



Comparisons Between Endoscopic Band Ligation, Radiofrequency Ablation and Endoscopic Thermal Therapy for Gastric Antral Vascular Ectasia: A Meta-Analysis

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Abstract

Background Endoscopic band ligation (EBL) and radiofrequency ablation (RFA) have emerged as alternative therapies of gastric antral vascular ectasia (GAVE) in addition to endoscopic thermal therapy (ETT), but the optimum choice remains inconclusive.

Aim We conducted a meta-analysis in order to compare these three treatments for GAVE.

Methods We searched the electronic databases of PubMed, Embase and Cochrane Central Register of Controlled Trials without any language restrictions and also performed a manual literature search of bibliographies located in both retrieved articles and published reviews for eligible publications prior to December 8, 2021. We included comparative trials which had evaluated the efficacy and safety of interventions in adults (aged ≥ 18 years) diagnosed with symptomatic GAVE and was confirmed according to clinical backgrounds and upper gastrointestinal endoscopy. We included reports that compared three interventions, ETT, EBL, and RFA. The study was comprised of adults diagnosed with GAVE and focused on overall mortality, bleeding cessation, endoscopic improvement, complications, hospitalization, hemoglobin improvement, number of sessions and transfusion requirements.

Results Twelve studies were performed involving a total of 571 participants for analysis. When compared with ETT, EBL achieved better bleeding cessation (OR 4.48, 95% CI 1.36–14.77, $p=0.01$), higher hemoglobin improvement (MD 0.57, 95% CI 0.31–0.83, $p<0.01$) and lower number of sessions (MD -1.44 , 95% CI -2.54 to -0.34 , $p=0.01$). Additionally, EBL was superior to ETT in endoscopic improvement (OR 6.00, 95% CI 2.26–15.97, $p<0.01$), hospitalization (MD -1.32 , 95% CI -1.91 to -0.74 , $p<0.01$) and transfusion requirement (MD -2.66 , 95% CI -4.67 to -0.65 , $p=0.01$) with statistical significance, with the exception of mortality (OR 0.58, 95% CI 0.19–1.77, $p=0.34$) and complication rate (OR 5.33, 95% CI 0.58–48.84, $p=0.14$).

Conclusion For GAVE, we suggest that EBL be initially recommended, and APC and RFA be used as alternative treatment choices based upon a very low quality of evidence.

Keywords Gastric antral vascular ectasia · Endoscopic thermal therapy · Endoscopic band ligation · Radiofrequency ablation · Meta-analysis

Abbreviations

APC	Argon plasma coagulation
CI	Confidence interval
EBL	Endoscopic band ligation
ETT	Endoscopic thermal therapy
GAVE	Gastric antral vascular ectasia
MD	Mean difference
ORs	Odds ratios

PRISMA	Preferred reporting items for systematic reviews and meta-analyses
RFA	Radiofrequency ablation
RoB 2.0 tool	Version 2 of the Cochrane tool for assessing Risk of Bias in randomised trials
ROBINS-I	Risk of bias in non-randomised studies—of interventions

Extended author information available on the last page of the article

Introduction

Gastric antral vascular ectasia (GAVE) is a capillary ectasia surrounding the gastric pits which radiates outward from the prepyloric gastric antrum [1–3]. It usually manifests itself with longitudinal stripes, diffuse punctate pattern or nodular types [1, 4]. Although GAVE accounts for only 4% of nonvariceal upper gastrointestinal bleeding [5], it is frequently associated with iron deficiency and transfusion-dependent anemia, and is accompanied by repeated blood transfusions and hospitalizations. Therefore, successful management of GAVE in clinical practice is an important issue regarding disease progression.

There are many treatment options both medically and endoscopically for GAVE, with endoscopy having recently become the first-line of therapy [6]. Endoscopic thermal therapy (ETT) using argon plasma coagulation (APC) has been widely used together with a non-contact device to destroy mucosal microvasculature, but a wide variability of endoscopic success rates and high recurrence rates have limited its efficacy in clinical practice. Endoscopic band ligation (EBL) has been in use since 2006 [7] and is applied distally from the pylorus to abnormal mucosa proximally as much as possible using ligation bands. Four meta-analyses [8–11] have been recently published with Mohan et al. [11] demonstrating that EBL exhibited a satisfying endoscopic success rate and GAVE recurrence rate of 81% and 15.4%, respectively. When compared to APC, EBL displayed better endoscopic eradication, less bleeding recurrence and the need for fewer blood transfusions with a lower requirement for therapeutic sessions [8–10]. Radiofrequency ablation (RFA) was first applied in patients with GAVE in 2008 [12] and included an energy generator and through-the-scope catheter, HALO60, HALO90, and HALO90 ULTRA, to achieve immediate hemostasis. One meta-analysis [13] enrolling 9 non-comparative studies on RFA and 24 studies on APC suggested that RFA exhibited similar efficacy and tolerability when compared to APC. There have been no comparative studies performed regarding the comparison between RFA and APC as well as meta-analysis which have discussed the optimum treatment choice amongst ETT, EBL and RFA. Therefore, the aim of our systematic review and meta-analysis was to compare the efficacy and clinical outcome parameters amongst ETT, EBL and RFA in the treatment of GAVE.

Materials and Methods

Search Strategy and Selection Criteria

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 statement [14] (Table S1). We

searched electronic databases including PubMed, Embase and Cochrane Central Register of Controlled Trials without any language restrictions and contained the keywords of Gastric antral vascular ectasia and its synonym. We also performed a manual literature search of bibliographies found in both retrieved articles and published reviews for eligible publications prior to December 8, 2021. Studies in abstract form were also enrolled for inclusion. A detailed description of the search strategies is provided in Table S2.

We included adults (aged ≥ 18 years) diagnosed with symptomatic GAVE, which was confirmed by symptoms, anemia, or gastrointestinal bleeding related to GAVE and required blood transfusion or endoscopic treatments. We compared the relative efficacy and safety of GAVE treatments among three interventions, ETT, EBL and RFA. We analyzed clinical outcomes including the overall mortality, bleeding cessation, complication, hospitalization, hemoglobin improvement, and transfusion requirement as well as endoscopic parameters of endoscopic improvement, and number of interventional sessions. Reports that involved pediatric patients, or patients with anemia or upper gastrointestinal bleeding other than GAVE, as well as those involving severe concurrent comorbidities were excluded.

Outcome Measures

For clinical outcome parameters, we determined the overall mortality rate, bleeding cessation rate, endoscopic improvement, complication rate, hospitalization, mean difference (MD) of hemoglobin, number of therapeutic sessions and requirement of blood transfusions during follow-up periods after completion of interventions from the enrolled studies. We defined cessation of bleeding as the absence of overt bleeding, endoscopic evidence of bleeding from GAVE or a requirement for transfusions, a hemoglobin drop < 2.0 g/dL per month, or no need for endoscopy within thirty days. Endoscopic improvement was judged subjectively by endoscopists, while adverse events were recorded if abdominal symptoms, fever, ulcer bleeding after endoscopic procedures, or post-therapeutic polyps occurred. Additionally, we analyzed the MD of hospitalization both before and after treatment, as well as hemoglobin change and requirement for blood transfusion, in order to investigate the therapeutic benefits. Ethical approval or informed consent from the participants was not necessary as there was no individual participant data involved.

Data Extraction and Quality Assessment

Two investigators (S-SI and C-CC) independently screened the titles and abstracts for eligibility, and full

texts were assessed to clarify the eligibility status of each article. All discrepancies were discussed and resolved through consultation with a third investigator (K-CW). Two reviewers (S-SI and C-CC) extracted data independently, with the data then checked by a third investigator (K-CW). The following variables were all extracted: country of study, participants' characteristics, inclusion criteria, details of comparative interventions and outcomes measurements.

Two investigators (S-SI and C-CC) evaluated the risk of bias in all studies independently and assessed the quality of the articles included in the analysis with version 2 of the Cochrane tool for assessing Risk of Bias in randomised trials (RoB 2.0 tool) [15, 16] and the Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I tool) [17]. Differences in opinion were discussed until a consensus was reached, with a third investigator (K-CW) being consulted when necessary.

Data Synthesis and Statistical Analysis

The results were analyzed using Review Manager V.5.3 software (Nordic Cochrane Centre, Copenhagen, Denmark). The pooled odds ratios (ORs) and 95% confidence interval (CI) were reported for binary variables and dichotomous variables, respectively. When we noted zero events, imputation for zero cell counts of 0.5 was performed. An OR with a 95% CI was used to present the overall mortality rate, bleeding cessation rate, endoscopic improvement and complication rate from the enrolled studies. The pooled MDs and 95% CI were reported for continuous variables, which consisted of hospitalization, Hb change, number of therapeutic sessions and requirement for blood transfusion. These were completely produced using a random effect model to allow for the expected heterogeneity amongst the enrolled studies.

Heterogeneity of the outcome measures was examined using the Cochrane I^2 statistic. We regarded an I^2 of less than 25% as mild heterogeneity, 25–50% as moderate heterogeneity, and higher than 50% as severe heterogeneity. If the χ^2 test showed $p > 0.05$ it was not considered significant in the heterogeneity test of the research. We checked for publication bias by carrying out a visual inspection of the funnel plot.

Subgroup Analysis

In addition, we performed subgroup analysis to determine the priority of procedures for GAVE in cirrhotic patients, as well as for those patients having a mean age older than 65 years.

Results

After primary screening of the titles and abstracts, 18 full-text articles were assessed for eligibility (Fig. 1 and Tables S3). Ultimately, we included 12 articles for both qualitative and quantitative analysis involving a total of 571 participants as summarized in the supplementary reference.

Characteristics of the Included Studies

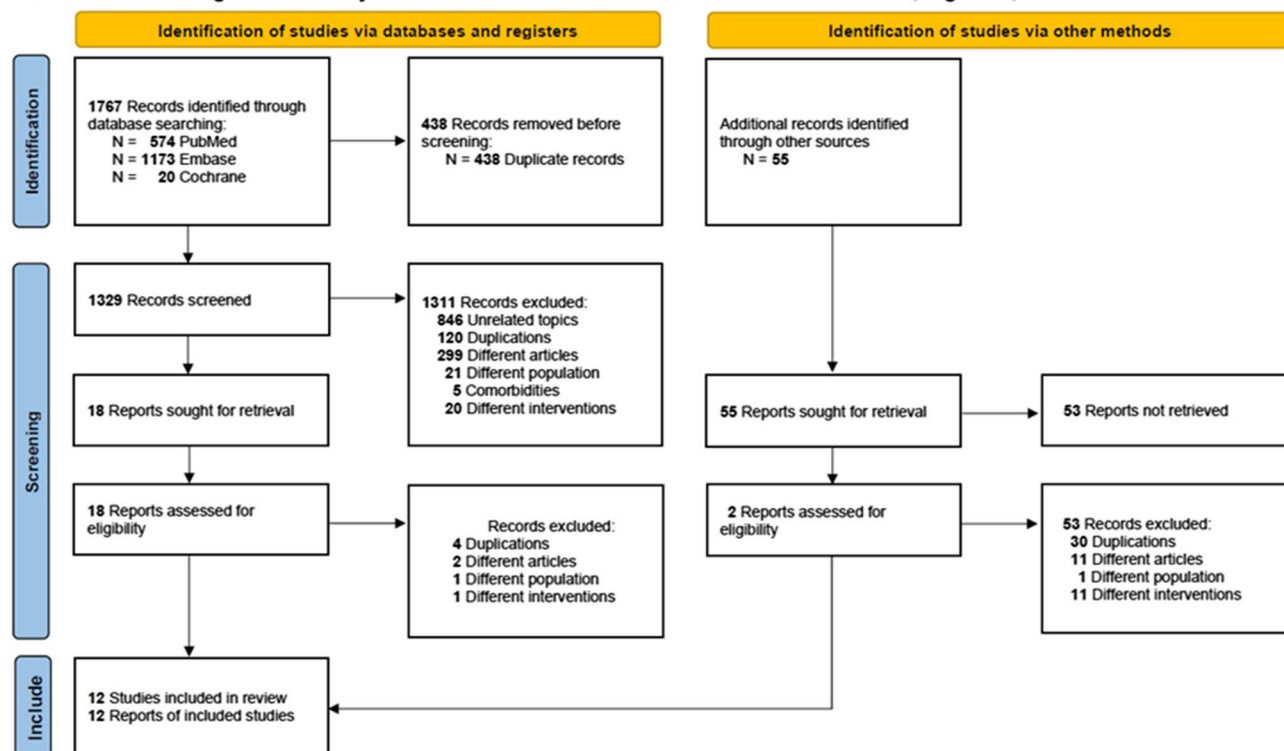
The methodology and characteristics of the study design and patient outcomes from the 4 randomized controlled studies plus 8 retrospective cohort trials are summarized in Tables S4, S5 and S6. A total of 4 randomized controlled studies and 6 retrospective cohort trials compared EBL to ETT while another two retrospective studies conducted head-to-head comparisons between RFA and ETT. Among these studies sample size ranged from 15 to 96 (median 38), while the ranges for age, percentage of male gender and cirrhosis were 27.0–74.0, 26.1–72.2 and 13.0–100.0, respectively. Most studies were performed in the Americas and Egypt (58.3%), with the remaining studies coming from the nations of Ireland, Hungary, Japan and Italy. ETT and EBL were the most common interventions seen in our review, followed by RFA with only 2 comparative trials.

Outcome Parameters: Efficacy and Safety

Traditional meta-analyses of the included regimens are shown in Figs. 2, 3 and 4. When compared with ETT (the reference regimen), EBL achieved better bleeding cessation (OR 4.48, 95% CI 1.36–14.77, $p=0.01$), higher hemoglobin improvement (MD 0.57, 95% CI 0.31–0.83, $p<0.01$), and a lower number of sessions (MD –1.44, 95% CI –2.54 to –0.34, $p=0.01$), while RFA showed no difference in these outcomes with a pooled OR of bleeding cessation of 4.88 (95% CI 0.29–82.08, $p=0.27$). St Romain et al. [18] reported that the mean number of sessions for RFA and ETT between non-cirrhotic and cirrhotic patients were 2.4–2.7, and 2.2–2.4, respectively, with no statistically significant hemoglobin change between these two groups.

Additionally, EBL was superior to ETT in endoscopic improvement (OR 6.00, 95% CI 2.26–15.97, $p<0.01$), hospitalization (MD –1.32, 95% CI –1.91 to –0.74, $p<0.01$), and transfusion requirement (MD –2.66, 95% CI –4.67 to –0.65, $p=0.01$), with statistical significance being seen except in mortality (OR 0.58, 95% CI 0.19–1.77, $p=0.34$) and complication rate (OR 5.33, 95% CI 0.58–48.84, $p=0.14$). Severe heterogeneity was disclosed in bleeding cessation ($I^2=63\%$), complication rate ($I^2=78\%$), number of sessions ($I^2=98\%$), and transfusion requirement ($I^2=73\%$).

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources



From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71.

Fig. 1 PRISMA 2020 Flow Diagram

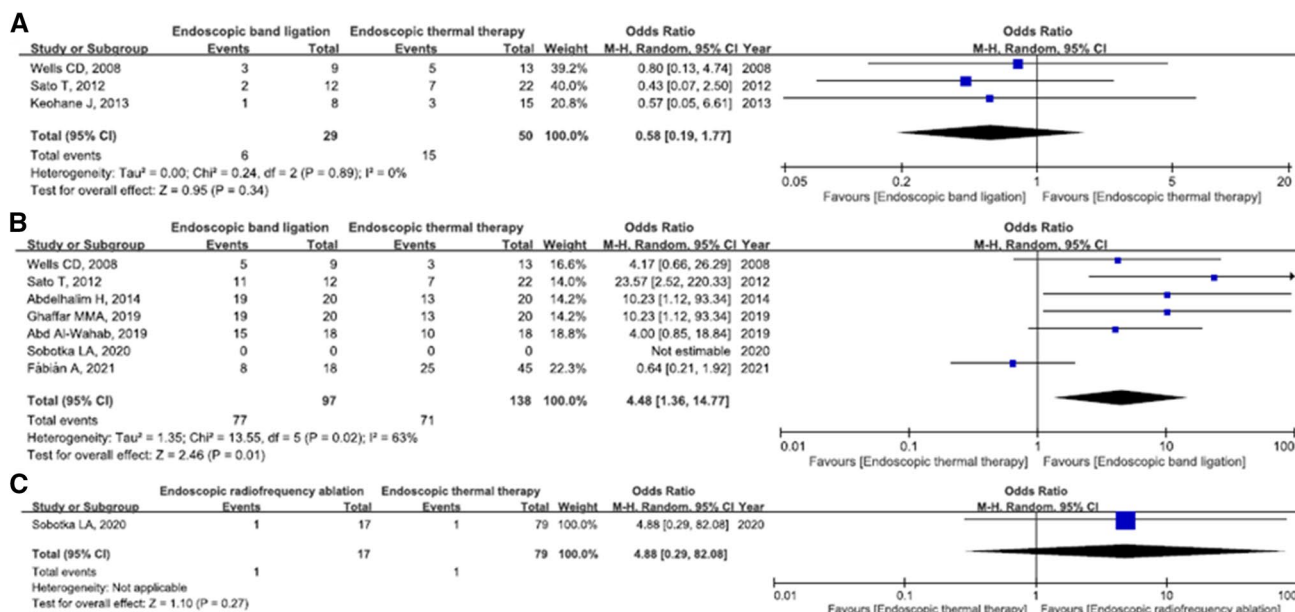


Fig. 2 Forest plot of direct comparisons (OR) of GAVE between endoscopic band ligation and endoscopic thermal therapy for overall mortality (A) and cessation of bleeding (B), as well as cessation of

bleeding between endoscopic radiofrequency ablation and endoscopic thermal therapy (C). GAVE gastric antral vascular ectasia, ORs odd ratios, CI confidence interval

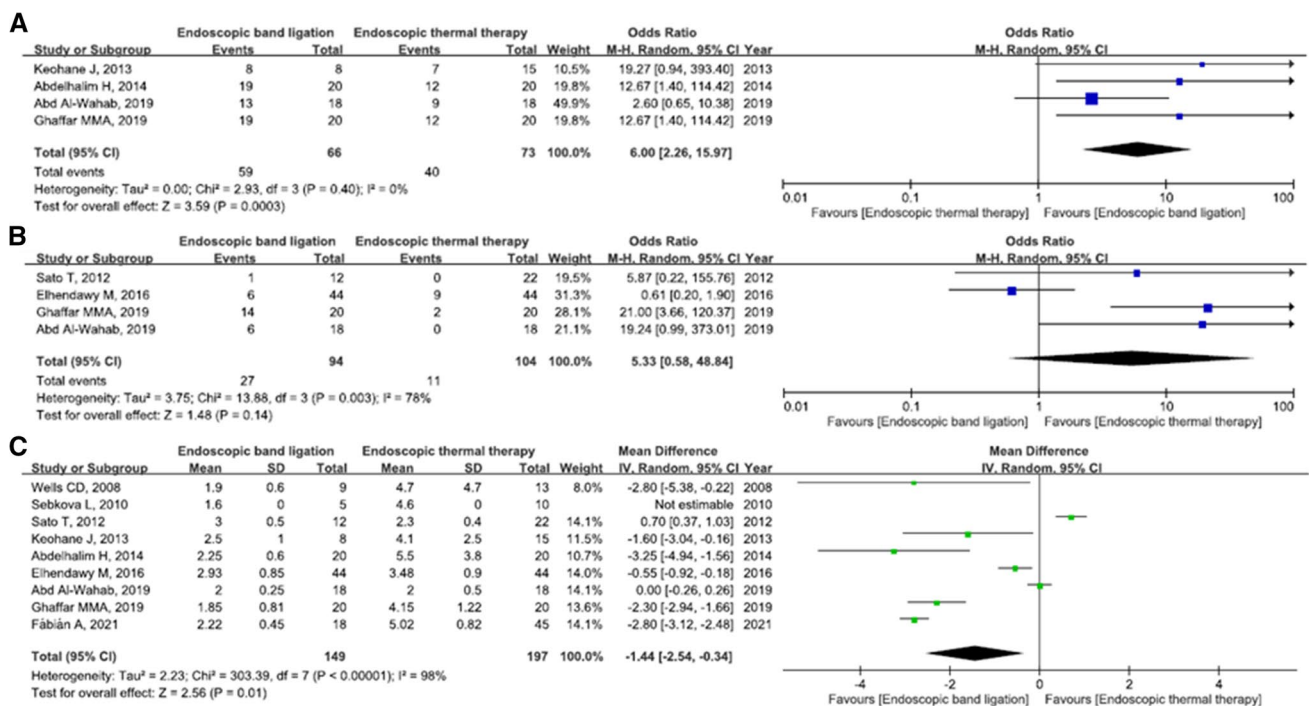


Fig. 3 Forest plot of direct comparisons (OR) of GAVE between endoscopic band ligation and endoscopic thermal therapy for endoscopic improvement (A), complication rate (B), and the direct com-

parison (MD) for number of therapeutic sessions (C). GAVE gastric antral vascular ectasia, ORs odd ratios, MD mean difference, CI confidence interval, SD standard deviation

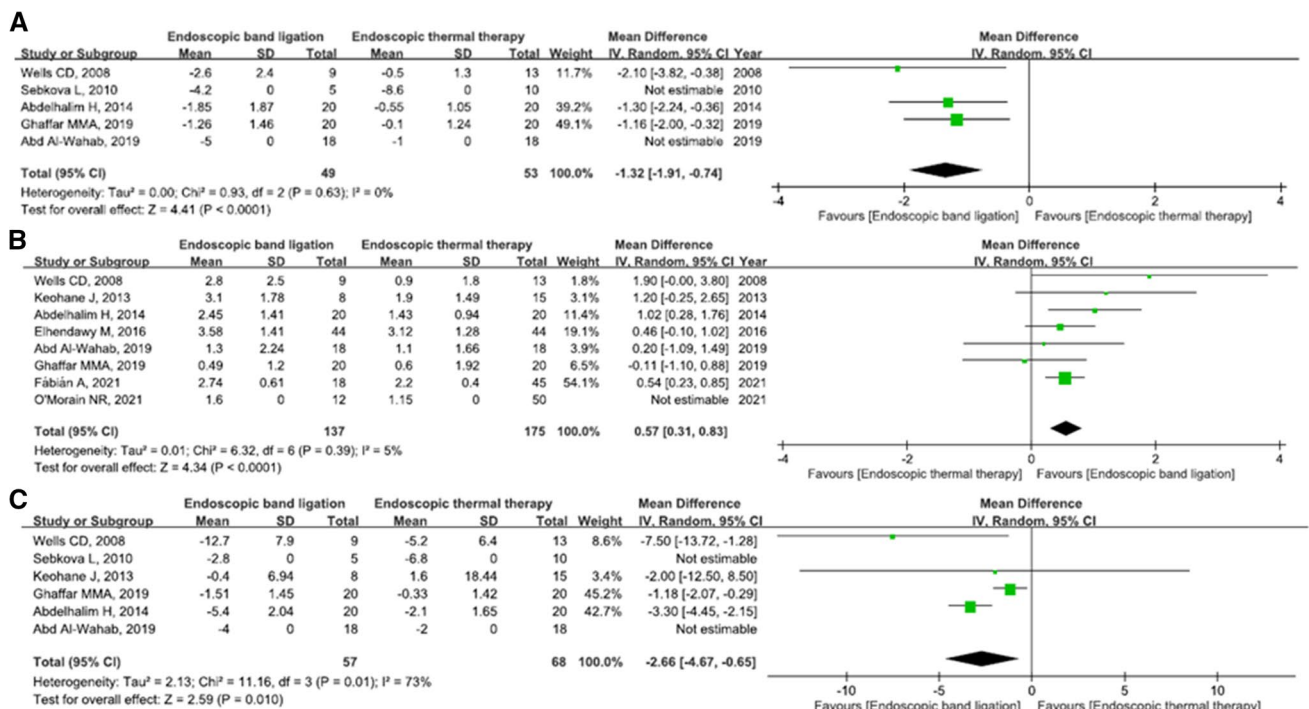


Fig. 4 Forest plot of direct comparisons (MD) of GAVE between endoscopic band ligation and endoscopic thermal therapy for hospitalization (A), hemoglobin improvement (B), and transfusion require-

ment (C). GAVE gastric antral vascular ectasia, MD mean difference, CI confidence interval, SD standard deviation

with significance. As for overall mortality ($I^2=0\%$), endoscopic improvement ($I^2=0\%$), hospitalization ($I^2=0\%$), and hemoglobin improvement ($I^2=5\%$), I^2 were less than 5% showing mild heterogeneity. Funnel plot revealed visually remarkable asymmetry in Figures S1B, E and G, while the rest of the funnel plots from this meta-analysis could not be judged due to less than 5 trials being held in each comparative outcome (Fig. S1A, C, D, F and H).

In subgroup analysis, we demonstrated that EBL was superior to ETT in cirrhotic patients with regards to bleeding cessation 6.37 (95% CI 2.12–19.15, $p < 0.01$), endoscopic improvement (OR 5.51, 95% CI 1.79–16.94, $p < 0.01$), hospitalization (MD –1.22, 95% CI –1.85 to –0.60, $p < 0.01$), hemoglobin improvement (MD 0.49, 95% CI 0.05–0.93, $p = 0.03$), and transfusion requirement (MD –2.21, 95% CI –4.28 to –0.13, $p = 0.04$) (Table 1). In patients older than 65 years, EBL was only better than ETT in hospitalization (MD –2.10, 95% CI –3.82 to –0.38, $p = 0.02$), hemoglobin improvement (MD 0.77, 95% CI 0.15–1.39, $p = 0.01$), and transfusion requirement (MD –6.07, 95% CI –11.42 to –0.72, $p = 0.03$).

Risk of Bias Assessment

The Cochrane Collaboration's Risk of Bias assessment is shown in Table S7. Some concern existed with regards to overall bias of the two trials [19, 20] because these studies did not describe the randomization process completely. ROBINS-I assessment is shown in Table S8, revealing that critical risks of bias were distributed in the domains of bias due to confounding, and that selection bias resulted in a critical risk of overall bias. Moderate to severe risks of bias were distributed in the domains of bias through the classification of interventions, bias due to missing data attrition and deviation from intended interventions.

Discussion

In this meta-analysis, we comprehensively investigated therapeutic efficacy amongst EBL, RFA and ETT in patients diagnosed with GAVE. We subsequently reported that EBL achieved better bleeding cessation, higher hemoglobin improvement, lower number of sessions, greater endoscopic improvement, shorter hospitalization and less transfusion requirement with statistical significance being seen when compared to ETT. There were exceptions however for both mortality and complications rates, while RFA showed no difference in any of these outcomes.

EBL is a widely used technique for esophageal varices with fewer adverse events being reported than treatment involving sclerotherapy alone for patients experiencing end-stage liver cirrhosis with decompensation [21]. Polski et al. [22] observed that histopathological changes in ischemic necrosis, superficial ulceration and submucosal fibrosis following esophageal varices ligation were due to vascular thrombosis, which may be postulated mechanisms for intervention of GAVE. Previous meta-analyses have shown that EBL was associated with a lower transfusion requirement [8–10], greater hemoglobin improvement [8, 9], fewer treatment sessions [8, 9], less recurrent bleeding [9, 10] and shorter hospitalization [10] when compared to ETT in clinical parameters except the mortality and complication rates, a finding which was consistent with our study. Furthermore, we also conducted subgroup analysis to demonstrate that EBL offered better hemoglobin improvement and less transfusion requirement and hospitalization course in patients older than 65 years when compared to ETT. Meanwhile, EBL was also superior to ETT in bleeding cessation, endoscopic improvement, hospitalization, hemoglobin improvement, and transfusion requirement in patients with cirrhosis, which had not been mentioned in previous studies. These studies also indicated that fewer treatment sessions of EBL were required, thus making it more cost-effective than other devices. Additionally, EBL requires less steep of a learning

Table 1 Subgroup analysis of GAVE between endoscopic band ligation and endoscopic thermal therapy

Cirrhosis				Older than 65 years			
Outcome	Sample size	OR (95% CI)	<i>p</i> -value	Outcome	Sample size	OR (95% CI)	<i>p</i> -value
Mortality	–	–	–	Mortality	79	0.58 (0.19–1.77)	0.34
Cessation of bleeding	116	6.37 (2.12–19.15)	<0.01	Cessation of bleeding	119	3.36 (0.40–28.09)	0.26
Endoscopic improvement	116	5.51 (1.79–16.94)	<0.01	Endoscopic improvement	23	19.27 (0.94–393.40)	0.05
Complication	198	5.33 (0.58–48.84)	0.14	Complication	34	5.87 (0.22–155.76)	0.29
Outcome	Sample size	MD (95% CI)	<i>p</i> -value	Outcome	Sample size	MD (95% CI)	<i>p</i> -value
Number of sessions	238	–0.85 (–1.75 to 0.05)	0.06	Number of sessions	142	–1.55 (–3.97 to 0.86)	0.21
Hospitalization	116	–1.22 (–1.85 to –0.60)	<0.01	Hospitalization	22	–2.10 (–3.82 to –0.38)	0.02
Hemoglobin improvement	204	0.49 (0.05–0.93)	0.03	Hemoglobin improvement	108	0.77 (0.15–1.39)	0.01
Transfusion requirement	80	–2.21 (–4.28 to –0.13)	0.04	Transfusion requirement	45	–6.07 (–11.42 to –0.72)	0.03

GAVE gastric antral vascular ectasia, ORs odd ratios, CI confidence interval, MD mean difference

curve for endoscopists in a user-friendly manner [9, 23], while ETT requires more detailed surgical skills to probe some distance away from the lesion, with time-consuming coagulation occurring depending on the surface of GAVE. GAVE is usually associated with chronic liver disease and cirrhosis, which may aggregate in the elderly, and our study has demonstrated that EBL is also safer for both cirrhotic and elderly patients.

RFA has been recommended for patients experiencing Barrett's esophagus with high-grade dysplasia [24] or low-grade dysplasia [25], as it can apply a high frequency alternating electrical current delivered locally to tissue resulting in a uniform ablation depth within the superficial layer of mucosa, thus providing a more balanced thermal injury than other modalities on a smooth surface. McCarty et al. [13] reported that RFA offered a better endoscopic success rate, fewer treatment sessions and less complications in a non-comparative analysis, with the exception of post-procedure hemoglobin and transfusion dependency which improved more for ETT than for RFA. As for our study, RFA showed no difference in bleeding cessation, hemoglobin improvement or number of sessions when compared with ETT based on the limited literature and low quality of evidence taken from retrospective studies. Therefore, RFA may be considered as salvage therapy when ETT is unavailable or has failed, except in cases of an uneven surface with nodularity.

There were still some limitations in our study. First of all, we enrolled 4 randomised controlled trials and 8 retrospective cohort trials in our analysis with visually remarkable asymmetry in funnel plot, which contributed to both selection bias and publication bias. We excluded most of the studies concerning RFA because of their noncomparative study designs, and in turn enrolled only 2 studies [18, 26] involving 148 participants, which may have accounted for any confounding factors and reporting bias. The certainty of the evidence is very low due to limitations in study design, inconsistency of results, and publication bias. Therefore, further randomized controlled studies are awaited, particularly regarding interventional comparisons of RFA and other modalities. Second, we did not perform meta-regression analysis according to GAVE subtypes or associated diseases such as chronic kidney disease or connective tissue disease, for the purpose of examining the impact of patient variables on study outcomes, due to missing characteristics. Instead, we performed subgroup analysis in cirrhotic and elderly patients to explore the impact of GAVE in a different population. Third, it is challenging to estimate the clinical outcomes of GAVE if no standard operating procedure exists for either EBL or RFA, as well as establishing a consensus of indication for repeat endoscopic therapy. Additionally, cost-effective analyses are warranted, from the preparation of equipment to treatment sessions of modalities, all of which are crucial when sharing decision-making options amongst the medical community in daily practice.

Conclusions

In this meta-analysis focusing on GAVE, we recommend that EBL be initially recommended, and APC and RFA be used as alternative treatment choices based on a very low quality of evidence. Additionally, EBL is a safer procedure for patients older than 65 years of age, as well as for cirrhotic patients.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s10620-023-08028-7>.

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Author's contributions SSI and CCC designed the meta-analysis, with input from all listed authors. SSI, CCC, KCW, TYK, and CCH contributed to data acquisition and drafted the article. SSI, CCC, TYK, and KCW contributed to data analysis and interpretation. All authors performed critical revision of the manuscript and approved the final draft of the article.

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Data availability All data relevant to the study are either included in the article or uploaded as supporting information.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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