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and meta-analysis

## Abstract

**Objectives:** Left-sided portal hypertension (LSPH) leads to life-threatening gastrointestinal (GI) bleeding. There are no recommendations or consensus about the management of GI bleeding caused by LSPH. This systematic review and meta-analysis were conducted to evaluate the incidence of GI bleeding and the mortality of patients with LSPH receiving different therapeutic strategies.

Splenectomy versus non-splenectomy for

gastrointestinal bleeding from left-sided

portal hypertension: a systematic review

**Design:** A systematic review and meta-analysis were performed to determine the efficacy of different therapeutic strategies for GI bleeding caused by LSPH.

**Data sources and methods:** All relevant studies were searched from PubMed, Embase, Web of Science, Cochrane Library, Scopus, ScienceDirect, MEDLINE, Google Scholar, CNKI, and Wanfang Data without language restriction through 15 November 2023. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated through RevMan5.3 software. (The Cochrane Collaboration, Copenhagen, Denmark).

**Results:** Seventeen retrospective studies and one prospective study involving 624 patients were included. This systematic review and meta-analysis found that: (1) splenectomy was more effective than non-splenectomy therapeutic strategies in reducing the incidence of GI bleeding caused by LSPH (OR: 0.12; 95% CI: 0.06–0.27); (2) splenectomy was superior to partial splenic artery embolism (PSAE) (OR: 0.06; 95% CI: 0.01–0.62) or endoscopic interventions (OR: 0.04; 95% CI: 0.01–0.19) in the prevention of GI bleeding, respectively; (3) no significant difference in the mortality was observed between splenectomy and non-splenectomy therapeutic strategies (OR: 0.46; 95% CI: 0.20–1.08); and (4) patients receiving preoperative PSAE followed by splenectomy had less intraoperative bleeding and shorter operative time than those receiving splenectomy.

**Conclusion:** This meta-analysis demonstrated that splenectomy is superior to nonsplenectomy therapeutic strategies in reducing the incidence of GI bleeding from LSPH, which revealed that splenectomy should be recommended in the management of these patients. **Trial registration:** This study has been registered on the PROSPERO database with the registration number CRD42023483764.

*Keywords:* endoscopic interventions, gastrointestinal bleeding, left-sided portal hypertension, partial splenic artery embolization, splenectomy

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#### Introduction

Left-sided portal hypertension (LSPH), a rare extrahepatic portal hypertension, is also known as

localized, regional, or sinistral portal hypertension.<sup>1,2</sup> LSPH is characterized by increased pressure on the left portal system secondary to the Correspondence to: Yuhu Song Department of Gastroenterology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022. China

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compression or the obstruction of splenic vein. Normal liver function and main portal vein patency are observed in patients with LSPH.<sup>3</sup> LSPH is caused mainly by pancreatic diseases, including chronic pancreatitis, pancreatic pseudocysts, pancreatic carcinoma, etc.<sup>4,5</sup> Isolated gastric varices are a typical manifestation of LSPH, which results in severe or persistent gastrointestinal (GI) bleeding.<sup>5–7</sup>

The main therapeutic goal for GI bleeding from gastric varices is to manage the occurrence and recurrence of the bleeding. Generally, therapeutic strategies for cirrhosis-derived gastric varices contain endoscopic interventions, balloon-occluded retrograde transvenous obliteration, transjugular intrahepatic portosystemic shunt, etc.<sup>8,9</sup> However, gastric varices derived from liver cirrhosis or LSPH have different vascular anatomy, which results in the difference in the management of GI bleeding. Therapeutic strategies for bleeding from LSPH include endoscopic interventions, partial splenic arterial embolization (PSAE), and splenectomy.<sup>10-13</sup> Endoscopic interventions are widely used for gastroesophageal varices in patients with liver cirrhosis but have a high failure rate in the management of GI bleeding caused by LSPH.<sup>12</sup> PSAE is a major therapeutic strategy for hypersplenism. Some studies demonstrated that PSAE was an effective approach for GI bleeding caused by LSPH.<sup>12,14,15</sup> However, the efficacy of PSAE needs to be investigated. Splenectomy is used for GI bleeding caused by LSPH by removing the spleen. Limited data demonstrated splenectomy were effective in reducing GI bleeding caused by LSPH.<sup>16</sup> In summary, there is no consensus guideline for the management of GI bleeding from LSPH. Additionally, meta-analyses evaluating the efficacy of different therapeutic strategies for GI bleeding from LSPH have not been reported until now.6 Therefore, this systematic review and meta-analysis aimed to determine the incidence of GI bleeding and the mortality of patients with LSPH after the patients had received different therapeutic strategies.

## Methods

#### Search strategy

This systematic review and meta-analysis were registered in PROSPERO (registration number: CRD42023483764) and performed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement<sup>17</sup> (Supplemental Table S1). The two authors independently searched English databases (PubMed, Embase, Web of Science, Cochrane Library, Scopus, ScienceDirect, MEDLINE, and Google Scholar) and Chinese databases (CNKI, Wanfang Data) from inception to 15 November 2023. Search keywords included LSPH, sinistral portal hypertension, bleeding, splenectomy, partial splenic artery embolization, and endoscopic interventions. The detailed search strategy was shown in Supplemental Table S2.

#### Selection criteria

Studies were included if they met the following criteria: (i) patients with LSPH; (ii) patients receiving different therapeutic strategies for LSPH; (iii) reported incidence of GI bleeding in patients after treatment; (iv) reported mortality in patients after treatment; (v) the patients with a minimum follow-up period of 6 months; (vi) odds ratios (ORs) or other data for the calculation of ORs and 95% confidence intervals (CIs) were reported. Studies presented as case series, reports, reviews, or comments were excluded. For the studies with overlapping cohorts, recent studies with comprehensive data were enrolled.

#### Data abstraction

We collected the first author's name, the publication year, and the type of research and extracted the number, age, sex, and etiology of the patients with LSPH from the cohorts. The number of patients, the surgical procedures for splenectomy, the rate of GI bleeding, and the mortality of patients in different treatment groups were collected for this meta-analysis.

#### Quality assessment

The Newcastle-Ottawa Scale (NOS) was utilized to evaluate the quality of included articles by two researchers.<sup>18</sup> If there were a disagreement between the two researchers, all the researchers would reach an agreement after careful discussion. The literature with an NOS score of <5 was considered to be low quality.<sup>19</sup>

#### Statistical analysis

Heterogeneity was assessed using the Chi-squarebased Q-tests and  $I^2$  statistic. Studies with an  $I^2$ 



Figure 1. Flow diagram of the selection.

statistics of 0%, 25%, 50%, and 75% corresponded to no, low, moderate, and high heterogeneity. *p* Value >0.10 or  $I^2 < 50\%$  indicates low heterogeneity and a fixed-effect model would be performed.<sup>20</sup> Publication bias was analyzed and represented by funnel plots and Egger's test.<sup>21</sup> State MP15 (Stata Corporation, College Station, TX, USA) was used to run Egger's test, and RevMan5.3 software (The Cochrane Collaboration, Copenhagen, Denmark) was used to produce all calculations and graphics.

## Results

## Search results and quality of included studies

Figure 1 illustrates the selection process of literature. After a comprehensive search, 523 papers were chosen, and 478 papers were excluded because the titles and the abstracts were not associated with the efficacy of therapeutic strategies for GI bleeding from LSPH, or the studies were presented as case series, reports, reviews, or comments.

Twenty-seven articles were removed due to no available data for the calculation of ORs and 95% CIs. Finally, a total of 18 studies were included in our meta-analysis. The results of the quality assessment were shown in Supplemental Table S3 and the quality scores of all included studies were  $\geq 5$  in this meta-analysis. Therefore, all included studies were considered to be high quality.

## Characteristics of included studies

A summary of characteristics of the included studies were showed in Table 1. These studies were published between 1992 and 2022. Included studies contained 1 prospective study<sup>22</sup> and 17 retrospective studies.<sup>16,23–38</sup> Two studies were

# THERAPEUTIC ADVANCES in Gastroenterology

Interpretation     Interp	E	ary of ch	aracteristics	of included stud	dies.				
Jost poly and	Countr	>	Number of	Characteristics o	f enrolled	patients	Surgical procedures of splenectomy	Therapeutic strategies	Duration of follow-un
22 $0.4 \pm 0.16$ $0.76$ Construction functionConstruction functionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstructionConstruction				Age (years)	Gender (M/F)	Etiology of LSPH			(months)
ad344119-7412111Unoring hardred with televaluated with the surgeryl555ad4.742/42/4Chronic parcentits 13155555ad10.742/42/4Chronic parcentits 10155555ad10.742/42/4Chronic parcentits 10155555ad10.742/42/4Chronic parcentits 101. State estil55555ad10.742/14Chronic parcentits 101. State estil555555ad10.742/14Chronic parcentits 101. Abronic action and any advine action and any advine action and advine action and action advine action action and advine action action advine action advine action advine action action advine action advin	Spain		22	$59.6\pm10.6$	17/5	Chronic pancreatitis (7), acute pancreatitis (7), pancreatic carcinoma (4), pancreatic surgery (3), pancreatic arteriovenous malformations (1)	Splenectomy (alone), splenectomy combined with other surgery (pancreatic resection or pseudocyst drainage)	Endoscopic interventions, PSAE, medications	24
33   4.4.1   2/4   Choncepantis (3)   Spence value (3)   Spenc	Amer	ca	34	46 [19–74]	23/11	Chronic pancreatitis [34]	Splenectomy (alone), splenectomy combined with other surgery [pancreatic surgery]	T	20
ica31250.350.3-Chronic parcreatitis (10), sister cut actronome 61, adenocarcinome 64, adenocarcinome	China		33	44.74	29/4	Chronic pancreatitis [33]	Splenectomy (alone)	Splenic vein stent implantation, medications	6
1 $17\pm 8$ $14/7$ Acute parcreatitis (1), chronic carcinoma (1), hening parcreatic parcreatic parcreatic parcreatic parcreatic parcreatic parcreatic parcreatic parcreatic parcreatic 	Amer	lica	37	50.3	I	Chronic pancreatitis (10), islet cell carcinoma (6), adenocarcinoma (4), acute pancreatitis (1), chronic pancreatitis and acute pancreatitis (1), unknown (15)	1	1	54
a5744.743/16Pancreatic peudocyt133, pancreatic paces [91, aute pancreatits [14, gastric uder [14], paces [91, aute pancreatits [14, gastric uder [14], paces [14], gastric uder [14], paces [14], gastric uder [14], paces [14], pancreatits [14], gastric uder [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], pancreatits [14], panc	Chin	ō	21	47±8	14/7	Acute pancreatitis (1), chronic pancreatitis (7), primary pancreatic carcinoma (11), benign pancreatic carcinoma (1), metastatic pancreatic carcinoma (1)	Splenectomy combined with other surgery (pancreatic duct-jejunum Roux-en-Y anastomosis, external drainage of the pancreatic cyst, or distal pancreatectomy)	PSAE, endoscopic interventions	72
a   45   M: 45,94 ± 6,92   31/14   Pancreatic pseudocyst [15] acute   Selenectomy [alone], splenectomy   Endoscopic   54     a   14   F: 43,64 ± 6,92   31/14   Pancreatic acritomen [1], Hodgkin (pericardial vascular vascular (pericardial vascular (pericard) pericardial vascular (pericardial vascular (	Chin	ŋ	59	44.7	43/16	Pancreatic pseudocyst (33), pancreatic abscess (9), acute pancreatitis (2), chronic pancreatitis (14), gastric ulcer (1)	Splenectomy (alone), preoperative PSAE followed by splenectomy	Preoperative PSAE followed by splenectomy	20
14   28.5 (3-65)   9/5   Chronic pancreatits (6), pancreatic carcinoma (3), gastric ulcer (1), pancreatic aneurysm (1), splenic tymph node tuberculosis (1), unknown (2)   Splenectomyl surgery (1), splenic tymph (subtotal gastrectomyl)   Igation of the splenic artery   18     1a   60   44.8   44/16   -   Splenctomy (alone), properative PSAE followed by splenectomy splenectomy   Properative splenectomy   Properative splenectomy   -     1a   47   41.4 (21-77)   41/6   -   Splenectomic and by splenectomy   Properative splenectomy   -     1a   47   41.4 (21-77)   41/6   -   Splenectomy (anone), properative proceedites (7), acute pancreatits (3), surgery (cardiac vascular dissection)   PSAE followed by splenectomy   -	Chir	e	45	M: 45.94 $\pm$ 9.42, F: 49.64 $\pm$ 6.92	31/14	Pancreatic pseudocyst (15), acute pancreatitis (1), chronic pancreatitis (22), pancreatic carcinoma (1), Hodgkin tymphoma (2), translocation of spleen (1), splenic aneurysm (1), arteriovenous malformations (1), abdominal trauma (1)	Splenectomy (alone), splenectomy combined with other surgery (pericardial vascular dissection)	Endoscopic interventions	54
Ia 60 44.8 44/16 - Splenectomy falone), prooperative PSAE followed by splenectomy Preoperative PSAE followed by splenectomy -   Ia 47 41.4 [21-77] 41/6 Pancreatic carcinoma [2], chronic pancreatitis [3], surgery lcardiac vascular dissection] PSAE followed by splenectomy -	Chir	ġ	14	28.5 (3–65)	9/5	Chronic pancreatitis (6), pancreatic carcinoma (3), gastric ulcer (1), pancreatic aneurysm (1), splenic lymph node tuberculosis (1), unknown (2)	Splenectomy (alone), splenectomy combined with other surgery (subtotal gastrectomy)	Ligation of the splenic artery	18
ia 47 41.4 (21–77) 41/6 Pancreatic carcinoma (2), chronic Splenectomy combined with other PSAE, conservative – pancreatitis (7), acute pancreatitis (33), surgery (cardiac vascular dissection) treatment autoimmune pancreatitis (5)	Chir	e	60	44.8	44/16	I	Splenectomy (alone), preoperative PSAE followed by splenectomy	Preoperative PSAE followed by splenectomy	I
	Chin	ŋ	47	41.4 (21–77)	41/6	Pancreatic carcinoma (2), chronic pancreatitis (7), acute pancreatitis (33), autoimmune pancreatitis (5)	Splenectomy combined with other surgery (cardiac vascular dissection)	PSAE, conservative treatment	1

First author,	Country	Number of	Characteristics	of enrolled	patients	Surgical procedures of splenectomy	Therapeutic	Duration of
Jear		handling	Age (years)	Gender (M/F)	Etiology of LSPH		סוומנכאוכס	(months)
Bei Sun, 2006 <sup>31</sup>	China	67	43.2 (15–79)	43/24	Pancreatic pseudocyst [19], pancreatic abscess [5], chronic pancreatitis [23], pancreatic carcinoma [14], pancreatic trauma [2], unknown [4]	Splenectomy (alone), splenectomy combined with other surgery (pericardial vascular dissection, Roux-en-Y anastomosis of cyst and jeJunum, or pancreatectomy)	PSAE, endoscopic interventions	33.1
Yu Tang, 2008 <sup>32</sup>	China	67	48 [16–78]	47/20	Pancreatic pseudocyst (10), pancreatic carcinoma (23), unknown (34)	Splenectomy (alone), splenectomy combined with other surgery (portal disconnection, pancreatectomy, or pseudocyst drainage)	Medications	1
Guangping Tu, 2019 <sup>33</sup>	China	32	49 ± 21	27/5	Pancreatic pseudocyst (1), acute pancreatitis (8), chronic pancreatitis (23)	splenectomy (alone), preoperative PSAE followed by splenectomy	Preoperative PSAE followed by splenectomy	25
Kai Wang, 2008 <sup>34</sup>	China	21	50.5 (34–72)	14/7	Pancreatic pseudocyst (4), pancreatic carcinoma (6), chronic pancreatitis (11)	Splenectomy (alone), splenectomy combined with other surgery (pericardial vascular dissection or internal drainage)	Ligation of the splenic artery	60
Qingsong Xie, 2020 <sup>35</sup>	China	24	47.6 (27-70)	14/10	Pancreatic pseudocyst (3), pancreatic carcinoma (4), acute or chronic pancreatitis (151, pancreatic duct stones (1), pancreatic injury (1)	Splenectomy (alone), splenectomy combined with other surgery (tail pancreatectomy, intestinal drainage, fenestration and drainage of pancreatic pseudocysts, residual cholecystectomy and choledocholithotomy and T-tube drainage, portal azygos vein disconnection or pancreatectomy]	PSAE, conservative treatment	128
Xiangyu Zhong, 2015³ <sup>6</sup>	China	23	46 (24-73)	14/9	Pancreatic pseudocyst (6), pancreatic carcinoma (5), chronic pancreatitis (10), acute pancreatitis (1), pancreatic injury (1)	Splenectomy (alone), splenectomy combined with other surgery (disconnection of gastric fundus blood vessels, disconnection of gastric fundus and cardiac blood vessels, cyst jējunal drainage, pancreaticoduodenectomy or	PSAE, conservative treatment	33.1
Yang Song, 2005 <sup>37</sup>	China	6	$41 \pm 10$	6/3	Pancreatic carcinoma (3), acute pancreatitis (1), chronic pancreatitis (5)	Splenectomy combined with other surgery (pancreatectomy)	Endoscopic interventions	48
Shugo Mizuno, 2019 <sup>38</sup>	Japan	6	61.3	5/4	Pancreatic carcinoma (9)	Splenectomy (alone)	PSAE, medications, endoscopic interventions	89
*Except for on PSAE, partial	le prospecti splenic art€	ive study, all th ery embolizatic	ne remaining artic on.	cles were re	strospective observational studies.			

performed in the United States,<sup>39,26</sup> one study was from Spain,<sup>23</sup> one study was from Japan,<sup>38</sup> and the rest of the studies were from China. A total of 624 patients were included in this metaanalysis. 71.72% of patients were male because LSPH is more common in men than in women, with a male-to-female ratio of nearly 2:1.27,40,41 The etiologies of enrolled patients with LSPH included acute pancreatitis, chronic pancreatitis, pancreatic pseudocvst, pancreatic carcinoma, etc.4,42 The patients with chronic pancreatitis were recruited in two studies,<sup>25,39</sup> while the other studies included patients with different pancreatic diseases. The follow-up times were variable among different studies, which ranged from 6 to 128 months. There are two types of splenectomy: splenectomy and splenectomy combined with pancreatic surgery. Major non-splenectomy therapeutic strategies include endoscopic interventions and PSAE. Endoscopic interventions include endoscopic sclerotherapy using N-butyl-2-cyanoacrylate and endoscopic variceal ligation. In addition, four studies determined the efficacy of preoperative PSAE followed by splenectomy and splenectomy.<sup>22,23,27,33</sup>

## Incidence of GI bleeding after treatment

*Meta-analysis.* A total of 12 studies provided evaluable data, involving 218 patients in the splenectomy group and 170 patients in the non-splenectomy group. Forest plots showed that splenectomy was more effective than non-splenectomy therapeutic strategies in reducing the incidence of GI bleeding caused by LSPH (OR: 0.12; 95% CI: 0.06-0.27; p=0.23;  $I^2=23\%$ , Figure 2). The difference was statistically significant and the heterogeneity among the 12 studies was low.

Subgroup analysis. Subgroup analyses were performed to determine the efficacy of splenectomy and non-splenectomy strategies containing endoscopic interventions and PSAE (Figure 2). Firstly, the patients undergoing splenectomy had a lower risk of GI bleeding than those undergoing endoscopic interventions (OR: 0.04; 95%CI: 0.01– 0.19; p=0.77;  $I^2=0\%$ ). Secondly, splenectomy was superior to PSAE in the prevention of GI bleeding (OR: 0.06; 95% CI: 0.01–0.62; p=0.63;  $I^2=0\%$ ). Additionally, pancreatic surgery leads to LSPH, and the mechanism underlying LSPH from pancreatic surgery is different from that of LSPH caused by pancreatitis.<sup>43,44</sup> Thus, the patients who underwent pancreatic surgery were excluded when a subgroup analysis was performed. The patients in the splenectomy group had a lower rate of GI bleeding than those in the non-splenectomy group (OR: 0.12; 95% CI: 0.04–0.39; p=0.52;  $I^2=0\%$ , Figure 2).

## All-cause mortality after treatment

*Meta-analysis.* There were 106 patients in the splenectomy group and 103 patients in the non-splenectomy group from eight studies. However, the result revealed no statistical difference in all-cause mortality between the splenectomy group and the non-splenectomy group (OR: 0.46; 95% CI: 0.20–1.08; p=0.63;  $I^2=0\%$ , Figure 3).

Subgroup analysis. Subgroup analyses were performed according to the etiology, operative approach, or therapeutic strategy. Firstly, patients with pancreatic carcinoma were excluded due to poor prognosis; then, the mortality was determined in patients who received splenectomy or non-splenectomy. There was no significant difference in mortality between the splenectomy group and the non-splenectomy group (OR: 0.08; 95% CI: 0.01–1.08; p = 0.49;  $I^2 = 0\%$ , Figure 3). Secondly, there was no statistically significant difference in all-cause mortality between the splenectomy group and the non-splenectomy group after removing patients who had received pancreatic surgery (OR: 0.76; 95% CI: 0.27-2.15; p=0.55;  $I^2=0\%$ , Figure 3). Finally, all-cause mortality of patients receiving the splenectomy was lower than that of those receiving PSAE (OR: 0.20; 95% CI: 0.04–0.97; p = 0.41;  $I^2 = 0\%$ , Figure 3).

## The efficacy and the safety of preoperative PSAE followed by splenectomy

Incidence of GI bleeding after treatment. A total of four studies provided evaluable data, with 89 patients who received splenectomy (splenectomy group) and 46 patients who received preoperative PSAE followed by splenectomy (preoperative PSAE group). The findings demonstrated no statistical difference in the incidence of bleeding between the splenectomy group and the preoperative PSAE group (OR: 3.01; 95% CI: 0.51– 17.54; p=0.56;  $I^2=0\%$ , Figure 4).

Intraoperative and postoperative outcomes. The intraoperative and postoperative outcomes of

## GI bleeding rate

(a)	Study or Subarrow	Splene	ctomy	Non-sple	nectomy	1 10/0	:	Odds Ratio		Odds I	Ratio		
	Alevendre Formendes 2015	Evenus		Events	1018	7	ignt i	Net estimable			u, 95% Ci		
	Alexandra Fernandes 2015	0	3	0	1/		20/						
	George Sekerates 1000	1	22	1	1	2 Z 1 A	00/	0.12 [0.00, 3.03]	←				
	Guijin Chon 2013	1	23	12	20	1 4 2 21	10%	0.13[0.01, 3.97]	<b>←</b>				
	linging Liu 2022	0	12	3	24	1 6	.1%	0.03 [0.00, 0.20]					
	John Loffus 1992	1	25	2	2	5 5	5%	0.21 [0.01, 4.40]					
	Kai Wang 2008	4	10	2	14	2 0	.5 /6	0.95 [0.15, 0.10]					
	Liting Liao 2019	0	10	8	15	2 1	1%	1 30 10 05 37 261					
		0	14	2	40	י כ ה ה	.4 /0	0 12 [0 01 2 74]	←				
	Xiangyu Zhong 2015	0	18	1	, i c	5 5	1%	0.12 [0.01, 2.74]	←				
	Vang Song 2005	0	6	2		5 3 7	2%	0.05 [0.00, 2.54]	← .		_		
	Yu Tang 2008	0	10	19	22	2 29	.2%	0.01 [0.00, 0.18]	←				
	Total (95% CI)		218		171	100	.0%	0.12 [0.06. 0.27]		◆			
	Total events	6		51				• • •					
	Heterogeneity: $Chi^2 = 11.69$	df = 9 (P =	= 0.23): l <sup>2</sup>	= 23%					H				
	Test for overall effect: Z = 5.2	22 (P < 0.0	00001)						0.01	0.1 1 Splenectomy	10 Non-splenect	1 omy	00
(b)		Splen	ectomy	Endosco	opic thera	nv		Odds Ratio		Odd	s Ratio		
` /	Study or Subaroup	Event	s Tota	Even	ts T	otal	Weiaht	M-H. Fixed, 95%	CI	M-H, Fiz	xed. 95% CI		
	Alexandra Fernandes 2015	5 (	) 3		0	5		Not estimat	le				
	Bei Sun 2006		1 65		0	2	5.5%	0.12 [0.00, 3.6	31 -		+		
	Guiiin Chen 2013		1 23		13	21	77.0%	0.03 [0.00, 0.2	51 —				
	Yang Song 2005	(	0 6		2	3	17.5%	0.05 [0.00, 1.5	6]		+		
	Total (95% CI)		97			31	100.0%	0.04 [0.01, 0.1	9]				
	Total events	2	2	1	15								
	Heterogeneity: $Chi^2 = 0.52$ , Test for overall effect: Z = 3	af = 2 (P = 3.98 (P < 0	= 0.77); I² .0001)	= 0%					0.001	0.1 Splenectomy	1 10 Endoscopio	c therap	1000 у
(a)		Spl	enectom	iv P	SAE			Odds Ratio		Odds	s Ratio		
$(\mathbf{U})$	Study or Subgroup	Eve	ents T	otal Ever	nts Total	Wei	aht M	M-H, Fixed, 95% C	1	M-H, Fix	ed, 95% Cl		
	Alexandra Fernandes 20	15	0	3	0 5		-	Not estimable					
	Bei Sun 2006		1	65	0 2	27	9%	0.12 [0.00, 3.63]			<u>+</u>		
	Liting Liao 2019		0	1	0 1			Not estimable					
	Qingsong Xie 2020		Ő	14	1 2	72	1%	0.03 [0.00, 1.28]	←		+		
	Xiangyu Zhong 2015		0	18	0 1			Not estimable					
	Total (95% CI)			101	11	100.	.0%	0.06 [0.01, 0.62]					
	Total events		1		1								
	Heterogeneity: Chi <sup>2</sup> = 0.2	24, df = 1 (	P = 0.63	); l² = 0%					H				
	Test for overall effect: Z	= 2.36 (P	= 0.02)						0.001	0.1 Splenectomy	PSAE		1000
(d)		Splenecto	omy M	lon-spler	nectomy			Odds Ratio		Odd	s Ratio		
(u)	Study or Subgroup	Events	Total	Events	Tota	l Wei	ight l	<u>M-H, Fixed, 95% C</u>		M-H, Fix	<u>ed, 95% Cl</u>		
	Bei Sun 2006	1	46	0	2	2 4	.3%	0.16 [0.01, 5.16]		•			
	Guijin Chen 2013	1	23	13	21	61	.6%	0.03 [0.00, 0.25]					
	Jingjing Liu 2022	0	12	3	21	11	.9%	0.21 [0.01, 4.46]					
	Kai Wang 2008	0	18	0	3	3		Not estimable					
	Liting Liao 2019	0	1	8	43	3 2	.6%	1.39 [0.05, 37.26]			•		2
	Qingsong Xie 2020	0	7	2	10	) 9	.4%	0.23 [0.01, 5.51]		•	<u> </u>		
	Xiangyu Zhong 2015	0	16	1	5	5 10	.2%	0.09 [0.00, 2.63]	•	•	<u> </u>		
	Total (95% CI)		123		105	5 100	.0%	0.12 [0.04, 0.39]	-				
	Total events	2		27									
	Heterogeneity: Chi <sup>2</sup> = 4.1	9, df = 5 (	P = 0.52	); I² = 0%							1 4	l	
	Test for overall effect: Z =	= 3.51 (P =	= 0.0005)	)					0.01	Splenectomy	Non-splene	ectomy	100

**Figure 2.** GI bleeding rate in patients with LSPH. (a) GI bleeding rate in patients receiving splenectomy or nonsplenectomy; (b) GI bleeding rate in patients receiving splenectomy or endoscopic interventions; (c) GI bleeding rate in patients receiving splenectomy or PSAE; (d) GI bleeding rate in patients receiving splenectomy or nonsplenectomy after excluding patients who underwent pancreatic surgery.

Events, the number of bleeding patients; GI, gastrointestinal; LSPH, left-sided portal hypertension; PSAE, partial splenic artery embolization; total, the number of patients enrolled in this group.

three studies were summarized in Table 2. $^{22,27,33}$ Less intraoperative bleeding was observed in the patients receiving preoperative PSAE followed by splenectomy compared with those receiving splenectomy only. Tu *et al.* demonstrated the difference in operative time between the two groups was not significant,<sup>33</sup> but other studies showed shorter operative time in the preoperative PSAE group compared with the splenectomy group. Postoperative pancreatic fistula (POPF)

#### Mortality

(2

(a)		Splenec	tomy	Non-splen	ectomy	/		Odds Ratio		Odd	ls Ratio	
("	Study or Subgroup	Events	Total	Events	To	tal We	ight	M-H, Fixed, 95% CI		M-H, Fi	xed, 95% Cl	
	George Sakorafas 1999	0	23	1		11 12	2.3%	0.15 [0.01, 3.97]	_	•		
	John Loftus 1992	10	25	5		12 25	5.5%	0.93 [0.23, 3.78]			•	
	Liting Liao 2019	0	1	2		46 1	1.0%	5.93 [0.19, 185.94]			· · · ·	
	Liushun Feng 1995	3	13	0		1 4	1.1%	1.00 [0.03, 30.62]			+	
	Qingsong Xie 2020	1	14	3		10 20	).5%	0.18 [0.02, 2.06]			+-	
	Quanda Liu 2014	0	10	2		11 14	1.4%	0.18 [0.01, 4.27]	-	•	+	
	Shugo Mizuno 2019	0	2	4		7 12	2.9%	0.16 [0.01, 4.40]	_		+	
	Xiangyu Zhong 2015	1	18	1		5 9	9.3%	0.24 [0.01, 4.62]		•		
	Total (95% CI)		106		10	03 100	0.0%	0.46 [0.20, 1.08]		-		
	Total events	15		18								
	Heterogeneity: Chi <sup>2</sup> = 5.2	5, df = 7 (P	= 0.63);	l² = 0%					0.001	01	1 10	1000
	Test for overall effect: Z =	= 1.79 (P = 0	0.07)						0.001	Splenectomy	/ Non-splene	ctomy
(1-)		Splenect	omv	PSAF				Odds Ratio		Odds	Ratio	
(D)	Study or Subgroup	Events	Total	Events T	otal V	Voiaht	м.	H Fixed 95% Cl		M-H Fixe	d 95% CI	
	Liting Line 2010		10101		1	reight	101-	Not optimoble		M-11, 11A		
	Liting Liao 2019	0	1	0	1	40.404		Not estimable				
	Liushun Feng 1995	3	13	0	1	10.4%	1	.00 [0.03, 30.62]				
	Quanda Liu 2014	0	10	1	6	27.8%		0.17 [0.01, 5.04]		-		
	Shugo Mizuno 2019	0	2	1	2	19.8%		0.20 [0.00, 8.82]	_	-		
	Xiangyu Zhong 2015	0	18	1	1	42.0%		0.01 [0.00, 0.64]				
	Total (95% CI)		44		11 1	00.0%	(	0.20 [0.04, 0.97]				
	Total events	3		3								
	Heterogeneity: Chi <sup>2</sup> = 2.	.89, df = 3	(P = 0.4	1); l <sup>2</sup> = 0%				E E	204			4000
	Test for overall effect: Z	= 2.00 (P	= 0.05)					0.0	JU1	Splenectomy	PSAE	1000
$\langle \rangle$												
(C)	Chudu on Cubanous	Spieneo	tomy	Non-spier	iectom	y		Odds Ratio				
` ´	Study of Subgroup	Events		Events	10			M-H, Fixed, 95% C	-	IVI-FI, F	IXed, 95% CI	
	George Sakoratas 1999	0	23	1		11 4	6.5%	0.15 [0.01, 3.97]		-		
	Liushun Feng 1995	0	10	0		1	0 50/	Not estimable				
	Quanda Liu 2014	0	1	1		1 5	3.5%	0.02 [0.00, 1.63]	•	-		
	Xiangyu Zhong 2015	0	15	0		3		Not estimable				
	Total (95% CI)		55			16 10	0.0%	0.08 [0.01, 1.08]	-		-	
	I otal events			2					<b></b>			
	Test for overall effect: Z =	18, df = 1 (P = 1.90 (P =	0.06) = 0.49	; 1² = 0%					0.001	0.1 Splenectom	1 10 y Non-splene	1000 ectomy
(d)		Splenect	omy	Non-splen	ectomy	y		Odds Ratio		Oc	lds Ratio	
(u)	Study or Subgroup	Events	Total	Events	To	tal We	eight	M-H, Fixed, 95% C	:	M-H, F	-ixed, 95% Cl	
	John Loftus 1992	10	25	5		12 5	0.0%	0.93 [0.23, 3.78]				
	Liting Liao 2019	0	1	2		46	1.9%	5.93 [0.19, 185.94]				
	Liushun Feng 1995	3	13	0		1	8.1%	1.00 [0.03, 30.62]			+	
	Qingsong Xie 2020	0	7	0		10		Not estimable				
	Quanda Liu 2014	0	3	2		11 1	3.5%	0.54 [0.02, 14,35]			• +	
	Xiangyu Zhong 2015	0 0	16	1		5 2	6.5%	0.09 [0.00, 2.63]	•	-	+	
	Total (95% CI)		65		:	85 10	0.0%	0.76 [0.27, 2.15]				
	Total events	13		10								
	Heterogeneity: Chi <sup>2</sup> = 3	8.05, df = 4	(P = 0.5	$(55);  ^2 = 0\%$					H		<u> </u>	+
	Test for overall effect: 2	Z = 0.52 (P	= 0.60)						0.01	0.1 Splenecton	1 ny Non-splen	10 100 lectomy

**Figure 3.** All-cause mortality in patients with LSPH. (a) All-cause mortality in patients receiving splenectomy or non-splenectomy; (b) all-cause mortality in patients receiving splenectomy or PSAE; (c) all-cause mortality in patients receiving splenectomy or non-splenectomy after excluding patients with pancreatic carcinoma; (d) all-cause mortality in patients receiving splenectomy or non-splenectomy or non-splenectomy after excluding patients who underwent pancreatic surgery.

Events, the number of dead patients; GI bleeding, gastrointestinal bleeding; LSPH, left-sided portal hypertension; PSAE, partial splenic artery embolization; total, the number of patients enrolled in this group.

was the most common complication of splenectomy, and no statistical difference in the occurrence of POPF was observed between the preoperative PSAE group and the splenectomy group. In Table 3, we provided a summary of the results of meta-analysis.



**Figure 4.** GI bleeding rate in patients receiving splenectomy or preoperative PSAE followed by splenectomy. GI bleeding, gastrointestinal bleeding; PSAE, partial splenic artery embolization.

**Table 2.** Intraoperative and postoperative outcomes of patients who received splenectomy or preoperative PSAE followed by splenectomy.

First	Splenector	ıy		Preoperativ	e PSAE followed	p Value				
autnor, year	Number of patients	Intraoperative blood loss (ml)	Operation time (min)	POPF	Number of patients	Intraoperative blood loss (ml)	Operation time (min)	POPF	Intraoperative blood loss	Operation time
Zhihe Wang, 2021 <sup>27</sup>	41	637.0 (416.5–1109.9)	174.0 (145–212)	7	18	420.3 (278.1–620.1)	141.5 (120–166.25)	6	0.041	0.012
Angzhi Li, 2021 <sup>22</sup>	42	858.3	174.9	1	18	559.2	146.8	1	0.035	0.027
Guangping Tu, 2019 <sup>33</sup>	3	728.0	214.3	-	8	541.6	201.2	-	-	-

POPF, Postoperative pancreatic fistula; PSAE, partial splenic artery embolization.

#### Table 3. Summary of meta-analysis results.

Group	No. studies	Pooled OR (95% CI)
Incidence of GI bleeding after treatment		
Splenectomy versus non-splenectomy	12	0.12 (0.06-0.27)
Subgroup		
Splenectomy versus endoscopic interventions	4	0.04 (0.01–0.19)
Splenectomy versus PSAE	5	0.06 (0.01-0.62)
Splenectomy versus non-splenectomy (pancreatic surgery excluded)	7	0.12 (0.04–0.39)
All-cause mortality after treatment		
Splenectomy versus non-splenectomy	8	0.46 (0.20–1.08)
Subgroup		
Splenectomy <i>versus</i> PSAE	5	0.20 (0.04–0.97)
Splenectomy versus non-splenectomy (pancreatic carcinoma excluded)	4	0.08 (0.01–1.08)
Splenectomy versus non-splenectomy (pancreatic surgery excluded)	6	0.76 (0.27–2.15)
Splenectomy versus preoperative PSAE followed by splenectomy		
Incidence of GI bleeding after treatment	4	3.01 (0.51–17.54)
GI bleeding, gastrointestinal bleeding; PSAE, partial splenic artery embolization.		

Sensitivity analysis and publication bias. According to the results of Chi-square-based Q-tests and  $I^2$  statistics, all meta-analyses showed low heterogeneity and the fixed-effect model was performed to pool ORs and 95% CIs. For the risk of potential heterogeneity, we performed subgroup analyses to eliminate this risk. p Value >0.10 and  $I^2 < 50\%$  were observed in all subgroup analyses, which revealed low heterogeneity. Funnel plots for meta-analysis were roughly symmetrical, showing that there was no obvious publication bias among the studies (Supplemental Figures S1-S3). p > 0.05 of Egger's test in all metaanalyses and no publication bias was observed (Supplemental Table S4).

## Discussion

Our systematic review and meta-analysis evaluated the efficacy of different therapeutic strategies for GI bleeding caused by LSPH. Our meta-analysis demonstrated that splenectomy reduced the incidence of GI bleeding more effectively than other therapeutic strategies containing PSAE and endoscopic interventions. These indicated that splenectomy should be recommended in the management of GI bleeding caused by LSPH. Additionally, the mortality in the splenectomy group was lower than that in the PSAE group. LSPH is caused by the obstruction or embolization of the splenic vein. Then, the blood in the splenic vein reverses into the fundal venous plexus through the short gastric veins, producing isolated fundal varices.<sup>3</sup> Gastric varices is a lifethreatening cause of bleeding in the upper GI tract. The management of bleeding gastric varices presents a challenge for patients with LSPH.45 In theory, the blockage of afferent veins is an effective strategy for gastric varices. Splenectomy removes the entire spleen and cuts off the blood supply from the spleen artery, which reduces blood flow in the splenic vein and the short gastric veins effectively. Endoscopic interventions is recommended in the management of bleeding gastric varices.<sup>46</sup> Although endoscopic interventions are effective in controlling bleeding gastric varices from LSPH, our meta-analysis revealed the incidence of bleeding in patients receiving endoscopic interventions was higher than that in those who received splenectomy. PSAE occludes the artery supply of the spleen peripherally, which results in ischemic necrosis of splenic tissue followed by a decrease in spleen size.<sup>11,14</sup> Thus, splenectomy and PSAE prevent bleeding by reducing the blood flow of the afferent vein (the short gastric veins). Because splenectomy reduces blood flow of the short gastric veins more efficiently than PSAE, our meta-analysis showed splenectomy was superior to PSAE in GI bleeding control and mortality improvement.

There was no significant difference in all-cause mortality between the splenectomy group and the non-splenectomy group. Since the patients with pancreatic carcinoma had a poor prognosis, the mortality of enrolled patients was determined after excluding the patients with pancreatic carcinoma. Similarly, statistical results showed no significance in mortality between the splenectomy group and the non-splenectomy group. However, the forest plot showed lower mortality in the splenectomy group compared with the non-splenectomy group. No statistical significance between the two groups was probably attributed to sample size and the quality of the study.

The resection and reconstruction of the portal vein and/or superior mesenteric vein has become a standard procedure when patients with pancreatic head carcinoma and venous invasion receive pancreatoduodenectomy.<sup>47,48</sup> The splenic vein has been ligated traditionally during mesenteric-portal venous reconstruction because it simplifies surgical operation and facilitates the removal of tissue.<sup>49</sup> However, this leads to LSPH.<sup>38</sup> Thus, the patients who underwent pancreatic surgery were excluded in our meta-analysis. Splenectomy was effective in preventing GI bleeding in the remaining patients.

PSAE followed by splenectomy was an alternative strategy for GI bleeding caused by LSPH.<sup>50–52</sup> Our meta-analysis found no significant difference in reducing the GI bleeding rate between the splenectomy group and the preoperative PSAE group. Additionally, the preoperative PSAE group exhibited less blood loss and shorter operation time; thus, PSAE followed by splenectomy could be performed in high-risk patients for splenectomy.<sup>53</sup>

The complications of splenectomy, including hemorrhage, infection, pancreatic injury, portal, and splenic vein thrombosis, are less common in patients with LSPH compared with patients with liver cirrhosis. Meanwhile, some new therapeutic strategies, such as splenic vein stenting and endoscopic ultrasound-guided coil and glue injection for obliteration of splenic artery, have emerged. More studies should be performed to assess their efficacy and safety in future.<sup>54,55</sup>

## Study limitations

There were several limitations existed in our meta-analysis. Firstly, it is difficult to evaluate the efficacy and the safety of therapeutic interventions through randomized controlled trials due to the low incidence of LSPH. Thus, there were 18 studies included in our meta-analysis and only one of them was a prospective study. Secondly, Chinese-language studies were included in this meta-analysis, which revealed further studies should be performed in future. Thirdly, only 624 patients were involved in this meta-study. Fourthly, the follow-up times were variable among different studies, which ranged from 6 to 128 months.

## Conclusion

In conclusion, splenectomy is effective in reducing the incidence of GI bleeding caused by LSPH, which revealed that splenectomy should be recommended in the management of these patients.

## Declarations

*Ethics approval and consent to participate* Not applicable.

*Consent for publication* Not applicable.

## Author contributions

**Minghui Liu:** Data curation; Formal analysis; Resources; Software; Writing – original draft.

**Ning Wei:** Methodology; Supervision; Validation; Writing – review & editing.

**Yuhu Song:** Conceptualization; Funding acquisition; Writing – review & editing.

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## Competing interests

The authors declare that there is no conflict of interest.

## Availability of data and materials

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

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## Supplemental material

Supplemental material for this article is available online.

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