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EUS–guided therapies for primary and secondary prophylaxis in gastric varices—An updated systematic review and meta-analysis

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ABSTRACT

Background and Objectives: Gastric varices (GVs) are associated with a higher risk of uncontrolled bleeding and death when compared with esophageal varices. While endoscopic glue injection therapy has been traditionally used for secondary prophylaxis in GV, data regarding primary prophylaxis continue to emerge. Recently, EUS–guided therapies have been used in GV bleeding.

Methods: We conducted a comprehensive search of several major databases from inception to June 2022. Our primary goals were to estimate the pooled rates of treatment efficacy, GV obliteration, GV recurrence, and rebleeding with EUS-guided therapy in primary and secondary prophylaxis. Overall adverse events and technical failures were assessed. Random-effects model was used for our meta-analysis, and heterogeneity was assessed using the I^2 % statistics.

Results: Eighteen studies with 604 patients were included. In primary prophylaxis, pooled rate of GV obliteration was 90.2% (confidence interval [CI], 81.1–95.2; $I^2 = 0$). With combination EUS–glue and coil therapy, the rate was 95.4% (CI, 86.7%–98.5%; $I^2 = 0$). Pooled rate of posttherapy GV bleeding was 4.9% (CI, 1.8%–12.4%; $I^2 = 0$). In secondary prophylaxis, pooled rate of treatment efficacy was 91.9% (CI, 86.8%–95.2%; $I^2 = 12$). With EUS-glue, EUS-coil, and combination EUS–glue and coil, the rates were 94.3% (CI, 88.9%–97.1%; $I^2 = 0$), 95.5% (CI, 80.3%–99.1%; $I^2 = 0$), and 88.7% (CI, 76%–95.1%; $I^2 = 14$), respectively. Pooled rate of GV obliteration was 83.6% (CI, 71.5%–91.2%; $I^2 = 74$). With EUS-glue, EUS-coil, and combination EUS–glue and coil, the rates were 84.6% (CI, 75.9%–90.6%; $I^2 = 31$), 92.3% (CI, 81.1%–97.1%; $I^2 = 0$), and 84.5% (CI, 50.8%–96.7%; $I^2 = 75$), respectively. Pooled rates of GV rebleeding and recurrence were 18.1% (CI, 13.1%–24.3%; $I^2 = 16$) and 20.6% (CI, 9.3%–39.5%; $I^2 = 66$), respectively.

Conclusion: Our analysis shows that EUS-guided therapy for GVs is technically feasible and clinically successful in both primary and secondary prophylaxis of GV.

Key words: EUS; Gastric varices; Variceal hemorrhage

BACKGROUND

Gastroesophageal variceal bleeding is a major complication of portal hypertension, especially in patients with cirrhosis, and accounts for 10% to 30% of all cases of bleeding from the upper gastrointestinal tract.[1] Development and growth of gastroesophageal varices each occur at a rate of approximately 7% per year among patients with cirrhosis.[2] While gastric varices (GVs) account for approximately 20% of all variceal bleeds, they are associated with more risk of uncontrolled bleeding, higher transfusion requirements, and higher rates of rebleeding and death when compared with esophageal varices.[3,4] According to the Sarin classification, GVs are categorized as gastroesophageal varices type 1 (GOV1), which extend over the cardia and lesser curvature, gastroesophageal varices type 2 (GOV2), which represent a continuation of esophageal varices (EVs) into the fundus of the stomach, isolated GV type 1 (IGV1), which are in the fundus of the stomach and isolated GV type 2 (IGV2), located anywhere in the stomach. Whereas GOV1 represents 75% of all the GVs, GOV2, IGV2, and IGV1 represent 21%, 4%, and less than 2%, respectively.

Gastric varices are further classified as primary and secondary GVs. Primary GVs are varices noted on initial endoscopic examination, before any therapy being performed. These are present in approximately 17% of patients with cirrhosis, and the prevalence is higher in bleeders than in nonbleeders: 24% versus 7%. Secondary GVs appear for the first time after therapy for esophageal

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varices has been applied and are seen in approximately 9% of patients with portal hypertension.[5] This classification has therapeutic implications as current guidelines recommend endoscopic therapy with tissue adhesives such as *N*-butyl-cyanoacrylate or thrombin as the preferred definitive modality for GV bleeding, that is, secondary prophylaxis. However, guidelines have not supported any form of treatment for primary prophylaxis for GV.[6,7]

Over the past few years, several EUS–guided options for both primary and secondary prophylaxis for GV have been reported. These include EUS-guided *N*-butyl-cyanoacrylate or glue therapy (EUS-glue), EUS-guided coil embolization (EUS-coil), EUS-guided sclerotherapy, EUS-guided thrombin injection, and EUS-coil injection with simultaneous use of glue (EUS-coil/glue). Although several previous studies have reported on the safety and efficacy of these approaches,[8–10] a global understanding of their overall efficacy is lacking.

We conducted an updated systematic review and meta-analysis to assess the safety and efficacy of EUS-guided treatments for both primary and secondary prophylaxis in GV.

METHODS

Search strategy

A comprehensive search of several databases from 2009 to May 24, 2019, limited to English language only and excluding animal studies, was conducted to evaluate for studies reporting on the outcomes of EUS-guided therapies in patients with GV. The same search was updated on June 13, 2022. The databases used (and their content coverage) is Ovid MEDLINE (1946 + and Epub Ahead of Print, In-Process, and Other Non-Indexed Citations), Ovid EMBASE (1988+), Ovid Cochrane Central Register of Controlled Trials (1991+), Ovid Cochrane Database of Systematic Reviews (2005+), and Scopus via Elsevier (1778+).

The search strategy was designed and conducted by a medical librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used. The full search strategy is available in Appendix 1, http://links.lww.com/ENUS/A338. In the case of non-English studies, electronic language translation service was used to convert the text to English.

As the included studies were observational in design, the MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist was followed[11] and is provided as Supplementary Appendix 2, http://links.lww.com/ENUS/A338. The quality of evidence presented in the randomized controlled trials (RCTs) was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology, outlined in Appendix 3 and Supplementary Figure 1, http://links.lww.com/ENUS/A338.[12] Reference lists of evaluated studies were examined to identify other studies of interest. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart for study selection is provided as Supplementary Figure 2, http://links.lww.com/ENUS/A338. Reference lists of evaluated studies were examined to identify other studies of interest.

Study selection

In this meta-analysis, we included studies that reported on the use of EUS-guided treatment modalities for GV as either a primary or secondary prophylaxis approach. Studies in which outcomes of EUS-guided therapies were reported either by themselves or in combination with outcomes of conventional endoscopic therapies were included in our analysis. Studies were included irrespective of patients with underlying liver cirrhosis, inpatient/outpatient setting, geography, and abstract/manuscript status, as long as they provided data needed for the analysis.

The following were our exclusion criteria[1]: studies reporting on only endoscopic guided therapy of GV[2] individual case reports,[3] studies performed in the pediatric population (age <18 years),[4] and studies that did not provide clear data on outcomes of interest (primary, secondary prophylaxis management of GV by EUS-guided treatment modalities).

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. Primary study authors were contacted via email in cases where any study-related clarification was needed.

Data abstraction and quality assessment

Data on study-related outcomes in the individual studies were abstracted onto a standardized form by at least 2 authors (S.C., B.P.M.), and 2 authors (B.P.M., D.R.) independently performed the quality scoring using the Newcastle-Ottawa scale.[13] The details can be found in Supplementary Table 1 (http://links.lww.com/ENUS/A338).

Outcomes assessed

I. In patients undergoing EUS-guided therapies for primary prophylaxis:

(1) Pooled rate of complete variceal obliteration, as confirmed by follow-up endoscopic and EUS examination

(2) Pooled rate of posttherapy GV bleeding as observed during the follow-up period

(3) Pooled rate of technical failures, defined as failure to successfully perform EUS-guided therapy

II. In patients undergoing EUS-guided therapies for secondary prophylaxis:

(1) Pooled rate of treatment efficacy, defined as complete cessation of bleeding during index procedure

(2) Pooled rate of complete variceal obliteration, as confirmed by follow-up endoscopic and EUS examination

(3) Pooled rate of GV rebleeding, including early and late rebleeding

(4) Pooled rate of GV recurrence as seen on follow-up endoscopic examination

(5) Pooled rate of technical failures, defined as failure to successfully perform EUS-guided therapy

In addition, where permissible, the results were further classified based on the type of EUS-guided treatment performed. Other outcomes assessed were the mean number of EUS-guided sessions performed, mean number of coils deployed, mean volume of cyanoacrylate (CYA) glue injected, overall pooled rate of adverse events, and overall pooled rate of rescue interventions needed.

Comparison of outcomes between EUS-guided versus endoscopic therapies

Statistical analysis

We used meta-analysis techniques to calculate the pooled estimates and relative risk (RR) in each case following the methods suggested by DerSimonian and Laird using the random-effects model.[14] 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.[15] We assessed heterogeneity between study-specific estimates by using the Cochran Q statistical test for heterogeneity, 95% confidence interval (CI), which deals with the dispersion of the effects,[16–18] and the I^2 statistics.[19] In this, values of <30%, 30% to 60%, 61% to 75%, and >75% were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively.[20] Publication bias was ascertained, qualitatively, by visual inspection of funnel plot and quantitatively, by the Egger test.[21] When publication bias was present, further statistics using the fail-safe N test and Duval and Tweedie's "trim and fill" test was used to ascertain the impact of the bias.[22]

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

RESULTS

Search results and population characteristics

Our initial search yielded 1706 results. After deduplication, 212 records were screened, and 172 full-length articles were assessed for eligibility. Eighteen studies (comprised of 27 cohorts) with 604 patients were included in our final analysis. Nine cohorts who were treated for primary prophylaxis, 13 for secondary prophylaxis and 5 cohorts reporting on combined primary + secondary prophylaxis outcomes were included in our analysis. EUS–guided therapies for primary GV prophylaxis were performed in 162 patients, whereas secondary prophylaxis for active and recent bleeding from GV was performed in 442 patients.

EUS–guided glue injection as monotherapy was performed in 4 studies,[23–26] EUS-coils were deployed as monotherapy in 5 studies,[24,27–30] combination EUS-coil + glue was performed in 9 studies,[26,28,30–36] EUS-guided thrombin injection was used in 1 study,[37] EUS-guided sclerosant (ethanolamine oleate) injection was used in 1 study[38] and EUS-guided coils and absorbable hemostatic gelatin sponge were used in 2 studies.[39,40]

There were 47 patients with GOV1, 190 patients with GOV2, 297 with IGV1, and 6 patients with IGV2. Overall, 348 male and 218 female patients were included in our analysis. Two studies did not report on patient sex. Follow-up time period ranged from 1.3 to 57 months.

Further study details including the type of EUS-modality used, number of sessions, volume of glue/number of coils deployed, and outcomes are reported in Tables 1 and 2.

Characteristics and quality of included studies

Two RCTs along with 6 case series[29,31,35,38–40] and 9 retrospective studies were included in our analysis. One RCT compared the outcomes of EUS-coil and EUS-coil + glue therapy,[28] whereas in the other, patients were randomized to EUS-guided or routine endoscopic-guided glue therapy.[32] Based on the Newcastle-Ottawa assessment system for study quality, there were 6 high-quality and 10 medium-quality studies. There were no low-quality studies in our analysis. Based on risk-of-bias assessment, the overall certainty of evidence was graded as high (grade A). The detailed assessment of study quality is given as Table 1 and Figure 2 in supplementary material, http://links.lww.com/ENUS/A338.

Meta-analysis outcomes

I. For patients undergoing EUS-guided treatment for primary prophylaxis:

(1) Pooled rate of complete variceal obliteration. The overall pooled rate of gastric variceal obliteration was 90.2% (95% CI, 81.1%–95.2%; I^2 = 0) [Figure 1]. Among patients undergoing combination EUS–glue and coil therapy, the rate was 95.4% (95% CI, 86.7%–98.5%; I^2 = 0).

(2) Pooled rate of posttherapy GV bleeding. The overall pooled rate of posttherapy bleeding was 4.9% (95% CI, 1.8%–12.4%; I^2 = 0) [Figure 2]. None of the patients had early (<48 hours) rebleeding. All patients who presented with GV bleeding did so more than 30 days after the index procedure.

(3) Pooled rate of technical failures. The overall pooled rate of technical failures was 10.1% (95% CI, 4.2%–22.6%; I^2 = 0) [Figure 3].

II. For patients undergoing EUS-guided treatment for secondary prophylaxis:

(1) Pooled rate of treatment efficacy. The overall pooled rate of treatment efficacy was 91.9% (95% CI, 86.8%–95.2%; I^2 = 12) [Figure 4]. Among patients undergoing EUS-glue,[23–26] EUS-coil,[28–30] and combination EUS–glue and coil,[27,28,30,31,35] the rates were 94.2% (95% CI, 88.9%–97.1%; I^2 = 0), 95.5% (95% CI, 80.3%–99.1%; I^2 = 0), and 88.7% (95% CI, 76%–95.1%; I^2 = 14), respectively.

(2) Pooled rate of complete variceal obliteration. The overall pooled rate of variceal obliteration was 83.6% (95% CI, 71.5%–91.2%; I^2 = 74; Supplementary Figure 3, http://links.lww.com/ENUS/A338). Among patients undergoing EUS-glue,[23–25] EUS-coil,[28–30] and combination EUS–glue and coil,[27,28,30,31,33] the rates were 84.6% (95% CI, 75.9%–90.6%; I^2 = 31), 91.6% (95% CI, 78.6%–97%; I^2 = 0), and 84.5% (95% CI, 50.8%–96.7%; I^2 = 75), respectively.

(3) Pooled rate of GV rebleeding. The overall pooled rate of variceal rebleeding was 18.1% (95% 13.1%–24.3%; I^2 = 16; Supplementary Figure 4, http://links.lww.com/ENUS/A338). Ten patients experienced early rebleeding, and 36 patients experienced late rebleeding.

(4) Pooled rate of GV recurrence. The overall pooled rate of GV recurrence on follow-up examination was 20.6% (95% CI, 9.3%–39.5%; I^2 = 66; Supplementary Figure 5, http://links.lww.com/ENUS/A338).

(5) Pooled rate of technical failures. The overall pooled rate of technical failure was 7.3% (95% CI, 3.3%–15.2%; I^2 = 33; Supplementary Figure 6, http://links.lww.com/ENUS/A338).

Among studies reporting outcomes of EUS-coil therapy, the mean number of coils used to achieve GV obliteration was 3 (95% CI, 2.6–3.5; I^2 = 96) (range, 1–8 coils). Among patients who were

Table 1

Study population characteristics

Study	Design	Type of Prophylaxis	Total n	EUS Modality Used (Coil/Glue/ Combination)	Volume/No. Coils	Volume/No. Coils	GV Type	No. Sessions	Male/ Female	Age, y
Lee et al,[23] 2000	Prospective, single center, July 1996 to October 1998, China	Secondary	54	EUS-glue	Median 3 doses of CYA (1–8)	NA	GOV1 20, GOV2 18, IGV1 16	2.2 ± 1.7	34/20	61 ± 14
Romero-Castro et al,[24] 2013	Retrospective, multicenter, February 2008 to May 2012, Spain and Germany	Primary/secondary (7/23)	30–19 (CYA); 11 (coil)	EUS-glue/EUS-Coil	1 mL/session (mean, 1.5 ± 0.1 mL; range, 1–3 mL)/ mean of 5.8 ± 1.2 coils (range, 2–13)	1.5 ± 0.1/ 5.8 ± 1.2	IGV1 15, GOV2 14, GOV1 1	1.4 ± 0.1 (range, 1–3)	22/8	60.6 ± 8.7
Gubler and Bauerfeind,[25] 2014	Retrospective, single center, 2006 to 2013, Switzerland	Primary Secondary	4/40 36/40	EUS-glue	1.9 mL (range, 1–10)	3.7 ± 2.6 (vol)	IGV1	2.7 ± 1.8	25/15	65 (14–79)
Bick et al,[26] 2019	Retrospective, single center, January 2013 and November 2017, USA	Primary Secondary	7 57	EUS-glue (62), glue + coil (2)	2 mL ± 0.8/2 coils	2 ± 0.8/2 ± 1	IGV1:30, GOV1: 2, GOV2: 32	1.2 ± 0.2	33/31	58.0 ± 12.5
Frost and Hebbar,[37] 2018	Retrospective, single center, October 2013 and January 2017, Ireland	Primary Secondary	5 3	EUS-thrombin EUS-thrombin	600–5000 IU of thrombin 4250–10,000 IU of thrombin	NA	GOV2: 4, IGV1: 4	NR NR	3/0 4/1	61.8 ± 10 61.8 ± 10
Mukkada et al,[27] 2018	Retrospective, single center, October 2013 to December 2016, India	Secondary	30	EUS-glue or coil	2 mL (1–10)/1–6 coils (1 [7n], 2 [13n], 3 [5n], 4 [3n], 5 [1n], 6 [1n])	3.75 ± 2.6/ 2.3 ± 1.5	GOV1: 12, GOV2: 8, IGV1: 10	"Multiple"	NR	57.5 ± 12.7
Khoury et al,[31] 2019	Case series, single center, March 2015 and March 2018, Israel	Secondary	10	EUS-glue + coil	1–2 mL/2–8 coils	1.5 ± 0.3/ 1.8 ± 1.5	GOV1: 2, GOV2: 5, IGV1: 3	1–4	7/3	46.7 ± 19.3
Lôbo et al,[32] 2019	Randomized controlled trial, single center, November 2014 to December 2016, Brazil	Primary + secondary (6/10)	16	EUS-glue + coil	1.40 ± 0.74 mL/1–3 coils (11/2/2)	1.4 ± 0.74/ 1.4 ± 0.5	GOV2 13, IGV1 3	1 session—6/16, 2 sessions—4/15	8/8	49.3 ± 14.8
Bazarbashi et al,[39] 2020	Retrospective, case series, single center, October 2017 and November 2018, USA	Secondary	10	EUS-coil/gelatin sponge	2.5 ± 0.7 mL absorbable sponge/ 8 ± 2.9 coils	2.5 ± 0.7/ 8 ± 2.9	GOV2: 3, IGV1: 7	NR	4/6	64 ± 11.5
Irisawa et al,[38] 2020	Prospective, single center, case series, Japan	Primary	8	EUS-guided coil with sclerotherapy	7.8 mL ± 6.7/5.6 ± 2.9 coils	7.8 ± 6.7/ 5.6 ± 2.9	IGV1	1.9 ± 1.0	6/2	69 ± 9
Koziel et al,[33] 2019	Retrospective, single center, Poland	Primary Secondary	6 10	EUS-glue + coil	2 mL (1–9)/1.7 (1–3) coils	3.5 ± 2.3/ 1.85 ± 0.6	GOV2 8, IGV1 6, IGV2 2	5	9/7	51 (29–75)
Robles-Medranda et al,[28] 2020 (a)	Randomized controlled trial, single center, March 2016 to October 2018, Ecuador,	Primary Secondary	4/30 21/30	EUS-coil	3 (1–7) coils	3.5 ± 1.7	GOV2 12, IGV 1 18	NR	19/11	61.6 (12.3)
Robles-Medranda et al,[28] 2020 (b)	Randomized controlled trial, single center, March 2016 to October 2018, Ecuador,	Primary Secondary	3/30 26/30	EUS-glue + coil	1.8 mL (1.2–2.4)/2 (1–3) coils	1.8 ± 0.4/ 2 ± 0.6	GOV2 19, IGV1 11	NR	16/14	61.8 (7.8)
Kouanda et al,[34] 2021	Retrospective, single center, June 2009 and December 2019, USA	Primary	80	EUS-glue + coil	2 mL (0.5–5)/1.5 (1–3) coils	2.4 ± 1.3/ 1.75 ± 0.6	IGV1 69, GOV2 8, GOV1 3	1.3 ± 0.5	55/25	60.5 ± 10.4
Mosquera-Klinger et al,[29] 2021	Retrospective, single center, case series, June 2014 to June 2018, Colombia	Secondary	4	EUS-guided hydrocoils	2 coils	2 ± 0.5	NR	NR	3/1	37 ± 12
Seven et al,[30] 2022 (a)	Retrospective, single center, January 1, 2011, and January 31, 2021, Turkey	Primary Secondary	8 11	EUS-coil	5 (3–9)	5.5 ± 1.7	— GOV2 8, IGV1 3	NR NR	— 7/4	55.9 ± 12.9

Seven et al,[30] 2022 (b)	Retrospective, single center, January 1, 2011, and January 31, 2021, Turkey	Secondary	9	EUS-glue + coil	5 (3–9)	5.5 ± 1.7	GOV2 7, IGV1 2	NR	5/4	52.1 ± 13.4
Alali et al,[35] 2022	Retrospective, case series, single center, October 2017 to October 2021, Kuwait	Primary + secondary (5/10)	15	EUS-glue + coil	1.5 mL (0.74)/1.5 (1.4) coils	1.5 ± 0.74/ 1.5 ± 1.4	GOV2 12, IGV1 3	1.25 ± 0.38	12/3	58 (12)
Bazarbashi et al,[40] 2022 (abs)	Retrospective case series, single center, 2018–2021, USA	Primary + secondary (11/68)	79	EUS-coils/coil/gelatin sponge	2.5 mL ± 2.05/4.29 ± 3.27 coils	2.5 ± 2.0/ 4.29 ± 3.27	IGV1 49, IGV2 4, GOV1 7, GOV2 19	NR	44/35	60.3 ± 13
Samanta et al,[36] 2022 (abs)	Prospective, multicenter, India-Italy	Primary + secondary (8/44)	52	EUS-glue + coil	2 mL (1–3)/2 (1–3) coils	2 ± 0.6/ 2 ± 0.6	NR	1 +/− 0.25	32/20	48.59 ± 13

abs, Abstract; CYA, cyanoacrylate; GV, gastric varices; IGV1, isolated gastric varices type 1; IGV2, isolated gastric varices type 2; GOV1, gastroesophageal varices type 1; GOV2, gastroesophageal varices type 2; NR, not reported.

treated with EUS-glue therapy, a mean volume of 2.1 mL of glue was used per patient (95% CI, 1.8–2.3 mL; I^2 = 93), ranging from 1.4 to 3.6 mL. The mean number of sessions to achieve GV obliteration was 1.4 (95% CI, 1.2–1.6; I^2 = 96) (range, 1–5 sessions).

Across all studies, the pooled rate of GV obliteration was 87% (95% CI, 78.8%–92.4%; I^2 = 72) and of GV recurrence was 12.3% (95% CI, 6.5%–22.2%; I^2 = 96). The overall pooled rate of adverse events was 11.9% (95% CI, 6.6%–20.3%; I^2 = 96), and the pooled rate of patients needing rescue or salvage therapy was 7.7% (95% CI, 4.8%–12.2%; I^2 = 0). Among these, 7 patients underwent transjugular intrahepatic portosystemic shunt, 3 patients required liver transplantation, 2 patients underwent creation of a distal splenorenal shunt, and 1 patient underwent balloon-occluded retrograde transvenous obliteration.

III. Comparison of EUS-guided vs conventional endoscopic therapy

Overall, 2 prospective,[23,36] 2 retrospective,[26,27] and 1 RCT[32] reported outcomes of EUS-guided verses conventional endoscopic therapies. Details of the studies are summarized in Table 3. Although there was no statistical difference between the rates of primary hemostasis (RR, 1.0 [95% CI, 0.97–1.034]; I^2 = 0; P = 0.84) and overall adverse events (RR, 0.869 [95% CI, 0.445–1.695]; I^2 = 47.32; P = 0.680), EUS-guided therapies resulted in a significantly lesser incidence of GV rebleeding compared with conventional endoscopic therapy (RR, 0.44 [95% CI, 0.31–0.62]; I^2 = 0; P < 0.001; Supplementary Figures 7–9, http://links.lww.com/ENUS/A338).

VALIDATION OF META-ANALYSIS RESULTS

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. Upon conclusion of the sensitivity analysis, we concluded that no single study significantly affected the outcomes for primary and secondary prophylaxis or the heterogeneity.

Heterogeneity

We assessed the dispersion of the calculated rates using the I^2 percentage values as reported in the meta-analysis outcomes section. We found low heterogeneity among all pooled outcomes for primary prophylaxis. Substantial heterogeneity was noted in pooled rates of GV obliteration and recurrence among patients undergoing secondary prophylaxis. Although there was low heterogeneity noted for GV obliteration rates with EUS-glue and EUS-coil–based therapy, combination glue and coil therapy continued to have substantial heterogeneity. This can likely be explained by the type of GV treated and the varying numbers of sessions performed, volume of glue injected by different users, and the different numbers of coils used in different patients and studies.

Publication bias

Based on visual inspection of the funnel plot as well as quantitative measurement that used the Egger regression test, there was no evidence of evidence of publication bias (z = −1.78, P = 0.18; Supplementary Figure 10, http://links.lww.com/ENUS/A338.

DISCUSSION

Our analysis shows that EUS-guided therapy for GVs is technically feasible and clinically successful in both primary and secondary

Table 2

Study outcomes and adverse events

Study	Treatment Efficacy	GV Obliteration (GV Subtypes or Interventions)	Technical Failure	Rebleeding			GV Recurrence	Rescue Therapy	Adverse Events	Follow-up, mo
				Total	Early (Time)	Late (Time)				
Lee et al,[23] 2000	52/54	43/54 (14/20, 14/18, 15/16)	11/54	14/54	4/14 (<48 h)	10/14 (>48 h)	14/54	4 (TIPS 2, DSRS 2)	0/54	24
Romero-Castro et al,[24] 2013	19/19 (Secondary)	29/30 (CYA19/19, coil 10/11)	1/30	0/30	—	—	0/11	—	12/30 (Fever 1, CP 1, EV bleed 1, glue PE 9)	17.2 ± 1.8 (6–41)
Gubler and Bauerfeind,[25] 2014	—	3/4	1/4	—	—	—	NR	6 (TIPS/OLT 3, others 3)	2/40 (GI bleed 1, bacteremia 1)	38
	36/36	30/36	0/36	6/36	0/36	6/36 (NR)				
Bick et al,[26] 2019	—	49/64	15/64	—	—	—	NR	1 (BRTO)	13/64 (Abdominal pain 5, fever 3, hypoxia 1, HE 1, splenic infarct 1, PE 1, bacteremia 1)	6.4 (1–36.3)
	52/57			5/57	3/57 (<30d)	2/57 (>30d)				
Frost and Hebbar,[37] 2018	—	4/5	1/5	0/5	0/5	0/5	NR	—	0/5	12
	2/3	2/3	1/3	1/3	1/3	0/3	NR	1 (TIPS)	0/3	
Mukkada et al,[27] 2018	24/30	8/20	0/30	6/30	0/30	6/30	NR	NR	0/30	1, 6, and 12
Khoury et al,[31] 2019	10/10	7/10	0/10	0/10	0/10	0/10	0/10	0/10	11/30 (Major bleeding 1, Minor bleeding 10)	9.7 (1–28)
Lôbo et al,[32] 2019	—	15/15	0/15	0/15	—	—	0/15	0/15	13 (Epigastric pain 7, PE 4, mild bleeding 2)	9.9 (1–26)
Bazarbashi et al,[39] 2020	10/10	10/10	0/10	0/10	—	—	0/10	0/10	2 (Postprocedure pain 1, fever 1)	6.4 ± 3.6
Irisawa et al,[38] 2020	—	7/8	1/8	1/8	0/8	1/8	1/8	0/8	0/8	57 (median) (3–67)
Koziel et al,[33] 2019	—	6/6	1/16	0/6	0/6	0/6	NR	—	6 (Pain 3, fever 2, minor bleeding 1)	10.7 (5.9–14.5)
	—	10/10		1/10	0/10	1/10	NR			
Robles-Medranda et al,[28] 2020 (a)	—	3/4	0/4	—	—	—	NR	NR	1/30 (Pain)	14.5 (range, 0.6–31.2)
	21/21	24/26	0/26	7/26	—	7/26	12/26			
Robles-Medranda et al,[28] 2020 (b)	—	3/3	0/3	—	—	—	NR	NR	2/30 (Pain 1, fever 1)	14.5 (range, 0.6–31.2)
	26/26	27/27	0/27	1/27	—	1/27	3/27			
Kouanda et al,[34] 2021	—	60/62	0/80	2/80	0/80	2/80	2/62	0/80	4 (PE 2, pain 2)	36 ± 28.8
Mosquera-Klinger et al,[29] 2021	4/4	4/4	0/4	0/4	0/4	0/4	NR	0	0/4	1.3–2.8
Seven et al,[30] 2022 (a)	—	8/8	0/8	—	—	—	—	—	1/19 (Retrosternal pain)	13.2 (range, 2.5—28.7)
	11/11	10/11	1/11	2/11	1/11	1/11	—	—		
Seven et al,[30] 2022 (b)	8/9	9/9	0/9	3/9	1/9	2/9	—	1/9 (TIPS)	1/9 (Fever)	12.6 (range, 1.6–42.2)
Alali et al,[35] 2022	10/10	15/15	0/15	0/15	0/15	0/15	0/15	0/15	1/15 (Pain)	5.7 (7.2)
Bazarbashi et al,[40] 2022 (abs)	68/79	39/53	0/79	13/79	1/79	12/79	12/79	NR	6 (Bleeding 1, systemic embolization 2, fever 2, pain 1)	2.46 (±2.21)
Samanta et al,[36] 2022 (abs)	52/52	48/52	NR	8/52	—	8/52	NR	NR	0/52	23.1 (IQR, 14.5)

abs, Abstract; BRTO, balloon-occluded retrograde transvenous obliteration; CYA, cyanoacrylate; DSRS, distal splenorenal shunt; EV, esophageal varices; GOV1, gastroesophageal varices type 1; GOV2, gastroesophageal varices type 2; GV, gastric varices; IGV1, isolated gastric varices type 1; IGV2, isolated gastric varices type 2; IQR, interquartile range; NR, not reported; TIPS, transjugular intrahepatic portosystemic shunt.

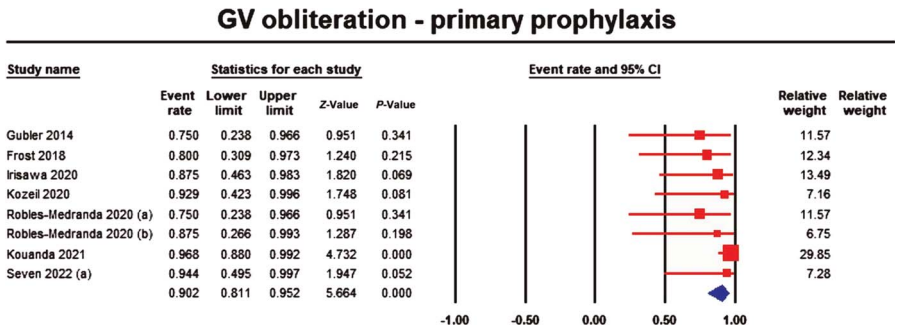

Figure 1. Forest plot, pooled rate, GV obliteration (primary prophylaxis). GV, gastric varices.

prophylaxis. We found that whereas the pooled rate of GV obliteration with combination EUS–glue and coil therapy was 95.4%, across all EUS-guided therapies, the pooled rate of successful GV obliteration was 90.2%. For secondary prophylaxis, EUS-guided therapies had treatment efficacy between 88.8% and 95.5%. Although endoscopic management of nonbleeding, actively bleeding or recently bled GVs can be technically challenging, our findings suggest that EUS-guided treatment is effective in all of the studied clinical scenarios.

Mortality associated with gastric variceal bleeding can be as high as 20% within 6 weeks of an index bleeding episode.[41] For secondary prophylaxis, consensus guidelines recommend endoscopic therapy with tissue adhesives such as *N*-butyl-cyanoacrylate or thrombin for IGV1 and GOV2, and endoscopic variceal ligation or tissue adhesive for bleeding GOV1.[7] A recent network meta-analysis showed that balloon-occluded retrograde transvenous obliteration was associated with a lower risk of rebleeding from GV when compared with β-blockers and endoscopic glue injection. For primary prophylaxis, however, although pharmacotherapy with nonselective β-blockers is recommended,[7,42] their use has not been shown to reduce the incidence or mortality of first bleeding from GV.[43] As such, therapeutic options for primary prophylaxis are not well established.

Endoscopic glue injection has shown efficacy in 70% to 90% of patients across published studies.[44,45] Gastric varices recurrence and rebleeding have been reported in as many as 20% to 30% of the patients undergoing glue injection.[46,47] In addition, CYA injection has been shown to cause site injection ulcers and lead to systemic adverse events such as cerebral stoke, splenic infarction, pulmonary emboli, and death.[48,49] In recent years, EUS-guided therapies including injection of coils alone, glue alone, or both in combination have been extensively reported in literature for GV bleeding. Although several studies and meta-analysis have shown high rates of GV obliteration and low rates of recurrence with these therapies,[8–10] cumulative outcomes based on clinical scenario, that is, primary or secondary prophylaxis, have not yet been evaluated.

In our analysis, we found that the overall rates of GV obliteration in patients undergoing primary and secondary prophylaxis were 90.2% and 84%, respectively. Successful hemostasis was achieved in 91.9% of patients, and the pooled rate of GV bleeding after successful primary prophylaxis was low at 4.9%. In addition, the rate of rebleeding after secondary prophylaxis across all studies was 18.1%. We found an overall pooled rate of adverse events of 11.9%, which included 11 patients with postprocedure fever, 24 patients with chest and/or abdominal pain, and 16 patients with pulmonary/systemic embolism. When comparing outcomes of EUS-guided and conventional endoscopic therapies, we found no statistical difference between the rates of primary hemostasis (RR, 1.0 [95% CI, 0.97–1.034]; $I^2 = 0$; $P = 0.84$) and overall adverse events (RR, 0.869 [95% CI, 0.445–1.695]; $I^2 = 47.32$; $P = 0.680$). Interestingly, EUS-guided therapies resulted in a significantly lesser incidence of GV rebleeding compared with conventional endoscopic therapy (RR, 0.45 [95% CI, 0.31–0.665]; $I^2 = 0$; $P < 0.001$).

Therapeutic gain from EUS-guided therapies must be weighed against the cost difference from conventional endoscopic therapy. Romero-Castro et al[24] reported that the average cost of 1 mL Histoacryl/Lipiodol was US $72.30, whereas that of one coil, independent of the length, was US $99.40. Furthermore, Kouanda et al[34] reported that based on the 2020 Medicare fee schedule,

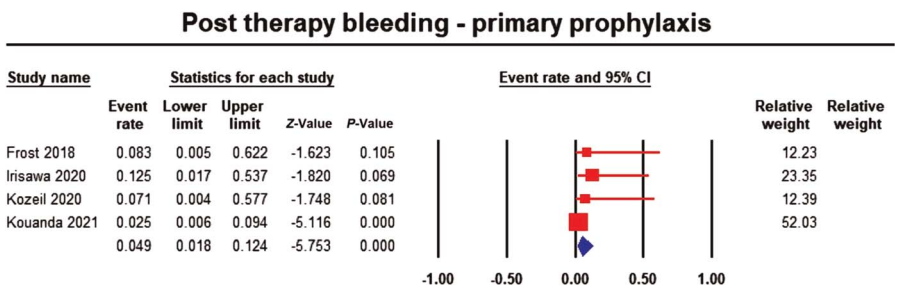

Figure 2. Forest plot, pooled rate, posttherapy GV bleeding (primary prophylaxis). GV, gastric varices.

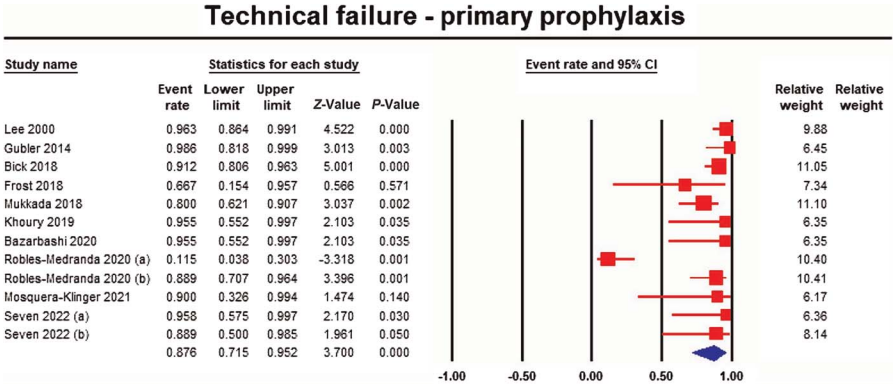

Figure 3. Forest plot, pooled rate, technical failures (primary prophylaxis).

the estimated cost of EUS-guided coil and CYA injection was $1831 (facility fee, $1557; physician fee, $274), and the cost of inpatient hospitalization for GV bleeding was $11,078. Although a comparative cost analysis between EUS-guided and conventional endoscopic therapy was beyond the scope of our study, future cost-effectiveness studies will be important to understand the economic value of EUS-guided interventions in comparison to endoscopic therapy, especially in resource-limited countries.

Our meta-analysis has several strengths. These include a thorough, updated, and 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. We reported separate outcomes for EUS-based therapies as they apply to primary and secondary prophylaxis in GV. This is particularly important as intervention is likely be more challenging in cases with active GV bleeding when compared with nonbleeding GV. Where permissible, we calculated pooled outcomes based on the type of EUS-based therapy used. A majority of our meta-analysis outcomes had low heterogeneity suggesting minimal between-study variability. Finally, we performed subgroup analysis to compare the outcomes of EUS-guided and conventional endoscopic therapy based on double-arm comparative studies. Although there was no statistical difference between the rates of primary hemostasis and overall adverse events, EUS-guided therapies resulted in a significantly lesser incidence of GV rebleeding compared with conventional endoscopic therapy.

There are also several limitations to this study, most of which are inherent to any meta-analysis. First, 5 of the included studies did not report outcomes separately for primary and secondary prophylaxis.[24,32,35,36,40] Although most of the studies included in our analysis were published as full-length articles, we included 2 recently published conference abstracts. Five of the included studies were case series, and although in the majority of the studies either EUS-coil, EUS-glue, or combination EUS–glue and coil were used, 2 studies reported use of coils and absorbable gelatin sponge, 1 study used thrombin, and 1 used sclerosant (ethanolamine oleate). Second, we were unable to report separate outcomes for EUS-glue, EUS-coil, and combination EUS–glue and coil therapy in patients undergoing primary prophylaxis due to paucity of data. Third, we were unable to assess the rate of GV obliteration based on the number of EUS sessions or the specific location of GV, given wide variation. Among patients undergoing EUS-guided therapies for secondary prophylaxis, we report that the rates of treatment efficacy with EUS-glue, EUS-coil, and combination EUS–glue and coil were 94.2%, 95.5%, and 88.7%, respectively. In addition, for GV obliteration, these were 84.6%, 91.6%, and 84.5%, respectively.

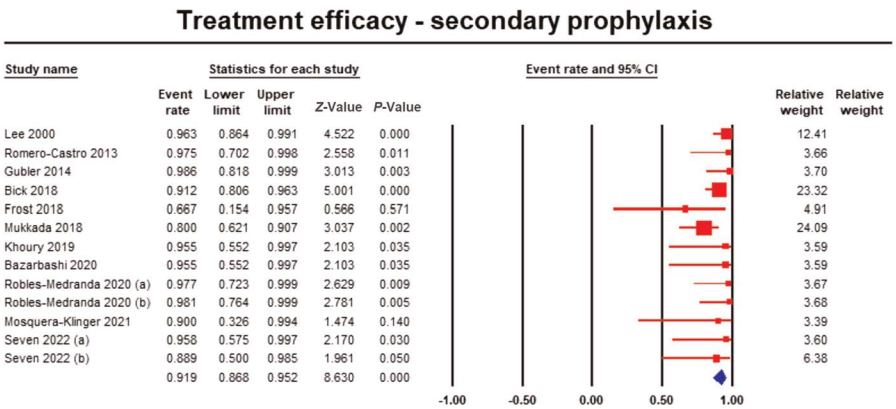

Figure 4. Forest plot, pooled rate, treatment efficacy (secondary prophylaxis).

Table 3

Comparison EUS-guided versus conventional endoscopic therapy

Study	Design	Interventions	Total Patients	GV Type	Primary Hemostasis	GV Obliteration	GV Rebleed	Adverse Events
Bick et al,[26] 2019	Retrospective, single center, January 2013 and November 2017, USA	EUS-guided	64	IGV1 30, GOV1 2, GOV2 32	NR	NR	5/57	13/64 (Abdominal pain 5, fever 3, hypoxia 1, hepatic encephalopathy 1, splenic infarct 1, PE 1, splenic infarct + bacteremia 1)
		END	40	IGV1 3, GOV1 6, GOV2 31	NR	NR	9/38	7/40 (Postprocedure GI bleed 7)
Lee et al,[23] 2000	Prospective, single center, July 1996 to October 1998, China	EUS-guided	54	GOV1 20, GOV2 18, IGV1 16	52/54	43/54	14/54 (Early 4, Late 10)	0/54
		END	47	GOV1 16, GOV2 20, IGV1 11	45/47	NR	27/47 (Early 6, late 21)	0/47
Mukkada et al,[27] 2018	Retrospective, single center, October 2013 to December 2016, India	EUS-guided	30	GOV1: 12, GOV2: 8, IGV1: 10	NR	NR	6/30	NR
		END	51	NR	NR	NR	26/51	NR
Lôbo et al,[32] 2019	Randomized controlled trial, single center, November 2014 to December 2016, Brazil	EUS-guided	16	NR	6/16	15/15	NR	13/16 (Epigastric pain 7, PE 4, mild bleeding 2)
		END	16	NR	8/16	12/13	NR	14/16 (Mental confusion 1, PE 8, epigastric pain 1, bleeding 2, Death 2)
Samanta et al,[36] 2022	Prospective, multi center, India-Italy	EUS-guided	52	NR	52/52	NR	8/52	0/52
		END	118	NR	117/118	NR	36/118	17/118 (Abdominal pain 16, embolization 1)

END, endoscopic therapy; GI, gastrointestinal; GOV1, gastroesophageal varices type 1; GOV2, gastroesophageal varices type 2; GV, gastric varices; IGV1, isolated gastric varices type 1; IGV2, isolated gastric varices type 2; PE, pulmonary embolism.

The difference in these outcomes, although not necessarily statistically significant, should be perceived with caution as the subgroup analysis was based on a small number of studies, only one of which was an RCT,[28] whereas the others were observational cohort studies and/or case series, which may have contributed to potential selection bias. Furthermore, there was variability in the number of coils and/or volume of glue used as well as endoscopist expertise and location of GV, all of which may have contributed to the difference in our outcomes. Finally, the included studies may not be entirely representative of the general population and community practice, with most studies being performed in tertiary-care referral centers.

Nonetheless, our study highlights that in expert hands EUS-guided therapy is safe and effective in primary as well as secondary prophylaxis for GV bleeding. Further prospective studies comparing specific EUS-based therapies may help guide future management of GV in primary and secondary prophylaxis clinical scenarios.

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Conflicts of Interest

The authors declare that they have no financial conflict of interest with regard to the content of this report. Douglas G. Adler is a Co-Editor-in-Chief of the journal. This article was subject to the journal's standard procedures, with peer review handled independently of the editor and his research group.

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Author Contributions

Saurabh Chandan and Douglas G. Adler did the conception and design, interpretation of the data, drafting of the article, and intellectual content and final approval of the manuscript. Andrew Khoi Nguyen conducted the study search, review, and selection and the drafting of the article. Babu P. Mohan and Smit Deliwala performed the statistical analysis of data and interpretation of results. Daryl Ramai and Lena L. Kassab did the study search, review, and selection. Arunkumar Muthusamy and Antonio Facciorusso managed the data collection and synthesis. Faisal Kamal also conducted the data collection and synthesis and drafting of the article. Mohammad Bilal and Jayanta Samanta provided the critical revision of the article for important intellectual content and final approval of the article.

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