Original Article

Comparing the protective effects of local and remote ischemic preconditioning against ischemia-reperfusion injury in hepatectomy: a systematic review and network meta-analysis

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Background: Local ischemic preconditioning (LIPC) has been proven to be a protective strategy against hepatic ischemia-reperfusion injury (HIRI) during hepatectomy. Growing evidence suggests remote ischemic preconditioning (RIPC) has the potential to reduce liver injury in hepatectomy. Few studies have directly compared the protective effects of these two mechanical preconditioning strategies. Therefore, we performed a network meta-analysis to compare the efficacy of LIPC and RIPC for hepatic injury during liver resection.

Methods: We searched Cochrane, PubMed, Embase, and China National Knowledge Infrastructure (CNKI) from the database inception to January 2023. We included studies directly comparing the effectiveness of LIPC and RIPC and those comparing LIPC or RIPC with no-preconditioning in liver resection. Postoperative liver function and surgical events were analyzed. Data were expressed as standardized mean differences (SMDs) or odds ratios (ORs) and analyzed using network meta-analysis with random effects model.

Results: Following the screening of 268 citations, we identified 26 eligible randomized clinical trials (RCTs) involving 1,476 participants (LIPC arm: 789, RIPC arm: 859, no-preconditioning arm: 1,072). LIPC and RIPC were superior to no-preconditioning in reducing postoperative serum transaminase levels [aspartate aminotransferase (AST): SMD RIPC versus no-preconditioning: −2.05, 95% confidence interval (CI): −3.39, −0.71; SMD LIPC versus no-preconditioning: −1.10, 95% CI: −2.07, −0.12; alanine aminotransferase (ALT): SMD RIPC versus no-preconditioning: −2.24, 95% CI: −4.15, −0.32; SMD LIPC versus no-preconditioning: −1.32, 95% CI: −2.63, −0.01]. No significant difference was observed between RIPC and LIPC in postoperative liver function and surgical outcomes (AST: SMD RIPC versus LIPC: −0.95, 95% CI: −2.52, 0.62; ALT: SMD RIPC versus LIPC: −0.91, 95% CI: −3.11, 1.28). In addition, the subgroup analysis revealed the potential benefits of RIPC in improving liver function, especially in patients who diagnosed with cirrhosis or underwent major resection.

Conclusions: RIPC and LIPC could serve as effective strategies in relieving HIRI during hepatectomy. No significant differences were observed between LIPC and RIPC, however, RIPC may be an easily applicable strategy to relieve liver injury in hepatectomy.

Keywords: Local ischemic preconditioning (LIPC); remote ischemic preconditioning (RIPC); hepatic ischemia-reperfusion injury (HIRI); liver resection

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Introduction

Hepatic resection has been used worldwide for treating both benign and malignant liver masses (1,2). However, intraoperative hepatic bleeding remains a significant challenge (3-5). The Pringle maneuver, involving intermittent inflow occlusion during hepatectomy could effectively reduce blood loss; whereas, it raises concern regarding hepatic ischemia-reperfusion injury (HIRI) during hepatectomy (6), especially when combined with low central venous pressure (7). The severity of HIRI is associated with higher rates of postoperative morbidity and mortality (8,9). Thus, finding effective strategies to mitigate HIRI in liver resection is recognized as a research priority.

Local ischemic preconditioning (LIPC) is a protective strategy that exposes the liver to a temporary period of ischemia before hepatectomy, enabling adaptation to subsequent long-term ischemic insults. Experimental and clinical evidence has revealed that LIPC can ameliorate hepatic injury (10-16). In addition, a recent network meta-analysis (17) demonstrated that LIPC resulted in multiple beneficial clinical endpoints during elective liver resection. Despite these promising results, LIPC has not gained widespread adoption in clinical practice. This may be partly due to the fact that LIPC can induce direct liver ischemia and necessitates additional surgical procedures, thereby increasing the surgical complexity and extending the operative time. Subsequently, remote ischemic preconditioning (RIPC), another mechanical preconditioning strategy, has been recognized for its effectiveness, as numerous studies have demonstrated its benefits within the same organ and in distant organs (18-21). RIPC involves one or more brief cycles achieved by inflating and deflating a standard blood pressure cuff placed on a limb before surgery to play a protective role in organ function. It offers several advantages such as user-friendly control, no need for additional surgical procedures, and no increase in surgical duration. These conveniences have facilitated its translation into clinical settings (22).

However, to our knowledge, no large randomized clinical trials (RCTs) have directly compared the effects of LIPC and RIPC on hepatic function in hepatectomy. Therefore, we performed a network meta-analysis to compare the efficacy of LIPC and RIPC for hepatic injury during liver resection. We present this article in accordance with the PRISMA-NMA reporting checklist (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-95/rc).

Highlight box

Key findings

- Remote ischemic preconditioning (RIPC) and local ischemic preconditioning (LIPC) could serve as effective strategies in relieving hepatic ischemia-reperfusion injury (HIRI) during hepatectomy. No significant differences were observed between LIPC and RIPC, however, RIPC may become an easily applicable protective strategy to relieve liver injury in hepatectomy.

What is known and what is new?

- HIRI is a major hurdle to the success of hepatectomy. LIPC is known to be a protective strategy but limited in clinical practice due to its poor feasibility and invasiveness in hepatectomy. Growing evidence suggests that RIPC has protective effects against HIRI. Few studies have directly compared the protective effects of the two mechanical preconditioning methods.
- This study provided new evidence that RIPC has protective effects against HIRI as LIPC does.

What is the implication, and what should change now?

- The severity of HIRI is associated with higher rates of postoperative morbidity and mortality.
- More clinical investigations are needed to find more effective strategies to mitigate HIRI in liver resection, especially combined measures.

Methods

This meta-analysis was prospectively registered on INPLASY (CRD202370007).

Search strategy

The following databases were searched: Embase, PubMed, Cochrane Library, and China National Knowledge Infrastructure (CNKI) from database inception until January 2023. In addition, meta-analysis and references cited in the included studies were examined. A detailed search strategy is provided in Appendix 1.

Study selection

First, duplicates were removed by Endnote X9. Subsequently, three reviewers (Y.C., J.Y., and K.W.) screened the titles and abstracts of trials independently to select the eligible inclusions based on the inclusion and exclusion criteria. Full-text articles and their relevant references were carefully selected for further assessment. Disagreements were resolved by an independent reviewer (Z.Z.).

Data extraction

Three authors (Y.C., J.Y., and K.W.) extracted data independently from the eligible studies, including study characteristics, participants' information, preconditioning types, and other interesting outcomes such as liver function and operative outcomes. Disagreements were settled by an independent reviewer (Z.Z.). All data were recorded in Microsoft Excel [2016].

Quality assessment

The methodological quality of included trials and risk of bias were evaluated by the Cochrane Collaboration's tool which includes seven domains: allocation concealment, random sequence generation, incomplete outcome data, selective outcome reporting, blinding of participants and personnel, blinding of outcome assessment, and other biases. The risk of bias was graded as high, unclear, or low. The risk of bias in each trial was evaluated independently by three authors (Y.C., J.Y., and K.W.), and disagreements were discussed with an independent reviewer (Z.Z.) to reach an agreement.

Selection criteria

Studies were selected based on specific inclusion criteria: (I) participants—humans with relevant diseases necessitating hepatectomy, aged over 18 years; (II) interventions—the intervention and comparator should include one of the following: LIPC versus RIPC, LIPC versus no-preconditioning, or RIPC versus no-preconditioning; (III) outcomes—reporting of outcome indicators reflecting liver function, such as aspartate aminotransferase (AST) or alanine aminotransferase (ALT), is required; and (IV) methodological criterion—prospective RCTs.

Exclusion criteria

The following exclusion criteria were used: (I) liver transplantation studies; and (II) cluster or crossover randomized trials.

Statistical analysis

We tried to contact study authors in cases where missing or unclear data were identified. When standard deviations (SDs) were unreported, they were computed from standard errors, P values, t values, confidence intervals (CIs), or graphical representations. Random effects models were used for the network meta-analyses. Summary odds ratios (ORs) for dichotomous outcomes and standardized mean differences (SMD) for continuous outcomes, along with their corresponding 95% CIs, were derived through network meta-analysis. The network meta-analysis was executed using the network meta package within Stata (version 16.1). Prior to conducting the network meta-analysis, an assessment of the transitivity assumption was conducted by scrutinizing the characteristics of the included studies. Statistical heterogeneity was probed via pairwise meta-analyses. Discrepancies between direct and indirect sources of evidence were assessed employing both global and local methodologies. Global inconsistency was evaluated through a design-by-treatment test, while local inconsistency was gauged using a side-splitting approach. Secondary metrics of treatment effect, such as surface under the cumulative rank curve (SUCRA) probabilities and treatment rankings, were also computed. Publication bias was explored by constructing funnel plots and detecting asymmetry. Subgroup analyses were performed between groups with cirrhotic and noncirrhotic livers, groups with major and minor hepatectomies, and groups with different times of vascular exclusion.

Outcomes

Primary outcomes: postoperative serum transaminase level, including AST and ALT on postoperative day 1 (POD1).

Secondary outcomes: other indicators to reflect liver function, like total bilirubin (TBIL) and outcomes presenting surgical process, including operative time, blood loss, and hospital stay.

Results

Study characteristics

In total, 268 studies were initially identified through the search strategy. After removing duplicates, 160 unique titles and abstracts were screened. Subsequently, 110 articles in the full-text review were assessed. Finally, 26 articles met eligibility for extraction (*Table 1*). The reasons for exclusion are shown in *Figure 1*.

Characteristics of the included studies

Among the trials included in this network meta-analysis, 13 studies were conducted in Asia, and 13 were conducted

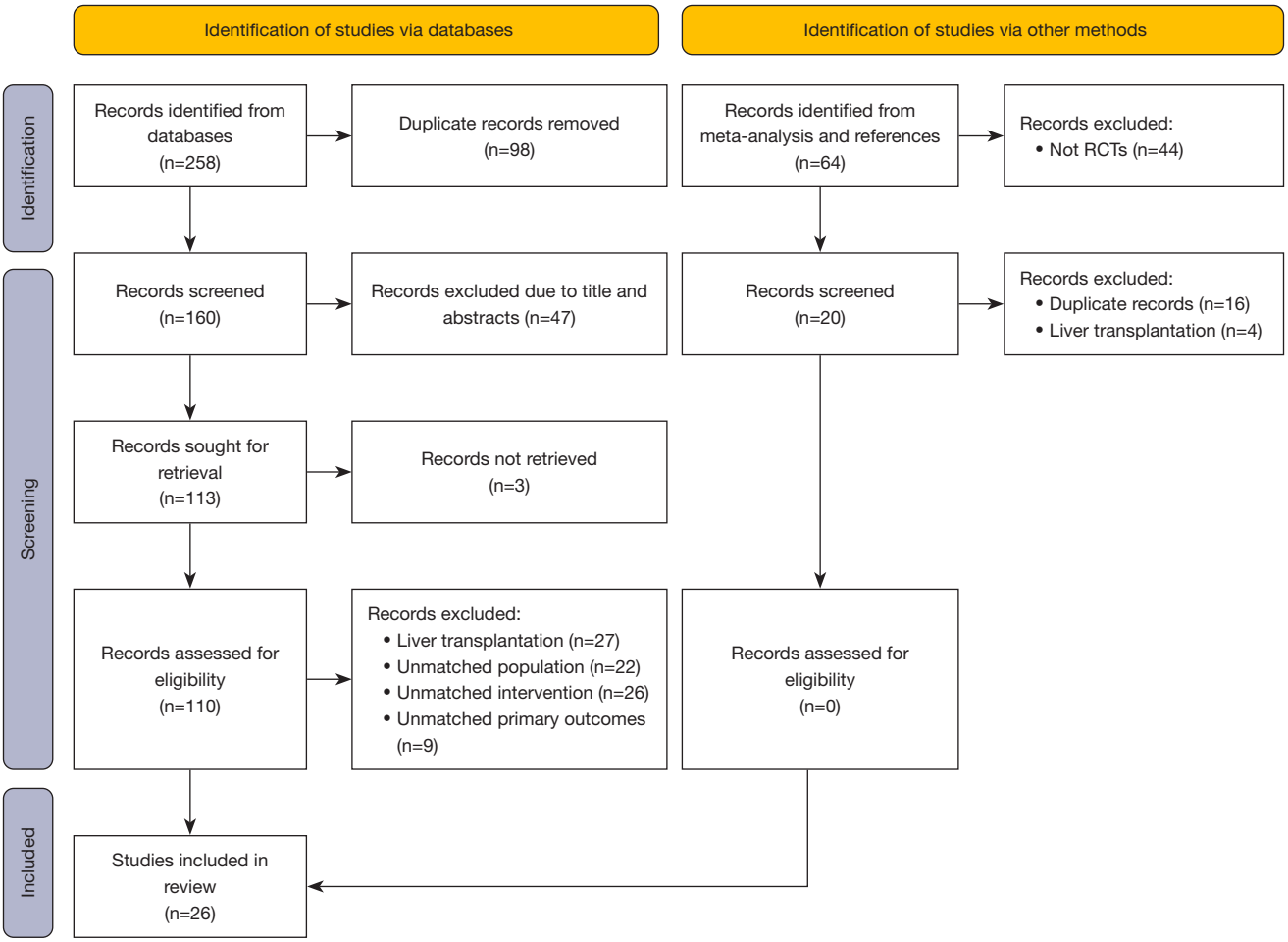

Figure 1 Study flow diagram. RCT, randomized clinical trial.

in Europe. These studies were published between 2002 and 2023. The mean age of the participants was 54 (12.7) years, and 484 (62.8%) of the patients were women. Of the 26 studies, six were limited to older adults (aged >60 years) and 10 (38%) enrolled patients undergoing major liver resection.

In ten trials (59%), LIPC was performed through 10 min of inflow occlusion followed by 10 min of reperfusion. In 6 (35%) studies in the LIPC group, the Pringle maneuver was preceded by 5 min of ischemia and 5 min of reperfusion. In 1 (6%) study, LIPC was done by inflow occlusion for 10 min followed by reperfusion for 15 min before continuous hepatic vascular exclusion.

Regarding RIPC, 7 trials (77%) were performed through three cycles of 5 min of inflow occlusion followed by 5 min of reperfusion. In one study, RIPC was conducted by three cycles of 10 min of inflow occlusion followed by 10 min of reperfusion. In another trial, RIPC was performed using four cycles of 5 min of inflow occlusion followed by 5 min of reperfusion.

We found no clear evidence of violations of the transitivity assumption when comparing characteristics of studies across comparisons (*Table 1*).

Meta-analysis

Figure 2 illustrates the network diagram of the total number of patients in each treatment. *Figures 3,4* illustrate the network of eligible comparisons for primary and secondary outcomes. *Figure 5* illustrates the ranking of treatments based on the SUCRA plot for each outcome.

Primary outcomes

AST: a total of 24 studies with 1,476 participants were

Table 1 Study and patient characteristics of included studies for analysis

ID	Source	Country	Type of preconditioning	Sample sizes, n	M/F, n	Age (years)	Ischemic time (min)	Resected volume	Cirrhosis, n	Steatosis, n
1	Choukèr *et al.* (14)	Germany	LIPC (10+10)×1	14	7/7	58±12	32±6.3	Minor resection	–	–
			No-preconditioning	34	23/11	61±10.8	35±11		–	–
2	Clavien *et al.* (23)	Switzerland	LIPC (10+10)×1	50	22/28	54±14	36±5.9	Major resection	–	13
			No-preconditioning	50	25/25	57±14	35±6.8		–	
3	Heizmann *et al.* (24)	Switzerland	LIPC (10+10)×1	31	19/12	55±13	33±12	Minor resection	–	10
			No-preconditioning	30	18/13	57±14	34±14		–	8
4	Li *et al.* (25)	China	LIPC (5+5)×1	14	12/2	50±10.7	18.0±3.6	Minor resection	13	–
			No-preconditioning	15	12/3	50±10.3	17.4±2.3		12	–
5	Azoulay *et al.* (26)	France	LIPC (10+10)×1	30	18/12	58±14.6	44.5±9.2	Major resection	1	4
			No-preconditioning	30	16/14	61±14	47.7±8.3		0	4
6	Winbladh *et al.* (27)	Sweden	LIPC (10+10)×1	16	8/8	64±14	39.5±11	Major resection	–	1
			No-preconditioning	16	10/6	64±9.4	44±10		–	3
7	Hahn *et al.* (28)	Hungary	LIPC (10+10)×1	80	42/38	57±2.2	33±2.9	Major resection	30	1
			No-preconditioning	80	37/43	55±1.8	28.5±6.2		30	2
8	Scatton *et al.* (29)	France	LIPC (10+10)×1	43	–	62±13.6	45±19.6	Major resection	–	–
			No-preconditioning	41	–	58.2±13	52.4±27.7		–	–
9	Arkadopoulos *et al.* (30)	Greece	LIPC (10+15)×1	41	–	–	42±10	Major resection	–	–
			No-preconditioning	43	–	–	42±11		–	–
10	Nuzzo *et al.* (31)	Italy	LIPC (10+10)×1	21	12/9	50±14	–	Minor resection	–	–
			No-preconditioning	21	11/10	57±11	–		–	–
11	Petrowsky *et al.* (32)	Switzerland	LIPC (10+10)×1	36	23/13	56.5±2.3	37.3±1.5	Major resection	–	15
			No-preconditioning	37	15/22	58.9±2.3	40.0±2.1		–	20
12	Ye *et al.* (33)	China	LIPC (5+5)×1	50	39/11	50±15.3	–	Minor resection	33	–
			No-preconditioning	50	37/13	53±11.4	–		34	–
13	Smyrniotis *et al.* (34)	Greece	LIPC (10+10)×1	27	20/7	63±13.75	41.4±4.3	Major resection	–	–
			No-preconditioning	27	18/9	62±14.75	42.5±6.3		–	–
14	Hou *et al.* (35)	China	LIPC (5+5)×1	24	–	47±14	–	Minor resection	12	–
			No-preconditioning	24	–	48±16	–		12	–
15	Ji *et al.* (36)	China	LIPC (5+5)×1	18	15/3	51.6±8.7	17.8±2.3	–	15	–
			No-preconditioning	16	12/4	48.6±8.6	17.9±1.8		13	–
16	Liang *et al.* (37)	China	LIPC (5+5)×1	14	12/2	50±10.7	18.0±3.6	Minor resection	13	–
			No-preconditioning	15	12/3	49.5±10.3	17.4±2.3		12	–
17	Jiang *et al.* (38)	China	LIPC (5+5)×1	35	25/10	47±11.2	24.8±9.5	–	30	–
			No-preconditioning	25	17/8	49±10.5	22.2±8.5		21	–

Table 1 (*continued*)

Table 1 (*continued*)

ID	Source	Country	Type of preconditioning	Sample sizes, n	M/F, n	Age (years)	Ischemic time (min)	Resected volume	Cirrhosis, n	Steatosis, n
18	Teo *et al.* (39)	China	RIPC (5+5)×4	24	20/4	64±11.2	37±18.7	Minor resection	11	–
			No-preconditioning	26	19/7	67±8.4	29±13.5		7	–
19	Kanoria *et al.* (40)	England	RIPC (10+10)×3	8	7/1	–	–	–	–	–
			No-preconditioning	8	6/2					
20	Liu *et al.* (41)	China	RIPC (5+5)×3	69	59/10	51.7±10.6	22±4.6	Minor resection	56	–
			No-preconditioning	67	59/8	52.1±10.9	22.3±5		51	–
21	Zou *et al.* (42)	China	RIPC (5+5)×3	20	7/13	47±11.03	49.6±5.14	Major resection	–	–
			No-preconditioning	20	9/11	52±8.22	47.5±3.72		–	–
22	Wu *et al.* (43)	China	RIPC (5+5)×3	10	–	52±8	17±4	–	–	–
			No-preconditioning	10	–	49±7	17±3	–	–	–
23	Li *et al.* (44)	China	RIPC (5+5)×3	30	17/13	39±8.5	–	–	–	–
			No-preconditioning	30	16/14	40±7.2	–	–	–	–
24	Cao *et al.* (45)	China	RIPC (5+5)×3	30	11/19	35±9.1	15.4±3.1	Major resection	–	–
			No-preconditioning	30	8/22	38±11	16.2±2.6		–	–
25	Kong *et al.* (46)	China	RIPC (5+5)×3	30	16/9	54±9.77	42.2±6.79	Minor resection	–	–
			LIPC (5+5)×3	30	15/13	54±10.68	39±28.84		–	–
			No-preconditioning	30	17/10	54±12.13	41±7.93		–	–
26	Rakić *et al.* (47)	Croatia	RIPC (5+5)×3	20	–	–	–	Minor resection	–	–
			LIPC (10+15)×1	20	–	–	–		–	–
			No-preconditioning	20	–	–	–		–	–

Values are presented as mean ± SD, unless otherwise indicated. Preconditioning types and implementation approaches were recorded. "(5+5)×3" indicates 5 min of ischemia followed by 5 min of reperfusion by three circles. n, number of events; M, male; F, female; LIPC, local ischemic preconditioning; RIPC, remote ischemic preconditioning; SD, standard deviation.

included in the network meta-analysis. RIPC and LIPC were more effective in preserving liver function than no-preconditioning (SMD RIPC versus no-preconditioning: –2.05, 95% CI: –3.39, –0.71; SMD LIPC versus no-preconditioning: –1.10, 95% CI: –2.07, –0.12). However, the network meta-analysis of indirect comparisons of RIPC and LIPC suggested no significant differences between RIPC and LIPC (SMD RIPC versus LIPC: –0.95, 95% CI: –2.52, 0.62). Furthermore, RIPC had the highest SUCRA value for AST reduction, followed by LIPC, and no-preconditioning.

ALT: in total, 23 studies with 1,466 participants were included in the network meta-analysis. Compared with no-preconditioning, RIPC (SMD RIPC versus no-preconditioning: –2.24, 95% CI: –4.15, –0.32) and LIPC (SMD LIPC versus no-preconditioning: –1.32, 95% CI: –2.63, –0.01) resulted in a significant reduction in ALT on POD1. However, no significant difference was observed between RIPC and LIPC (SMD RIPC versus LIPC: –0.91, 95% CI: –3.11, 1.28). Similarly, RIPC had the highest SUCRA value for ALT reduction on POD1, followed by LIPC, and no-preconditioning.

Secondary outcomes

TBIL: a total of 17 studies with 924 participants were included in the network meta-analysis. Compared with no-preconditioning, RIPC or LIPC exhibited no protective effect on liver function (SMD RIPC versus no-

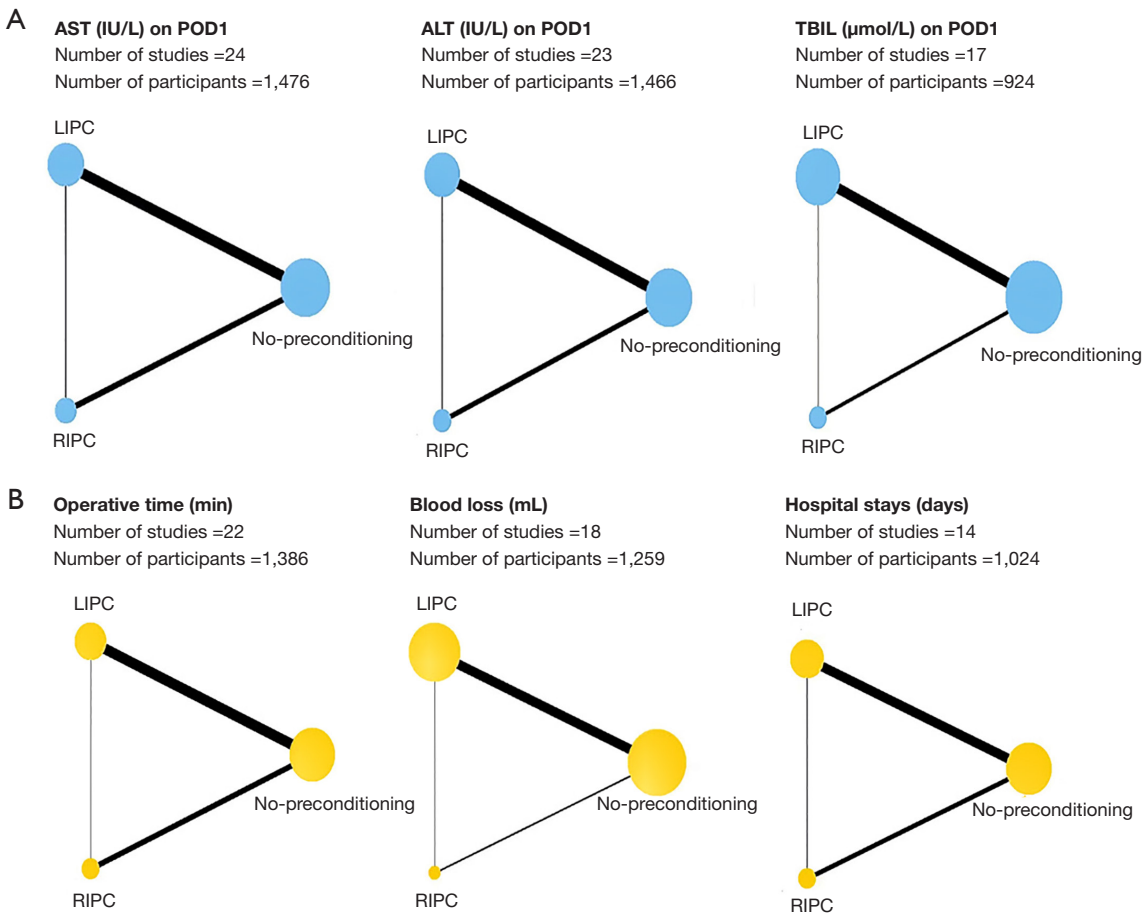

Figure 2 Network diagram depicting the total number of patients analyzed in each treatment arm. (A) AST, ALT, and TBIL on POD1. (B) Operative time, blood loss, and hospital stays. Circles represent the intervention as a node in the network; lines represent direct comparisons using RCTs; thickness of lines represents the number of RCTs included in each comparison, also represented by the numbers. AST, aspartate aminotransferase; POD1, postoperative day 1; LIPC, local ischemic preconditioning; RIPC, remote ischemic preconditioning; ALT, alanine aminotransferase; TBIL, total bilirubin; RCT, randomized controlled trial.

preconditioning: –0.28, 95% CI: –0.73, 0.16; SMD LIPC versus no-preconditioning: –0.21, 95% CI: –0.49, 0.07). Furthermore, the comparison between RIPC and LIPC revealed no decline in TBIL (SMD RIPC versus LIPC: –0.07, 95% CI: –0.57, 0.42).

Surgical time: 22 studies with 1,386 participants were included in the network meta-analysis. No significant difference was observed between the three pairwise comparisons (SMD RIPC versus LIPC: 0.11, 95% CI: –0.19, 0.42; SMD RIPC versus no-preconditioning: 0.05, 95% CI: –0.21, 0.30; SMD LIPC versus no-preconditioning: –0.06, 95% CI: –0.24, 0.11). LIPC had the highest SUCRA value for reducing surgical time.

Blood loss: 18 studies with 1,259 participants were included in the network meta-analysis. LIPC caused less blood loss compared with no-preconditioning (SMD LIPC versus no-preconditioning: –0.24, 95% CI: –0.44, –0.03). However, the Network meta-analysis of indirect comparisons of RIPC and LIPC also suggested no difference in bleeding (SMD RIPC versus LIPC: 0.10, 95% CI: –0.39, 0.60). LIPC had the highest SUCRA value, followed by RIPC, and no-preconditioning.

Hospital stays: This network meta-analysis analyzed 14 studies with 1,024 participants. No statistical difference was observed between LIPC and no-preconditioning or RIPC and no-preconditioning or LIPC and RIPC (SMD LIPC versus no-preconditioning: –0.18, 95% CI: –0.54, 0.19; SMD RIPC versus no-preconditioning: –0.06, 95%

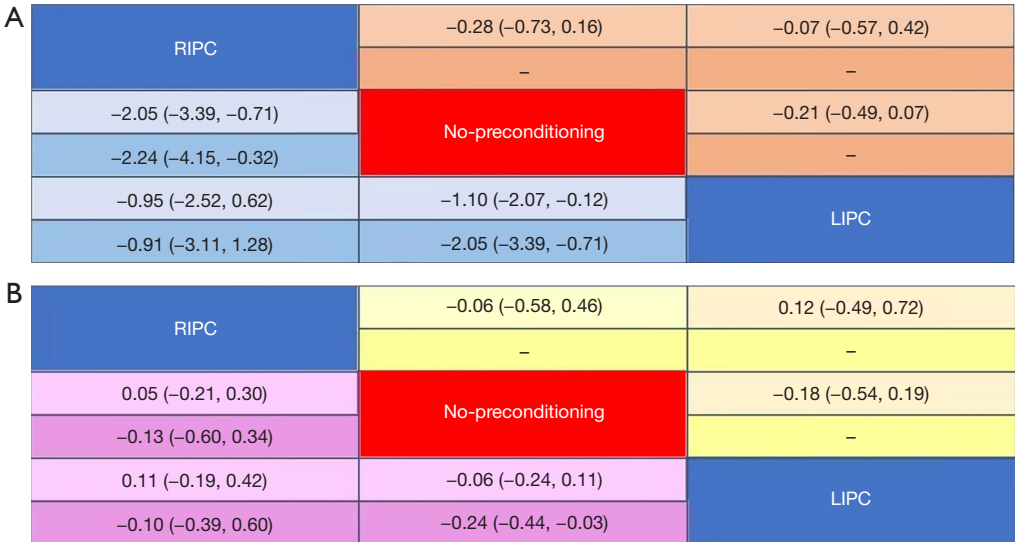

Figure 3 Network meta-analysis. (A) AST, ALT, and TBIL on POD1. (B) Operative time, blood loss, and hospital stays. Comparisons should be read from left to right. The levels of AST, ALT, TBIL, operative time, blood loss, and hospital stays are located at the intersection between the column-defining treatment and the row-defining treatment. Data are in SMD (95% CI), and data below 0 favor the column-defining treatment. Light blue represents AST levels, dark blue represents ALT levels, and orange represents TBIL levels. Light pink represents operative time; pink represents blood loss; light yellow represents hospital stays. LIPC, local ischemic preconditioning; RIPC, remote ischemic preconditioning; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; POD1, postoperative day 1; SMD, standardized mean difference, CI, confidence interval.

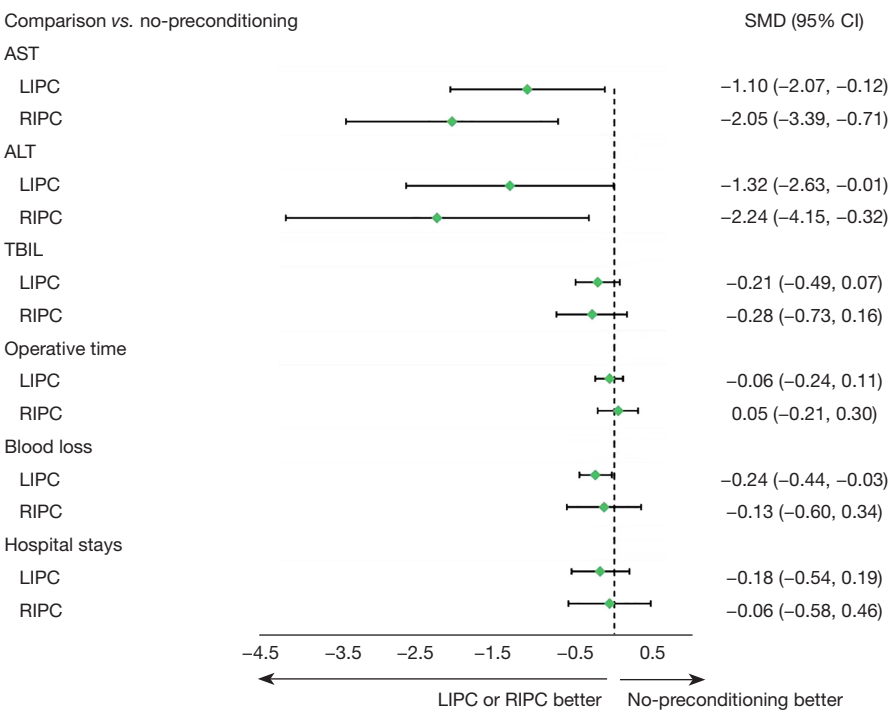

Figure 4 Forest plots for network metanalysis. SMD, standardized mean difference; CI, confidence interval; AST, aspartate aminotransferase; LIPC, local ischemic preconditioning; RIPC, remote ischemic preconditioning; ALT, alanine aminotransferase; TBIL, total bilirubin.

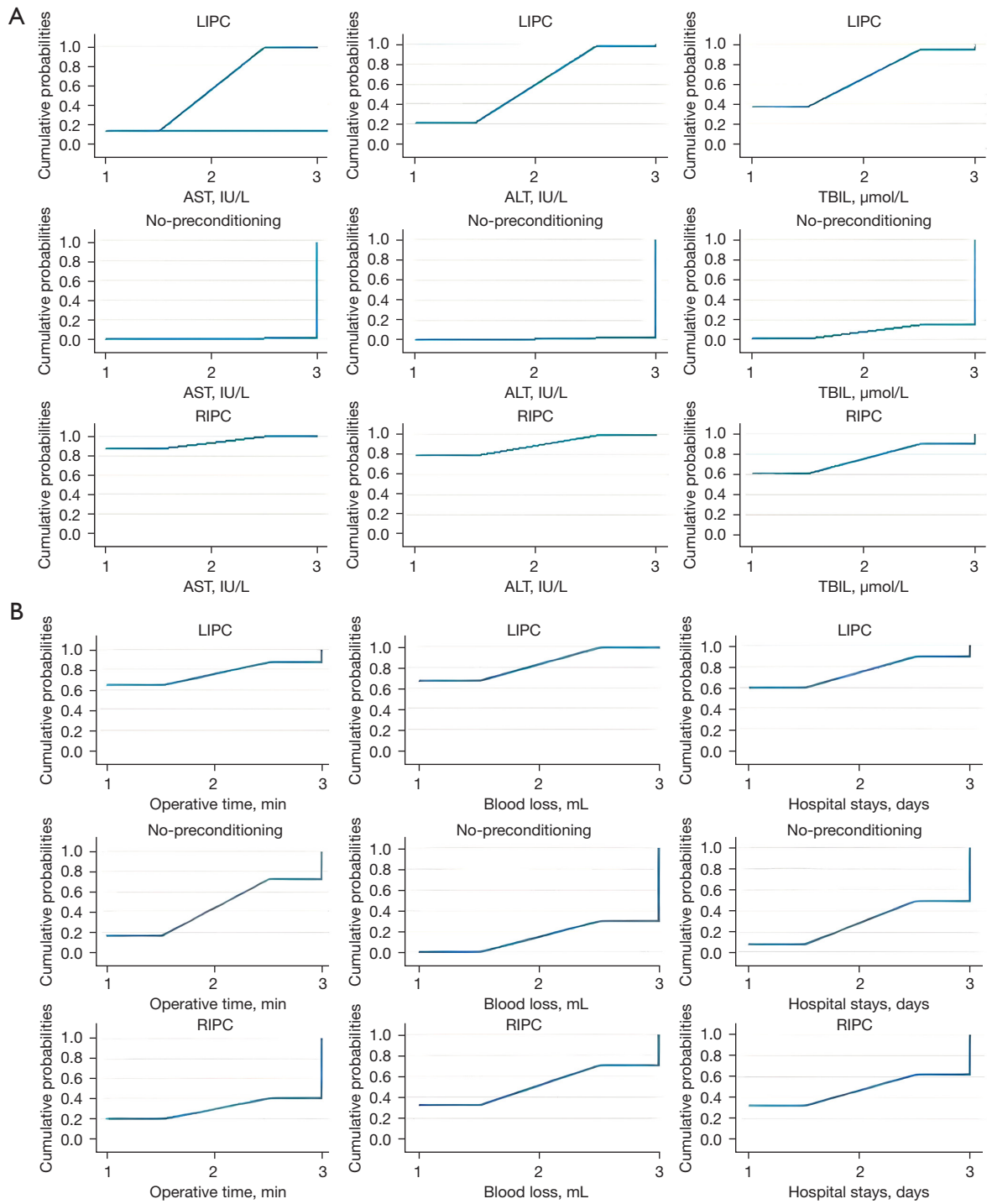

Figure 5 SUCRA plot. (A) AST, ALT, TBIL on POD1. (B) Operative time, blood loss, and hospital stays. LIPC, local ischemic preconditioning; RIPC, remote ischemic preconditioning; AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBIL, total bilirubin; SUCRA, surface under the cumulative rank curve; POD1, postoperative day 1.

CI: –0.58, 0.46; SMD RIPC versus LIPC: 0.12, 95% CI: –0.49, 0.72). However, our results showed that LIPC had the highest SUCRA value, followed by RIPC, and no-preconditioning.

No inconsistency was found in our study, and the evaluation of local inconsistency for each primary outcome was presented in Appendix 2. Moreover, the ranking of treatments based on the SUCRA plot for each outcome was shown in *Figure 5*. Subsequently, we conducted subgroup analyses to explore cirrhosis, resected liver volume, and inflow occlusion time (*Figure 6*). These results did not substantially differ from those of the primary analyses for most of the comparisons. RIPC demonstrated protective effects in terms of AST and ALT levels on POD1, especially in terms of patients who had cirrhosis or undergone major resection (*Figure 6*). The Cochrane Collaborative bias risk tool was used to assess the risk of bias of the included studies. *Figure 7* shows the bias assessment of each methodological component of the eligible studies.

Discussion

To our knowledge, this is the first meta-analysis study to directly compare the efficiency of LIPC and RIPC in patients undergoing hepatectomy. We found that LIPC and RIPC were superior to no-preconditioning in alleviating liver injury. Moreover, no significant difference was observed between the effect of LIPC and RIPC. Furthermore, in subgroup analysis, RIPC demonstrated potential protective effects on liver function after major liver resection or when patients diagnosed with cirrhosis. These findings provided evidence that RIPC had the potential to reduce HIRI during liver resection as well as LIPC did.

LIPC has been confirmed to have beneficial effects in relieving HIRI in animals and humans over the past three decades (48-51). Our study also found that LIPC offers protection in liver function which is consistent with the findings of the latest meta-analysis (52). This protection could be further enhanced by manipulation of apoptotic pathways, activating related signaling pathways or inhibiting hepatocyte apoptosis (53). While laboratory and experimental evidence is favorable, a major limitation to clinical application of LIPC is the potential to damage to the portal vein and its small branches. Furthermore, prior studies have not reached a consensus on the standardization of ischemia and reperfusion durations for LIPC. Most studies have followed a standardized protocol of 10 min of ischemia followed by 10 min of reperfusion; however, the protocol remains controversial. Therefore, it is necessary to discover better ways to mitigate liver damage.

RIPC, as another form of mechanical preconditioning, can be achieved noninvasively by simple inflating and deflating a standard blood pressure cuff placed on a limb, which facilitates RIPC translation into the clinical settings. Initially demonstrated in the canine heart (54), its protective effect on heart was later confirmed in humans. Subsequent studies have shown that RIPC protects muscle flaps, brain, kidneys, and heart from ischemic injury (55-62). In recent years, numerous animal experiments have shown the protective effects of RIPC on the liver (63,64). Several small clinical trials have presented evidence supporting the potential benefit of RIPC during hepatectomy (40,43), but two trials with small samples failed to demonstrate liver protection with RIPC (41,65). Thus, the role of RIPC in liver protection remains controversial. Interesting, our study provides new insight into the potential effectiveness of RIPC in liver resection. This may be linked to the ability of RIPC to promote the regeneration of marginal liver remnants, leading to improved survival after extended hepatectomy in a vascular endothelial growth factor (VEGF) dependent manner (66).

Our study demonstrated that no significance difference was observed between LIPC and RIPC. Currently, there are only two RCTs directly comparing RIPC and LIPC. Our result aligns with the latest clinical trial designed by Kong *et al.* (46), while it contradicts to the findings of the other study (47). We speculate that this may be related to several possible reasons. Firstly, anesthesia may be a confounding factor in the role of RIPC in liver surgery. Many studies supported that volatile but not propofol was a positive influencing factor in RIPC for myocardial protection (67-69). Similar results were confirmed in kidney protection during cardiac surgery (55,70). Unfortunately, due to a lack of sufficient data, subgroup analysis of anesthetic methods was not conducted in our study. Nevertheless, five eligible studies in our study indicated the beneficial impact of RIPC on liver function, all of which utilized propofol. Therefore, propofol may enhance the effects of RIPC. As Kong' trial, patients in RIPC group received invasive anesthesia by propofol which had lower AST and ALT levels, while the anesthesia mode in another RCT directly comparing RIPC and LIPC was not clear. Future research is needed to confirm the impact of anesthesia on RIPC in liver resection. Secondly, different ischemic preconditioning protocols may influence the effects of these two strategies, including

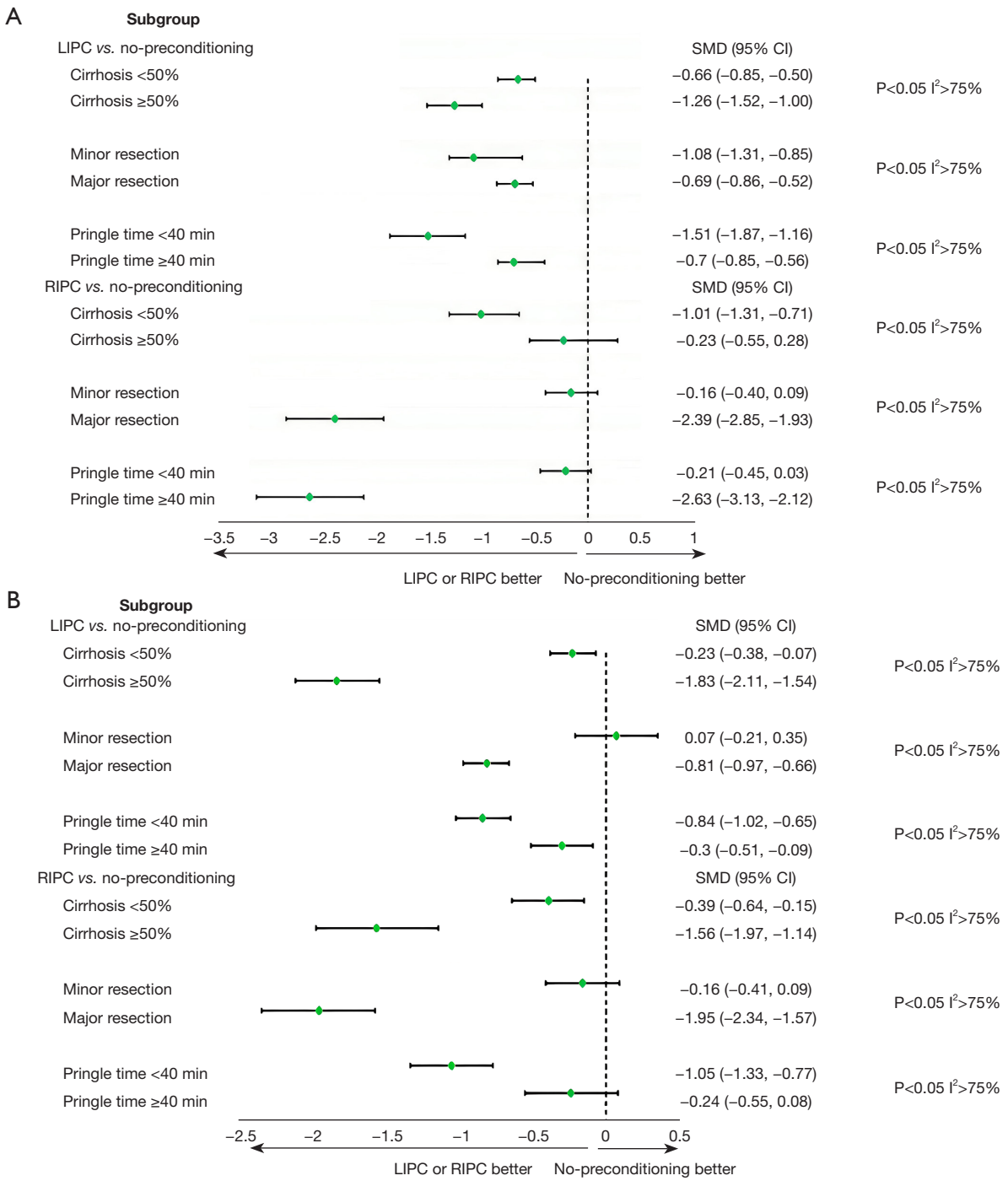

Figure 6 Forest plots for subgroup analyses. (A) AST on POD1. (B) ALT on POD1. I^2 is employed to assess the heterogeneity of study results. I^2 ranges from 0% to 100%, where 0% indicates no observed heterogeneity, and 100% signifies the maximum degree of heterogeneity. SMD, standardized mean difference; CI, confidence interval; LIPC, local ischemic preconditioning; RIPC, remote ischemic preconditioning; AST, aspartate aminotransferase; POD1, postoperative day 1; ALT, alanine aminotransferase.

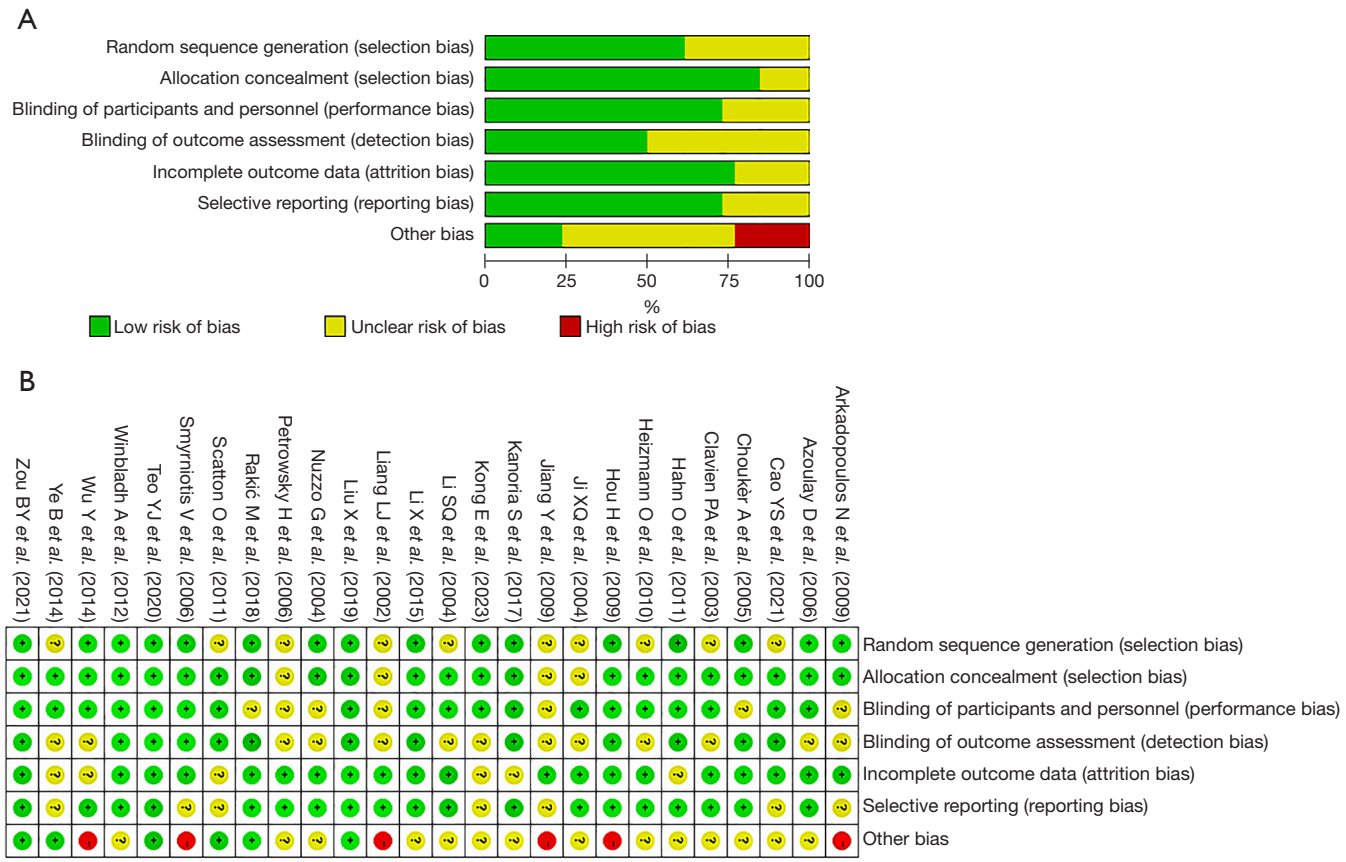

Figure 7 Assessment of risk of bias in the RCTs. (A) Risk of bias graph. (B) Risk of bias summary. Green represents low risk of bias; yellow represents unclear risk of bias; red represents high risk of bias. RCT, randomized controlled trial.

variations in the site, duration, intensity (71). Further research is needed to confirm the relationship between these factors and the effectiveness of LIPC and RIPC. Moreover, whether participants have other complications, the severity of diseases, and other factors can be crucial. Thus, individual differences may have an impact on the therapeutic efficacy.

There were some limitations that must be considered. First, laboratory indicators such as AST and ALT are commonly used as primary outcomes in clinical trials; however, they may not provide a comprehensive assessment of short-term recovery and clinical outcomes following liver surgery. Therefore, lacking sensitive and specific indicators reflecting liver function remains a significant concern in clinical studies, which needs to attract enough attention in future investigations. Additionally, given differences between eligible studies, clinical and statistical heterogeneity may exist. While SUCRA plots were utilized to determine the ranking of relative outcomes, caution is warranted in interpreting their values, as the comparisons of SMD were not significant for most outcomes. Finally, due to insufficient data, the role of anesthetic methods as a confounding factor in the efficacy of RIPC and LIPC was not analyzed in our study.

Conclusions

RIPC and LIPC could serve as effective strategies in relieving HIRI during hepatectomy. No significant differences were observed between LIPC and RIPC, however, RIPC may become an easily applicable protective strategy to relieve liver injury in hepatectomy. More large-scale clinical trials are needed in the future to confirm the application of LIPC and RIPC in hepatectomy.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tgh.amegroups.com/article/view/10.21037/tgh-23-95/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Appendix 1

Search strategy

Embase

#1 ('randomized controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR 'prospective study'/de OR 'double blind procedure'/de OR 'clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de
#2 'hepatectomy':ab,ti
#3 'hepatectomies':ab,ti
#4 'liver resection':ab,ti
#5 'liver surgery':ab,ti
#6 'liver operation':ab,ti
#7 'hepatic surgery':ab,ti
#8 'hepatic resection':ab,ti
#9 'hepatic operation':ab,ti
#10 'portal clamping':ab,ti
#11 'Pringle maneuver':ab,ti
#12 'pedicle clamping':ab,ti
#13 #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
#14 'ischemic preconditioning':ab,ti
#15 'pre-conditioning, ischemic':ab,ti
#16 'ischemic pre conditioning':ab,ti
#17 'ischemic pre-conditioning':ab,ti
#18 'preconditioning, ischemic':ab,ti
#19 'remote ischemic preconditioning':ab,ti
#20 'remote ischemic pre conditioning':ab,ti
#21 'remote ischemic pre-conditioning':ab,ti
#22 #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #1 AND #13 AND #22

PubMed

#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 randomized [tiab]
#4 randomly [tiab]
#5 trial [tiab]
#6 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#7 animals [mh] NOT humans [mh]
#8 #6 NOT #7
#9 hepatectomy[mh]
#10 liver resection[tiab]
#11 liver surgery[tiab]
#12 liver operation[tiab]
#13 hepatic resection[tiab]
#14 hepatic operation [tiab]
#15 hepatic surgery[tiab]
#16 portal clamping [tiab]
#17 pringle maneuver [tiab]

https://dx.doi.org/10.21037/tgh-23-95

#18 pedicle clamping[tiab]
#19 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 ischemic preconditioning[mh]
#21 remote ischemic preconditioning [tiab]
#22 remote ischemic pre-conditioning[tiab]
#23 remote ischemic pre conditioning[tiab]
#24 #20 OR #21 OR #22 OR #23
#8 AND #19 AND #24

Cochrane
#1 (hepatectomy):ti,ab,kw
#2 (liver resection) :ti,ab,kw
#3(liver surgery) :ti,ab,kw
#4(liver operation) :ti,ab,kw
#5(hepatic resection):ti,ab,kw
#6(hepatic operation) :ti,ab,kw
#7(hepatic surgery) :ti,ab,kw
#8(portal clamping):ti,ab,kw
#9(pringle maneuver):ti,ab,kw
#10(pedicle clamping):ti,ab,kw
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
#12(ischemic preconditioning):ti,ab,kw
#13(remote ischemic preconditioning):ti,ab,kw
#14(remote ischemic pre-conditioning):ti,ab,kw
#15(remote ischemic pre conditioning):ti,ab,kw
#16 #12 OR #13 OR #14 OR #15
#17 #11 AND #16

https://dx.doi.org/10.21037/tgh-23-95

Appendix 2

Testing for inconsistency in AST on POD1

Side	Direct		Indirect		Difference			Tau
	Coef.	Std. err.	Coef.	Std. err.	Coef.	Std. err.	P>|z|	
AB†	–203.3363	78.60285	–374.5607	462.9102	171.2244	469.5621	0.715	308.8483
AC†	–122.4227	104.6508	185.5192	430.5762	–307.942	443.1355	0.487	307.5374
BC†	226.319	229.1751	54.6338	143.4103	171.6852	270.4668	0.526	307.7871

†, no statistal difference. A, local ischemic preconditioning; B, remote ischemic preconditioning; C, no-preconditioning. AST, aspartate aminotransferase; POD1, postoperative day 1; coef., coefficient; std., standard; err., error.

Testing for inconsistency in ALT on POD1

Side	Direct		Indirect		Difference			Tau
	Coef.	Std. err.	Coef.	Std. err.	Coef.	Std. err.	P>|z|	
AB†	–211.2279	49.93275	–192.1612	284.1783	–19.06676	288.5791	0.947	186.225
AC†	–85.73231	65.21929	284.6784	252.4141	–370.4108	260.6811	0.155	178.9054
BC†	241.4087	136.0542	105.4986	92.86104	135.9101	164.9099	0.410	184.2372

†, no statistal difference. A, local ischemic preconditioning; B, remote ischemic preconditioning; C, no-preconditioning. ALT, alanine aminotransferase; POD1, postoperative day 1; coef., coefficient; std., standard; err., error.

Testing for inconsistency in TBIL on POD1

Side	Direct		Indirect		Difference			Tau
	Coef.	Std. err.	Coef.	Std. err.	Coef.	Std. err.	P>|z|	
AB†	–1.855024	1.32136	–5.267894	4.712489	3.41287	4.899134	0.486	2.891924
AC†	–1.837898	1.763721	1.574979	4.5654	–3.412877	4.899138	0.486	2.891928
BC†	3.43	4.370001	0.0171233	2.21465	3.412877	4.899141	0.486	2.89193

†, no statistal difference. A, local ischemic preconditioning; B, remote ischemic preconditioning; C, no-preconditioning. TBIL, total bilirubin; POD1, postoperative day 1; coef., coefficient; std., standard; err., error.

Testing for inconsistency in operative time

Side	Direct		Indirect		Difference			Tau
	Coef.	Std. err.	Coef.	Std. err.	Coef.	Std. err.	P>|z|	
AB†	–2.736956	3.961458	4.251029	23.15934	–6.987985	23.48583	0.766	9.068104
AC†	2.298342	4.763723	–0.725592	22.21443	2.370901	22.688	0.917	9.123404
BC†	2.298523	11.93202	5.501991	6.638106	–3.203467	13.64996	0.814	9.10892

†, no statistal difference. A , local ischemic preconditioning; B, remote ischemic preconditioning; C, no-preconditioning. Coef., coefficient; std., standard; err., error.

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Testing for inconsistency in hospital stays

Side	Direct		Indirect		Difference			Tau
	Coef.	Std. err.	Coef.	Std. err.	Coef.	Std. err.	P>|z|	
AB[†]	–1.546786	8.175444	2.80285	4.457999	–4.349635	4.537369	0.338	2.058672
AC[†]	–1.418028	1.066095	–1.207996	4.381216	1.066194	4.512721	0.813	2.168374
BC[†]	–0.945779	2.261839	1.766025	1.48499	–1.860603	2.705558	0.492	2.123976

[†], no statistal difference. A, local ischemic preconditioning; B, remote ischemic preconditioning; C, no-preconditioning. Coef., coefficient; std., standard; err., error.

Testing for inconsistency in blood loss

Side	Direct		Indirect		Difference			Tau
	Coef.	Std. err.	Coef.	Std. err.	Coef.	Std. err.	P>|z|	
AB[†]	–38.90878	16.07758	60.63274	111.8554	–99.54152	112.6244	0.377	35.21156
AC[†]	–4.358502	30.04253	–98.36853	82.60391	94.01003	87.73031	0.284	35.47823
BC[†]	–15.82048	41.41671	56.5381	40.25386	–72.35858	57.86942	0.211	33.38502

[†], no statistal difference. A, local ischemic preconditioning; B, remote ischemic preconditioning; C, no-preconditioning. Coef., coefficient; std., standard; err., error.

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