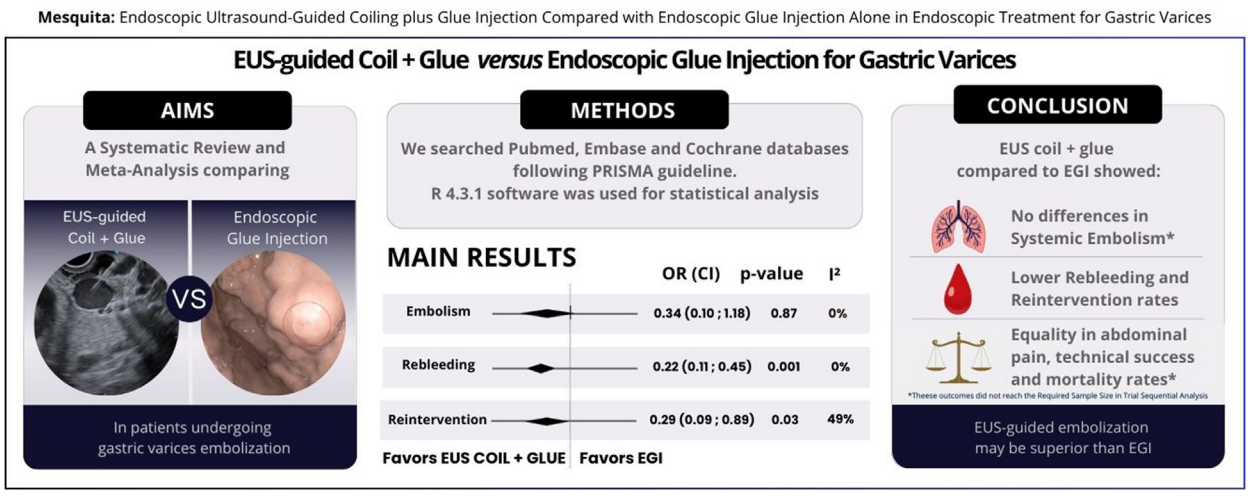
EUS-guided coiling plus glue injection compared with endoscopic glue injection alone in endoscopic treatment for gastric varices: a systematic review and meta-analysis

Cynthia Florencio de Mesquita,[1] Vanio L. J. Antunes,[2] Natalia Junkes Milioli, MD,[3] Matheus Vanzin Fernandes, MD,[2] Tulio L. Correa, MD,[4] Otavio Cosendey Martins,[5] Radhika Chavan, MD, DNB, FISG, FASGE,[6] Stefano Baraldo, MD[7]

Recife, Porto Alegre, Juiz de Fora, Barretos, Brazil; Boston, Massachusetts, USA; Gujarat, India

GRAPHICAL ABSTRACT



Background and Aims: EUS-guided coil plus glue injection has emerged as a safe and effective modality for gastric varices (GVs). Very few studies have compared EUS embolization with the direct endoscopic glue injection (EGI) technique for its safety and effectiveness. In this systematic review and meta-analysis, we compared the outcomes of EUS-guided coil plus glue injection versus EGI.

Methods: MEDLINE, EMBASE, and Cochrane databases were searched for studies that compared EUS and EGI for GVs, and 1454 articles were screened following the Preferred Reporting Items for Systematic reviews and Meta-Analyses protocol. Endpoints were pulmonary embolism, recurrent bleeding rate, reintervention rate, technical success, abdominal pain, and mortality rate. A restricted maximum likelihood random-effects model with odds ratios (ORs) and 95% confidence intervals (CIs) was used for binary endpoints. Heterogeneity was evaluated through Cochrane's Q statistic and Higgins and Thompson's I^2 statistic. Significance was defined as $P < .05$.

Results: We included 6 studies with 445 patients treated for GVs. Mean patient age was 49 years, and 43% were women. EUS was associated with a reduction in recurrent bleeding rate (OR, .22; 95% CI, .11-.45; $P < .001$; $I^2 = 0$) and reintervention rate (OR, .29; 95% CI, .09-.89; $P = .03$; $I^2 = 49\%$) compared with EGI. There were no differences between groups in pulmonary embolism (OR, .34; 95% CI, .10-1.18; $P = .09$; $I^2 = 0\%$), mortality rate (OR, .78; 95% CI, .28-2.13; $P = .63$; $I^2 = 0\%$), technical success (OR, 3.50; 95% CI, .60-20.49; $P = .16$; $I^2 = 0\%$), fever (OR, 1.49; 95% CI, .42-5.21 days; $P = .5$; $I^2 = 0\%$), and abdominal pain (OR, .96; 95% CI, .31-2.95; $P = .94$; $I^2 = 32\%$).

Conclusions: In patients with GVs, EUS-guided coil plus glue injection is associated with lower recurrent bleeding and reintervention rates than EGI with no difference in pulmonary embolization rate, abdominal pain, technical success, and mortality rate. (Gastrointest Endosc 2025;101:331-40.)

(footnotes appear on last page of article)

Gastric variceal bleeding is severe and associated with a high risk of recurrent bleeding, morbidity, and mortality.[1] The risk of recurrent bleeding after an initial episode can range from 35% to 90%, with associated mortality rates notably high, often between 30% and 50%.[2] Effective management of gastric variceal bleeding typically involves a combination of endoscopic treatments, such as cyanoacrylate glue, and radiologic interventions.[3] Despite these interventions, the condition remains challenging because of the complex anatomy and high vascular pressure involved.[4]

Therefore, the implementation of effective strategies is crucial. Because of the availability of heterogeneous data on the management of gastric varices (GVs), guidelines suggest endoscopic injection of acrylate polymers like cyanoacrylate as the primary treatment and interventional radiologist-guided balloon retrograde transvenous obliteration for refractory or severe bleeding.[1] Although endoscopic cyanoacrylate injection is widely used, it is associated with systemic embolization risk, bleeding from needle site ulcers, peritonitis, recurrent bleeding, and even death.[1,5]

EUS-guided gastric variceal embolization is now increasingly used because of its safety profile.[5] EUS offers optimal visualization of varices along with feeder vessels, allowing the injection of coil and glue, as well as real-time Doppler confirmation of variceal obliteration.[6] However, EUS-guided embolization is not widely available because it demands expertise and dedicated accessories. Moreover, in many regions, including Brazil, endoscopic glue injection (EGI) is still the standard option for treatment of GVs because of the easy availability of the glue and the long-standing practice of EGI. At major centers such as the University of São Paulo, Brazil, it is estimated that only about 10 EUS-guided embolization procedures for GVs are performed annually.[7]

Although multiple studies have reported the safety of EUS-guided embolization of GVs, the literature is uncertain whether it is more effective than cyanoacrylate injection.[5,7-11] Therefore, we performed a systematic review and meta-analysis of studies assessing the safety and efficacy of EUS-guided embolization in comparison with EGI in patients with GVs.

METHODS

This systematic review and meta-analysis was performed and reported following the Cochrane Collaboration Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic reviews and Meta-Analysis[12] statement guidelines (Appendix 1, available online at www.giejournal.org). The meta-analysis protocol was registered with the International Prospective Register of Systematic Reviews (CRD42024505740).

Data source and search strategy

We systematically searched PubMed, EMBASE, Cochrane, and ClinicalTrials.gov from inception to May 2024. The search terms used were "endoscopic," "endoscopic ultrasound," "EUS," "coil," "cyanoacrylate," "glue," and "gastric varices." The complete search strategy for each database is provided in Appendix 2 (available online at www.giejournal.org). Two authors (C.F.M. and V.L.J.A.) independently screened titles and abstracts and evaluated the articles in full for eligibility based on prespecified criteria. A third author (T.L.C.) resolved discrepancies in a panel discussion. Additionally, we used backward snowballing (ie, review of references) to certify that no relevant texts were left behind.

Eligibility criteria

We considered studies eligible for inclusion if they were randomized controlled trials or cohort studies comparing EUS-guided embolization with EGI for GVs and presented the data regarding prespecified endpoints. Conference abstracts, editorials, reviews, controls with coiling alone, and studies with no primary intention to compare glue plus coil versus glue alone were excluded from the analysis.

Data extraction

Two authors (C.F.M. and V.L.J.A.) independently extracted the data from each study using a standardized study form to determine authors, enrollment period, study publication year, main inclusion and exclusion criteria, sample size, follow-up period, baseline patient characteristics, medications used at baseline, and endpoint definitions. Discrepancies were resolved in a panel discussion with the senior author.

Endpoints

Our efficacy endpoints were pulmonary embolism, recurrent bleeding, and reintervention rates. Secondary endpoints were technical success, abdominal pain incidents, fever, and all-cause mortality rates.

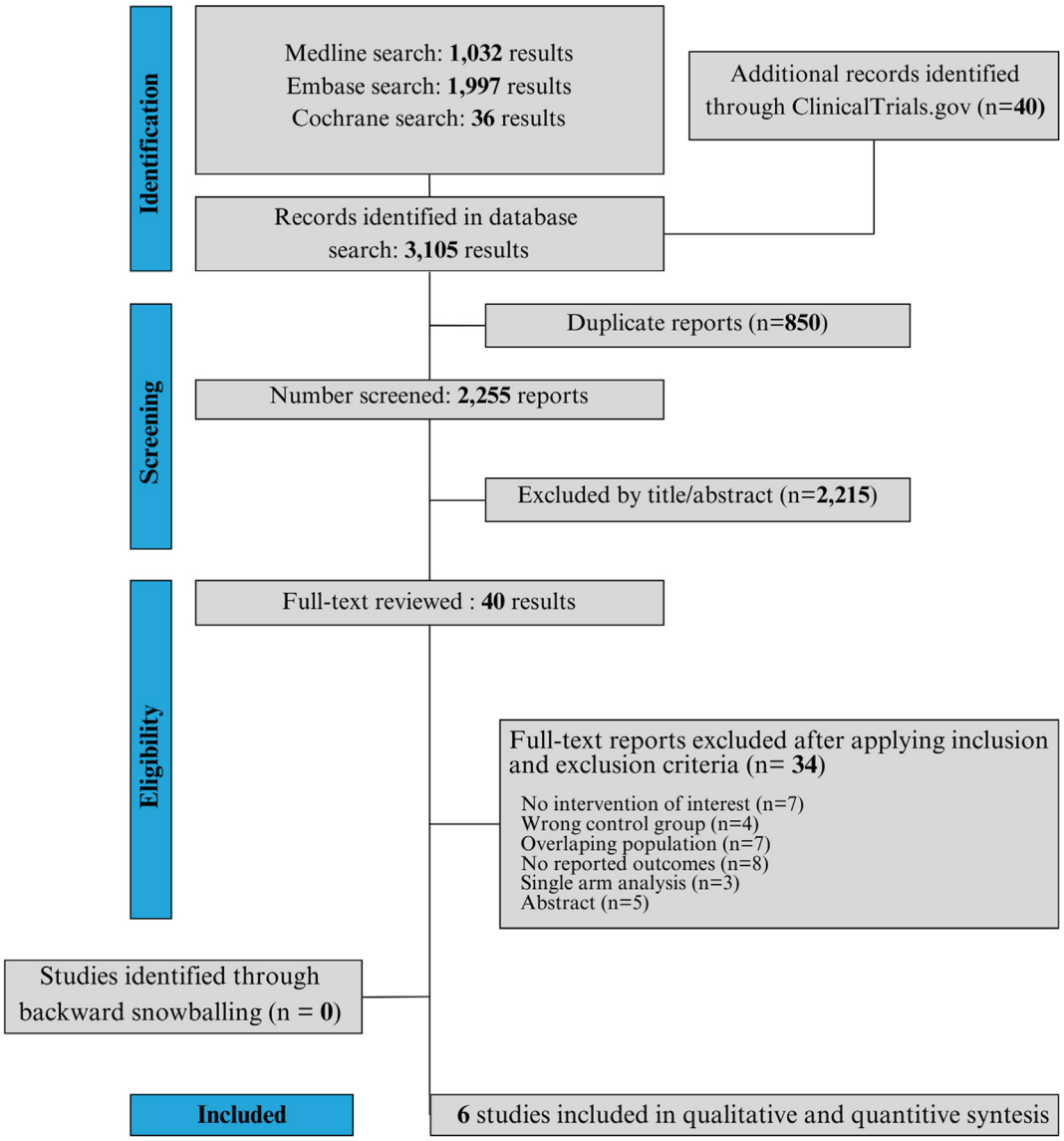


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram of study screening and selection.

Quality assessment and evidence quality assessment

Two independent authors assessed the risk of bias in the included randomized controlled trials using the Cochrane Collaboration tool for assessing the risk of bias in randomized trials (Risk of Bias Assessment Tool [RoB 2])[13] and using the Cochrane Collaboration's Risk Of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool for observational studies.[14] Any disagreements were resolved by consensus between authors. Publication bias was investigated by funnel plot analysis of point estimates in relation to study weights. The certainty in evidence and strength of findings were assessed using the Grading of Recommendations, Assessment, Development, and Evaluation tool.[15]

Statistical analysis

We summarized binary endpoints using the Mantel-Haenszel random-effects model (restricted maximum likelihood estimator for t^2) with odds ratio (OR) and 95% confidence interval (CI) as a measure of effect size. When necessary, we performed a leave-one-out sensitivity analysis in which each study is omitted to evaluate the impact of heterogeneity and robustness of our findings. We assessed heterogeneity with Cochrane's Q statistic and Higgins and Thompson's I^2 statistic with $P \leq .10$ indicating statistical significance. We determined the consistency of the studies based on I^2 values of 0%, $\leq$25%, $\leq$50%, and >50% indicating none observed, low, moderate, and substantial heterogeneity, respectively. All tests were 2-tailed, and $P < .05$ was considered statistically significant. If

TABLE 1. Baseline characteristics of included studies

Study	Type of study	Follow-up	Sample size	Age (y)	No. (%) of women	Alcoholic cirrhosis etiology (%)
Galvis-García, 2022[10]	Prospective	221 days	I: 15 C: 53	63.1 ± 9.8 54.3 (9.4)	19 (60) 32 (60)	33 45
Jamwal, 2023[5]	Retrospective	1 y	I: 40 C: 40	44.1 ± 8.23 43.2 ± 7.88	10 (25) 12 (30)	50 45
Lôbo, 2019[7]	Randomized controlled trial	1 y	I: 16 C: 56	49.31 ± 14.83 57.69 ± 11.56	8 (50) 11 (69)	19 19
Robles-Medranda, 2021[9]	Retrospective	10 mo	I: 17 C: 19	63.29 ± 8.8 62.83 ± 11.5	7 (41) 9 (47)	
Samanta, 2023[11]	Retrospective propensity matching	6 mo	I: 58 C: 218 I: 58 C: 118	44.33 ± 12.1 48.95 ± 13.4 44.33 ± 12.1 46.63 ± 13.6		43 35
Chen, 2024[8]	Retrospective	13 mo	I: 21 C: 36	57.5 ± 7.7 58.8 ± 8.0	7 (33) 9 (25)	9 11

Values are mean ± standard deviation, n (%), or median (interquartile range).
C, control group; *GOV*, Gastroesophageal varices; *I*, intervention group; *IGV*, Isolated gastric varices.

(continued on the next page)

necessary, means and standard deviations were estimated.[16] We used R version 4.3.1 software (R Foundation for Statistical Computing, Vienna, Austria) and the extension package "meta" for all calculations and graphics.

Trial sequential analysis

Meta-analyses can only assess the combined effect size, and using the standard 95% CI or the 5% significance level may result in false-positive (Type I error) or false-negative (Type II error) outcomes. Trial sequential analysis (TSA) is a frequent method that helps balance Type I and II errors and determines when the effect is strong enough to be unlikely to be changed by more studies.[17]

TSA was performed on the main outcomes using TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen, Denmark).[18] The effect measure (OR) was used, and a random-effects model using the DerSimonian and Laird method was selected. No continuity correction was applied in the case of a zero event. We estimated the required sample size on the calculated effect size for the intervention considering a Type I error of 5% and a power of 99%; benefit, harm, and inner wedge boundaries were drawn using the O'Brien-Fleming spending function. Heterogeneity correction was performed using model variance-based.

RESULTS

Study selection and characteristics

Our systematic search yielded 3105 potential articles (Fig. 1). After removing duplicates and excluding articles by title or abstract, 40 articles were retrieved and reviewed in full for possible inclusion. Of these, 6 studies met all inclusion criteria and were included in the primary analysis. We included 589 patients, with 30% of patients in the EUS group and 70% of patients in the EGI group. Table 1 summarizes the main characteristics of the included studies.

Mean patient age was 49 years (range, 43-63 years), and 64% were men. Most patients (62.9%) had isolated GVs type 1, 36.5% had gastroesophageal varices type 1, and <1% had gastroesophageal varices type 2 as per the Sarin classification.[19] Follow-up duration ranged from 6 to 13 months, with a mean of 310 days.

The expertise of the centers in the included studies varied considerably. Five centers reported having at least 2 experienced faculty members for EUS-guided embolization. Among these, 2 centers reported 70 to 80 cases of EUS-guided embolization annually out of a total of more than 20,000 endoscopy cases. Other centers reported significantly fewer EUS-embolization, with only 3 to 5 cases annually, as detailed in Supplementary Table 1 (available online at www.giejournal.org). Although most centers have training programs and fellows, the fellows were involved primarily in basic and intermediate-risk procedures, such as EUS-guided FNA and cyst drainage.

Efficacy endpoints

Compared with EGI, EUS-guided coil plus glue injection was statistically similar in systemic embolization rates (OR, .34; 95% CI, .10-1.18; $P = .09$; $I^2 = 0\%$) (Fig. 2A). There was a significant reduction in recurrent bleeding rates (OR, .22; 95% CI, .11-.45; $P < .001$; $I^2 = 0\%$) (Fig. 2B) and reintervention rates (OR, .29; 95% CI, .09-.89; $P = .03$; $I^2 = 49\%$) (Fig. 2C) when using EUS. There were no statistically significant differences between groups in all-cause mortality (OR, .78; 95% CI, .28-2.13; $P = .63$; $I^2 = 0\%$) (Fig. 3A), technical success (OR, 3.50; 95% CI, .60-20.49; $P = .16$; $I^2 = 0\%$) (Fig. 3B), fever (OR, 1.49; 95% CI,

TABLE 1. Continued

Nonalcoholic steatohepatitis (%)	Cyanoacrylate volume (mL)	Sarin classification		
		GOV1	GOV2	IGV1
66	2	0 (0)	15 (100)	0 (0)
56	2	0 (0)	33 (62)	20 (38)
30	2 ± .91			
25	6 ± 2.31			
		0 (0)	13 (81)	13 (81)
		0 (0)	3 (19)	3 (19)
	1.8 (1.2-2.4)	0 (0)	12 (70)	12 (63)
	1.8 (.6-6.6)	0 (0)	5 (30)	7 (37)
72		0 (0)	31 (53)	128 (59)
79		0 (0)	27 (47)	90 (41)
	2.0 (1.0-4.0)			
	2.0 (1.0-12.0)			
80	1.64 ± .67	1 (0)	13 (62)	7 (33)
82	2.38 ± .72	2 (0)	19 (53)	15 (42)

.42-5.21; $P = .53$; $I^2 = 0\%$) (Fig. 3C), and abdominal pain (OR, .96; 95% CI, .31-2.95; $P = .94$; $I^2 = 32\%$) (Fig. 3D).

A leave-one-out sensitivity analysis was performed on endpoints with moderate and high heterogeneity (I^2 >25%). This assessment revealed similar reintervention rates if individually omitting 3 of 4 available studies for the analysis: Samanta et al[11] (OR, .47; 95% CI, .12-1.82; $P = .27$; $I^2 = 29\%$), Galvis-García et al[10] (OR, .33; 95% CI, .09-1.27; $P = .11$; $I^2 = 65\%$), or Chen et al[8] (OR, .31; 95% CI, .06-1.55 ; $P = .15$; $I^2 = 66\%$) (Supplementary Fig. 1, available online at www.giejournal.org). The other sensitivity analyses required for the pain assessment remained consistent after the omission of each study (Supplementary Fig. 2, available online at www.giejournal.org).

Trial sequential analysis

In the TSA of recurrent bleeding rates, the cumulative Z-line crossed the boundary for effect and reached the required sample size (Supplementary Fig. 3, available online at www.giejournal.org). These findings suggest that the pooled effect is statistically significant and the sample size sufficient to suggest a definitive result, and future studies are not necessary to be conclusive about the use of EUS to reduce this outcome compared with EGI in patients with GVs.

For the remaining outcomes, TSA showed that the pooled analysis did not reach the minimum population, because the cumulative Z-line did not reach the required sample size (Supplementary Fig. 4A-E, available online at www.giejournal.org). Therefore, no conclusions of the meta-analysis pooled effect can be made, and more studies are necessary to evaluate them.

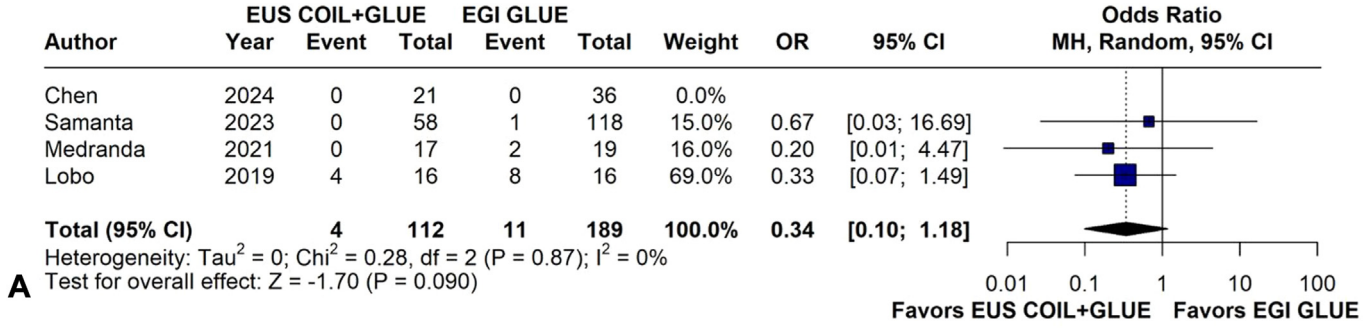
Quality assessment and publication bias

RoB 2 identified the randomized study as low risk of bias (Fig. 4), whereas ROBINS-I showed a moderate risk in all studies except for Samanta et al,[11] mainly because of its propensity score matching reduction in cofounding on the first domain (Fig. 5). Funnel plot evaluation showed symmetric distribution, suggesting a low risk of small study effects, and publication bias (Supplementary Fig. 5, available online at www.giejournal.org).

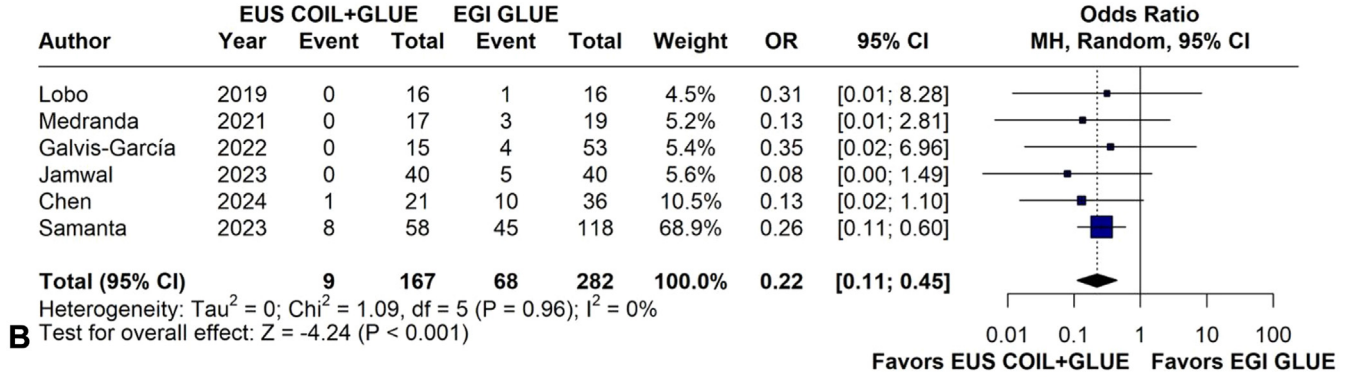
DISCUSSION

This systematic review and meta-analysis of 6 studies assessed the efficacy and safety of EUS-guided coil plus glue injection versus direct endoscopic glue alone in patients with GVs. Our main findings were that coiling plus cyanoacrylate injection does not decrease pulmonary embolisms, EUS is related to lower recurrent bleeding rates and reintervention rates, and there were no differences in terms of other adverse events.

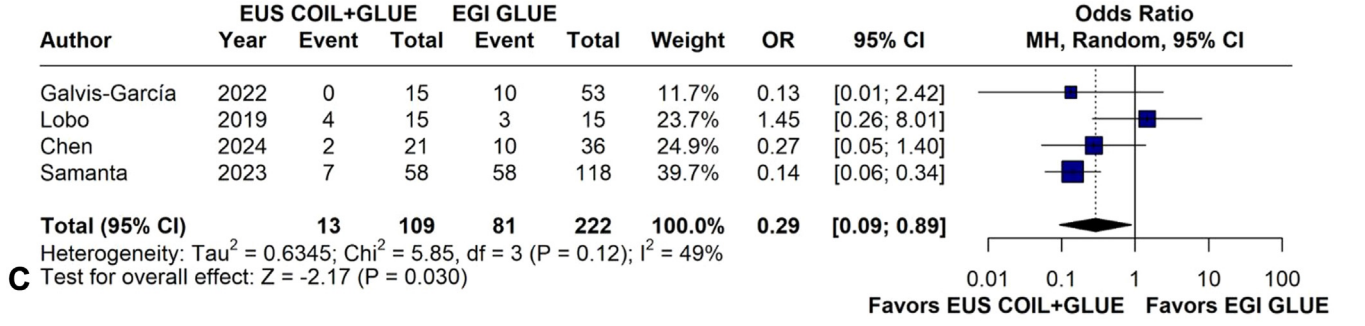
A previous meta-analysis[20] evaluated EUS-guided obliteration techniques (cyanoacrylate glue and/or coil and/or thrombin) compared with an historical control group of EGI. Recurrence rates were estimated at 9.1% in the EUS group and 18% in the EGI group. Although our data did not analyze recurrence specifically, our reintervention rates were 11.9% and 36.4%, respectively, with a treatment effect significantly favoring the EUS group. Early recurrent bleeding rates were 7% in EUS and 5% in EGI, whereas our overall recurrent bleeding rates were 5% and 24%, respectively. Although the previous meta-analysis did not make direct comparisons for mortality, it found a higher incidence for the EUS-guided group of 13.1% versus 7.7%. In contrast, our study showed a statistical equivalent in all-cause mortality among the groups, with a higher incidence in the EGI group of 13.3% compared with 6.9% in the EUS group. As discussed in this previous study, GV



A



B



C

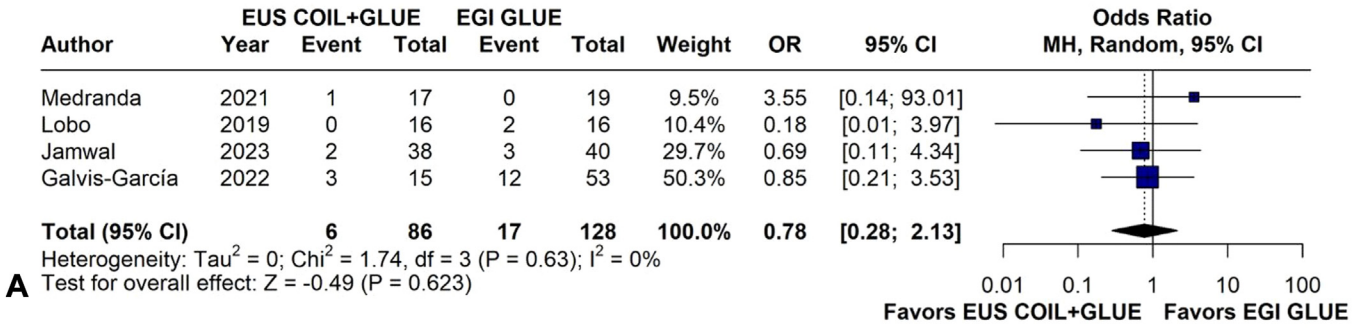
Figure 2. Pooled analysis of primary outcomes. **A,** Embolism rates. **B,** Recurrent bleeding rates. **C,** Reintervention rates. *EGI*, Endoscopic glue injection; *OR*, odds ratio; *CI*, confidence interval.

management by obliteration therapies varies with a range of treatments in addition to EUS coil and glue and EGI.

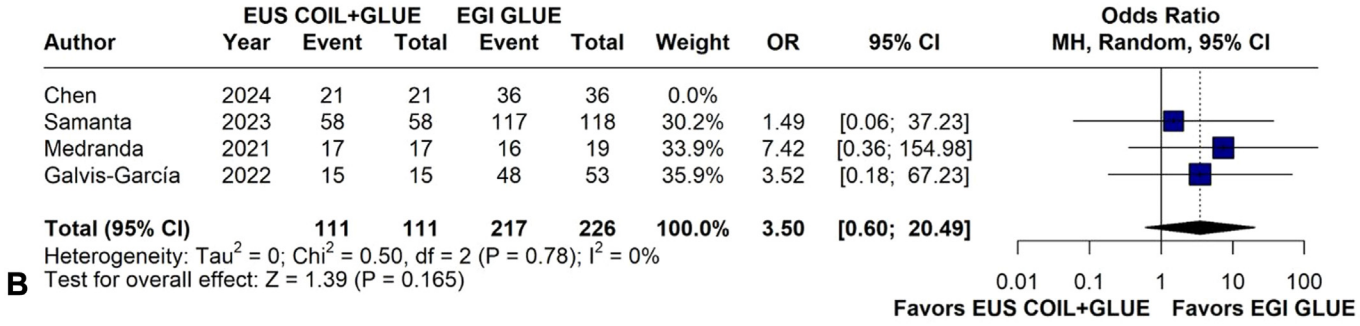
It is important to acknowledge that other options, such as thrombin obliteration through EUS, are also alternatives suggested to be effective and safe both alone[21] and combined with coils.[22] Thrombin can also be used in non–EUS-guided procedures and has shown promising results in these settings as well.[23] Further studies are required to see the efficacy and safety of these in comparison with conventional agents (including glue and/or coil) used during the EUS technique as well as with EGI.[24]

EUS guidance allows real-time visualization of complete GVs and injection of coils, which was unable to be done with conventional gastroscopic techniques. Coils reduce the volume of glue required, thus potentially reducing the systemic embolization risk. We found a numerical difference of systemic embolization between groups of 3.5% in the EUS group versus 5.8% in the EGI group, but there was no significant difference in pulmonary embolism rates. TSA suggested an insufficient statistical power to assess this outcome confidentially, and more studies are necessary to confirm the hypothesis of lower embolization in the EGI group.

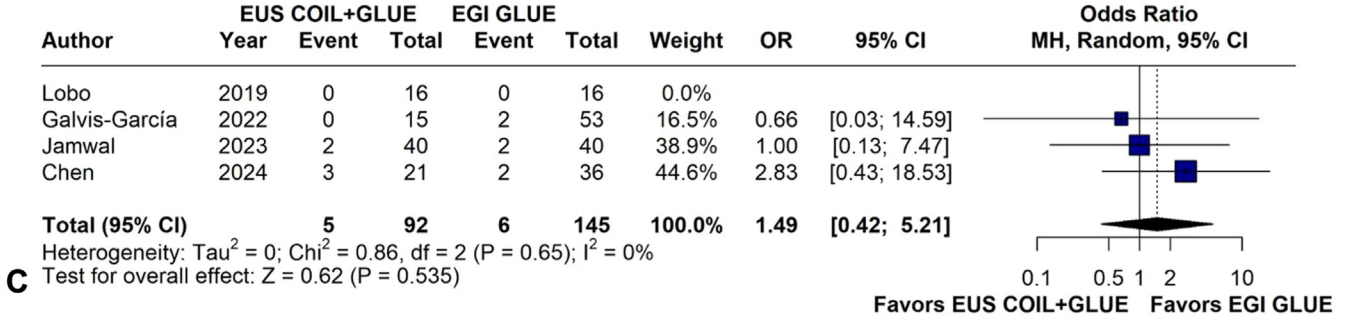
In a single-arm meta-analysis[25] evaluating the treatment of GVs with EUS guidance, the variceal obliteration rate was 78.3% after the first session and increased to 96.8% with multiple sessions. Hemorrhage occurred in 4.9% of



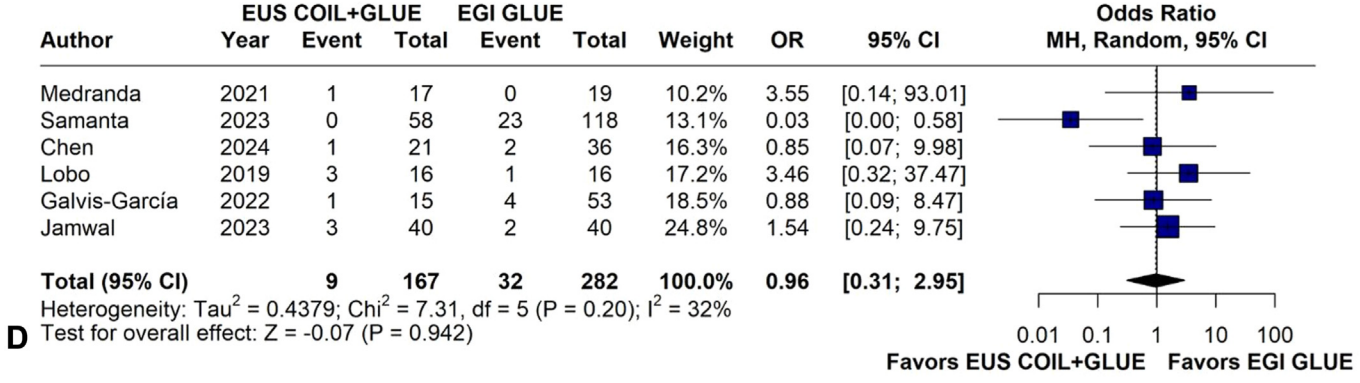
A



B



C



D

Figure 3. Pooled analysis of secondary outcomes. **A,** All-cause mortality. **B,** Technical success. **C,** Fever. **D,** Abdominal pain. *EGI*, Endoscopic glue injection; *OR*, odds ratio; *CI*, confidence interval.

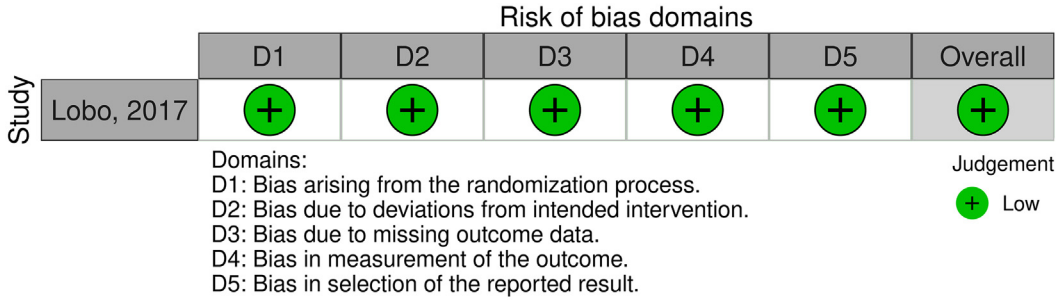


Figure 4. Risk of bias of the included randomized controlled trial assessed through Cochrane's Collaboration tool 2 (RoB 2).

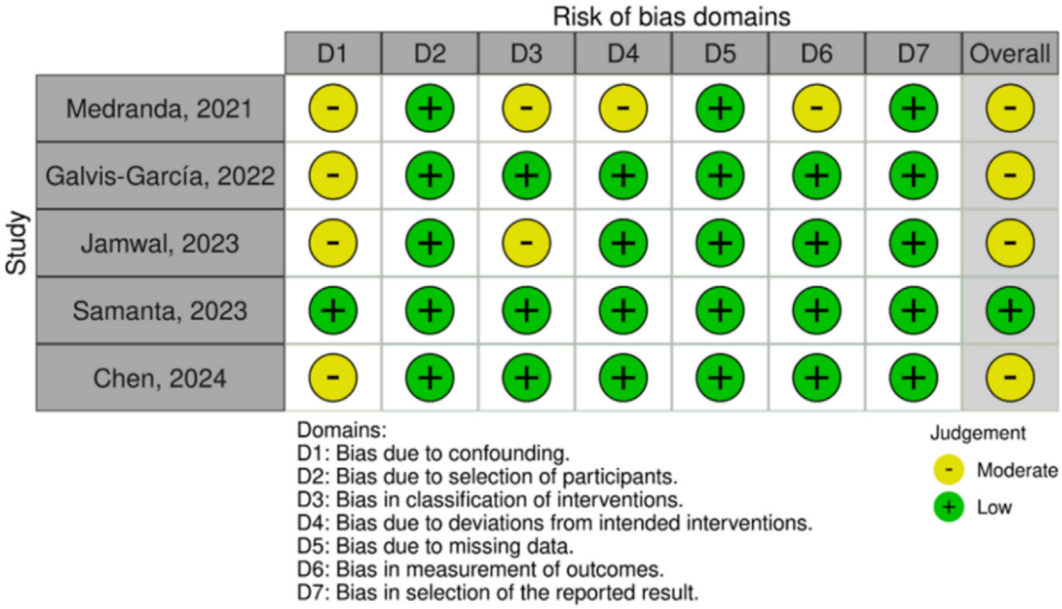


Figure 5. Risk of bias of all included cohort studies assessed through Cochrane's ROBINS-I tool.

cases. Adverse events included abdominal pain (9.8%), pulmonary embolism (2.2%), febrile episodes (1.2%), and procedure-related bleeding (2.62%). In our study, pain was observed in 5.3% of EUS patients and 11% of EGI patients. Regarding fever, a 5% prevalence in the EUS group was recorded, compared with 4% in the EGI group.

One important finding of our study is that EUS therapy has demonstrated superior results in reducing recurrent bleeding rates. TSA with a power of 99% confirmed that this is a feasible evaluation with the population grouped, and this perceived reduction is unlikely to be a Type I error. Although other outcomes did not reach the minimum required sample size, the observed reduction in recurrent bleeding rates is significant and should influence medical practices. Future studies are necessary to explore whether EUS can also provide benefits in other outcomes.

EUS-guided interventions require more specialized training,[26] which introduces a potential nonmeasurable bias that may not be fully captured by the tools used to assess risk of bias, such as ROBINS-I and RoB 2. Although some included studies in our analysis used strategies to reduce this issue, such as randomization or interventions in both groups made by a single endoscopist, this inherent bias likely favors EUS in comparison with EGI, because faculty with more expertise may demonstrate better outcomes because of proficiency rather than the technique itself. Nevertheless, we believe that training and credentialing in therapeutic EUS are essential and should be conducted within multidisciplinary settings at tertiary care centers. These should be offered after assessing trainees' basic EUS skills.

Furthermore, EUS-guided embolization techniques need to be standardized in relation to the size and number of coils and the use of glue. Our study did not directly compare the efficacy of glue with coils versus glue alone, because it introduces an additional variable with the use of EUS in the intervention group. Nevertheless, it prompts a valid discussion regarding whether even with the

integration of this newer and more advanced technology like EUS alongside coils and glue, lower rates of embolization could not be achieved compared with using glue alone.

Our study has some limitations. First, we were unable to stratify patients according to severity, which could potentially affect the relative efficacy of EUS versus EGI. However, our main analysis showed no heterogeneity for the efficacy endpoints. Additionally, our inclusion of 4 retrospective studies and 1 prospective study introduces a potential confounding bias. Moreover, limited data prevented us from performing subgroup analysis. TSA and funnel plots were made despite including only 6 studies. We also acknowledge the limitation of not being able to accurately quantify all included centers' procedural volume and expertise in GVs embolization. Finally, our study novelty poses challenges, such as a limited number of studies available for comparison and a restricted number of patients to include in the analysis.

In conclusion, in patients with GVs, EUS-guided embolization of GVs reduced recurrent bleeding and reintervention rates. There were no significant differences in terms of systemic embolism and adverse events compared with direct endoscopic glue injection.

DISCLOSURE

All authors disclosed no financial relationships.

ACKNOWLEDGMENTS

We thankfully acknowledge the Meta-Analysis Academy for its methodologic support.

REFERENCES

1. Gralnek IM, Camus Duboc M, Garcia-Pagan JC, et al. Endoscopic diagnosis and management of esophagogastric variceal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) guideline. Endoscopy 2022;54:1094-120.
2. Philips CA, Ahamed R, Rajesh S, et al. Beyond the scope and the glue: update on evaluation and management of gastric varices. BMC Gastroenterol 2020;20:361.
3. Goral V, Yılmaz N. Current approaches to the treatment of gastric varices: glue, coil application, TIPS, and BRTO. Medicina 2019;55:335.
4. Baliss M, Patel D, Madi MY, et al. EUS-guided vascular interventions. J Clin Med 2023;12:2165.
5. Jamwal KD, Padhan RK, Sharma A, et al. Endoscopic ultrasound-guided coiling and glue is safe and superior to endoscopic glue injection in gastric varices with severe liver disease: a retrospective case control study. Clin Endosc 2023;56:65-74.
6. Chavan R, Baraldo S, Patel N, et al. Technical tips for EUS-guided embolization of varices and pseudoaneurysms. VideoGIE 2024;9:211-9.
7. Lôbo MR de A, Chaves DM, DE Moura DTH, et al. Safety and efficacy of EUS-guided coil plus cyanoacrylate versus conventional cyanoacrylate technique in the treatment of gastric varices: a randomized controlled trial. Arq Gastroenterol 2019;56:99-105.
8. Chen D, Fu S, Shen R. Efficacy and safety of EUS-guided coil embolization in combination with cyanoacrylate injection versus conventional endoscopic cyanoacrylate injection in the treatment of gastric varices with spontaneous portosystemic shunts. Gastroenterol Rep 2024;12:goae026.
9. Robles-Medranda C, Nebel JA, Puga-Tejada M, et al. Cost-effectiveness of endoscopic ultrasound-guided coils plus cyanoacrylate injection compared to endoscopic cyanoacrylate injection in the management of gastric varices. World J Gastrointest Endosc 2021;13:13-23.
10. Galvis-García ES, Zárate-Guzmán ÁM, Reding-Bernal A, et al. Embolización guiada por ultrasonido endoscópico con cianoacrilato solo o combinado con endo-coil para las várices gástricas (Spanish). Cir Cir 2022;90:7677.
11. Samanta J, Nabi Z, Facciorusso A, et al. EUS-guided coil and glue injection versus endoscopic glue injection for gastric varices: International multicentre propensity-matched analysis. Liver Int 2023;43:1783-92.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
13. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
14. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919.
15. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336:1106-10.
16. Luo D, Wan X, Liu J, et al. Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018;27:1785-805.
17. De Cassai A, Tassone M, Geraldini F, et al. Explanation of trial sequential analysis: using a post-hoc analysis of meta-analyses published in *Korean Journal of Anesthesiology*. Korean J Anesthesiol 2021;74:383-93.
18. Imberger G, Thorlund K, Gluud C, et al. False-positive findings in Cochrane meta-analyses with and without application of trial sequential analysis: an empirical review. BMJ Open 2016;6:e011890.
19. Sarin SK, Kumar A. Gastric varices: profile, classification, and management. Am J Gastroenterol 1989;84:1244-9.
20. Mohan BP, Chandan S, Khan SR, et al. Efficacy and safety of endoscopic ultrasound-guided therapy versus direct endoscopic glue injection therapy for gastric varices: systematic review and meta-analysis. Endoscopy 2020;52:259-67.
21. Frost J, Hebbar S. EUS-guided thrombin injection for management of gastric fundal varices. Endosc Int Open 2018;06:E664-8.
22. O'Rourke J, Todd A, Shekhar C, et al. EUS-guided thrombin injection and coil implantation for gastric varices: feasibility, safety, and outcomes. Gastrointest Endosc 2024;100:549-56.
23. Lo GH, Lin CW, Tai CM, et al. A prospective, randomized trial of thrombin versus cyanoacrylate injection in the control of acute gastric variceal hemorrhage. Endoscopy 2020;52:548-55.
24. Bhurwal A, Makar M, Patel A, et al. Safety and efficacy of thrombin for bleeding gastric varices: a systematic review and meta-analysis. Dig Dis Sci 2022;67:953-63.
25. Bhat YM, Weilert F, Fredrick RT, et al. EUS-guided treatment of gastric fundal varices with combined injection of coils and cyanoacrylate glue: a large U.S. experience over 6 years (with video). Gastrointest Endosc 2016;83:1164-72.
26. Wani S, Keswani RN, Petersen B, et al. Training in EUS and ERCP: standardizing methods to assess competence. Gastrointest Endosc 2018;87:1371-82.

FURTHER READING REFERENCES

27. Binmoeller KF, Weilert F, Shah JN, et al. EUS-guided transesophageal treatment of gastric fundal varices with combined coiling and cyanoacrylate glue injection (with videos). Gastrointest Endosc 2011;74:1019-25.
28. Fujii-Lau LL, Law R, Wong Kee Song LM, et al. Endoscopic ultrasound (EUS)-guided coil injection therapy of esophagogastric and ectopic varices. Surg Endosc 2016;30:1396-404.
29. Romero-Castro R, Ellrichmann M, Ortiz-Moyano C, et al. EUS-guided coil versus cyanoacrylate therapy for the treatment of gastric

varices: a multicenter study (with videos). Gastrointest Endosc 2013;78:711-21.

Abbreviations: CI, confidence interval; EGI, endoscopic glue injection; GV, gastric varix; RoB 2, Risk of Bias Assessment Tool; ROBINS-I, Risk Of Bias in Nonrandomized Studies of Interventions; OR, odds ratio; TSA, trial sequential analysis.

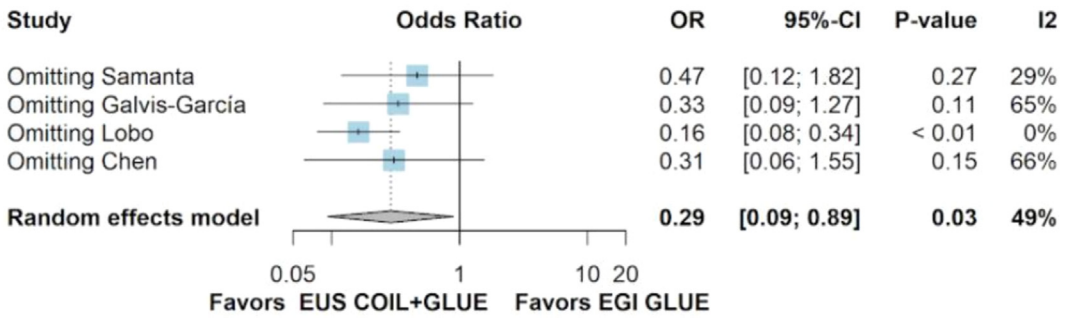
Use your mobile device to scan this QR code and watch the author interview. Download a free QR code scanner by searching "QR Scanner" in your mobile device's app store.

0016-5107/$36.00
https://doi.org/10.1016/j.gie.2024.10.005

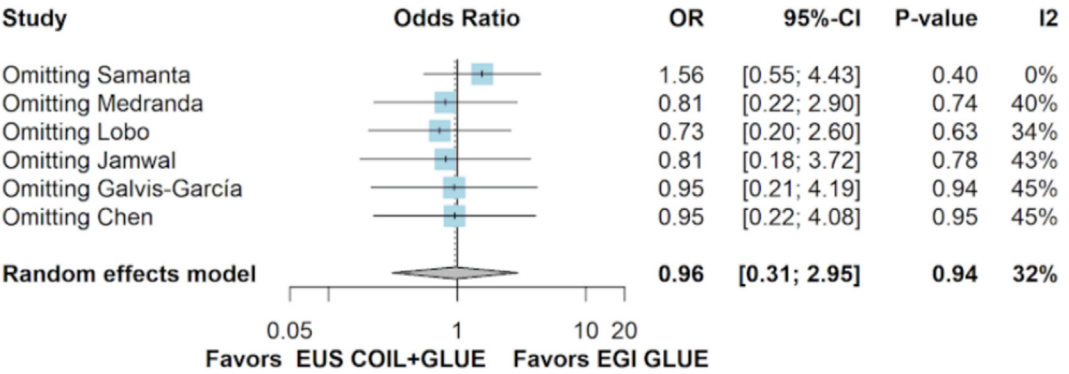
Received July 12, 2024. Accepted October 2, 2024.

Current affiliations: Center for Medical Sciences, Federal University of Pernambuco, Recife, Brazil (1), Federal University of Health Sciences of Porto Alegre, Porto Alegre, Brazil (2), Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil (3), Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA (4), Federal University of Juiz de Fora, Juiz de Fora, Brazil (5), Department of Gastroenterology and Advanced Endoscopy, Ansh Clinic, Gujarat, India (6), Department of Endoscopy, Barretos Cancer Hospital, Barretos, Brazil (7).

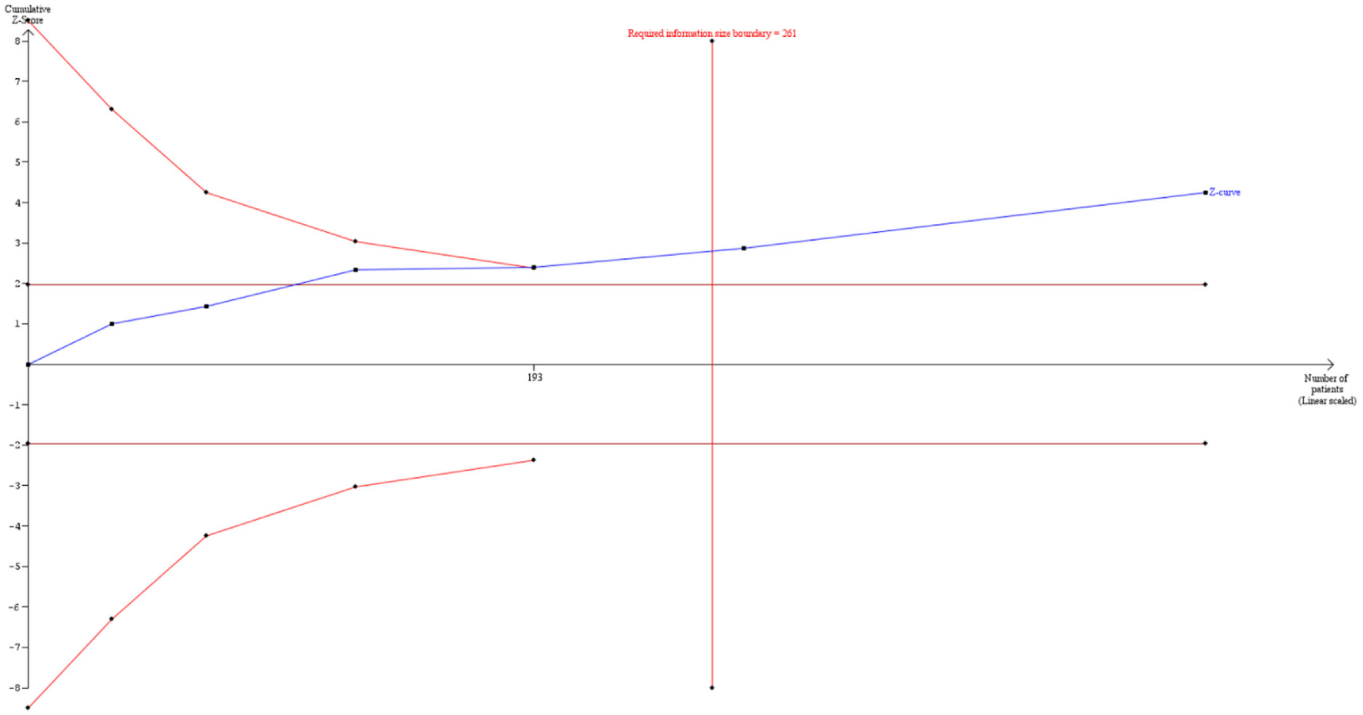
Corresponding author: Cynthia Florêncio de Mesquita, Federal University of Pernambuco, Av. Prof. Moraes Rego, Av. da Engenharia, 531-611 - Cidade Universitária, Recife - Pernambuco, Brazil 50670-901.



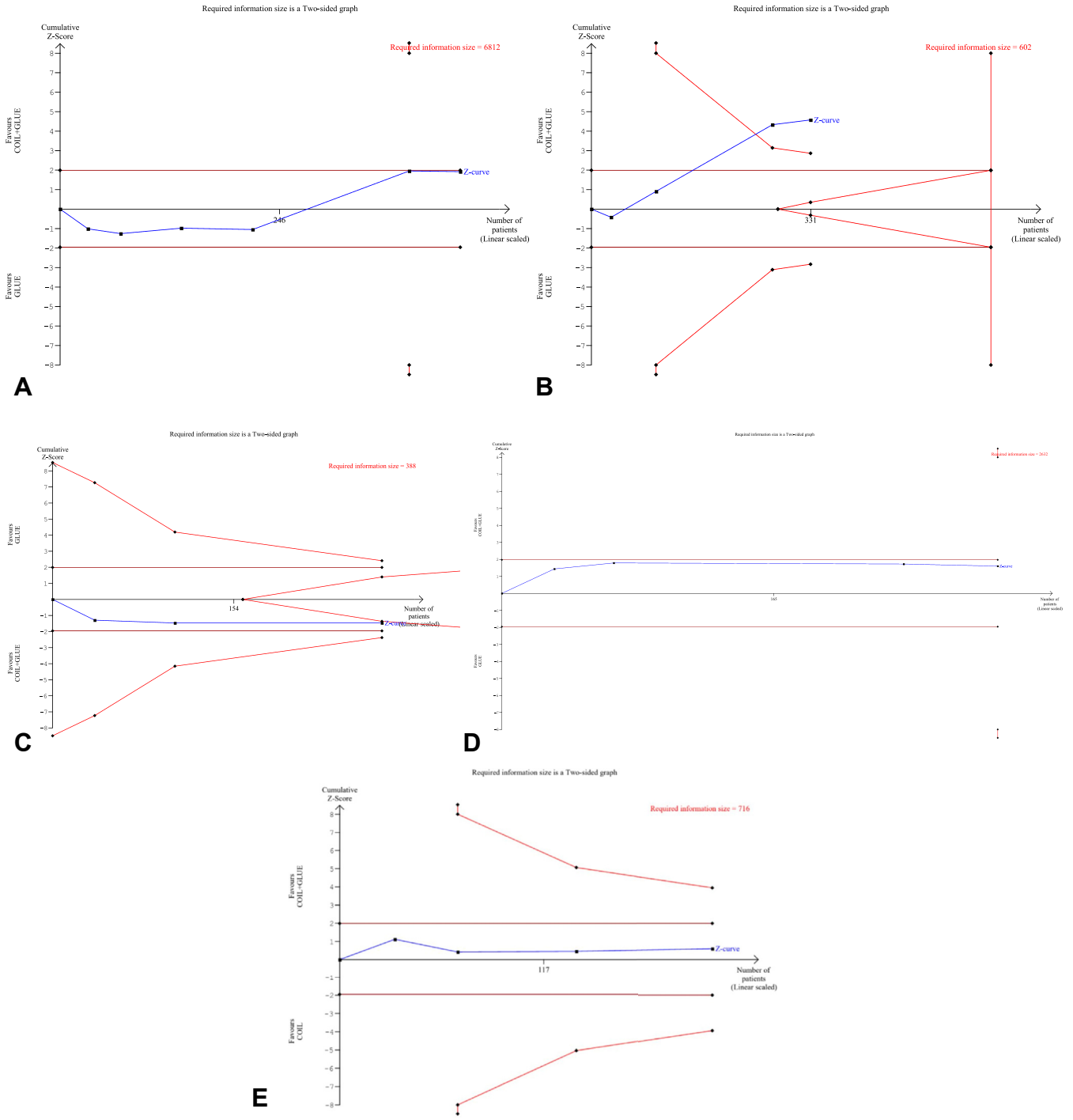
Supplementary Figure 1. Leave-one-out analysis sensitivity analysis for reintervention rates. *EGI*, Endoscopic glue injection; *OR*, odds ratio; *CI*, confidence interval.



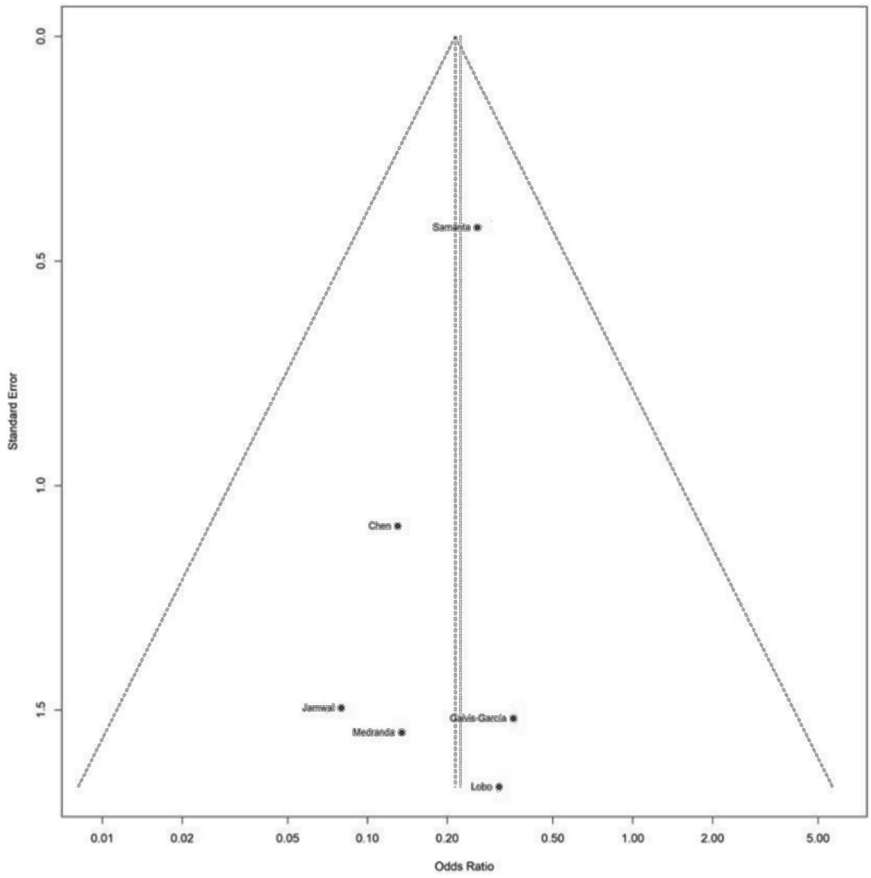
Supplementary Figure 2. Leave-one-out analysis sensitivity analysis for abdominal pain. *EGI*, Endoscopic glue injection; *OR*, odds ratio; *CI*, confidence interval.



Supplementary Figure 3. Trial sequential analysis of recurrent bleeding rates.



Supplementary Figure 4. Trial sequential analysis of the remaining outcomes. **A,** Abdominal pain. **B,** Reintervention rates. **C,** Technical success. **D,** Systemic embolism. **E,** Death.



Supplementary Figure 5. Funnel plot for recurrent bleeding.

APPENDIX 1. PRISMA 2020 main checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	p. 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	Not available
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	p. 4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	p. 4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	p. 5
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	p. 5
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used.	p. 7 in supplement
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and, if applicable, details of automation tools used in the process.	p. 5-6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and, if applicable, details of automation tools used in the process.	p. 4-5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (eg, for all measures, time points, analyses), and, if not, the methods used to decide which results to collect.	p. 6-7
	10b	List and define all other variables for which data were sought (eg, participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	p. 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and, if applicable, details of automation tools used in the process.	p. 7
Effect measures	12	Specify for each outcome the effect measure(s) (eg, risk ratio, mean difference) used in the synthesis or presentation of results.	p. 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (eg, tabulating the study intervention characteristics and comparing against the planned groups for each synthesis [item 5]).	Table 1
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	p. 5-7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	p. 8
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	p. 6-8
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (eg, subgroup analysis, meta-regression).	p. 6-7
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	p. 5-7 in supplement

(*continued on the next page*)

APPENDIX 1. Continued

Topic	No.	Item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias because of missing results in a synthesis (arising from reporting biases).	p. 5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	p. 5
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Not available
Study characteristics	17	Cite each included study and present its characteristics.	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	p. 16
Results of individual studies	19	For all outcomes, present, for each study (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (eg, confidence/credible interval), ideally using structured tables or plots.	Figures 2-4
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	p. 7
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (eg, confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	p. 7-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	p. 6
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	p. 6-7
Reporting biases	21	Present assessments of risk of bias because of missing results (arising from reporting biases) for each synthesis assessed.	p. 16
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Not available
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	p. 7-8
	23b	Discuss any limitations of the evidence included in the review.	p. 9
	23c	Discuss any limitations of the review processes used.	p. 9
	23d	Discuss implications of the results for practice, policy, and future research.	p. 8-9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Prospective Register of Systematic Reviews: CRD42024505740
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023453779
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or nonfinancial support for the review, and the role of the funders or sponsors in the review.	None
Competing interests	26	Declare any competing interests of review authors.	p. 1
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not available

PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses.

APPENDIX 2. Details of the search strategy

Database	Search strategy
PubMed	("gastric varices" OR "gastroesophageal varices" OR "variceal bleeding" OR "portal hypertension" OR "Varices of the Stomach" OR "stomach varices" OR "Gastric Vein Varices" OR "Portal Hypertensive Gastropathy" OR "Gastric Vascular Abnormalities" OR "Gastric Varicosities" OR "Stomach Varicosities" OR "Esophageal and Gastric Varices" OR "Varicose Veins of the Stomach" OR "Porto-gastric Varices" OR "EUS-guided coil and glue injection" OR "coil" OR "coiling" OR "hybrid approach" OR "Endoscopic Spirals" OR "Endoscopic Coiling System" OR "Endoscopic Coil Implant" OR "Endoscopic Helical Device" OR "Endoscopic Coil Delivery System" OR "Endoscopic Spiral") AND ("endoscopic glue injection" OR "endoscopic cyanoacrylate" OR " methyl 2-cyanoacrylate" OR "MCA" OR "ethyl 2-cyanoacrylate" OR "ECA" OR "Super Glue" OR "Krazy Glue" OR "n-butyl cyanoacrylate" OR "n-BCA" OR "octyl cyanoacrylate")
EMBASE	("gastric varices" OR "gastroesophageal varices" OR "variceal bleeding" OR "portal hypertension" OR "Varices of the Stomach" OR "stomach varices" OR "Gastric Vein Varices" OR "Portal Hypertensive Gastropathy" OR "Gastric Vascular Abnormalities" OR "Gastric Varicosities" OR "Stomach Varicosities" OR "Esophageal and Gastric Varices" OR "Varicose Veins of the Stomach" OR "Porto-gastric Varices" OR "EUS-guided coil and glue injection" OR "coil" OR "coiling" OR "hybrid approach" OR "Endoscopic Spirals" OR "Endoscopic Coiling System" OR "Endoscopic Coil Implant" OR "Endoscopic Helical Device" OR "Endoscopic Coil Delivery System" OR "Endoscopic Spiral") AND ("endoscopic glue injection" OR "endoscopic cyanoacrylate" OR " methyl 2-cyanoacrylate" OR "MCA" OR "ethyl 2-cyanoacrylate" OR "ECA" OR "Super Glue" OR "Krazy Glue" OR "n-butyl cyanoacrylate" OR "n-BCA" OR "octyl cyanoacrylate")
Cochrane	("gastric varices" OR "gastroesophageal varices" OR "variceal bleeding" OR "portal hypertension" OR "Varices of the Stomach" OR "stomach varices" OR "Gastric Vein Varices" OR "Portal Hypertensive Gastropathy" OR "Gastric Vascular Abnormalities" OR "Gastric Varicosities" OR "Stomach Varicosities" OR "Esophageal and Gastric Varices" OR "Varicose Veins of the Stomach" OR "Porto-gastric Varices" OR "EUS-guided coil and glue injection" OR "coil" OR "coiling" OR "hybrid approach" OR "Endoscopic Spirals" OR "Endoscopic Coiling System" OR "Endoscopic Coil Implant" OR "Endoscopic Helical Device" OR "Endoscopic Coil Delivery System" OR "Endoscopic Spiral") AND ("endoscopic glue injection" OR "endoscopic cyanoacrylate" OR " methyl 2-cyanoacrylate" OR "MCA" OR "ethyl 2-cyanoacrylate" OR "ECA" OR "Super Glue" OR "Krazy Glue" OR "n-butyl cyanoacrylate" OR "n-BCA" OR "octyl cyanoacrylate")
ClinicalTrials.gov	endoscopic AND "gastric varices" AND ("glue" OR "cyanoacrylate")

SUPPLEMENTARY TABLE 1. Details in center volume and training

Study	Center	No. of faculty with experience in performing EUS-guided embolization	Total endoscopy cases per year	No. of fellows	Estimation of EUS-guided embolization of gastric varices cases per y
Robles-Medranda, 2021[9]	Instituto Ecuatoriano de Enfermedades Digestivas	At least 1 (Carlos Robles-Medranda)*	NI	NI	NI
Galves-García, 2022[10]	Hospital General de México Dr Eduardo Liceaga	NI	NI	NI	NI
Lôbo, 2019[7]	Hospital das Clínicas, Serviço de Endoscopia Gastrointestinal	3	+10,000	2	10
Jamwal, 2023[5]	Institute of Liver and Biliary Sciences, New Delhi, India	2	+30,000	12	40-50
Samanta, 2023[11]	• Postgraduate Institute of Medical Education and Research, Chandigarh	5	+20,000	18	70-80
	• Asian Institute of Gastro-enterology, Hyderabad	5	+40,000	30†	70-80
	• Universita degli Studi di Foggia, Foggia	NI	NI	NI	NI
	• Humanitas Mater Domini, Castellanza	1	+12,000	5	0
Chen, 2024[8]	Ningbo Medical Center Lihuili Hospital, Zhejiang, China	3	36,000	2-3 endoscopy students on rotation	3-5

NI, No significant difference.
*Endoscopist responsible for the EUS in the study.
†Fellow does basic endoscopy only.