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Meta-analysis of ischemic preconditioning (IP) on postoperative outcomes after liver resections

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Abstract

Background: The protective role (decrease ischemia-reperfusion injury) of ischemic preconditioning (IP) before continuous vascular occlusion in liver resection is controversial. This meta-analysis aimed to compare the advantages and any potential disadvantages of IP maneuver.

Methods: A systematic search in the Embase, Medline, PubMed databases, and the Cochrane Library was performed using both medical subject headings (MeSH) and truncated word searches to identify all randomized controlled trials (RCTs) published on this topic. The primary outcomes were postoperative morbidity, mortality, postoperative aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, and total bilirubin (TB) level. Pooled odds ratios (ORs) and weighted mean differences (WMDs) with 95% confidence intervals (95% CIs) were calculated using either the random effects model or fixed effects model.

Results: Thirteen RCTs involving 918 patients were analyzed to achieve a summated outcome. The patients have been divided into IP group (n = 455) and no IP group (n = 463) before continuous vascular occlusion. No significant difference was found in postoperative mortality between both groups ($P = .30$). Subgroup analysis revealed that the postoperative morbidity in the cirrhosis subgroup was significantly less for the IP group compared with the control group ($P = .01$). In the cirrhosis subgroup, the result was stable ($P = .04$), without heterogeneity ($P = .59$; $I^2 = 0\%$). Meta-analysis of AST level on postoperative day (POD) 1 indicated lower postoperative AST level in the IP group ($P = .04$). The analysis of ALT level showed lower ALT level in the IP group versus control group ($P = .02$). However, there was no difference in postoperative AST and ALT level after excluding 1 study with statistical heterogeneity (all $P > .05$). With respect to postoperative TB level, there was no significant difference between 2 groups.

Conclusion: IP cannot decrease the hospital mortality for patients undergoing hepatectomy. IP may be beneficial for patients with cirrhosis due to less morbidity in patients with liver cirrhosis. However, we cannot conclude that IP can decrease ischemia-reperfusion injury because it did not significantly decrease postoperative AST, ALT, and TB levels.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CENTRAL = Cochrane Central Register of Controlled Trials, CI = confidence intervals, ICU = intensive care center, IP = ischemic preconditioning, IRI = ischemia-reperfusion injury, MeSH = medical subject headings, OR = odds ratios, POD = postoperative day, RCT = randomized controlled trials, TB = total bilirubin, WMD = weighted mean differences.

Keywords: hepatectomy, ischemic preconditioning, meta-analysis, vascular exclusion

1. Introduction

Hepatic inflow occlusion is usually needed in liver resections. Pringle maneuver (in a manner of 15 minutes of occlusion and 5 minutes of reperfusion repetitively) is one the most commonly used techniques to achieve blood loss control during liver parenchymal transection.[1] Although Pringle maneuver can reduce ischemia-reperfusion injury (IRI) significantly,[2] it is still necessary to reduce this damage further. It has been proved that IP was beneficial to IRI reduction on some animal models.[3,4] Moreover, IP has decreased the adverse effects of hepatic inflow occlusion such as instable hemodynamics.[5] However, the superiority of IP before continuous vascular exclusion is controversial in several randomized controlled trials (RCTs) comparing IP maneuver to control methods (Pringle maneuver only or other methods, used for control of blood loss without IP).[6–8]

To our knowledge, only 1 meta-analysis (including 4 trials) evaluating the role of IP was performed 7 years ago.[9] Several RCTs have been published to date comparing IP maneuver to the control (no IP maneuver before continuous vascular exclusion).[10–21] The objective of this study was to perform a meta-analysis of all published RCTs and demonstrate the effect of IP

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for intraoperative parameters (such as blood loss) and postoperative characteristics (including overall morbidity and mortality, liver function after surgery, and hospital or ICU stay) in patients undergoing liver resections.

2. Methods

2.1. Data sources and searches

Embase, Medline, the Cochrane Hepato-Biliary Group Controlled Trials Register, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to December 2016 were searched using a highly sensitive filter for detection of RCTs. The MeSH terms included ischemic preconditioning, ischemia, liver, liver neoplasms, liver diseases, hepatectomy, liver transplantation. The other free-text search terms and truncated words included occlusion, clamping, exclusion, vascular, vessel, arter*, venous, hepatic, portal, pringle, ischaemi*, ischemi*, precondition*, segmentectomy, resection, transplant*, and graft*. No limitations such as publication date or filters for Journal categories were used in the search strategies. The date of the most recent search was September 1, 2014. Ovid was used for searches, and the computer program Endnote X7 was used for reference management. The references from the included trials were searched to identify additional studies. This study was approved by the Ethical Committee of our hospital.

2.2. Study selection and extraction

Two authors (Guo XJ and Liu GP) carried out the searches and identifications of studies independently. We identified studies with patients who underwent liver resection for both malignant and benign conditions in both normal and cirrhotic livers. The included studies should be RCTs evaluating the potential role of IP (irrespective of the liver status, duration, timing of the vessel occluded to provide the IP stimulus) to reduce IRI in hepatectomy. According to the protocol, Cochrane Collaboration guidelines were used for risk of bias assessment (including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting).[22]

We extracted the data on baseline characteristics of included trials (i.e., study period, indications for surgery), studying patients (i.e., gender, age), and perioperative parameters (i.e., duration of surgery, intraoperative blood loss, no. of patients transfused). The primary outcomes were postoperative morbidity, mortality, postoperative aspartate aminotransferase (AST) level, alanine aminotransferase (ALT) level, and total bilirubin (TB) level. The other outcomes included parameters such as blood loss, operative time, time of vascular occlusion and duration of hospital stay, or intensive care unit (ICU) stay. Morbidity was defined as complications directly associated with the liver resection or other general complications such as renal insufficiency, pulmonary infection, pleural effusion, surgical site infection, and vein thrombosis. Operative mortality was defined as death within 30 days after liver resection.

2.3. Statistical analysis

Meta-analyses of RCTs were performed by Review Manager 5.3 software (Cochrane Collaboration). Postoperative morbidity and mortality were calculated as odds ratio (OR) with 95% confidence interval (95% CI). Weighted mean difference (WMD) was effect measure for the other continuous data. Data presenting as median (range) were excluded of meta-analysis. Clinical and statistical heterogeneity of the included studies were checked carefully. Heterogeneity was determined by χ^2 test, with significance set at $P < .05$. And I^2 values of 50% or more indicated the presence of heterogeneity. A fixed-effects model was utilized to synthesize data when heterogeneity was not presented, otherwise the random effects model would be employed. In all analyses, P value $< .05$ for overall effect was considered statistically significant.

Publication bias was explored by constructing funnel plots and detecting asymmetry. Sensitivity analysis was carried out to test the validity of the meta-analyses and a single trial involved in the pooled meta-analysis was excluded each time to observe if the corresponding ORs or WMDs were changed significantly. Forest plots were used to present the data of meta-analyses. Subgroup analyses were performed between groups with cirrhotic and noncirrhotic livers, groups with major and minor hepatectomies, and among groups with different methods of vascular exclusion.

3. Results

The flow diagram of electronic searches is displayed in Fig. 1. After reviewing the abstracts and titles of the 445 RCTs acquired by the literature search, 23 studies were selected for detailed evaluation. After excluding studies with inadequate study intervention and insufficient data, 13 studies with a cumulative sample size of 918 patients were finally included in the analysis. A risk of bias summary table is shown in Fig. 2 and the risk of each category was expressed as a plus (high risk of bias), question mark (unclear), and minus (low risk of bias), respectively. Pooled data were analyzed by combining the results of the 13 RCTs.

3.1. Characteristics of RCTs

The baseline characteristics are summarized in Tables 1–3. The included 13 RCTs were published between 2002 and 2014 from Greece, France, Germany, Switzerland, Hungary, Sweden, and China.[5,10–21] All the studies (Tables 1–3) included comparisons of 2 methods (IP vs no IP before continuous vascular occlusion). Six trials enrolled both cirrhotic and noncirrhotic patients[11,13–16,21] and 7 trials included only noncirrhotic patients.[5,10,12,17–20] In 6 trials, more than half of patients underwent hemi-hepatectomy or extended hemi-hepatectomy.[11–13,17–19] In 3 trials,[15,16,21] IP was performed through 5 minutes of inflow

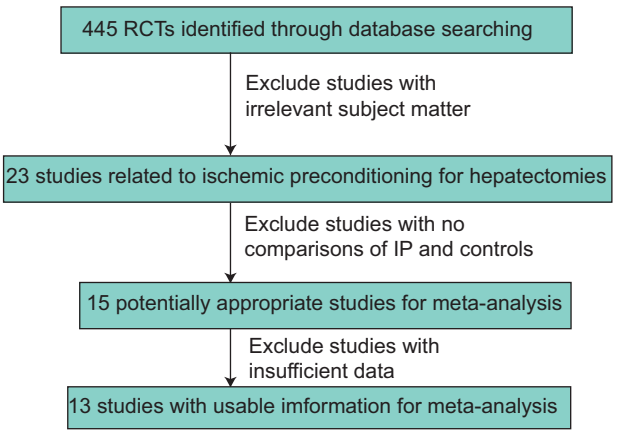

Figure 1. PRISMA Flowchart describing literature search strategy.

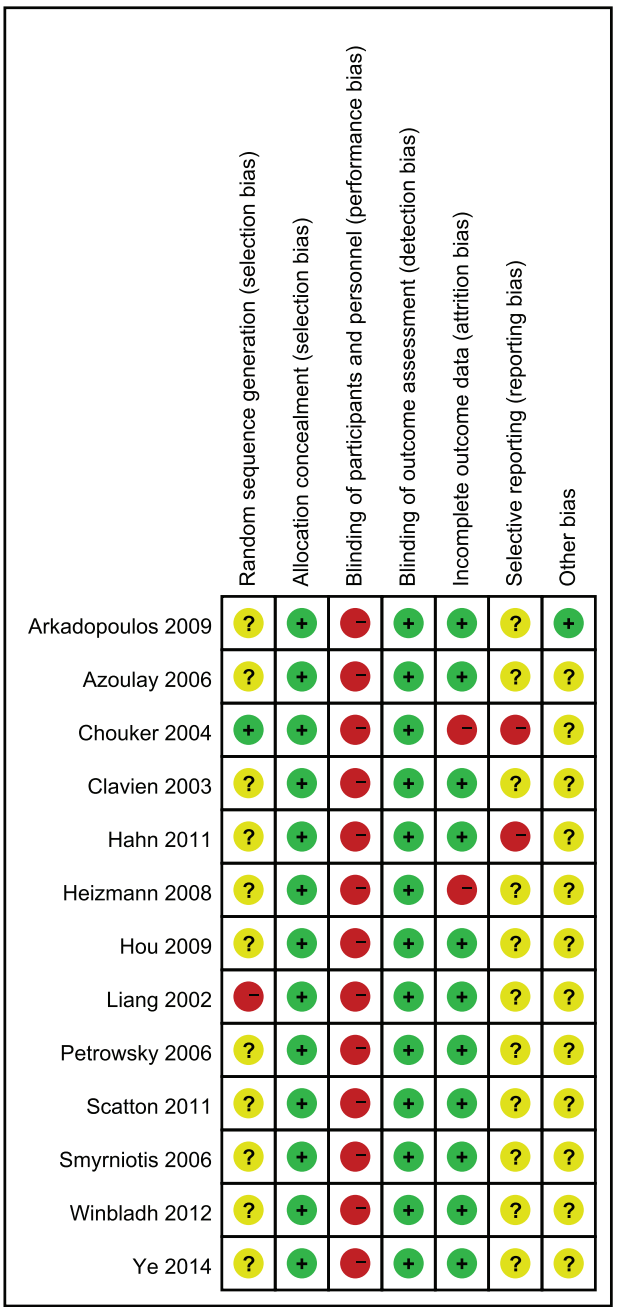

Figure 2. Risk of bias in RCTs.

occlusion followed by 5 minutes of reperfusion before the latter Pringle maneuver (the control group was performed Pringle maneuver only). In 7 studies of IP group,[5,11,13,14,18–20] the Pringle maneuver was preceded by 10 minutes of ischemia and 10 minutes of reperfusion (the control group was performed Pringle maneuver only). In 2 trials,[12,17] IP was carried out through 10 minutes of inflow occlusion and 10 minutes of reperfusion, prolonged 30 minutes of ischemia (patients from the control group in 1 trial[12] have undergone 30 minutes of ischemia before 30 minutes of reperfusion without IP, and patients from the control group in another trial[17] have undergone only Pringle maneuver). In 1 study,[10] IP was done by inflow occlusion of 10 minutes followed by reperfusion of 15 minutes before continuous hepatic vascular exclusion. Funnel plot to evaluate publication bias for outcomes of hospital morbidity and mortality did not demonstrate strong asymmetry, and there was no evidence of publication bias.

3.2. Meta-analysis of intraoperative outcomes

Twelve trials[5,10–14,16–21] provided data for operative time. There was no statistically significant difference in the operative time between the 2 groups (WMD 1.63; 95% CI −3.92 to 7.18; $P=.57$; $I^2=64\%$). Statistical heterogeneity was presented and $P=.001$. Twelve trials[5,10–14,16–21] provided usable data on duration of vascular occlusion and the IP group had significantly shorter hepatic inflow occlusion time (WMD −2.00; 95% CI −3.63 to −0.36; $P=.02$; $I^2=78\%$). Meta-analyses of all 10 trials[5,11–14,16–19,21] found that patients from IP group had less blood loss (WMD −63.71; 95% CI −105.27 to −22.15; $P=.003$; $I^2=52\%$) than from the control one (Table 4).

3.3. Meta-analysis of postoperative outcomes

Seven trials[5,10,15,16,19–21] provided data of AST levels on POD 1. In the random-effects model, meta-analysis of AST levels on POD 1 indicated lower postoperative AST level in the IP group (WMD −128.98; 95% CI −253.31 to −4.66; $P=.04$; $I^2=75\%$). Data from 6 trials[5,14–16,20,21] were included in the analysis of ALT level on POD 1 and lower ALT level was found in IP group versus control group (WMD −168.24; 95% CI −307.54 to −28.94; $P=.02$; $I^2=50\%$). Meta-analysis of AST (4 studies)[15–17,19] and ALT (3 studies) [15,16,20] levels on POD 3 showed no significant difference between IP group and control group (AST: WMD −22.16; 95% CI −158.87 to 114.55; $P=.75$; $I^2=89\%$. ALT: WMD −51.58; 95% CI −250.50 to 147.34; $P=.61$; $I^2=82\%$). Meta-analysis (including 3 studies)[11,15,16] of AST and ALT levels on POD7 showed no significant difference between IP group and control group (AST: WMD 4.17; 95% CI −4.84 to 13.18; $P=.36$; $I^2=0\%$. ALT: WMD −1.69; 95% CI −43.70 to 40.31; $P=.94$; $I^2=75\%$). Meta-analyses of TB levels on POD 1 (which includes 4 studies)[14–16,20] and POD3 (which includes 3 studies) [15,16,20] indicated no significant difference between the IP group and control group (POD 1: WMD 0.14; 95% CI −3.79 to 4.08; $P=.94$; $I^2=0\%$. POD3: WMD −0.91; 95% CI −19.52 to 17.71; $P=.92$; $I^2=80\%$). In 3 trials[11,15,16], a meta-analysis of TB levels on POD 7 indicated lower postoperative TB level in the IP group (WMD −9.86; 95% CI −18.33 to −1.38; $P=.02$; $I^2=0\%$).

Seven studies[11,13,16–19,21] provided data on hospital stay and no significant difference was found (WMD −1.60; 95% CI −4.08 to 0.88; $P=.21$; $I^2=90\%$) between IP group and control group in a random-effects model. Five studies[11,13,14,17,18] provided data on ICU stay and no significant difference was found (WMD −0.26; 95% CI −2.42 to 1.89; $P=.81$; $I^2=97\%$) between 2 groups. Data from 11 trials[10–12,14–21] were included in the analysis of postoperative mortality and no significant difference was found between both groups (OR 1.75; 95% CI 0.60–5.06; $P=.30$; $I^2=0\%$). The analysis of 10 trials[10,13–21] providing data on morbidity found lower postoperative morbidity rate in the IP group than in the control group (OR 0.62; 95% CI 0.39–0.99; $P=.04$; $I^2=38\%$) (Table 4).

3.4. Sensitivity analyses

The primary outcomes were used to conduct sensitivity analyses to examine the stability and reliability of pooled WMDs or ORs by sequential omission of individual studies. After excluding the

Table 1

Characteristics of the included studies.

Ref.	Study period	Group	Indications	No. of patients	M/F	Age, y	Cirrhosis (n)	Preoperative AST, IU/L	Preoperative ALT, IU/L	Preoperative TB, μmol/L
Azoulay et al[11]	2001–2004	No IP	CLM = 14; HCC = 4; ICC = 8; Other = 4	30	16/14	60.7 ± 14.0	2	43.3 ± 32.2	52.1 ± 56.5	31.3 ± 48.9
		IP	CLM = 13; HCC = 5; ICC = 8; Other = 4	30	18/12	58.3 ± 14.6	3	34.7 ± 17.9	37.9 ± 28.6	15.5 ± 29.1
Chouker et al	1999–2001	No IP	Malignant:19; Benign:0	19	13/6	59.4 (28–76)	0	16.9 ± 12.8	22.9 ± 18.3	/
		IP	Malignant:13; Benign:1	14	7/7	57.7 (34–82)	0	23.3 ± 18.0	13.7 ± 7.6	/
Clavien et al[12]	1999–2001	No IP	CLM = 43; HCC = 16; ICC = 4; Benign:29; Other metastatic liver tumor: 8	50	25/25	57 ± 14	0	/	/	/
		IP		50	28/22	59 ± 14	0	/	/	/
Heizmann et al[14]	1999–2000	No IP	Malignant:28; Benign:3	31	19/12	55 ± 13 (28–77)	/	/	/	/
		IP	Malignant:26; Benign:4	30	18/12	57 ± 14 (26–81)	/	/	/	/
Hou et al[15]	2004–2006	No IP	Metastic liver tumor = 4; HCC = 33; Hemangioma: 7; Other = 4	24	37/11	48.4 ± 16.0	12	52.3 ± 41.9	53.1 ± 32.2	15.6 ± 4.2
		IP		24		47.2 ± 14.1	12	69.5 ± 42.9	73.8 ± 33.5	14.3 ± 4.5
Scatton et al[18]	2005–2007	No IP	Malignant: 38; Benign:1; Other: 2	41	/	58.2 ± 13.0	0	53.5 ± 61.7	55.5 ± 70.9	12.0 ± 10.9
		IP	Malignant: 38; Benign: 2; Other: 3	43	/	62.0 ± 13.6	0	39.2 ± 22.5	38.6 ± 24.8	12.1 ± 9.1
Smymiotis et al[1]	2003–2004	No IP	All liver malignancy	27	18/9	62 (19–78)	0	/	/	/
		IP		27	20/7	63 (23–78)	0	/	/	/
Winbladh et al[20]	2008–2009	No IP	Malignant:13; Benign:3	16	10/6	64	/	47.5 ± 71.67	32.5 ± 15.69	16.8 ± 2.40
		IP	Malignant:15; Benign:1	16	8/8	63.5	/	41 ± 24.29	25.5 ± 8.99	9.66 ± 9.41
Arkadopoulos et al[10]	2002–2006	No IP	Malignant: 38; Benign: 5	43	/	61 (16–82)	0	36 ± 21	/	/
		IP	Malignant: 37; Benign: 4	41	/	63 (42–84)		41 ± 28	/	/
Hahn et al[13]	2004–2008	No IP	CLM = 27; HCC = 24; ICC = 14; Other = 15	80	42/38	56.76	30	/	/	/
		IP	CLM = 24; HCC = 25; ICC = 13; Other = 18	80	37/43	54.99	30	/	/	/
Liang et al[16]	2001	No IP	HCC	15	12/3	49.5 ± 10.3	12	64.7 ± 39.2	56.7 ± 53.9	22.6 ± 13.1
		IP		14	12/2	50.4 ± 10.7	13	60.1 ± 55.4	54.8 ± 45.0	18.9 ± 7.4
Petrowsky et al[17]	2005	No IP	Malignant: 28; Benign: 9	37	15/22	58.9 ± 2.3	0	37.5 ± 4.9	56.8 ± 11.7	12.7 ± 1.7
		IP	Malignant: 22; Benign: 14	36	23/13	56.5 ± 2.3	0	41.4 ± 4.7	54.1 ± 9.9	14.9 ± 2.1
Ye et al[21]	2005–2008	No IP	Malignant: 42; Benign: 8	50	37/13	52.8 ± 11.4	34	43.8 ± 28.5	43.8 ± 28.5	14.2 ± 6.4
		IP	Malignant: 44; Benign: 6	50	39/11	50.2 ± 15.3	33	45.7 ± 29.3	45.7 ± 29.3	14.5 ± 6.9

Values are mean ± (SD).

ALT = alanine aminotransferase; ASA = American Society of Anesthesiologists; AST = aspartate aminotransferase; CLM = colorectal liver metastasis; F = female; HCC = hepatocellular carcinoma; ICC = intrahepatic cholangiocarcinoma; M = male; TB = total bilirubin.

Table 2

Intraoperative results of the included studies.

Ref.	Group	Tumor size, cm	Liver segments resected	Operative time, min	Vascular exclusion time, min	Blood loss, mL	Blood transfusion, U
Azoulay et al[11]	No IP	/	4.4±0.9	309±99	47.7±8.3	1066±748	1.4±2.1
	IP	/	4.2±0.8	289±85	44.5±9.2	1005±850	1.1±2.3
Chouker et al	No IP	/	5/14 (n) (hemi/segment)	257±83	35±11	600±448	0
	IP	/	4/10 (n) (hemi/segment)	251±46	32±6.3	550±341	0
Clavien et al[12]	No IP	/	40±19.9 (% resected volume)	240±92	45±6.8	225±325	/
	IP	/	57±22.7 (% resected volume)	225±73	36±5.9	240±92	/
Heizmann et al[14]	No IP	/	2.7±1.1	271±58	33±12	1940±760	0.90±1.24
	IP	/	2.7±1.3	260±63	34±14	1280±910	0.47±1.31
Hou et al[15]	No IP	8.2±4.0	11/13 (n) (hemi/segment)	/	/	600 (50–1500)	/
	IP	8.9±4.8	5/19 (n) (hemi/segment)	/	/	400 (50–2000)	/
Scatton et al[18]	No IP		33/8 (n) (hemi/segment)	299.2±122.8	52.4±27.7	562.0±382.3	12.5±8.2
	IP		38/5 (n) (hemi/segment)	281.7±107.4	45.0±19.6	792.9±1134.4	13.2±15.2
Smyrniotis et al[1,19]	No IP	/	13/14 (n) (major/minor)	236.8±27.8	41.4±4.3	720±220	0 (0–4)
	IP	/	14/13 (n) (major/minor)	210.8±30.9	42.5±6.3	520±247	0 (0–3)
Winbladh et al[20]	No IP	/	/	310±96.12	44±7.0		/
	IP	/	/	267±62.15	39.5±11.17		/
Arkadopoulos et al[10]	No IP	/	3.6±0.9	190±27	42±10	480 (260–1950)	1 (0–6)
	IP	/	3.7±0.8	185±34	42±11	550 (220–2350)	1 (0–7)
Hahn et al[13]	No IP	43.5 cm^3	46/34 (n) (hemi/segment)	152±54.49	29.5±3.40	408.75±64.76	2.46±0.30
	IP	49.75 cm^3	48/32 (n) (hemi/segment)	161±39.34	28.5±2.71	355±61.00	1.34±0.35
Liang et al[16]	No IP	7.9±2.9	2/13 (n) (hemi/segment)	208.2±45.3	17.4±2.3	602.0±310.6	/
	IP	7.1±3.6	2/12 (n) (hemi/segment)	191.3±74.9	18.0±3.6	469.2±292.6	/
Petrowsky et al[17]	No IP	/	major	300±19	40.0±2.1	492±75	2.9±0.5
	IP	/	Major	316±21	37.7±1.5	426±75	1.7±0.3
Ye et al[21]	No IP	/	17/33 (n) (hemi/segment)	185±60	29.4±12.6	298±250	2.67±1.25
	IP	/	12/38 (n) (hemi/segment)	197±54	30.1±15.6	257±203	2.0±0.58

Values are presented as mean±SD or median (range).
IP = ischemic preconditioning.

study of Liang et al,[16] pooled outcomes of ALT-POD3, AST-POD3, and ALT-POD7 have not been changed along with reduced heterogeneity (I^2=0%). However, when excluding this study, the analytical results of AST and ALT on POD1 were changed considerably (the statistical difference between IP group and control group has disappeared) with reduced heterogeneity (AST on POD1: WMD −84.22; 95% CI −193.50 to 25.06; P=.13; I^2=62%; ALT on POD1: WMD −102.25; 95% CI −216.46 to 11.96; P=.08; I^2=0%) (Figs. 3, 4).

After excluding the study of Hahn et al,[13] the result of hospital morbidity was changed considerably (the statistical difference between IP group and control group disappeared) along with reduced heterogeneity (OR 0.74; 95% CI 0.52–1.06; P=.10; I^2=0%) (Fig. 5). The other corresponding WMDs or ORs were not significantly changed, when a single trial, involved in the pooled meta-analysis, has being excluded each time in sensitivity analyses (data not shown).

3.5. Subgroup analyses

3.5.1. Postoperative morbidity. Meta-analysis stratified by bias-risk cannot be performed, as all the trials were of high bias-risk. Subgroup analyses were carried out on groups with cirrhotic and noncirrhotic livers, on groups with major and minor hepatectomies, and on groups with different methods of vascular occlusion. In the cirrhotic-liver group, subgroup analysis revealed that the postoperative morbidity rate was significantly lower in the IP group than in the control group (OR 0.37; 95% CI 0.17–0.81; P=.01; I^2=46%). After excluding the study of Hahn et al[13] in the cirrhotic-liver group, the pooled result has been unchanged (OR 0.53; 95% CI 0.29–0.98; P=.04), with no heterogeneity (P=.59; I^2=0%) (Fig. 6). However, in the noncirrhotic-liver group, the subgroup analysis found no statistical difference between morbidity rates in IP group and control one (OR 0.89; 95% CI 0.57–1.40; P=.63; I^2=0%).

On the basis of the difference between IP methods, included studies have been divided into 2 subgroups: subgroup 1 (IP group: 10 minutes of ischemia + 10 minutes of reperfusion + Pringle maneuver; control group: Pringle maneuver) and subgroup 2 (IP group: 5 minutes of ischemia + 5 minutes of reperfusion + Pringle maneuver; control group: Pringle maneuver). The morbidity rate in IP and control groups presented no significant difference in both subgroups (subgroup 1: OR 0.48; 95% CI 0.20–1.11; P=.08; I^2=63%; subgroup 2: OR 0.67; 95% CI 0.33–1.39; P=.77; I^2=0%) (Fig. 7). After excluding study of Hahn et al,[13] the heterogeneity in subgroup 1 was reduced without changing the pooled outcome (Table 5).

3.5.2. AST on POD1. The analytical results for both cirrhotic- and noncirrhotic-liver subgroups showed that AST on POD1 had no significant difference between the IP and control groups (cirrhotic group: WMD −195.57; 95% CI −456.11 to 64.98; P=.14; I^2=77%; noncirrhotic group: WMD −84.76; 95% CI −232.33 to 62.82; P=.26; I^2=76%). One study[16] in the cirrhotic-liver subgroup obviously influenced the statistical heterogeneity; thus, we excluded this study and performed the combined analysis of the other 2 studies. The meta-analysis of the 2 studies revealed that the value of AST on POD1 also had no statistical difference between 2 groups (WMD −71.01; 95% CI −231.36 to 89.34; P=.39), with no heterogeneity (I^2=0%; P=.76).

When subgroup analyses were performed, basing on the different IP methods, both analyses of subgroup 1 (IP group: 10

Table 3

Postoperative results of the included studies.

Ref.	Group	TB, μmol/L	AST, IU/L	ALT, IU/L	Postoperative hospital stay, (ICU stay), d	Morbidity n (%)	Mortality (n)
Azoulay et al[11]	No IP	Peak in 10 d: 81.2±71.0; Day 7: 56.1±64.0; At discharge: 28.5±22.9; Day 30: 27.8±43.3	Peak in 10 d: 427±166; Day 7: 55.1±32.0; At discharge: 56.9±34.7; Day 30: 51.0±58.0	Peak in 10 d: 403±200; Day 7: 86.8±58.1; At discharge: 77.7±60.5; Day 30: 36.8±26.9	17.2±10.7 (3.3±4.1)	1.0±1.0 (per patient) (n)	0
	IP	Peak in 10 d: 63.0±60.0; Day 7: 45.1±71.0; At discharge: 25.6±33.9; Day 30: 28.4±68.2	Peak in 10 d: 851±1733; Day 7: 55.0±37.1; At discharge: 55.1±53.9; Day 30: 43.7±45.0	Peak in 10 d: 717±995; Day 7: 112.5±69.2; At discharge: 81.5±54.1; Day 30: 41.2±47.9	14.1±4.8 (2.4±1.6)	0.8±0.9 (per patient) (n)	2
Chouker et al	No IP		POD1: 408.4±322.5; POD2: 258.6±416.0	POD1: 549.8±749.1; POD2: 560.8±919.1	/	/	/
	IP		POD1: 237.2±155.1; POD2: 141.3±105.0	POD1: 254.6±135.3; POD2: 205.3±133.6	/	/	/
Clavien et al[12]	No IP	46±43 (peak)	520 (peak)	519 (peak) (in 3 d)	7 (3–54); ICU: 1 (0–16)	15%	0
	IP	56±51 (peak)	364 (peak)	406 (peak) (in 3 d)			0
Heizmann et al[14]	No IP	Day 1: 24.62±29.58 (6.84–168.09)	/	Day 1: 450±650 (54–2888)	2.68±5.57 (ICU stay)	14 (45%)	0
	IP	Day 1: 23.94±21.55 (3.93–95.59)	/	Day 1: 247±210 (45–852)	2.43±3.70 (ICU stay)	6 (20%)	1
Hou et al[15]	No IP	Day 1: 15.7±8.2; Day 3: 15.6±4.8; Day 7: 26.3±24.8	Day 1: 713.4±445.0; Day 3: 140.6±80.5; Day 7: 51.3±11.5	Day 1: 743.0±549.9; Day 3: 434.8±216.2; Day 7: 145.5±72.3	17 (10–33)	9 (37.5%)	0
	IP	Day 1: 16.1±8.4; Day 3: 25.5±22.4; Day 7: 19.9±9.5	Day 1: 687.1±695.3; Day 3: 202.1±229.2; Day 7: 57.0±23.6	Day 1: 652.6±428.3; Day 3: 527.1±483.9; Day 7: 156.1±80.0	20 (13–50)	8 (33.3%)	1
Scatton et al[18]	No IP	38 (Day 1 and peak)		510 (Day 1 and peak)	15.0±9.9 (3.3±5.4)	28 (68.3%)	2
	IP	33 (Day 1 and peak)		520 (Day 1 and peak)	15.0±12.0 (2.3±2.4)	24 (55.8%)	2
Smyrniotis et al[1,19]	No IP	/	Day 1: 594.4±200.8; Day 3: 239.7±107.5; Day 6: 46.4±8.66	/	11±3 ICU: 0 (0–3)	10 (37.0%)	0
	IP	/	Day 1: 614.6±232; Day 3: 310.1±193; Day 6: 45±9.49	/	10±4 ICU: 0 (0–4)	9 (33.3%)	0
Winbladh et al[20]	No IP	Day 1: 26.33±13.13; Day 3: 23.09±13.80; Day 4: 19.84±13.25	Day 1: 452±247.76; Day 3: 152±103.80; Day 4: 78±30.66	Day 1: 457±404.70; Day 3: 358.5±293.47; Day 4: 252.5±184.51	/	5 (31.3%)	0
	IP	Day 1: 33.01±25.65; Day 3: 30.01±30.27; Day 4: 18.72±14.30	Day 1: 575±554.93; Day 3: 175.5±127.48; Day 4: 71.5±34.15	Day 1: 512±410.64; Day 3: 373±103.8; Day 4: 260±30.66	/	7 (43.8%)	0
Arkadopoulos et al[10]	No IP	/	Day 1: 498±255	/	8 (4–19); ICU: 1 (0–8)	14 (32.6%)	0
	IP	/	Day 1: 288±140;	/	9 (5–21); ICU: 1 (0–9)	12 (29.3%)	0
Hahn et al[13]	No IP		Day 1: 320	Day 1: 285	13.58±6.35 (3.38±2.41)	22 (27.5%)	/
	IP		Day 1: 160	Day 1: 135	9.73±3.57 (1.85±0.92)	3 (3.75%)	/
Liang et al[16]	No IP	Day 1: 33.1±23.9; Day 3: 49.1±35.4; Day 7: 39.7±29.3	Day 1: 856.4±310.9; Day 3:409.6±197.4; Day 7:85.3±45.5	Day 1: 802.9±280.1; Day 3:417.3±162.6; Day 7: 130.1±49.0	18.6±9.1	3 (20%)	0
	IP	Day 1: 26.7±10.3; Day 3:25.9±9.2; Day 7: 22.8±8.0	Day 1: 433.8±143.8; Day 3: 156.7±52.5; Day 7: 56.5±18.9	Day 1: 430.9±179.4; Day 3:200.9±88.6; Day 7:89.9±42.8	12.8±3.1	1 (7.14%)	0
Petrowsky et al[17]	No IP	48.6±13.4 (peak)	528±58 (peak)	522±62 (peak)	12.7±1.4 (1.8±0.5)	14 (37.8%)	0
	IP	50.4±6.9 (peak)	645±65 (peak)	414±60 (peak)	14.7±1.6 (4.0±1.2)	15 (41.7%)	1
Ye et al[21]	No IP	/	Day 1:629.4±527.15	Day1: 638.65±517.48	14±7	11 (22%)	1
	IP	/	Day 1: 544.58±399.9	Day 1: 585.02±490.67	13±5	8 (16%)	0

Values are mean±(SD) or median (range).

ALT=alanine aminotransferase; AST=aspartate aminotransferase; IP=ischemic preconditioning; TB=total bilirubin.

Table 4

Meta-analysis of intra- and postoperative outcomes.

Parameters (IP group vs control group)	Number of studies	WMDs or ORs	95% CI	*P*	I^2
Operative duration	12	1.63	−3.92 to 7.18	.57	64%
Duration of vascular exclusion	12	-2.00	−3.63 to −0.36	.02	78%
Blood loss	10	−63.71	−105.27 to −22.15	.003	52%
AST-POD1	7	−128.98	−253.31 to −4.66	.04	75%
ALT-POD1	6	−168.24	−307.54 to −28.94	.02	50%
AST-POD3	4	−22.16	−158.87 to 114.55	.75	89%
ALT-POD3	3	−51.58	−250.50 to 147.34	.61	82%
AST-POD7	3	4.17	−4.84 to 13.18	**.36**	**0%**
ALT-POD7	3	−1.69	−43.70 to 40.31	.94	75%
TB-POD1	4	0.14	−3.79 to 4.08	**.94**	**0%**
TB-POD3	3	−0.91	−19.52 to 17.71	.92	80%
TB-POD7	3	−9.86	−18.33 to −1.38	**.02**	**0%**
Hospital stay	7	−1.60	−4.08 to 0.88	.21	90%
ICU stay	5	−0.26	−2.42 to 1.89	.81	97%
Postoperative mortality	11	1.75 (OR)	0.60 to 5.06	**.30**	**0%**
Postoperative morbidity	10	0.62 (OR)	0.39 to 0.99	.04	38%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; IP = ischemic preconditioning; CI = confidence intervals; POD = postoperative day; OR = odds ratios; TB = total bilirubin; WMD = weighted mean differences.

Bold values signify no heterogeneity between studies.

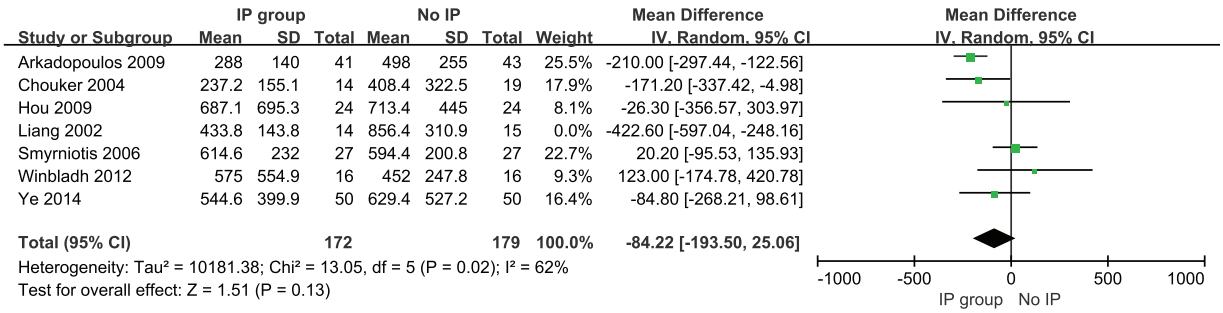

Figure 3. The analytical results of AST on POD1 when excluding 1 study [16] with data heterogeneity.

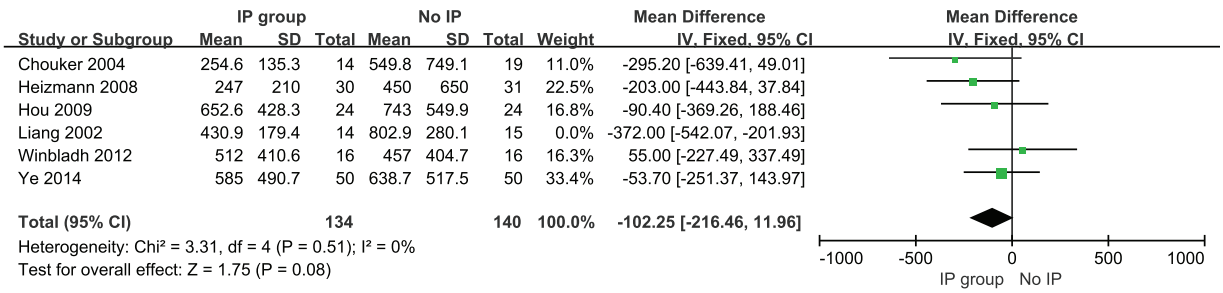

Figure 4. The analytical results of ALT on POD1 when excluding 1 study[16] with data heterogeneity.

minutes of ischemia + 10 minutes of reperfusion + Pringle maneuver; control group: Pringle maneuver) and subgroup 2 (IP group: 5 minutes of ischemia + 5 minutes of reperfusion + Pringle maneuver; control group: Pringle maneuver) revealed that AST level on POD1 had no significant difference (subgroup 1: WMD −29.14; 95% CI −183.22 to 124.93; $P = .71$; $I^2 = 56\%$; subgroup 2: WMD −195.57; 95% CI −456.11 to 64.98; $P = .14$; $I^2 = 77\%$) between 2 groups. However, the analytical results for the subgroup 3 (IP group: 10 minutes of ischemia + 15 minutes of reperfusion + TVE; control group: TVE) showed that values of AST on POD1 in the IP group were significantly lower (WMD −210.00; 95% CI −297.44 to −122.56; $P < .00001$). After excluding 1 study[5] in subgroup 1 and 1 study[16] in subgroup 2, which significantly influenced the heterogeneity of the data, the meta-analyses of the residual studies showed that values of AST on POD1 in IP groups and control groups still had no significant difference with no heterogeneities (subgroup 1: WMD 33.69; 95% CI −74.18 to 141.56; $P = .54$; $I^2 = 0\%$;

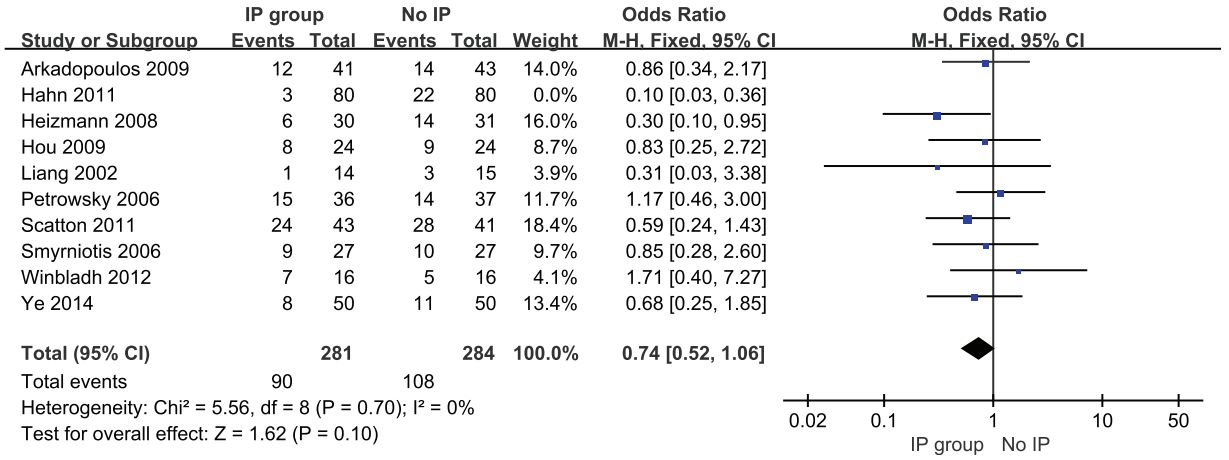

Figure 5. The analytical results of hospital morbidity when excluding 1 study[13] with data heterogeneity.

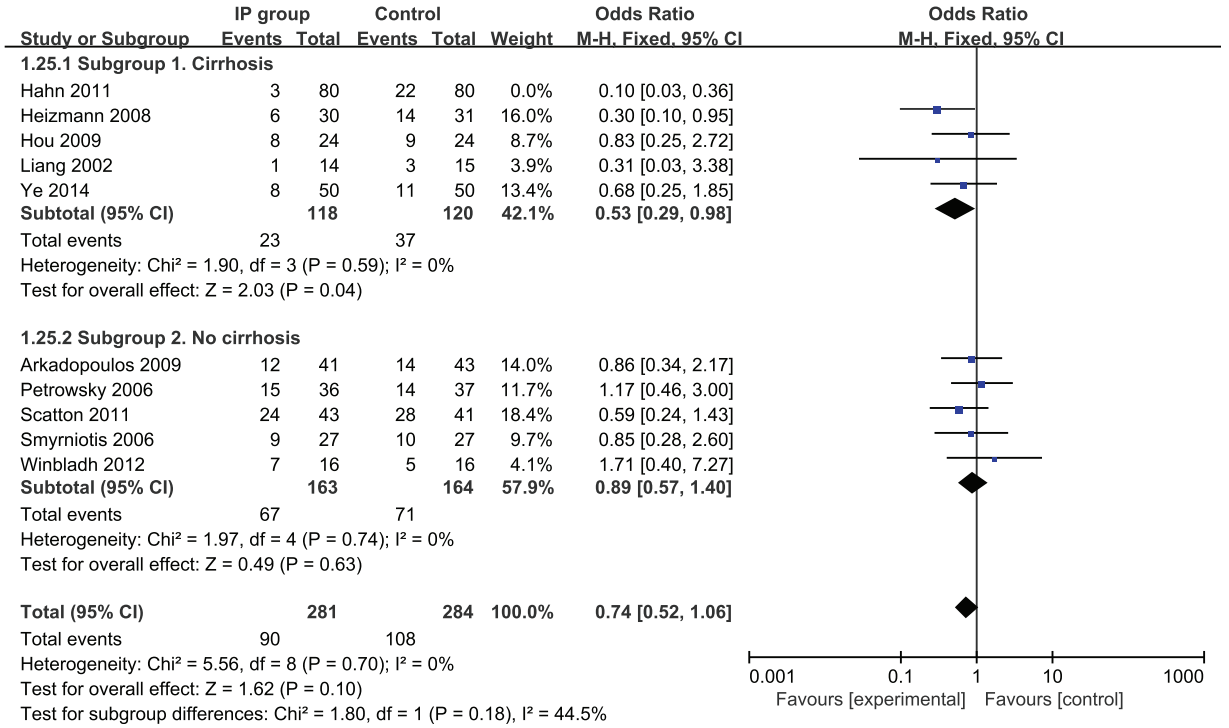

Figure 6. Subgroup analysis revealed that the postoperative morbidity in the cirrhotic-liver group was significantly less for the IP group compared with the control group.

subgroup 2: WMD −71.01; 95% CI −231.36 to 89.34; $P=.39$; $I^2=0\%$) (Table 5).

For different liver resection volume, analysis of subgroup A (more than half of patients, undergone hemi- or extended hemihepatectomy) showed that the different values of AST on POD1 in both groups exhibited no statistical significance (WMD 20.20; 95% CI −95.53 to 135.93; $P=.73$). However, for subgroup B (less than half of patients, undergone hemi- or extended hemihepatectomy), the analysis revealed that the values of AST on POD1 in the IP group were significantly lower than that in the control group (WMD −167.08; 95% CI −288.77 to −45.38; $P=.007$; $I^2=63\%$). However, only 1 trial was included in subgroup A.

3.5.3. ALT on POD1. For values of ALT on POD1, after excluding 1 study [16] (in cirrhotic group) significantly influencing the statistical heterogeneity, the analytical results of both cirrhotic and noncirrhotic liver subgroups showed no significant difference between the IP and control groups (cirrhotic group: WMD −108.39; 95% CI −242.39 to 25.61; $P=.11$; $I^2=0\%$; noncirrhotic group: WMD −105.72; 95% CI −447.76 to 236.31; $P=.54$; $I^2=58\%$).

For the different IP methods, analysis of subgroup 1 (IP group: 10 minutes of ischemia + 10 minutes of reperfusion + Pringle maneuver; control group: Pringle maneuver) and subgroup 2 (IP group: 5 minutes of ischemia + 5 minutes of reperfusion + Pringle maneuver; control group: Pringle

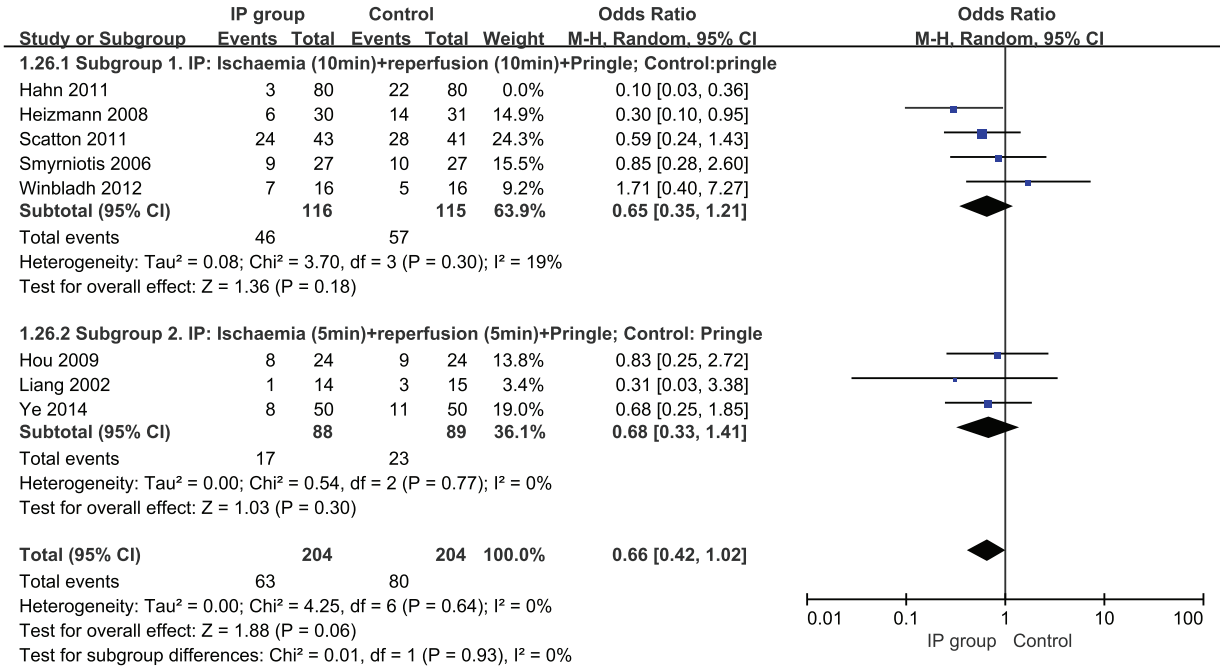

Figure 7. The morbidity presented no significant difference in subgroup 1 (IP group: 10 min of ischemia + 10 min of reperfusion + Pringle; control group: Pringle) and subgroup 2 (IP group: 5 min of ischemia + 5 min of reperfusion + Pringle; control group: Pringle).

maneuver) indicated that values of ALT on POD1 had no significant difference (subgroup 1: WMD −139.64; 95% CI −336.48 to 57.21; P=.16; I^2=30%; subgroup 2: WMD −183.66; 95% CI −405.00 to 37.69; P=.10; I^2=70%). After excluding 1 study, [16] which obviously influenced the statistical heterogeneity, the result of subgroup 2 revealed that different values of ALT on POD1 in both groups were still statistically insignificant (WMD −65.97; 95% CI −227.24 to 95.29; P=.42), with no heterogeneity (P=.83; I^2=0%) (Table 5).

Table 5

Subgroup analysis.

Subgroup	Number of studies	WMDs or ORs	95% CI	P	I^2
Postoperative morbidity					
Liver cirrhosis					
Cirrhotic liver	4*	0.53 (OR)	0.29–0.98	.04	0%
Noncirrhotic liver	5	0.89 (OR)	0.57–1.40	.63	0%
IP methods					
Subgroup 1	4	0.64 (OR)	0.37–1.10	.30	19%
Subgroup 2	3	0.67 (OR)	0.33–1.39	.77	0%
AST on POD1					
Liver cirrhosis					
Cirrhotic liver	2†	−71.01	−231.36 to 89.34	.39	0%
Noncirrhotic liver	4	−84.76	−232.33 to 62.82	.26	76%§
IP methods					
Subgroup 1	2‡	−29.14	−183.22 to 124.93	.71	0%
Subgroup 2	2†	−71.01	−231.36 to 89.34	.39	0%
ALT on POD1					
Liver cirrhosis					
Cirrhotic liver	3†	−108.39	−242.39 to 25.61	.11	0%
Noncirrhotic liver	2	−105.72	−447.76 to 236.31	.54	58%‖
IP methods					
Subgroup 1	3	−139.64	−336.48 to 57.21	.16	30%
Subgroup 2	2†	−65.97	−227.24 to 95.29	.42	0%

Subgroup 1: (IP group: 10 min of ischemia + 10 min of reperfusion + Pringle; control group: Pringle); Subgroup 2: (IP group: 5 min of ischemia + 5 min of reperfusion + Pringle; control group: Pringle).
IP = ischemic preconditioning; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CI = confidence interval; OR = odds ratios; POD = postoperative day; WMD = weighted mean differences.
* Exclude study of Hahn et al.[13]
† Exclude study of Liang et al.[16]
‡ Exclude study of Chouker et al.
§ The sensitivity analysis did not find out the source of heterogeneity.
‖ Only 2 studies were included in this subgroup and sensitivity analysis was not performed.

4. Discussion

No significant difference has been found in the analysis of postoperative mortality in both groups, while in our meta-analysis, ischemic preconditioning did decrease the morbidity of the patients undergoing hepatectomy with continuous hepatic inflow occlusion. However, after excluding the study lead to the data heterogeneity, the conclusion was changed significantly (IP had no impact on decreasing of postoperative morbidity in the total included patients). The excluded study was a randomized trial from Hahn et al.[13] In this study, including patients with both normal and cirrhotic liver, the authors demonstrated that IP could decrease the IRI of the liver obviously with less postoperative morbidity, especially in patients with cirrhosis. They also found that IP significantly reduced the level of serum free radicals and liver enzymes and decreased the consumption of antioxidants (more obviously in patients with cirrhosis). Through the subgroup analysis, pooled data of the studies, including cirrhotic-liver patients, indicated that the morbidity was less in IP group than in the control group before and after excluding the study of Hahn et al.[13] We proposed that patients with cirrhosis benefit most from IP before continuous vascular occlusion. Nevertheless, IP did not decrease postoperative morbidity of the patients with noncirrhotic liver. Consequently, intermittent vascular occlusion during liver resection in patients with cirrhosis should be carried out with caution due to the limited compensatory function of the cirrhotic liver.

Liver failure is a severe complication after intraoperative hepatic inflow occlusion, especially in cirrhotic liver.[23] However, due to the limitation of the included trials in our meta-analysis and the low rates of liver failure in these studies, we cannot analyze the difference between liver failure rates in 2 groups. The pooled results of postoperative TB level (one of the components of liver failure definitions)[24] on POD 1 and 3 also showed no statistical difference. Specially, TB level on POD7 in IP group was lower, but it is insufficient to illustrate the superiority of IP maneuver. Whereas there was a trend toward lower AST and ALT level on POD1, which may be due to the protective role of IP maneuver in blood reperfusion after liver inflow occlusion. However, the sensitivity analyses indicated that IP maneuver cannot decrease ALT and AST level on POD1 when excluding study of Liang et al.[16] This study was carried out in 2002 and the quality score was low due to the loss of randomization and the low sample size. This study was the source of hepatectomy when pooling postoperative ASTs and ALTs.

We did not analyze the data of the peak levels of these enzymes between the 2 groups because only 2 trials provided complete data on it. Intraoperative blood loss in IP group was less and the reason was not found. The operative duration of IP group was shorter, though it may be time-consuming when performing IP maneuver. There was no difference in the hospital stay and ICU stay between the groups.

There are several limitations in the present analysis. Unlike the previous meta-analysis on the role of IP,[9] our meta-analysis included RCTs that did not include only cirrhotic or noncirrhotic patients. In subgroup analysis, the cirrhotic-liver group did not include trials only studying cirrhotic-liver patients (we divided the studies into cirrhotic-liver group when cirrhotic patients accounted for more than or nearly half of the total cases).[13–16,21] Moreover, the included studies had different methods of IP maneuver (with different hepatic exclusion time and reperfusion time). It is not clear whether or not the difference between IP methods can influence the effectiveness of IP in liver resections. More RCTs should be carried out for illustration of this issue. Further trials for demonstration of the mechanism of IP are also needed. In addition, though most of the patients in the included studies underwent major hepatectomies, studies recruiting a small number of patients underwent minor hepatectomies in this review may not have difference in outcomes between IP group and control group.[14,16] All these factors can influence the stability of the conclusion. All the trials in the present analysis were of high risk of bias according to the standard of the Cochrane Collaboration. Blinding was not carried out in any of the trials due to the difficulty to blind the surgeons to the groups. Some of the included trials did not provide the primary outcomes related to our meta-analyses, which results in high risk of bias.

In conclusion, IP cannot decrease hospital mortality of patients undergoing hepatectomy, and IP may be beneficial for patients with cirrhosis because of less morbidity among cirrhotic-liver patients. However, IP may not decrease IRI because it did not significantly decrease postoperative AST, ALT, and TB levels. In addition, some factors including IP methods and extent of hepatectomy may also influence the role of IP maneuver in liver resections. Some high-quality trials are needed to illustrate the role of IP maneuver in patients with different liver background, different liver diseases, different extent of liver resections, and different hepatectomy methods (open or laparoscopic).

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