World Journal of Gastroenterology, Hepatology and Endoscopy ISSN: 2766-788X

Research Article Open Access

Optimal Secondary Prophylaxis for Esophageal and Gastric Variceal Bleeding: A Network Meta-Analysis of Surgery, TIPS, and Endoscopy

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Received Date: 10 Mar 2026
Accepted Date: 28 Mar 2026
Published Date: 30 Mar 2026 J
Short Name: WJGHE

Keywords: Esophageal and Gastric Variceal Bleeding; Surgery; TIPS; Endoscopy; Network Meta-Analysis

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Abstract

1.1. Background

Liver cirrhosis with gastroesophageal variceal bleeding is a major cause of morbidity and mortality worldwide. Secondary prophylaxis to prevent variceal rebleeding remains a clinical challenge. Although surgery, trans jugular intrahepatic portosystemic shunt (TIPS), and endoscopic therapy are widely used, their comparative efficacy and optimal treatment sequence remain controversial.

1.2. Aims

To compare the surgery, TIPS, and endoscopy as secondary prophylactic interventions for patients with a history of variceal bleeding.

1.3. Methods

We systematically searched PubMed, Embase, the Cochrane Library, Web of Science, and Ovid MEDLINE from inception to March 2026. Randomized controlled trials and retrospective studies comparing surgery, TIPS, or endoscopic therapy as secondary prophylaxis were included. Two researchers independently screened studies, extracted data, and assessed quality using ROB2 or the Newcastle-Ottawa Scale (NOS). Bayesian network meta-analysis was performed to calculate pooled odds ratios and ranking probabilities.

1.4. Results

30 studies were included. For rebleeding, surgery ranked best, followed by TIPS and endoscopy. Surgery significantly reduced rebleeding risk compared with endoscopy (OR 0.104, 95% CI 0.044–0.238) and TIPS (OR 0.370, 95% CI 0.171–0.790). For all-cause mortality, surgery remained the best, while TIPS ranked worst, with significantly higher mortality than surgery (OR 2.03, 95% CI 1.22–3.32). For HE, TIPS ranked worst, with significantly higher risk versus surgery (OR 0.143, 95% CI 0.0532–0.344) and endoscopy (OR 0.260, 95% CI 0.123–0.497). Subgroup analysis revealed no differences between endoscopy alone and endoscopy combined with medication across all outcomes. Shunt surgery was superior to devascularization for rebleeding control, whereas devascularization surgery showed advantages in HE prevention.

1.5. Conclusion

Surgery is the most effective intervention for preventing rebleeding and reducing mortality, while TIPS carries the highest risk of HE. The choice between shunt and devascularization surgery should be individualized.

1.6. Core Tips

This first network meta-analysis comparing surgery, TIPS,

and endoscopy for variceal rebleeding shows surgery is most effective in preventing rebleeding and reducing mortality. TIPS carries the highest hepatic encephalopathy risk. Choice between shunt and devascularization should be individualized based on rebleeding risk and encephalopathy considerations.

2. Introduction

Liver cirrhosis represents a significant global health burden, affecting millions of individuals worldwide and contributing substantially to morbidity and mortality [1]. Among the most severe and life-threatening complications of portal hypertension in cirrhotic patients is the development of oesophageal and gastric varices, with an estimated prevalence of approximately 50% in patients with compensated cirrhosis and up to 85% in those with decompensated disease [2,3]. Acute variceal bleeding constitutes a medical emergency associated with substantial mortality, with reported six-week mortality rates ranging from 10% to 20% despite advances in therapeutic interventions [4-6]. For patients who survive an initial bleeding episode, the risk of recurrent variceal haemorrhage without secondary prophylactic treatment is alarmingly high, approaching 60% within one to two years, with each rebleeding episode carrying significant mortality risk and decreased quality of life [7-9].

The current armamentarium for secondary prophylaxis of variceal bleeding encompasses several therapeutic modalities, primarily including endoscopic therapy, trans jugular intrahepatic portosystemic shunt (TIPS), and surgical interventions [10-14]. Endoscopic approaches, including endoscopic variceal ligation and sclerotherapy, either alone or in combination with non-selective beta-blockers, have traditionally served as first-line options due to their minimally invasive nature and widespread availability [15-17]. TIPS, a radiological intervention creating an intrahepatic shunt between the portal and hepatic veins, effectively reduces portal pressure and has demonstrated efficacy in preventing variceal rebleeding, particularly in patients who fail endoscopic therapy [18, 19]. Surgical options, including various shunt procedures (such as distal splenorenal shunt) and devascularization operations (such as esophagogastric devascularization with splenectomy), offer definitive portal decompression or variceal obliteration but carry the inherent risks of major abdominal surgery and postoperative complications [20-22].

Despite the availability of these treatment modalities, the optimal strategy for secondary prevention of variceal bleeding remains a subject of ongoing debate [23]. Furthermore, existing studies have predominantly focused on rebleeding as the primary endpoint, with less attention paid to other critical outcomes such as mortality and the development of hepatic encephalopathy (HE)-a devastating complication particularly associated with shunt procedures [24]. Importantly, previous meta-analyses have been limited by traditional pairwise approaches that cannot simultaneously compare multiple treatments, and they have rarely addressed the heterogeneity within treatment categories, such as the distinction between shunt and devascularization surgery or between endoscopy alone versus endoscopy combined with pharmacotherapy [25]. Additionally, inconsistencies in study design, patient populations, and follow-up durations across individual trials have hindered the synthesis of evidence and the establishment of clear treatment hierarchies.

Given these knowledge gaps, a comprehensive network meta-analysis that integrates direct and indirect evidence while accounting for treatment heterogeneity and multiple clinically relevant outcomes is urgently needed to guide clinical decision-making and inform future research directions.

3. Materials And Methods

3.1. Search Strategy

Two researchers independently screened the titles and abstracts of the articles in accordance with the selection criteria. The literature search was performed in multiple electronic databases, including PubMed, Embase, the Cochrane Library, Web of Science, and Ovid MEDLINE, from their inception to March 2026. A combination of free-text terms and medical subject headings (MeSH/Emtree) were used for the subject search, as follows: “liver cirrhosis,” “portal hypertension,” “oesophageal and gastric varices,” “surgery,” “trans jugular intrahepatic portosystemic shunt (TIPS),” “endoscopy,” “haemorrhage,” “HE,” and “survival rate.” The article type was restricted to randomized controlled trials.

3.2. Study Selection

Two researchers independently screened the titles and abstracts of all retrieved records against the eligibility criteria. Full-text articles of potentially relevant studies were then

obtained and further assessed for inclusion. Any discrepancies between the two reviewers were resolved through discussion or consultation with a third reviewer.

Studies were considered eligible if they met the following criteria: (1) patients with clinically or pathologically confirmed liver cirrhosis and a history of gastroesophageal variceal bleeding who received corresponding secondary prophylactic treatment after the first bleeding episode; (2) age ≥ 18 years, regardless of sex; (3) randomized controlled trials (RCTs) or retrospective studies comparing surgery, trans jugular intrahepatic portosystemic shunt (TIPS), or endoscopic therapy (with or without concomitant medication) as secondary prophylactic interventions; (4) studies reporting rebleeding and mortality as primary outcomes.

The exclusion criteria were as follows: (1) articles not written in English; (2) non-human studies; (3) non-clinical articles, such as case reports, letters, basic research, or systematic reviews; (4) studies lacking sufficient or qualified data; (5) duplicate publications or studies with fewer than 20 participants in any group.

3.3. Data Extraction and Quality Assessment

Data included in the analysis were independently extracted by two researchers, with a third researcher participating when necessary to reach a majority decision. The following information was incorporated into the subsequent analysis: (1) authors' names, year of publication, intervention measures, country of study, number of patients, and follow-up time; (2) clinical outcomes, with all-cause rebleeding during the follow-up period as the primary outcome variable, and mortality and the occurrence of HE as secondary outcome variables. This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2009 statement[26]. The methodological quality of randomized controlled trials (RCTs) and retrospective studies was evaluated using ROB2 or the Newcastle-Ottawa Scale (NOS) [27, 28].

3.4. Subgroup Analysis

Among the three specific interventions, the endoscopic treatment group was divided into the endoscopy-only group (Endoscope_only) and the endoscopy plus drug group (Endoscope+Drug) based on whether vasoactive drugs such as somatostatin were administered; surgery was classified according to its nature, with procedures including splenectomy combined with pericardial devascularization categorized as devascularization surgery , and procedures including splenorenal shunt categorized as shunt surgery.

4. Statistical Analysis

This study used the gemtc package (version 1.1-0) to perform Bayesian network meta-analysis using the Markov chain Monte Carlo (MCMC) method [29]. The mtc.run function was applied to generate samples, with 5,000 simulations set as the "burn-in" period for each chain, yielding 20,000 iterations based on three Markov chains to obtain the odds ratios (ORs) for the model parameters. Rank probabilities were calculated to determine the hierarchical position of each treatment, and rank probability plots were created. Brooks-Gelman-Rubin plots, trace plots, and density plots were used to assess model convergence [30,31]. The mtc. anohe command was used to evaluate global heterogeneity. The mtc. nodesplit command was used to perform consistency testing. The net meta package (version 3.3-1) was used to generate funnel plots for assessing publication bias. $p<0.05$ is considered as statistically significant [32].

5. Results

5.1. Studies Included in Meta Analysis

The literature search yielded 5517 clinical studies. After title and abstract screening by two researchers, duplicate removal, and eligibility assessment, 1439 articles were excluded, and the remaining articles underwent full-text review for secondary screening. Finally, 30 randomized controlled studies and retrospective studies met the inclusion criteria and were selected for the meta-analysis. The detailed screening process is shown in Figure 1.

5.2. Study Characteristics and Quality

The basic characteristics of the selected studies are summarized in Table 1. Among 30 studies, 19 were conducted in Asia, 4 in Europe, 5 in America, 1 in Africa and 1 Multi-center. Interventions were mainly categorized into the endoscopy group (including endoscopy-only and endoscopy combined with drugs), TIPS, and surgical operations (including devascularization surgery mainly consisting of pericardial

Table 1: Characteristics of studies included in Meta-analysis.

References	Country	alcohol/ Hepatitis/ others	Age (range or SD	Male/ female	Treatment	SampleSize	(A/B/C)	(range or SD)
Chen B, 2024[38]	China	4/77/16	54.8±11.6	60/37	TIPS	97	32/65/0	37.9 months
Chen B, 2024	China	6/87/11	52.7±10.3	68/36	Devascularization surgery	104	48/56/0	57.2 months
G Pomier-Layrargues, 2001[39]	Canada	NA	52.9±13.3	29/12	TIPS	41	NA	678 days
G Pomier-Layrargues, 2001	Canada	NA	54.3±10.9	27/12	Endoscope	39	NA	581 days
G.-H. Lo, 2007[40]	Taiwan,China	NA	NA	NA	TIPS	35	NA	NA
G.-H. Lo, 2007	Taiwan,China	NA	NA	NA	Endoscope	37	NA	NA
Guo H, 2021[41]	China	6/31/9	54.67±11.72	28/18	Endoscope	46	22/24/0	11.5 months
Guo H, 2021	China	4/21/2012	53.92±12.62	23/14	TIPS	37	16/19/2	13.2 months
Gülberg, 2002[42]	Germany	22/3/3	57±2	20/8	TIPS	28	11/15/2002	1.8 years
Gülberg, 2002	Germany	23/3/0	56±2	19/7	Endoscope	26	10/12/2004	2.0 years
J. MICHAEL HENDERSON, 2006[43]	USA	43/NA/NA	53±10	42/31	Shunt surgery	73	41/32/0	45 months
J. MICHAEL HENDERSON, 2006	USA	37/NA/NA	52±1	44/23	TIPS	67	39/28/0	45 months
Juan G. Abraldes 2013[44]	Multi-center	18/4/8	55±9	18/12	Endoscope	30	0/10/20	14.6±12 months
Juan G. Abraldes 2013	Multi-center	25/5/15	56±12	34/11	TIPS	45	0/18/27	13.1±12 months
Junyuan Zhu, 2025[45]	China	5/13/2012	56.6±11.1	19/11	TIPS	30	12/15/2003	24.5 months
Junyuan Zhu, 2025	China	7/15/2008	55.0±11.3	19/11	Endoscope	30	12/16/2002	22.4 months
Kai Zhang, 2019[46]	China	5/23/2015	50.40±11.91	24/19	Devascularization surgery	43	22/15/6	33.4±18.0 months
Kai Zhang, 2019	China	3/18/2010	50.06±12.45	23/8	TIPS	31	8/14/2009	25.3±13.9 months
Lu Ning Li, 2019[47]	China	NA	47.3 ± 13.4	16/5	TIPS	21	NA	21.0 ± 9.1 months
Lu Ning Li, 2019	China	NA	46.2 ± 11.5	19/7	Endoscope	26	NA	27.0 ± 19.3 months
Ma JL, 2021[48]	China	0/151/0	48.0±10.1	113/38	Endoscope	151	76/69/6	38.8 months
Ma JL, 2021	China	0/151/0	47.2±8.8	106/45	Devascularization surgery	151	76/68/7	57.0 months
Marshall J. Orloff, 2014[49]	USA	NA	49	56/22	TIPS	78	NA	NA
Marshall J. Orloff, 2014	USA	NA	49.1	60/16	Shunt surgery	76	NA	NA
P. Sauer, 2002[50]	Germany	29/9/5	53.5±11.8	27/16	TIPS	43	15/16/12	4.1±0.26 years
P. Sauer, 2002	Germany	24/9/6	55.1±12.5	23/19	Endoscope	42	10/19/2013	3.64±0.25 years
Roberto Santambrogio, 2006[51]	Italy	NA	NA	NA	Shunt surgery	40	NA	109 ± 58 months
Roberto Santambrogio, 2006	Italy	NA	NA	NA	Endoscope	40	NA	87 ± 61 months
Sagnik Biswas, 2025[52]	India	18/10/17	45.2±12.8	35/10	Endoscope	45	16/22/7	17.9 months
Sagnik Biswas, 2025	India	7/23/2015	45.6±12.1	27/18	Devascularization surgery	45	16/24/5	16.4 months
Shin Jae Lee, 2017[53]	South Korea	41/45/9	59.4±10.9	73/22	Devascularization surgery	95	NA	30.6±30.1 months
Shin Jae Lee, 2017	South Korea	22/22/3	55.6±9.0	42/5	TIPS	47	NA	23.4±24.1 months
Spela Korsic, 2021[54]	Slovenia	49/NA/NA	53.56±11.15	45/25	TIPS	70	15/41/14	47 months
Spela Korsic, 2021	Slovenia	30/NA/NA	57.57±11.69	34/22	Endoscope	56	8/31/2017	40 months
Su AP, 2017[55]	China	45/146/11	50.4±10.4	135/61	TIPS	196	101/95/0	29.2±7.6 months
Su AP, 2017	China	53/223/20	47.3±9.9	175/108	Devascularization surgery	283	148/135/0	28.7±8.3 months
Wenfeng Zhu, 2023[56]	China	8/57/18	50 (44-62)	66/17	Devascularization surgery	83	NA	NA
Wenfeng Zhu, 2023	China	12/57/14	47 (44-63)	65/18	TIPS	83	NA	NA
Wenyue Wu, 2023[57]	China	4/19/2019	57.17±11.72	25/17	Endoscope	42	22/20/0	12 months

Wenyue Wu, 2023	China	3/28/2008	54.62±9.59	25/14	TIPS	39	14/24/1	12 months
Yong Lv, 2018[58]	China	NA	49	13/11	TIPS	24	9/13/2002	30.9 months
Yong Lv, 2018	China	NA	46	16/9	Endoscope	25	10/14/2001	30.4 months
Yong Lv, 2019[59]	China	2/65/17	50.7±11.6	53/31	TIPS	84	0/65/19	24 months
Yong Lv, 2019	China	4/38/3	50.9±10.4	34/11	Endoscope	45	0/35/10	24 months
Zhang H, 2021[60]	China	4/34/12	55±11	32/18	TIPS	50	21/26/3	21 months
Zhang H, 2021	China	5/20/2022	56±13	26/21	Endoscope	47	12/31/2004	18 months
Fouad Harras, 2010[61]	Egypt	NA	NA	NA	Endoscope+Drug	50	NA	NA
Fouad Harras, 2010	Egypt	NA	NA	NA	Endoscope	50	NA	NA
Zhuang Zeng, 2024[62]	China	3/39/18	56 (50.00-67.75)	38/22	TIPS	60	21/32/7	NA
Zhuang Zeng, 2024	China	2/30/13	51 (45.50-59.00)	31/14	Endoscope	45	20/23/2	NA
Syed Mohsin Ali, 2017[63]	China	4/37/23	51.5±13.1	51/13	Endoscope+Drug	64	20/33/11	24 months
Syed Mohsin Ali, 2017	China	3/39/18	53.1±11.2	45/15	Endoscope	60	22/29/9	24 months
ASHISH KUMAR, 2009[64]	India	NA	42 ± 14	NA	Endoscope+Drug	84	35/31/10	15 ± 12 months
ASHISH KUMAR, 2009	India	NA	41 ± 14	NA	Endoscope	83	26/34/15	15 ± 11 months
Héctor Orozco, 2000[65]	Mexico	NA	NA	NA	Endoscope	46	21/14/8	45 months
Héctor Orozco, 2000	Mexico	NA	NA	NA	Surgical Operation	30	21/3/3	45 months
Julio Argonz, 2000[66]	Argentina	20/12/9	53.4±1.4	32/9	Endoscope	41	14/23/4	11.2 months
Julio Argonz, 2000	Argentina	24/6/9	52.9±2.2	30/9	Endoscope	39	11/26/2002	12.9 months
Yeong-Shan Cheng, 2001[67]	Taiwan,China	10/27/2005	52.7±10.2	30/12	Endoscope	42	14/17/11	2 years
Yeong-Shan Cheng, 2001	Taiwan,China	9/31/4	55.2±9.8	29/15	Endoscope	44	18/14/12	2 years

Table 2: League table with rebleeding, death rate and HE as the outcome variables.

Rebleeding			
	Endoscope	Surgical_Operation	TIPS
Endoscope	-	0.1 (0.04, 0.24)	0.28 (0.15, 0.51)
Surgical_ Operation	9.58 (4.19, 22.73)	-	2.7 (1.27, 5.85)
TIPS	3.55 (1.95, 6.63)	0.37 (0.17, 0.79)	-
Death			
	Endoscope	Surgical_Operation	TIPS
Endoscope	-	0.61 (0.35, 1.08)	1.23 (0.79, 1.94)
Surgical_ Operation	1.65 (0.92, 2.86)	-	2.03 (1.22, 3.32)
TIPS	0.81 (0.52, 1.27)	0.49 (0.3, 0.82)	-
HE			
	Endoscope	Surgical_Operation	TIPS
Endoscope	-	0.55 (0.19, 1.59)	3.85 (2.01, 8.16)
Surgical_ Operation	1.82 (0.63, 5.22)	-	7.01 (2.9, 18.81)
TIPS	0.26 (0.12, 0.5)	0.14 (0.05, 0.34)	-

devascularization and splenectomy, and shunt surgery mainly consisting of distal splenorenal shunt). All studies were two-arm trials. Detailed results of the bias risk assessment are shown in Supplementary Tables 1 and 2.

5.3. Clinical Outcomes of Different Interventions for Treating EGVB

The interventions in the trials were first categorized into three types, namely endoscopic therapy, TIPS, and surgical operations. Network structure diagrams were applied to depict the direct associations among the treatment strategies. The thickness of the lines is proportional to the number of comparisons, and the diameter of the circles is proportional to the number of treatments included in the meta-analysis. Brooks–Gelman–Rubin diagnostic plots, trace plots, and density plots were used to assess the convergence of the model, and satisfactory convergence was achieved in all studies. In the density plots, smooth curves conforming to the normal distribution indicated good convergence of the model. Furthermore, the potential scale reduction factor for each analysis in the Brooks–Gelman–Rubin diagnostic plots was close to 1.0 (Supplementary Figures 1–3).

In studies with rebleeding as the primary outcome variable, 818, 1,206, and 1,023 patients received endoscopic therapy,

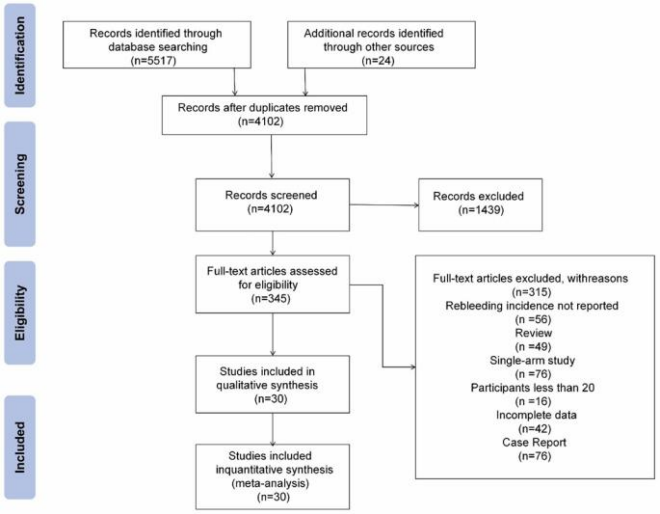

Figure 1: Flow diagram of the meta-analysis. A total of 5,517 articles were identified through searches of PubMed, Embase, and the Cochrane Library. After title and abstract screening and full-text assessment, 30 clinical studies were included.

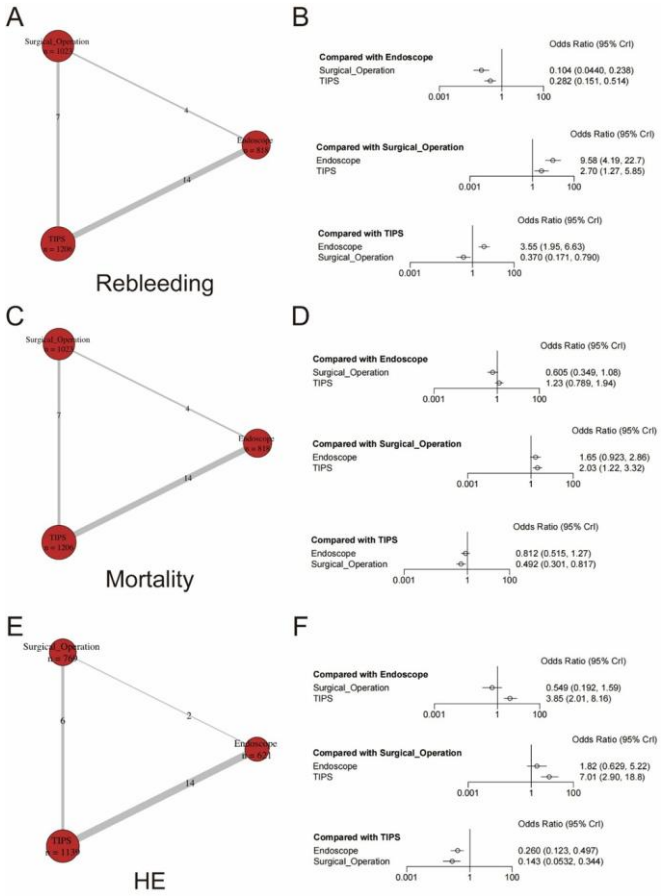

Figure 2: Comparative efficacy of the three non-pharmacological interventions for different outcomes in esophageal and gastric variceal bleeding. (A) Network plot for rebleeding; (B) Comparative efficacy of the three interventions for controlling all-cause rebleeding; (C) Network plot for all-cause mortality; (D) Comparative efficacy of the three interventions for reducing all-cause mortality; (E) Network plot for HE; (F) Comparative efficacy of the three interventions for controlling the incidence of HE.

TIPS, and surgical operations, respectively. Compared with endoscopic therapy, the risk of rebleeding was significantly reduced after surgical operations and TIPS interventions (Surgical Operation vs. Endoscope, OR 0.104, 95% CI 0.044–0.238; TIPS vs. Endoscope, OR 0.282, 95% CI 0.151–0.514). Moreover, the effect of surgery in preventing rebleeding was also significantly better than TIPS (OR 0.370, 95% CI 0.171–0.790) (Figures 2A, B).

In studies regarding all-cause mortality, the number of cases included for the three interventions was the same as in the rebleeding studies. However, compared with endoscopic therapy, the other two interventions did not significantly reduce all-cause mortality (Surgical Operation vs. Endoscope, OR 0.605, 95% CI 0.349–1.08; TIPS vs. Endoscope, OR 1.23, 95% CI 0.789–1.94). However, compared with surgical operations, TIPS showed significantly higher all-cause mortality (OR 2.03, 95% CI 1.22–3.32) (Figures 2C, D).

In studies on HE, as some trials did not report the incidence of HE, only 621, 1,139, and 769 cases receiving endoscopic therapy, TIPS, and surgical operations, respectively, were included (Figure 2E). The incidence of HE was significantly higher in patients after TIPS intervention compared with the other two interventions (Surgical Operation vs. TIPS, OR 0.143, 95% CI 0.0532–0.344; Endoscope vs. TIPS, OR 0.260, 95% CI 0.123–0.497). There was no significant difference between surgery and endoscopic therapy (Surgical Operation vs. Endoscope, OR 0.549, 95% CI 0.192–1.59) (Figure 2F).

5.4. Probability Rankings of Non-Pharmacological Interventions for Different Outcomes

To determine the prognostic superiority among the three treatment modalities, we calculated the ranking probabilities to establish the hierarchical position of each therapy. In descending order, Surgical Operation ranked best for controlling all-cause rebleeding, followed by TIPS and Endoscope. In contrast, Surgical Operation ranked best for reducing all-cause mortality and controlling the incidence of postoperative HE, followed by Endoscope and TIPS (Figure 3, Supplementary Table 3).

5.5. Sensitivity Analysis, Inconsistency, and Publication Bias

To assess the robustness of this study, we conducted sensitivity analysis, inconsistency testing using the node-splitting method, and publication bias assessment. The results of the sensitivity analysis indicated that after sequentially excluding individual studies, the majority of pooled effect sizes for the three outcomes—rebleeding, all-cause mortality, and HE—did not exhibit directional changes, suggesting that the network meta-analysis results were relatively stable and reliable, and not disproportionately driven by any single study. However, notable differences were observed between TIPS and surgical operation. Regarding heterogeneity, taking all-cause rebleeding as an example, the pooled direct comparison results (Surgical Operation vs. Endoscope) showed high heterogeneity (pair-wise, I2=82.5; network, I2=86.6%), whereas the direct comparison for TIPS vs. Endoscope demonstrated relatively lower heterogeneity (pair-wise, I2=37.4%; network, I2=35.7%), suggesting some degree of clinical or methodological heterogeneity among certain comparison groups (Figure 4). Inconsistency was evaluated using the node-

Table 3: League table for risks of rebleeding, mortality, and hepatic encephalopathy in the endoscopic subgroup analysis.

Rebleeding				
	Endoscope and Drug	**Endoscope only**	**Surgical Operation**	**TIPS**
Endoscope and Drug	-	0.9 (0.41, 2.02)	0.1 (0.04, 0.24)	0.27 (0.15, 0.51)
Endoscope only	1.12 (0.5, 2.42)	-	0.11 (0.04, 0.27)	0.3 (0.14, 0.66)
Surgical Operation	9.97 (4.19, 24.34)	8.95 (3.67, 22.7)	-	2.72 (1.33, 5.72)
TIPS	3.66 (1.97, 6.85)	3.28 (1.51, 7.38)	0.37 (0.17, 0.75)	-
Mortality				
	Endoscope and Drug	Endoscope only	Surgical Operation	TIPS
Endoscope and Drug	-	1.05 (0.61, 1.87)	0.62 (0.35, 1.13)	1.24 (0.79, 1.98)
Endoscope only	0.95 (0.53, 1.64)	-	0.59 (0.32, 1.07)	1.18 (0.67, 2.05)
Surgical Operation	1.63 (0.88, 2.87)	1.71 (0.93, 3.13)	-	2.02 (1.25, 3.19)
TIPS	0.8 (0.5, 1.26)	0.85 (0.49, 1.49)	0.5 (0.31, 0.8)	-
HE				
	Endoscope and Drug	Endoscope only	Surgical Operation	TIPS
Endoscope and Drug	Endoscope and Drug	0.81 (0.21, 3.13)	0.51 (0.17, 1.6)	3.66 (1.81, 8.35)
Endoscope only	1.24 (0.32, 4.71)	Endoscope only	0.63 (0.16, 2.6)	4.53 (1.37, 16.48)
Surgical Operation	1.95 (0.63, 5.95)	1.58 (0.39, 6.32)	Surgical Operation	7.12 (2.95, 18.92)
TIPS	0.27 (0.12, 0.55)	0.22 (0.06, 0.73)	0.14 (0.05, 0.34)	TIPS

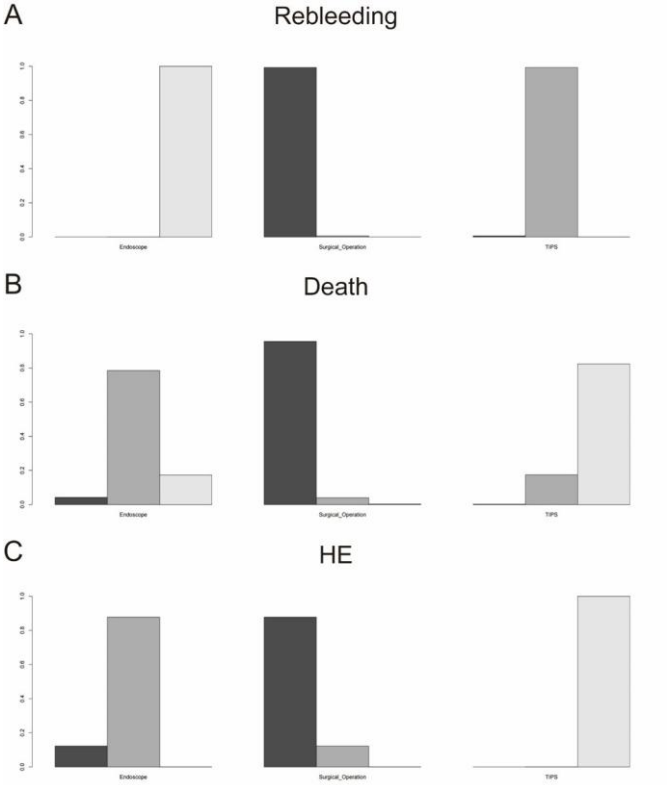

Figure 3: Probability rankings of the three non-pharmacological interventions for different outcomes in esophageal and gastric variceal bleeding. (A) For all-cause rebleeding, surgical operation ranked as the optimal intervention, while endoscopy ranked worst; (B) For all-cause mortality, surgical operation ranked as the optimal intervention, while TIPS ranked worst; (C) For HE incidence, surgical operation ranked as the optimal intervention, while TIPS ranked worst.

splitting method to assess the agreement between direct and indirect evidence. For the outcomes of all-cause rebleeding, all-cause mortality, and HE, the differences between direct and indirect comparisons across treatment groups were not statistically significant, indicating that the direct and indirect evidence were generally consistent, supporting the validity of the consistency assumption (Figure 5A, C, E). Regarding publication bias, comparison-adjusted funnel plots were used for detection. The funnel plots for rebleeding and all-cause mortality showed roughly symmetric distribution of scattered points, suggesting no significant publication bias (Figure 5B, D). However, the funnel plot for HE exhibited some asymmetry (P=0.0396), indicating potential publication bias or small-study effects for this outcome (Figure 5F).

5.6. Subgroup Analysis of Endoscopic Therapy and Surgical Operation

To further explore the sources of heterogeneity, we performed subgroup analyses for the endoscopic group and the surgical group, respectively, with the specific grouping methods as described previously. The subgroup analysis of endoscopic treatment revealed that endoscopic therapy alone and endoscopy combined with medication did not show statistically significant differences in preventing all-cause rebleeding, reducing all-cause mortality, or decreasing the incidence of HE. The relationships among the three interventions remained consistent with the prior analysis (Figure 6). Regarding all-cause mortality, regardless of whether medication was combined, the control effect of endoscopy remained inferior to both surgical operation and TIPS (Figure 7A). In terms of all-cause mortality reduction, both endoscopic subgroups were still superior to TIPS but inferior to surgical operation (Figure 7B). The incidence of HE also yielded results consistent with previous findings (Figure 7C), and the probability rankings between the two subgroups were similar (Supplementary Table 4). Some heterogeneity

Table 4: League table for risks of rebleeding, mortality, and hepatic encephalopathy in the surgery subgroup analysis.

Rebleeding				
	Devascularization surgery	**Endoscope**	**Shunt surgery**	**TIPS**
Devascularization surgery	-	5.92 (2.47, 14.56)	0.12 (0.02, 0.66)	1.66 (0.76, 3.67)
Endoscope	0.17 (0.07, 0.4)	-	0.02 (0, 0.1)	0.28 (0.16, 0.48)
Shunt surgery	8.32 (1.5, 44.53)	49.19 (10.32, 235)	-	13.81 (3.04, 61.29)
TIPS	0.6 (0.27, 1.32)	3.57 (2.08, 6.22)	0.07 (0.02, 0.33)	-
Mortality				
	Devascularization surgery	Endoscope	Shunt surgery	TIPS
Devascularization surgery	-	1.56 (0.75, 3.12)	0.73 (0.22, 2.33)	1.88 (0.99, 3.53)
Endoscope	0.64 (0.32, 1.33)	-	0.47 (0.16, 1.37)	1.21 (0.76, 1.97)
Shunt surgery	1.38 (0.43, 4.57)	2.14 (0.73, 6.25)	-	2.59 (0.96, 7.12)
TIPS	0.53 (0.28, 1.01)	0.83 (0.51, 1.32)	0.39 (0.14, 1.05)	-
HE				
	Devascularization surgery	Endoscope	Shunt surgery	TIPS
Devascularization surgery	-	2.82 (0.83, 9.71)	3.72 (0.52, 30.04)	10.19 (3.65, 32.55)
Endoscope	0.35 (0.1, 1.21)	-	1.31 (0.24, 7.96)	3.61 (1.89, 7.73)
Shunt surgery	0.27 (0.03, 1.93)	0.76 (0.13, 4.13)	-	2.74 (0.5, 15.6)
TIPS	0.1 (0.03, 0.27)	0.28 (0.13, 0.53)	0.37 (0.06, 2.01)	-

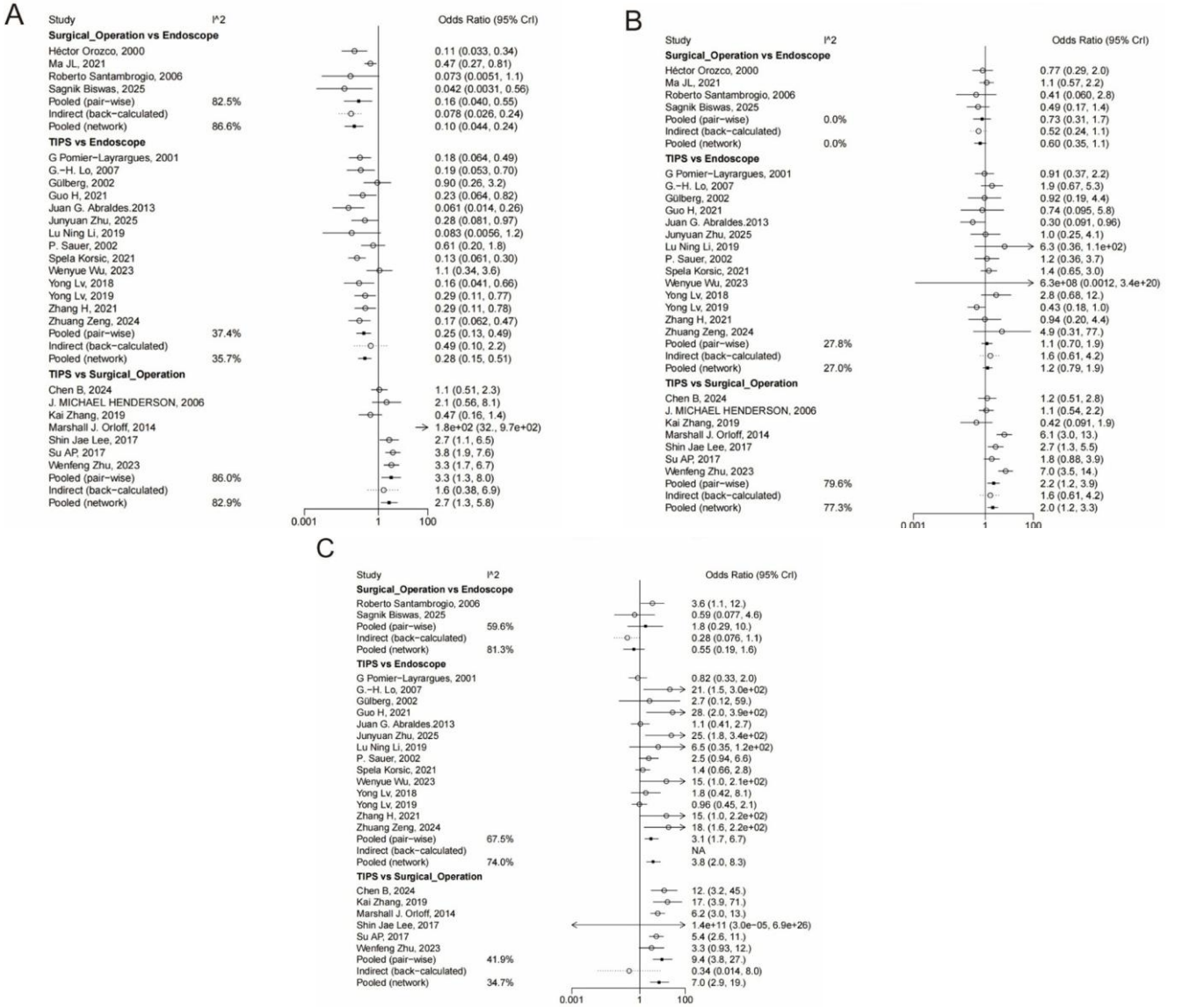

Figure 4: Sensitivity analysis and heterogeneity assessment of the three non-pharmacological interventions. (A) Rebleeding; (B) All-cause mortality; (C) HE incidence. Heterogeneity was considered present when $I^2 > 50\%$.

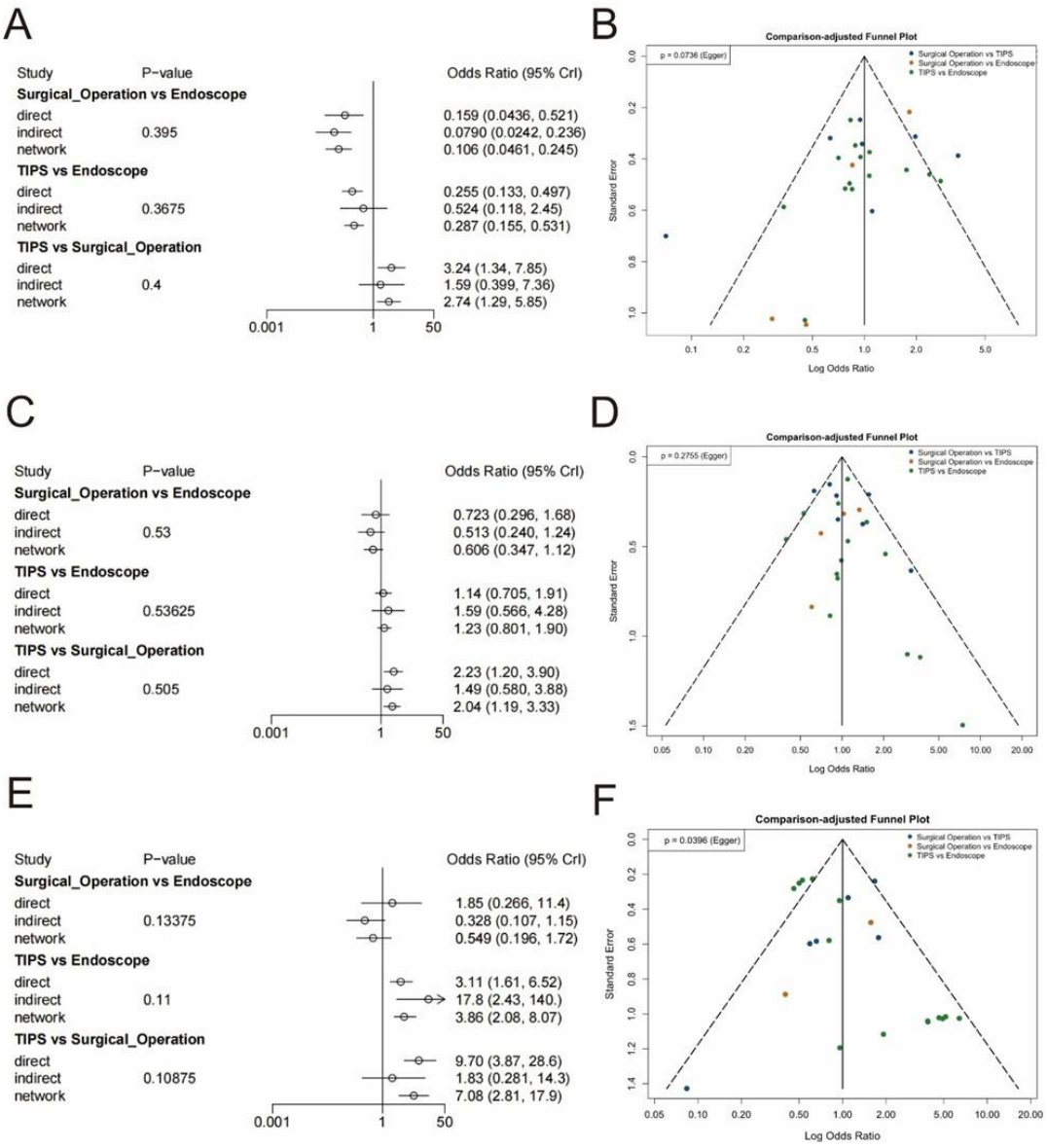

Figure 5: Consistency testing and publication bias assessment. (A) Consistency test for rebleeding; (B) Publication bias assessment for rebleeding; (C) Consistency test for all-cause mortality; (D) Publication bias assessment for all-cause mortality; (E) Consistency test for HE incidence; (F) Publication bias assessment for HE incidence. Egger's test was used to evaluate publication bias, with $p < 0.05$ considered statistically significant.

persisted in certain comparisons, no significant inconsistency was detected across all studies, and publication bias for HE remained present (Supplementary Figure 4).

In the subgroup analysis of the surgical group, notable differences were observed between shunt surgery and devascularization surgery. In the analysis using all-cause rebleeding as the outcome variable, a total of 189 and 804 patients who underwent shunt surgery and devascularization surgery, respectively, were included in the study (Figure 8A). Compared with devascularization surgery, shunt surgery was associated with a significantly lower risk of rebleeding (Shunt vs. Devascularization, OR 0.120, 95% CI 0.0225–0.665), and was significantly superior to all other treatments. Devascularization surgery resulted in a significantly lower rebleeding risk compared with endoscopy, while showing no significant difference versus TIPS (Devascularization vs. TIPS, OR 0.169, 95% CI 0.0687–0.404; Devascularization vs. Endoscope, OR 0.602, 95% CI 0.273–1.32) (Figure 8B, Table 4). The number of cases included for all-cause mortality was identical to that for rebleeding (Figure 8C), and no significant difference was observed between the two surgical approaches in terms of mortality control (Shunt vs. Devascularization, OR 0.727, 95% CI 0.219–2.33) (Figure 8D, Table 4). For the incidence of HE, a total of 116 and

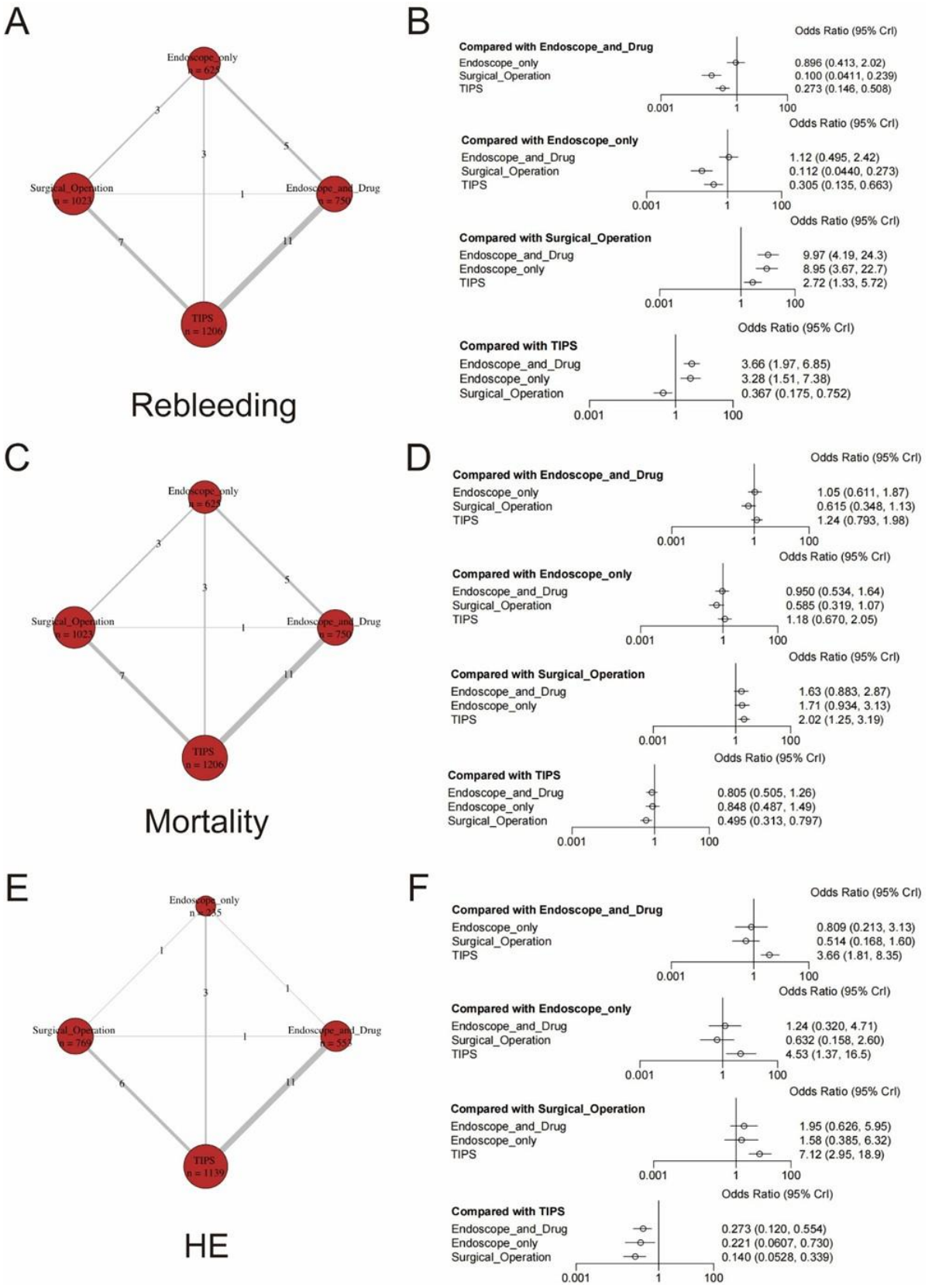

Figure 6: Subgroup analysis results for endoscopic therapy. (A) Network plot for rebleeding; (B) Comparison of the two endoscopic treatment modalities with the other two interventions for controlling all-cause rebleeding; (C) Network plot for all-cause mortality; (D) Comparison of the two endoscopic treatment modalities with the other two interventions for reducing all-cause mortality; (E) Network plot for HE; (F) Comparison of the two endoscopic treatment modalities with the other two interventions for controlling HE incidence.

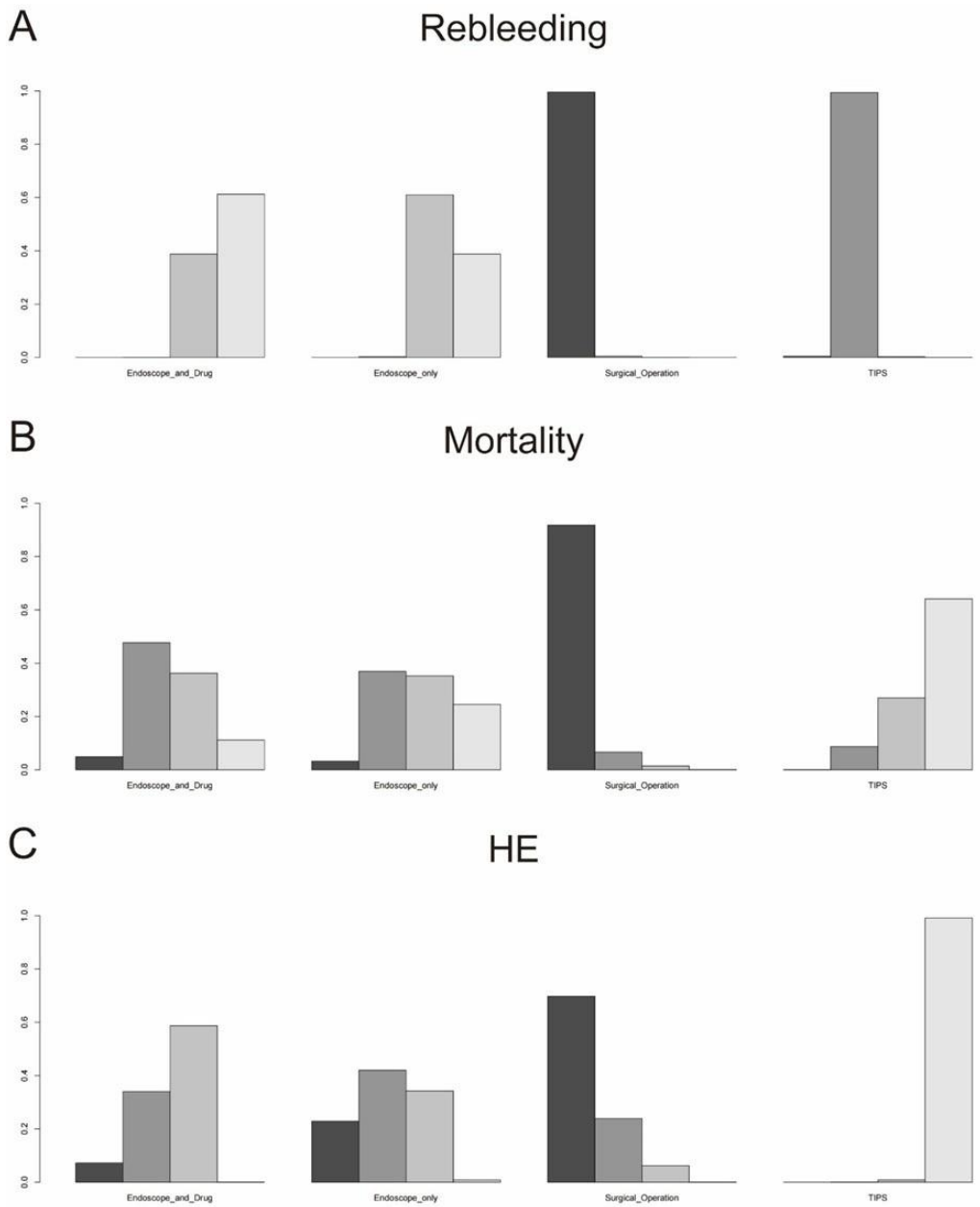

Figure 7: Probability rankings of the two endoscopic treatment modalities and the other two interventions for different outcomes in esophageal and gastric variceal bleeding. (A) For all-cause rebleeding, surgical operation ranked as the optimal intervention, while endoscopy ranked worst, with no significant difference between the two endoscopic modalities; (B) For all-cause mortality, surgical operation ranked as the optimal intervention, while TIPS ranked worst, with similar efficacy between the two endoscopic modalities; (C) For HE incidence, surgical operation ranked as the optimal intervention, while TIPS ranked worst, with similar efficacy between the two endoscopic modalities.

653 patients receiving shunt surgery and devascularization surgery, respectively, were analyzed (Figure 8E). Although no significant difference was found between the two surgical types (Shunt vs. Devascularization, OR 3.72, 95% CI 0.518–30.0), devascularization surgery demonstrated a significant advantage over TIPS (Devascularization vs. TIPS, OR 0.0981, 95% CI 0.0307–0.274), whereas shunt surgery did not differ significantly from TIPS (Shunt vs. TIPS, OR 0.365, 95% CI 0.0641–2.01) (Figure 8F, Table 4). Some heterogeneity persisted in certain comparisons, no significant inconsistency was detected across all studies, and publication bias for HE remained present (P = 0.0026) (Supplementary Figure 5). The probability ranking results are presented in Figure 9 and Supplementary Table 5, Shunt surgery had the highest probability of being ranked the best for controlling all-cause rebleeding and all-cause mortality, whereas devascularization surgery appeared to be more advantageous for the prevention and control of HE.

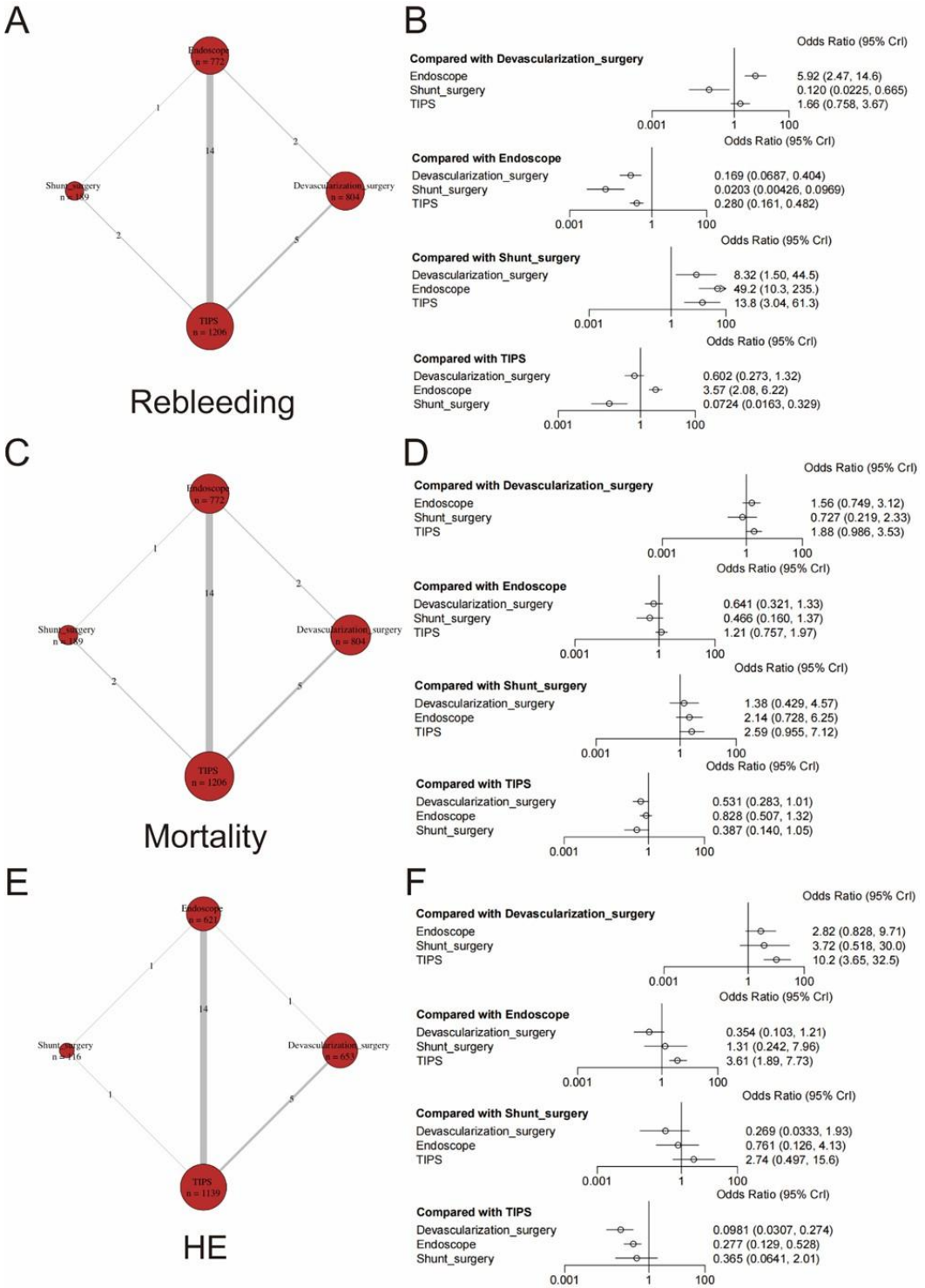

Figure 8: Subgroup analysis results for surgical treatment. (A) Network plot for rebleeding; (B) Comparison of shunt surgery and devascularization surgery with the other two interventions for controlling all-cause rebleeding; (C) Network plot for all-cause mortality; (D) Comparison of shunt surgery and devascularization surgery with the other two interventions for reducing all-cause mortality; (E) Network plot for HE; (F) Comparison of shunt surgery and devascularization surgery with the other two interventions for controlling HE incidence.

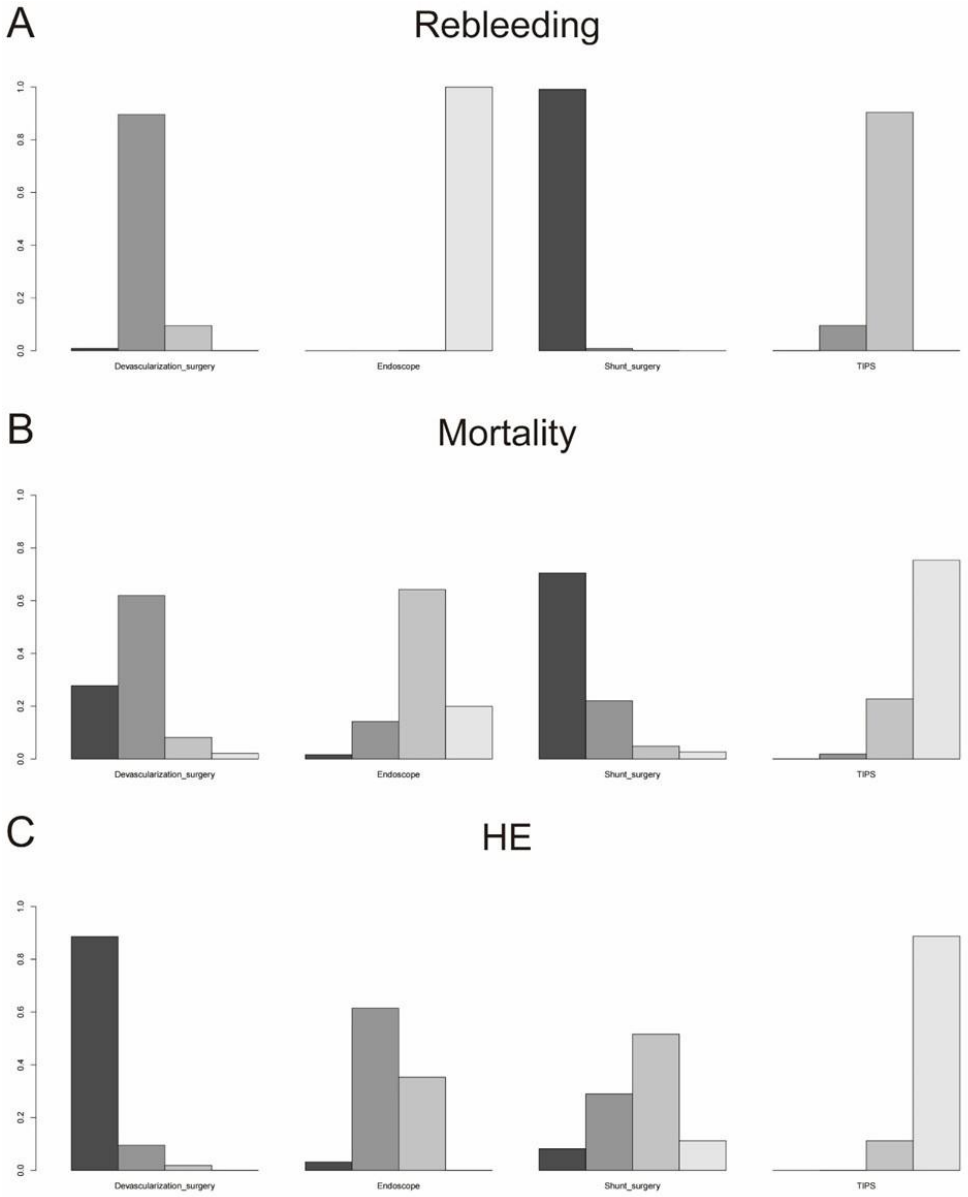

Figure 9: Probability rankings of the two surgical treatment modalities and the other two interventions for different outcomes in esophageal and gastric variceal bleeding. (A) For all-cause rebleeding, shunt surgery ranked as the optimal intervention, followed by devascularization surgery, while endoscopy ranked worst; (B) For all-cause mortality, shunt surgery remained the optimal intervention, while TIPS ranked worst, with devascularization surgery showing a favorable probability ranking compared with endoscopy; (C) For HE incidence, devascularization surgery ranked as the optimal intervention, while TIPS ranked worst, with endoscopy showing a favorable probability ranking compared with shunt surgery.

6. Discussion

This study provides the first systematic comparison of surgery, TIPS, and endoscopic therapy as secondary prophylactic interventions for esophageal and gastric variceal bleeding in patients with liver cirrhosis through a Bayesian network meta-analysis, incorporating three critical clinical outcomes: rebleeding, all-cause mortality, and incidence of HE. Our findings demonstrate that surgery ranked best for preventing all-cause rebleeding, followed by TIPS and endoscopy. For reducing all-cause mortality, surgery also performed optimally, while TIPS ranked worst. Regarding HE control, TIPS was associated with the highest risk, with no significant difference observed between surgery and endoscopy. Subgroup analyses further revealed no significant differences between endoscopy alone and endoscopy combined with medication across all outcomes[33]. Shunt surgery was superior to devascularization for rebleeding control, whereas devascularization surgery demonstrated advantages in preventing HE [34, 35]. Previous pairwise meta-analyses have largely focused on direct comparisons between two interventions, often yielding inconsistent conclusions.

For instance, earlier meta-analyses suggested that TIPS was superior to endoscopy in preventing rebleeding but at the cost of a higher incidence of HE, which aligns with our findings [36]. However, these studies were unable to simultaneously compare all three interventions or establish treatment hierarchies. Although several network meta-analyses have recently attempted to compare multiple interventions, most did not distinguish between surgical subtypes (shunt vs. devascularization) or endoscopic regimens (with or without concomitant medication), and paid insufficient attention to mortality and HE outcomes [37]. By incorporating subgroup analyses and multiple clinically relevant endpoints, the present study addresses these evidence gaps.

The superior performance of surgery in controlling both rebleeding and mortality warrants further exploration. From a pathophysiological perspective, both shunt and devascularization procedures fundamentally address portal hypertension or directly obliterate varices. Shunt surgery reduces portal pressure, thereby decreasing the driving force for rebleeding, while devascularization surgery achieves local hemostasis by disrupting pericardial vessels. Our subgroup analysis demonstrated that shunt surgery was superior to devascularization for rebleeding control, likely attributable to more effective portal decompression [34]. However, shunt surgery was associated with a higher risk of HE compared with devascularization (although not statistically significant), suggesting that shunt procedures may be more suitable for patients at extremely high risk of rebleeding who can tolerate potential encephalopathy [35].

TIPS demonstrated superior rebleeding prevention compared with endoscopy but was inferior to surgery, reflecting the degree of portal pressure reduction achieved. TIPS effectively lowers portal pressure below the threshold for variceal bleeding, yet its shunting effect may be less durable or complete than surgical shunts. More importantly, TIPS carried the highest risk of HE, representing its major clinical limitation. The development of encephalopathy is associated with shunt diameter, baseline liver function reserve, and direct entry of intestinal toxins into the systemic circulation. Although covered stents have reduced TIPS dysfunction rates, they have not significantly decreased encephalopathy incidence, highlighting the need to balance rebleeding prevention against quality of life.

Endoscopic therapy, traditionally considered a first-line option, ranked lowest for both rebleeding and mortality control in this analysis. However, this does not negate its clinical value. Endoscopy offers advantages including minimal invasiveness, repeatability, and no increased risk of HE. Our subgroup analysis revealed that combining medication with endoscopy did not significantly improve clinical outcomes, which contrasts with some previous studies. Potential explanations include heterogeneity in medication regimens (e.g., somatostatin, propranolol) across included studies, variable patient adherence, and possible masking of additional benefits by baseline treatment efficacy. Nevertheless, endoscopic therapy remains appropriate for patients with poor liver function who cannot tolerate surgery or TIPS, or as a bridging strategy to other treatments.

The subgroup findings carry important clinical implications. First, the absence of significant differences between endoscopy alone and endoscopy combined with medication suggests that endoscopic monotherapy may be acceptable when medications are contraindicated or unavailable. Second, the differential efficacy between shunt and devascularization procedures supports individualized surgical selection: shunt surgery may be preferred for patients at extremely high rebleeding risk with preserved liver function, whereas devascularization may be more appropriate for those at heightened risk of HE or requiring preserved portal perfusion. These findings provide novel evidence to guide clinical decision-making.

Substantial heterogeneity was observed for the rebleeding outcome in the surgery versus endoscopy comparison ($I^2 > 80\%$), likely attributable to variations in surgical techniques, baseline patient characteristics, and evolving endoscopic practices across studies. Subgroup and sensitivity analyses were performed to explore heterogeneity sources, and the results remained robust. Publication bias was detected for the HE outcome, suggesting potential underreporting of small studies or negative findings, warranting cautious interpretation.

Several limitations should be acknowledged. First, the inclusion of retrospective studies introduces potential selection and confounding biases, although quality assessment using the Newcastle-Ottawa Scale and sensitivity analyses were performed. Second, heterogeneity in surgical techniques, endoscopic modalities, TIPS stent types, and medication regimens across studies may contribute to clinical

heterogeneity. Third, definitions and follow-up durations for outcomes such as HE varied among included studies. Fourth, due to limited data, subgroup analyses based on cirrhosis etiology (e.g., alcoholic, viral) could not be performed. Fifth, the presence of publication bias may affect the robustness of findings for HE.

Future large-scale, multicenter, prospective randomized controlled trials with standardized intervention protocols and outcome definitions are warranted to validate these findings. Particular attention should be directed toward detailed comparisons between shunt and devascularization procedures, as well as evaluation of endoscopy combined with novel pharmacological agents. Patient-reported outcomes, including quality of life, and cost-effectiveness analyses should also be incorporated into future research to comprehensively inform clinical practice.

Funding

This work is supported by Fundamental research program funding of Ninth People's Hospital affiliated to Shanghai Jiao Tong University School of Medicine (JYZZ282).

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