Partial Splenic Embolization has Beneficial Effects for the Management of Gastroesophageal Variceal Hemorrhage

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ABSTRACT

Background/Aims: Partial splenic embolization (PSE) is used in the management of gastroesophageal variceal hemorrhage (GEVH). However, it is uncertain whether it has beneficial effects for GEVH patients in preventing variceal recurrence and variceal hemorrhage, as well as promoting overall survival (OS), when it is combined with conventional therapies. **Materials and Methods:** The databases including PubMed, EMBASE, Web of Science, Google scholar, and Cochrane Central Register of Controlled Trials were searched up to 11th of November, 2015. Meta-analyses were performed by using Review Manager 5.3 software for analyzing the risk of bias, Newcastle-Ottawa Scale for assessing the bias of cohort studies, and GRADEprofiler software for assessing outcomes obtained from the meta-analyses. **Results:** A total of 1505 articles were reviewed, and 1 randomized controlled trial and 5 cohort studies with 244 participants were eligible for inclusion. The pooled hazard ratio (HR) of variceal recurrence is 0.50 (95% confidence interval (CI) 0.37, 0.68; $P < 0.00001$; $I^2 = 0\%$). The pooled HR of variceal hemorrhage is 0.24 (95% CI 0.15, 0.39; $P < 0.00001$; $I^2 = 0\%$). The pooled HR of OS is 0.50 (95% CI 0.33, 0.67; $P < 0.00001$; $I^2 = 0\%$). Meta-analyses demonstrated statistically significant superiority of combinational therapies over conventional therapies in preventing variceal recurrence and variceal hemorrhage and prolonging OS. The complications related to PSE were mild or moderate and nonfatal. **Conclusions:** The results indicate that PSE has beneficial effects for GEVH patients, however, future investigation with a larger number of subjects in clinical trials is warranted.

Key Words: Gastroesophageal variceal hemorrhage, hypersplenism, overall survival, partial splenic embolization, variceal recurrence

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Gastroesophageal varices are present in almost half of the patients with liver cirrhosis, and 25% to 35% of them suffer from gastroesophageal variceal hemorrhage (GEVH).[1] GEVH is a very serious medical emergency with high morbidity and mortality. In the past three decades, due to the development of new therapeutic technology, the mortality of GEVH at 6 weeks has significantly dropped from 60 to 20%.[2]

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However, variceal recurrence and re-bleeding are still big challenges after the initial treatment. In a recent consensus conference (the 6th Consensus Workshop, Baveno, Italy, April 2015), it was declared that the endpoint for GEVH patients with variceal hemorrhage and other complications is death, indicating the severity of GEVH.[3]

Pharmacological, endoscopic and angiographic treatments, and surgery are four main therapeutic strategies for GEVH. These strategies are designed to achieve three different therapeutic goals, namely, primary prophylaxis, managing

acute variceal bleeding, and second prophylaxis; each one has its own advantages and disadvantages.[4] In general, the patients with mild and moderate GEVH undergo endoscopic treatments, such as endoscopic variceal ligation (EVL), endoscopic injection sclerotherapy (EIS), and pharmacological therapies.[1] Transjugular intrahepatic portosystemic shunt (TIPS) and ballooned-transjugular retrograde obliteration (B-RTO) are used for patients with severe GEVH or those in whom endoscopic treatments have failed to control bleeding. Endoscopy is normally used to control most esophagus variceal bleeding, isolated gastric variceal bleeding, or gastroesophageal varices that extend beyond the cardia. On the other hand, TIPS, B-RTO, and percutaneous transhepatic variceal embolization (PTVE), and even surgery are used for the remaining cases of gastroesophageal varices.[3,4] The common mechanism of the above mentioned treatments in controlling GEVH is to change the hemodynamics of gastric and esophagus varices.

Partial splenic embolization (PSE) was initially used in the management of hypersplenism.[5] However, PSE had not been widely accepted for treating GEVH due to its unacceptably high rate of complications, such as sepsis, pneumonia rupture, progressive liver failure, or even death,[5] until the introduction of new embolization techniques and embolic materials. PSE reduces portal pressure and the size of the spleen, thus attenuating hypersplenism induced by thrombocytopenia.[6] PSE can also improve liver function, ameliorate encephalopathy, and promote liver regeneration.[7]

Furthermore, as a nonsurgical procedure, PSE can be applied in patients with various conditions and has been used in combination with conventional therapies in the management of GEVH.[8-13] However, the beneficial effects of PSE for GEVH have not been validated. Therefore, we designed this study to analyze whether combinational therapies are more effective than conventional therapies in reducing variceal recurrence, variceal hemorrhage, and occurrence of serious complications, as well as in promoting overall survival (OS) in GEVH patients using systematic review and meta-analyses.

MATERIALS AND METHODS

Data sources and searches

This systematic review and meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement checklist.[14] Literature search was focused on identifying randomized controlled trials (RCTs) and cohort studies, in which GEVH patients were treated with combinational therapies versus conventional therapies. The primary outcome was variceal recurrence, and the secondary outcomes were variceal hemorrhage and OS. The studies comparing only hemodynamics indexes, such as hepatic venous pressure gradient or portal pressure, were excluded from this study. Considering 6-week mortality to be an important clinical index,[15] studies with less than 6-weeks of follow-up were also excluded.

A systematic review of English articles was performed by 3 investigators by searching PubMed, EMBASE, Web of Science, Google scholar, and Cochrane Central Register of Controlled Trials (CENTRAL) (up to Nov 11, 2015). Search terms included numerous descriptors for PSE and GEVH (e.g., varic*, embolization*). The detailed search strategy used for PubMed is summarized in Table 1. This search strategy was also modified to accommodate the controlled vocabulary for EMBASE and CENTRAL databases. Text words were used for Google scholar. In addition, we reviewed references of eligible studies and searched the cited articles on Web of Science. We contacted several content experts and inquired about the knowledge of any studies that were not on our list of eligible studies or of any unpublished data pertinent to our research question. Finally, we searched the following clinical trial registries: Clinicaltrials.gov, clinicaltrialregister.eu, and anzctr.org.au.

Study selection

Two investigators working independently determined the eligibility of each of the abstracts that resulted from the search strategy. When an abstract met inclusion criteria, the

Table 1: Searching strategies for PubMed database

Number	Strategies
#1	randomized controlled trial [pt]
#2	controlled clinical trial [pt]
#3	randomized [tiab]
#4	placebo [tiab]
#5	drug therapy [sh]
#6	randomly [tiab]
#7	trial [tiab]
#8	groups [tiab]
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#10	animals [mh] NOT humans [mh]
#11	#9 NOT #10
#12	Esophageal and Gastric Varices.mp. or exp Esophageal and Gastric Varices/
#13	varic*
#14	#12 or #13
#15	embolisation*
#16	embolization*
#17	#15 or #16
#16	#11 and #14 and #17

Note: A total of 171 articles were extracted by this strategy published upto Nov 11, 2015

full-text was reviewed. Full-text articles were obtained unless both reviewers determined that the abstract was ineligible for this study. When disagreement appeared between the 2 reviewers about advancing to the full-text review, a third investigator was asked to further assess the abstract. If 2 of the 3 reviewers recommended a full-text review, additional efforts were made to obtain the full-text article. Full-text review was also performed in duplicate, and disagreements on inclusion of full-text articles were harmonized by consensus. If consensus was not reached, arbitration by an additional content expert was arranged.

Data extraction and quality assessment

Data were extracted by 2 investigators using a standardized form including the number of participants enrolled in each study arm, the study setting, the type of varices, the trial location, the methods of intervention, the infarction volume of the spleen, the mean times of PSE, the funding, and the follow-up period. The data of hazard ratio (HR) on variceal recurrence, variceal hemorrhage, and OS were obtained from this standardized form. No matter how many episodes of variceal hemorrhage occurred in one patient during a fixed period, we defined these episodes as once. If detailed data mentioned above could not be found in the text section, the method introduced by Tierney[16] was used to calculate the HR, the logrank Observed minus Expected events (O-E), variance, and 95% confidence interval (CI). Engauge Digitizer 5.2 was used to obtain time to event data from the cumulative frequency polygon in the article. If there was no cumulative frequency polygon or the data were missing in the paper, we advised the authors. Data extraction was performed in duplicate by 2 independent investigators, and disagreements were resolved by consensus. We assessed the following study characteristics to judge methodological quality of the RCT studies; how the randomization sequence was generated, how allocation was concealed, whether there were important imbalances in prognostic factors at baseline, which groups were blinded, and how missing outcome data were reported and analyzed. The risk of bias was assessed by using the Cochrane Collaboration risk of bias tool[17] for RCTs by 2 independent investigators. The Newcastle–Ottawa Scale (NOS)[18] was used to assess the bias in cohort studies. Disagreements on risk of bias assessments were harmonized by consensus.

Data synthesis and analysis

A fixed-effects model was used to calculate the pooled HR for attributing data including the ratio of variceal recurrence, variceal hemorrhage, and mortality. The inconsistency was measured by using the I^2 test, in which a higher I^2 score suggests a greater inconsistency. GRADEprofiler 3.6 software (The GRADE working group)[19] was applied to assess the outcomes obtained from meta-analyses.

RESULTS

Selected studies

Our initial search strategy identified 1451 articles. By using the additional strategy of reviewing bibliographies, lists of works cited, clinical trial registries, and contacting experts, we identified an additional 121 citations. After the duplicates were deducted, a total of 1505 citations were identified, 44 of which met the criteria for full-text review. Of the 44 full-text citations considered, 6 met the criteria for inclusion.[8-13] The PRISMA template[14] for study selection is shown in Figure 1. The most common reasons for excluding the studies were that they were either not RCT or cohort studies or they only investigated hemodynamics indexes. Among the 6 studies, 1 was RCT[11] and the other 5 were cohort studies.[7-10] Their characteristics are shown in Table 2. The conventional therapies used in these studies included EVL, B-RTO, TRO, and PTVE.

Quality assessment

The RCT study[11] was shown to have either a low or unclear risk of bias, as assessed by the Cochrane Risk of Bias tool[17] [Figure 2]. The 5 cohort studies were shown to have no significant high risk bias, as assessed by an NOS analysis[18] [Table 3].

Table 2: Characteristics of six included studies

Studies	Study type	Trial location	Type of varices	No. of patients		Conventional therapeutic methods	Infarction volume of spleen	Follow-up periods (years)
				Conventional therapy	Combinational therapy			
Taniai 1999[9]	cohort	Japan	esophageal	25	31	EVL	≈50%	3
Chikamori 2008[12]	cohort	Japan	gastric	19	14	B-RTO TRO	>70%	3.67
Ohmoto 2006[8]	RCT	Japan	esophageal	42	42	EVL	60-80%	8
Ohmoto 2003[11]	cohort	Japan	esophageal	26	26	EVL	60-80%	8.1
Waguri 2012[13]	cohort	Japan	gastric	9	10	B-RTO	60-90%	5
Duan 2014[10]	cohort	China	esophageal	34	31	PTVE	50-70%	2

PSE was performed for more than one time in all the 6 studies. None of the studies acknowledged funding support. Conventional therapy refers to EVL, B-RTO or PTVE, and combinational therapy, the conventional therapy plus PSE. RCT, randomized controlled trial; PSE, partial splenic embolization; EVL, endoscopic variceal ligation; B-RTO, balloon-occluded retrogradetransvenous obliteration; PTVE, percutaneous transhepatic variceal embolization

Overall analyses of outcomes

The pooled HR of variceal recurrence is 0.50 (95% CI 0.37, 0.68; $P < 0.00001$; $I^2 = 0\%$ [Figure 2a]. Among the 5 studies included in this analysis, 3 studies[8,9,11] investigated esophagus varices, whereas the other 2 studies[12,13] investigated gastric varices. The 2 studies of gastric varices did not differ from the 3 studies of esophagus varices with regard to the precision and size of samples. In the 3 studies,[8,10,11] the pooled HR of variceal hemorrhage is 0.24 (95% CI 0.15, 0.39; $P < 0.00001$; $I^2 = 0\%$) [Figure 2b], and the pooled HR of OS is 0.50 (95% CI 0.33, 0.67; $P < 0.00001$; $I^2 = 0\%$) [Figure 2c]. All the outcomes of comparisons were significantly different in terms of overall effects, and 2 arms of each had a low level of heterogeneity. The studies are distributed closely within the 95% CI axis by Reviewer Manager 5.3 on recurrence of varices, variceal hemorrhage, and OS. The representative funnel plot on variceal recurrence is shown in Figure 3.

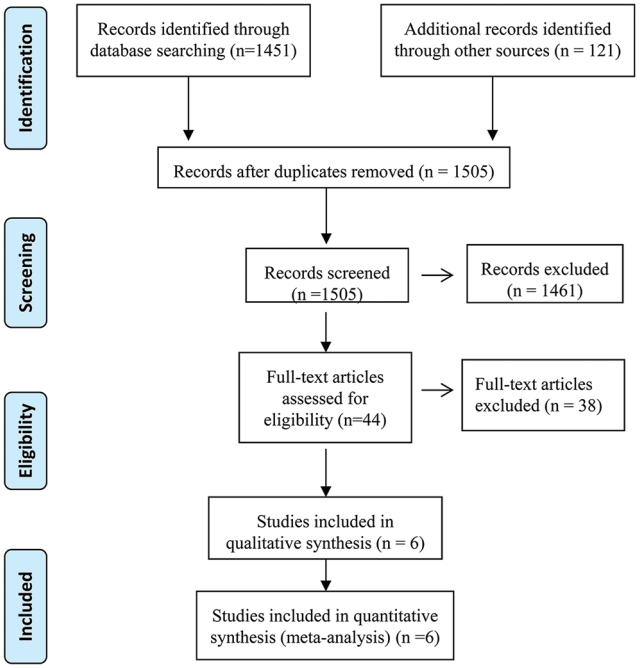

Figure 1: PRISMA flow diagram describing the steps of study selection. PRISMA, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

The two studies by Ohmoto *et al.*[8,11] are from the same institution, and hence their patient populations may have been overlapping, or a subpopulation of the former study[8] may be included in the latter study.[11] Therefore, we performed another analysis by excluding the former study.[8] As shown in Figure 4, the results from the new analysis on the pooled HR of variceal recurrence, variceal hemorrhage, and OS are similar to those from the analysis mentioned above. The pooled HR of variceal recurrence is 0.49 (95% CI 0.35,

Table 3: Evaluation of the cohort studies by Newcastle–Ottawa Scale

Authors and year of publication	Selection				Comparability	Outcome		Total score
	a	b	c	d	e	f	g‡	
Taniai 1999[9]	*	*	*	*	**	*	/	7*
Chikamori 2008[12]	*	*	*	*	**	*	/	7*
Ohmoto 2003[11]	*	*	*	*	**	*	*	8*
Waguri 2012[13]	/	/	*	*	*	*	*	5*
Duan 2014[10]	*	*	*	*	**	*	/	7*

All the 5 studies were prospective ones. "a" indicates representativeness of exposed cohort; "b," selection of the nonexposed cohort; "c," ascertainment of cohort; "d," demonstration that outcome of interest not present at the start of the study; "e," comparability; "f," assessment of outcome; "g," follow-upped long enough until outcomes occur. None of the study met the adequacy of follow-up of cohorts. "‡" indicates follow-up≥5 years is considered as "*"

Table 4: Incidence of complications after treatments in the six studies

Studies	Serious/Major complications	Incident rates		*P* value
		Combinational therapy	Conventional therapy	
Taniai 1999[9]	No serious complications described†	0	0	/
Chikamori 2008[12]	Major complications ∆	14/14	14/19	<0.05
	Mild to moderate abdominal pain	14/14	12/19	NS
Ohmoto 2006[8]	No serious complications described ‡	0	0	/
Ohmoto 2003[11]	No serious complications described§	0	0	/
Waguri 2012[13]	Serious complications described$	4/10	3/9	NS
Duan 2014[10]ϕ	Ascites	3/31	20/34	0.003
	Portal hypertensive gastropathy	2/31	13/34	0.014
	Hepatic encephalopathy	0/31	1/31	NS
	Portal vein thrombosis	2/31	1/34	NS

Combinational therapy refers to conventional therapy plus PSE. "†," Mild complications included fever≥38°C, left chest pain, anorexia and nausea. "∆," Major complications included mild to moderate abdominal pain, ascites, and worsening of portal hypertensive gastropathy. Minor complications included fever≥38°C, hematuria and small amount of pleural effusion. "‡," Mild complications including transient fever, left-sided chest pain and anorexia were observed in all patients. "§," Mild complications including transient fever, left-sided chest pain and anorexia were observed in all patients to some extent. "$," Serious complications included symptomatic ascites, pleural effusion, spontaneous bacterial peritonitis and portal thrombus. Mild complications included fever≥38°C and abdominal pain. "ϕ," No definite word of "serious" or "major" was used for describing complications. The Chi-square test was used for statistical analyses

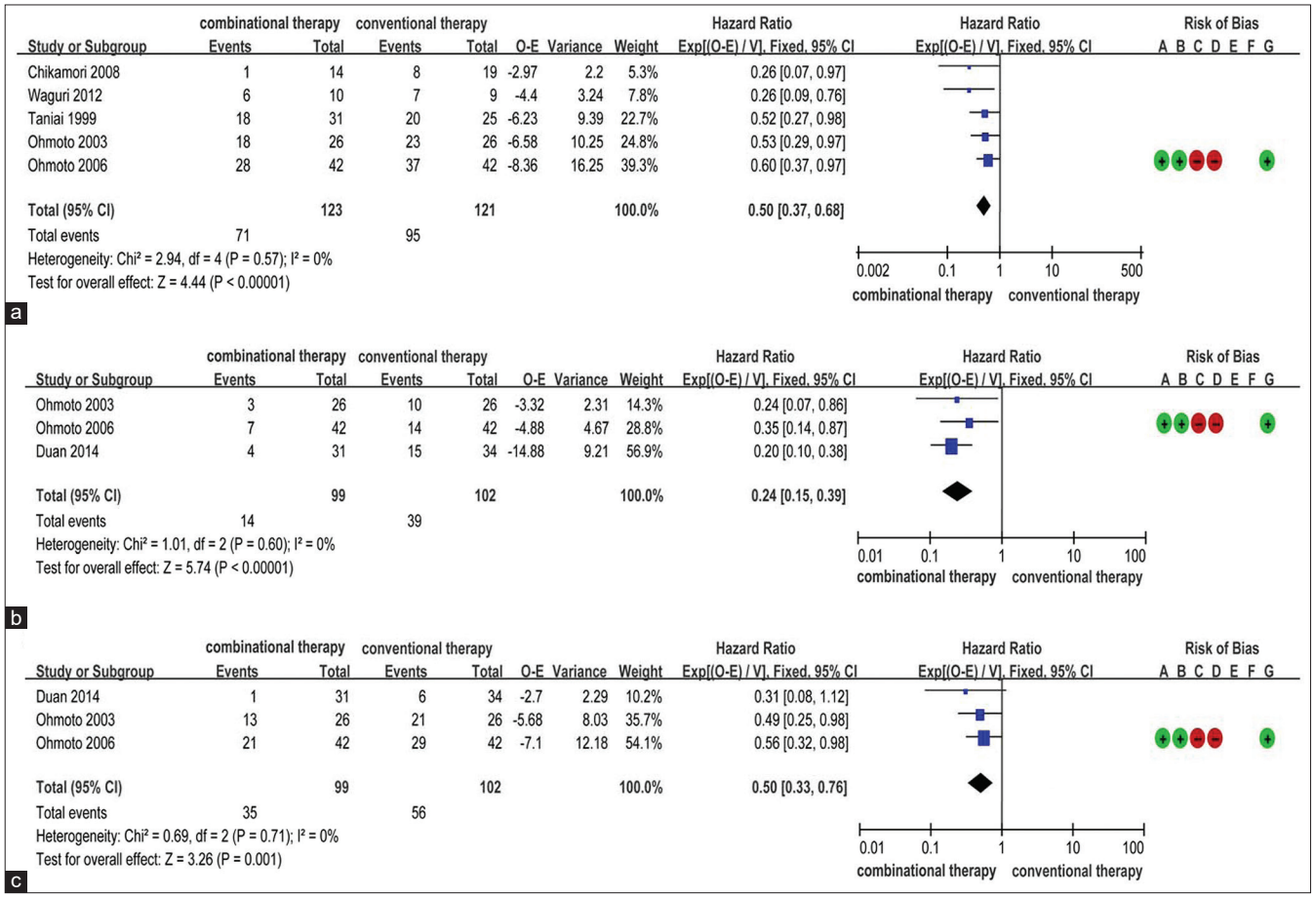

Figure 2: Forest plot of comparisons by risk of bias analyses. The analyses were performed by using Review Manager 5.3 on variceal recurrence (a) variceal hemorrhage, (b) overall survival, (c) and risk of bias. Types of risk of bias: (A) random sequence generation (selection bias), (B) allocation concealment (selection bias), (C) blinding of participants and personnel (performance bias), (D) blinding of outcome assessment (detection bias), (E) incomplete outcome data (attrition bias), (F) selective reporting (reporting bias), and (G) other bias

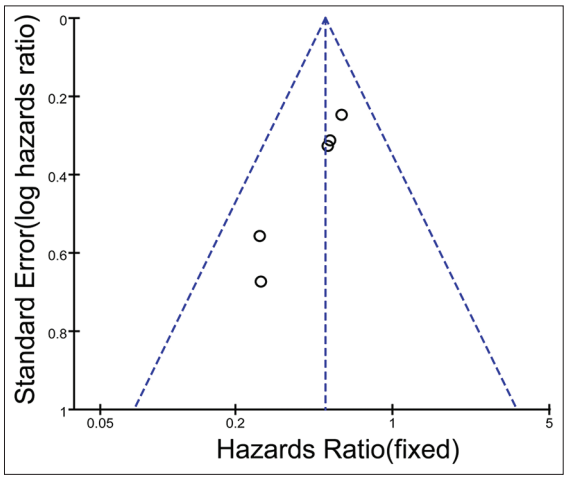

Figure 3: Funnel plot for comparisons on variceal recurrence. The analyses were performed by using Reviewer Manager 5.3 on variceal recurrence in the 5 cohort studies

0.70; $P < 0.00001$; I2 = 0% [Figure 4a], the pooled HR of variceal hemorrhage is 0.24 (95% CI 0.14, 0.41; $P < 0.00001$; $I^2 = 0\%$) [Figure 4b], and the pooled HR of OS is 0.51 (95% CI 0.30, 0.85; $P < 0.00001$; $I^2 = 0\%$) [Figure 4c].

The data of complications in the 6 studies are summarized in Table 4. The definition of serious complications varied significantly among different studies; therefore, we were unable to perform meta-analyses for this issue. However, most of the complications were usually mild or moderate and nonfatal.

Grade assessment

The GRADEprofiler 3.6 software was used to assess the outcome acquired from meta-analyses [Table 5]. All the outcomes were given moderate quality.

DISCUSSION

Splenic embolization was first introduced by Maddison in 1973,[20] when autologous blood clot was used as an embolus to produce splenic artery embolization for

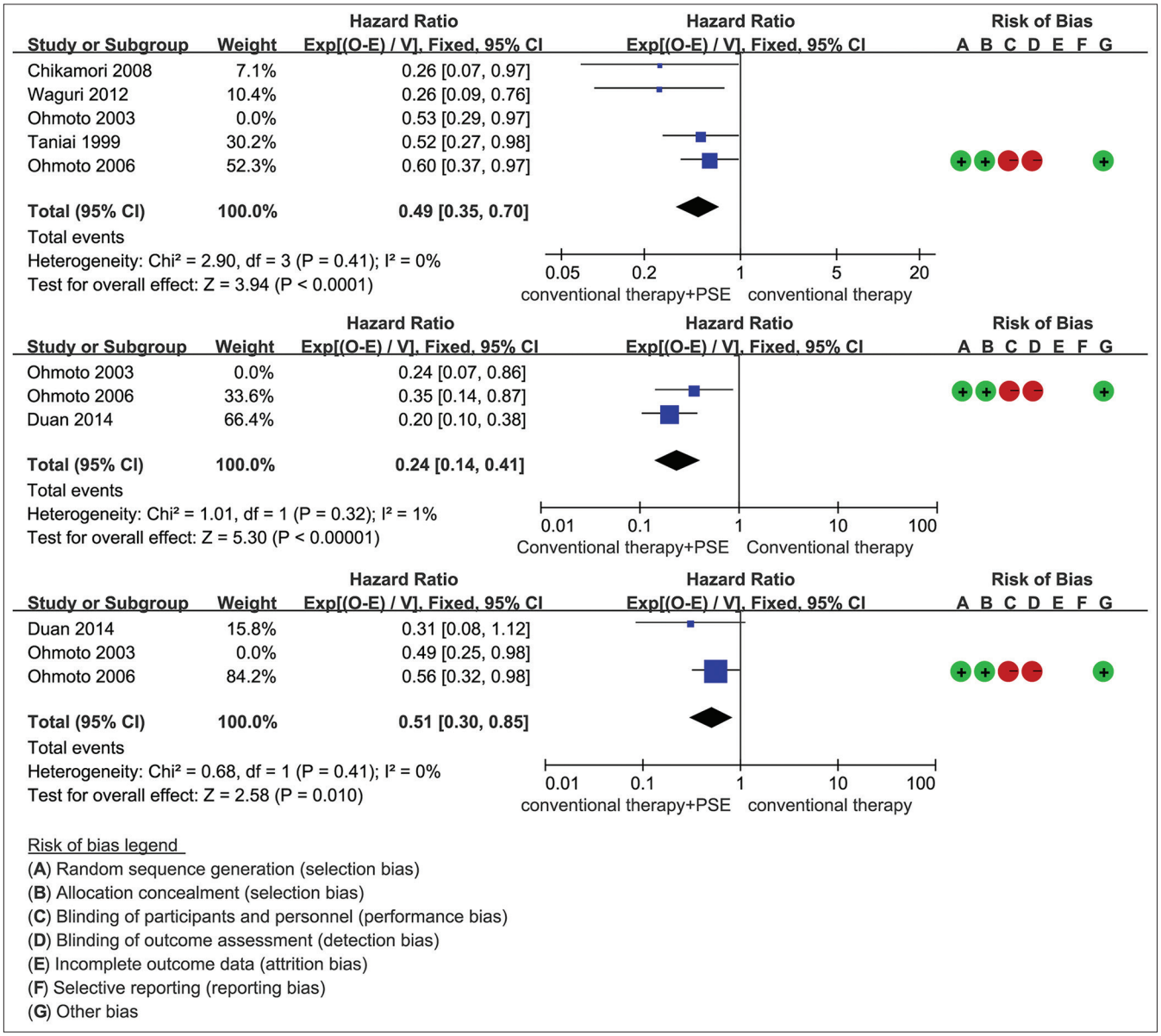

Figure 4: Forest plot of comparisons by risk of bias analyses (The study (Ohmoto K, *et al*. Hepatogastroenterology, 2003; 50: 1766-1769) is excluded). The analyses were the same as in Figure 2

hypersplenism. Transcatheter PSE was developed by Spigos in the late 1970s.[21,22] With the development of interventional radiology, particularly the invention of new embolic materials, the application of PSE has been extended from hypersplenism to various diseases such as hereditary spherocytosis, thalassemia, autoimmune hemolytic anemia, and splenic trauma.[23] The first systemic review on PSE in the management of portal hypertension was published in 2007, and the most contemporary study noted in this review was reported in 2005.[24] This article thoroughly summarized the English-language literature and the benefits of PSE.[24] Later, Smith and Ray[25] published a review of PSE in portal hypertension in 2012, and Hadduck and McWilliams[26] published a review on PSE in cirrhosis in 2014. These reviews focus on the application of PSE in cirrhosis and/or portal hypertension.

GEVH is a catastrophic episode for patients with cirrhosis accompanied with portal hypertension, and PSE has been used in the management of GEVH alone or in combination with conventional therapies. However, we have not spotted a systemic review on this topic after searching the available databases. A few clinical trials have been conducted on the use of PSE in the management of GEVH, and the results have been promising.[8-13] However, it has not been systematically analyzed whether PSE do

Table 5: Grade assessment on variceal recurrence, variceal hemorrhage, and survival between combinational therapy vs. conventional therapy

	No. of studies	Quality assessment		Summary of findings				Quality	Importance
		Limitations, Inconsistency Indirectness, Imprecision	Association	No of patients		Effects			
				Combinational therapy	Conventional therapy	Relative (95% CI)	Absolute		
Variceal recurrence	5	None	Strong [a]	71/123 (78.50%)	95/121 (78.50%) 80%	HR 0.50 (0.37-0.68)	249 (137-351) fewer per 1000 247 (135-351) fewer per 1000	⊕⊕⊕◯ Moderate	CRITICAL
Variceal hemorrhage	3	None	Strong [b]	14/99 (44.1%)	39/102 (38.20%) 38.50%	HR 0.24 (0.15-0.39)	273 (211-313) fewer per 1000 275 (212-315) fewer per 1000	⊕⊕⊕◯ Moderate	CRITICAL
Survival	3	None	Strong [c]	35/99 (35.4%)	56/102 (54.90%) 74.90%	HR0.50 (0.33-0.76)	221 (95-318) fewer per 1000 250 (99-383) fewer per 1000	⊕⊕⊕◯ Moderate	CRITICAL

have beneficial effects of management of GEVH without severe complications when it is combined with conventional therapies. The present study, to our knowledge, is the first one to address this issue by using meta-analyses to compare the outcomes of combinational therapies versus conventional therapies in the management of GEVH. The results of our meta-analyses have demonstrated that PSE is efficacious in preventing variceal recurrence, variceal bleeding, and prolonging OS. Most complications were mild or moderate and nonfatal. The results indicate that PSE appears to be an effective and safe procedure in the management of GEVH when it is combined with conventional therapies.

The three studies on esophagus varices[8,9,11] were highly homogeneous, so were the two studies of gastric varices.[12,13] However, when the two groups were compared, HR was significantly lower in the group of gastric varices studies than those of esophagus varices. This heterogeneity could be explained by two reasons. First, esophagus and gastric varices are formed through different mechanisms; second, EVL was mainly used for patients with esophagus varices, whereas B-RTO was the main conventional therapy for gastric varices.

Serious complications used to be the main factor restricting the wide application of PSE. We have carefully extracted and analyzed the data from all the 6 studies. Although we were unable to use meta-analyses because of different definitions of serious complications among the studies, most complications after PSE were usually mild or moderate. In general, the incidence rate of serious complications in patients treated with combinational therapies was less than those treated with conventional therapies. Specifically, the study by Duan[10] showed that patients treated with PTVE plus PSE had either less incidence rates of ascites and portal hypertensive gastropathy or no significantly different incidence rates of hepatic encephalopathy and portal vein thrombosis compared with PTVE alone. By searching published literature, we found that the serious complications reported previously[5] were rare in the past decades. Multiple applications of PSE to induce a minimum of 50% infarction volume of the spleen, the development of interventional radiology, and the use of new embolic materials may have led to this dramatic reduction in the onset of serious complications.[25,26]

The relatively small size of samples may be the biggest limitation of the present study. Although the results of this meta-analysis indicate the beneficial effects of PSE in patients with GEVH, an international and multicentered study with a large number of subjects is needed. If the results presented here could be verified by future studies, the application of PSE, particularly when it is combined with conventional therapies, may be included in the clinical guidelines of GEVH treatment.

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Conflicts of interest

There are no conflicts of interest.

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