Review article

Embolization of spontaneous portosystemic shunts for refractory hepatic encephalopathy in cirrhosis patients: A meta-analysis

Running head: SPSS embolization for HE

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Abstract

Background and Aims: Hepatic encephalopathy (HE) is an important cause of morbidity in cirrhosis patients. The presence of spontaneous portosystemic shunts (SPSS) is associated with an increased risk of recurrent/refractory HE. Embolization of SPSS has been shown to improve HE symptoms, but it may worsen portal hypertension and related complications. The aim of this study is to determine the efficacy of SPSS embolization for recurrent/refractory HE.

Materials and Methods: Five databases were screened to identify studies assessing the efficacy of SPSS embolization for HE. The random-effects model was used to calculate the pooled rates, and I^2 values were used to assess heterogeneity.

Results: Twenty-one studies met the inclusion criteria, comprising a total of 331 patients with recurrent or refractory HE despite medical management. The etiology of cirrhosis includes ethanol abuse, chronic viral hepatitis, MASH, and others. Following embolization, 82% of patients had HE-related clinical improvement, and 71% of patients became free from HE-related hospitalization. The mean difference in pre- and post-embolization serum ammonia level was 104 [77–130], $p < 0.01$. Worsening portal hypertension following embolization presented as gastrointestinal bleed (10%), new or aggravated varices (15%), and new or aggravated ascites (15%).

Conclusions: SPSS embolization demonstrated improvement in HE-related clinical symptoms with a decreased need for hospitalization, but it exacerbates portal hypertension, increasing the risks of ascites, varices, and gastrointestinal bleeding. Future randomized controlled trials are needed to evaluate SPSS embolization efficacy against standard medical management.

Introduction

Hepatic encephalopathy (HE) is a reversible syndrome encompassing neuropsychiatric pathologies resulting from the accumulation of neurotoxins in the bloodstream.[1] HE occurs in patients with acute or advanced liver disease, as well as in those with portosystemic shunting, even in the absence of liver disease.

Overt HE, characterized by a noticeable decline in cognitive and neurological function, affects 30–45% of patients with cirrhosis and leads to approximately 20,000 hospitalizations annually in the United States.[2–4] Inpatient management of HE is costly, with an average of $35,000 per hospital stay.[5] Morbidity is further complicated by increased risk of falls, the inability to safely drive, and caregiver burden.[5]

Management of HE focuses on identifying precipitating factors, administering ammonia-lowering therapies, and preventing recurrence.[6] According to the American Association for the Study of Liver Diseases (AASLD), lactulose is recommended as the first-line therapy for treating overt HE, with rifaximin added for preventing recurrence.[2]

Patients with overt HE who do not respond to medical management are classified as having refractory HE. These patients may have developed spontaneous portosystemic shunts (SPSS), which are abnormal connections between the portal vein and systemic circulation.[6] While SPSS can act as "release valves" to reduce portal pressure, they bypass normal liver blood flow, increasing the risk of recurrent or refractory HE. Embolization of large SPSS is being investigated as a potential preventive measure for HE recurrence and may offer survival benefits.[7]

Although data on the clinical performance of SPSS embolization are currently limited to case series and small studies, we conducted a meta-analysis to comprehensively evaluate the efficacy of shunt embolization in managing persistent or recurrent HE.

Materials and Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist to identify the efficacy of SPSS embolization for the management of refractory/recurrent HE (Supplementary Appendix A).

Search Strategy

The literature was searched by authors (PP, ME) for the concepts of spontaneous portosystemic shunts, HE, embolization, portal hypertension, and cirrhosis. Search strategies were created using a combination of keywords and standardized index terms. Searches were conducted in Embase (81), Scopus (8), PubMed (103), Web of Science (58), and Medline (43). Full search strategies are provided in Supplementary Appendix B.

The titles and abstracts of the identified studies were independently screened by two authors (PP and ME). Based on predetermined inclusion and exclusion criteria, studies that did not address our specific research question were excluded. The full texts of the selected articles were then reviewed for relevant information. Any discrepancy in article selection was resolved by mutual consensus, after discussion with the third co-author (EZ). Additional relevant articles were manually searched from the bibliographic sections of the selected articles, as well as the systematic and narrative articles on the topic.

Study Selection

For the purpose of this meta-analysis, we included studies that evaluated the efficacy and safety of SPSS embolization for persistent or recurrent HE. Studies reporting data on adult patients (>18 years) with cirrhosis complicated by persistent or recurrent HE were included.

The exclusion criteria were as follows: (1) single-patient case reports, review articles, and editorials; (2) studies done in the pediatric (<18 years) population; (3) non-English language studies; (4) non-human/animal studies; (5) non-clinical laboratory studies.

Data Abstraction and Quality Assessment

Two authors (E.Z. and H.K.) independently abstracted data from the studies using a pre-approved standardized form. Two authors (M.A.E., P.P.) independently assessed the quality of the studies to ascertain the risk of bias.

This was done using the National Institute of Health (NIH) quality assessment tool for before-after (pre-post) studies with no control group (Table 1).

Outcomes Assessed

The outcomes assessed included clinical improvement in HE, changes in HE medication requirements, the need for HE-related hospitalization, changes in Model for End-Stage Liver Disease (MELD) score, serum ammonia levels, and serum creatinine levels. We also evaluated the development or worsening of varices and/or ascites, and the incidence of gastrointestinal bleeding (GIB) following SPSS embolization for the management of persistent or recurrent HE.

Statistical Analysis

Standard meta-analysis statistics were used, following the methods suggested by DerSimonian and Laird. The pooled efficacy rates with the corresponding 95% confidence interval were calculated by logit transformation using a random-effects model. Heterogeneity between study-specific estimates was assessed using the Cochrane Q test and the I^2 statistic. Publication bias assessment is discussed under validation of the meta-analysis. All analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 4 (BioStat, Englewood, NJ).

Results

Search Results and Population Characteristics

The initial search yielded 270 references. After the removal of duplicates, a total of 194 studies, including full articles and abstracts, underwent formal title and abstract screening. Based on our inclusion and exclusion criteria, 21 studies involving a total of 331 patients were included (Fig. 1).

The final analysis included 331 patients (205 male, mean age: 60.8±9.3) with recurrent or refractory HE despite medical management. The most common etiology for cirrhosis was ethanol use/abuse (30%), followed by chronic viral hepatitis (Hepatitis B or Hepatitis C, 30%), metabolic dysfunction-associated steatohepatitis (27%), and other causes (13%, including primary biliary cholangitis, autoimmune hepatitis, and cryptogenic cirrhosis). Mean MELD and Child-Pugh scores were 14.2±2.3 and 8.8±1.1, respectively. One or more types of shunts were present in each patient, and the most common type of shunt was splenorenal, which was present in 64% of patients. One or more procedures for SPSS embolization were performed in each patient, with techniques including, but not limited to, coils, glue, vascular plugs, and sclerosant injection via various transvenous approaches. Refer to Table 1 for characteristics of included studies.

Characteristics and Quality of Included Studies

Two authors (P.P. and M.E.) conducted an independent and blinded quality assessment of the included studies. Despite encountering some discrepancies, these were resolved by a third author (P.L.) in an independent and blinded manner. Our systematic review employed three types of quality assessment using the NIH scale: pre-post studies without control groups, controlled intervention studies, and case series assessments. The NIH scale was chosen for its comprehensive evaluation criteria suitable for diverse study designs.[8] According to the NIH scale, eleven studies received a score of 9, indicating high quality, whereas seven studies were deemed fair quality, with scores ranging from 5 to 8, as shown in Supplementary Table 1 and Table 2. Fair-quality studies had insufficient data, as they were based on abstracts rather than full-text articles. Despite this limitation, these abstracts were included due to their relevance to the research question and the lack of available full-text studies. In the case series studies, two of the included studies were regarded as high quality. Regarding the randomized controlled trial, one study was deemed high quality with 11 points out of 14 in different aspects as per the NIH quality assessment for controlled intervention trials.

Pooled Outcomes

Clinical Success

Nineteen of the twenty-one studies reported HE-related clinical improvement. A total of 261 (82%) patients experienced improvement in HE symptoms following one or more embolization procedures (I^2=46%) (Fig. 2). Six studies reported the need for HE-related hospitalization following embolization (Supplementary Fig. 1). Fifty-three (71%) patients became free from HE-related hospitalization (I^2=55%). The change in serum ammonia level was reported by seven studies. There was a significant reduction noted between pre- and post-embolization serum ammonia levels (mean difference = 104 [77–130] mcg/dL, p<0.01, I^2=77%) (Fig. 3). There was no significant difference in pre- and post-embolization MELD scores (0.428 [–2.5 to 3.3], p=0.8; 5 studies) (Table 2).

Adverse Events

Sixteen studies reported the incidence of new or worsening portal hypertension following embolization. Thirty-three (15%) patients developed new or aggravated esophageal and/or gastric varices (I^2=62%), and thirty-four (15%) patients developed new or worsening ascites (I^2=2.5%) (Supplementary Fig. 2). The post-embolization course was complicated by GIB in 15 (10%) patients, as reported by 13 studies (I^2=11%) (Fig. 4). Twenty-six (15%) patients from 12 studies developed post-embolization fever and/or leukocytosis (I^2=70%). No significant difference was noted between pre- and post-embolization serum creatinine levels (mean difference = 0.17 [–0.36 to 0.03] mg/dL, p=0.09, I^2=56%) (Table 2).

Validation of Meta-Analysis

Sensitivity Analysis

To assess whether any one study had a dominant effect on the meta-analysis, we excluded one study at a time and analyzed its effect on the main summary estimate. No single study significantly affected the outcome or heterogeneity.

Heterogeneity

We assessed the dispersion of the calculated rates using the I^2 percentage values. Based on I^2 analysis for heterogeneity, considerable heterogeneity was noted for the pooled difference in pre- and post-embolization change in serum ammonia level and MELD score. The I^2 values for the pooled rates are summarized in Table 2.

Prediction Interval

This meta-analysis was conducted using the random-effects model. Therefore, we calculated the prediction interval, which deals with the dispersion of the effects. The calculated prediction interval of the difference in means between pre- and post-embolization ammonia was 104 (95% interval: 18.5 to 189.5); for new or aggravated varices, it was 0.148 (95% interval: 0.016 to 0.656).

Publication Bias

Based on visual inspection of the funnel plot, as well as quantitative measurement using the Egger regression test, there is evidence of publication bias for pre- and post-embolization ammonia (Egger's 2-tailed p-value = 0.04). There is also evidence of publication bias for overall clinical success (Egger's 2-tailed p-value = 0.001). The funnel plot for publication bias is illustrated in Supplementary Figure 3.

Discussion

This study evaluated the efficacy of SPSS embolization for patients with HE refractory to medical management. A total of 21 studies meeting the inclusion criteria were analyzed. SPSS embolization demonstrated efficacy through clinical improvement in HE symptoms, reduced need for HE-related hospitalization, and a statistically

significant decrease in ammonia levels. Adverse events included post-embolization fever/leukocytosis, GIB, and the development or worsening of pre-existing esophageal or gastric varices and/or ascites.

In our analysis of 19 studies, 82% of patients had clinical improvement in persistent or recurrent HE, reported as increased autonomy, improvement in cognitive symptoms, and decreased need for HE medications after SPSS embolization. GIB and development of new or exacerbated varices were reported in 10% and 15% of patients, respectively, following embolization. GIB following embolization may result from worsened portal hypertension or the progression of underlying cirrhosis. However, it is unclear whether SPSS embolization directly worsens portal hypertension, as the relationship between SPSS and the risk of GIB remains ambiguous.[30–32]

In our study, 15% of patients developed new-onset ascites or experienced a worsening of pre-existing ascites after SPSS embolization, likely due to increased portal hypertension. A recent study found that an elevation of the hepatic venous pressure gradient (HVPG) by >4 mm Hg from baseline and an absolute increase to >16 mm Hg immediately post-embolization were significant predictors of early- and late-onset ascites, respectively.[33]

Overt HE is one of the major complications of Transjugular Intrahepatic Portosystemic Shunt (TIPS).[34] Moreover, the presence of SPSS further increases the risk of overt HE following TIPS.[35] In their meta-analysis, Yang et al.[35] reported an increased risk of overt HE in patients undergoing TIPS without concurrent SPSS embolization compared to those with concurrent SPSS embolization, with no significant differences in mortality, variceal bleeding, or shunt dysfunction. A recent meta-analysis reported decreased risk of overt HE in patients undergoing TIPS along with concurrent large SPSS embolization compared to TIPS alone, without a significant increase in recurrent variceal bleeding.[36] Our findings are consistent with these studies in that SPSS embolization decreases the risk of recurrent/refractory HE in patients with or without TIPS.

The presence and size of SPSS increase with liver dysfunction, as indicated by higher MELD scores.[37] Our analysis revealed no significant difference in MELD scores before and after SPSS embolization (Table 2). However, the MELD score does not account for post-SPSS embolization complications related to portal hypertension, and its impact on other serious outcomes remains uncertain.[7]

In our analysis, 15% of patients developed fever and/or leukocytosis following SPSS embolization. Post-embolization fever is a common occurrence, primarily attributed to transient bacteremia following the injection of sclerosing agents.[38] In the majority of patients, fever subsided with conservative management.

To our knowledge, this is the first meta-analysis that investigates the efficacy of embolization of SPSS for patients with persistent or recurrent HE. This analysis includes a diverse patient population with various shunt types and encompasses different embolization techniques. Given that embolization remains a key treatment option for many patients in the absence of liver transplantation, our results demonstrating acceptable levels of heterogeneity are particularly significant. This consistency across the included studies enhances the robustness of our findings in this patient group.

Our study is constrained by the following limitations. First, the prevalence of retrospective studies introduces inherent biases from historical data, which may affect the robustness of our findings. Second, 5 out of 21 studies included in the analysis originate from conference abstracts, which, by their nature, lack the comprehensive inspection and peer-review process characteristic of full-length publications. Third, the limited data on long-term and survival-related outcomes highlights the need for further research. Finally, data on shunt diameter, post-procedure changes in HVPG, and stratified outcomes based on MELD score were unavailable in the included studies and thus could not be analyzed. This highlights the necessity for further research to address these critical gaps in understanding.

Conclusion

SPSS embolization is an effective treatment for patients with recurrent or refractory HE. Careful patient selection is important to balance long-term benefits with potential complications. Future randomized controlled trials are needed to compare its efficacy against standard medical management and to address technical factors and outcomes.

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Table 1. Characteristics of the included studies

Study ID	Study type	Patients (n) / Male(n)	Age (mean)	Etiology of cirrhosis/shunt	Shunt anatomy	Embolization method	Embolization route	Follow up period	Outcomes studied
Sakurabayasi[9], 1997	Prospective	7 / 3	66	Etoh(1), HCV(4), cryptogenic(2)	Splenorenal Shunts(5); Gastrorenal Shunt(1); İntrahepatic Porto-Hepatic Vein Shunt(1)	Stainless steel coil (7)	Percutaneous transhepatic vein(4); transrenal vein(3)	3-4 months	Improvement in HE, change in ammonia level, new/worsening PHTN
chikamori[10], 2000	Case Series	5 / 2	60.2±6	Etoh(2); HCV(2); crypto(2)	Gastrorenal(5)	5% ethanolamine oleate with iopamidol(EOI) and absolute ethanol	transjugular retrograde obliteration (TJO)	17-74 months	improvement in HE, change in portal flow volume, change in ammonia level, new/worsening PHTN
Zidi[11], 2007	Case Series	7 / NR	66±9.2	HCV(4); Etoh(3)	Splenorenal(7)	steel coils ± histoacryl	transfemoral(6), tranhepatic(1)	3 months	improvement in HE, survival, new/worsening PHTN
Mukund[12], 2012	Retrospective	7 / 7	56	MASH(2), Etoh(2), HBV(1), crypto(2)	Splenorenal(7)	vascular plug or balloon occluder	BRTO with sodium tetradecyl sulphate foam	4 months	improvement in HE, change in ammonia levels, new/worsening PHTN
Laleman[13], 2013	Retrospective, Multicenter	37 / 21	60±12.7	MASH(3), Etoh(17), HCV(13), PBC(2), AIH(1),cryptogenic(1)	Splenorenal(20), Meso-Caval(7), Periumbilical(9), Meseo-Renal Shunt(1)	coils, Amplatzer plugs, matrix	transhepatic (7); percutaneous (6); transfemoral or transjugular (23)	23±5 months	improvement in HE, new/worsening PHTN
Young[14], 2013	Retrospective	8 / 2	55.5±10.1	MASH, PBC , HCV, AIH, PSC, crypto	Na	coil, occluder, liquid agents	common femoral vein(3); internal jugular vein(1); and transhepatic approach(3); recanalized	3-28 mo; mean: 15.5±9.9	Improvement in HE, change in HE medications, new/worsening PHTN

							paraumbilical vein(2)		
An et al[15], 2014	Retrospective Cohort	17 / 11	61.6± 2.6	HBV (9) HCV (2) Alcohol (5) Others (1)	Splenorenal(14); Paraumbilical(3)	vascular plugs or coils + gelatin sponge	femoral vein(14); percutaneous for paraumbilical vein(3)	17 months (6–37)	improvement in HE, survival, change in liver function
Naeshiro[16], 2014	Retrospective	14 / 9	68.7± 5.6	HBV(1), HCV(9), alcohol(4)	Splenorenal(3); Gastrorenal(4), Meso-Caval(5); Porto-Caval(2)	ethanolamine oleate (EO) OR EO+coils OR EO + coils OR EO, coils + n-butyl 2-cyanoacrylate (NBCA) OR coils+NBCA	combination of these	27 (12-29 mo)	improvement in HE, change in ammonia level, new/worsening PHTN, survival
Inoue[17] 2014	Retrospective	19 / 8	66.9± 2.2	HCV(12), HBV(1), ALD(4), schistosomiasis (1), crypto(1)	Splenorenal(19)	5% ethanolamine oleate with iopamidol(EOI) or coil occluder	BRTO	28.4±2.4 months.	improvement in HE, change in hepatic function reserve, survival, new/worsening PHTN
C. Parra-Farinas[24] ,2016	Prospective	35 / 18	60.7± 15	MASH(4), Etoh(11), HCV(8), PBC(2), AIH(2),cryptogenic(8)	Spleno-Renal Shunts (24), Meso-Caval/Renal (7), Gastric Azygos/Renal (3), Recanalized Paraumbilical Veins (1)	coil or occluder and/or liquid agents	common femoral vein (21), internal jugular vein (9), transhepatic (3), trans-splenic approaches (1).	3-31 months	improvement in HE, new/worsening PHTN
Lynn[18], 2016	Retrospective	20 / 10	60.9± 8.1	MASH (8), Etoh (5), HCV (2), AIH (1), PSC (1), A1AT (1), crypto(n)	Splenorenal (12); IMV-Ovarian (2); SMV-Ovarian (1); Portal-Right Gonadal (1); IMV-Left Renal (1); Periumbilical-Portosystemic (1); Multiple (2)	coil (15); occluder (4); coil+occluder (1)	transhepatic (5); right femoral vein (6); internal jugular vein (5), umbilical vein (1); right axillary vein (3)	12 months	hospitalization requirements, change in HE medications, change in ammonia level, new/worsening PHTN

Aw et al[19], 2017	Retrospective	7 / 5	62.5	Etoh (3), chronic hepatitis (3), MASH (1)	Nr	combination of a vascular plug, coils and sclerosant	retrograde transvenous obliteration.	3-6 months	improvement in HE, change in ammonia level, new/worsening PHTN
Choudhary[20], 2017	Retrospective	5 / 5	61±7	MASH (3), Etoh (1), HBV (1)	Splenorenal (4); Mesocaval(1)	vascular plugs ± sclerosant	right femoral vein(4); right internal jugular vein (2)	9.8 months	improvement in HE, change in ammonia level, new/worsening PHTN
Philips[21], 2017	retrospective	21 / 17	56±10.6	MASH (13), Etoh (6), crypto(2)	splenorenal(17); mesocaval(7), other(6)	coil, cyanoacrylate glue	PARTO, BRTO with or without cyanoacrylate glue embolization, or a combination of these	1-9 months	improvement in HE, change in ammonia levels, new/worsening PHTN
He et al[22] 2018	retrospective cohort	44 / 31	51.2 ± 11.6	HBV (29), HCV (2), Alcoholic liver disease (3), Others (2), Cryptogenic (8)	splenorenal (29); mesocaval(2), gastroesophageal(13), recanalized paraumbilical vein(1)	coil or vascular plug	transjugular (44)	20.7 months (15.5–31.0)	improvement in HE, new/worsening PHTN
Philips[23], 2020	retrospective	45 / 38	57.2± 9.1	MASH(28), Etoh(15), HBV(1), HCV(1)	paraumbilical vein(4); coronary vein(3); splenorenal(25); multiple(13)	vascular plugs or coils or occluders ± glue	transfemoral(2);transhepatic(8);transjugular(36)	9 months	improvement in HE, change in ammonia level, new/worsening PHTN
Alvarez-lopez[25],2022	retrospective	5 / 3	57.1± 8	HCV (4) Etoh(1)	mesocaval(2); splenorenal(2); gastroesophageal(1), gastrorenal(1)	Coils + Onyx 34 (3)/ Glue + Amplatzer (1) / Coils (1) / Glue (1)	right internal jugular vein(5)	4.4 years (range 1.0-5.0)	Improvement in HE, change in HE medications, new/worsening PHTN
Sahay[26], 2022 -ab	retrospective	15 / 7	NR	MASH(4), Etoh(2), HCV(5), multifactorial (2), crypt (2)	Natural shunt or TIPS	NA	NA	12 months	number of hospitalizations, change in renal function, new/worsening PHTN
Fujimoto[27], 2023	retrospective cohort	30 / NR	NR	NR	NR	NR	NR	24 months	improvement in HE, new/worsening PHTN

Gurtatta[28] et al 2023	retrospective	9 / 5	62	NR	NR	NR	NR	3 months	improvement in HE, new/worsening PHTN
Mukund[29] 2023	RCT	18 / 12	55.4 ± 10.9	MASH(10), Etoh(3), viral(3), crypto(2)	spleno-renal(15); gastro-renal(8), large paraumbilical(5); gastro-spleno-renal shunt(3)	vascular plug or balloon occluder	BRTO; PARTO	5 months	improvement in HE, change in liver volume, change in ammonia levels, new/worsening PHTN

HBV: Hepatitis B Virus; HCV: Hepatitis C Virus; Etoh: Ethanol; MASH: Metabolic dysfunction associated steatohepatitis; PBC: Primary Biliary Cholangitis; AIH: Autoimmune Hepatitis; BRTO: balloon-occluded retrograde transvenous obliteration; PARTO: plug-assisted retrograde transvenous obliteration; CARTO: Coil-assisted retrograde transvenous occlusion; PHTN: Portal hypertension; TIPS: Transjugular Intrahepatic Portosystemic Shunt.

Table 2. Pooled outcomes

Outcomes	**Percentage**	**Mean difference**	**I2%**	**Studies (n)**
Improvement in HE symptoms/clinical success	81.7 (73-87) %	-	46	19
Free from HE medications	12.3 (3-37)%	-	58	5
Decrease in need for HE medications	17.5 (7-35)%	-	42	5
Free from HE related hospitalizations	71.7(48-87)%	-	55	6
No change in HE medications	22 (7-51)%	-	67	5
Development of new or worsening of pre-existing ascites	15.4 (11-21)%	-	2.5	16
Development of new or worsening of pre-existing varices	14.8 (8-26)%	-	62	16
Post-embolization gastrointestinal bleeding	10 (6-16)%	-	11	13
Post-embolization sepsis	15.2 (6-32)%	-	70	12

Serum creatinine	-	-0.17(-0.4 - 0.03), p=0.09	56	5
Serum ammonia	-	104(77-130), p <0.001	77	7
MELD score	-	0.4(-2.5 - 3.4), p=0.7	96	5

HE: Hepatic encephalopathy; MELD: Model for End stage Liver Disease.

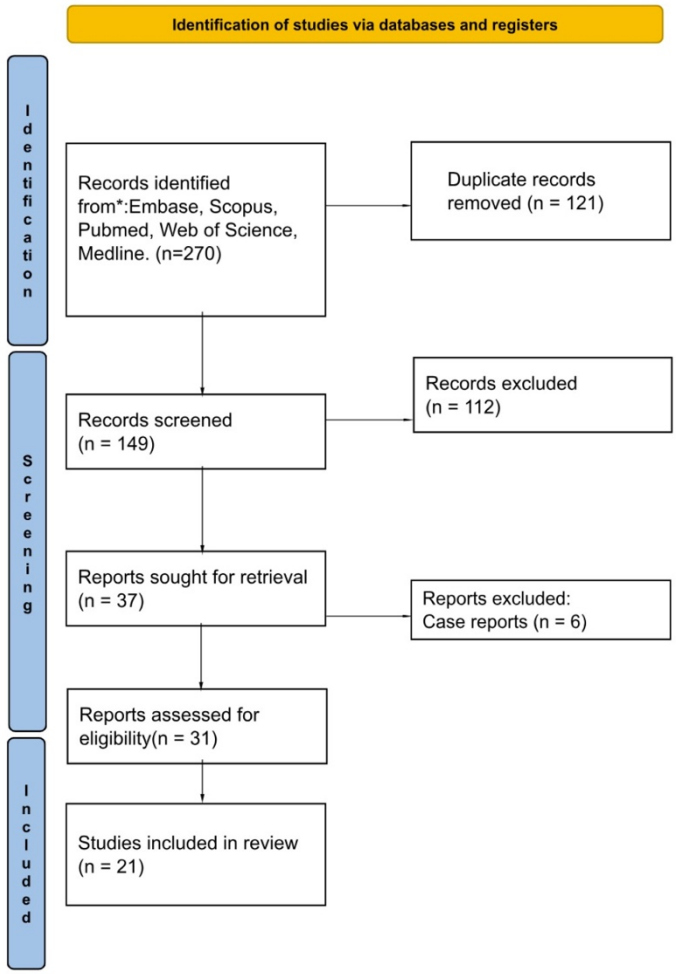

Figure 1. Study selection flow chart

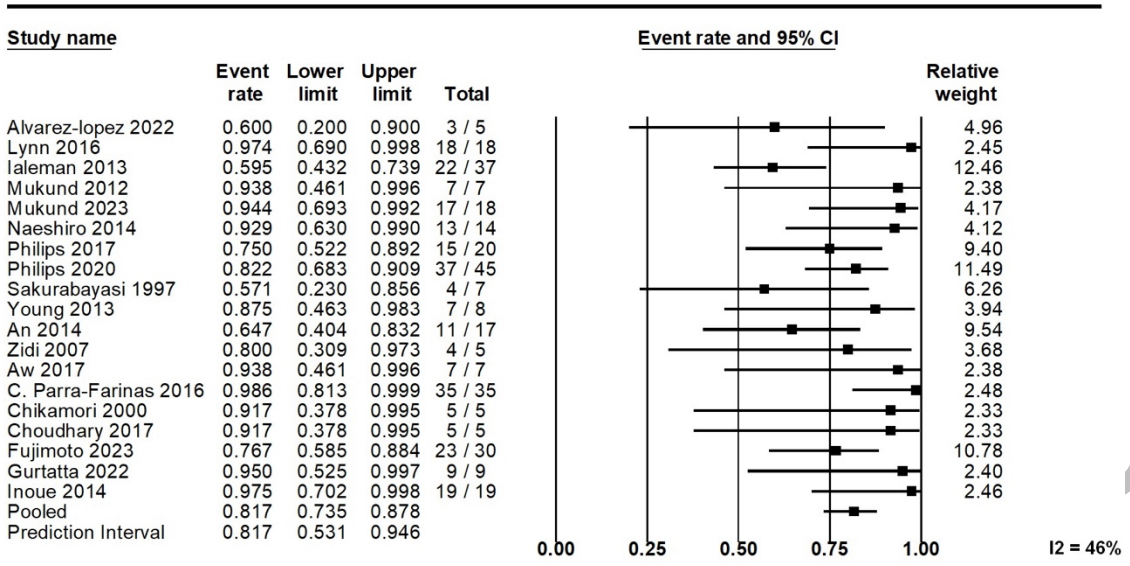

Figure 2. Clinical success

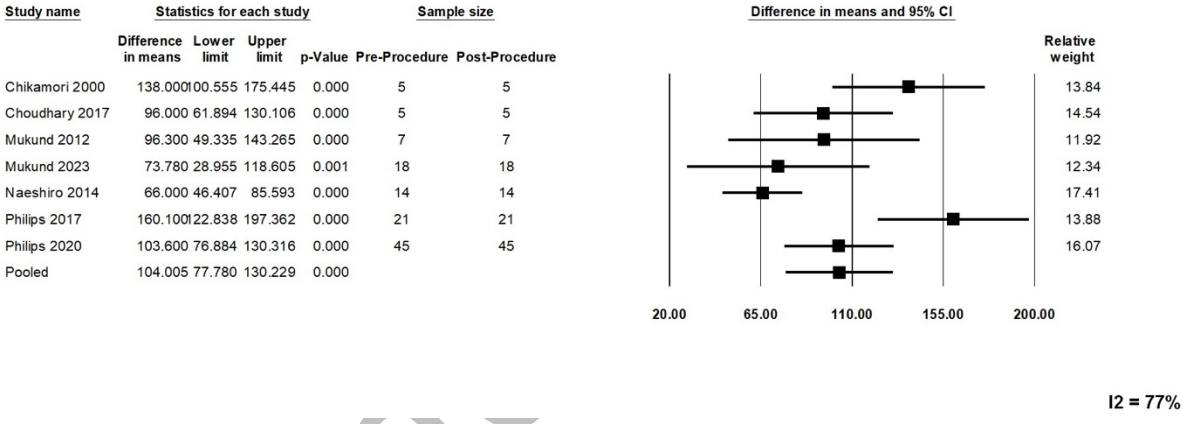

Figure 3. Mean difference in serum ammonia

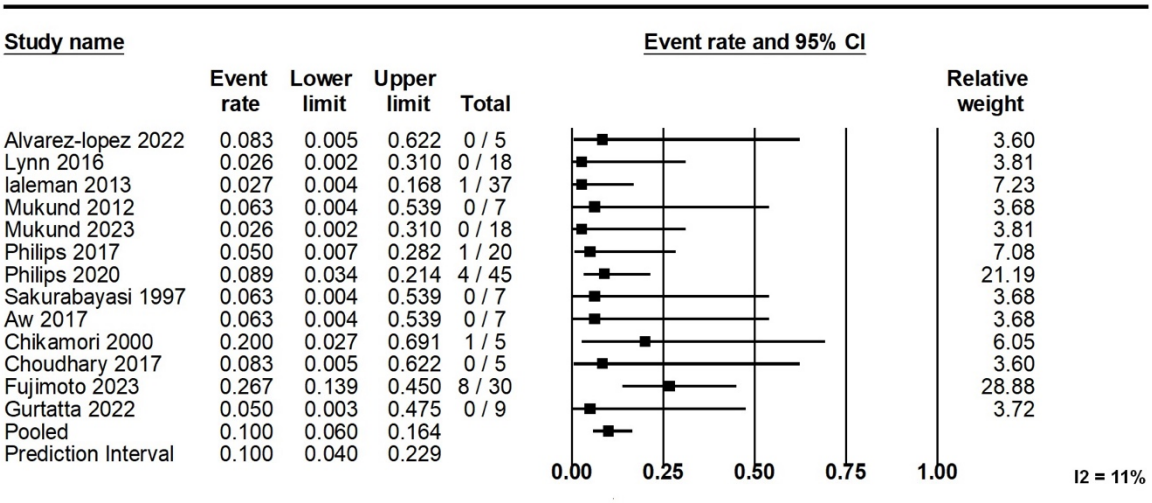

Figure 4. Post embolization gastrointestinal bleeding