Effectiveness and safety of endoscopic treatment for duodenal variceal bleeding: a systematic review

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Duodenal varix is a rare condition that involves massive bleeding, diagnostic difficulties, and a high rate of rebleeding and mortality. The purpose of this study was to systematically review endoscopic treatment for duodenal variceal bleeding to evaluate its effectiveness and safety. We searched PubMed, Embase, Web of Science, and the Cochrane Library up to 21 November 2019. Ninety-two studies containing 156 patients were finally included, and individual data from 101 patients (mean age: 52.67 ± 13.82 years, male: 64.4%) were collected and further analyzed. We used an analysis of variance and χ^2 or Fisher's exact tests to analyze individual data from 101 patients. The cause of duodenal variceal bleeding was cirrhosis-related intrahepatic portal hypertension (IPH) in 76.2% of patients. The overall rates of initial hemostasis and treatment success of endoscopic treatment for duodenal variceal bleeding were 89.1 and 81.2%, respectively. The median duration of follow-up was 4.5 (1.0, 12.0) months. The overall rates of rebleeding and mortality were 8.9 and 13.9%, respectively. Among a variety of endoscopic treatments available, only the initial hemostasis rate was significantly different between the endoscopic injection sclerotherapy and endoscopic tissue adhesive (ETA) groups (72.7 vs. 94.7%, $P = 0.023$); differences in treatment success, rebleeding, mortality, and adverse events were not statistically significant among the four groups. Endoscopic intervention is a feasible, well tolerated, and effective modality for the treatment of duodenal variceal bleeding. Among the variety of endoscopic treatments available, ETA with cyanoacrylate may be preferable for duodenal variceal bleeding. Eur J Gastroenterol Hepatol 33: 461–469

Introduction

Duodenal varix is the development of collateral veins between the portal vein trunk or superior mesenteric vein and the inferior vena cava [1,2] and is one form of ectopic varices. Previous studies suggested that duodenal varices were responsible for 1–3% of all varices in patients with cirrhosis [2,3]. In a large population who underwent upper endoscopy, the prevalence of duodenal varices was 0.2% [4]. In patients with portal hypertension who underwent upper endoscopy, the prevalence of duodenal varices was 0.4% [5]. Duodenal varices have a prevalence of up to 40% in patients with intrahepatic portal hypertension (IPH) who underwent angiography [6]. In patients with extrahepatic portal hypertension (EPH), duodenal varices seem to be even more prevalent [7]. Duodenal varices accounted for 17–32.9% of all ectopic varices [8–10]. Overall, duodenal varices is a rare condition, and its prevalence varies greatly due to different modalities of detection and etiologies of the patients studied.

Bleeding from duodenal varices occurs at a low frequency but is generally massive and fatal. The condition is often difficult to diagnose and control, with high mortality rates of up to 40% for initial bleeding [1,11,12]. However, the optimal modality for bleeding duodenal varices has not yet been established due to a lack of strong evidence from prospective, large-sample randomized controlled trials (RCTs). Currently available treatment modalities for bleeding duodenal varices include medications, endoscopic treatments, radiological interventions, and surgical procedures [13–16]. Published evidence from case reports and case series showed that transjugular intrahepatic portosystemic shunt (TIPS) and balloon-occluded retrograde transvenous obliteration (BRTO) effectively achieved hemostasis in patients with bleeding duodenal varices [11,17,18]. However, these therapies are more invasive and associated with a high risk of hepatic encephalopathy [10]. In addition, both modalities remain limited to hospitals with technical expertise in radiological intervention. Previous studies have demonstrated that surgical procedures were associated with a high rate of rebleeding and mortality for bleeding ectopic varices, particularly in patients with cirrhosis and portal hypertension [12,19]. Surgical modality is rarely performed. Medication alone has limited efficacy in cases of duodenal variceal bleeding [17].

To date, only case reports and case series about the effectiveness of endoscopic treatment for bleeding duodenal varices have been published. Moreover, endoscopic treatment is now one of the most common therapeutic

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modalities for bleeding duodenal varices and is less invasive compared with radiological interventions and surgical procedures [9,20]. However, previous studies showed that endoscopic treatment provided variable results for effectiveness and safety in the management of bleeding duodenal varices. Some studies showed that a satisfactory outcome was achieved after endoscopic treatment for bleeding duodenal varices [21,22]. Gabr *et al*. [22] found that successful treatment was achieved in all 18 patients after endoscopic injection of cyanoacrylate for duodenal variceal bleeding. Neither rebleeding nor death was observed during follow-up. Chaudhari *et al*. [21] reported a case series in which all 25 patients with duodenal variceal bleeding were treated via cyanoacrylate injection, and neither rebleeding nor death occurred in any patients during follow-up. In contrast, previous studies found that endoscopic treatment had a poor outcome in cases of duodenal variceal bleeding [20,23]. Mora-Soler *et al*. [23] reported five patients who underwent endoscopic injection of cyanoacrylate, 2 (40%) of whom experienced rebleeding, and 3 (60%) died (the causes of death were bleeding, acute liver failure, and severe infection, separately). The purpose of our study is to evaluate the effectiveness and safety of endoscopic treatments for bleeding duodenal varices using a systematic review of all currently published evidence.

Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-analysis statement guidelines (Supplement 1, supplement digital content 1, *http://links.lww.com/EJGH/A557*). A protocol has been registered (registration No. CRD42020167542).

Data sources and search strategy

We searched for suitable studies containing information on endoscopic treatment for patients with bleeding duodenal varices in four databases (PubMed, Embase, Web of Science, and the Cochrane Library) using the terms 'Duodenal varice', 'Duodenal variceal bleeding', 'Ruptured duodenal varice', 'Endoscopic band ligation', 'Tissue adhesives', 'Cyanoacrylates', and 'Ethanolamine and sclerotherapy'. The last search was performed on 21 November 2019. Per the requirement of different databases, the terms were adjusted to different retrieval expressions. The search strategy was restricted to clinical studies in humans. There was no date of publication restriction. The specific search strategy used is presented in Supplement 2, supplement digital content 2, *http://links.lww.com/EJGH/A558*. The reference list of relevant publications based on the search strategy was obtained and downloaded into EndNote 7.5 (Thompson ISI ResearchSoft, Philadelphia, Pennsylvania, USA), a bibliographic database manager.

Inclusion and exclusion criteria

The following inclusion criteria were employed. All clinical studies that assessed the effectiveness and safety of endoscopic treatment for duodenal variceal bleeding were eligible for inclusion. Endoscopic therapeutic modalities included only endoscopic band ligation (EBL), endoscopic injection sclerotherapy (EIS), endoscopic tissue adhesive (ETA), and combination treatment. Combination treatment was defined as the endoscopic injection of sclerosant and tissue adhesive or endoscopic injection of sclerosant combined with band ligation. If key information, such as demographic characteristics, endoscopic findings, definite diagnosis, interventional modality, and clinical outcomes, was available and could be collected, studies published only as abstracts were also included. The exclusion criteria were as follows: other interventions (surgery and radiological intervention alone, such as TIPS, BRTO, and double balloon-occluded embolotherapy) for duodenal variceal bleeding; full text or abstract not available; insufficient data available in the article; non-English studies and reviews; duplicated studies; and reviews, editorials, or author responses.

Study selection and data extraction

First, any duplicate publications were identified and removed automatically using EndNote software. Then, the titles and abstracts of each study were manually screened by two independent reviewers (W.Y.P. and L.C.) to select potentially relevant full-text articles. The second step further analyzed the full-text articles according to inclusion and exclusion criteria. When duplications were found, the largest dataset was used for our study. Data extraction was performed independently by the two independent reviewers. The extracted data included the journal of publication, year of publication, title, first author, country of origin, demographic characteristics (sex and age), and clinical characteristics of the included individuals (manifestation, cause, comorbidity, previous therapy), endoscopic findings, outcomes of endoscopic treatment, and follow-up. When disagreement between the reviewers occurred, a third reviewer (Z.X.) was responsible for resolving discrepancies in study selection and data extraction.

Quality assessment

The quality appraisal of included case reports was conducted according to the CASE (Case REport) guidelines [24]. The 13 items of the CASE guideline included the title, keywords, abstract, introduction, patient information, clinical findings, timeline, diagnostic assessment, therapeutic intervention, follow-up and outcomes, discussion, patient perspective, and informed consent.

Outcomes and definitions

The primary outcomes included treatment success, rebleeding, and mortality for endoscopic treatment of duodenal variceal bleeding. The secondary outcomes were initial hemostasis and adverse events.

Initial hemostasis was defined as the cessation of active bleeding at the time of therapeutic endoscopy followed by stable vital signs, no drop in hemoglobin (Hb), and no rebleeding within 24 h [25,26].

Treatment success was defined as no death or need to change therapy, which was defined by the occurrence of one of the following (based on the Baveno criteria) within 120 h: (1) fresh hematemesis or nasogastric aspiration of at least 100 mL of fresh blood at least 2 h after therapeutic endoscopy, (2) the development of hypovolemic shock, or (3) a 3-g decrease in Hb (9% drop of hematocrit) within any 24-h period if no transfusion was administered [25].

Rebleeding was defined as a single episode of or recurrent hematemesis or melena after 120 h resulting in any of the following: (1) hospital admission, (2) blood transfusion, (3) a 3-g decrease in Hb, or (4) death within 6 weeks [25].

Adverse events were defined as all conditions possibly caused by the endoscopic procedure.

Statistical analysis

Data analyses were performed using SPSS software, version 23.0 (SPSS Inc., Chicago, Illinois, USA). Continuous variables are expressed as the mean ± SD and qualitative data are expressed as numbers (percentages). Categorical variables were evaluated using χ^2 or Fisher's exact tests. Analysis of variance was used to compare the means among the multiple groups. We used the Cox proportional hazards regression model to analyze factors associated with rebleeding and mortality. On univariate analysis, all variables with P less than 0.1 were further analyzed in multivariate analysis. All tests were two-tailed, and P-values less than 0.05 were considered statistically significant.

Results

Search results

We retrieved 645 potentially relevant publications from four databases using the search strategy, and an additional 12 records were identified through references. A total of 230 duplicate publications were excluded, and 283 articles were excluded after the title and abstract review. A total of 144 full texts were retrieved, of which 52 articles were excluded after full-text analysis. Finally, 92 articles met our inclusion criteria, including 9 case series and 83 case reports. A flowchart is presented in Fig. 1.

Study characteristics

Cases were aggregated from 21 countries around the world, including Austria, Brazil, Canada, China, France, Germany, India, Italy, Japan, Korea, Malaysia, Pakistan, Portugal, Saudi Arabia, Singapore, Spain, Switzerland, Turkey, the UK, the USA, and Egypt. The literature was mainly reported from the USA, Japan, India, China, Germany, and Korea (25.0, 18.5, 8.7, 7.6, 5.4, and 5.4%, respectively). A total of 156 patients with duodenal varices were included, and detailed individual data of 101 patients were collected from 88 case reports and case series and are presented in Supplement 3, supplement digital content 3, *http://links.lww.com/EJGH/A559*. The data from four published case series, including 55 patients with bleeding duodenal varices, could not be extracted individually for each patient and were simply described.

The quality of all 83 case reports was assessed, yielding a mean score of 8.1 points based on the CASE guideline. The following items were recorded from all case reports patient information, diagnostic assessment, therapeutic interventions, and clinical outcomes. The items of title, keywords, abstract, introduction, clinical findings, timeline, discussion, and informed consent were described in 17 (20.5%), 25 (30.1%), 39 (47.0%), 57 (68.7%), 51 (61.4%), 72 (86.7%), 70 (84.3%), and 7 (8.4%) studies, respectively. The item of patient perspective was not provided in all case reports. The quality assessment of case studies is presented in Supplement 4, supplement digital content 4, *http://links.lww.com/EJGH/A560*.

Demographic and clinical characteristics of 101 individual patients with Duodenal variceal bleeding

The characteristics of the 101 patients are summarized in Table 1. All 101 patients with bleeding duodenal varices underwent endoscopic treatment. The mean age was 52.67 ± 13.82 years. There were 65 (64.4%) male and 31 (30.7%) female, and the sex of 5 (4.9%) patients were not provided. The most common cause of duodenal varix was cirrhosis-related intrahepatic portal hypertension (IPH) (77, 76.2%). Of the 77 patients with IPH, 3 had hepatocellular carcinoma (HCC), and 2 patients had Budd–Chiari syndrome. Twenty-two (21.8%) patients had noncirrhosis-related EPH, including four patients with cavernous transformation of the portal vein, five patients with portal vein thrombosis (PVT), three patients with portal vein tumor thrombosis, four patients with vascular abnormalities caused by abdominal surgery, two patients with idiopathic portal hypertension, one patient with inferior vena cava thrombophlebitis with thrombosis, and three patients with specific causes of extrahepatic portal venous obstruction (EHPVO) not mentioned in the studies. The causes of duodenal varix in the remaining 2 (2.0%) patients were not recorded in the studies.

The most common cause of cirrhosis was alcoholic liver disease in 33 patients (33/77, 42.8%) followed by hepatitis C virus (HCV), hepatitis B virus (HBV), idiopathic cirrhosis, HCV + alcoholism, HBV + alcoholism, HCV + HBV + alcoholism, and primary biliary cirrhosis in 15 (19.5%), 5 (6.5%), 4 (5.2%), 4 (5.2%), 2 (2.6%), 1 (1.3%), and 1 (1.3%) case, respectively. Moreover, the causes in 12 (15.6%) patients with cirrhosis were not described in the studies. Ninety-nine (98.0%) patients with duodenal varices presented with gastrointestinal bleeding (GIB) and specific manifestations of 15 of these cases were not described. The remaining 2 (1.9%) patients were admitted with hepatic encephalopathy. The location of 97 patients with duodenal variceal bleeding was recorded, but this information was not reported for 4 patients.

Endoscopic treatment effectiveness

In total, 30 (29.7%), 22 (21.8%), 38 (37.6%), and 11 (10.9%) patients received EBL, EIS, ETA, and the combination treatment, respectively. The baseline characteristics of patients with duodenal variceal bleeding were comparable among the four groups ($P > 0.05$) (Table 1). The clinical outcomes of patients who underwent endoscopic treatments for duodenal variceal bleeding are summarized in Table 2. The overall rate of initial hemostasis and treatment success was 89.1% (90/101) and 81.2% (82/101) after initial endoscopic treatment, respectively. Among a variety of endoscopic treatments available, only the rate of initial hemostasis was significantly different between the EIS and ETA groups (72.7 vs. 94.7%, $P = 0.023$), but no significant difference was noted between the other groups ($P > 0.05$). The differences in treatment success rates were not statistically significant among the four groups ($P = 0.367$).

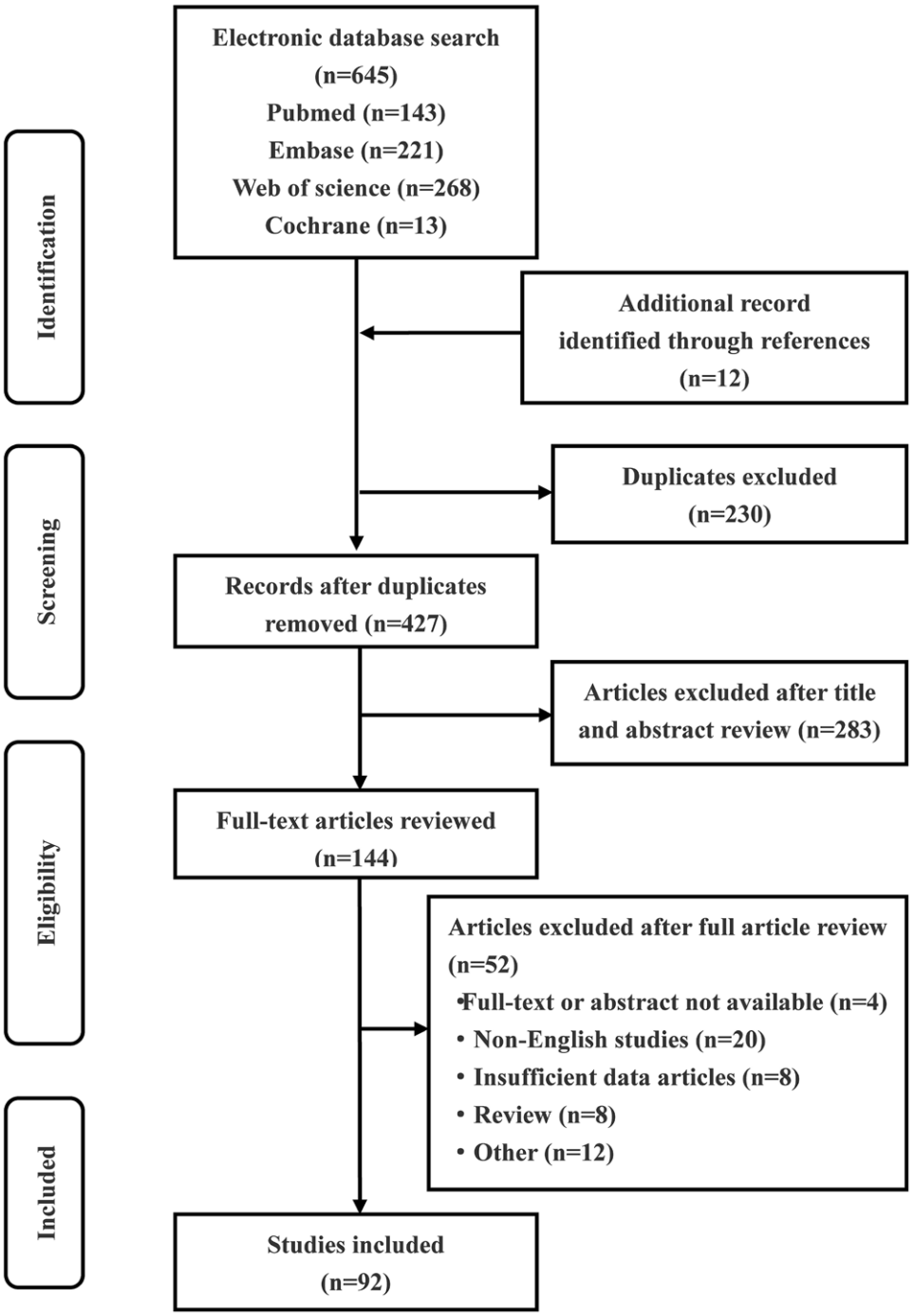

Fig. 1. PRISMA diagram of the study search and selection process. PRISMA, Preferred Reporting Items for Systematic Review and Meta-analysis statement.

The median follow-up time of these patients who underwent endoscopic treatment for duodenal variceal bleeding was 4.5 (interquartile range: 1.0, 12.0) months. Nine (8.9%) patients developed rebleeding after initial endoscopic treatment; of these nine patients, seven patients experienced rebleeding due to ruptured duodenal varices. The remaining two patients developed endoscopic treatment-induced ulcer bleeding. The rebleeding rates were comparable among the four groups ($P = 0.647$). The number of patients experiencing rebleeding within 6 weeks accounted for 66.7% of the total number of patients experiencing rebleeding (Table 2). In addition, the rate of rebleeding was increased in patients with cirrhosis (10.4%, 8/77) compared with those with noncirrhotic EPH (4.5%, 1/22), while the difference between the two groups was not statistically significant ($P > 0.05$).

Fourteen (13.9%) patients died during the follow-up period. The most common cause of death was liver failure in 5 (35.7%) patients followed by bleeding, multiple organ dysfunction syndrome, respiratory failure, and HCC in 4 (28.6%), 2 (14.3%), 2 (14.3%), and 1 (7.1%) patients, respectively. Differences in the mortality rates were not considered statistically significant among the four groups ($P = 0.214$). The number of patients who died within 6 weeks accounted for 78.6% of the total number of patients who died (Table 2). Furthermore, mortality was

Table 1. Demographic and clinical characteristics of patients who were treated with endoscopy for duodenal variceal bleeding

	All patients ($N=101$)	EBL ($n=30$)	EIS ($n=22$)	ECA ($n=38$)	Combination ($n=11$)	P
Age (mean ± SD) (years)	52.67 ± 13.82	55.13 ± 13.42	48.90 ± 13.69	52.50 ± 14.11	56.54 ± 13.88	0.336
Sex [*n* (%)]						0.87
Male	65 (64.4%)	19 (63.3)	15 (68.2)	25 (65.8)	6 (54.5)	
Female	31 (30.7%)	10 (33.3)	5 (22.7)	12 (31.6)	4 (36.4)	
Cause of duodenal varix						0.105
Cirrhosis-related IPH [*n* (%)]	77 (76.2)	23 (66.7)	18 (81.8)	25 (63.2)	11 (100)	
Noncirrhosis-related EPH [*n* (%)]	22 (21.8)	7 (33.3)	3 (13.6)	12 (34.2)	0 (0)	
The presentation of duodenal variceal bleeding						0.892
Hematemesis only	12 (11.9)	4 (13.3)	2 (9.1)	5 (13.2)	1 (9.1)	
Melena or hematochezia only	51 (50.5)	18 (60.0)	11 (50.0)	17 (44.7)	5 (45.5)	
Hematemesis and hematochezia/melena	21 (20.8)	6 (20.0)	2 (9.1)	10 (26.3)	3 (27.3)	
Previous history of other varices [*n* (%)]	34 (33.7)	9 (30.0)	11 (50.0)	11 (28.9)	3 (27.3)	0.353
Esophageal varices	20 (19.8)	4 (13.3)	8 (36.4)	7 (18.4)	1 (9.1)	
Gastric varices	6 (5.9)	2 (6.7)	2 (9.1)	2 (5.3)	0 (0)	
Esophageal varices + gastric varices	8 (7.9)	3 (10.0)	1 (4.5)	2 (5.3)	2 (18.2)	
Previous history of endoscopic treatments [*n* (%)]	25 (24.8)	4 (13.3)	9 (40.9)	9 (23.7)	3 (27.3)	0.161
Locations of duodenal varices [*n* (%)]						0.437
Bulb part	23 (22.8)	5 (16.7)	4 (18.2)	12 (31.6)	2 (18.2)	
Descending part	55 (54.5)	20 (66.7)	12 (54.5)	16 (42.1)	7 (63.6)	
Other part	19 (18.8)	3 (10.0)	5 (22.7)	9 (23.7)	2 (18.2)	
Duodenal varices coexisting with other varices [*n* (%)]	54 (53.5)	11 (36.7)	11 (50.0)	25 (65.8)	7 (63.6)	0.101
Need for further treatment [*n* (%)]	23 (22.8)	7 (23.3)	6 (27.3)	8 (21.0)	2 (18.2)	0.9464

EBL, endoscopic band ligation; EIS, endoscopic injection sclerotherapy; ECA, endoscopic cyanoacrylate; Combination, EIS combined with EBL or ECA; duodenal varix, duodena varices.

Table 2. Clinical outcome of patients who underwent endoscopic treatments for duodenal variceal bleeding

	All patients ($N=101$)	EBL ($n=30$)	EIS ($n=22$)	ECA ($n=38$)	Combination treatment (n=11)	P
Initial hemostasis [*n* (%)]	90 (89.1)	28 (93.3)	16 (72.7)	36 (94.7)	10 (90.9)	0.066
Treatment success [*n* (%)]	82 (81.2)	25 (83.3)	15 (68.2)	33 (86.8)	9 (81.8)	0.367
Rebleeding [*n* (%)]	9 (8.9)	3 (10.0)	3 (13.6)	2 (5.3)	1 (9.1)	0.647
5 days–6 weeks	6 (5.9)	2 (6.7)	3 (13.0)	0 (0)	1 (9.1)	0.82
>6 weeks	3 (3.0)	1 (3.3)	0 (0)	2 (5.3)	0 (0)	
Mortality [*n* (%)]	14 (13.9)	3 (10.0)	5 (22.7)	3 (7.9)	3 (27.3)	0.179
5 days–6 weeks	11 (10.9)	2 (6.7)	5 (22.7)	2 (5.3)	2 (18.2)	0.124
>6 weeks	3 (3.0)	1 (3.3)	0 (0)	1(2.6)	1 (9.1)	
Adverse events [*n* (%)]	28 (27.7)	6 (20.0)	6 (27.3)	14 (36.8)	2 (18.2)	0.388
Follow-up [months (IQR)]	4.5 (1.0, 12.0)	2.0 (1.0, 11.25)	5 (0.25, 13.0)	6.5 (2.0, 12.5)	3.0 (1.0, 13.0)	0.469

EBL, endoscopic band ligation; EIS, endoscopic injection sclerotherapy; ECA, endoscopic cyanoacrylate; combination treatment, EIS combined with EBL or ECA; IQR, interquartile range.

higher in patients with cirrhosis (16.9%, 13/77) compared with noncirrhosis patients (4.5%, 1/22), but the difference between the two groups was not statistically significant ($P>0.05$).

On univariate analysis, age, duodenal varix location, and duodenal varices coexisting with other varices have *P*-values less than 0.1. Subsequently, all variables with *P* less than 0.1 were further assessed in multivariate analysis, revealing that only age (hazard ratio 1.006; 95% confidence interval, 1.006–1.129; $P=0.03$) was an independent predictor of mortality (Table 3).

Adverse events

Twenty-eight (27.7%) patients developed adverse events related to endoscopic treatment. Endoscopic treatment-induced ulcer, endoscopic treatment-induced ulcerative bleeding [20,27–29], biliary obstruction [30–32], PVT [20,33], pulmonary embolism [34,35], abdominal pain [36], cerebral infarction [37], right atrium embolism [38], sepsis [39], and pneumonia [40] were noted in 12 (11.9%, 12/101), 4 (4.0%, 4/101), 3 (3.0%, 3/101), 2 (2.8%, 2/71), 2 (2.8%, 2/71), 1 (1.0%, 1/101), 1 (1.4%, 1/71), 1 (1.4%, 1/71), 1 (1.0%, 1/101), and 1 (1.0%, 1/101) patients, respectively. The majority of adverse events were endoscopic treatment-induced ulcer or ulcerative bleeding (15.8%, 16/101). The systemic embolization rate due to injection sclerotherapy with sclerosants or tissue adhesives was 5.6% (4/71). The rate of adverse events was comparable among the four groups ($P=0.395$) (Table 2).

Review of 55 patients with duodenal variceal bleeding

For four published case series including 55 patients with duodenal variceal bleeding, individual data could not be extracted for each patient and were simply reviewed. Chaudhari *et al*. [21] reported 25 patients with duodenal variceal bleeding who underwent endoscopic cyanoacrylate (ECA). The most common cause of duodenal varix was EHPVO in 19 (76%) patients and chronic liver disease in 5 (20.0%) patients. The follow-up time ranged from 6 to 44 months. This study showed that 5 (20.0%) patients developed rebleeding after initial treatment, and death was not observed during the follow-up period. Gabr *et al*. [22] studied 18 patients with cirrhosis-related IPH with duodenal variceal bleeding who underwent ECA. All 18 patients successfully achieved hemostasis, and 6 (33.3%) patients experienced adverse events (endoscopic treatment related to ulcers). Moreover, rebleeding and death were not observed in any of the patients with

Table 3. Cox-regression analysis for mortality

	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age (years)	1.069	1.015–1.127	0.012	1.066	1.006–1.129	0.03
Sex	2.226	0.747–7.311	0.145			
Causes	0.156	0.029–1.762	0.121			
Previous history of other varices	3.448	0.761–15.62	0.118			
Locations of duodenal varices (bulb vs. descending part)	0.099	0.009–1.111	0.061	0.147	0.013–1.713	0.126
Duodenal varices coexisting with esophageal varices and/or gastric varices	3.352	1.002–11.210	0.050	2.707	0.821–8.924	0.102
Endoscopic therapeutic modalities	1.140	0.632–2.055	0.664			
Need for further treatment	2.133	0.664–6.852	0.203			

CI, confidence interval.

duodenal varices during the 1-year follow-up. Matsui *et al*. [41] enrolled eight patients with duodenal variceal bleeding. Of these patients, five were treated with ECA, one with EBL, and two with a combination of EBL with EIS. The results showed that hemostasis was successfully achieved in all eight patients, and rebleeding and death were not observed. Liu *et al*. [42] investigated 14 patients with duodenal varices (13 with cirrhosis-related IPH and 1 with PVT-related EPH), 4 of whom were treated with ECA. Follow-up ranged from 7 to 30 months, and rebleeding was not observed. However, death occurred in two patients in the 7th and 24th months after initial treatment.

Discussion

In our systematic review, the clinical characteristics of patients with duodenal variceal bleeding included the following: (1) cirrhosis-related IPH (76.2%) was the main cause of patients with duodenal variceal bleeding; (2) the most frequent location of duodenal varices was the descending portion of the duodenum (54.5%); (3) a majority of patients with duodenal variceal bleeding (53.5%) occurred in conjunction with gastric varices or esophageal varices, which was comparable with results of a previous report that suggested 50–60% patients with duodenal varices coexisting with esophageal varices or gastric varices [43]. Furthermore, this study demonstrated that endoscopic treatment is feasible, well tolerated, and effective for duodenal variceal bleeding.

The cause and location of duodenal varices remain controversial. In Western countries, duodenal varices located in the duodenal bulb were found most frequently followed by duodenal varices located in the descending part of the duodenum [11,44]. In contrast, in Asian countries, such as Japan and China, the descending part of the duodenum was the main location of duodenal varices followed by the duodenal bulb [1,9,42]. Interestingly, in Western countries, EPH was the most common cause of ectopic varices; on the other hand, cirrhosis-related IPH was the most frequent cause in Asian countries [9,42]. This discrepancy may be associated with the different causes and ethnicities of patient populations [45]. In the systematic review based on data from 21 countries, we found that the descending part of the duodenum (54.5%) was the most frequent site of duodenal varices, and the most common cause of duodenal variceal bleeding was IPH due to cirrhosis. Therefore, we suggest that when endoscopists encounter acute GIB, especially in patients with cirrhosis, the descending part of the duodenum and then the distal portion should be observed under endoscopy.

With regard to treatment of bleeding duodenal varices, currently only case reports and case series are available in the published literature. In our systematic review analyzing 101 individual patient data on endoscopic treatment of bleeding duodenal varices, the overall rates of initial hemostasis, treatment success, rebleeding, and mortality were 89.1, 81.2, 8.9, and 13.9%, respectively, suggesting that endoscopic treatment was an effective modality in cases of bleeding duodenal varices. Notably, the rate of rebleeding and mortality was significantly reduced in our study compared with the previously reported rebleeding and mortality rates of 20–40% [21,23,46] and 25–60% [23,42,46], respectively. This discrepancy may be attributed to the following reasons. First, the definition of 'rebleeding' varies in the published literature. In our study, rebleeding was defined according to the Baveno V consensus. Second, the severity of liver function may be different among patient populations. Furthermore, our study found that the rate of rebleeding and mortality was increased in patients with cirrhosis compared with those with noncirrhosis-related EPH, which was consistent with previous results [47], suggesting that patients with cirrhosis have a worse prognosis than noncirrhosis patients. In addition, this study showed that the first 6 weeks after initial endoscopic treatment was a high-risk period of rebleeding and mortality, accounting for 66.7 and 78.6% of all cases of rebleeding and death, respectively. Therefore, we think patients who underwent endoscopic treatment for duodenal variceal bleeding should be closely monitored and given more supportive treatment within the first 6 weeks. These measures may reduce the risk of rebleeding and mortality of bleeding duodenal varice.

Endoscopic therapies include mechanical therapies (band ligation) and injection therapies (sclerotherapy with sclerosants or tissue adhesives). Endoscopic intervention was more challenging in the treatment of bleeding duodenal varices compared with bleeding esophageal varices because the inherent duodenal anatomy made identifying the extent of varix and maintaining full visualization of the lesion difficult [48,49]. An extensive literature review by Gunnerson *et al*. [46] evaluated 19 patients with duodenal variceal bleeding who underwent EBL and found that successful hemostasis was achieved in only 3 (15.8%) patients who rebled after initial treatment. Two (10.5%) of these patients died of liver failure and complications of not related to endoscopic treatment. This study suggested that EBL appears to be effective for duodenal variceal

bleeding. Nevertheless, if the band does not completely ligate large varix, especially those greater than 15 mm, which may potentially create a wide defect in the variceal wall after sloughing of the band, thus aggravating the bleeding [50,51]. In addition, given the usual proximity to the ampulla, there is a risk of papilla within the banded tissue, resulting in biliary obstruction [52]. To date, the largest sample study on endoscopic treatment of bleeding duodenal varices reported 25 patients who underwent ETA. The study found that only 5 (20.0%) patients rebled, and no death was observed during the follow-up [21]. Seo *et al*. [53] reviewed some previous reports about injection sclerotherapy (including EIS and ETA) for duodenal variceal bleeding. In the study, serious adverse events were not observed, and the treatment response was relatively good. These studies showed that EIS and ETA may be effective for bleeding duodenal varices. However, both EIS and ETA techniques can be complicated by tissue damage, mucosal ulceration, perforation, and subsequent serious distant embolisms, such as pulmonary embolism and cerebral embolism [37,40,46,54]. Although these endoscopic treatments appeared to be useful in the management of bleeding duodenal varices, the best endoscopic treatment modality remains unclear because no study has evaluated the comparative effectiveness and safety of various endoscopic interventions for duodenal variceal bleeding. In this systematic review, we found that initial hemostasis was significantly increased in the ETA group compared with the EIS group ($P = 0.023$), whereas treatment success, rebleeding, and mortality were not significantly different among the four groups ($P > 0.05$). These results suggest that the effectiveness of endoscopic treatment for duodenal variceal bleeding appears to be comparable among the four endoscopic treatment strategies. Notably, compared with the other groups, the EIS group had higher rates of rebleeding and mortality and a lower rate of treatment success; however, these differences were not statistically significant. Therefore, studies comparing the effectiveness and safety of various endoscopic therapies in the future should be performed to assess the optimal endoscopic treatment for duodenal variceal bleeding. This work is very challenging because it is difficult for a single center to collect sufficient samples; thus, multicenter collaboration may be a useful way to solve the problem.

Although the absence of directly comparative data among various endoscopic treatment strategies, we think that ETA with cyanoacrylate may be preferable in the treatment of bleeding duodenal varices based on the following reasons. First, because duodenal varices may cause massive bleeding, a safer, easier, and faster therapy was considered to be preferable. Endoscopic intervention is effective, less invasive, and easier and faster to perform compared with interventional radiology and surgical procedures [43,53,55]. Second, given the anatomical characteristics of duodenal varix that are often located deep in the serosal layer of the duodenum, it is difficult to achieve long-term eradication of varices with EBL alone given the insufficient effect of EBL on the feeding collateral vessels [40,51,53,56]. In addition, some cases may be refractory to the band given the anatomy of the duodenal varices [46]. Sclerosants and tissue adhesives were injected into target intravarices or feeding collateral vessels to obtain the eradication of varices [57–59]. Third, in published studies, sclerosants and tissue adhesives included ethanolamine oleate, sodium morrhuate, absolute alcohol, polidocanol, thrombin, cyanoacrylate, and sodium tetradecyl sulfate; in addition, cyanoacrylate and ethanolamine oleate are frequently used. Ethanolamine oleate interferes with endothelial cells, causing coagulation and necrosis, and directly promote thrombus formation, causing penetration, or perforation of the thin duodenal wall. Cyanoacrylate rapidly polymerizes upon contact with blood and embolizes varix [48,51]. Therefore, many investigators prefer cyanoacrylate rather than ethanolamine oleate in the treatment of variceal bleeding because *N*-butyl-2-cyanoacrylate causes less tissue damage than other agents [43,55,60].

Endoscopic treatment techniques theoretically increase the risk of mucosal ulcers, perforations, or other complications given the relative thinness of the duodenal wall compared to the other parts of the upper gastrointestinal tract [46,57,61]. In this systematic review, the overall rate of adverse events was 27.7%, which was comparable with 19–38% previously reported for endoscopic treatments for gastric varices [62–64]. Moreover, major adverse events included endoscopic treatment-induced ulceration or ulcerative bleeding, which is consistent with the results of previous studies [22,45]. In addition, previous studies have shown that in patients with bleeding gastric varices who were treated with cyanoacrylate injection, the risk of severe and fatal systemic embolisms, such as pulmonary embolism and cerebral infarction, was 0–2% [63,65–67], which was lower than our findings (5.6%). Nevertheless, the incidence of serious adverse events of endoscopic treatment of bleeding duodenal varices was still relatively low. Therefore, we think that endoscopic therapy is a relatively well-tolerated modality in the management of duodenal variceal bleeding.

Several limitations of this review should be noted. First, duodenal varix is a rare condition, and all studies included were case reports and case series and not prospective RCTs. Second, although the studies retrieved were comprehensive, it is still possible that unpublished case reports were not found, resulting in publication bias. Third, there was a selection bias in the systematic review of case reports, including patients with different ethnicities and different underlying diseases. In addition, the results of the study may be affected by the exclusion of non-English publications. Fourth, in this review, the studies we included used different types and volumes of sclerosants and tissue adhesives, as well as different ratios of mixed lipiodol and tissue adhesives, which may have an impact on the results. Theoretically, the higher the ratio of lipiodol to tissue adhesive (the greater the volume of lipiodol injected), the higher the risk of ectopic embolism [37,45]. Previous studies have shown that the use of different ratios of lipiodol to tissue adhesive (from 1/1 to 0.3/1 volume ratio) could reduce the risk of distant embolism from 0.7 to 0% [67]. Despite these limitations, there are several strengths that should be noted in our systematic review. First, the current study is the first structured systematic review evaluating the effectiveness and safety of endoscopic treatment for duodenal variceal bleeding. Second, this remains the only study to analyze comparative endoscopic treatment modalities in the therapy of bleeding duodenal varices. Guidelines and consensus are not

available for the treatment of bleeding duodenal varices, so the choice of treatment strategy depends on the local facilities and expertise available. We evaluated some specific data on various endoscopic treatments for duodenal variceal bleeding, including hemostasis, treatment success, rebleeding, mortality, and adverse events, which perhaps may guide clinicians to make decisions in the future.

Conclusion

Endoscopic intervention is a feasible, well-tolerated, and effective modality for the treatment of bleeding duodenal varices. Among a variety of endoscopic treatments available, ETA with cyanoacrylate may be preferable in the management of duodenal variceal bleeding. Due to the lack of studies on cumulative and directly comparative endoscopic treatments of duodenal variceal bleeding, the conclusions need to be further validated by large-scale, prospective, RCTs in the future.

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Conflicts of interest

There are no conflicts of interest.

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