-enhanced delivery system ideal for EUS-GBD. Due to its "all-in-one" nature, the direct introduction of the device into the GB without prior placement of a guidewire eliminates the need for multiple steps and accessory exchanges[9]. The one step procedure with cautery-enhanced (hot) LAMS decreases the procedure time and the need for fluoroscopic assistance. The complications are further decreased by the hemostatic effect of cautery and absence of need for tract dilation likely reduces risk of bleeding and bile leak[12,13]. Deployment of non-cautery enhanced (cold) LAMS is wire guided and carries the risk of loss of wire access and attendant problems which do not apply to cautery enhanced LAMS. Hence, the cautery-enhanced LAMS is expected to have lesser rate of AEs as compared to non-cautery enhanced.

In our study, we did not observe any significant difference in the technical and clinical success between the cautery enhanced and non-cautery enhanced LAMS in EUS-GBD. No significant difference was observed in the rate of AEs between the two approaches when studies with both arms only were analyzed; however, a significant difference (P < 0.01) was noted in the rate of AEs when all the studies were included in the analysis, with the AEs being higher in non-cautery enhanced compared to cautery-enhanced LAMS.

There are several limitations to our study. The number of included studies was small due to data sparsity; thus, the results of this study might be underpowered. Additionally, the studies were done at several different centers, and the heterogeneity amongst various centers weakens the reliability of the results. Furthermore, since the number of studies was less than 10, publication bias is difficult to address. In addition to publication bias, selection bias, lead-time bias, and

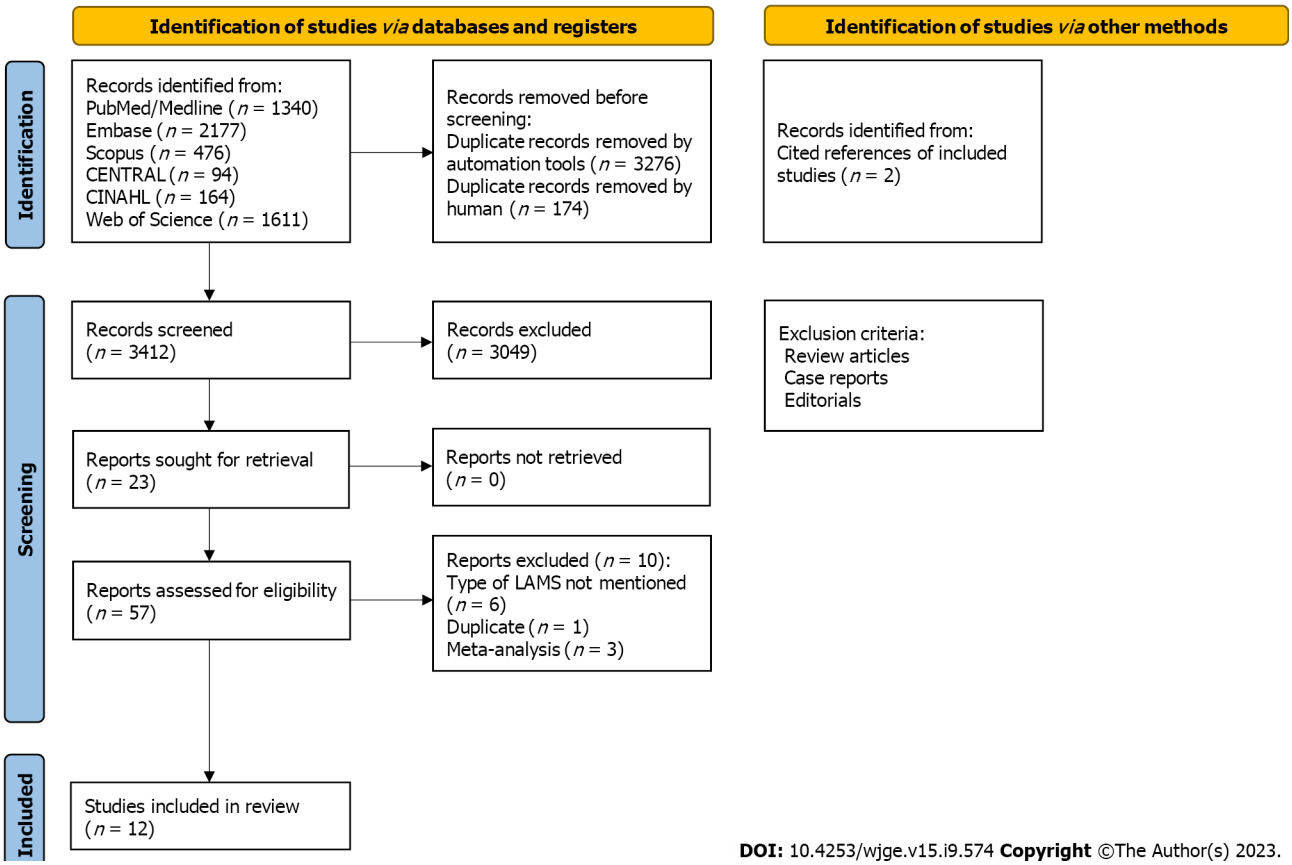

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Figure 2 PRISMA flow diagram elucidating the screening and selection of studies for comparison or cautery-enhanced *vs* non-cautery enhanced approaches.

confounding factors cannot be excluded. Several studies reported their experience with EUS-GBD but did not aim to compare TD/TV *vs* TG approaches. With first method of analyzing studies with both arms, we were able to compare TD/TJ approach *vs* TG approach by the same operator. This helped reduce performance bias and data heterogeneity. However, these studies were not conducted with the primary aim of comparing both approaches. Some of the findings from our analysis did not reach statistical significance due to data sparsity. When we used the second method and included all studies in our analysis, due to the increase in available data, some findings were statistically significant. However (as some case series reported one approach only and pooled data included multiple operators) the analyzed data was quite heterogeneous. Given the sparse data and heterogeneity of the data we are unable to perform GRADE analysis and make recommendations based on GRADE methodology. Sufficiently powered randomized control trial should be done to compare the clinical outcomes of TD/TJ *vs* TG approach. Given the significantly reduced procedure time and ease of deployment of cautery enhanced LAMS for EUS-GBD, it is unlikely that a randomized controlled trial will be conducted to compare cautery enhanced *vs* and non-cautery enhanced LAMS to validate our findings.

CONCLUSION

Based on our study findings, cautery-enhanced LAMS deployment appears safer than non-cautery enhanced stent deployment for EUS-GBD. The TD/TJ approach may be associated with a more favorable AE profile with equal efficacy when compared to TG approach for EUS-GBD. While decision regarding approach to trans-luminal GB drainage depends on endoscopist preference and patient-specific anatomic considerations such as proximity of GB to the gastrointestinal tract lumen, it would be helpful to know which approach (trans-gastric *vs* trans-duodenal) has a favorable AEs profile especially when both approaches are feasible in a given patient. If EUS-GBD is a bridge to cholecystectomy, surgery appears feasible with both TG and TD/TJ approaches[21,22] but data regarding preferred approach is lacking[6].

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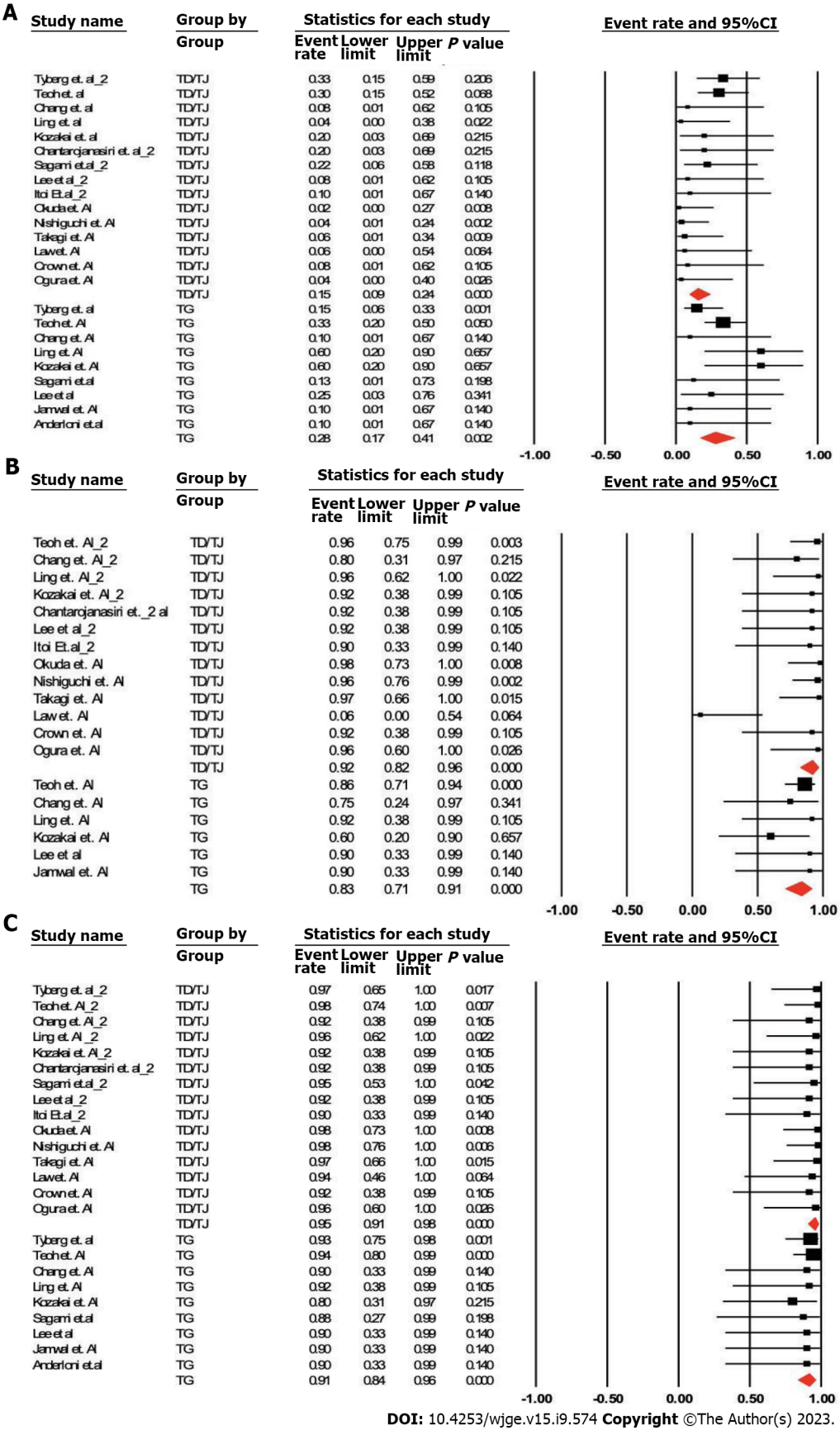

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Figure 3 Forrest plot. A-C: Forrest plot illustrating the comparison of rate of adverse events (A), clinical success (B), and technical success (C) between transduodenal/transjejunal *vs* transgastric approaches including studies with patients in both arms only (method 1). TG *vs* TD/TJ: Transduodenal/transjejunal *vs* transgastric; 95%CI: 95% confidence interval.

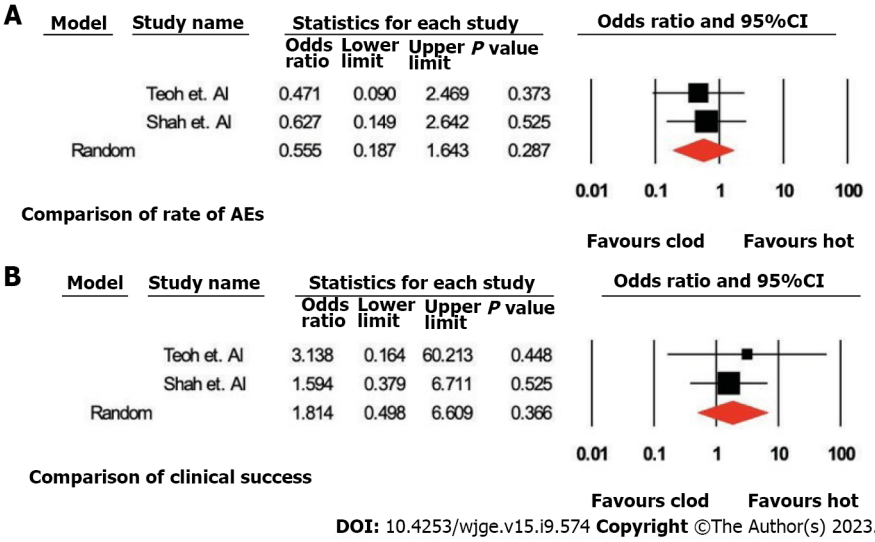

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Figure 4 Forrest plot. A and B: Forrest plot illustrating the comparison of parameters between cautery enhanced (hot) *vs* non-cautery enhanced (cold) approaches including with studies with patients in both arms only (method 1). AEs: Adverse events; 95%CI: 95% confidence interval.

ARTICLE HIGHLIGHTS

Research background

Adequately powered RCTS are need to confirm the findings in our retrospective study.

Research motivation

Transduodenal endoscopic ultrasound guided gallbladder drainage (EUS-GBD) appeard to be safer than transgastric drainage. Hot lumen apposing metallic stents (LAMS) is better than cold LAMS.

Research objectives

As per out study transduodenal approach appeared to have a more favorable adverse event (AE) profile with comparable technical and clinical success when compared to transgastric approach. Cautery enhanced LAMS has a more favorable AE and shorter procedure time than cold LAMS.

Research methods

Literature search was done using PubMed, Embase, Scopus, CENTRAL, CINAHL, and Web of Science database. The inclusion criteria included randomized or nonrandomized controlled clinical trials and prospective and retrospective studies. Due to a lack of data, abstracts presented at conferences and case series (with four or more patients) were also included in the study. Reviews, meta-analyses, animal studies, letters from the editor, case reports, opinion articles, and editorials were not included. The other exclusion criteria included animal studies and studies in languages other than English. No age and gender restrictions were applied. A post-hoc analysis was done to compare the cautery-enhanced (hot) *vs* non-cautery enhanced approach and only twelve studies met the above-mentioned inclusion criteria. Manuscripts were reviewed for the data collection: Rate of AEs, clinical success, and technical success. The search was conducted again couple of days prior to the submission of this manuscript for the emerging data. Random effects models were estimated using Comprehensive Meta-Analysis (Biostat Inc.) software. A *P* value of less than 0.05 was considered significant.

Research results

Compare trans-gastric *vs* trans-enteric EUS-GBD based on available literature. Compare AE profile, technical success and clinical success of both approaches. As a secondary outcome compare cautery enhanced LAMS use *vs* non-cautery enhanced (cold) LAMS.

Research conclusions

Identify if any transgastric or transenteric EUS-GBD is better based on existing literature.

Research perspectives

EUS-GB being increasingly used either as bridge to cholecystectomy or as destination therapy. GB can be accessed by transgastric or transenteric route. However, it is unclear if one approach is better than the other.

FOOTNOTES

Author contributions: Grover D and Fatima I contributed to literature search, literature inclusion for the study, and drafting of article; Dharan M contributed to conceptualization of research, literature search, critical revision of article and rewriting the discussions.

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