Effects of shunt embolization on hepatic encephalopathy recurrence in patients with major portosystemic shunts: A systematic review and meta-analysis

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Abstract. This study addresses the effects of shunt embolization on the recurrence of hepatic encephalopathy (HE) in patients with major portosystemic shunts. MEDLINE via PubMed, Google Scholar, and Scopus was searched to find the relevant full-text articles published from inception until August 2024. The primary outcome was the degree of HE or mental state change determined by the West-Heaven classification system. Dichotomous data were compared using odds ratios (OR). 95% confidence (CI) intervals were provided for each outcome in the report. The random-effects model was used to analyze the data. Trim and fill, Egger's regression and funnel plot were employed to evaluate publication bias in this body of literature. A total of 7 articles and 254 patients were included in the present meta-analysis. It was found that shunt embolization significantly reduced the recurrence of HE in patients with portosystemic shunts due to liver cirrhosis. Overall analysis showed that the pooled OR was 0.253 and the overall heterogeneity of the data was substantial (95% CI: 0.117-0.550, I^2=60.52% and P=0.001). The funnel plot was reasonably symmetrical and no study was trimmed to either side of the mean. Begg's (P=0.229) and Egger's tests (P=0.273) showed no significant risk of publication bias. Quality assessment showed that the majority of the included studies were of low quality. In conclusion, the present meta-analysis indicates that shunt embolization after portosystemic shunt significantly reduces the recurrence of HE in patients with liver cirrhosis. However, the findings should be interpreted with caution due to the low quality and low number of the included studies. Future research should prioritize higher-quality trials to validate these results and explore long-term outcomes.

Introduction

Hepatic encephalopathy (HE) is a general term for a wide range of neurological or psychiatric conditions, ranging from preclinical abnormalities to coma, which are suggestive of either brain dysfunction caused by portal-systemic shunting or liver failure (1). From an epidemiological perspective, HE is currently recognized as the most prevalent cirrhosis consequence, leading to frequent readmissions, hospital stays, and a higher risk of mortality (2).

Numerous factors contribute to the complex pathophysiology of HE, including abnormal brain energy metabolism, increased oxidative stress in astrocytes, changed gut flora, impaired metabolism of intestinally generated neurotoxins, and altered blood-brain barrier and neurotransmission. Through several mechanisms, including increased intracellular osmolality in astrocytes, impaired transport of amino acids from the blood to the brain, and abnormal neuronal electrical activity, intestinal neurotoxin ammonia affects neurological function at multiple sites (3,4).

HE is classified into three primary categories based on the underlying cause. Individuals with portosystemic shunting without intrinsic liver disease develop type B, those with acute liver failure develop type A and those with cirrhosis are categorized as type C (5,6). The first-pass hepatic clearance of neurotoxins generated from the gut, including ammonia, is reduced during portosystemic shunt. In addition, intestinal glutaminase activity is elevated, increasing ammonia production in the gut (7). Polytetrafluoroethylene-coated stents significantly improve patency and reduce the likelihood of shunt malfunction. However, HE following portosystemic shunts, such as the transjugular intrahepatic portosystemic shunt (TIPS), remains a significant cause of concern (8-10).

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According to several previous studies, angiographic embolization of large shunts in patients with recurrent HE has been linked to improved neurological symptoms (11-14). Furthermore, shunt embolization may increase patient survival and liver function by restoring hepatic blood flow (12). This systematic review and meta-analysis addresses the effects of shunt embolization on HE recurrence in patients with major portosystemic shunts.

Materials and methods

Data sources and search strategy. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement approach was used to perform this systematic review and meta-analysis (15). A medical librarian at the teaching hospital conducted a comprehensive computerized search of relevant literature in MEDLINE via PubMed (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.com/) and Scopus (https://www.scopus.com/search/form.uri?display=basic) to find the full-text articles that assessed the effects of shunt embolization on refractory HE in patients with major portosystemic shunts from inception until August 2024. Unpublished publications were examined by searching the World Health Organization International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform). Auto-alerts were set up to track down recently published documents. In addition, the reference lists of the papers were manually searched to find other studies. The search was performed using the key terms 'hepatic encephalopathy', 'embolization', and 'portosystemic shunt' and the following search strategy: [TITLE-ABS-KEY (hepatic AND encephalopathy) AND TITLE-ABS-KEY (embolization) AND TITLE-ABS-KEY (portosystemic AND shunt)] AND [LIMIT-TO (DOCTYPE, 'ar')] AND [LIMIT-TO (LANGUAGE, 'English')]. The medical librarian only retrieved the studies and was not involved in the subsequent steps of the study.

Study selection. Studies that met the following standards were considered: i) Population: Adults (aged >18 years) with confirmed liver cirrhosis and a history of HE; ii) interventions: Embolization, independent of region, frequency, or duration; iii) comparators: Placebo or other interventions; and iv) the primary outcomes: The degree of HE or mental state change as determined by the West-Heaven classification system. This grading system distinguishes among four clinically distinct HE gradings. Patients in grade I exhibit inattention and mild personality changes that are primarily apparent to their family members. The most common finding in grade II is disorientation for time when combined, for instance, with inappropriate behavior and lethargy. Patients in grade III are comatose but react to stimuli. They may also behave strangely and are confused about where they are and what to do. Patients in grade IV are unconscious (16); and (5) study design: Clinical trials [both randomized and non-randomized (prospective or retrospective cohorts)].

Additionally, and based on this system, there are two different forms of refractory HE: Recurrent HE and persistent HE. The hallmark of recurrent HE is recurrent episodes that happen more than once within 6 months (16). When overt HE recurs, an ongoing pattern of behavioral changes that persists and coexists with it is referred to as persistent HE (16). Grade ≥II was designated as overt HE (16).

The exclusion criteria were as follows: i) Studies where the population was either pregnant or had congenital or autoimmune liver diseases; ii) where no specific intervention or comparator was mentioned; and iii) case series, case reports, conference proceedings; or studies lacking the necessary data.

Data extraction and quality assessment. After performing independent searches of all eligible studies' titles and abstracts to identify any that may be pertinent, two reviewers (JS and WL) skimmed through the full text of those studies and collected the necessary data. Disagreements among reviewers were resolved via discussions with a third reviewer (JJ). Each chosen study's first author's name, publication year, trial design, patient age, cirrhosis etiology, HE grades, Child-Pugh (CP) score or classification, intervention, comparison, and length of therapy were extracted. When data in articles were not provided, it was attempted to contact the authors.

Using the Cochrane Risk of Bias Tool (17), the methodological quality of the studies was assessed. It was determined whether an article had a low, uncertain, or high quality for each item. The following areas were covered in this assessment: Blinding of allocations, random sequence generation, selective reporting, inadequate outcome data, blinded outcome evaluation, blinding of participants and staff, and other risks of bias. For a study to be categorized as having a low risk of bias, it must have had a low grade across all domains. The experiment's overall risk of bias was classified as unclear whenever at least one area had the label 'uncertain'. If at least one domain demonstrated a high risk of bias, the trial's overall risk was likewise considered high.

Statistical analysis. The data were analyzed using the Comprehensive Meta-Analysis Software program, version 2.0 (Biostat). Dichotomous factors were compared using odds ratios (OR). 95% confidence intervals (CI) were provided for each reported outcome. The pooled OR and 95% CI were estimated using the Mantel-Haenszel method for dichotomous data. Data heterogeneity was evaluated using the I^2 test and was deemed high if I^2 was >50%. The random-effects model was used to analyze the data due to their high heterogeneity (I^2>50%). Random-effects models are advantageous when there is significant heterogeneity across studies, as they provide a more realistic and generalizable estimate of the overall effect size while accounting for the variability in the underlying true effects (17). Trim and fill, Begg's analysis Egger's regression, and funnel plot were employed to evaluate publication bias in this body of literature. A funnel plot visually represents the effect sizes of individual studies against their precision, ideally forming a symmetrical shape; asymmetry suggests potential bias, often due to smaller studies with non-significant results being unpublished. The trim-and-fill method addresses this issue by first trimming away studies that contribute to asymmetry and then filling in hypothetical missing studies to restore symmetry, thereby providing an adjusted overall effect estimate. Furthermore, Egger's regression test assesses funnel

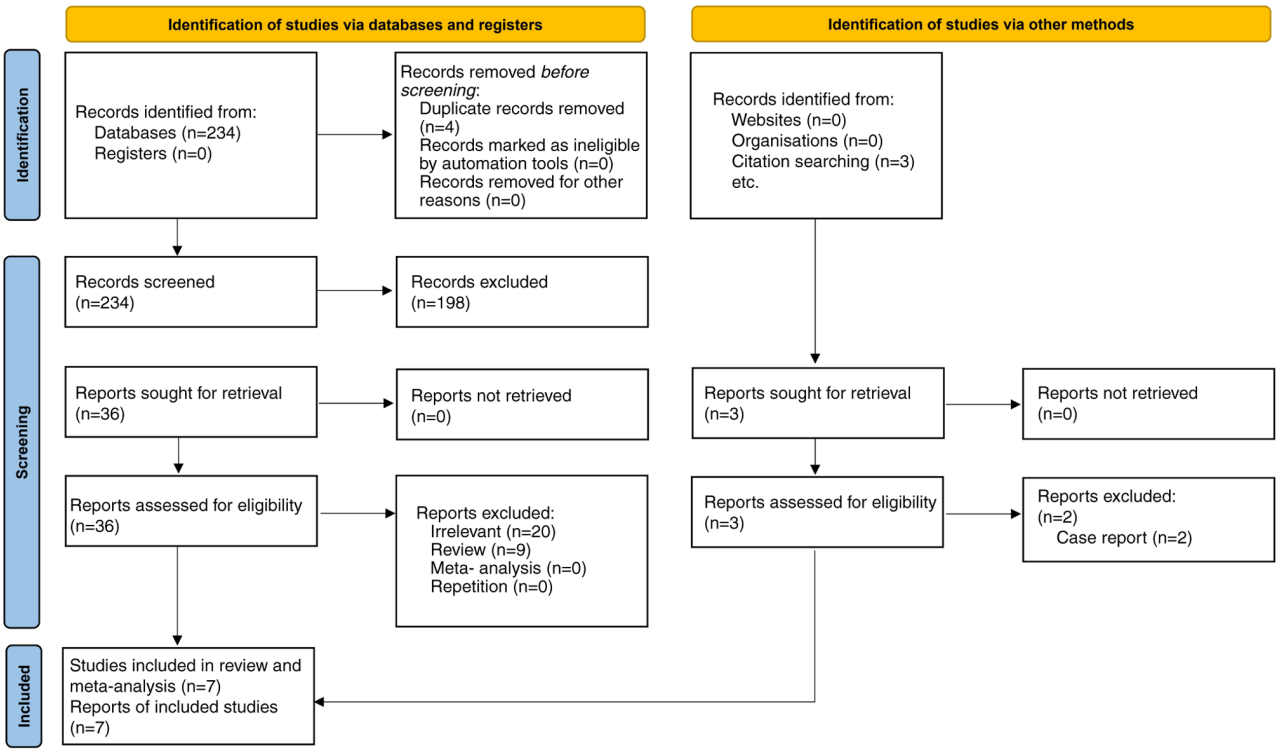

Figure 1. Flowchart of study inclusion according to the PRISMA guidelines.

plot asymmetry by performing a weighted regression of the effect sizes on their standard errors. A significant intercept in this regression indicates potential publication bias, suggesting that smaller studies with non-significant results are missing from the analysis. Conversely, Begg's analysis, specifically the Begg and Mazumdar rank correlation test, evaluates the correlation between the ranks of effect sizes and their variances. A significant correlation suggests that smaller studies report different results than larger ones, which can also indicate publication bias (18).

Leave-one-out sensitivity analysis is a robust technique used in meta-analysis to evaluate the influence of individual studies on the overall effect size. This method systematically excludes one study at a time from the analysis and recalculates the overall effect size and heterogeneity for each iteration. By doing so, it is identified whether any single study disproportionately affects the results. Significant changes in the effect size or a marked decrease in heterogeneity upon exclusion indicate that the omitted study may be an influential outlier (19). $P<0.05$ was utilized as the threshold for statistical significance.

Results

Study selection. During the initial search of the mentioned databases, 234 studies were found. After four duplicate articles were excluded, 230 papers were evaluated based on their titles and abstracts. Accordingly, 128 publications (case reports, case series, correspondences, review articles, *in vitro* experiments or animal studies) were excluded. Thus, 36 publications were retained for full-text examination. Following a thorough assessment, three descriptive studies lacking comparative analysis were excluded.

Furthermore, 29 other papers were excluded for failing to disclose pertinent data. Thus, six studies fulfilled the inclusion and not the exclusion criteria (11-14,20,21). Another study was identified in a manual search and added (22). Hence, seven studies were included in this meta-analysis. Only one study was a randomized clinical trial (RCT) (14), while the remaining studies were retrospective cohort studies. A total of 254 patients were included in the present meta-analysis. The literature review process is depicted in Fig. 1. Table I presents the characteristics of the included studies.

Effect of shunt embolization on portosystemic refractory HE. It was found that shunt embolization significantly reduced HE recurrence in patients with portosystemic shunts due to liver cirrhosis (the pooled OR=0.253, 95% CI: 0.117-0.550; Fig. 2). The overall heterogeneity of the data was found to be high (I^2=60.52% and P=0.001).

Safety. An *et al* (12) reported no major procedure-related complications in the embolization group. Patients with either a Model for End-stage Liver Disease (MELD) score ≥15 or hepatocellular carcinoma at baseline experienced all severe sequelae throughout the follow-up. Two of these six patients had persistent hepatorenal syndrome and all six patients died within a year following embolization. These patients complained of either mild stomach bloating or fever, which all disappeared a week after embolization with conservative therapy. Laleman *et al* (11) noticed one major complication. This study reported eight early procedure-related complications, seven minor and symptomatically addressed (two episodes of self-limiting fever, one contrast-induced nephropathy, three localized hematomas at the puncture site,

Table I. Characteristics of included studies in the meta-analysis.

Author(s), year	Design	No. of patients	Age, years	CTP score	MELD score	No. of HE episodes	Maximum HE grade	Outcome(s)	(Refs.)
An *et al*, 2016	Retrospective cohort	17	62 (56-65.5)[a]	9 (8-10)[b]	13 (11-15)[a]	1-2 (n=9); ≥3 (n=8)	II (n=6); III-IV (n=11)	The 2-year HE recurrence rate in the embolization group was considerably lower than in the control group (39.9 vs. 79.9%, P=0.02)	(12)
He *et al*, 2018	Retrospective cohort	44	51.2±11.6	7.2±1.9	11.2±4.0	15	III-IV (n=5)	The SPSS group had a higher risk of HE compared with the SPSS + ES groups	(13)
Laleman *et al*, 2013	Retrospective cohort	37	61.0±2.0	7.9±0.3	13.2±0.9	-	IV	Improved severity of the worst HE episode after embolization in three-quarters of the patients	(11)
Lv *et al*, 2022	RCT	27	48.0 (43-56.5)[a]	7.0 (6.0-8.0)[b]	10.0 (8.0-13.0)[b]	1	-	Concurrent large SPSS embolization decreased the chance for overt HE in cirrhotic patients receiving TIPS for variceal bleeding without worsening other complications	(14)
Philips *et al*, 2013	Retrospective cohort	21	56.6±10.6	9.6±1.9	15.7±4.1	-	1-2 (n=15); ≥3 (n=6)	Recurrent and persistent HE markedly improved in the short (n=20, 1 to 3 months), intermediate (n=12, 3 to 6 months) and long (n=7, 6 to 9 months) follow-up	(20)
Zhang *et al*, 2022	Retrospective cohort	13	57.5±10.0	11.0	12.0	-	-	When treating SPSS-induced refractory HE, the 6-month mortality decreased following SESV (in comparison to ES)	(21)
Ke *et al*, 2024	Retrospective cohort	95	56.4±9.5	9.0±2.0	13.0 (11.0-16.0)[a]		II (n=30); III-IV (n=4)	Embolization seems to be a safe therapeutic approach for individuals with cirrhosis who have refractory HE linked to large SPSS	(22)

The data are expressed as the mean ± standard deviation, median ([a]interquartile range or [b]range) or n (%). RCT, randomized clinical trial; HE, hepatic encephalopathy; CTP, Child-Pugh score; MELD, model for end-stage liver disease; SPSS, spontaneous portosystemic shunt; SESV, selective embolization of the splenic vein; ES, embolization of the shunt; TIPS, transjugular intrahepatic portosystemic shunt.

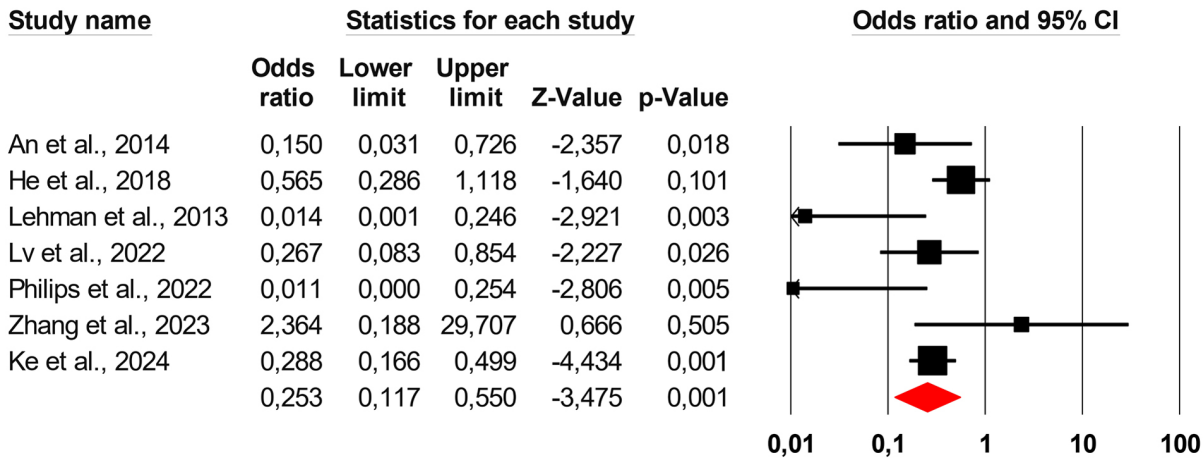

Figure 2. Forest plots of studies comparing the effect of shunt embolization on hepatic encephalopathy incidence in patients with major portosystemic shunts. The odds ratio pertains to the hepatic encephalopathy recurrence (for the pooled analysis: I^2=60.523%; degrees of freedom, 6; χ^2=0.517; P=0.019). CI, confidence interval.

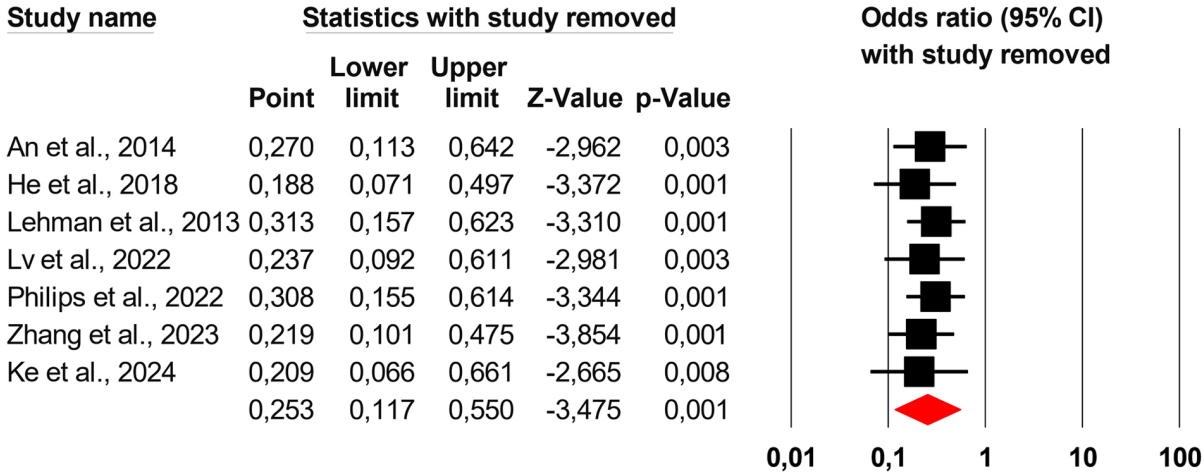

Figure 3. Leave-one-out sensitivity analysis of the included studies. The odds ratio pertains to the hepatic encephalopathy recurrence.

and a cutaneous infection at the puncture site). Throughout the monitoring period, the authors found no significant worsening of portal hypertension (11). In the study by Philips *et al* (20) (n=21), the procedure caused the following immediate problems: Two patients (9.52%) experienced negative outcomes that were specifically connected to the surgery. One of these patients experienced a local site hematoma of grade 1 Common Terminology Criteria for Adverse Events (CTCAE) event, which was treated conservatively; the other patient, however, experienced events of grade 5 CTCAE (hemoperitoneum and multiple organ failures), which resulted in death within 24 h of the procedure (20). Ke *et al* (22) found no early procedure-related complications in the embolization group. Throughout the follow-up, the two groups exhibited no significant difference in the incidence of long-term complications. Only two patients (or 5.9%) required additional embolization due to postoperative follow-up imaging revealing recanalization of the initial embolic shunt (22).

Sensitivity analysis. To test the robustness of the findings, an iterative leave-one-out sensitivity analysis was used, removing one study at a time and recalculating the overall OR. This analysis showed consistent results, proving that leaving out any one study would not significantly change the study's overall conclusions. Consequently, it is improbable that a single study will have a major impact on the OR in either direction (Fig. 3).

Publication bias and study quality. Publication bias was assessed using funnel plot and trim and fill analysis. A funnel plot plots the effect size of individual studies against a measure of their precision, typically the standard error. If the funnel plot is asymmetrical, it may indicate potential publication bias, where studies with non-significant results are less likely to be published. This can lead to overestimating the intervention effect in the meta-analysis (23). The funnel plot was reasonably symmetrical and no study was trimmed to either side of the mean.

Begg's and Egger's tests are statistical methods that help determine whether the results of studies are systematically skewed due to selective publication (23). Begg's test (P=0.229), Egger's test (P=0.273), and the funnel plot showed no significant risk of publication bias (Fig. 4). Quality appraisal showed

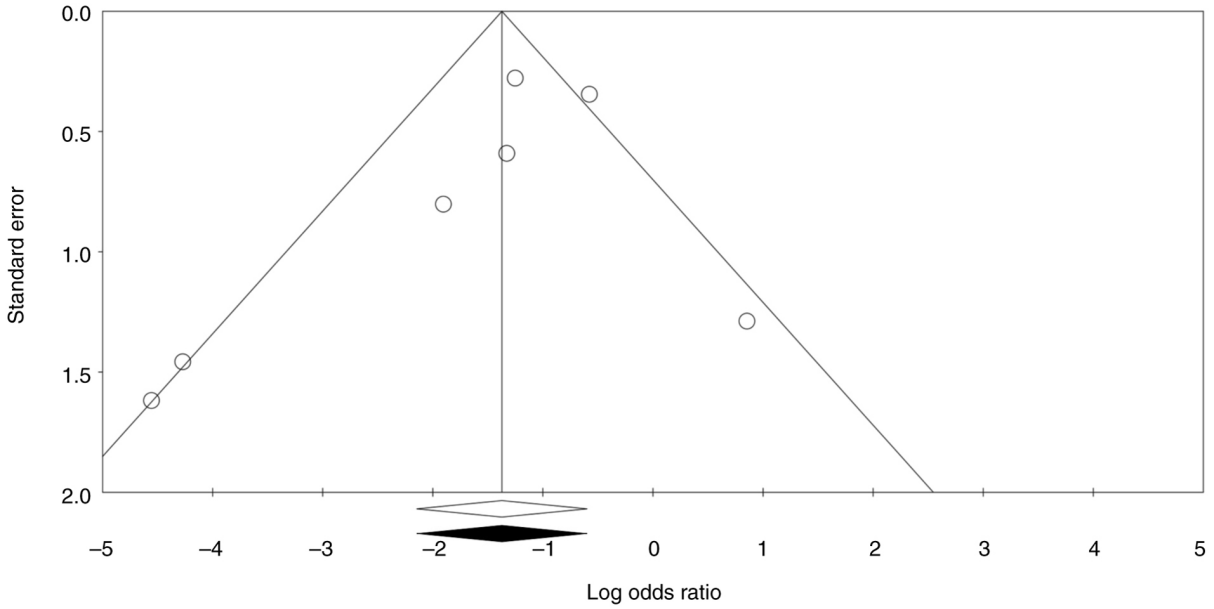

Figure 4. Funnel plot to explore the publication bias in the meta-analysis regarding the incidence of hepatic encephalopathy. The white and black diamonds represent the pooled effect size of the studies before and after trim and fill analysis, respectively.

that all included studies were of low quality, except the study by Lv *et al* (14), in which the patients were randomized into two groups of intervention and control (Fig. 5).

Discussion

From asymptomatic portal hypertension to recurrent and refractory HE, the portosystemic shunt syndrome comprises a spectrum of clinical symptoms that, in patients with cirrhosis and accompanying large portosystemic shunts, eventually lead to progressive liver failure. The splenorenal, gastrorenal, and dilated paraumbilical veins are frequently seen in cirrhosis and can all present with recurrent or refractory HE (24). After ruling out other neurological conditions, HE in patients with cirrhosis with periods of persistent cognitive impairments and a poor MELD score may merit examination for significant spontaneous portosystemic shunt (25).

Large shunts with a diameter of >8 mm can be embolized using several different methods. The proposed portosystemic shunt embolization aims to enhance portal blood flow to the liver, improving liver metabolism and function and decreasing brain exposure to neurotoxic compounds (26-28). The surgical closure of portosystemic shunts has been proven to be beneficial in correcting chronic persistent hepatic encephalopathy, but it is also linked with significant mortality (29). It is also a concern that the embolization surgery worsens portal hypertension (30).

A promising series of five patients with chronic portosystemic encephalopathy who were chosen for radiological interventional therapy was initially described by Uflacker *et al* (31) in 1987. Two patients were subjected to direct splenic artery embolization by the authors, two patients underwent progressive venous shunt occlusion through a transhepatic route utilizing steel coils and one patient underwent surgical mesocaval shunt occlusion using a 'home-made' big detachable balloon. One patient died as a direct result of increased portal pressure and subsequent intra-abdominal bleeding. However, permanent encephalopathy control was

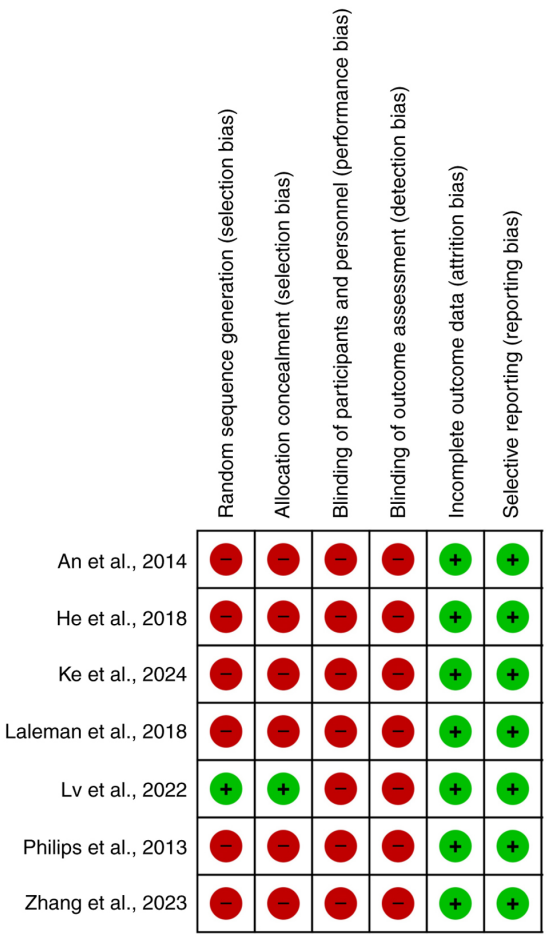

Figure 5. Quality appraisal of the included studies based on the Cochrane risk of bias tool.

achieved in four patients with a longer life (8-37 months) (31). In another study by An *et al* (12) on cirrhotic individuals with recurrent HE and marginally retained liver function, embolization of a large spontaneous portosystemic shunt enhanced survival and liver function and reduced the incidence of HE. He *et al* (13) confirmed that a pre-existing big portosystemic shunt syndrome was linked to a higher risk of HE among cirrhotic patients with TIPS.

On the other hand, portosystemic shunt embolization lowered that risk. There was no conclusive link between the existence or embolization of the portosystemic shunt and death, shunt malfunction or portosystemic shunt syndrome clinical recurrence (13). In a multicenter European cohort study by Laleman *et al* (11), the efficiency and safety of embolizing portosystemic shunts were supported, assuming there was sufficient functional liver reserve. In a randomized clinical trial by Lv *et al* (14), it was found that concurrent large portosystemic shunt embolization decreased the risk for overt HE without worsening adverse events in patients with cirrhosis who were receiving TIPS for variceal bleeding. Therefore, they suggested that concurrent large portosystemic shunt embolization should be considered to prevent TIPS-related HE (14). These findings were replicated in the studies by Philips *et al* (20) and Zhang *et al* (21). The findings from these studies were in line with the results of the present meta-analysis, which showed a decrease in the incidence of HE after shunt embolization in patients with chronic portosystemic shunts.

While portosystemic shunt embolization has already been clinically established for numerous years, the present meta-analysis aims to systematically synthesize the existing literature, providing a comprehensive overview of the effectiveness of this intervention across various studies and allowing for a quantitative assessment of the treatment's effectiveness that may not be evident from individual reports. The present meta-analysis confirms the effectiveness of portosystemic shunt embolization and highlights the variability in methodologies and patient populations across studies. This variability underscores the need for a systematic review to evaluate the robustness of the existing evidence and identify gaps in the current understanding of the procedure's effectiveness.

Of note, the present study had several limitations and areas for improvement. First, the embolization methods and embolic agents used in the included publications varied. The degree of embolization and choice of embolic agents may impact the recurrence of HE. The sustained variceal perfusion through collaterals may be enabled by proximal embolization of the afferent arteries employing coils alone. As they aid in occluding or causing thrombosis of the variceal cavity, liquid agents such as cyanoacrylate and ethanol may be used in distal embolization, which may be more successful. To avoid the development of new collateral veins and reperfusion, a combination of coils and liquid agents may be advised to generate a long-acting embolization of proximal and peripheral collateral veins (32). Second, each included trial had a distinct form of varices or collateral vessels. The effectiveness of variceal embolization may thus differ depending on the structure and hemodynamics of the varices. Third, the papers considered varied in their indications of variceal embolization. Fourth, even though a thorough literature search was performed using three databases without any publication language restrictions, only seven articles were included in the present meta-analysis. When the number of included studies is low (e.g., <5), the overall sample size needs to be bigger, limiting the statistical power to detect effects of interest (33). Low power increases the risk of false-negative results, where the meta-analysis fails to find an effect even if one truly exists (34). Fifth, only one study was of good quality and the remaining studies had a high risk of quality-related bias. Studies with poor design or execution may yield results that do not accurately reflect the true effect being measured, thereby misleading researchers and practitioners about the efficacy of an intervention (34). Here, the results should be interpreted with caution. The findings may need to be more generalizable to broader populations or real-world settings, as the limitations of the included studies may heavily influence them. This can lead to erroneous conclusions about the effectiveness of treatments or interventions in practice (35). Despite the low quality of certain included studies, the meta-analysis employed robust statistical methods, including random-effects modeling and assessment of publication bias through funnel plots and Egger's test. These methodologies help mitigate the impact of individual study limitations and provide a more reliable pooled estimate of the treatment effect. Sixth, in the present study, mostly observational (and only 1 RCT) studies were included. However, the inclusion of observational studies can provide valuable insights, particularly in fields where RCTs are limited or unavailable. Finally, the majority of the patients had cirrhosis with a viral origin; as a result, no firm conclusions can be made for individuals with other chronic liver illnesses. While the limitation in the generalizability of the present findings is acknowledged, it is important to note that the pathophysiology of HE is partially dependent on the specific etiology of cirrhosis. The development of HE is primarily driven by the presence of portosystemic shunts and the accumulation of neurotoxins, which can occur in various types of cirrhosis (36).

In conclusion, the present meta-analysis of seven trials suggests that shunt embolization following TIPS or other portosystemic shunts may help reduce the frequency of HE. However, it is essential to interpret these findings cautiously due to the limitations associated with the low quality of the included studies and the small sample size. The variability in embolic agents, types of varices, and methods of variceal embolization across the studies further complicates the interpretation of the results. Future research should focus on conducting higher-quality RCTs that can provide more definitive conclusions to strengthen the evidence base. Additionally, exploring the long-term outcomes of shunt embolization would be valuable in understanding its effectiveness and safety in HE management.

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Availability of data and materials

The pooled dataset prepared and used in the present study may be requested from the corresponding author.

Authors' contributions

JS, WL, SY, FW, ZZ and JJ developed the study protocol. JS and WL were responsible for data collection. SY and FW analyzed the data. JS and JJ checked and confirmed the authenticity of the raw data (pertaining to the pooled dataset). All authors contributed to the writing of the manuscript and read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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