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Efficacy and safety of endoscopic ultrasound-guided therapy versus direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis

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ABSTRACT

Background Gastric variceal bleeding carries significant mortality in the setting of portal hypertension. Among the endoscopic treatment options, endoscopic ultrasound (EUS)-guided glue and/or coil injection is a novel approach, but its role in the treatment of gastric varices is not established due to a lack of robust data.

Methods We conducted a comprehensive search of several databases (inception to June 2019) to identify studies evaluating EUS in the treatment of gastric varices. Our primary goals were to estimate the pooled rates of treatment efficacy, obliteration and recurrence of gastric varices, early and late rebleeding, and adverse events with EUS-guided therapy in gastric varices. We also searched for studies that evaluated direct endoscopic glue (END-glue) injection for treatment of gastric varices, and used the pooled rates as comparators.

Results 23 studies (851 patients) evaluating EUS-guided therapy were included. The pooled treatment efficacy was 93.7 % (95 % confidence interval [CI] 89.5 – 96.3, I^2 = 53.7), gastric varices obliteration was 84.4 % (95 %CI 74.8 – 90.9, I^2 = 77), gastric varices recurrence was 9.1 % (95 %CI 5.2 – 15.7, I^2 = 32), early rebleeding was 7.0 % (95 %CI 4.6 – 10.7, I^2 = 0), and late rebleeding was 11.6 % (95 %CI 8.8 – 15.1, I^2 = 22). The rates were comparable to END-glue therapy (28 studies, 3467 patients) except for obliteration, which was significantly better with EUS-guided therapy. On subgroup analysis, EUS-coil/glue combination showed superior outcomes.

Conclusions EUS-guided therapy demonstrated clinical efficacy for treatment of gastric varices in terms of obliteration, recurrence, and long-term rebleeding, and may be superior to END-glue.

Introduction

Gastric varices are a cause of significant morbidity and mortality. An actively bleeding gastric varix can be catastrophic in the setting of portal hypertension and cirrhosis, the most common scenario in which it arises. Gastric varices can be present in 20 % – 30 % of patients with portal hypertension, irrespective of cirrhosis. The reported rebleeding rate of gastric varices is 44 % – 65 % within 5 years, with an estimated 1-year mortality rate of over 50 % [1 – 3]. Effective treatment is therefore important and relies on early diagnosis and prompt therapy.

Treatment options include a combination of fluid resuscitation, administration of medications that reduce portal pressure such as octreotide, balloon-retrograde transvenous obliteration, emergent transjugular intrahepatic portosystemic shunt, and endoscopic or interventional radiology approaches to target the source of bleeding using cyanoacrylate glues.

Endoscopic options to deliver cyanoacrylate glue include: 1) direct endoscopic injection of glue using catheters inserted through a standard upper endoscope to obliterate the varices (END-glue), and 2) endoscopic ultrasound (EUS)-guided variceal injection via a fine-needle aspiration (FNA) device (EUS-glue). A third intervention in the treatment of gastric varices is to directly deliver embolization coils into gastric varices under EUS guidance (EUS-coil), also through FNA needles. EUS-coil injection of gastric varices has been attempted without and with simultaneous use of glue (EUS-coil/glue). Endoscopic and EUS images of gastric varices are shown in ▶ **Fig. 1** and ▶ **Fig. 2**, respectively.

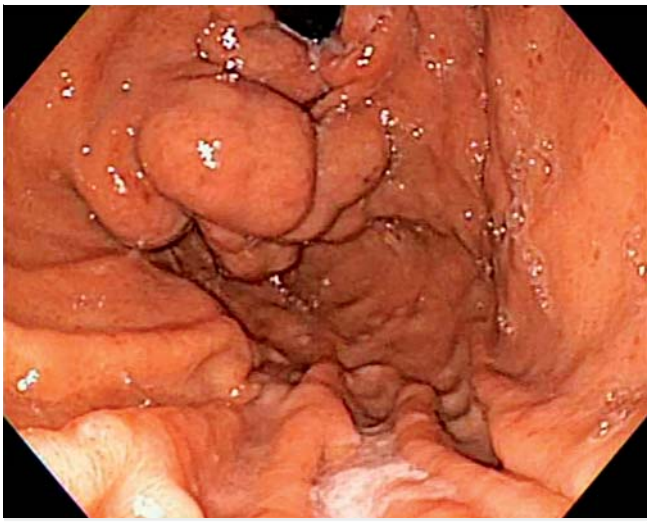
Data on the clinical outcomes of EUS-guided treatment in gastric varices is limited to a handful of small-sized studies; hence, the role of EUS in the treatment of gastric varices is not defined. There has been no meta-analysis evaluating EUS therapy in the treatment of gastric varices. We, therefore, conducted this meta-analysis to delineate the efficacy and safety of EUS-guided management of gastric varices, and used the pooled outcomes of END-glue therapy as a comparator.

Methods

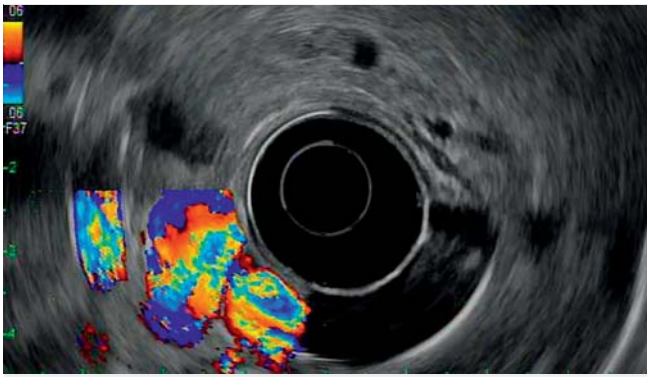
Search strategy

A comprehensive search of several databases from inception to 17 June 2019, limited to the English language only and excluding animal studies, was conducted. The databases included Ovid MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus.

The search strategy was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for studies describing the role of EUS in the treatment of gastric varices. The full search strategy is available in Appendix 1 s in the online-only Supplementary material.



▶ **Fig. 1** Endoscopic image of a gastric varix.



▶ **Fig. 2** Endoscopic ultrasound image of a gastric varix.

Study selection

In this meta-analysis, we included studies that reported on the outcomes of EUS-guided treatment in the management of gastric varices. Studies, irrespective of patients with active and/or recent gastric variceal bleeding, type of obliterant used (cyanoacrylate glue and/or coil and/or thrombin), use of concomitant medical therapy, underlying liver cirrhosis, inpatient/outpatient setting, geography, and abstract/manuscript status were included as long as they provided data needed for the analysis.

Exclusion criteria were studies conducted in a pediatric population (< 18 years) and studies not published in the English language.

In cases of multiple publications from the same cohort and/or overlapping cohorts, data from the most recent and/or most appropriate comprehensive report were included.

Study selection for the comparator group included studies that reported on the outcomes of END-glue injection therapy for gastric varices. Inclusion criteria were studies published as full manuscripts, noncomparative cohort studies, and minimum sample size of 40 (as this is the minimum sample size to

score 1 on the study quality assessment). Exclusion criteria were studies published in abstract form only, studies published prior to the earliest EUS study included in this analysis so that the time frame of the studies were comparable, and studies with a sample size of < 40 patients.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form by at least three authors (S.R.K., B.P.M., S.T.), and two authors (B.P.M., S.C.) independently checked the data collected to ensure accuracy. The primary authors of the studies were contacted via email for any data collection and/or clarification as and when needed. Two authors (B.P.M., S.R.K.) performed independent quality scoring using the Newcastle – Ottawa scale.

Outcomes assessed

Assessed outcomes were the pooled rates of: 1) treatment efficacy, 2) obliteration of gastric varices, 3) recurrence of gastric varices, 4) early rebleeding of gastric varices, 5) late rebleeding of gastric varices, 6) adverse events, distant organ embolism, all-cause mortality, and mortality due to bleeding gastric varices.

Subgroup analysis

The EUS treatment was categorized as: EUS-glue, EUS-coil, and EUS-coil/glue, and the pooled rates were stratified according to the subgroups. The pooled outcomes of END-glue therapy were used as the comparator.

Definitions

The endoscopic criteria for bleeding gastric varices included: 1) active spurting and/or oozing of blood from a gastric varix, and 2) presence of fibrinous clot (nipple sign) and/or erosive cherry red spots and/or blackish ulcer over a gastric varix with no other obvious active source of bleeding.

Treatment efficacy was defined by complete cessation of bleeding from the gastric varices as seen endoscopically, and/or cessation of bleeding with no blood flow on color Doppler as seen on EUS, with stable vital signs, no drop in hemoglobin, and no rebleeding within 24 hours. Obliteration of the varix was defined by the absence of Doppler flow on EUS. Early rebleeding was defined by rebleeding that was noted within 5 days (120 hours) of treatment, as manifested by the following: 1) a fresh hematemesis or nasogastric tube aspiration of at least 100 mL fresh blood at least 2 hours after the therapeutic endoscopy; 2) development of hypovolemic shock; and 3) a 3-g drop in hemoglobin within a 24-hour period (Baveno V consensus) [4]. Late rebleeding was defined as clinically significant bleeding after 5 days (120 hours), manifested as hematemesis and/or melena resulting in hospital admission and/or blood transfusion and/or 3-g drop in hemoglobin (Baveno V consensus) [4]. In studies where this definition was not followed, the bleeding event was considered as late rebleeding for the purposes of this analysis.

Adverse events were categorized into mild, moderate, and severe based on the American Society for Gastrointestinal Endoscopy lexicon of adverse events [5]. Information on distant organ embolism (pulmonary embolism and splenic infarcts), all-cause mortality, and mortality due to bleeding gastric varices were collected as reported in the primary studies.

Statistical analyses

We used meta-analysis techniques to calculate the pooled estimates in each case following the methods suggested by DerSimonian and Laird using the random-effects model. When the incidence of an outcome was zero in a study, a continuity correction of 0.5 was added to the number of incident cases before statistical analysis. *P* values of < 0.05 were considered statistically significant and all tests were two-sided. We assessed heterogeneity between study-specific estimates by using the Cochran Q statistical test for heterogeneity, 95 % prediction interval (PI), which deals with the dispersion of the effects, and the I^2 statistics. I^2 values of < 30 %, 30 % – 60 %, 61 % – 75 %, and > 75 % were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively. Publication bias was ascertained qualitatively by visual inspection of a funnel plot, and quantitatively by the Egger test. When publication bias was present, further statistics using the Fail-Safe N test and Duval and Tweedie's "Trim and Fill" test were used to ascertain the impact of the bias. Three levels of impact were reported based on the concordance between the reported results and the actual estimate if there was no bias; the impact was reported as minimal if both versions were estimated to be the same, modest if the effect size changed substantially but the final finding remained the same, and severe if the basic final conclusion of the analysis was threatened by the bias.

All analyses were performed using Comprehensive Meta-Analysis software, version 3 (BioStat, Englewood, New Jersey, USA).

Results

Search results and population characteristics

From an initial total of 1286 studies, 180 records were screened and 144 full-length articles and abstracts were assessed. A total of 23 studies (851 patients) were included in the final analysis of EUS-guided therapy [6 – 28], including 12 cohorts treated with EUS-coil/glue [10 – 12, 14, 16, 17, 19, 20, 23, 26 – 28], 9 cohorts treated with EUS-glue therapy [6, 7, 9, 15, 17 – 19, 24, 25], 3 cohorts with EUS-coil placement [17, 21, 24], and 1 each treated with EUS-thrombin [13], EUS-coil/thrombin [22], and EUS-coil/gelatin sponge [8]. We encountered three EUS-guided studies that were from the same cohort and/or overlapping cohorts [29 – 31]; data from only the most recent and/or most appropriate comprehensive report were included. The schematic diagram of study selection is illustrated in **Fig. 1s**. For the comparator group, a total of 28 studies (3467 patients) were included based on our inclusion/exclusion criteria [6, 11, 18, 21, 32 – 55].

Basic study and population characteristics are described in **Table 1s**. The range of mean ages was 40 – 65 years, and 42 % of patients were male. N-butyl-2-cyanoacrylate was the most commonly used glue. Use of lipiodol varied among the studies.

▶ **Table 1** Pooled results of outcomes.

Intervention/outcomes, pooled rate, % (95 %CI, I^2)	All EUS modalities	EUS-glue	EUS-coil	EUS-coil/glue	END-glue (comparator group)
Treatment efficacy	93.7 (89.5 – 96.3, 53.7) 29 cohorts	91 (80 – 96.2, 40) 9 cohorts	84.2 (54.5 – 96, 6.5) 3 cohorts	96.7 (93 – 98.5, 55) 14 cohorts	91.4 (82.8 – 95.9, 97) 28 cohorts; P = 0.4
Obliteration of gastric varices	84.4 (74.8 – 90.9, 77) 21 cohorts	90 (71.3 – 97, 0) 5 cohorts	N/C	86.2 (75.5 – 92.7, 74) 12 cohorts	62.6 (42.6 – 79.1, 97); 13 cohorts; P = 0.02
Recurrence of gastric varices	9.1 (5.2 – 15.7, 32) 16 cohorts	15 (8.8 – 24.5, 0) 5 cohorts	N/C	5.2 (2.6 – 9.8, 0) 6 cohorts. P = 0.01	18 (11.4 – 27.2, 89) 8 cohorts; P = 0.06
Early rebleeding	7 (4.6 – 10.7, 0) 20 cohorts	6 (3.1 – 11.1, 0) 8 cohorts	N/C	7.7 (3.9 – 14.9, 46) 7 cohorts	5 (3.3 – 7.4, 72) 23 cohorts; P = 0.7
Late rebleeding	11.6 (8.8 – 15.1, 22) 26 cohorts	16.3 (9.7 – 26.1, 65) 8 cohorts	16.8 (7.3 – 34.1, 0) 3 cohorts)	9.2 (6.4 – 13, 0) 12 cohorts	17 (12.3 – 22.9, 92) 27 cohorts; P = 0.1
Adverse events					
Embolism	5.6 (3.1 – 9.8, 56) 28 cohorts	8.4 (3 – 21.3, 66) 9 cohorts	4 (0.5 – 25.7, 0) 3 cohorts	4.3 (1.8 – 9.8, 59) 13 cohorts; P = 0.33	–
Mild adverse events	5.9 (4.1 – 8.3, 0) 28 cohorts	4.7 (2.1 – 10.6, 0) 9 cohorts	3.9 (0.8 – 18.1, 0) 3 cohorts	5.3 (3.2 – 8.6, 35) 13 cohorts	–
Moderate adverse events	5.7 (3.2 – 9.8, 53) 28 cohorts	9 (3.5 – 21.6, 66) 9 cohorts	4 (0.5 – 25.1, 0) 3 cohorts	4 (1.7 – 9.2, 57) 13 cohorts	
Mortality (all-cause)	13.1 (8.3 – 20.2, 68); 19 cohorts	27.9 (16.3 – 43.5, 75); 5 cohorts	N/C	9 (5.1 – 15.2, 0); 9 cohorts; P = 0.003	
Mortality due to gastric varices rebleed	7.7 (4.9 – 11.9, 29) 18 cohorts	12 (5.2 – 25.6, 58) 5 cohorts	N/C	4.5 (2 – 9.8, 21) 8 cohorts; P = 0.09	

EUS, endoscopic ultrasound; END, direct endoscopic glue injection; CI, confidence interval; N/C, not calculated due to limited studies.

Overall, 28 % of included patients had gastroesophageal varices type 1 (GOV1), 48 % had GOV2, 24 % had isolated gastric varix type 1 (IGV1), and 63 % of patients had cirrhosis. In total, 30 % of varices were due to alcohol, 31 % were due to viral hepatitis, and 11 % of the included patients had hepatocellular carcinoma.

Characteristics and quality of included studies

Four of the included studies were prospective in nature [6, 19, 20, 26]. There were no population-based studies. Ten of the studies were published as abstracts at the time of the analysis [6 – 9, 14, 20, 22, 26 – 28]. Based on the Newcastle – Ottawa assessment system for study quality, there were no low quality studies in our analysis: 11 of the studies were considered to be of high quality and the rest were of medium quality [10 – 12, 18 – 21, 23, 24, 26, 27]. All studies included in the comparator group were considered to be of high quality. The assessment of study quality is detailed in **Table 2s**.

Meta-analysis outcomes

The pooled rate of treatment efficacy with EUS-guided therapy was 93.7 % (95 % confidence interval [CI] 89.5 – 96.3, I^2 = 53.7) (▶ **Fig. 3**), which was comparable to the treatment efficacy of END-glue (91.4 %, 95 %CI 82.8 – 95.9, I^2 = 97, P = 0.4) (▶ **Table 1**). The pooled rate of obliteration with EUS-guided therapy was 84.4 % (95 %CI 74.8 – 90.9, I^2 = 77) (▶ **Fig. 4**), which was significantly superior to END-glue therapy (62.6 %, 95 %CI 42.6 – 79.1, I^2 = 97, P = 0.02). The pooled rate of recurrence with EUS-guided therapy was 9.1 % (95 %CI 5.2 – 15.7, I^2 = 32) (▶ **Fig. 5**), which was comparable to END-glue (18 %, 95 %CI 11.4 – 27.2, I^2 = 89, P = 0.06).

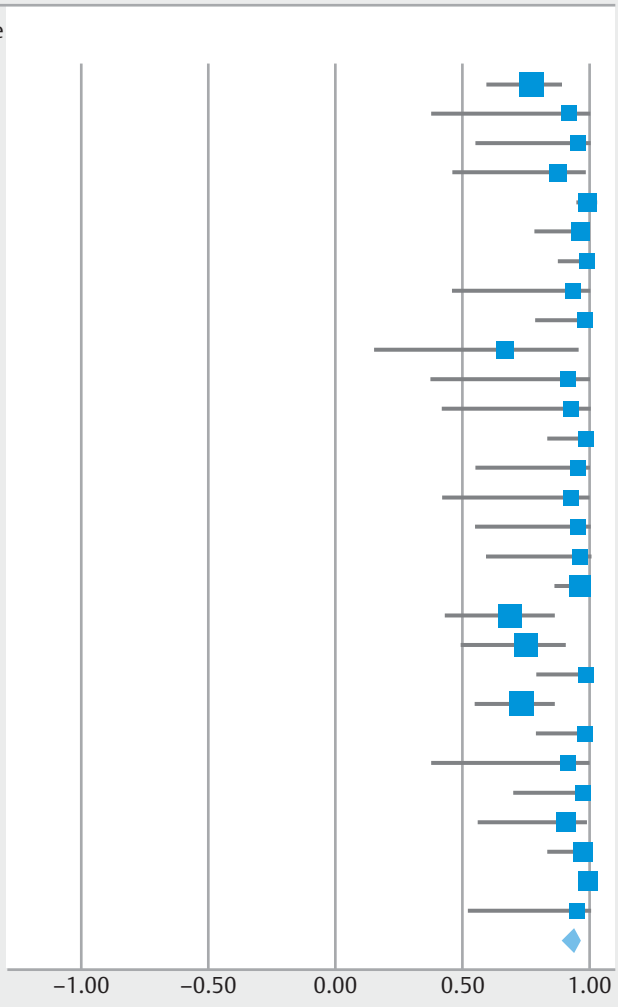
The pooled rate of early rebleeding was 7.0 % (95 %CI 4.6 – 10.7, I^2 = 0) with EUS-guided treatment and 5 % (95 %CI 3.3 – 7.4, I^2 = 72, P = 0.7) with END-glue treatment. The pooled rate of late rebleeding was 11.6 % (95 %CI 8.8 – 15.1, I^2 = 22) with EUS-guided therapy and 17 % (95 %CI 12.3 – 22.9, I^2 = 92, P = 0.1) with END-glue.

The pooled rate of mild adverse events with EUS-guided therapy was 5.9 % (95 %CI 4.1 – 8.3, I^2 = 0) and the pooled rate of moderate adverse events was 5.7 % (95 %CI 3.2 – 9.8, I^2 = 53). The pooled rate of distant organ embolism with EUS-guided therapy was 5.6 % (95 %CI 3.1 – 9.8, I^2 = 56). The pooled rate of all-cause mortality with EUS-guided therapy was 13.1 % (95 % CI 8.3 – 20.2, I^2 = 68) and the pooled rate of mortality due to gastric variceal bleeding was 7.7 % (95 %CI 4.9 – 11.9, I^2 = 29) (▶ **Table 1**).

Subgroup analysis

The subgroups of EUS-guided therapy analyzed were EUS-glue, EUS-coil/glue, and EUS-coil. Subgroup analysis revealed that

Study name	Event rate	Lower limit	Upper limit	*P*-value
Bang, 2015	0.774	0.596	0.888	0.004
Baptista, 2017	0.917	0.378	0.995	0.105
Bazarbashi, 2019	0.955	0.552	0.997	0.035
Bertoli, 2011	0.875	0.463	0.983	0.069
Bhat, 2016	0.993	0.995	0.999	0.000
Bhat, 2016p	0.964	0.789	0.995	0.001
Bick, 2018	0.991	0.877	0.999	0.001
Bick, 2018p	0.938	0.461	0.996	0.064
Binmoeller, 2011	0.984	0.789	0.999	0.004
Frost, 2018	0.667	0.154	0.957	0.571
Frost, 2018	0.917	0.378	0.995	0.105
George, 2017	0.929	0.423	0.996	0.081
Gubler, 2014	0.988	0.833	0.999	0.002
Khoury, 2019	0.955	0.552	0.997	0.035
Krill J T, 2018	0.929	0.423	0.996	0.081
Krill J T, 2018	0.955	0.552	0.997	0.035
Krill J T, 2018	0.962	0.597	0.998	0.026
Lee, 2000	0.963	0.864	0.991	0.000
Lobo, 2019	0.688	0.433	0.864	0.144
Lobo, 2019	0.750	0.492	0.903	0.057
Mathew, 2018	0.984	0.794	0.999	0.004
Mukkada, 2018	0.733	0.550	0.861	0.014
Robles-Medranda, 2018	0.984	0.789	0.999	0.004
Romero-Castro, R 2007	0.917	0.378	0.995	0.105
Romero-Castro, R 2013	0.975	0.702	0.998	0.011
Romero-Castro, R 2013	0.909	0.561	0.987	0.028
Singla, 2018	0.974	0.835	0.996	0.000
Weilert, 2015	0.994	0.955	0.999	0.000
Yague, 2009	0.950	0.525	0.997	0.042
	0.937	0.895	0.963	0.000



▶ **Fig. 3** Forest plot – treatment efficacy of endoscopic ultrasound-guided therapy. CI, confidence interval.

EUS-coil/glue had significantly fewer incidences of recurrence (5.2%, 95%CI 2.6–9.8, $I^2=0$, $P=0.01$) when compared with the other groups. The pooled results are summarized in ▶ **Table 1**.

Sensitivity analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. On this analysis, no single study significantly affected the outcome or the heterogeneity.

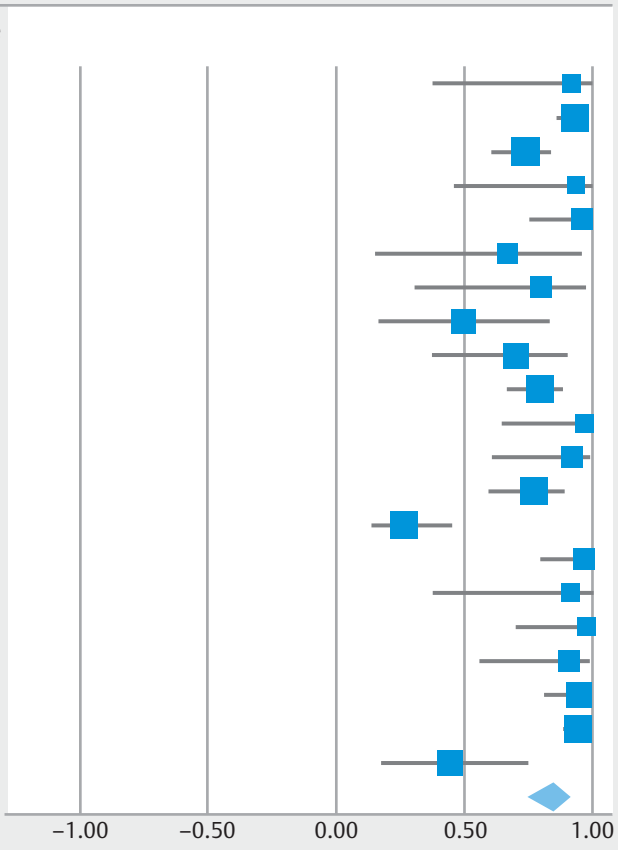
Heterogeneity

We assessed dispersion of the calculated rates using the PI and I^2 percentage values. The PI gives an idea of the range of the dispersion and I^2 tell us what proportion of the dispersion is true vs. chance [56]. The pooled rates of primary outcomes with EUS-guided therapy had narrow PIs with respect to the treatment efficacy rate (68.1–99). A wide PI was noted in the EUS-guided obliteration rate (16.7–99.4), recurrence rate (0.5–44.7), and late rebleeding rate (2.8–33.1). Subgroup analysis based on the publication status of the studies (full manuscripts and abstracts), primary and/or secondary prophylaxis treatment of gastric varices, and study quality (medium and high) did not change the outcomes or explain the heterogeneity. A meta-regression analysis based on the presence of underlying cirrhosis did not change the outcomes or explain the heterogeneity.

Publication bias

Based on visual inspection of the funnel plot, as well as quantitative measurement that used the Egger regression test, there was evidence of publication bias (Egger's two tailed $P=0.01$). Further statistics using the Fail-Safe N test and Duval and Tweedie's "Trim and Fill" test revealed that the impact of the possible publication bias appeared to be minimal and would not change the calculated estimate or the conclusion of the meta-analysis.

Study name	Event rate	Lower limit	Upper limit	*P*-value
Baptista, 2017	0.917	0.378	0.995	0.105
Bhat, 2016	0.930	0.860	0.966	0.000
Bick, 2018	0.737	0.608	0.835	0.001
Bick, 2018	0.938	0.461	0.996	0.064
Binmoeller, 2011	0.958	0.756	0.994	0.002
Frost, 2018	0.667	0.154	0.957	0.571
Frost, 2018	0.800	0.309	0.973	0.215
George, 2017	0.500	0.168	0.832	1.000
Khoury, 2019	0.700	0.376	0.900	0.220
Lee, 2000	0.796	0.668	0.883	0.000
Lobo, 2019	0.969	0.650	0.998	0.017
Lobo, 2019	0.923	0.609	0.989	0.017
Mathew, 2018	0.774	0.596	0.888	0.004
Mukkada, 2018	0.267	0.139	0.450	0.014
Robles-Medranda, 2018	0.967	0.798	0.995	0.001
Romero-Castro, R 2007	0.917	0.378	0.995	0.105
Romero-Castro, R 2013	0.975	0.702	0.998	0.011
Romero-Castro, R 2013	0.909	0.561	0.987	0.028
Singla, 2018	0.947	0.813	0.987	0.000
Weilert, 2015	0.945	0.889	0.973	0.000
Yague, 2009	0.444	0.177	0.749	0.739
	0.844	0.748	0.909	0.000



▶ **Fig. 4** Forest plot – gastric varices obliteration in endoscopic ultrasound-guided therapy. CI, confidence interval.

Discussion

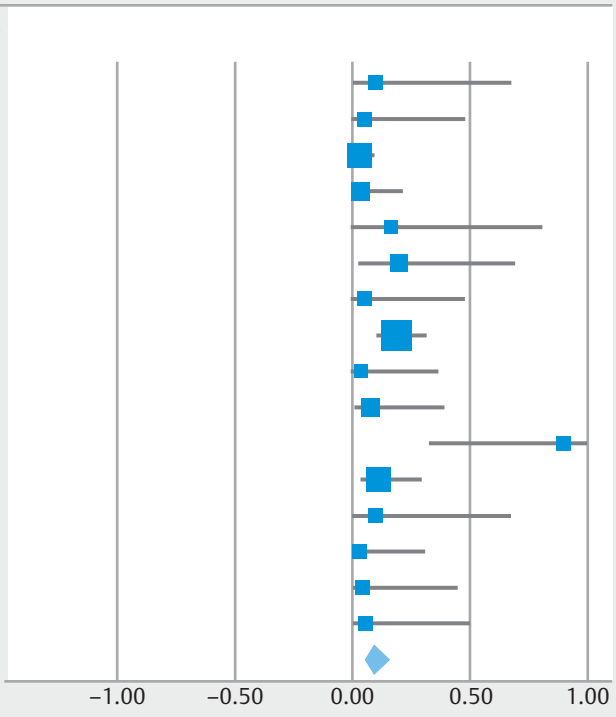
Based on current guidelines, endoscopic variceal ligation is the first-line treatment for GOV1 varices, and transjugular intrahepatic portosystemic shunt is the first-line treatment for GOV2 and IGV1 varices [57,58]. Tissue adhesive injection by endoscopy continues to be the conventional method of obliterating gastric varices [4,56,57]. The role of EUS in the treatment of gastric varices is not established but remains an area of active investigation. In this systematic review and meta-analysis of 23 studies and 851 patients, the pooled rate of gastric varices treatment efficacy with EUS-guided therapy was 94%, complete obliteration was 84%, recurrence was 9%, early rebleeding was 7%, and late rebleeding was 12%. EUS-guided therapy modalities included EUS-coil/glue, EUS-glue, EUS-coil, EUS-thrombin, EUS-coil/thrombin, and EUS-coil/gelatin foam.

The current study represents the first systematic review and meta-analysis evaluating the role of EUS-guided therapy for gastric varices, and puts the findings in perspective by comparing results with the pooled outcomes of END-glue therapy for gastric varices (28 studies, 3467 patients). Based on our analysis, the pooled treatment efficacy (94% and 91%, $P=0.4$), early rebleeding (7% and 5%, $P=0.7$), and late rebleeding (12% and 17%, $P=0.1$) were comparable between EUS-guided and END-glue groups. However, EUS-guided therapy was superior in terms of obliteration (84% vs. 63%, $P=0.02$), and almost reached superiority in the rate of recurrence (9% vs. 18%, $P=0.06$) when compared with END-glue therapy, limited most likely by the sample size.

Our subgroup analysis revealed that EUS-guided therapy with combined coil/glue had a pooled treatment efficacy rate of 97%, pooled obliteration rate of 86%, pooled recurrence rate of 5%, pooled early rebleeding rate of 8%, and pooled late rebleeding rate of 9%. The gastric varices recurrence rate and late rebleeding rate with EUS-coil/glue were the lowest among the subgroups. The combination of coil/glue appears to provide a more sustained treatment effect than that of glue alone, probably due to the fact that the coil concentrates and retains the glue at the site of coil deployment.

Our analysis of adverse events showed that the pooled rates of mild or moderate adverse events with EUS-guided therapy were approximately 6%. The most commonly reported events were sepsis and/or bacteremia, distant organ embolism, post-procedure fever, and post-procedure pain. The use of coil/glue in EUS-guided therapy of gastric varices has been postulated to reduce the incidence of glue-related distant organ embolism. However, based on our study, although the rate of distant organ embolism with EUS-glue was more than with EUS-coil/glue

Study name	Event rate	Lower limit	Upper limit	*P*-value
Baptista, 2017	0.100	0.006	0.674	0.140
Bazarbashi, 2019	0.050	0.003	0.475	0.042
Bhat, 2016	0.030	0.010	0.089	0.000
Bhat, 2016	0.036	0.005	0.214	0.001
Frost, 2018	0.167	0.010	0.806	0.299
Frost, 2018	0.200	0.027	0.691	0.215
Khoury, 2019	0.050	0.003	0.475	0.042
Lee, 2000	0.185	0.103	0.311	0.000
Lobo, 2019	0.033	0.002	0.366	0.019
Lobo, 2019	0.077	0.011	0.391	0.017
Orourke, 2018	0.900	0.326	0.994	0.140
Robles-Medranda, 2018	0.111	0.036	0.293	0.001
Romero-Castro, R 2007	0.100	0.006	0.674	0.140
Romero-Castro, R 2013	0.026	0.002	0.310	0.012
Romero-Castro, R 2013	0.045	0.003	0.448	0.035
Yague, 2009	0.056	0.003	0.505	0.052
	0.091	0.052	0.157	0.000



▶ **Fig. 5** Forest plot – gastric varices recurrence in endoscopic ultrasound-guided therapy. CI, confidence interval.

(8% and 4%, $P=0.33$), the difference failed to reach significance. There were a total of 115 deaths reported in the EUS-guided therapy cohorts, 32 of which were due to gastric variceal bleeding. The pooled rate of all-cause mortality with EUS-guided therapy was 13% and the pooled rate of mortality due to gastric variceal bleeding was approximately 8%. The all-cause and gastric variceal bleeding mortality rates were comparable to the pooled rates of END-glue cohort.

How does our study compare to other published works in the literature? A previous work by Bang et al. [6] published only in abstract form, compared direct endoscopic injection of cyanoacrylate glue into the gastric varices with EUS-guided injection of cyanoacrylate glue. The authors reported higher rates of recurrent rebleeding events and overall adverse events in the direct endoscopic injection group compared with the EUS group. In their comparative study, Bick et al. [11] showed a lower rate of gastric variceal rebleeding with EUS compared with direct endoscopic injection, with comparable adverse events, whereas the study by Lôbo et al. showed similar efficacy in the obliteration of varices [19]. Our late rebleeding rates with EUS-guided coil/glue therapy, when compared with END-glue therapy, are comparable to these studies. However, we are the first to report pooled data on recurrence and complete obliteration with either of the treatment modalities.

The strengths of this review are as follows: systematic literature search with well-defined inclusion criteria, careful exclusion of redundant studies, inclusion of good quality studies with detailed extraction of data, rigorous evaluation of study quality, and statistics to establish and/or refute the validity of the results of our meta-analysis. Overall heterogeneity was moderate for the outcomes of EUS-guided therapy. We used a comparator group comprising high quality studies using the current standard of care.

There are some limitations, however, most of which are inherent to any meta-analysis. The included studies were not entirely representative of the general population and community practice, with most studies being performed in tertiary-care referral centers. Our analysis included studies that were retrospective in nature, which contributes to selection bias. There is very limited precision in our estimates, as reflected in the wide confidence intervals, which are most likely due to limited sample sizes; limited and varied sample sizes and the number of included studies contributed to the observed heterogeneity. We were not able to analyze our results based on the severity of cirrhosis in terms of the Child – Pugh and/or Model for End-stage Liver Disease score. We were not able to ascertain predictors of treatment success and/or failure in terms of the etiology, varix type, and/or size, and the differences in types of glue.

In conclusion, EUS-guided therapy demonstrated treatment efficacy in 94% of patients compared with 91% of patients treated with END-glue. However, EUS-guided therapy seemed to be superior to END-glue therapy in terms of gastric varices obliteration, and EUS-guided therapy with coil/glue was superior in terms of recurrence. Furthermore, EUS-coil/glue, in particular, appeared to be the best modality, although this is

the least commonly performed procedure given the need for specialized equipment and training.

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Competing interests

The authors declare that they have no conflict of interest.

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