## Review Article Pringle maneuver versus hemihepatic blood flow occlusion during hepatectomy: a systematic review and meta-analysis

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Abstract: The Pringle maneuver (PM) and hemihepatic blood flow occlusion (HHO) are used worldwide to reduce blood loss during liver resection surgery; however, it is unknown which is the optimal technique for vascular occlusion during hepatectomy. Thus, a systematic review and meta-analysis was performed to evaluate the clinical outcomes in patients undergoing hepatectomy using the PM compared to those using the HHO technique. Methods: Two authors independently assessed trials for inclusion and independently extracted the data. Risk ratio with its 95% confidence intervals (CI) were calculated for the extracted data. Results: Eight randomized controlled trials (RCTs) involving 688 patients met the predefined inclusion criteria. A total of 343 patients were treated with PM and 345 with HHO. Meta-analysis showed HHO is better than PM groups during hepatectomy on total peri-operative morbidity (RR = 1.52, 95% CI = [1.17, 1.96], P = 0.001), qualitative transfusion (ml) (standard mean difference [SMD] = 0.45, 95% CI = [0.07, 0.83], P = 0.02), total bilirubin (TBIL) levels on the postoperative days three and seven (the third day, SMD = 0.33, 95% CI = [0.13, 0.52], P = 0.001; the seventh day, SMD = 0.31, 95% CI = [0.08, 0.54], P = 0.009), albumin (ALB) levels on the postoperative day three (SMD = -0.38, 95% Cl = [-0.57, -0.18], P < 0.001), prealbumin (PAB) levels on the postoperative days three and seven(the third day, SMD = -0.34, 95% CI = [-0.57, -0.12], P = 0.003; the seventh day, SMD = -0.39, 95% CI = [-0.68, -0.10], P = 0.008), alanine aminotransferase (ALT) on the postoperative days one, three, and seven (the first day, SMD = 0.69, 95% Cl = [0.31, 1.07], P < 0.001; the third day, SMD = 0.83, 95% CI = [0.47, 1.20], P < 0.001; the seventh day, SMD = 0.74, 95% CI = [0.50, 0.98], P < 0.001), and aspartate aminotransferase (AST) levels on the postoperative days one, three, and seven (the first day, SMD = 0.66, 95% CI = [0.46, 0.86], P < 0.001; the third day, SMD = 0.75, 95% CI = [0.42, 1.08], P < 0.001; the seventh day, SMD = 0.81, 95% CI = [0.32, 29], P = 0.001). No significant differences were found between the two groups in mortality, hepatic insufficiency, infection, bile leakage, splanchnocoel effusion, postoperative hemorrhage, qualitative transfusion (person), hospital stay, operating time, ischemic duration and operative blood loss. Conclusion: Our results suggested that the HHO technique is more efficacious compared to PM during hepatic resection surgery.

Keywords: Pringle maneuver, hemihepatic blood flow occlusion, hepatectomy

#### Introduction

Selective liver resection is performed mainly for liver tumors, hepatic trauma, and hepatolith, especially for early stage hepatocellular carcinoma [1, 2]. Despite abundant experience and advanced techniques for hepatectomy, bleeding remains the main concern during parenchymal transection [3, 4]. Bleeding has been found to increase tumor recurrence and reduce the survival rate in patients undergoing partial hepatectomy for liver malignancy [5, 6]. Besides, Blood loss and transfusions have been shown to have a deleterious impact on short- and longterm outcomes [7, 8]. Therefore, many methods of hepatic vascular control have been developed in the past decades to control intraoperative blood loss. In 1908, Pringle described the efficacy of total hepatic inflow occlusion (THO) in cases of liver trauma for the first time. The Pringle method (PM) is a technique of encircling the hepatoduodenal ligament with a tape, and

then applying a tourniquet or a vascular clamp until the hepatic arterial pulse disappears distally [9]. It has been the standard for hepatic resection surgery for a long time. The major flaw of this procedure is resultant ischemic damage of the liver and intestinal congestion, especially in patients with chronic liver diseases [10, 11]. To avoid the ischemia reperfusion injury, Makuuchi, in 1987, proposed the hemihepatic vascular occlusion (HHO) technique, which allows for normal blood supply to the contralateral hemi-liver [12]. The advantages of the HHO maneuver are no ischemic reperfusion injury to the remnant liver, avoidance of splanchnic congestion and better hemodynamic tolerability, because considerable portal blood flco is preserved and only portions of the liver are rendered ischemic and anoxic [13]. However, portal vein and artery dissection to perform selective clamping is time consuming and may result in more blood loss from the other hemi-liver, thus causing serious complications [14].

Though there are many studies and meta-analyses comparing the safety and efficacy of the PM and HHO methods [15-17], due to their small sample size, it is difficult to draw a definitive conclusion on the best technique of hepatic vascular control. The optimal method of vascular control during hepatic resection continues to be debated. The objective of this metaanalysis study was to establish the relative safety and efficacy of the HHO versus PM, or total hepatic inflow occlusion, during hepatectomy.

### Material and methods

### Literature and search strategy

Two authors independently searched Pubmed, Embase, Cochrane Library, Ovid, Web of Science Scopus, WANFANG, China National Knowledge Internet, and China Biology Medicine disc until December 2015. Details of the search strategies can be found in <u>Supplementary</u> <u>Table 1</u>. The searches were conducted in English and Chinese.

### Inclusion and exclusion criteria

The following inclusion and exclusion criteria were applied: (a) Types of studies: only randomized clinical trials (RCTs) were considered for this review. Animal studies, observational studies, basic research, retrospective studies, case-control studies, semi-random control, case reports, and cohort studies were excluded. (b) Types of participants: We focused on adults (> 18 years) who needed selective hepatectomy due primarily to liver cancer, hepatolith, or hepatic trauma, which are the most common diseases requiring hepatectomy irrespective of age, gender, cirrhosis, tumor size, and nodule numbers. (c) Types of interventions: We included trials comparing the PM versus HHO during hepatectomy irrespective of ischemic preconditioning before vascular occlusion. (d) Types of outcome measures: (a) Primary outcomes: Mortality, hepatic insufficiency, peri-operative morbidity (total infection, wound infection, bile leakage, splanchnocoel effusion, cardiac insufficiency, postoperative hemorrhage) and transfusion requirements (number of patients, volume). (b) Secondary outcomes: Hospital stay, operating time, ischemic duration, operative blood loss, markers of liver function (total bilirubin [TBIL], albumin [ALB], and prealbumin [PAB] levels) and biochemical markers of liver injury (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels).

### Data collection and quality assessment

The records from the initial search were scanned by two authors to exclude any irrelevant studies. Two authors subsequently performed a full-text review to apply the inclusion and exclusion criteria; discrepancies were resolved by the third author. All data were independently extracted by two authors, and each study's corresponding author was contacted to obtain additional information when missing or incomplete data were encountered. Study quality was estimated using an adaptation of the Cochrane Handbook for Systematic Reviews of Interventions [18] via the following characteristics: method of randomization, allocation concealment, patients' baseline characteristics, blinding, intention-to-treat analysis, and loss to follow-up.

### Statistical analysis

Statistical heterogeneity was assessed using I<sup>2</sup> [19] and *P*-value statistics, and consideration was given for appropriateness of the pooling and meta-analysis. A fixed effects model [20] was adopted if there was no evidence of signifi-



Figure 1. Flowchart of filtering of studies.

cant heterogeneity ( $I^2 \le 50\%$  and  $P \ge 0.1$ ), and a random effects model [21] was used in all other instances ( $l^2 > 50\%$  or P < 0.1). If possible, we explored the heterogeneity, and performed subgroup analyses based on patients' age, study area, and disease. Different models were used to detect sensitivity and evaluate the stability of the result. For dichotomous data, relative risk (RR) was adopted, while continuation outcomes were converted to the mean difference (MD) through the inverse variance method. Potential publication bias was evaluated by Egger's test. The meta-analysis was considered to have significant publication bias if the P-value was less than 0.05. All statistical calculations were performed by Review Manager 5.3 (Cochrane collaboration. Copenhagen). The Egger's tests were conducted using the STATA software (Version 12.0; STATA Corporation, College Station, TX, USA).

### Results

### Literature search

Our search initially reached 15798 studies, although 8974 studies were subsequently

excluded due to duplication. After a review of the titles and abstracts, we excluded an additional 6781 studies. Then, by scanning the full-text (as necessary), we further excluded 35 studies (15 animal studies, three reviews and metaanalyses, one with data repeatability, eight with no clear randomization method, and eight retrospective and cohort studies). Therefore, eight RCTs [22-29] were included in our analysis (Figure 1).

# Characteristics of included studies

Features of the eligible RCTs [22-29] are presented in **Table 1.** The RCTs were published between 2002 and 2015, involving 688 patients. All the trials compared HHO (n = 345) with PM (n = 343). Five papers

[22-24, 26, 27] were written in English while the other three [25, 28, 29] were in Chinese. Seven [22-27, 29] concluded that HHO is better than PM during hepatectomy except one trial [28] that did not provide a conclusion either way. Patients were generally well-matched in the studies according to sex, age and the tumor size.

### Risk of bias in included studies

The risk of bias in the included studies is summarized in **Figure 2** and **Table 2**. They include randomization, allocation concealment, patients' baseline characteristics, blinding, intention-to-treat analysis and loss to follow-up.

### Primary outcomes

### <u>Mortality</u>

Mortality was defined as death that occurred within 30 days after the operation or during the same hospitalization. Four studies [22-24, 28] including 350 patients reported mortality. The fixed model showed no difference between groups (RR = 1.02, 95% confidence interval [CI]

First author (yrs.)	Journal	Sample size (n)	PM/ HHO (n)	Age (mean yrs.) PM/ HHO	Sex (male: female) PM/ HHO	Tumor size (mean yrs.) PM/HHO	Outcome
Figueras J (2005)	Ann Surg	80	39/41	61.8/62	31:8/28:13	ND	HHO > PM
Wu CC (2002)	Arch Surg	58	28/30	53.2/57.5	23:5/25:5	9.3/8.8	HHO > PM
Fu SY (2011)	Am J Surg	120	60/60	48.6/49.3	46:14/41:19	6.8/6	HHO>PM
Liang G (2009)	Hepatogastroenterology	80	40/40	49.55/49.40	27:13/31:9	6.93/7.58	HHO > PM
Ni JS (2013)	J Gastrointest Surg	120	60/60	55.2/56.1	45:15/47:13	5.4/4.7	HHO > PM
Xiao J (2015)	Chin J Clinical Rational Drug Use	100	50/50	51.8/50.8	28:22/29:21	ND	HHO > PM
Luo Y (2011)	Chin J postgrad Med	60	31/29	50.5/51.3	ND	ND	HHO > PM
Wu ZY (2014)	Chin J Hepatopancreatobiliary Surgery	70	35/35	ND	ND	ND	ND
Total	-	688	343/345	-	-	-	-

Table 1. Characteristics of included studies

PM: Pringle maneuver; HHO: Hemihepatic vascular occlusion; ND: The study did not describe.



Figure 2. Flowchart of risks of bias.

= [0.14, 7.25], P = 0.98) without significant heterogeneity (P = 0.35, I<sup>2</sup> = 0%) (**Figure 3A**).

### Hepatic insufficiency

Hepatic insufficiency was defined as the presence of serum bilirubin levels greater than 50  $\mu$ mol/L on postoperative day seven or thereafter or prothrombin time less than 50% of normal, or encephalopathy. Six studies [22-26, 28] including 530 patients reported severe liver dysfunction. The fixed model showed there was no difference between groups (RR = 2.11, 95% CI = [0.84, 5.31], P = 0.11) without significant heterogeneity (P = 0.33, I<sup>2</sup> = 14%) (**Figure 3B**).

### Peri-operative morbidity

Peri-operative morbidity was defined as complications that occurred within thirty days after the operation or during the same hospitalization. Seven trials [22-24, 26-29] including 628 patients reported peri-operative morbidity. The fixed model showed, without significant heterogeneity (P = 0.37,  $l^2 = 7\%$ ), that the PM group had a statistically significant, higher rate of peri-operative morbidity than the HHO group

# $(\mathsf{RR} = 1.52, \ 95\% \ \mathsf{CI} = [1.17, \ 1.96], \ \mathsf{P} = 0.001) \ (\textbf{Figure 3C}).$

Infection: Infection referred to any infection documented in the postoperative period, including wound infection, which means an infection in the tissues of the incision and operative area. Four trials [23, 26, 27, 29] including 398 patients reported total infection, and three studies [23, 26, 27] with

298 patients reported wound infection. There was no significant heterogeneity (total infection: P = 0.19,  $I^2 = 36\%$ , wound infection: P = 0.44,  $I^2 = 0\%$ ). And the fixed model showed both parameters were not significantly different between the two groups (total infection: RR = 1.12, 95% CI = [0.53, 2.37], P = 0.77; wound infection: RR = 1.02, 95% CI = [0.28, 3.75], P = 0.97) (Figure 3D, 3E).

*Bile leakage:* Bile leakage was defined as any drainage through the catheter with a bilirubin content higher than that in the plasma. Seven studies [22-24, 26-29] including 628 patients reported bile leakage. The fixed model showed there was no difference between the two groups (RR = 1.22, 95% CI = [0.64, 2.34], P = 0.55) without significant heterogeneity (P = 0.87,  $l^2 = 0\%$ ) (**Figure 3F**).

Splanchnocoel effusion: Pleural effusion was defined as a fluid collection that required pleuracentesis to be controlled. Postoperative ascites was defined as an abdominal output greater than 500 ml/d or ascites that required treatment to be controlled. Five trials [23, 24,

First author (yrs.)	Randomization	Random sequence	Allocation concealment	Patient baseline characteristics	Blinding	Intention- to-treat analysis	Follow- up
Figueras J (2005)	Yes	Sortition and stratification	Yes	Yes	Single	Yes	100%
Wu CC (2002)	Yes	Sortition	Yes	Yes	ND	Yes	100%
Fu SY (2011)	Yes	Sortition	Yes	Yes	ND	Yes	100%
Liang G (2009)	Yes	ND	ND	Yes	ND	Yes	100%
Ni JS (2013)	Yes	Sortition	Yes	Yes	ND	Yes	100%
Xiao J (2015)	Yes	Dice rolling	ND	Yes	ND	Yes	100%
Luo Y (2011)	Yes	Randomized number table	ND	Yes	ND	Yes	100%
Wu ZY (2014)	Yes	Computer randomization	ND	Yes	ND	Yes	100%

 Table 2. Risk of bias of included studies

ND: The study did not describe.

26, 27, 29] including 478 patients reported pleural effusion, and six trials [22-24, 26, 27, 29] including 558 patients reported ascites. There was no significant heterogeneity (pleural effusion: P = 0.87,  $I^2 = 0\%$ ; ascites: P = 0.82,  $I^2 = 0\%$ ) and the fixed model showed both of the parameters were not significantly different between the two groups (pleural effusion: RR = 1.42, 95% CI = [0.79, 2.55], P = 0.24; ascites: RR = 1.31, 95% CI = [0.67, 2.58], P = 0.43) (Figure 4A, 4B).

Postoperative hemorrhage: Postoperative hemorrhage was defined as bleeding after a surgical procedure. Five trials [23, 25-28] including 428 patients reported total bleeding, and two trials [27, 28] including 128 patients reported gastrointestinal bleeding. There was no significant heterogeneity (total bleeding: P = 0.96, I<sup>2</sup> = 0%; gastrointestinal bleeding: P = 0.58, I<sup>2</sup> = 0%) and the fixed model showed both of the parameters were not significantly different between the two groups (total bleeding: RR = 2.17, 95% CI = [0.63, 7.50], P = 0.22; gastrointestinal bleeding: RR = 1.72, 95% CI = [0.24, 12.55], P = 0.59) (Figure 4C, 4D).

Qualitative transfusion (person): Blood transfusion was performed when intraoperative hematocrit was less than 0.24 in patients with normal cardiopulmonary function or below 0.27 in patients aged 70 years or older or with correctable heart or lung diseases. This was continued until the early postoperative period, when fresh frozen plasma, albumin, or both were infused to keep the serum albumin level at 30 g/L or higher. Five studies [22-24, 26, 27] including 458 patients reported this parameter. The fixed model showed no difference between the two groups (RR = 1.14, 95% Cl = [0.77, 1.68], P = 0.53) without significant heterogeneity (P = 0.27,  $I^2$  = 22%) (**Figure 4E**).

*Quantitative Transfusion (ml):* Five studies [22-24, 26, 29] including 500 patients reported this parameter. The random model showed the PM group had statistically significant more blood transfusions than the HHO group (standard mean difference [SMD] = 0.45, 95% CI = [0.07, 0.83], P = 0.02) with significant heterogeneity (P = 0.001, I<sup>2</sup> = 78%) (Figure 4F).

### Secondary outcomes

### Hospital stay (day)

Hospital stay was defined as the length of stay of the patient at the hospital. Four studies [22-24, 27] including 338 patients reported this parameter. The random model showed no difference between the two groups (SMD = -0.03, 95% CI = [-0.75, 0.69], P = 0.94) with significant heterogeneity (P < 0.001, I<sup>2</sup> = 90%) (**Figure 5A**).

# Operation time (min) and ischemic duration (min)

Operation time was measured from the beginning to the end of liver transection. Seven trials [22-24, 26-29] with 628 patients reported the operation time. Due to significant heterogeneity (P < 0.001, I<sup>2</sup> = 79%), the random model was applied, and no significant difference was found between the two groups (SMD = -0.21, 95% CI = [-0.57, 0.14], P = 0.24) (**Figure 5**). Ischemic duration was defined as the total time required for the administration of the PM for the PM group, from the beginning of the ipsilateral portal vein and the artery occlusion to the release of the portal vein and the artery for the

Α		Total hepatic inflow occlusio	on (THO)	Hemihepatic vascular occ	clusion (HHO)		<b>Risk Ratio</b>		Risk Ratio	
· ^ _	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
	Figueras, J 2005	0	39	1	41	74.5%	0.35 [0.01, 8.34]			
	Fu, SY 2011	1	60	0	60	25.5%	3.00 [0.12, 72.20]			
	Liang, GL 2009	0	40	0	40		Not estimable			
	Wu, ZY 2014	0	35	0	35		Not estimable			
	Total (95% CI)		174		176	100.0%	1.02 [0.14, 7.25]			
	Total events	1		1						
	Heterogeneity: Chi <sup>2</sup> = I	0.88, df = 1 (P = 0.35); l <sup>2</sup> = 0%						0.001	01 1 10	1000
	Test for overall effect: 2	Z = 0.02 (P = 0.98)						0.001	Favours [THO] Favours [HHO]	1000
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в	Charles California	I otal hepatic inflow occlusion	on (THO)	Heminepatic vascular oc	clusion (HHO)	Intellected	RISK Ratio		RISK Ratio	
-	Study of Subgroup	Events	Total	Events	Total	50.00	M-H, FIXed, 95% CI	-	M-H, FIXEd, 95% CI	
	Figueras, J 2005	0	39	3	41	2 000	0.15 [0.01, 2.81]			
	Liang GL 2009	2	40	1	40	15 6%	3.00 [0.12, 72.20]			
	Luo V 2011	0	31	0	29	15.0%	Not estimable			
	Ni .IS 2013	1	60	0	60	7.8%	3 00 0 12 72 201			
	Wu ZY 2014	7	35	1	35	15.6%	7 00 10 91 53 951			
						10.070				
	Total (95% CI)		265		265	100.0%	2.11 [0.84, 5.31]		-	
	Total events	12		5						
	Heterogeneity: Chi <sup>2</sup> =	4.64, df = 4 (P = 0.33); I <sup>2</sup> = 14%	5					0.002	01 1 10	500
	Test for overall effect:	Z = 1.58 (P = 0.11)						0.002	Favours [THO] Favours [HHO]	500
-										
С		Total hepatic inflow occlusi	on (THO)	Hemihepatic vascular oc	clusion (HHO)		Risk Ratio		Risk Ratio	
	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M-H, Fixed, 95% Cl	
	Figueras, J 2005	15	39	12	41	16.6%	1.31 [0.71, 2.44]		and the second	
	FU, SY 2011	19	60	12	60	17.1%	1.58 [0.85, 2.97]		1 miles - 1 mile	
	Liang, GL 2009	24	40	12	40	10.5%	1 95 [1 04 2 27]			
	Mu CC 2002	24	28	10	30	13 7%	0.86 (0.40, 1.86)			
	Wu, ZY 2014	17	35	10	35	14.2%	1.70 [0.91, 3.18]			
	Xiao, J 2015	15	50	5	50	7.1%	3.00 [1.18, 7.63]			
				-						
	Total (95% CI)		312		316	100.0%	1.52 [1.17, 1.96]		•	
	Total events	106		71						
	Heterogeneity: Chi <sup>2</sup> =	6.48, df = 6 (P = 0.37); I <sup>2</sup> = 7%						0.05	0.2 1 5	20
	Test for overall effect:	Z = 3.18 (P = 0.001)							Favours [THO] Favours [HHO]	
Б		Total bonatic inflow occlusi	on (THO)	Hamihanatia wascular oc	alusion (UUO)		Diek Datio		<b>Bick Batic</b>	
υ	Study or Subgroup	Evente	Total	Evente	Total	Weight	M H Eived 05% CL		M H Fixed 95% CI	
	Ful SY 2011	2	60	1	60	8 5%	2 00 10 19 21 471		11.11.20, 35 / Cl	
	Ni JS 2013	2	60	1	60	8.5%	2.00 [0.19, 21.47]			
	Wu, CC 2002	3	28	8	30	65.9%	0.40 [0.12, 1.36]			
	Xiao, J 2015	6	50	2	50	17.1%	3.00 [0.64, 14.16]			
	1.1									
	Total (95% CI)		198		200	100.0%	1.12 [0.53, 2.37]		<b>•</b>	
	Total events	13		12						
	Heterogeneity: Chi <sup>2</sup> =	4.71, df = 3 (P = 0.19); I <sup>2</sup> = 369	6					0.002	0.1 1 10	500
	Test for overall effect:	Z = 0.29 (P = 0.77)							Favours [THO] Favours [HHO]	
-		Total banadia influence and	THON	Hamilton Hannahan			Diale Datis		Dials Datia	
E	Study or Subgroup	Fuente	Total	Fuente	Total	Weight	M H Eived 05% CI		M H Eived 95% Cl	
	Ful SY 2011	2	60	1	60	22.6%	2 00 00 19 21 471			
	Ni, JS 2013	2	60	1	60	22.6%	2.00 (0.19, 21, 47)		<b>_</b>	
	Wu, CC 2002	0	28	2	30	54.7%	0.21 [0.01, 4.27]			
	Total (95% CI)		148		150	100.0%	1.02 [0.28, 3.75]		-	
	Total events	4		4						
	Heterogeneity: Chi <sup>2</sup> =	1.66, df = 2 (P = 0.44); I <sup>2</sup> = 0%						0.002	0.1 1 10	500
	Test for overall effect:	Z = 0.03 (P = 0.97)							Favours [THO] Favours [HHO]	
-		Total banatic inflaw cookie	in (THO)	Hamiltonatio una cular ou	achusian (IIIIO)		Diale Datio		Diel: Datie	
F	Study or Subarous	Funte	Total	Evente	Total	Weight	MH Fixed 05% C		MH Fixed 05% CI	
	Figuerae 12005	Events	20	Lvents 0	41	3 2%	2 15 10 12 75 09		m-n, rixed, 55% Cl	
	Fu. SY 2011	2	59	2	60	131%	1.00 [0.15, 75.08]			
	Liang, GL 2009	1	40	2	40	13.1%	0.50 [0.05, 5.30]			
	Ni, JS 2013	4	60	3	60	19.6%	1.33 [0.31, 5.70]			
	Wu, CC 2002	4	28	5	30	31.5%	0.86 [0.26, 2.87]			
	Wu, ZY 2014	2	35	2	35	13.1%	1.00 [0.15, 6.71]			
	Xiao, J 2015	4	50	1	50	6.5%	4.00 [0.46, 34.54]		2 A Kar	
			1000							
	Total (95% CI)		312		316	100.0%	1.22 [0.64, 2.34]		<b>T</b>	
	I otal events	18 2 40 df = 6 /D = 0.07\-12 - 00		15				+	Y	
	Test for overall effect	- 2.46, 01 = 0 (F = 0.87); F = 0%	,					0.002	0.1 1 10	500
	reactor overall ellect	. 2 = 0.00 (P = 0.00)							Favours [THO] Favours [HHO]	

**Figure 3.** Forest plots of the Pringle maneuver (PM) versus hemihepatic blood flow occlusion (HHO) during hepatectomy. They are mortality (A), hepatic insufficiency (B), peri-operative morbidity (C), total infection (D), wound infection (E) and bile leakage (F) respectively.

HHO group. Eight studies [22-29] with 688 patients reported the ischemic duration. The random model showed no difference between the two groups (SMD = 0.09, 95% CI = [-0.15, 0.32], P = 0.46) with significant heterogeneity (P = 0.02,  $I^2 = 58\%$ ) (Figure 5B, 5C).

#### Operative blood loss (ml)

Blood loss was measured by estimating the weight of the soaked gauze and the blood collected in the suction apparatus containers. Five studies [22-24, 28, 29] including 450 patients

А		Total hepatic inflow of	cclusion (THO)	Hemihepatic v	ascular occl	usion (HHO)		<b>Risk Ratio</b>		Risk Ratio	
· ` .	Study or Subgroup	Events	Total	E	vents	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl	
	Fu, SY 2011	10	60		8	60	47.2%	1.25 [0.53, 2.95]			
	Liang, GL 2009	1	40		2	40	11.8%	0.50 [0.05, 5.30]			
	Ni, JS 2013	9	60		5	60	29.5%	1.80 [0.64, 5.06]			
	Wu, CC 2002	2	28		1	30	5.7%	2.14 [0.21, 22.35]			
	Xiao, J 2015	2	50		1	50	5.9%	2.00 [0.19, 21.36]		20 A 80 A	
	Total (95% CI)		238			240	100.0%	1.42 [0.79, 2.55]		•	
	Total events	24	200		17	210				-	
	Heterogeneity: Chi2 =	1.24, df = 4 (P = 0.87); I	<sup>2</sup> = 0%						+		-
	Test for overall effect:	Z = 1.17 (P = 0.24)							0.002		500
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В		Total hepatic inflow of	occlusion (THO)	Hemihepatic	ascular occl	usion (HHO)		Risk Ratio		Risk Ratio	
	Study or Subgroup	Events	Total	E	vents	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl	
	Figueras, J 2005	3	39		4	41	28.2%	0.79 [0.19, 3.30]			
	Liang GL 2009	2	40		2	40	14 5%	1.00 [0.06, 15.62]			
	Ni . IS 2013	2 8	40		4	40	28 9%	2 00 0 64 6 29			
	Wu CC 2002	1	28		2	30	14.0%	0.54 (0.05, 5.59)			
	Xiao, J 2015	3	50		1	50	7.2%	3.00 [0.32, 27,87]			
								,			
	Total (95% CI)		277			281	100.0%	1.31 [0.67, 2.58]		+	
	Total events	18			14				12		15
	Heterogeneity: Chi <sup>2</sup> =	2.21, df = 5 (P = 0.82);	²=0%						0.002	0.1 1 10	500
	Test for overall effect:	Z = 0.78 (P = 0.43)								Favours [THO] Favours [HHO]	
~		Total honatic inflow	colucion (THO)	Homibonatic	accular occl	ucion (UUO)		Dick Patio		Pick Patio	
C	Study or Subaroup	Events	Total	E	vents	Total	Weight	M-H. Fixed, 95% Cl		M-H. Fixed, 95% Cl	
	Fu. SY 2011	1	60		0	60	14.4%	3.00 [0.12, 72,20]			
	Luo, Y 2011	0	31		0	29		Not estimable			
	Ni, JS 2013	1	60		0	60	14.4%	3.00 [0.12, 72.20]			
	Wu, CC 2002	1	28		0	30	13.9%	3.21 [0.14, 75.61]			
	Wu, ZY 2014	3	35		2	35	57.4%	1.50 [0.27, 8.43]			
	Tatal (OFM CD		244			244	100.00	2 47 10 62 7 501			
	Total (95% CI)	c	214		2	214	100.0%	2.17 [0.63, 7.50]			
	Heterogeneitr Chi <sup>2</sup> =	0.31  df = 3 (P = 0.96)	<sup>2</sup> = 0%		2				+	T T	
	Test for overall effect:	Z = 1.22 (P = 0.22)	- 0 /0						0.002	0.1 1 10	500
		,								Favours [THO] Favours [HHO]	
D		Total hepatic inflow	occlusion (THO)	Hemihepatic	vascular occl	lusion (HHO)		Risk Ratio		Risk Ratio	
_	Study or Subgroup	Events	Total	E	vents	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% Cl	
	Wu, CC 2002	1	28		0	30	32.6%	3.21 [0.14, 75.61]			
	VVu, ZY 2014	1	35		1	35	67.4%	1.00 [0.07, 15.36]			
	Total (95% CI)		63			65	100.0%	1.72 [0.24, 12,55]			
	Total events	2			1						
	Heterogeneity: Chi <sup>2</sup> =	0.30, df = 1 (P = 0.58);	l <sup>2</sup> = 0%						-		
	Test for overall effect	Z = 0.53 (P = 0.59)							0.002	Eavours [THO] Eavours [HHO]	500
_											
Е	Chudu on Cubanaun	Total hepatic inflow	occlusion (THO)	Hemihepatic	ascular occl	usion (HHO)	Malabe	Risk Ratio		Risk Ratio	
	Study of Subgroup	Events	20		ents	10101	16 4%	0 70 10 21 2 201		M-H, FIXed, 95% CI	
	Figueras, 5 2005	4	60		4	60	11 2%	1 50 [0.21, 2.30]			
	Liang GL 2009	14	40		15	40	42.0%	0.93 [0.52, 1.67]			
	Ni, JS 2013	4	60		6	60	16.8%	0.67 [0.20, 2.24]			
	Wu, CC 2002	12	28		5	30	13.5%	2.57 [1.04, 6.37]			
	Wu, CC 2002	12	28		5	30	13.5%	2.57 [1.04, 6.37]			
	Wu, CC 2002 Total (95% CI)	12	28		5	30 231	13.5% 100.0%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68]		+	
	Wu, CC 2002 Total (95% CI) Total events	12 40	28 227		5 36	30 231	13.5% 100.0%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68]		•	
	Wu, CC 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> =	12 40 5.13, df = 4 (P = 0.27);	28 227 1 <sup>2</sup> = 22%		5 36	30 231	13.5% 100.0%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68]	0.005	0.1 1 10	200
	Wu, CC 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect:	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53)	28 227 <sup>2</sup> = 22%		5 36	30 231	13.5%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68]	0.005	0.1 1 10 Favours [THO] Favours [HHO]	200
F	Wu, CC 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect:	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow o	28 227 <sup>12</sup> = 22% cclusion (THO)	Hemihepatic v	5 36 rascular occlu	30 231 usion (HHO)	13.5% 100.0%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference	0.005	0.1 1 10 Favours [HHO] Favours [HHO] Std. Mean Difference	200
F	Wu, CC 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study or Subgroup	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow on Mean	28 227 F = 22% Colusion (THO) SD Total	Hemihepatic v Mean	5 36 ascular occlu SD	30 231 usion (HHO) Total	13.5% 100.0% Weight	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference IV, Random, 95% C	0.005	0.1 1 10 Favours [THO] Favours [HHO] Std. Mean Difference IV. Random, 95% CL	200
F	Wu, CC 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>a</sup> = Test for overall effect: <u>Study or Subgroup</u> Figueras, J 2005	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow on <u>Mean</u> 72	28 227 F = 22% Colusion (THO) SD Total 200 39	Hemihepatic v Mean 68	5 36 ascular occlu SD 180	30 231 usion (HHO) <u>Total</u> 41	13.5% 100.0% Weight 19.3%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference <u>IV. Random, 95% C</u> 0.02 [-0.42, 0.46	0.005	0.1 1 10 Favours [THO] Favours [HHO] Std. Mean Difference IV. Random. 95% CI	200
F	Wu, CC 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: <u>Study or Subgroup</u> Figueras, J 2005 Fu, SY 2011	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow or <u>Mean</u> 72 260	28 227 F = 22% SD Total 200 39 20 60	Hemihepatic v Mean 68 240	5 36 ascular occlu <u>SD</u> 180 100	30 231 usion (HHO) <u>Total</u> 41 60	13.5% 100.0% Weight 19.3% 21.0%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference <u>IV. Random, 95% C</u> 0.02 [-0.42, 0.46 0.28 [-0.08, 0.64	0.005	0.1 1 10 Favours [THO] Favours [HHO] Std. Mean Difference IV. Random, 95% Cl	200
F	Wu, CC 2002 Total (95% CI) Total events Heterogeneity. Chi≇= Test for overall effect <u>Study or Subaroup</u> Figueras, J 2005 Fu,SY 2011 Ling, GL 2009	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow on Mean 72 260 592,86 381	28 227 P = 22% Colusion (THO) SD Total 200 39 20 60 .22 40	Hemihepatic v <u>Mean</u> 68 240 546.67	5 36 ascular occlu SD 180 100 232.58	30 231 usion (HHO) <u>Total</u> 41 60 40	13.5% 100.0% Weight 19.3% 21.0% 19.3%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference IV. Random. 95% C 0.28 [-0.88, 0.64 0.28 [-0.88, 0.64 0.14 [-0.29, 0.58	0.005	0.1 1 10 Favours [THO] Favours [HHO] Std. Mean Difference IV, Random, 95% CI	200
F	Wu, CC 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>2</sup> = Test for overall effect: Study or Subaroup Figueras, J 2005 Fu, SY 2011 Liang, GL 2009 Ni, JS 2013 Yoo 12015	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow o <u>Mean</u> 72 260 592.86 381 280 611 2 592.86	28 227 F = 22% SD Total 200 39 20 60 22 40 80 60 06 50	Hemihepatic v Mean 68 240 546.67 240	5 36 ascular occlu SD 180 100 232.58 40 200 1	30 231 usion (HHO) <u>Total</u> 41 60 40 60	13.5% 100.0% Weight 19.3% 21.0% 19.3% 20.9%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference <u>IV. Random, 95% C</u> 0.02 [-0.42, 0.46 0.28 [-0.08, 0.64 0.14 (-0.29, 0.58 0.63 [0.26, 1.00 1.45 [-0.29, -52]	0.005	0.1 1 10 Favours (THO) Favours (HHO) Std. Mean Difference IV, Random, 95% Cl	200
F	Wu, CC 2002 Total (95% CI) Total events Heterogeneity: Chi <sup>#</sup> = Test for overall effect: <u>Study or Subaroup</u> Figueras, J 2005 Fu, SY 2011 Liang, GL 2009 Ni, JS 2013 Xiao, J 2015	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow on Mean 72 260 592.86 381 280 611.2 15	28 227 227 228 200 20 20 20 20 20 20 20 20 20 20 20 20	Hemihepatic v Mean 68 240 546.67 240 405.2	5 36 ascular occlu SD 180 100 232.58 40 200.1	30 231 <u>Total</u> 41 60 40 60 50	13.5% 100.0% <u>Weight</u> 19.3% 21.0% 19.3% 20.9% 19.6%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference <u>IV. Random. 95%</u> C 0.02 [-0.42, 0.46 0.28 [-0.08, 0.44 0.14 [-0.29, 0.58 0.63 [0.26, 1.00 1.15 [0.73, 1.58]	0.005	0.1 1 10 Favours [THO] Favours [HHO] Std. Mean Difference IV. Random, 95% Cl	200
F	Wu, CC 2002 Total (95% CI) Total events Heterogeneity. Chi <sup>2</sup> = Test for overall effect: <u>Study or Subaroup</u> Figueras, J 2005 Fu, SY 2011 Liang, GL 2009 Ni, JS 2013 Xiao, J 2015 Total (95% CI)	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow or <u>Mean</u> 72 260 592.86 381 280 611.2 15	28 227 P <sup>2</sup> = 22% cclusion (THO) <u>SD Total</u> 20 60 22 40 80 60 0.6 50 249	Hemihepatic v Mean 68 240 546.67 240 405.2	5 36 ascular occlu 50 180 100 232.58 40 200.1	30 231 2500 (HHO) Total 41 60 40 60 50 251	13.5% 100.0% Weight 19.3% 21.0% 19.3% 20.9% 19.6% 100.0%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference IV. Random, 95% C 0.02 [-0.42, 0.46 0.28 [-0.08, 0.64 0.14 [-0.29, 0.58 0.63 [0.73, 1.58 0.45 [0.07, 0.83	0.005	0.1 1 10 Favours [THO] Favours [HHO] Std. Mean Difference IV. Random, 95% CI	200
F	Wu, CC 2002           Total (95% CI)           Total events           Heterogeneity: ChiP =           Test for overall effect:           Study of Subgroup           Figueras, J 2005           Fu, SY 2011           Liang, GL 2009           NI, JS 2013           Xiao, J 2015           Total (95% CI)           Heterogeneity: Tai <sup>2</sup> =	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow or Mean 72 280 592.86 381 280 611.2 15 0.15; Chi <sup>2</sup> = 17.92, df = 4	28 227 P = 22% cclusion (THO) <u>SD</u> Total 20 60 .22 40 80 60 0.6 50 249 (P = 0.001); F= 71	Hemihepatic 1 Mean 68 240 546.67 240 405.2	5 36 ascular occlu SD 180 100 232.58 40 200.1	30 231 rsion (HHO) <u>Total</u> 41 60 60 50 251	13.5% 100.0% 19.3% 21.0% 19.3% 20.9% 19.6% 100.0%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference IV. Random, 95% C 0.28 [-0.88, 0.64 0.28 [-0.08, 0.64 0.14 [-0.29, 0.58 0.63 [0.26, 1.00 1.15 [0.73, 1.58 0.45 [0.07, 0.83]	0.005	0.1 1 10 Favours [HHO] Favours [HHO] Std. Mean Difference IV, Random, 95% CI	200
F.	Wu, CC 2002 Total (95% CI) Total events Heterogeneity. Chi <sup>a</sup> = Test for overall effect: Study or Subaroup Figueras, J 2005 Fu, SY 2011 Liang, OL 2009 Ni, JS 2013 Xiao, J 2015 Total (95% CI) Heterogeneity. Tau <sup>a</sup> = Test for overall effect 2	12 40 5.13, df = 4 (P = 0.27); Z = 0.63 (P = 0.53) Total hepatic inflow o Mean 72 260 592.86 381 280 611.2 15 0.15; Chi <sup>2</sup> = 17.92, df = 4 Z = 2.29 (P = 0.02)	28 227 P = 22% SD Total 200 39 20 60 80 60 0.6 50 249 (P = 0.001); P = 74	Hemihepatic v Mean 68 240 546.67 240 405.2	5 36 <b>ascular occlu</b> 5D 180 100 232.58 40 200.1	30 231 sision (HHO) Total 41 60 40 60 50 251	13.5% 100.0% 19.3% 21.0% 19.3% 20.9% 19.6% 100.0%	2.57 [1.04, 6.37] 1.14 [0.77, 1.68] Std. Mean Difference IV. Random, 95% C 0.02 [0.42, 0.46 0.28 [0.08, 0.64 0.14 [-0.29, 0.58 0.63 [0.26, 1.00 1.15 [0.73, 1.58 0.45 [0.07, 0.83]	0.005	0.1 1 10 Favours [THO] Favours [HHO] Std. Mean Difference IV. Random, 95% CI	200

**Figure 4.** Forest plots of the Pringle maneuver (PM) versus hemihepatic blood flow occlusion (HHO) during hepatectomy. They are pleural effusion (A), ascites (B), total bleeding (C), gastrointestinal bleeding (D), qualitative transfusion (person) (E), quantitative transfusion (ml) (F) respectively.

reported this parameter. The data showed no difference between the two groups (SMD = -0.02, 95% Cl = [-0.32, 0.27], P = 0.88) with significant heterogeneity (P = 0.04, I<sup>2</sup> = 59%) (**Figure 5D**).

### Markers of liver function: TBIL (µmol/L), ALB (g/L), PAB (g/L)

Four studies [23, 26, 28, 29] including 410 patients reported TBIL of the first and third

days after operation, and three trials [23, 28, 29] with 290 patients reported TBIL of the seventh day post-operation. TBIL level on the first day showed significant heterogeneity (P = 0.03,  $I^2 = 67\%$ ), and the random model showed no significant difference between the two groups (SMD = 0.17, 95% CI = [-0.17, 0.52], P = 0.33). There was no significant heterogeneity about the parameters of the third (P = 0.73,  $I^2 = 0\%$ ) and seventh (P = 0.59,  $I^2 = 0\%$ ) days after oper-

А		Total hepatic in	flow occlusion	(THO)	Hemihepatic v	ascular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
· · .	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Figueras, J 2005	9.38	4.9	39	8.15	3.8	41	25.2%	0.28 [-0.16, 0.72]	1-
	Fu, SY 2011	13.7	5.2	60	10.2	4.1	60	25.9%	0.74 [0.37, 1.11]	
	Liang, GL 2009	9.85	3.55	40	10.12	2.41	40	25.2%	-0.09 [-0.53, 0.35]	
	Wu, CC 2002	14.8	1.4	28	16.4	1.4	30	23.8%	-1.13 [-1.68, -0.57]	
	Total (95% CI)			167			171	100.0%	.0.03 [.0 75 0 69]	-
	Heterogeneity Tau? -	0.49 Chi2 = 31.43	7 df = 3 (P < 0 )	00001) 12-	90%		1/1	100.0%	-0.05 [-0.15, 0.09]	<del> </del>
	Test for overall effect	Z = 0.08 (P = 0.94	) )							-2 -1 0 1 2 Favours [THO] Favours [HHO]
в		Total hepatic in	flow occlusion	(THO)	Hemihepatic v	ascular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
Ξ.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Figueras, J 2005	207	48	39	219	45	41	14.2%	-0.26 [-0.70, 0.18]	
	Fu, SY 2011	114.2	37.2	60	133.5	44.6	60	15.2%	-0.47 [-0.83, -0.10]	
	Liang, GL 2009	203.98	38.36	40	236.15	49.2	40	14.0%	-0.72 [-1.18, -0.27]	
	Ni, JS 2013	116	65	60	136	45	60	15.3%	-0.36 [-0.72, 0.01]	
	Wu, CC 2002	409.2	19.2	28	399	15.6	30	12.9%	0.58 [0.05, 1.10]	
	WU, ZY 2014	123.1	15.2	35	130.1	23.8	30	13.0%	-0.04 [-1.13, -0.16]	
	XIa0, J 2015	295	181.8	50	225.0	141	50	14.8%	0.42 [0.03, 0.82]	
	Total (95% CI)			312			316	100.0%	-0.21 [-0.57, 0.14]	•
	Heterogeneity: Tau <sup>2</sup> =	0.18: Chi <sup>2</sup> = 28.98	6. df = 6 (P < 0.0	0001): 17 =	79%		010	1001011		
	Test for overall effect:	Z = 1.18 (P = 0.24	)							-2 -1 0 1 2 Favours [THO] Favours [HHO]
С		Total hepatic in	flow occlusion	(THO)	Hemihepatic v	ascular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
-	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Figueras, J 2005	41	14	39	47	18	41	12.3%	-0.37 [-0.81, 0.07]	
	Fu, SY 2011	16.6	8.7	60	14.9	4.5	60	14.5%	0.24 [-0.12, 0.60]	1
	Liang, GL 2009	40.17	13.3	40	42.38	12.79	40	12.4%	-0.17 [-0.61, 0.27]	
	Luo, Y 2011	35	15	31	26	19	29	10.6%	0.52 [0.01, 1.04]	
	NI, JS 2013	21	11	60	19	7	60	14.5%	0.22 [-0.14, 0.57]	
	WU, CC 2002	96	10.9	28	94.2	9.9	30	10.6%	0.17 [-0.35, 0.69]	
	Viao 12014	13.6	3.5	35	15.2	4.4	35	11.6%	-0.40 [-0.87, 0.08]	
	Ald0, J 2015	24.9	4.0	50	21.8	8.6	50	13.5%	0.45 [0.05, 0.84]	
	Total (95% CI)			343			345	100.0%	0.09 [-0.15, 0.32]	+
	Heterogeneity Tau <sup>2</sup> =	0.06: Chi <sup>2</sup> = 16.54	4. $df = 7 (P = 0.0)$	12): 12 = 58	*		545			
	Test for overall effect	Z = 0.74 (P = 0.46	0							-2 -1 0 1 2
										Favours [THO] Favours [HHO]
D		Total hepatic in	flow occlusion	(THO)	Hemihepatic v	ascular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
۲.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Figueras, J 2005	671	533	39	735	397	41	19.3%	-0.14 [-0.57, 0.30]	
	Fu, SY 2011	339.5	205.1	60	354.4	240.3	60	22.6%	-0.07 [-0.42, 0.29]	-
	Liang, GL 2009	569.8	285.56	40	649.35	279.05	40	19.2%	-0.28 [-0.72, 0.16]	
	Wu, ZY 2014	323.4	115	35	347.1	98.9	35	18.1%	-0.22 [-0.69, 0.25]	
	Xiao, J 2015	370	141.7	50	301.2	112	50	20.8%	0.53 [0.14, 0.93]	
	Total (05% CD			224			320	100.05	FC 0 CC 0 1 C0 0	<b></b>
	Hotorogonoity Tour	0.07: Chiz - 0.76	df = 1 /P = 0.04	12 - 50%			220	100.0%	-0.02 [-0.32, 0.27]	
	Heterogeneity. Tau-=	0.07, $Chr = 9.75$ , 7 = 0.16 /P = 0.99	$a_1 = 4 (P = 0.04)$	1), 1~= 59%						-2 -1 0 1 2
	restror overall effect.	2 = 0.15 (F = 0.86	9							Favours [THO] Favours [HHO]
F		Total hepatic in	flow occlusion	(THO)	Hemihepatic v	ascular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
Е.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Xiao, J 2015	29.8	21.3	50	28.5	2.7	50	25.2%	0.08 [-0.31, 0.48]	
	Wu, ZY 2014	37.2	29.4	35	30.1	17.2	35	22.0%	0.29 [-0.18, 0.76]	+
	Ni, JS 2013	22.4	11.5	60	25.2	13.7	60	26.6%	-0.22 [-0.58, 0.14]	
	Fu, SY 2011	32	10.6	60	26.9	7.5	60	26.3%	0.55 [0.19, 0.92]	
	Total (95% CI)			205			205	100.0%	0.17 [-0.17, 0.52]	· · · · · ·
	Heterogeneity: Tau <sup>2</sup> =	0.08; Chi <sup>2</sup> = 9.18,	df = 3 (P = 0.03	3);   <sup>2</sup> = 67%	0					-2 -1 0 1 2
	Test for overall effect	Z = 0.98 (P = 0.33	0							Favours [THO] Favours [HHO]
E.		Total honatic in	flow occhucies	THON	Hamihanatia	accular occhied			Std Moon Difference	Std Mann Difference
F	Study or Subarous	I dan nepatic in	SD S	Total	Hennepatic v	ascular occlusio	Total	Weight	N Fixed Off C	V Fixed 05% CI
	Ful SY 2011	22.7	14.6	60	27.2	11.6	FOI BO	29.9%	0.49 (0.13, 0.95)	IV, FIAEU, 95% CI
	Ni JS 2013	28.3	177	00	24.2	9.5	00	29.5%	0.25[-0.11_0.61]	+
	Wu, ZY 2014	39.7	29	35	31.1	18	35	17.1%	0.35 -0.12 0.82	
	Xiao, J 2015	26.5	20.6	50	23.4	2.1	50	24.6%	0.21 [-0.18, 0.60]	
		20.0	20.0	50	20.4	4.1	50	24.070	0.21 [ 0.10, 0.00]	
	Total (95% CI)			205			205	100.0%	0.33 [0.13, 0.52]	•
	Heterogeneity: Chi <sup>2</sup> =	1.29, df = 3 (P = 0	.73); 12 = 0%							1 06 0 06 1
	Test for overall effect:	Z = 3.29 (P = 0.00	1)							-1 -0.5 0 0.5 1 Eavours [THO] Eavours [HHO]
										ravous (THO) ravous (HHO)
G		Total hepatic in	flow occlusion	(THO)	Hemihepatic v	ascular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
	Fu, SY 2011	26.3	17	60	19.6	13.7	60	41.0%	0.43 [0.07, 0.79]	
	WU, ZY 2014	32.9	11	35	29.2	11	35	24.1%	0.33 [-0.14, 0.80]	
	Ala0, J 2015	19.3	13	50	17.3	12.9	50	34.9%	0.15 [-0.24, 0.55]	
	Total (95% CI)			145			145	100.0%	0.31 [0.09.0.54]	•
	Heterogeneity Chi?=	1.05 df = 2 (P = 0)	59)· I <sup>2</sup> = 0%	140			140	100.0%		
	Test for overall effect	7 = 2 62 (P = 0.00	(9)							-1 -0.5 0 0.5 1
	. Sou tor overall enect.	= - 2.02 (r = 0.00								Favours [THO] Favours [HHO]

**Figure 5.** Forest plots of the Pringle maneuver (PM) versus hemihepatic blood flow occlusion (HHO) during hepatectomy. They are hospital stay (A), operative time (B), ischemic duration (C), operative blood loss (D), total bilirubin (TBIL) levels on the first (E), third (F) or seventh (G) day respectively.

ation. The fixed model showed that the PM group had a statistically significant, higher TBIL level (the third day, SMD = 0.33, 95% CI = [0.13, 0.52], P = 0.001; the seventh day, SMD = 0.31, 95% CI = [0.08, 0.54], P = 0.009) (Figure 5E-G).

In four studies [23, 26, 28, 29], including 410 patients ALB levels on the first and third days after operation were reported. Three trials [23, 28, 29] with 290 patients revealed ALB levels on the seventh day post-operation. The ALB

Α		Total hepatic inf	low occlusion	(THO)	Hemihepatic vas	cular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
· · ·	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Fu, SY 2011	36.6	14.7	60	37.6	15.8	60	26.6%	-0.07 [-0.42, 0.29]	-
	Ni, JS 2013	34.6	3.5	60	39.3	8.2	60	26.1%	-0.74 [-1.11, -0.37]	
	Wu, ZY 2014	33.7	5.3	35	35.2	2.5	35	22.1%	-0.36 [-0.83, 0.11]	
	Xiao, J 2015	30.2	2.5	50	30.2	1.7	50	25.2%	0.00 [-0.39, 0.39]	
	Total (95% CI)			205			205	100.0%	-0.29 [-0.64, 0.06]	•
	Heterogeneity: Tau <sup>2</sup> = Test for overall effect: 2	0.09; Chi <sup>2</sup> = 9.39, ( Z = 1.62 (P = 0.10)	df = 3 (P = 0.02	!); I² = 68%					-	-2 -1 0 1 2 Favours [THO] Favours [HHO]
R		Total hepatic inf	low occlusion	(THO)	Hemihepatic vas	cular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
۲.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	Fu, SY 2011	30.2	14.6	60	35.6	15.1	60	29.5%	-0.36 [-0.72, -0.00]	
	Ni JS 2013	34.2	4.2	60	38.6	8.5	60	28.4%	-0.65[-1.02 -0.28]	
	Wu 7Y 2014	32.3	51	35	34.2	5	35	17.2%	-0.37 (-0.84 0.10)	
	Xiao, J 2015	32.1	2.5	50	32.3	2.3	50	25.0%	-0.08 [-0.47, 0.31]	
	Total (95% CI)			205			205	100.0%	-0.38 [-0.57, -0.18]	•
	Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	4.32, df = 3 (P = 0.1 Z = 3.76 (P = 0.000	23); I² = 31% 02)							-2 -1 0 1 2 Favours (THO) Favours (HHO)
c		Total hepatic int	flow occlusion	(THO)	Hemihepatic vas	cular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
C	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Eu. SY 2011	31.7	167	60	37.4	16.6	60	37.0%	-0.34 (-0.70, 0.02)	
	1801 ZV 2014	22.0	5.2	25	26.7	5.2	35	29.5%	-0.53 [ 1.1 01 -0.06]	
	Xiao, J 2015	34.9	2.5	50	34.7	2.1	50	34.5%	0.09 [-0.31, 0.48]	
	Total (95% CI)			145			145	100.0%	-0.25 [-0.60, 0.10]	•
	Heterogeneity: Tau <sup>2</sup> = Test for overall effect:	0.05; Chi <sup>2</sup> = 4.39, Z = 1.40 (P = 0.16)	df = 2 (P = 0.11	l); l² = 54%						-2 -1 0 1 2 Favours (THO) Favours (HHO)
п		Total hepatic in	flow occlusion	(THO)	Hemihepatic vas	cular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	Eu SY 2011	146	61	60	154	87	60	38.8%	-0.11 (-0.46 0.25)	
	Ni .18 2013	158.9	40.2	60	152	51.7	60	38.7%	0 15 60 21 0 511	
	Wu, ZY 2014	226.4	89.4	35	208.3	83.5	35	22.5%	0.21 [-0.26, 0.68]	
	Total (95% CI)			155			155	100.0%	0.06 [-0.16, 0.29]	+
	Heterogeneity: Chi <sup>2</sup> =	1.43, df = 2 (P = 0.	49); l² = 0%							-1 -0.5 0 0.5 1
	Test for overall effect:	Z = 0.55 (P = 0.58)								Favours [THO] Favours [HHO]
Е		Total hepatic in	flow occlusion	n (THO)	Hemihepatic vas	cular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
Ξ.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	Fu, SY 2011	174	73	60	197	114	60	39.3%	-0.24 [-0.60, 0.12]	
	Ni, JS 2013	93	26.2	60	99.4	30.3	60	39.3%	-0.22 [-0.58, 0.13]	
	Wu, ZY 2014	154.8	38.3	35	191.7	56.5	35	21.4%	-0.76 [-1.24, -0.27]	
	Total (95% CI)			155			155	100.0%	-0.34 [-0.57, -0.12]	•
	Heterogeneity: Chi <sup>2</sup> = Test for overall effect:	3.52, df = 2 (P = 0. Z = 3.00 (P = 0.00)	17); I² = 43% 3)							-2 -1 0 1 2 Favours [THO] Favours [HHO]
F		Total hepatic in	flow occlusion	n (THO)	Hemihepatic vas	cular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
Г	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed, 95% CI	IV. Fixed, 95% CI
	Fu SY 2011	193	107	60	245	146	60	631%	-0.40 (-0.77 -0.04)	
	Wu, ZY 2014	178.4	63.5	35	204.7	78.1	35	36.9%	-0.37 [-0.84, 0.11]	
	Total (95% CI)			95			95	100.0%	-0.39 [-0.68, -0.10]	•
	Heterogeneity: Chi <sup>2</sup> =	0.02, df = 1 (P = 0	90);   <sup>2</sup> = 0%							
	Test for overall effect:	Z = 2.66 (P = 0.00	8)							-2 -1 0 1 2 Favours [THO] Favours [HHO]

**Figure 6.** Forest plots of the Pringle maneuver (PM) versus hemihepatic blood flow occlusion (HHO) during hepatectomy. They are albumin (ALB) levels on the first (A), third (B) or seventh (C) day and prealbumin (PAB) levels on the first (D), third (E) or seventh (F) day respectively.

level of the first day showed significant heterogeneity (P = 0.02, I<sup>2</sup> = 68%), and the random model showed no significant difference between the two groups (SMD = -0.29, 95% CI = [-0.64, 0.06], P = 0.10). ALB data of the third day showed no significant heterogeneity (P = 0.23, I<sup>2</sup> = 31%), and the fixed model showed a statistically significant difference between the two groups (SMD = -0.38, 95% CI = [-0.57, -0.18], P < 0.001). However, the ALB level of the seventh day showed no statistical difference between the two groups (SMD = -0.25, 95% CI = [-0.60, 0.10], P = 0.16) by the random model with heterogeneity (P = 0.11, I<sup>2</sup> = 54%) (**Figure 6A-C**).

Three trials [23, 26, 28] including 310 patients reported the PAB on the first and third days

after operation, and two trials [23, 28] with 190 patients for the seventh day. The data showed no significant heterogeneity of PAB on the first day (P = 0.49,  $I^2$  = 0%), and the fixed model showed no significant difference between the two groups (SMD = 0.06, 95% CI = [-0.16, 0.29], P = 0.58). The third day data showed heterogeneity (P = 0.17,  $I^2$  = 43%), and the fixed model showed a statistically significant, lower level of PAB in the PM group (SMD = -0.34, 95% CI = [-0.57, -0.12], P = 0.003) compared to the HHO group. PAB level of the seventh day showed that the PM group had a statistically significant, lower pre-ALB level by fixed model (SMD = -0.39, 95% CI = [-0.68, -0.10], P = 0.008) with no significant heterogeneity (P =  $0.90, l^2 = 0\%$ ) (Figure 6D-F).

Δ		Total hepatic in	flow occlusion	(THO)	Hemihepatic vas	scular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
·``.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Fu, SY 2011	1,013.6	654.4	60	369.4	347.2	60	25.6%	1.22 [0.83, 1.61]	
	Ni, JS 2013	619.6	516.8	60	451.4	337.1	60	26.6%	0.38 [0.02, 0.74]	
	Wu, ZY 2014	435.2	177.1	35	350.5	156.1	35	22.6%	0.50 [0.03, 0.98]	
	Xiao, J 2015	264.4	154.1	50	166.5	152.4	50	25.2%	0.63 [0.23, 1.04]	
	Total (95% CI)			205			205	100.0%	0 60 0 31 1 071	•
	Heterogeneity Tau <sup>2</sup> =	0.11: Chi2 - 10.5	6 df = 3 /P = 0.0	1): 12 = 720	*		205	100.0%	0.03 [0.51, 1.07]	
	Test for overall effect:	Z = 3.55 (P = 0.00	0, u1 = 3 (F = 0.0 )04)	1),1 = 72	20					-2 -1 0 1 2 Favours ITHO1 Favours IHHO1
Б		Total honatic in	flow occlusion	THON	Homibonatic var	ecular occlusiv			Std Moon Difforence	Std Mean Difference
в	Study or Subgroup	Mean	SD	Total	Mean	SD SD	Total	Weight	IV. Random, 95% CI	IV. Random, 95% CI
	Fu. SY 2011	592.2	416.4	60	218.4	185.3	60	26.0%	1.15 (0.77, 1.54)	
	Ni, JS 2013	534.4	501	60	376.4	329.6	60	27.1%	0.37 [0.01, 0.73]	
	Wu, ZY 2014	369.5	122.4	35	277.3	88.1	35	22.1%	0.86 [0.36, 1.35]	
	Xiao, J 2015	220.3	96.8	50	134.3	75.2	50	24.9%	0.98 [0.57, 1.40]	
	Total (95% CI)			205			205	100.0%	0.83 [0.47, 1.20]	•
	Heterogeneity: Tau <sup>2</sup> =	0.09; Chi <sup>2</sup> = 9.41,	df = 3 (P = 0.02)	; I <sup>2</sup> = 68%						
	Test for overall effect:	Z = 4.50 (P < 0.00	0001)							Favours [THO] Favours [HHO]
С		Total hepatic in	flow occlusion	(THO)	Hemihepatic vas	scular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
Υ.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	Fu, SY 2011	172.4	125.8	60	79.6	55.3	60	40.0%	0.95 [0.57, 1.33]	
	Wu, ZY 2014	121.6	72.5	35	97.1	51.2	35	25.5%	0.39 [-0.09, 0.86]	
	Xiao, J 2015	72.5	48.4	50	42.9	24	50	34.5%	0.77 [0.36, 1.18]	
	Total (95% CI)			145			145	100.0%	0.74 [0.50, 0.98]	•
	Heterogeneity: Chi <sup>2</sup> =	3.34, df = 2 (P = 0	1.19); I <sup>2</sup> = 40%							
	Test for overall effect:	Z = 6.09 (P < 0.00	0001)							Favours [THO] Favours [HHO]
р		Total hepatic in	flow occlusion	(THO)	Hemihepatic vas	scular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
Ξ.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
	Fu, SY 2011	812.6	475.3	60	447.6	210.3	60	27.7%	0.99 [0.61, 1.37]	
	Ni, JS 2013	630.3	571.8	60	366.2	229	60	29.7%	0.60 [0.24, 0.97]	
	Wu, ZY 2014	453.6	284.9	35	380.7	160.5	35	17.9%	0.31 [-0.16, 0.78]	
	Xiao, J 2015	258.2	153	50	162.3	150.4	50	24.7%	0.63 [0.23, 1.03]	
	Total (95% CI)			205			205	100.0%	0.66 [0.46, 0.86]	•
	Heterogeneity: Chi <sup>2</sup> =	5.06, df = 3 (P = 0	1.17); I <sup>2</sup> = 41%							
	Test for overall effect:	Z = 6.51 (P < 0.00	0001)							Favours [THO] Favours [HHO]
E		Total hepatic in	flow occlusion	(THO)	Hemihepatic va	scular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
Ξ.	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Fu, SY 2011	423.7	265.4	60	207.5	79.3	60	26.1%	1.10 [0.71, 1.48]	
	Ni, JS 2013	206.6	204	60	135.6	119	60	27.2%	0.42 [0.06, 0.78]	
	Wu, ZY 2014	345.6	102.2	35	283.4	126.9	35	21.9%	0.53 [0.06, 1.01]	
	Xiao, J 2015	218.3	100	50	133.8	76	50	24.7%	0.94 [0.53, 1.36]	
	Total (95% CI)			205			205	100.0%	0.75 [0.42, 1.08]	•
	Heterogeneity: Tau <sup>2</sup> =	0.07; Chi <sup>2</sup> = 7.90,	df = 3 (P = 0.05)	; I² = 62%						-2 -1 0 1 2
	Lear IOL Overall Ellect.	2 - 4.47 (F < 0.00	,001)							Favours [THO] Favours [HHO]
F		Total hepatic in	nflow occlusion	(THO)	Hemihepatic vas	scular occlusio	on (HHO)		Std. Mean Difference	Std. Mean Difference
· .	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
	Fu, SY 2011	143.6	87.5	60	64.2	29.4	60	34.7%	1.21 [0.82, 1.60]	
	Wu, ZY 2014	114.3	75.2	35	88.9	76.3	35	31.4%	0.33 [-0.14, 0.80]	
	Xiao, J 2015	73	48.1	50	41.2	23.9	50	33.9%	0.83 [0.42, 1.24]	
	Total (95% CI)			145			145	100.0%	0.81 [0.32, 1.29]	•
	Heterogeneity: Tau <sup>2</sup> =	0.14; Chi <sup>2</sup> = 7.89.	df = 2 (P = 0.02)	; I2 = 75%						
	Test for overall effect:	Z = 3.26 (P = 0.00	01)	4.5						Favours [THO] Favours [HHO]

**Figure 7.** Forest plots of the Pringle maneuver (PM) versus hemihepatic blood flow occlusion (HHO) during hepatectomy. They are alanine aminotransferase (ALT) levels on the first (A), third (B) or seventh (C) day and aspartate aminotransferase (AST) levels on the first (D), third (E) or seventh (F) day respectively.

### Biochemical markers of liver injury: ALT, AST

Four studies [23, 26, 28, 29] including 410 patients for ALT on the first and third days after operation, and three trials [23, 28, 29] with 290 patients for the seventh day post-operation. Significant heterogeneity was observed for the parameters of the first (P = 0.01, I<sup>2</sup> = 72%) and third (P = 0.02, I<sup>2</sup> = 68%) days after operation. The random model showed that the PM group had a statistically significant, higher ALT level (the first day, SMD = 0.69, 95% CI = [0.31, 1.07], P < 0.001; the third day, SMD = 0.83, 95% CI = [0.47, 1.20], P < 0.001) than the HHO group. ALT level of the seventh day showed no

significant heterogeneity (P = 0.19,  $l^2 = 40\%$ ), and the fixed model showed the same result as the first and third days after operation (SMD = 0.74, 95% Cl = [0.50, 0.98], P < 0.001) (**Figure 7A-C**).

Four trials [23, 26, 28, 29] including 410 patients for AST on the first and third days after operation, and three trials [23, 28, 29] with 290 patients for the seventh day post-operation. The data showed no significant heterogeneity for AST levels on the first day post-operation (P = 0.17,  $I^2 = 41\%$ ). The fixed model showed a statistically significant higher AST level in the PM group compared to the HHO group on the

Outcomes	SMD/OR Fluctuation	95% CI Fluctuation	Publication Bias (P value)
Primary Outcomes			
Mortality	0.34~3.05	0.01~76.39	Ν
Hepatic insufficiency	1.21~4.70	0.38~16.82	Ν
Peri-operative morbidity	1.62~1.96	1.11~2.87	0.453
Total infection	0.70~2.62	0.25~8.58	0.451
Wound infection	0.73~2.03	0.14~11.32	Ν
Bile leakage	1.02~1.41	0.48~3.17	0.799
Pleural effusion	1.30~1.63	0.58~3.91	0.832
Ascites	1.03~1.56	0.42~3.56	0.485
Postoperative hemorrhage	-0.16~0.04	-0.41~0.38	0.851
Total bleeding	2.07~3.14	0.49~20.23	Ν
Gastrointestinal bleeding	1.00~3.32	0.06~85.11	Ν
Quantitative transfusion (ml)	0.29~0.55	-0.09~0.99	0.245
Qualitative transfusion (person)	0.89~1.34	0.50~2.49	0.888
Secondary Outcomes			
Hospital stay	-0.30~0.32	-1.17~1.00	0.868
Operation time	-0.33~-0.13	-0.66~0.25	0.067
Ischemic duration	0.03~0.15	-0.21~0.38	0.552
TBIL			
1st day	0.02~0.32	-0.31~0.69	0.241
3rd day	0.26~0.37	0.03~0.59	0.085
7th day	0.23~0.40	-0.07~0.69	0.828
ALB			
1st day	-0.39~-0.11	-0.83~0.20	0.048
3rd day	-0.48~-0.27	-0.70~-0.04	0.265
7th day	-0.41~-0.14	-0.82~0.40	0.275
PAB			
1st day	0.01~0.17	-0.28~0.46	0.911
3rd day	-0.43~-0.23	-0.71~-0.14	0.342
7th day	-0.41~-0.40	-0.84~0.10	Ν
ALT			
1st day	0.50~0.75	0.17~1.25	0.205
3rd day	0.73~1.03	0.30~1.32	0.568
7th day	0.61~0.87	0.30~1.15	0.869
AST			
1st day	0.54~0.74	0.30~0.96	0.266
3rd day	0.63~0.89	0.26~1.24	0.099
7th day	0.60~1.03	-0.08~1.65	0.689

Table 3. Publication bias
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Note: P < 0.05: The existence of publication bias; N: Insufficient observations for analysis; SMD: Standardized mean difference.

first day after operation (SMD = 0.66, 95% CI = [0.46, 0.86], P < 0.001). Significant heterogeneity for the parameters of the third (P = 0.05,  $I^2 = 62\%$ ) and the seventh day (P = 0.02,  $I^2 = 75\%$ ) after operation was manifest. The random model showed that the PM group had a statistically significant, higher AST level than the HHO group (the third day, SMD = 0.75, 95%)

 $\label{eq:solution} \begin{array}{l} {\sf CI} = [0.42, \ 1.08], \ {\sf P} < 0.001; \ the \ seventh \ day, \\ {\sf SMD} = 0.81, \ 95\% \ {\sf CI} = [0.32, \ 29], \ {\sf P} = 0.001) \\ (\mbox{Figure 7D-F}). \end{array}$ 

Sensitivity analysis and publication bias

The sensitivity analysis [30] showed that, except for TBIL on the first and seventh days,

ALB on the seventh day, PAB on the third and seventh days, AST on the seventh day, and quantitative transfusion (ml), all results were consistently reported in all included studies, which means most of the study parameters are stable and reliable. To assess publication bias, we used the Egger's test [31, 32]. Only ALB on the first day had a low *P* value (< 0.05) (**Table 3**), but both the fixed and random effects model results of ALB data were unchanged by the trim and fill method. Therefore, as shown, the results in our study are stable and valid.

### Discussion

This systematic review summarizes the best available evidence relating to the safety and effectiveness of the PM versus HHO during hepatectomy. After an extensive search of the literature, eight RCTs were identified and included in this review and analysis.

In our analysis, we mainly evaluated primary and secondary outcomes. The primary outcomes consisted of mortality, hepatic insufficiency, peri-operative morbidity, and transfusion requirements. The evidence regarding mortality, hepatic insufficiency, and the number of patients who needed transfusion suggests that there is no significant difference between PM and HHO, which is supported by the results of a retrospective study [33] and a meta-analysis [17]. However, Tanaka K et al. reported that a slightly lower proportion of patients needed transfusion in the PM group than in HHO group [13]. In addition, Yu W et al. found that more patients needed transfusion in the PM group than in HHO group because the average clamping frequency was  $1.6 \pm 0.7$  min and the average clamping period was  $17.1 \pm 4.7$  min in PM group, while one-time clamping was adopted and the mean clamping duration was 20.9  $\pm$ 5.3 min in HHO group [34]. As for transfusion volume, our study suggests that there is a little difference between the two groups, similar to the findings of a retrospective study by Li MH et al. [33]. Regarding peri-operative morbidity, our results showed that there was no significant difference between groups in any type of complication. However, the overall peri-operative morbidity rate in the PM group was significantly higher than that in the HHO group, similar to that found by Zhang Y and his team [35]. Yi B et al. found that the incidence of complications in the PM group (18.9%) was significantly higher than that of the HHO group [36]; however, they did not perform further research for any other type of complications.

The secondary outcomes included hospital stay, operating time, ischemic duration, operative blood loss, markers of liver function, and biochemical markers of liver injury. There was no difference between the PM and HHO group in hospital stay, which contradicts the findings of a retrospective study, that revealed the average hospitalization days for the PM and HHO groups were  $18.9 \pm 4.4$  and  $16.2 \pm 3.2$ , respectively, which represented a statistically significant difference between groups [34]. There was no significant difference between the PM and HHO groups in operating time, ischemic duration and operative blood loss, which contradicts the conclusions of previous retrospective studies [35, 36]. Zhang Y et al. showed that the mean amount of intraoperative blood loss in the PM group was significantly greater than that in the HHO group (568.2 ± 325.1 vs. 420.7 ± 307.2 mL, P = 0.0444) [35]. However, Li MH and his team found that the volume of blood loss was greater in the HHO group than in the PM group, but the difference was not significant (P > 0.05) [33]. In addition, a meta-analysis by Wang HQ et al. suggested that blood loss in three trials showed no significant difference between the PM group and HHO group, further supporting our conclusion.

In our analysis, we used TBIL, ALB, and PAB to reflect post-operative liver function. Although TBIL showed no significant difference between the PM and HHO groups before the surgery and on day one, TBIL increased much more in the PM group than in the HHO group on days three and seven. ALB was lower in the PM group than in the HHO group on day three and PAB was lower in the PM group than in the HHO group on days three and seven. All of the post-operative liver function findings indicate that PM surgery can significantly induce ischemia reperfusion injury of the liver. The outcomes regarding biochemical markers of liver injury such as ALT and AST further support the above conclusion. Our analysis suggested that ALT and AST in the PM group were much higher than in the HHO group on days one, three, and seven. This conclusion is supported by many retrospective studies [33, 34, 36, 37]. For instance, Li MH et al. found that ALT, AST, and TBIL increased much more in the PM group than in the HHO group [33]. However, Zhang Y et al. arrived at a different conclusion that no significant differences between the two groups were observed in ALT and AST levels on postoperative days one and three. Only on the postoperative day seven, the PM group showed significantly higher ALT and AST levels than the HHO group and the finding was against the authors' expectations mainly due to the dramatic variance in ALT and AST levels and the statistical variation of a small sample size [35].

Our results highlight the need for a high level, good quality research into the safety and effectiveness of the PM versus HHO maneuver during hepatectomy. Only RCTs were included in this systematic review and meta-analysis. We analyzed many trials, and the studies that met our inclusion criteria spanned a period from 1990 to 2013. Most of our parameters are stable as shown in our sensitivity analysis, and only one parameter showed publication bias, which means our result is reliable. This systematic review and meta-analysis has some limitations. First, incomplete reporting of important methodological issues, such as sample size calculations, randomization processes, and blinding assessment of trial quality, might raise doubts about the adequate power of these studies. Second, we did not analyze the indicator to reflect the hemodynamic change between the PM and HHO groups, which is an important part of evaluating the safety and effectiveness of PM versus HHO during hepatectomy, because no data is available. Lastly, although we searched for unpublished data, no unpublished data were available; therefore, our data analysis is based on published data only.

### Conclusions

In conclusion, the evidence shows a great advantage of the HHO over the PM, in terms of transfusion volume, peri-operative morbidity, markers of liver function, and biochemical markers of liver injury. However, no statistical difference was found in mortality, hepatic insufficiency, any type of complications, number of patients who need transfusion, hospital stay, operating time, ischemic duration, and operative blood loss between the PM and HHO groups. Our findings highlight the need for more rigorous RCTs comparing PM versus HHO during hepatectomy and more robust, more convincing meta-analyses as well as uniformity in data selection and reporting.

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### Disclosure of conflict of interest

None.

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### Supplementary Table 1. Search strategies

Database	Amount	Search strategy used
Pubmed	2340	(((Hemihepatic[Title/Abstract] OR half-hepatic[Title/Abstract] OR selective[Title/Abstract] OR portal[Title/Abstract] OR alternative[Title/Abstract] OR selectional[Title/Abstract] OR elective[Title/Abstract] OR preferential[Title/ Abstract] OR optional[Title/Abstract]) AND (occlusion[Title/Abstract] OR control[Title/Abstract] OR clamping[Title/ Abstract] OR interdict[Title/Abstract] OR cut off[Title/Abstract] OR Blocking[Title/Abstract] OR Infibulation[Title/ Abstract] OR interdict[Title/Abstract] OR cut off[Title/Abstract] OR Blocking[Title/Abstract] OR Clamping[Title/ Abstract] OR Liver[Title/Abstract] AND Pringle[Title/Abstract] OR Control[Title/Abstract] OR Clamping[Title/ Abstract] OR Liver[Title/Abstract] OR cut off[Title/Abstract] OR Blocking[Title/Abstract] OR Clamping[Title/ Abstract] OR interdict[Title/Abstract] OR cut off[Title/Abstract] OR Blocking[Title/Abstract] OR Infibulation[Title/ Abstract] OR interdict[Title/Abstract] OR vein[Title/Abstract] OR artery[Title/Abstract] OR portal[Title/Ab- stract] OR venous[Title/Abstract] OR vein[Title/Abstract] OR flow[Title/Abstract] OR portal[Title/Abstract]) OR hepatic[Title/Abstract] OR vessel[Title/Abstract] OR Surgery[Title/Abstract] OR Blocking[Title/Abstract] OR Blocking[Title/Abstract]] OR hepatic[Title/Abstract] OR excision[Title/Abstract] OR Surgery[Title/Abstract] OR Segmentectomy[Title/ Abstract]) OR (Hepatectomy[MeSH Terms] OR Liver Transplantation[MeSH Terms]) AND (Clinical Tial[Publication Type] OR Multicenter Study [Publication Type] OR Clinical Tials as Topic[MeSH Terms]) OR Perspect*[Title/Abstract] OR Meta-Analysis[Title/Abstract] OR follow-up[Title/Abstract] OR Blow[Title/Abstract] OR Random*[Title/Abstract] OR Stochastic[Title/Abstract] OR (Meta[Title/Abstract] OR Blind[Title/Abstract] OR Blinding[Title/Abstract] OR Control*[Title/Abstract] OR Placebo*[Title/Abstract] OR Blind[Title/Abstract] OR Blinding[Title/Abstract] OR Control*[Title/Abstract] OR Placebo*[Title/Abstract] OR Blinding[Title/Abstract] OR Control*[Title/Abstract] OR Compa
Embase	3967	(((Hemihepatic:ti,ab OR half-hepatic:ti,ab OR selective:ti,ab OR portal:ti,ab OR alternative:ti,ab OR selectional:ti,ab OR elective:ti,ab OR preferential:ti,ab OR optional:ti,ab) AND (occlusion:ti,ab OR control:ti,ab OR clamping:ti,ab OR interdict:ti,ab OR (cut:ti,ab AND off:ti,ab) OR Blocking:ti,ab OR Infibulation:ti,ab) OR (half:ti,ab AND Pringle:ti,ab)) AND (Pringle:ti,ab OR ((Hepatic:ti,ab OR Liver:ti,ab OR Infibulation:ti,ab) OR (half:ti,ab OR elective:ti,ab OR (cut:ti,ab AND off:ti,ab) OR Blocking:ti,ab OR Infibulation:ti,ab) OR (half:ti,ab OR verse); (t),ab OR (cut:ti,ab AND off:ti,ab) OR Blocking:ti,ab OR Infibulation:ti,ab))) AND (Vascular:ti,ab OR Vein:ti,ab OR artery:ti,ab OR portal:ti,ab OR verse); (t),ab OR flow:ti,ab OR forwiti,ab)) AND (('Liver'/exp OR 'liver timor'/exp OR 'liver disease'/exp OR liver:ti,ab OR hepatic:ti,ab OR flow:ti,ab) AND (('Liver'/exp OR 'liver transplantation'/exp)) AND ('comparative study'/exp OR 'controlled study'/exp OR 'first in human study'/exp OR 'human versus animal comparison'/exp OR 'field study'/exp OR 'clinical study'/exp OR 'numan'/exp OR 'in vivo culture'/exp OR 'methodology'/exp OR 'prevention study'/exp OR 'validation study'/exp OR 'replication study'/exp OR Perspect*:ti,ab OR Multicent*:ti,ab OR follow-up:ti,ab OR Follow:ti,ab OR follow:ti,ab OR Stochastic:ti,ab OR follow:ti,ab OR Blind:ti,ab OR Blinding:ti,ab OR Control*:ti,ab OR Compar*:ti,ab OR Contrast:ti,ab OR EDCC:ti,ab OR group:ti,ab OR groups:ti,ab) AND [embase]/lim
Cochrane Library	197	(((Hemihepatic:ti,ab OR half-hepatic:ti,ab OR selective:ti,ab OR portal:ti,ab OR alternative:ti,ab OR selectional:ti,ab OR elective:ti,ab OR preferential:ti,ab OR optional:ti,ab) AND (occlusion:ti,ab OR control:ti,ab OR clamping:ti,ab OR interdict:ti,ab OR (cut:ti,ab AND off:ti,ab) OR Blocking:ti,ab OR Infibulation:ti,ab) OR (half:ti,ab AND Pringle:ti,ab)) AND (Pringle:ti,ab OR (thepatic:ti,ab OR Live:ti,ab) AND (occlusion:ti,ab OR control:ti,ab OR clamping:ti,ab OR interdict:ti,ab OR (cut:ti,ab AND off:ti,ab) OR Blocking:ti,ab OR Infibulation:ti,ab) OR (half:ti,ab AND Pringle:ti,ab) OR interdict:ti,ab OR (thepatic:ti,ab OR Live:ti,ab) AND (occlusion:ti,ab OR control:ti,ab OR clamping:ti,ab OR interdict:ti,ab OR (cut:ti,ab AND off:ti,ab) OR Blocking:ti,ab OR Infibulation:ti,ab)) AND (Vascular:ti,ab OR veni:ti,ab OR entery:ti,ab OR portal:ti,ab OR venous:ti,ab OR vessel:ti,ab OR flow:ti,ab OR inflow:ti,ab) AND ((([mh Liver] OR [mh "Liver Neoplasms"] OR [mh "Liver Transplantation"]))
Ovid	2739	(((Hemihepatic.ti,ab OR half-hepatic.ti,ab OR selective.ti,ab OR portal.ti,ab OR alternative.ti,ab OR selectional. ti,ab OR elective.ti,ab OR preferential.ti,ab OR optional.ti,ab) AND (occlusion.ti,ab OR control.ti,ab OR clamping. ti,ab OR interdict.ti,ab OR (cut.ti,ab AND off.ti,ab) OR Blocking.ti,ab OR Infibulation.ti,ab) OR (half.ti,ab AND Pringle. ti,ab)) AND (Pringle.ti,ab OR (cut.ti,ab AND off.ti,ab) OR Blocking.ti,ab OR Infibulation.ti,ab) OR (half.ti,ab AND Pringle. ti,ab)) AND (Pringle.ti,ab OR (cut.ti,ab AND off.ti,ab) OR Blocking.ti,ab OR Infibulation.ti,ab)) AND (vascular.ti,ab OR clamping.ti,ab OR interdict.ti,ab OR (cut.ti,ab AND off.ti,ab) OR Blocking.ti,ab OR Infibulation.ti,ab))) AND (Vascular.ti,ab OR vein.ti,ab OR artery.ti,ab OR portal.ti,ab OR venous.ti,ab OR vessel.ti,ab OR flow.ti,ab OR finfow.ti,ab)) AND (((exp Liver/OR exp Liver Neoplasms/OR exp Liver Diseases/OR liver.ti,ab OR hepatic.ti,ab AND (Operation.ti,ab OR surgery.ti,ab OR Segmentectomy.ti,ab OR resection.ti,ab OR excision.ti,ab OR transplant*.ti,ab OR graft*.ti,ab)) OR (exp Hepatecto- my/OR exp Liver Transplantation/)) AND (Exp Clinical Trial/OR exp Multicenter Study/OR exp Clinical Trials as Topic/ OR Perspect*.ti,ab OR Multicent*.ti,ab OR follow-up.ti,ab OR Follow.ti,ab OR Following.ti,ab OR Meta-Analysis.ti,ab OR (Meta.ti,ab AND Analysis.ti,ab) OR Random*.ti,ab OR Stochastic.ti,ab OR Placebo*.ti,ab OR Blind.ti,ab OR Blind. ing.ti,ab OR Control*.ti,ab OR Compar*.ti,ab OR Contrast.ti,ab OR EDCC.ti,ab OR group.ti,ab OR groups.ti,ab)
WOS	2918	(((TS=Hemihepatic OR TS=half-hepatic OR TS=selective OR TS=portal OR TS=alternative OR TS=selectional OR TS=elective OR TS=preferential OR TS=optional) AND (TS=occlusion OR TS=control OR TS=clamping OR TS=interdict OR TS=(cut AND off) OR TS=Blocking OR TS=Infibulation) OR TS=(half AND Pringle)) AND (TS=Pringle OR ((TS=Hepatic OR TS=Liver) AND (TS=occlusion OR TS=control OR TS=clamping OR TS=interdict OR TS=(cut AND off) OR TS=Blocking OR TS=Infibulation))) AND (TS=Vascular OR TS=Vein OR TS=artery OR TS=portal OR TS=venous OR TS=vessel OR TS=finflow) AND ((TS=Liver OR TS=(Liver AND Neoplasms) OR TS=(Liver AND Diseases) OR TS=hepatic) AND (TS=Operation OR TS=Surgery OR TS=cgmentectomy OR TS=resection OR TS=excision OR TS=tansplant* OR TS=graft*)) OR (TS=Hepatectomy OR TS=(Liver AND Transplantation))) AND ((TS=(Perspect* OR Multicent* OR Follow-up OR Follow OR Following OR Meta-Analysis OR (Meta AND Analysis) OR Random* OR Stochastic OR Placebo* OR Blind OR Blinding OR Control* OR Compar* OR Contrast OR EDCC OR group OR groups))

Scopus	3106	(((TITLE-ABS(Hemihepatic) OR TITLE-ABS(half-hepatic) OR TITLE-ABS(selective) OR TITLE-ABS(portal) OR
•		TITLE-ABS(alternative) OR TITLE-ABS(selectional) OR TITLE-ABS(elective) OR TITLE-ABS(preferential) OR TITLE-
		ABS(optional)) AND (TITLE-ABS(occlusion) OR TITLE-ABS(control) OR TITLE-ABS(clamping) OR TITLE-ABS(interdict)
		OR TITLE-ABS(cut AND off) OR TITLE-ABS(Blocking) OR TITLE-ABS(Infibulation)) OR TITLE-ABS(half AND Pringle))
		AND (TITLE-ABS(Pringle) OR ((TITLE-ABS(Hepatic) OR TITLE-ABS(Liver)) AND (TITLE-ABS(occlusion) OR TITLE-
		ABS(control) OR TITLE-ABS(clamping) OR TITLE-ABS(interdict) OR TITLE-ABS(cut AND off) OR TITLE-ABS(Blocking)
		OR TITLE-ABS(Infibulation)))) AND (TITLE-ABS(Vascular) OR TITLE-ABS(Vein) OR TITLE-ABS(artery) OR TITLE-
		ABS(portal) OR TITLE-ABS(venous) OR TITLE-ABS(vessel) OR TITLE-ABS(flow) OR TITLE-ABS(inflow))) AND ((((TITLE-
		ABS(Liver) OR TITLE-ABS(Liver AND Neoplasms) OR TITLE-ABS(Liver AND Diseases) OR TITLE-ABS(hepatic)) AND
		(TITLE-ABS(Operation) OR TITLE-ABS(Surgery) OR TITLE-ABS(Segmentectomy) OR TITLE-ABS(resection) OR TITLE-
		ABS(excision) OR TITLE-ABS(transplant*) OR TITLE-ABS(graft*))) OR (TITLE-ABS(Hepatectomy) OR TITLE-ABS(Liver
		AND Transplantation))) AND (TITLE-ABS(Perspect* OR Multicent* OR follow-up OR Follow OR Following OR Meta-
		Analysis OR Random* OR Stochastic OR Placebo* OR Blind OR Blinding OR Control* OR Compar* OR Contrast OR
		EDCC OR group OR groups) OR TITLE-ABS(Meta AND Analysis))
WANFANG	317	Adjust according search strategy of Pubmed (search in Chinese)
CNKI	126	Adjust according search strategy of Pubmed (search in Chinese)
CBM	88	Adjust according search strategy of Pubmed (search in Chinese)
Total	15798	