

# Selective Hepatic Vascular Exclusion versus Pringle Maneuver in Major Hepatectomy: A Systematic Review and Meta-Analysis

Shahd Mobarak<sup>1</sup>, Martyn C. Stott<sup>1</sup>, Munir Tarazi<sup>2</sup>\*, Rebecca J. Varley<sup>1</sup>, Madhav S. Davé<sup>1</sup>, Minas Baltatzis<sup>3</sup> and Thomas Satyadas<sup>1</sup>

<sup>1</sup>Department of Hepato-Pancreato-Biliary Surgery, Manchester Royal Infirmary, Manchester, UK, <sup>2</sup>Department of Surgery and Cancer, Imperial College London, London, UK, <sup>3</sup>Department of Upper GI Surgery, Salford Royal Hospital, Salford, UK

**Objectives:** Mortality and morbidity following hepatic resection is significantly affected by major intra-operative blood loss. This systematic review and meta-analysis evaluates whether selective hepatic vascular exclusion (SHVE) compared to a Pringle maneuver in hepatic resection reduces rates of morbidity and mortality.

#### **OPEN ACCESS**

Edited by: Francesco Pata, Nicola Giannettasio Hospital, Italy

#### Reviewed by:

Nicolas Jarufe, Las Condes Clinic, Chile, Luis Rafael Moscote-Salazar, Latinamerican Council of Neurocritical Care (CLaNi), Colombia, Marcello Di Martino, Princess University Hospital, Spain

> \***Correspondence:** Munir Tarazi m.tarazi@imperial.ac.uk

#### Speciality section:

This article was submitted to Visceral Surgery, a section of the journal Frontiers in Surgery

> Received: 23 January 2022 Accepted: 24 March 2022 Published: 06 April 2022

#### Citation:

Mobarak S, Stott MC, Tarazi M, Varley RJ, Davé MS, Baltatzis M and Satyadas T (2022) Selective Hepatic Vascular Exclusion versus Pringle Maneuver in Major Hepatectomy: A Systematic Review and Meta-Analysis. Front. Surg. 9:860721. doi: 10.3389/fsurg.2022.860721 **Methods:** A systematic review and meta-analysis were conducted according to the PRISMA guidelines by screening EMBASE, MEDLINE/PubMed, CENTRAL and SCOPUS for comparative studies meeting the inclusion criteria. Pooled odds ratios or mean differences were calculated for outcomes using either fixed- or random-effects models.

**Results:** Six studies were identified: three randomised controlled trials and three observational studies reporting a total of 2,238 patients. Data synthesis showed significantly decreased rates of mortality, overall complications, blood loss, transfusion requirements, air embolism, liver failure and multi-organ failure in the SHVE group. Rates of hepatic vein rupture, post-operative hemorrhage, operative and warm ischemia time, length of stay in hospital and intensive care unit were not statistically significant between the two groups.

**Conclusion:** Performing SHVE in major hepatectomy may result in reduced rates of morbidity and mortality when compared to a Pringle maneuver. The results of this metaanalysis are based on studies where tumors were adjacent to major vessels. Further RCTs are required to validate these results.

**Clinical Trial Registration:** PROSPERO (CRD42020212372) https://www.crd.york.ac.uk/ prospero/display\_record.php?RecordID=212372.

Keywords: pringle, selective hepatic vascular exclusion (SHVE), hepatectomy, liver resection, Systematic (Literature) Review

# INTRODUCTION

Over the past two decades, improvements in safety have allowed hepatic resection to play a significant role in the management of benign and malignant hepatobiliary disease (1-4). Due to the liver's specialized blood supply, major intra-operative hemorrhage can significantly affect morbidity and mortality (5, 6). Most hepatic resections require vascular occlusion, especially where tumors are sizeable or lie close to major vessels.

1

The Pringle maneuver, first described in 1908 as a technique to minimize blood loss during hepatic surgery, is the most common technique of vascular occlusion in surgical practice (7-9). It involves clamping of the hepatoduodenal ligament and occluding the portal triad, which minimizes the blood inflow into the liver via the portal vein and hepatic artery. Blood outflow from the liver is not affected, therefore Pringle maneuver cannot prevent backflow bleeding from the hepatic veins. Furthermore, if the tumor lies close to the inferior vena cava or at the confluence of one or more of the major hepatic veins, major hemorrhage as well as air embolism can occur, as a result of injury of these vessels. Total hepatic vascular exclusion (THVE) was developed in an attempt to reduce these complications, occluding both hepatic inflow and outflow by performing a Pringle maneuver and clamping the inferior vena cava (IVC) above and below the liver (10-12). However, this causes significant hemodynamic disturbance due to the interruption of venous blood flow in the IVC (13, 14).

Selective hepatic vascular exclusion (SHVE) is a newer technique which involves clamping the hepatic veins without clamping the IVC (15, 16). This can control hepatic inflow and outflow, preserving caval flow and therefore avoiding major hemodynamic disturbance. SHVE is not widely used by surgeons despite the theoretical advantage it offers, as it is technically challenging and can be complicated by laceration of the hepatic veins during dissection resulting in major hemorrhage.

The safest type of vascular occlusion to perform in hepatectomy remains a contested topic of discussion. The aim of this systematic review and meta-analysis is to compare morbidity and mortality between SHVE and Pringle maneuver in major hepatectomy surgery.

# **METHODS**

## **Study Design**

This systematic review and meta-analysis was registered at PROSPERO (CRD42020212372). It was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

## **Data Sources and Search Strategy**

The following electronic databases were searched: MEDLINE/ PubMed (1946 to June 2021), EMBASE (1947 to June 2021), Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) from The Cochrane Library (2020, Issue 7) on 26 June 2021. This was done by two independent authors (SM, MT). A combination of medical subject headings (MeSH) and free-text terms were used to form the search strategy for each database. This is displayed in Supplementary Table S1 (Online Resource 1).

In order to identify relevant studies that did not get included in the initial database searches, the reference lists of selected articles were examined. The World Health Organization International Clinical Trials Registry, ClinicalTrials.gov, ISRCTN Register and PROSPERO were also searched to identify any unpublished studies.

# **Study Selection**

Our inclusion criteria included: randomized controlled trials (RCTs) or comparative observational studies in the English language; human studies; studies including patients aged 18 years or older of any gender; studies where a hepatectomy was performed; studies where a Pringle maneuver was performed for hepatic inflow occlusion in the SHVE group.

Our exclusion criteria included: non-English studies; nonmedical, non-human studies; studies in patients under the age of 18 years old and conference abstracts, editorials, expert opinion, case reports and non-comparative observational studies.

The studies that were identified by the initial search strategy were reviewed by two independent authors (RV, MT). Duplicated were removed. Rayyan software was used to screen titles and abstracts of identified studies for inclusion into the review (17). If the study abstract was not sufficient to make a decision for inclusion, the full paper was screened. Any conflicts that arose were resolved through discussion, and a third author (MD) made the final decision where necessary.

# **Data Extraction**

The data was extracted from studies using an electronic data extraction spreadsheet. This was done by two independent authors (SM, MCS). Any conflicts that arose were resolved through discussion, and a third author (MD) made the final decision where necessary. Collected data included: study-related data, patient demographics, peri-operative management and relevant outcome measures.

# **Outcome Measures**

Intra-operative outcome measures included: operative time (minutes), warm ischemia time (minutes), blood loss (milliliters), patients requiring blood transfusion, blood transfusion (units), air embolism and hepatic vein rupture.

Post-operative outcome measures included: overall mortality, intra-operative mortality, in-hospital mortality, overall complication rate (%), hospital stay (days), intensive care unit (ICU) stay (days), post-operative hemorrhage, liver failure and multi-organ failure.

Where studies reported outcomes as median with range, the mean and standard deviation were estimated using the validated method described by Hozo et al. (18).

## Assessment of Risk of Bias

Risk of bias was assessed by two independent authors (SM, MCS). This was carried out using the revised Cochrane riskof-bias tool (RoB 2) for RCTs and the Cochrane Risk Of Bias In Non-Randomized Studies – of Interventions tool (ROBINS-I) for non-randomized studies. Where there were disagreements between the two authors, this was discussed and the final decision was made by a third independent author (MD).

### **Data Synthesis and Statistical Analysis**

The software Review Manager (RevMan) (The Cochrane Collaboration; Version 5.3.5, The Nordic Cochrane Centre, Copenhagen, Denmark) was used for data synthesis (19). This was done by one independent author (MB) who entered the extracted data into the software. A second independent author (MD) then reviewed the entered data.

To estimate treatment effects, relevant outcome parameters that were extracted from the included studies were assessed. For dichotomous variables, the Mantel-Haenszel method was used to pool the odds ratio (OR). For continuous variables, the mean difference (MD) was calculated between the two groups (20). A forest plot was generated for each outcome measure with 95% confidence intervals (CIs) and its associated p-value. Statistical significance was defined as p < 0.05.

The Cochran Q test  $(\chi^2)$  was used to assess the heterogeneity between studies. This was then further quantified by generating an inconsistency statistic  $(I^2)$  for each outcome measure. Low heterogeneity was defined as an  $I^2$  of 0–50% and fixed-effects modelling was used. Conversely, high heterogeneity was defined as an  $I^2$  of 51–100% and random-effects modelling was used.

To explore potential sources of heterogeneity, sensitivity analyses were carried out. For each outcome parameter with high inter-study heterogeneity, individual studies were removed and the analysis would be repeated to assess that study's contribution to the overall effect size and heterogeneity. In order to explore potential changes in the effect size, subgroup analyses of the RCTs and observational studies were carried out.

The independent (unpaired) samples t-test was performed on the Pringle and SHVE groups to assess statistical significance between patient demographics. This was done using the software IBM SPSS Statistics (IBM Corp; Version 23.0, Armonk, NY, USA) (21). Statistical significance was defined as p < 0.05.

## RESULTS

### **Study Selection**

The literature search identified 2,411 studies, which became 1,267 following removal of duplicated studies. Abstracts were then assessed for eligibility and 1,253 studies were excluded. From the remaining 15 studies, six met the inclusion criteria. Therefore the study population for this systematic review is comprised of three RCTs, two retrospective cohort studies and one case-control study reporting a total of 2,238 patients. PRISMA flowchart is demonstrated in **Figure 1**.

## **Study Characteristics**

All studies were published between the years 2003 and 2019. One study was undertaken in Greece (22), four in China (23–26) and one in Thailand (27). All RCTs were single-center studies. Study durations ranged from 11 to 96 months. In total, there were 1,288 patients in the Pringle group and



950 in the SHVE group. Study characteristics are presented in Table 1.

Baseline demographics of the study populations are presented in **Table 2**. There was no statistically significant difference in the mean age and gender between the Pringle and SHVE groups. Tumor size, number of patients with cirrhosis (including Child-Pugh Grade) and hepatitis B status were only reported in a few of the studies, but where they were reported, they were comparable across the two groups. The extent of tumor invasion of the hepatic veins was reported by the four studies from China and remained comparable across the two groups (23–26). These studies only selected patients with tumors encroaching on the hepatic veins. Zhou et al. (23) and Tongsiri et al. (27) reported the number of hepatic veins involved rather than named veins therefore it was not possible to assess whether there were differences between the Pringle and SHVE groups.

Other than one study that solely looked at outcomes in hemangioma (25), malignancy was the most common indication for resection, and hepatocellular carcinoma (HCC) accounted for the majority of malignant lesions in both groups. The number of patients with HCC were similar across the two groups. The most commonly performed resections were right and left hepatectomy, with very few numbers reported for the various segmentectomies, and this remained comparable across the two groups. All studies reported the use of a clamp-crushing technique for liver resection, except Tongsiri et al. which used ultrasonic dissection (27), and all studies used additional polypropylene 3-0 and 4-0 sutures for hemostasis.

 TABLE 1 | Summary of characteristics of included studies.

Author	Year	Journal	Country	Study design	Retrospective or prospective	Study period	Study duration (months)	<i>n</i> , total	<i>n</i> , Pringle	n, SHVE
Smyrniotis et al.	2003	World Journal of Surgery	Greece	RCT	Prospective	1995–2002	84	110	55	55
Zhou et al.	2008	European Journal of Surgical Oncology	China	Case-control	Retrospective	2000–2005	58	235	110	125
Zhang et al.	2012	British Journal of Surgery	China	Cohort	Retrospective	2003–2010	84	1420	870	550
Yang et al.	2014	American Surgeon	China	Cohort	Retrospective	2003–2011	96	273	153	120
Si-Yuan et al.	2014	International Journal of Surgery	China	RCT	Prospective	2008–2010	24	160	80	80
Tongsiri et al.	2020	Journal of The Medical Association of Thailand	Thailand	RCT	Prospective	2018–2019	11	40	20	20

RCT, randomized controlled trial; SHVE, selective hepatic vascular exclusion.

TABLE 2	Baseline patient	demographics	of included	studies.
---------	------------------	--------------	-------------	----------

Author	Average age (years)		<i>n</i> , m	ale	Tumou (cr		<i>n</i> , cirr	hosis	n, Chilo Grad	•	n, Child Grad		n, HBs/	Ag + ve
	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE	Pringle	SHVE
Smyrniotis et al.	62	61	44	43	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Zhou et al.	52.3	51.6	77	86	11.8	12.4	65	74	102	113	8	12	71	90
Zhang et al.	53	51	630	406	8.6	8.9	604	393	580	379	24	14	621	427
Yang et al.	41.9	45.8	62	41	12.9	14.2	2	1	N/R	N/R	N/R	N/R	N/R	N/R
Si-Yuan et al.	48.3	49.2	63	61	8	8.2	48	50	43	45	5	5	N/R	N/R
Tongsiri et al.	57.4	61.1	4	11	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	1	0
Independent samples t-test	<i>p</i> = 0	.840	<i>p</i> = 0	.743	<i>p</i> = 0	.758	p = 0.	.776	<i>p</i> = 0	.771	p = 0	.780	<i>p</i> = 0	.815

Statistical significance defined as p < 0.05.

HBsAg, hepatitis B surface antigen; N/R, not reported.

Two studies performed a continuous Pringle maneuver for all patients in both groups (22–25) and Tongsiri et al. performed intermittent Pringle maneuver for both groups (27). Si-Yuan et al. performed a continuous Pringle maneuver for the SHVE group only (26) and two studies performed a continuous Pringle maneuver either if the liver was cirrhotic (24) or developed cirrhosis (23) in both groups. Zhang et al. (24) and Yang et al. (25) converted to THVE in the Pringle group in 34 and 11 patients respectively. Si-Yuan et al. converted to THVE in one patient in the SHVE group as the tumor had invaded the IVC (26). Tongsiri et al. converted two patients in the SHVE group to Pringle (27). All studies described clamping the right, middle and left hepatic veins in all cases regardless of the type of resection. Operative techniques are presented in Supplementary Table S2 (Online Resource 1).

## Data Synthesis

#### Hemorrhage and Transfusion

The pooled analysis demonstrated a statistically significant decrease in blood loss (MD: -353.13, 95% CI: -380.80--325.46, *p* < 0.00001); number of patients requiring blood

transfusion (OR: 0.31, 95% CI: 0.20–0.50, p < 0.00001); and number of units transfused (MD: -1.59, 95% CI: -1.70– -1.49, p < 0.00001) in the SHVE group compared to the Pringle group. Forest plots for these outcomes are presented in **Table 3**. Rates of post-operative hemorrhage remained similar between the two groups (OR: 0.55, 95% CI: 0.17–1.78, p = 0.32). This is presented in Supplementary Figure S3 (Online Resource 1). Heterogeneity between studies for blood loss ( $I^2 = 0\%$ , p = 0.72); units of blood transfused ( $I^2 = 0\%$ , p =0.48); and rates of post-operative hemorrhage ( $I^2 = 22\%$ , p =0.27) was low. There was high heterogeneity between studies for number of patients requiring blood transfusion ( $I^2 = 74\%$ , p = 0.004).

#### Morbidity and Mortality

There was a statistically significant decrease in overall mortality (OR: 0.12, 95% CI: 0.03–0.55, p = 0.005) and in-hospital mortality (OR: 0.09, 95% CI: 0.01–0.68, p = 0.02) in the SHVE group compared to the Pringle group. Heterogeneity remained low between the studies for both overall mortality ( $I^2 = 0\%$ , p = 0.81) and in-hospital mortality. ( $I^2 = 0\%$ , p = 0.41).

Blood loss		SHV			Pringle			Mean Di				Mean Difference
	Study or Subgroup 1.3.1 RCTs	Mean	SD Tot	al Mean	SD	Total	Weight	IV,	, Fixed, 9	95% CI	Year	IV, Fixed, 95% Cl
	Smyrniotis et al	420	475 5	55 880	417	55	2.7%	-460.00 [-62	27.04, -2	92.96]	2003	
	Si-Yuan et al			30 776.9		80	1.1%	-248.20 [-				
	Tongsiri et al Subtotal (95% Cl)	923.5 1,21	9.5 1	20 1,109 55	1,223	20 155	0.1%	-185.50 [-9 -392.08 [-53			2020	•
	Heterogeneity: Chi <sup>2</sup> = Test for overall effect :		P = 0.36)	I <sup>2</sup> = 3%					, -			
	1.3.2 Observational											
	Zhou et al			25 1,160				-480.00 [-1				
	Zhang et al Yang et al		210 55 250 12	50 830 20 1.000			93.6% 2.2%	-350.00 [-37				
	Subtotal (95% CI)		79		.,	1133		-351.51 [-37				•
	Heterogeneity: Chi <sup>2</sup> = Test for overall effect .											
	Total (95% CI)		95	50		1288	100.0%	-353.13 [-38	0.80, -3	25.46]		•
	Heterogeneity: Chi <sup>2</sup> =											-1000 -500 0 500 10
	Test for overall effect: Test for subgroup diffe				0.57), I	*= 0%						Favours SHVE Favours Pringle
Patients requiring		SHV	Æ	Pring	ile			Odds Ratio				Odds Ratio
transfusion	Study or Subgroup			-		Weigh		Random, 9	5% CI	Year		M-H, Random, 95% Cl
	1.4.1 RCTs											
	Smyrniotis et al	18	55	32	55	16.29	б	0.35 [0.16,				
	Si-Yuan et al	13	80	22	80	16.39		0.51 [0.24,		2014		
	Subtotal (95% CI) Total events	31	135	54	135	32.5	76	0.42 [0.25,	0.73]			-
	Heterogeneity: Tau Test for overall effe	= 0.00; Ch		6, df = 1 (	(P = 0.5	i0);  ² =	0%					
	1.4.2 Observationa	l.										
	Zhou et al	40	125	89	110	19.59	Х	0.11 [0.06,	0.20]	2008		
	Zhang et al	83	550	278	870	26.39		0.38 [0.29,				-
	Yang et al Subtotal (95% CI)	35	120 795	77	153 1133			0.41 [0.25, 0.27 [0.13,		2014		•
	Total events	158		444								
	Heterogeneity: Tau Test for overall effe				(P = 0	.0009);	I² = 86%	•				
	Total (95% CI)		930		1268	100.0	%	0.31 [0.20,	0.50]			•
	Total events	189		498								
	Heterogeneity: Tau				(P = 0	.004); I²	= 74%				0.01	0.1 1 10 10
	Test for overall effe Test for subgroup o				1 (P =	0.31), P	<sup>e</sup> = 4.8%					Favours SHVE Favours Pingle
Units of blood	Church and Carlos		HVE		Pring			Mean D				Mean Difference
transfused	Study or Subgroup	) Mean	SD TO	otal Me	an Si	J 10ta	i weig	nt IV, FD	xed, 95	% CI		IV, Fixed, 95% Cl
	1.22.1 RCTs Si-Yuan et al	0	2	55	1 2.3	3 55	5 17	% -1.00[-	1 91 -	1 1 01		
	Smyrniotis et al Subtotal (95% CI)	1	2		2.2		0.8	% -1.20[- % -1.20[- !% -1.06[-	2.38, -	0.02]		•
	Heterogeneity: Chi Test for overall effe				= 0%							
	1.22.2 Observation	nal										
	Yang et al		1.3	120	4 5.	5 153	3 1.3	% -2.00[-	2.90, -	1.10]		<u> </u>
	Zhang et al	1.3			2.9 1.4			% -1.60[-		-		
	Zhou et al	2.2	4	125	4.3 1:	2 110		% -2.10				+

Zhou et al Subtotal (95% CI) 125 795 2.2 4 110 0.2% -2.10 [-4.45, 0.25] 1133 97.6% -1.61 [-1.71, -1.50] Heterogeneity: Chi<sup>2</sup> = 0.92, df = 2 (P = 0.63); l<sup>2</sup> = 0% Test for overall effect: Z = 30.03 (P < 0.00001)

Total (95% CI) 930 1268 100.0% -1.59 [-1.70, -1.49] Heterogeneity: Chi<sup>2</sup> = 3.49, df = 4 (P = 0.48); l<sup>2</sup> = 0% Test for overall effect: Z = 30.15 (P < 0.00001) Test for subgroup differences:  $Chi^2 = 2.50$ , df = 1 (P = 0.11),  $l^2 = 59.9\%$ 

(continued)

٠

-4

4 -2 0 2 4 Favours SHVE Favours Pringle

#### TABLE 3 | Continued

Overall mortality	~			Pring			Odds Ratio		Odds Ratio
	Study or Subgroup	LTUINS	I VIUI	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl
	1.9.1 RCTs					0.50			
	Smyrniotis et al	0	55	1	55	8.5%	0.33 [0.01, 8.21]		-
	Si-Yuan et al Tongsiri et al	0	80 20	0	80 20		Not estimable Not estimable		
	Subtotal (95% CI)	-	155	-	155	8.5%	0.33 [0.01, 8.21]	2020	
	Total events	0		1					
	Heterogeneity: Not ap Test for overall effect:		P = 0.5	0)					
	1.9.2 Observational								
	Zhou et al	0	125	2	110	15.1%	0.17 [0.01, 3.64]	2008	
	Zhang et al	0	550	14	870	64.0%	0.05 [0.00, 0.90]	2012	<b>_</b>
	Yang et al Subtotal (95% CI)	0	120 795	2	153 1133	12.5% 91.5%	0.25 [0.01, 5.29] 0.10 [0.02, 0.55]	2014	
	Total events	0		18					
	Heterogeneity: Chi <sup>2</sup> = Test for overall effect:				= 0%				
	Total (95% CI)		950		1288	100.0%	0.12 [0.03, 0.53]		-
	Total events	0		19					
	Heterogeneity: Chi <sup>2</sup> =	0.97, df =	3 (P =	0.81); l² =	= 0%				0.001 0.1 1 10 1000
	Test for overall effect:	Z = 2.80 (	P = 0.0	05)					Favours SHVE Favours Pringle
	Test for subgroup diff	erences: (	Chi <sup>2</sup> = (	).41, df=	1 (P =	0.52), l <sup>2</sup> =	: 0%		, accare en la reneater ingle
Overall									
		SHVE		Pring	le		Odds Ratio		Odds Ratio
complications	Study or Subgroup		2	-		Weight	Odds Ratio M-H, Fixed, 95% Cl	Year	Odds Ratio M-H, Fixed, 95% Cl
	Study or Subgroup 1.11.1 RCTs		2	-		Weight		Year	
			2	-		Weight 6.7%			
	1.11.1 RCTs	Events	Total	Events	Total		M-H, Fixed, 95% CI	2003	
	1.11.1 RCTs Smyrniotis et al	Events 29	Total 55	Events 33	Total 55	6.7%	M-H, Fixed, 95% Cl 0.74 [0.35, 1.58]	2003 2014	
	<b>1.11.1 RCTs</b> Smyrniotis et al Si-Yuan et al Tongsiri et al	Events 29 16	Total 55 80 20	Events 33 24	Total 55 80 20	6.7% 8.2% 1.5%	M-H, Fixed, 95% Cl 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43]	2003 2014	
	1.11.1 RCTs Smyrniotis et al Si-Yuan et al Tongsiri et al Subtotal (95% CI)	Events 29 16 12 57	Total 55 80 20 155	Events 33 24 9 66	Total 55 80 20 155	6.7% 8.2% 1.5%	M-H, Fixed, 95% Cl 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43]	2003 2014	
	1.11.1 RCTs Smyrniotis et al Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events	29 16 12 57 2.40, df=	Total 55 80 20 155 2 (P =	Events 33 24 9 66 0.30); I <sup>2</sup> =	Total 55 80 20 155	6.7% 8.2% 1.5%	M-H, Fixed, 95% Cl 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43]	2003 2014	
	1.11.1 RCTs         Smyrniotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational	29 16 12 57 2.40, df= Z = 1.09 (0	55 80 20 155 2 (P = P = 0.2	33 24 9 66 0.30);  ² = 7)	Total 55 80 20 155 = 17%	6.7% 8.2% 1.5% <b>16.5</b> %	M-H, Fixed, 95% Cl 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24]	2003 2014 2020	
	1.11.1 RCTs         Smyrniotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational         Zhou et al	Events 29 16 12 57 2.40, df= Z = 1.09 (0 49	Total 55 80 20 155 2 (P = P = 0.2 125	Events 33 24 9 66 0.30); I <sup>≠</sup> = 7) 57	Total 55 80 20 155 = 17%	6.7% 8.2% 1.5% <b>16.5</b> %	M-H, Fixed, 95% Cl 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01]	2003 2014 2020 2020	
	1.11.1 RCTs         Smymiotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% Cl)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational         Zhou et al         Zhou et al	Events 29 16 12 57 2.40, df = Z = 1.09 (0 49 102	Total 55 80 20 155 2 (P = P = 0.2 125 550	Events 33 24 9 66 0.30); I <sup>a</sup> = 7) 57 198	Total 55 80 20 155 = 17% 110 870	6.7% 8.2% 1.5% <b>16.5</b> % 15.8% 53.6%	M-H, Fixed, 95% CI 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01] 0.77 [0.59, 1.01]	2003 2014 2020 2020 2008 2012	
	1.11.1 RCTs         Smyrniotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational         Zhou et al	Events 29 16 12 57 2.40, df= Z = 1.09 (0 49	Total 55 80 20 155 2 (P = P = 0.2 125	Events 33 24 9 66 0.30); I <sup>≠</sup> = 7) 57	Total 55 80 20 155 = 17%	6.7% 8.2% 1.5% <b>16.5</b> %	M-H, Fixed, 95% Cl 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01]	2003 2014 2020 2020 2008 2012	
	1.11.1 RCTs         Smymiotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% Cl)         Total events         Heterogeneity: Chi <sup>2</sup> =         Test for overall effect:         1.11.2 Observational         Zhou et al         Zhang et al         Yang et al	Events 29 16 12 57 2.40, df = Z = 1.09 (0 49 102	Total 55 80 20 155 2 (P = P = 0.2 125 550 120	Events 33 24 9 66 0.30); I <sup>a</sup> = 7) 57 198	Total 55 80 20 155 = 17% 110 870 153	6.7% 8.2% 1.5% 16.5% 15.8% 53.6% 14.0%	M-H, Fixed, 95% CI 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01] 0.77 [0.59, 1.01] 0.59 [0.34, 1.04]	2003 2014 2020 2020 2008 2012	
	1.11.1 RCTs         Smymiotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% Cl)         Total events         Heterogeneity: Chi <sup>2</sup> =         Test for overall effect:         1.11.2 Observational         Zhou et al         Zhang et al         Yang et al         Subtotal (95% Cl)	29 16 12 57 2.40, df= Z = 1.09 () 49 102 25 176 1.19, df=	Total 55 80 20 155 2 (P = P = 0.2 125 550 120 795 2 (P =	Events           33           24           9           66           0.30);  *=           7)           57           198           47           302           0.55);  *=	Total 55 80 20 155 = 17% 110 870 153 1133	6.7% 8.2% 1.5% 16.5% 15.8% 53.6% 14.0%	M-H, Fixed, 95% CI 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01] 0.77 [0.59, 1.01] 0.59 [0.34, 1.04]	2003 2014 2020 2020 2008 2012	
	1.11.1 RCTs         Smymiotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational         Zhou et al         Zhang et al         Yang et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =	29 16 12 57 2.40, df= Z = 1.09 () 49 102 25 176 1.19, df=	Total 55 80 20 155 2 (P = P = 0.2 125 550 120 795 2 (P =	Events           33           24           9           66           0.30);  *=           7)           57           198           47           302           0.55);  *=	Total 55 80 20 155 = 17% 110 870 153 1133 = 0%	6.7% 8.2% 1.5% 16.5% 15.8% 53.6% 14.0%	M-H, Fixed, 95% CI 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01] 0.77 [0.59, 1.01] 0.59 [0.34, 1.04]	2003 2014 2020 2020 2008 2012	
	1.11.1 RCTs         Smymiotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational         Zhou et al         Zhang et al         Yang et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:	29 16 12 57 2.40, df= Z = 1.09 () 49 102 25 176 1.19, df=	Total 55 80 20 155 2 (P = P = 0.2 125 550 120 <b>795</b> 2 (P = P = 0.0	Events           33           24           9           66           0.30);  *=           7)           57           198           47           302           0.55);  *=	Total 55 80 20 155 = 17% 110 870 153 1133 = 0%	6.7% 8.2% 1.5% 16.5% 15.8% 53.6% 14.0% 83.5%	M-H, Fixed, 95% CI 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01] 0.77 [0.59, 1.01] 0.59 [0.34, 1.04] 0.71 [0.57, 0.88]	2003 2014 2020 2020 2008 2012	
	1.11.1 RCTs         Smymiotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational         Zhou et al         Zhang et al         Yang et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total (95% CI)	29 16 12 57 2.40, df = Z = 1.09 (J 49 102 25 176 1.19, df = Z = 3.07 (J 233	Total           55         80           20         155           2 (P =         P = 0.2           125         550           120         795           2 (P =         P = 0.0           950         950	Events 33 24 9 66 0.30);   <sup>2</sup> = 7) 57 198 47 302 0.55);   <sup>2</sup> = 02) 368	Total 55 80 20 155 = 17% 110 870 153 1133 = 0% 1288	6.7% 8.2% 1.5% 16.5% 15.8% 53.6% 14.0% 83.5%	M-H, Fixed, 95% CI 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01] 0.77 [0.59, 1.01] 0.59 [0.34, 1.04] 0.71 [0.57, 0.88]	2003 2014 2020 2020 2008 2012	M-H, Fixed, 95% Cl
	1.11.1 RCTs         Smymiotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% Cl)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational         Zhou et al         Zhang et al         Yang et al         Subtotal (95% Cl)         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total (95% Cl)         Total events	29 16 12 57 2.40, df= Z = 1.09 (0 49 102 25 176 1.19, df= Z = 3.07 (0 233 3.67, df=	Total           55         80           20         155           2 (P =         P = 0.2           125         550           120         795           2 (P =         P = 0.0           950         950           5 (P =         5 (P =	Events           33           24           9           66           0.30);  *=           7)           57           198           47           302           0.55);  *=           02)           368           0.60);  *=	Total 55 80 20 155 = 17% 110 870 153 1133 = 0% 1288	6.7% 8.2% 1.5% 16.5% 15.8% 53.6% 14.0% 83.5%	M-H, Fixed, 95% CI 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01] 0.77 [0.59, 1.01] 0.59 [0.34, 1.04] 0.71 [0.57, 0.88]	2003 2014 2020 2020 2008 2012	M-H, Fixed, 95% CI
	1.11.1 RCTs         Smymiotis et al         Si-Yuan et al         Tongsiri et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         1.11.2 Observational         Zhou et al         Zhang et al         Yang et al         Subtotal (95% CI)         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total events         Heterogeneity: Chi² =         Test for overall effect:         Total events         Heterogeneity: Chi² =         Total events         Heterogeneity: Chi² =	29 16 12 57 2.40, df= Z = 1.09 (J 49 102 25 176 1.19, df= Z = 3.07 (J 233 3.67, df= Z = 3.25 (J	Total           55         80           20         155           2 (P =         P = 0.2           125         550           795         2 (P =           950         550           5 (P =         P = 0.0	Events           33           24           9           66           0.30);  *=           7)           57           198           47           302           0.55);  *=           02)           368           0.60);  *=           01)	Total 55 80 20 155 = 17% 1100 870 153 1133 = 0% 1288 = 0%	6.7% 8.2% 1.5% 16.5% 16.5% 53.6% 14.0% 83.5%	M-H, Fixed, 95% CI 0.74 [0.35, 1.58] 0.58 [0.28, 1.21] 1.83 [0.52, 6.43] 0.77 [0.47, 1.24] 0.60 [0.36, 1.01] 0.77 [0.59, 1.01] 0.59 [0.34, 1.04] 0.71 [0.57, 0.88] 0.72 [0.59, 0.88]	2003 2014 2020 2020 2008 2012	M-H, Fixed, 95% Cl

(continued)

The forest plot for overall mortality is presented in **Table 3**. Inhospital mortality is presented in a forest plot in Supplementary Figure S4 (Online Resource 1).

The meta-analysis of complication rate demonstrated a statistically significant decrease in the SHVE group compared to the Pringle group (OR: 0.72, 95% CI: 0.59–0.88, p = 0.001) with low heterogeneity ( $I^2 = 0\%$ , p = 0.60). There was no statistically significant difference in hepatic vein rupture (OR: 0.92, 95% CI: 0.73–1.17, p = 0.52) or bile leak (OR: 1.15, 95% CI: 0.75–1.76, p = 0.53) between the two groups. Heterogeneity

was low for both hepatic vein rupture ( $I^2 = 0\%$ , p = 0.97) and bile leak ( $I^2 = 0\%$ , p = 0.77). There was a statistically significant decrease in air embolism (OR: 0.08, 95% CI: 0.02–0.36, p =0.0008); liver failure (OR: 0.31, 95% CI: 0.12–0.81, p = 0.02); and multi-organ failure (OR: 0.15, 95% CI: 0.03–0.83, p =0.03) in the SHVE group compared to the Pringle group. Heterogeneity between studies for air embolism ( $I^2 = 0\%$ , p =0.97); liver failure ( $I^2 = 0\%$ , p = 0.98); and multi-organ failure ( $I^2 = 0\%$ , p = 0.78) remained low. The forest plots for these outcomes are presented in **Table 3**. Hepatic vein rupture

Bile leak

#### TABLE 3 | Continued

	SHV	E	Pring	le		Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
1.5.1 RCTs								
Smyrniotis et al	0	55	0	55		Not estimable	2003	
Si-Yuan et al	18	80	20			0.87 [0.42, 1.81]	2014	
Subtotal (95% CI)		135		135	11.1%	0.87 [0.42, 1.81]		
Total events	18		20					
Heterogeneity: Not a	pplicable							
Test for overall effect	: Z = 0.37	(P = 0.7	'1)					
1.5.2 Observational								
Zhou et al	18	125	17	110	11.1%	0.92 [0.45, 1.89]	2008	
Zhang et al	84	550	144	870	67.5%	0.91 [0.68, 1.22]	2012	
Yang et al	16	120	19	153	10.3%	1.09 [0.53, 2.21]	2014	
Subtotal (95% CI)		795		1133	88.9%	0.93 [0.72, 1.20]		<b>+</b>
Total events	118		180					
Heterogeneity: Chi <sup>2</sup> =	= 0.20, df =	2 (P =	0.90); l <sup>z</sup> =	= 0%				
Test for overall effect	: Z = 0.56	(P = 0.5	58)					
Total (95% CI)		930		1268	100.0%	0.92 [0.73, 1.17]		•
Total events	136		200					
Heterogeneity: Chi <sup>2</sup> =	= 0.23, df =	3 (P =	0.97); l <sup>2</sup> =	= 0%				0.01 0.1 1 10 100
Test for overall effect	: Z = 0.65	(P = 0.5	52)					0.01 0.1 1 10 100 Favours SHVE Favours Pringle
Test for subgroup dif	fferences:	Chi <sup>z</sup> =	0.03, df=	1 (P=	0.87), I <sup>z</sup> =	0%		ravouis serve ravouis rinigie
	SHV		Pring			Odds Ratio		Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
1.20.1 RCTs								
Smyrniotis et al	6	50	5	50	11.3%	1.23 [0.35, 4.32]	2003	
Tax maini at al	0	20	-	00	7400	2 15 10 01 0 201	0000	



(continued)

#### Duration of Surgery and Hospital Stay

There was no statistically significant difference in warm ischemia (MD: -0.84, 95% CI: -2.18-0.51, p = 0.22) or operative time (MD: 6.44, 95% CI: -2.65-15.54, p = 0.16) in the SHVE group compared to the Pringle group. Heterogeneity was high for both warm ischemia time ( $I^2 = 69\%$ , p = 0.01) and operative time ( $I^2 = 84\%$ , p < 0.00001).

Similarly, there was no statistically significant difference in length of stay in hospital (MD: -3.04, 95% CI: -8.06-1.98, p = 0.24) or ICU (MD: 0.66, 95% CI: -0.53-1.86, p = 0.28) in the SHVE group compared to the Pringle group. Heterogeneity was high for both hospital stay ( $I^2 = 99\%$ , p < 0.00001) and ICU stay ( $I^2 = 99\%$ , p < 0.00001). The forest plots for these outcomes are presented in Supplementary Figures S5–S8 (Online Resource 1).

## **Sensitivity and Subgroup Analysis**

Random-effects modelling was applied to patients requiring transfusion, operative time, warm ischemia time, ICU stay and hospital stay due to the high heterogeneity between studies. This did not affect the pooled effect size or heterogeneity. Sensitivity analyses were also performed. Excluding the Si-Yuan study resulted in the operative time becoming significantly shorter in the Pringle group, excluding the Si-Yuan study resulted in warm

#### TABLE 3 | Continued

Air embolism		SHV	E	Pring	le		Odds Ratio		Odds Ratio	
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl	
	1.7.1 RCTs									
	Si-Yuan et al Subtotal (95% Cl)	0	80 80	3	80 80	13.9% <b>13.9</b> %	0.14 [0.01, 2.71] 0.14 [0.01, 2.71]	2014		
	Total events	0		3						
	Heterogeneity: Not applicable Test for overall effect: Z = 1.31 (P = 0.19)									
	1.7.2 Observational									
	Zhou et al	0	125	3	110	14.8%	0.12 [0.01, 2.40]			
	Zhang et al	0	550	14	870	44.9%	0.05 [0.00, 0.90]			
	Yang et al Subtotal (95% CI)	0	120 <b>795</b>	7	153 1133	26.3% <b>86.1</b> %	0.08 [0.00, 1.43] <b>0.07 [0.01, 0.39]</b>	2014	•	
	Total events	0		24						
	Heterogeneity: Chi² = Test for overall effect:				:0%					
	Total (95% CI)		875		1213	100.0%	0.08 [0.02, 0.36]		•	
	Total events	0		27						
	Heterogeneity: Chi <sup>2</sup> =				:0%				0.001 0.1 1 10 100	
	Test for overall effect:								Favours SHVE Favours Pringle	
			Chi <sup>z</sup> = I	J.13. df=	1 (P =	0.72), I*=	0%			
	Test for subgroup dif	erences.	0111 -							
Lines follows	l est for subgroup dif	SHV		Pring	le		Odds Ratio		Odds Ratio	
Liver failure	Study or Subgroup	SHV	E	Pring		Weight	Odds Ratio M-H, Fixed, 95% Cl	Year	Odds Ratio M-H, Fixed, 95% Cl	
Liver failure		SHV	E	Pring		Weight		Year		
Liver failure	Study or Subgroup	SHV	E	Pring		Weight 7.9%				
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al	SHV Events	E <u>Total</u> 80 20	Pring Events	Total 80 20	7.9%	M-H, Fixed, 95% Cl 0.33 [0.01, 8.20] Not estimable	2014		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al	SHV Events 0 0	E Total 80	Pring Events 1 0	Total 80		M-H, Fixed, 95% Cl 0.33 [0.01, 8.20]	2014		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events	SHV Events 0 0	E <u>Total</u> 80 20	Pring Events	Total 80 20	7.9%	M-H, Fixed, 95% Cl 0.33 [0.01, 8.20] Not estimable	2014		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events Heterogeneity: Not ag	SHV Events 0 0 0 pplicable	E Total 80 20 100	Pring Events 1 0	Total 80 20	7.9%	M-H, Fixed, 95% Cl 0.33 [0.01, 8.20] Not estimable	2014		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect:	SHV Events 0 0 0 0 0 0 0 0 0 0 2 = 0.68	E Total 80 20 100	Pring Events 1 0	Total 80 20	7.9%	M-H, Fixed, 95% Cl 0.33 [0.01, 8.20] Not estimable	2014		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: 1.16.2 Observational	SHV Events 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	E Total 20 100 P = 0.5	Pring Events 1 0 1	Total 80 20 100	7.9%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20)	2014 2020		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: 1.16.2 Observational Zhou et al	SHV Events 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 2 2 0.68 0 7 2 2 0.68 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	E Total 20 100 P = 0.5	Pring <u>Events</u> 1 0 1 :0) 3	Total 80 20 100	7.9% <b>7.9</b> %	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 [0.01, 8.20] Not estimable	2014 2020 2008		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events Heterogeneity: Not ag Test for overall effect: 1.16.2 Observational Zhou et al Zhang et al Yang et al	SHV Events 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	E Total 80 20 100 P = 0.5 0 550 120	Pring Events 1 0 1	Total 80 20 100 110 870 153	7.9% 7.9% 85.2% 6.9%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20] Not estimable 0.30 (0.10, 0.87) 0.42 (0.02, 10.45)	2014 2020 2008 2012		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: 1.16.2 Observational Zhou et al Zhou et al Yang et al Subtotal (95% Cl)	SHV Events 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	E Total 80 20 100 P = 0.5 0 550	Pring Events 1 0 1 50) 3 21 1	Total 80 20 100 110 870	7.9% <b>7.9</b> % 85.2%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 [0.01, 8.20] Not estimable 0.30 (0.10, 0.87]	2014 2020 2008 2012		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events Heterogeneity: Not ag Test for overall effect: 1.16.2 Observational Zhou et al Zhang et al Yang et al Subtotal (95% CI) Total events	SHV <u>Events</u> 0 0 0 0 0 0 0 0 0 125 4 0 129	E Total 80 20 100 P = 0.5 0 550 120 670	Pring Events 1 0 1 0) 3 21 1 25	Total 80 20 100 110 870 153 1133	7.9% 7.9% 85.2% 6.9%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20] Not estimable 0.30 (0.10, 0.87) 0.42 (0.02, 10.45)	2014 2020 2008 2012		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% Cl) Total events Heterogeneity: Not a; Test for overall effect: 1.16.2 Observational Zhou et al Zhang et al Yang et al Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> =	SHV <u>Events</u> 0 0 0 0 0 0 0 0 0 0 125 4 0 129 0.04, df=	E Total 80 20 100 P = 0.5 0 550 120 670 1 (P =	Pring Events 1 0 1 50) 3 21 1 25 0.84);   <sup>2</sup> =	Total 80 20 100 110 870 153 1133	7.9% 7.9% 85.2% 6.9%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20] Not estimable 0.30 (0.10, 0.87) 0.42 (0.02, 10.45)	2014 2020 2008 2012		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events Heterogeneity: Not ap Test for overall effect: 1.16.2 Observational Zhou et al Zhang et al Yang et al Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	SHV <u>Events</u> 0 0 0 0 0 0 0 0 0 0 125 4 0 129 0.04, df=	E Total 80 20 100 P = 0.5 550 120 670 1 (P = P = 0.0	Pring Events 1 0 1 50) 3 21 1 25 0.84);   <sup>2</sup> =	Total 80 20 100 870 153 1133 = 0%	7.9% 7.9% 85.2% 6.9% 92.1%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20) Not estimable 0.30 (0.10, 0.87) 0.42 (0.02, 10.45) 0.31 (0.11, 0.85)	2014 2020 2008 2012		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% Cl) Total events Heterogeneity: Not ap Test for overall effect: 1.16.2 Observational Zhou et al Zhang et al Yang et al Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Total (95% Cl)	SHV Events 0 0 0 0 0 0 0 0 0 0 0 125 4 0 129 0.04, df= Z = 2.28 (	E Total 80 20 100 P = 0.5 0 550 120 670 1 (P =	Pring Events 1 0 1 i0) 3 21 1 25 0.84);   <sup>2</sup> = (2)	Total 80 20 100 870 153 1133 = 0%	7.9% 7.9% 85.2% 6.9%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20] Not estimable 0.30 (0.10, 0.87) 0.42 (0.02, 10.45)	2014 2020 2008 2012		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events Heterogeneity: Not ag Test for overall effect: 1.16.2 Observational Zhou et al Zhang et al Yang et al Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Total (95% CI) Total events	SHV <u>Events</u> 0 0 0 0 0 0 0 0 125 4 0 129 0.04, df= Z = 2.28 129	E Total 80 20 100 P = 0.6 550 120 670 1 (P = P = 0.0 770	Pring Events 1 0 1 1 50) 3 21 1 25 0.84); I <sup>*</sup> = (2) 26	Total 80 20 100 110 870 153 1133 :0% 1233	7.9% 7.9% 85.2% 6.9% 92.1%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20) Not estimable 0.30 (0.10, 0.87) 0.42 (0.02, 10.45) 0.31 (0.11, 0.85)	2014 2020 2008 2012		
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% Cl) Total events Heterogeneity: Not ag Test for overall effect: 1.16.2 Observational Zhou et al Zhou et al Yang et al Subtotal (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Total (95% Cl) Total events Heterogeneity: Chi <sup>2</sup> =	SHV <u>Events</u> 0 0 0 0 0 0 0 125 4 0 129 0.04, df= 2 = 2.28 ( 129 0.04, df= 2 = 0.64, df= 129 0.04, df= 129	E Total 80 20 100 P = 0.5 550 120 670 1 (P = P = 0.0 770 2 (P =	Pring Events 1 0 1 50) 3 21 1 25 0.84);   <sup>2</sup> = (2) 26 0.98);   <sup>2</sup> =	Total 80 20 100 110 870 153 1133 :0% 1233	7.9% 7.9% 85.2% 6.9% 92.1%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20) Not estimable 0.30 (0.10, 0.87) 0.42 (0.02, 10.45) 0.31 (0.11, 0.85)	2014 2020 2008 2012	M-H, Fixed, 95% Cl	
Liver failure	Study or Subgroup 1.16.1 RCTs Si-Yuan et al Tongsiri et al Subtotal (95% CI) Total events Heterogeneity: Not ag Test for overall effect: 1.16.2 Observational Zhou et al Zhang et al Yang et al Subtotal (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Total (95% CI) Total events	SHV <u>Events</u> 0 0 0 0 0 0 125 4 0 129 0.04, df= Z = 2.28 129 0.04, df= Z = 2.38 ( 129 0.04, df= Z = 2.38 ( 129 0.04, df= ( 129 0.04, df= ( 129 0,	E Total 80 20 100 P = 0.6 550 120 670 1 (P = P = 0.0 770 2 (P = P = 0.0	Pring Events 1 0 1 0 3 21 1 25 0.84);   <sup>2</sup> = (2) 26 0.98);   <sup>2</sup> = (2)	Total 80 20 100 110 153 1133 0% 1233 : 0%	7.9% 7.9% 85.2% 6.9% 92.1%	M-H, Fixed, 95% Cl 0.33 (0.01, 8.20) Not estimable 0.33 (0.01, 8.20) Not estimable 0.30 (0.10, 0.87) 0.42 (0.02, 10.45) 0.31 (0.11, 0.85) 0.31 (0.12, 0.81)	2014 2020 2008 2012	M-H, Fixed, 95% Cl	

(continued)

ischemia time became significantly shorter in the SHVE group and excluding the Zhang study resulted in the hospital stay becoming significantly shorter in the SHVE group.

Subgroup analyses separating RCTs from observational studies had no effect on the meta-analysis of all outcomes, except complication rate which did not show a significant difference between the SHVE and Pringle groups in RCTs alone and hospital stay which became significantly reduced in the SHVE group.

# Methodological Quality of Included Studies

Overall, risk of bias was low for all randomized controlled trials included in this review. Double blinding was not possible as

surgeons knew whether they were performing performed SHVE or Pringle maneuver. Since knowledge of assigned intervention did not affect objectively measured post-operative endpoints, this did not add risk of observer bias. Additionally, there was no bias from missing outcome data and any deviations from intended interventions were equally distributed between both groups. Measurement of outcomes and reporting of results did not confer a significant risk of bias.

Overall, risk of bias was moderate for all observational studies. This was mainly due to issues with confounding bias as studies did not account for important variables or make reasonable adjustments to prevent this. All studies were found to have moderate risk of bias in the selection of reported

#### TABLE 3 | Continued

		SHV	E	Pring	le		Odds Ratio		Odds Ratio					
Multi-organ failure	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year	M-H, Fixed, 95% Cl					
	1.17.1 RCTs													
	Smyrniotis et al Subtotal (95% CI)	0	55 55	1	55 55	13.5% <b>13.5</b> %	0.33 [0.01, 8.21] 0.33 [0.01, 8.21]	2003						
	Total events	0		1										
	Heterogeneity: Not applicable													
	Test for overall effect:	Z = 0.68	(P = 0.5	i0)										
	1.17.2 Observational													
	Zhang et al	0	550	9	870	66.7%	0.08 [0.00, 1.42]	2012						
	Yang et al	0	120	2	153	19.9%	0.25 [0.01, 5.29]	2014						
	Subtotal (95% CI)		670		1023	86.5%	0.12 [0.02, 0.95]							
	Total events	0		11										
	Heterogeneity: Chi <sup>2</sup> =	0.29, df =	1 (P =	0.59); l² :	= 0%									
	Test for overall effect:	Z = 2.01	(P = 0.0	14)										
	Total (95% CI)		725		1078	100.0%	0.15 [0.03, 0.83]							
	Total events	0		12										
	Heterogeneity: Chi <sup>2</sup> =	0.51, df=	2 (P =	0.78); F	= 0%			F	.001 0.1 1 10 1000					
	Test for overall effect:	Z= 2.17	(P = 0.0)	(3)				U	Favours SHVE Favours Pringle					
	Test for subgroup diff	erences:	Chi <sup>2</sup> = 1	0.26, df=	1 (P=	0.61), I²=	:0%		rated softe rated stringle					

Cl, confidence interval; M-H, Mantel-Haenszel test; RCT, randomized controlled trial.

results. Zhang et al. and Yang et al. had serious issues with deviation from intended interventions. The risk of bias assessment of both RCTs and observational studies is presented in Supplementary Figure 9 (Online Resource 1).

# DISCUSSION

Mortality following major hepatic resection has markedly improved in recent years due to advancements in surgical and anesthetic techniques (1–4). Resection of tumors lying adjacent to the hepatic veins can result in major hemorrhage or venous air embolism. Therefore, hepatic vascular control has been recognized as an important aspect of reducing morbidity in these patients. Whilst portal triad clamping (Pringle maneuver) can control hepatic inflow, it does not prevent backflow from the hepatic veins. THVE may prevent massive bleeding from lacerated veins but causes significant hemodynamic disturbance due to obstruction of blood returning via the IVC. SHVE combines the advantages of both the Pringle and THVE techniques, reducing blood in the hepatic field whilst maintaining caval flow (7–14).

This systematic review and meta-analysis was conducted to compare the mortality and morbidity when using SHVE versus a Pringle maneuver in hepatectomy. Meta-analysis of the data revealed significantly decreased rates of mortality, overall complications, blood loss, blood transfusion rates, units of blood transfused, air embolism, liver failure and multiorgan failure when performing SHVE compared to a Pringle maneuver. The heterogeneity between studies for all these outcomes except blood transfusion rates were low suggesting that these outcomes are robust and reliable. Rates of hepatic vein rupture, post-operative hemorrhage, operative time, warm ischemia time, hospital stay and ICU stay were not statistically significant between the two techniques. All of these outcomes, except for hepatic vein rupture, had high heterogeneity between studies.

The results of this study are consistent with a meta-analysis reported in 2008 comparing techniques of vascular exclusion with Pringle (28). The study by Smyrniotis et al. (22) reported a subgroup analysis of SHVE versus Pringle and showed a significant decrease in blood loss and patients requiring blood transfusion in the SHVE group. There are no registered ongoing trials comparing SHVE to Pringle. Therefore, this review remains the most up to date review of the evidence.

Three of the studies in this review, including one RCT, selected patients who had tumors lying adjacent to the major hepatic veins (24–26). These studies were included the most frequently in the meta-analyses for all outcomes and therefore it is likely that these results suggest that SHVE may be a more appropriate technique to perform in this population of patients.

### Limitations

This review is limited largely by heterogeneity of included studies. Several selection bias can be identified: status of the liver pre-operatively, number and location of resected liver nodules, continuous versus intermittent Pringle maneuver, transection techniques and peri-operative chemotherapy. As chemotherapy affects the quality of the liver parenchyma and subsequently the blood loss, the lack of this information increases the heterogeneity in the results.

Although SHVE describes the technique of hepatic outflow occlusion, there are different methods in which inflow occlusion can be performed. In this review, studies were only included if they performed a Pringle maneuver as part of the hepatic inflow. This minimized the heterogeneity between the studies, but in doing so, reduced the number of good quality studies that could be included in this review. Further studies with a standardized definition of SHVE are required. This review demonstrated that rates of hepatic vein injury during both liver parenchymal and hepatic vein dissection remains comparable between Pringle and SHVE techniques. However, the studies included reported three different methods for outflow occlusion (ligation, clamping and tourniquet). Although different outflow occlusion techniques increases heterogeneity amongst the studies, this had no effect on rates of hepatic vein laceration.

SHVE is not widely practiced as it is considered technically challenging owing to the difficulty in isolating the major hepatic veins from the vena cava and the risk of injury associated with it. In clinical practice, SHVE is is much less reproducible than the Pringle maneuver, especially in centers with low volume and experience. SHVE has also become less practiced since the publication of many of these studies, partly due to the advance of the laparoscopic approach. Due to the difficulty in comparing existing variables and the low numbers of studies included in this review, wider conclusions for clinical practice cannot be drawn.

# CONCLUSION

This systematic review and meta-analysis of best available evidence revealed that performing SHVE in major hepatectomy resulted in a lower overall mortality, lower complication rates including air embolism and liver failure and lower amounts of blood loss and transfusion requirement. The results of this meta-analysis are based on few high-quality studies where tumors were adjacent to major vessels, which

## REFERENCES

- Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg. (2000) 191(1):38–46. doi: 10. 1016/S1072-7515(00)00261-1
- Jarnagin WR, Gonen M, Fong Y, DeMatteo RP, Ben-Porat L, Little S, et al. Improvement in perioperative outcome after hepatic resection: analysis of 1,803 consecutive cases over the past decade. *Ann Surg.* (2002) 236 (4):397–406. doi: 10.1097/0000658-200210000-00001
- Imamura H, Seyama Y, Kokudo N, Maema A, Sugawara Y, Sano K, et al. One thousand fifty-six hepatectomies without mortality in 8 years. *Arch Surg.* (2003) 138(11):1198–206. doi: 10.1001/archsurg.138.11.1198
- Fan ST, Mau Lo C, Poon RT, Yeung C, Leung Liu C, Yuen WK, et al. Continuous improvement of survival outcomes of resection of hepatocellular carcinoma: a 20-year experience. *Ann Surg.* (2011) 253 (4):745–58. doi: 10.1097/SLA.0b013e3182111195
- Shimada M, Matsumata T, Akazawa K, Kamakura T, Itasaka H, Sugimachi K, et al. Estimation of risk of major complications after hepatic resection. *Am J Surg.* (1994) 167:399–403. doi: 10.1016/0002-9610(94)90124-4
- Wei AC, Tung-Ping Poon R, Fan ST, Wong J. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. *Br J Surg.* (2003) 90(1):33–41. doi: 10.1002/bjs.4018
- Pringle JHV. Notes on the arrest of hepatic hemorrhage due to trauma. Ann Surg. (1908) 48(4):541–9. doi: 10.1097/00000658-190810000-00005
- Dixon E, Vollmer Jr CM, Bathe OF, Sutherland F. Vascular occlusion to decrease blood loss during hepatic resection. *Am J Surg.* (2005) 190(1): 75–86. doi: 10.1016/j.amjsurg.2004.10.007

seems the most suitable situation to utilize this technique. Due to the limitations of this review, it is difficult to draw conclusions for clinical practice. Larger studies are required to identify which groups of patients, tumors and types of resection benefit the most from the use of SHVE.

# DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

# **AUTHOR CONTRIBUTIONS**

Conception and design: TS, MS, MT. Literature search and study selection: MT, RV. Data extraction: SM, MS. Methodological appraisal: SM, MS. Statistical analysis: MB, MD, SM. Writing of the article: SM, MS. Critical revision of the article: All authors. Final approval of the article: All authors. All authors contributed to the article and approved the submitted version.

# SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fsurg.2022.860721/full#supplementary-material.

- Belghiti J, Noun R, Malafosse R, Jagot P, Sauvanet A, Pierangeli F, et al. Continuous versus intermittent portal triad clamping for liver resection: a controlled study. *Ann Surg.* (1999) 229(3):369–75. doi: 10.1097/00000658-199903000-00010
- Heaney JP, Stanton WK, Halbert DS, Seidel J, Vice T. An improved technic for vascular isolation of the liver: experimental study and case reports. *Ann Surg.* (1989) 163:237–41. doi: 10.1097/0000658-196602000-00013
- Bismuth H, Castaing D, Garden OJ. Major hepatic resection under total vascular exclusion. Ann Surg. (1989) 210:13–9. doi: 10.1097/00000658-198907000-00002
- Berney T, Mentha G, Morel P. Total vascular exclusion of the liver for the resection of lesions in contact with the vena cava or the hepatic veins. *Br J Surg.* (1998) 85:485–58. doi: 10.1046/j.1365-2168.1998.00659.x
- Delva E, Barberousse JP, Nordlinger B, Ollivier JM, Vacher B, Guilmet C, et al. Hemodynamic and biochemical monitoring during major liver resection with use of hepatic vascular exclusion. *Surgery*. (1984) 95(3): 309–18.
- Belghiti J, Noun R, Zante E, Ballet T, Sauvanet A. Portal triad clamping or hepatic vascular exclusion for major liver resection. A controlled study. Ann Surg. (1996) 224:155–61. doi: 10.1097/00000658-199608000-00007
- Elias D, Lasser P, Debaene B, Doidy L, Billard V, Spencer A, et al. Intermittent vascular exclusion of the liver (without vena cava clamping) during major hepatectomy. *Br J Surg.* (1995) 82(11):1535–9. doi: 10.1002/ bjs.1800821126
- Cherqui D, Malassagne B, Colau PI, Brunetti F, Rotman N, Fagniez PL. Hepatic vascular exclusion with preservation of the caval flow for liver resections. *Ann Surg.* (1999) 230(1):24–30. doi: 10.1097/00000658-199907000-00004

- Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan a web and mobile app for systematic reviews. Syst Rev. (2016) 5:210. doi: 10.1186/ s13643-016-0384-4
- Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. (2005) 5:13. doi: 10.1186/1471-2288-5-13
- Review Manager (RevMan) [computer program]. Version 5.4. The Cochrane Collaboration (2020).
- 20. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. (1959) 22(4):719-48.
- 21. IBM SPSS Statistics for Windows [computer program]. Version 23.0. Armonk, NY (2015).
- Smyrniotis VE, Kostopanagiotou GG, Contis JC, Farantos CI, Voros DC, Kannas DC, et al. Selective hepatic vascular exclusion versus Pringle maneuver in major liver resections: prospective study. *World J Surg.* (2003) 27(7):765–9. doi: 10.1007/s00268-003-6978-8
- Zhou W, Li A, Pan Z, Fu S, Yang Y, Tang L, et al. Selective hepatic vascular exclusion and Pringle maneuver: a comparative study in liver resection. *Eur J Surg Oncol.* (2008) 34(1):49–54. doi: 10.1016/j.ejso.2007.07.001
- 24. Zhang J, Lai EC, Zhou WP, Fu S, Pan Z, Yang Y, et al. Selective hepatic vascular exclusion versus Pringle maneuver in liver resection for tumors encroaching on major hepatic veins. *Br J Surg.* (2012) 99(7):973–7. doi: 10. 1002/bjs.8764
- 25. Yang Y, Zhao LH, Fu SY, Lau WY, Lai EC, Gu FM, et al. Selective hepatic vascular exclusion versus pringle maneuver in partial hepatectomy for liver hemangioma compressing or involving the major hepatic veins. *Am Surg.* (2014) 80(3):236–40. doi: 10.1177/000313481408000317
- 26. Si-Yuan F, Yee LW, Yuan Y, Sheng-Xian Y, Zheng-Guang W, Gang H, et al. Pringle maneuver versus selective hepatic vascular exclusion in partial hepatectomy for tumors adjacent to the hepatocaval junction: a

randomized comparative study. Int J Surg. (2014) 12(8):768-73. doi: 10. 1016/j.ijsu.2014.05.068

- 27. Tongsiri N, Siripornadulsilp S, Impool T. Comparison of early clinical outcomes between intermittent vascular inflow occlusion versus intermittent selective hepatic vascular exclusion in hepatic resections for cholangiocarcinoma patients: a prospective randomized controlled trial study. J Med Assoc Thai. (2020) 103:521–8. doi: 10.35755/jmedassocthai. 2020.06.11023
- Rahbari NN, Koch M, Mehrabi A, Weidmann K, Motschall E, Kahlert C, et al. Portal triad clamping versus vascular exclusion for vascular control during hepatic resection: a systematic review and meta-analysis. *J Gastrointest Surg.* (2009) 13(3):558–68. doi: 10.1007/s11605-008-0588-6

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Publisher's Note:** All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Mobarak, Stott, Tarazi, Varley, Davé, Baltatzis and Satyadas. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.