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# **Does intermittent Pringle maneuver loss its clinical value in reducing bleeding during hepatectomy? A systematic review and meta-analysis**

**Running title: IPM for hepatectomy**

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**Study type:** Review

**Does the intermittent Pringle's maneuver lose its clinical value in reducing bleeding during hepatectomy? A systematic review and meta-analysis**

**ABSTRACT**

**Background:** The intermittent Pringle's maneuver (IPM) is conducted mainly during the procedure of hepatectomy to control intraoperative blood loss (IBL), but it has been questioned since improvement of surgical technology and intraoperative management. Hence, we conducted a systematic review and meta-analysis to validate the clinical value of IPM.

**Materials and Methods:** Eligible studies that were designed to evaluate the IPM in the procedure of hepatectomy were searched for on PubMed, Medline, and other databases from establishment of the database to October 2019. The primary endpoints were IBL and intraoperative blood transfusion (IBT). The risk ratio (RR) with 95% confidence interval (CI) was used to determine the effect size.

**Results:** A total of 16 studies with six randomized controlled trials (RCTs) were enrolled in this meta-analysis, including 1,770 cases in the IPM group and 1,611 cases in the non-IPM group. Overall, there were no significant differences between the IPM and non-IPM groups in the amount of IBL and the incidence of IBT (RR=0.96, 95% CI 0.67-1.37,  $P=0.82$ ), which was also confirmed in the subgroups of RCTs ( $P>0.05$ ). However, subgroup analyses showed that for patients with colorectal liver metastasis (CRLM), the amount of IBL was generally higher in the IPM group than in the non-IPM group, and the incidence of IBT was significantly higher in the IPM group (RR= 7.17, 95% CI 1.91-26.94,  $P=0.004$ ). In addition, no significant differences were observed in terms of postoperative complications between the two groups (all

24  $P>0.05$ ).

25 **Conclusion:** With the current data, we concluded that IPM had lost its value in  
26 patients with CRLM, although it remained controversial in patients with  
27 hepatocellular carcinoma.

28 **Keywords** intermittent Pringle's maneuver; liver cancer; intraoperative blood loss;  
29 intraoperative blood transfusion; liver failure; meta-analysis.

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## 48 **1.0 Introduction**

49 The intermittent Pringle's maneuver (IPM) is one of the most common types of  
50 vascular control strategies which is widely conducted worldwide<sup>1,2</sup>. However, worries  
51 on ischemia-reperfusion injury (IRI) never lessen<sup>3,4</sup>. In addition, IPM has been losing  
52 its effect on intraoperative blood loss (IBL) with the improvements in surgical  
53 technology and intraoperative management, but it has also been reported to increase  
54 the risk of postoperative complications and recurrence<sup>3,5,6</sup>.

55 In recent decades, non-IPM has been tried in highly experienced hepatobiliary centers,  
56 mainly owing to the development of state-of-the-art equipment<sup>7</sup>, promotion of  
57 controlled low central venous pressure (CVP)<sup>5</sup>, and the advent of precise hepatectomy.  
58 In a recent randomized controlled trial (RCT), non-IPM was identified to be not  
59 inferior to IPM in the control of IBL<sup>8</sup>, which was completely different from earlier  
60 findings<sup>9,10</sup>. Considering that the sample sizes of the current studies were generally  
61 small, a comprehensive systematic review and meta-analysis is warranted to  
62 investigate the clinical value of IPM.

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## 65 **2.0 Methods**

66 This systematic review was performed according to the guidelines of the Preferred  
67 Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>11</sup> and

Assessing the Methodological Quality of Systematic Reviews (AMSTAR) Guidelines.

## **2.1 Literature search**

A comprehensive search was conducted by two independent researchers using databases including PubMed, MedLine, Embase, the Cochrane Library, and Google Scholar from establishment of the database to October 2019. Studies evaluating the clinical value of IPM in the procedure of hepatectomy were eligible. The following terms and strategies were used to seek the eligible studies: (“liver” OR “hepatic”) AND (“liver resection” OR “hepatectomy” OR “surgical resection”) AND (“blood occlusion” OR “intermittent Pringle’s maneuver” OR “IPM” OR “hepatic pedicle clamp” OR “intermittent inflow occlusion” OR “hilar clamping”). Furthermore, any potentially eligible studies were searched for manually from the included studies, reviews, letters, and comments. Of note, only studies written in English, either retrospective or prospective, were enrolled in this study.

## **2.2 Selection criteria**

The inclusion criteria were as follows: 1) patients who underwent hepatectomy, 2) comparison between non-IPM and IPM, and 3) outcomes including at least IBL and intraoperative blood transfusion (IBT).

The exclusion criteria were as follows: 1) repeat hepatectomy, 2) selective PM or continuing PM, 3) in animal studies, 4) case reports, letters, reviews, and conference abstracts, and 5) unavailable data.

In the case of results reported from the same center more than once, the latest was

extracted.

### **2.3 Data extraction**

All data were extracted and assessed by two independent investigators with predefined forms, which were as follows: 1) general data including title, first author, journal, publication data, and study design, 2) baseline characteristics, such as tumor type, patient number, cirrhosis, ischemia time, hepatectomy strategy, and so on and 3) outcomes including IBL IBT, and postoperative complications including pleural effusion, ascites, and liver dysfunction. In the case of disagreement, a third investigator intervened for a conclusion.

### **2.4 Intervention and outcome definition**

IPM was carried out by tightening a rubber tube encircling the hepatoduodenal ligament. The procedure was usually clamping within 15 min of ischemia followed by 5 min of reperfusion, but it varied slightly among different centers.

Non-IPM in this study was defined as hepatectomy without any modality of blood flow blocking.

IBL was calculated by assessing the volumes in suction bottles or the weight of soaked gauze.

IBT was defined as transfusion of any of the following within the perioperative period (except the preoperative period): whole blood, red blood cell, plasma, blood platelet owing to IBL, but not for preoperative thrombocytopenia or impaired clotting.

### **2.5 Quality assessment**

Both RCTs and non-RCTs were included in this study, then they were evaluated using the Cochrane risk assessment tool and the Newcastle-Ottawa Scale (NOS), respectively. For RCTs, any studies that were assessed to have a high risk of bias and would be reevaluated. For non-RCTs, studies scoring above 5 were considered of high quality.

## 2.6 Statistical analysis

The systematic review and meta-analysis was registered at <https://www.crd.york.ac.uk/> (CRD42019125050) and performed using RevMan version 5.3 and Stata 15. The incidence of IBL between the IPM and non-IPM groups was evaluated by risk ratio (RR) with 95% confidence intervals (CI). Considering that the included studies spanned a long period and patients included both primary liver cancer and metastatic liver cancer, the random-effects model was used for the cases with significant heterogeneity. Begg's and Egger's tests were conducted to evaluate the publication bias, if the publication bias was taken away, the trim and fill method was used to assess the stability of the result.

## 3.0 Results

### 3.1 Basic characteristics of the included studies

Initially, 730 records were identified by two independent reviewers, and then 714 records were excluded according to the established inclusion and exclusion criteria. Of note, one study that assessed the IPM in a repeat hepatectomy was excluded<sup>12</sup>. Finally, 16 records<sup>9, 10, 13-26</sup> including 6 RCTs<sup>14, 16, 18, 20, 21</sup> remained to be analyzed in



this study. Details are depicted in Fig 1.

The total number of patients from all the included studies was 3,381, with the sample size of the included studies ranging from 20 to 1,330, including 1,770 patients (52.35%) in the IPM group and 1,611 patients (47.65%) in the non-IPM group. Of the included studies, hepatectomy was performed for hepatocellular carcinoma (HCC) in four<sup>9, 23, 24, 26</sup>, and for colorectal liver metastasis (CRLM) in four studies<sup>15, 19, 20, 22</sup>. All non-RCTs were scored above 5, and all the RCTs were assessed to have a low risk of bias, indicating that all of them were of high quality. Details are shown in Table 1.

### **3.2 Primary endpoints: intraoperative blood loss**

IBL was evaluated in 13 studies<sup>9, 10, 13, 15, 16, 18, 20-26</sup>, including five western series<sup>15, 18, 20, 22, 25</sup> and eight eastern series<sup>9, 10, 13, 16, 21, 23, 24, 26</sup>. However, IBL data were presented as median (range) in seven studies<sup>10, 13, 16, 21, 22, 25, 26</sup>, mean (standard deviation) in five studies<sup>9, 15, 20, 23, 24</sup>, and range (quartile) in one study<sup>18</sup>. Therefore, RR could not be pooled using meta-analysis.

Details of IBL in each included study are depicted in Table 2. The findings were as follows: 1) the amount of IBL was found to be lower as time went by, 2) the amount of IBL in the eastern series was greatly higher than that in the western series, 3) apparent differences in IBL between the IPM and non-IPM groups were only observed in seven studies<sup>9, 10, 15, 16, 23-25</sup>, but the results were distinct.

### **3.3 Primary endpoints: intraoperative blood transfusion**

IBT was evaluated in 13 included studies<sup>9, 13-18, 20, 21, 23-26</sup>. The incidence of IBT in the IPM and non-IPM groups was 16.7% and 23.2% respectively. Considering the

apparent heterogeneities among the included studies, the pooled RR for the occurrence of IBT was 0.96 (95% CI: 0.67–1.37,  $P=0.82$ , Fig 2) using a random-effect model.

Subgroup analyses stratified by study design showed that the incidence of IBT was comparable between the two groups in both RCTs (RR=1.30, 95% CI: 0.62–2.71,  $P=0.49$ ) . Fig 3A) and RCSs (RR=0.91, 95% CI: 0.55–1.50,  $P=0.70$ . Fig 3B).

IBT was evaluated in three included studies on CRLM<sup>15, 19, 20</sup> and four studies on HCC<sup>9, 23, 24, 26</sup>. Subgroup analysis stratified by different tumors showed that for CRLM, the incidence of IBT was significantly higher in the IPM group than that in the non-IPM group (17.1% vs. 1.7%, RR= 7.17, 95% CI: 1.91–26.94,  $P=0.004$ , Fig 4A), while it was the reverse for HCC (15.5% vs. 22.2%), although there was no significant difference (RR=0.69, 95% CI: 0.29–1.63,  $P=0.40$ , Fig 4B).

### 3.4 Secondary endpoints: postoperative complications

Pleural effusion was evaluated in five studies including three RCTs<sup>14, 20, 21</sup> and two non-RCTs<sup>9, 23</sup>. No significant difference was observed in the occurrence of pleural effusion between the IPM and non-IPM groups in a whole (RR=1.55, 95% CI: 0.84–2.87,  $P=0.16$ , Table 3), which was confirmed in the subgroups of RCTs and non-RCTs (RR=1.47, 95% CI: 0.70–3.08,  $P=0.30$ ; RR=1.73, 95% CI: 0.57–5.30,  $P=0.34$ , respectively, Table 3).

Ascites was evaluated in four studies including two RCTs<sup>21, 26</sup> and two non-RCTs<sup>9, 24</sup>. No significant difference was observed in the incidence of ascites between the IPM and non-IPM groups across the whole (RR=1.09, 95% CI: 0.68–1.74,  $P=0.73$ , Table

3), which was confirmed in the subgroups of RCTs and non-RCTs (RR=2.52, 95% CI: 0.72–7.07,  $P=0.16$ ; RR=0.92, 95% CI: 0.54–1.56,  $P=0.76$ ; respectively, Table 3).

Liver dysfunction was evaluated in nine studies including four RCTs<sup>18, 20, 21, 26</sup> and five non-RCTs<sup>9, 17, 22-24</sup>. No significant difference was observed in the incidence of liver dysfunction between the IPM and non-IPM groups as a whole (RR=0.43, 95% CI: 0.13–1.40,  $P=0.16$ , Table 3), which was confirmed in the subgroups of RCTs and non-RCTs (RR=0.87, 95% CI: 0.30–2.53,  $P=0.79$ ; RR=0.78, 95% CI: 0.35–1.73,  $P=0.54$ ;, respectively, Table 3).

### 3.5 Publication bias analysis

Publication bias analysis was conducted on the pooled RR for the incidence of IBT compared between the IPM and non-IPM groups, and significant publication bias was found using the Begg's test ( $P=0.015$ ). After “trim and fill” analysis, four more studies were enrolled, and IBT was still comparable between the IPM and non-IPM groups ( $P>0.05$ ), which indicated that the unpublished studies would not change the results.

## 4.0 Discussion

IPM is mostly done during hepatectomy to decrease the amount of IBL, but its efficacy has been questioned<sup>8, 27</sup>. To the best of our knowledge, this is the first systematic review and meta-analysis evaluating the efficacy of IPM in hepatectomy procedures. Sixteen studies including six RCTs were identified, and the results showed that no significant difference was observed in the amount of IBL between

groups of IPM and non-IPM. In addition, there was no significant difference in the incidence of IBT and postoperative complications between the IPM and non-IPM groups (all  $P>0.05$ ), which was also confirmed by the subgroup analysis of RCTs and non-RCTs (all  $P>0.05$ ). Hence, we concluded that IPM might have lost its efficacy in hepatectomy.

PM was first introduced in clinical practice in 1908 to prevent massive IBL in the procedure of hepatectomy<sup>1</sup>, but it would inevitably cause I/R injury. IPM was a modified PM, which was found not inferior to PM in vascular control but was superior to PM in the prophylaxis of I/R injury<sup>28, 29</sup>. However, things have changed in recent decades: 1) IPM was reported to be inefficient in the vascular control<sup>20, 21, 26</sup>, 2) IPM might decrease, but not eliminate I/R injury<sup>30, 31</sup>, and 3) IPM was found to increase the risk of postoperative complications<sup>4, 32</sup>. In this study, we found that the amount of IBL in the hepatectomy procedure decreased over time, mainly due to the development of state-of-the-art equipment such as the CUSA<sup>33</sup> and LigaSure<sup>34</sup>, the promotion of LVCP, and the advent of precise hepatectomy.

Hepatectomy without vascular control has been conducted in more and more hepatobiliary centers. Recently, the non-inferiority of non-IPM in the reduction of IBL has been confirmed in several RCTs<sup>20, 21, 26</sup>, but worries on the IBL never lessen. The reasons were as follows: 1) IBL, especially massive IBL and corresponding IBT, were the two important risk factors of postoperative complications and long-term prognosis, and 2) the sample sizes of recent RCTs were generally small. In this systematic review, we identified 16 studies involving 3,381 patients and found that the amount of IBL

was comparable between the IPM and non-IPM groups in most of the included studies. The corresponding IBT was evaluated in 13 of the included studies, and meta-analysis showed that no significant difference was observed between the two groups ( $P>0.05$ ), which was also confirmed by the subgroup analysis of both RCTs and non-RCTs (both  $P>0.05$ ). Hence, the conclusion that IPM might have lost its efficacy in the procedure of hepatectomy was convicting.

However, findings worthy of further investigation were observed in the subgroup analysis stratified by pathogenesis. For patients with HCC, the amount of IBL in the IPM group was often slightly smaller than that in the non-IPM group, and the incidence of IBT in the IPM group was comparable with that in the non-IPM group (15.2% vs. 24.9%,  $P>0.05$ ). However, for patients with CRLM, the amount of IBL in the IPM group was often larger than that in the non-IPM group, and the incidence of IBT in the IPM group was significantly higher than that in the non-IPM group (17.1% vs. 1.7%,  $P<0.05$ ). A possible reason was that patients with hepatocellular carcinoma (HCC) were more likely to suffer massive IBL mainly due to the combination of cirrhosis and damaged liver function<sup>35, 36</sup>. Hence, we recommended that IPM should not be routinely used in the procedure of hepatectomy for patients with CRLM, but for patients with HCC, it needed further validation.

Pleural effusion, ascites, and liver dysfunction are common complications following hepatectomy. In this systematic review, the total incidences of pleural effusion, ascites, and liver dysfunction after hepatectomy were 5.4%, 4.2%, and 1.5% respectively, and no significant differences were found in the incidences of pleural effusion and ascites

between groups of IPM and non-IPM (all  $P>0.05$ ). Besides, the results were confirmed by the subgroup analysis of RCTs and non-RCTs (all  $P>0.05$ ), which is consistent with the results of previous studies<sup>12, 21, 26</sup>.

There were several restrictions of this systematic review and meta-analysis. First, the data of IBL could not be pooled using the meta-analysis, which would weaken the conclusion. Secondly, the procedure of IPM was similar worldwide, but the duration of each PM was from 15 min to 20 min. Thirdly, confounding factors such as anatomic and non-anatomic hepatectomy, cirrhosis, HBsAg status, Child-Pugh class, major or minor hepatectomy, and open or laparoscopic hepatectomy were inevitable, but relevant subgroup analysis was not conducted due to the unavailability of data. Finally, publication bias was found, although the potentially unpublished studies did not change the results using “trim and fill” analysis.

## 5.0 Conclusion

With the current data, we concluded that IPM had lost its value in patients with MLC, although it remained controversial in patients with HCC. In the future, RCTs with larger samples and multi-centers should be conducted to identify the clinical value of IPM in the procedure of hepatectomy for patients with HCC. Currently, prophylactic IPM is still recommended for patients with HCC, especially for those with poor liver function and severe cirrhosis.

## 6.0 Acknowledgments

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## **7.0 Conflicts-of-interests statement:**

The authors deny any conflict of interest.

## **8.0 Provenance and peer review**

Not commissioned, externally peer-reviewed

### **Figure legends**

Figure 1. PRISMA flow diagram showing selection of articles for meta-analysis

Figure 2. Forest plot of the incidence of intraoperative blood transfusion.

Figure 3. Subgroup analysis of the incidence of intraoperative blood transfusion stratified by study design. (A). Randomized controlled trials (RCTs). (B). non-Randomized controlled trials (non-RCTs).

Figure 4. Subgroup analysis of the incidence of intraoperative blood transfusion stratified by disease. (A). Hepatocellular carcinoma (HCC). (B). Colorectal liver metastasis (CRLM).

Figure 5. Egger's test for publication bias.

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Table 1. Basic characteristic of the included studies

Study	Country	Study Period	Study type	Patient		Liver cirrhosis		Multiple tumors		Tumor size (cm)		L/O	Ischemia Time(min)	Major resection	
				P	N	P	N	P	N	P	N			P	N
Taniguchi 1992	Japan	-	RCS	27	32	14	12	-	-	-	-	O	-	-	-
Man 1997	China	1995-1997	RCT	50	50	13	16	-	-	6.8 (2-23)	6.5 (0.3-15)	O	88 (24-101)	34	35
Buell 2001	U.S.A.	1994-2000	RCS	85	15	-	-	-	-	5.1±3.7	3.8±2.2	O	-	-	-
Man 2003	China	2000-2000	RCT	20	20	17	12	14	12	6 (1.5–20)	4.1 (1.2–14)	-	65 (40–108)	14	12
Miller 2004	Italy	2001-2003	RCS	15	19	-	-	-	-	-	-	O	31±9	-	-
Chau 2005	China	1991-2002	RCS	41	30	31	22	13	9	3.4 ± 1.7	3.5 ± 3.9	O	40 ± 19	-	-
Capussotti 2006	Italy	2002-2004	RCT	63	63	6	13	25	31	-	-	-	49.0(44.0,57.3)	25	31
Wong 2008	England	1993-2006	RCS	289	274	-	-	150	143	-	-	-	22(2-104)	150	143
Ferrero 2010	Italy	2002-2004	RCT	39	41	-	-	-	-	-	-	-	47.8 ± 17.2	20	19
Lee 2012	China	2008-2011	RCT	63	63	26	28	-	-	-	-	O	45 (15–87)	30	32
De 2013	Italy	2002-2010	RCS	60	60	-	-	24	26	4.6 (1.5-5)	3.7 (0.5-5)	-	-	24	26
Huang 2014	China	2009-2013	RCS	158	200	158	200	-	-	-	-	-	41.9±12.3	158	200
Huang# 2014	China	1998-2008	RCS	712	618	518	322	199	185	8.6±7.8	7.7±5.1	O	47.4±38.7	338	289
Dua 2014	U.S.A.	2007-2013	RCS	88	66	20	21	-	-	3(1.9-3.9)	2(1.4-3.2)	L	24 (15–34.3)	15	10
Takatsuki 2015	Japan	-	RCS	10	10	-	-	-	-	-	-	O	-	-	-
Lee 2018	China	2013-2016	RCT	50	50	28	25	13	12	3.3(1.0–12.0)	3.5 (1.0–12.0)	O	45 (15.0–60)	35	34

P, intermittent Pringle maneuver; N, non- intermittent Pringle maneuver; L, laparoscopic liver resection; O, open liver resection; RCS, retrospective study; RCT, randomized controlled study, -, no mention

Study	Tumor type	Blood loss (ml)	
		P	N
Western Country			
Buell 2001*	Metastases -	625.9±637.2	303.2±293.2
Capussotti 2006*	Mixed	184.1(122.8,245.5)	204.1(158.4,249.8)
Ferrero 2010	CRLM	210.6 ± 281.3	175.8 ± 180.7
De 2013	CRLM	210 (50-910)	190(65-535)
Dua 2014*	Mixed	100 (50–200)	50 (25–200)
Eastern Country			
Taniguchi 1992	Mixed	1665 (80-10689)	1700 (110-10689)
Chau 2005*	HCC	1488 ± 1506	2259 ± 1630
Man 2003	Mixed	436.1(42-3897.6)	520.8(54.6-6825.6)
Lee 2012*	Mixed	370 (50–3600)	335 (40–3160)
Huang 2014*	HCC	518.06451.0	638.26426.8
Huang# 2014*	HCC	1146.3±895.2	1428.6±1123.7
Takatsuki 2015	LDD	303 (170-480)	720 (360-2200)
Lee 2018*	HCC	310.0(50.0–500.0)	300.0(50.0–2176.0)

P, Pringle maneuver; N, Non-Pringle maneuver; LLD: Living Liver Donors; HCC, hepatocellular carcinoma; CRLM, colorectal liver metastases; Mixed, including any kinds of hepatic tumor.

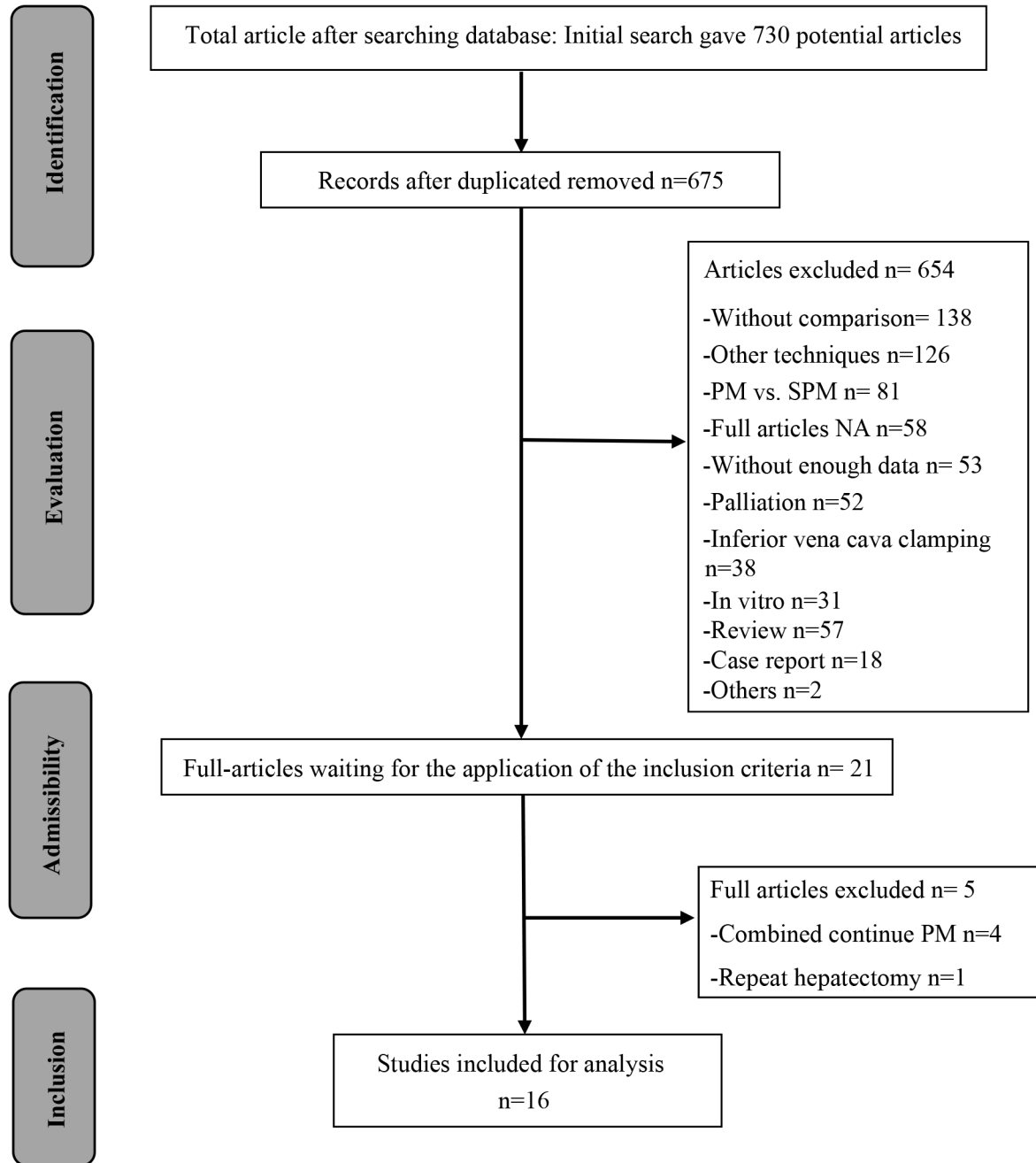
**Table 2. Intraoperative blood loss and tumor type between Western and Eastern country.**

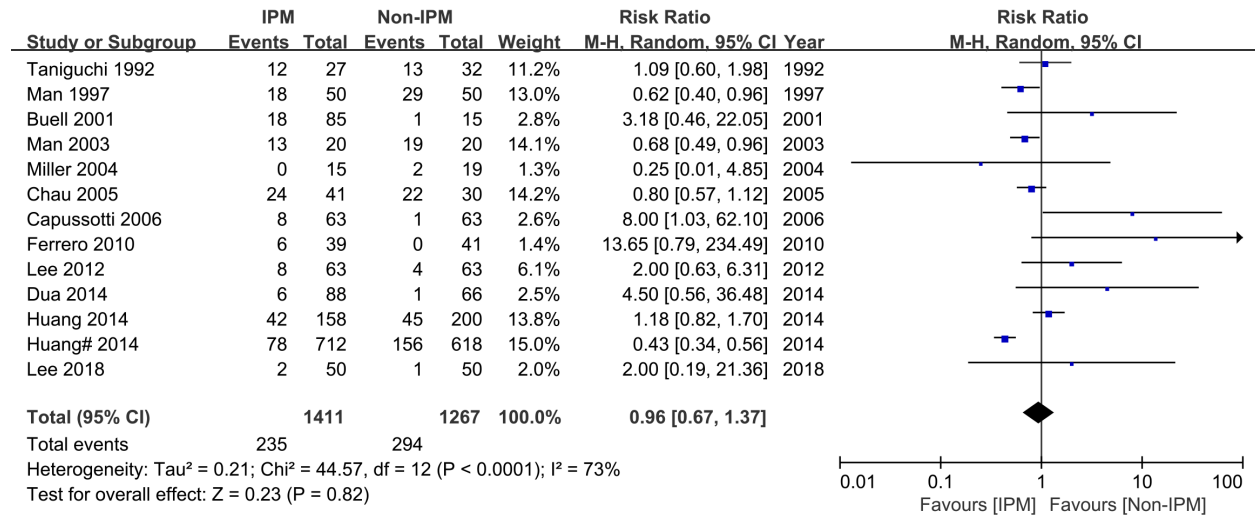


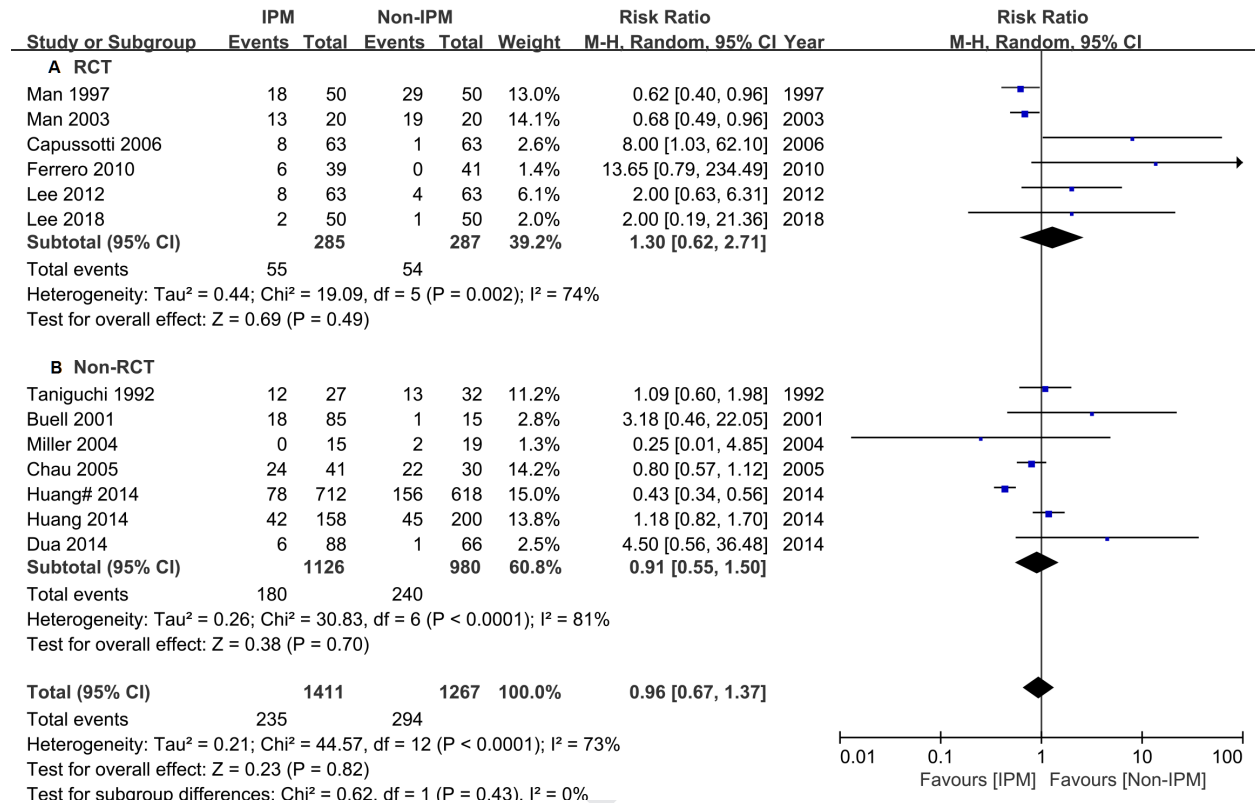
**Table 3. Subgroup analysis of postoperative complications.**

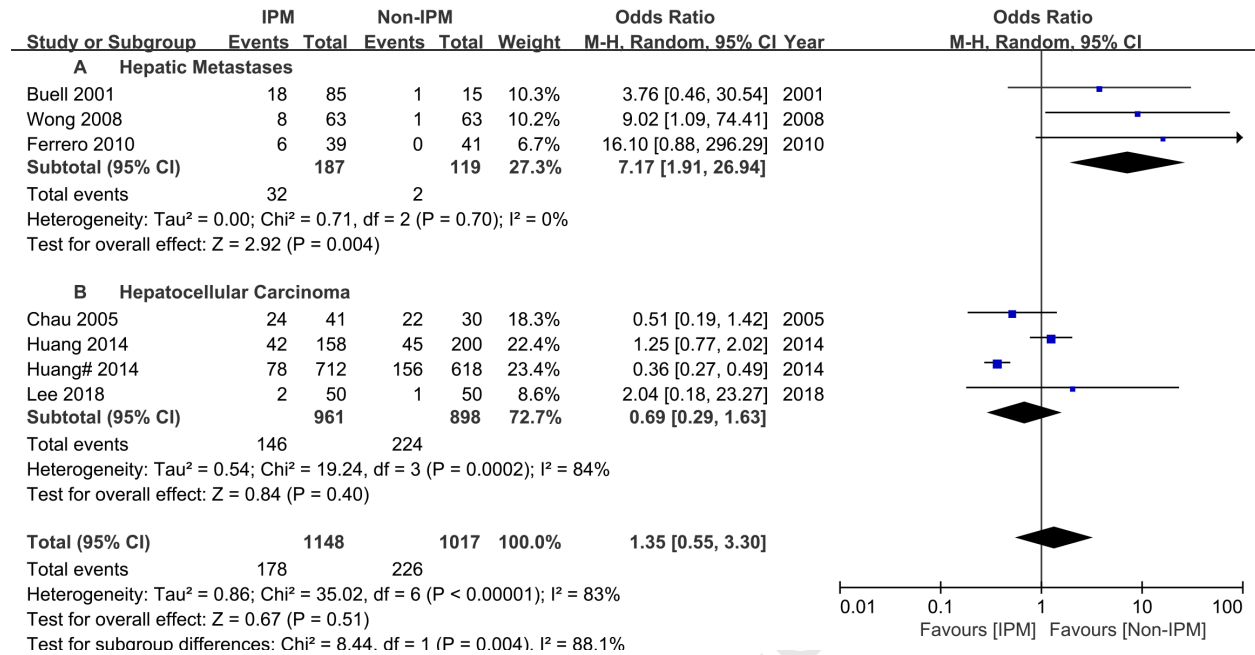
<b>Complication</b>	<b>RCT</b>			<b>RCS</b>			<b>Combined</b>	
	Included studies	RR (95%CI)	P value	Included studies	RR (95%CI)	P value	RR (95%CI)	P value
Pleura effusion	3	1.47(0.70,3.08)	0.30	2	1.73(0.57,5.30)	0.34	1.55(0.84,2.87)	0.16
Ascites	2	2.52(0.72,7.07)	0.16	2	0.92(0.54,1.56)	0.76	1.09(0.68,1.74)	0.73
Liver disfunction	4	0.87(0.30,2.53)	0.79	5	0.78(0.35,1.73)	0.54	0.43(0.13,1.40)	0.16

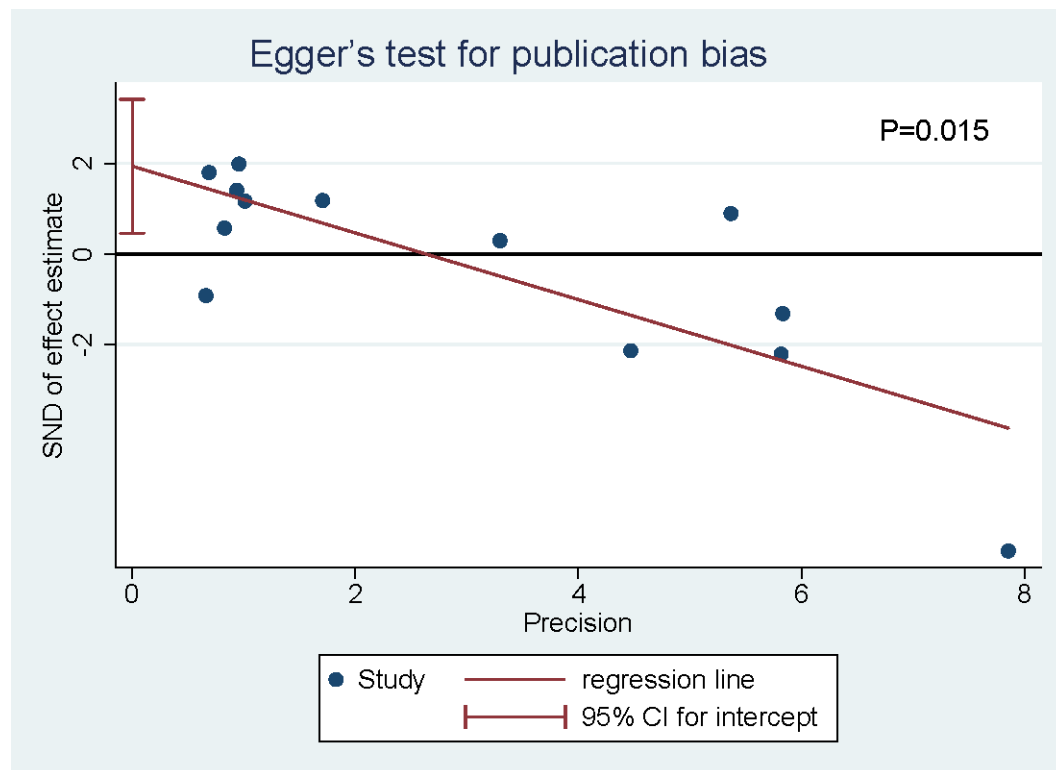
RCS, retrospective study; RCT, randomized controlled study; RR, risk ratio.











### **High lights**

1. Intermittent pringle maneuver (IPM) is conducted prevalently in the procedure of hepatectomy, but its clinical value has been questioned since the improvement of surgical technology and intraoperative management.
2. This is the first meta-analysis designed to evaluate the effect of IPM on the complication, especially in blood loss. Results showed that IPM might have lost its efficacy in the prevention of intraoperative blood loss.

## International Journal of Surgery Author Disclosure Form

The following additional information is required for submission. Please note that failure to respond to these questions/statements will mean your submission will be returned. If you have nothing to declare in any of these categories then this should be stated.

### Please state any conflicts of interest

No

### Please state any sources of funding for your research

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### Please state whether Ethical Approval was given, by whom and the relevant Judgement's reference number

No.

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The name of the registry: PROSPERO  
Identifying number: CRD 42019125050  
Hyperlink: [www.crd.york.ac.uk](http://www.crd.york.ac.uk)



**Author contribution**

Please specify the contribution of each author to the paper, e.g. study design, data collections, data analysis, writing. Others, who have contributed in other ways should be listed as contributors.

Nanping Lin acquisition of data, analysis and interpretation of data, drafting the article, final approval; Jingrong Li and Qiao Ke acquisition of data, analysis and interpretation of data, drafting the article; Lei Wang and Jingfeng Liu conception and design of the study, critical revision, final approval.

**Guarantor**

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Jingfeng Liu

**Biostatistics statement:**

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The statistical methods of this study were reviewed by Zhiqiang Liu, master of epidemiology and health statistics.

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