

# Remote ischemic conditioning in experimental hepatic ischemia-reperfusion: A systematic review and meta-analysis

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**Abstract.** Remote ischemic conditioning (RIC), including pre-conditioning (RIPC, before the ischemic event), per-conditioning (RIPerC, during the ischemic event), and post-conditioning (RIPostC, after the ischemic event), protects the liver in animal hepatic ischemia-reperfusion injuries models. However, several questions regarding the optimal timing of intervention and administration protocols remain unanswered. Therefore, the preclinical evidence on RIC in the HIRI models was systematically reviewed and meta-analyzed in the present review to provide constructive and helpful information for future works. In the present review, 39 articles were identified by searching the PubMed, OVID, Web of Science and Embase databases spanned from database inception to July 2024. According to the preferred reporting items for systematic reviews and meta-analyses guidelines, data were extracted independently by two researchers. The primary outcomes evaluated in this study were those directly related to liver injury, such as alanine transaminase (ALT), aspartate transaminase (AST) and liver histopathology. The risk of bias was assessed using the risk of bias tool of the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE). The findings were expressed as standardized mean difference (SMD) and analyzed using random-effects models. Egger's test was used to evaluate the publication bias. RIC significantly reduced the changes in ALT, AST and liver histopathology (all  $P < 0.00001$ ). These effects had two peaks, with the first peak of RIPerC/RIPostC occurring earlier, regardless of models and species. RIPerC/RIPostC exerted significant effects on changes in ALT and AST [ALT SMD (95% confidence interval (CI)): RIPC -1.97 (-2.40, -1.55) vs.

-2.78 (-3.77, -1.78);  $P = 0.142$ ; AST SMD (95%CI): RIPC -1.45 (-1.90, -0.99) vs. -2.13 (-2.91, -1.34);  $P = 0.142$ ], and RIPC had a greater effect on liver histopathology change [SMD (95%CI): RIPC -2.68 (-3.67, -1.69) vs. -1.58 (-2.24, -0.92);  $P = 0.070$ ]; however, no interactions were observed between the two groups in the meta-regression analysis. RIC is the most effective in experimental HIRI, using a 10-25-min dose. These outcomes suggest that RIC may be a promising strategy for treating HIRI; however, future studies using repeated doses in animal models with comorbidities will present novel ideas for its therapeutic application. The protocol of present study was registered with PROSPERO (CRD42023482725).

## Introduction

Ischemic conditioning intervention therapy originated for the management of cardiovascular diseases in the 1980s, conferring cardiac protection from a subsequent or ongoing ischemia-reperfusion injury (IRI) (1). Subsequently, organ protection in brain and liver diseases has also been investigated, but its apparent preclinical benefits have not been consistently translated into clinical practice (2,3). Remote ischemic conditioning (RIC) can activate ischemia tolerance through transient, non-fatal induction of remote or limb ischemia by simply inflating a blood pressure cuff on a leg or arm (4). This highly attractive treatment strategy is beneficial in terms of economy, safety, non-invasion and ease of promotion.

RIC, including three types of pre-conditioning (RIPC, before the ischemic event), per-conditioning (RIPerC, during the ischemic event) and post-conditioning (RIPostC, after the ischemic event) based on the timing of induction, has shown promise in treating several cardiovascular and cerebrovascular diseases (5,6). RIC protects the liver from IRI via several mechanisms such as neuro-humoral, mitochondrial autophagy and exosomal gene mechanisms (4). Although RIC has a strong short-term hepatoprotective effect against hepatic ischemia-reperfusion injuries (HIRIs) during liver-related surgeries, it is neutral in improving long-term outcomes such as hepatocyte apoptosis index, duration of hospital stay and survival rate (2). The potential explanation is interactions with liver-protecting anesthetics.

Although RIC does not cause harm in patients undergoing liver-related surgery and has elevated to human trials,

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human clinical evidence is limited. Importantly, there are still several unanswered questions about the optimal timing of intervention and administration protocols (such as one compared with two limbs and the number and duration of cycles, among others). Therefore, the preclinical evidence on RPreC, RPerC and RPostC in the HIRI models was systematically reviewed and meta-analyzed in the present review to provide constructive and helpful information for future works.

## Materials and methods

This systematic review was prepared in accordance with the recommendations of preferred reporting items for systematic reviews and meta-analyses (PRISMA) to assess the methodological quality. Preclinical (non-human) studies were included to compare the effects of RIC on HIRI animal models. This systematic review has been registered with PROSPERO, registration number: CRD42023482725.

**Search strategy.** A comprehensive literature search was conducted on July 26, 2024 using the PubMed (<https://pubmed.ncbi.nlm.nih.gov>), OVID (<https://ovidsp.ovid.com>), Web of Science (<https://clarivate.com>) and Embase databases (<https://www.embase.com>) for articles published from the inception to July 2024. Search terms comprised various combinations of 'remote ischemic conditioning' or 'limb ischemic conditioning' or 'remote ischemic treatment' or 'remote ischemic adaptation' or 'remote ischemic preconditioning' or 'distant ischemic preconditioning' or 'limb ischemic preconditioning' or 'remote ischemic preconditioning' or 'limb ischemic preconditioning' or 'remote ischemic postconditioning' or 'limb ischemic postconditioning' or 'RIC' or 'RIP' or 'RIPC' or 'RPC' or 'RPerC' or 'IperC' or 'RPostC', 'hepatic ischemia-reperfusion' or 'liver graft' or 'liver transplantation' or 'liver resection' or 'hepatectomy'. The search terms were adjusted according to different search engines. There were no language restrictions for the articles that were included. In addition, the authors manually searched the references of included studies and other existing meta-analyses to obtain more eligible studies. A specific search strategy is presented in Table SI.

**Inclusion and exclusion criteria.** The authors CT and AW independently reviewed and retrieved the full-text articles simultaneously. Different views were discussed among all authors, and duplicate articles in all databases were merged. The latest and most complete study was included when duplicate studies were from the same population.

The inclusion criteria are as follows: i) Any non-human species, any sex, in the models of hepatic ischemia-reperfusion; ii) interested intervention was limb RIC compared with the control group without RIC; iii) controlled studies with a separate control group; and iv) interested outcomes were postoperative liver synthetic function and liver histopathological injury.

The exclusion criteria are as follows: i) Human subjects, *in vitro* or computer studies; ii) retrospective or single-arm studies; iii) case studies, cross-over studies, studies without a separate control group, editorials, meta-analyses and reviews; iv) only the abstract of a study was available; and v) no reports

of postoperative aminotransferase levels or data were from review articles.

**Data extraction.** The authors CT and AW independently extracted data from each article. Any disagreements were resolved by the consensus of a third reviewer (YK). The following information was extracted from the included articles: First author; year of publication; country or region of studies; animal model (species, sex, sample size, the method of ischemic induction, the duration of ischemia); parameters of RIC (body part, unilateral or bilateral, number of cycles per treatment, duration of occlusion and release per cycle) and interested outcomes. The published graphs were enlarged and measured using Grab software (2) if the information was unavailable in the text. If data were not reported or unclear, the reviewers tried to contact the respective study authors by e-mail (maximum of two attempts). Furthermore, it should be stated that it was impossible to separate the RPerC and RPostC groups easily; hence, these were combined to form one group.

**Quality assessment.** The included animal model studies were assessed using the risk of bias tool of the SYstematic Review Centre for Laboratory animal Experimentation (SYRCLE). This assessment was performed independently by CT and AW. Any disagreements were resolved by consensus. Categories for the quality investigation included sequence generation, baseline characteristics, allocation concealment, random housing, blinding for the performance bias, random outcome assessment, blinding for the detection bias, incomplete outcome data, selective outcome data and other sources of bias. Each category was classified as high, low or uncertain risk.

The methodological quality of the results was evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) guidelines (2). Ultimately, the quality of evidence for each outcome was rated as high, moderate, low or very low.

**Primary and secondary outcomes.** The primary outcomes evaluated in this study were those directly related to liver injury, such as alanine transaminase (ALT), aspartate transaminase (AST) and liver histopathology. The secondary outcomes assessed were lactate dehydrogenase (LDH), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL) -6, IL-10, IL-1 $\beta$ , apoptosis and other possible outcomes.

**Statistical analysis.** The analysis was performed using the Review Manager version 5.4 software (The Nordic Cochrane Center; The Cochrane Collaboration, 2020). The continuous outcomes were reported as standardized mean difference (SMD) with 95% confidence interval (CI). The dichotomous outcomes were presented as odds ratio (OR) with 95%CI, and the random-effects model was used for analysis. Subgroup meta-regression or sensitivity analyses were then performed using Stata/MP (version 17.0; StataCorp LLC), and descriptive analysis was conducted if meta-analysis was inappropriate. Publication bias was assessed using Egger's linear regression test.  $P < 0.05$  was considered to indicate a statistically significant difference.

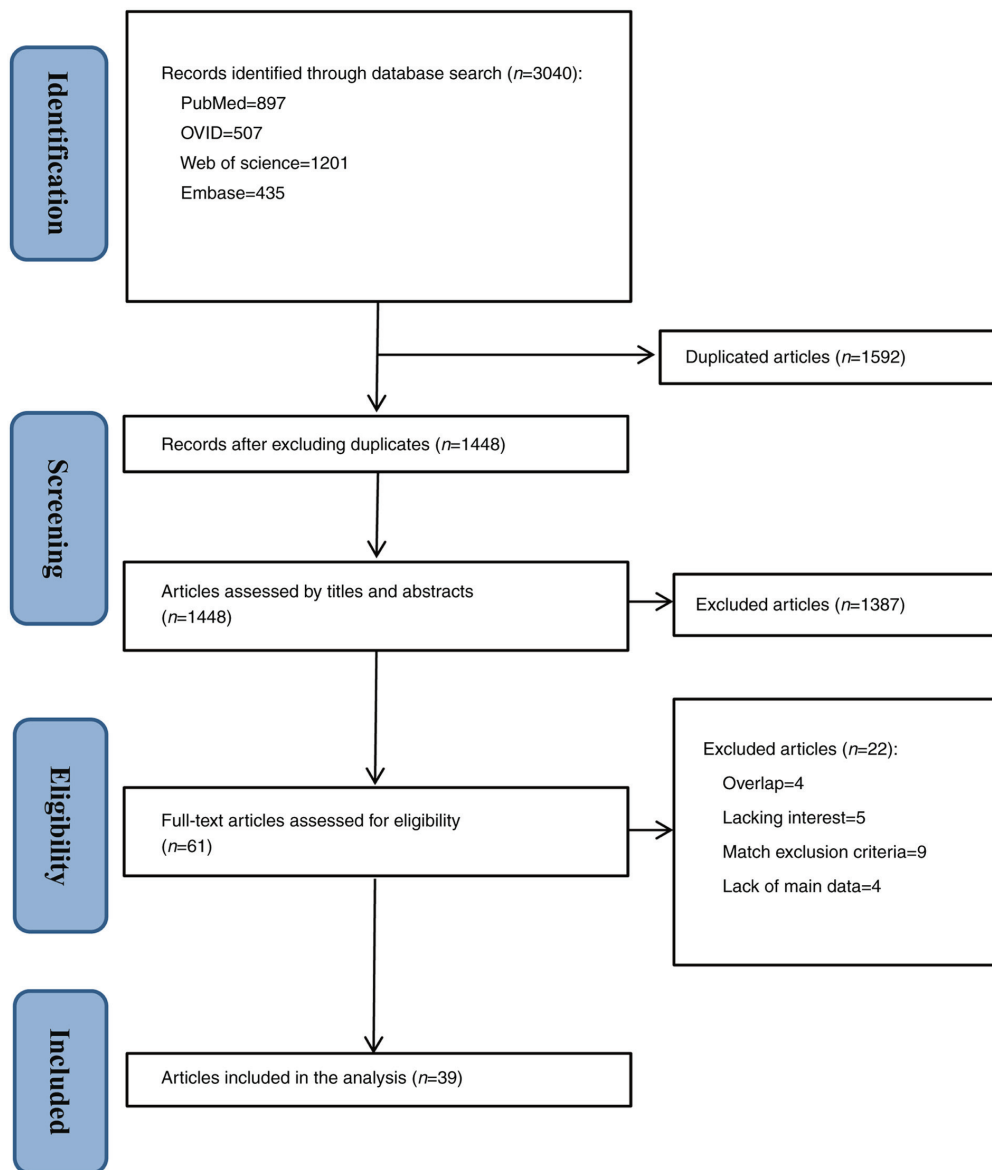


Figure 1. PRISMA flowchart of the papers selection. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

## Results

**Study characteristics.** The reviewers initially identified 3,040 relevant articles, of which 1,592 were duplicates. Excluding duplicates, a total of 1,448 studies were left for analysis. After analyzing the titles and abstracts, 1,387 articles that did not fulfil the criteria were also excluded, and the remaining 61 studies were selected for a full reading. After reviewing the full texts, 39 animal model studies met the eligibility criteria for data synthesis (Fig. 1).

All 39 included articles/studies (101 animal experiment records) were published between 2006 and 2023 and conducted in 10 countries (China, n=15; United Kingdom, n=5; Brazil, n=3; Korea, n=3; Hungary, n=3; Switzerland, n=3; Germany, n=2; Canada, n=2; Sweden, n=2; and Turkey, n=1). In total, 32 of 101 animal experiments studied Sprague Dawley rats (n=337), 12 used Wistar rats (n=178), 16 tested Lewis rats (n=144), 28 examined C57BL/6 mice (n=270), five used wild-type mice (n=82) and eight studied New Zealand

white rabbits (n=50). To induce HIRI, various animal models, such as orthotopic liver transplantation (OLT), 70% liver I/R, total hepatic ischemia (THI), hemorrhagic shock-resuscitation (HSR) I/R or hindlimb I/R, were used. RIC was primarily performed by occluding the femoral vascular bundle, femoral artery or hind limbs. Table I summarizes the experimental characteristics of all the involved studies (7-45).

**Quality assessment.** The SYRCLE's risk of bias tool was used to evaluate the risk of bias in the included animal experiments studies (Fig. 2). In quality assessment, 15 studies (7,9,18,22,26, 27,31,32,36-40,44,45) were analyzed with the same baseline characteristics among groups, but none of them conducted random sequence generation or allocation concealment. A total of 30 studies (7-12,14,15,17-28,31,32,34,35,37-41,44) had complete outcome data and they also demonstrated a low risk of attrition and reporting biases. Furthermore, blind bias could not be evaluated in most studies because of the characteristics of animal experiments.

Table I. Characteristics of the included studies.

| First author/s,<br>year                   | Country | Species                   | Model (min)               | Method of RIC                                        | Number and<br>duration of<br>cycles                          | Time of<br>administration                                                 | Time of<br>assessment <sup>a</sup> | Interested outcomes                                                                                | (Refs.) |
|-------------------------------------------|---------|---------------------------|---------------------------|------------------------------------------------------|--------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------|---------|
| Mukkala <i>et al</i> ,<br>2023            | Canada  | M, wild-type<br>mice      | HSR-I/R<br>(150)          | Right hind limb,<br>non-invasive                     | RIPC,<br>4x5/5 min                                           | RIPC, 30 min<br>pre-HSR                                                   | 2 h                                | ALT, liver<br>histopathology<br>(liver necrosis area)<br>TNF- $\alpha$ , IL-6, IL-10               | (7)     |
| Li <i>et al</i> , 2023                    | China   | M, Sprague<br>Dawley rats | OLT (75)                  | Hind limbs,<br>non-invasive                          | RIPerC,<br>3x5/5 min                                         | RIPerC, at<br>the onset of<br>the recipient<br>anhepatic phase            | 3 h                                | ALT, AST, liver<br>histopathology<br>(Suzuki classification)                                       | (8)     |
| Zhou <i>et al</i> , 2021<br>(ex1-5)       | China   | M, Sprague<br>Dawley rats | HSR-I/R (60)              | Left hind limb<br>(femoral artery),<br>invasive      | Ex1-5, RIPC,<br>3x5/5 min                                    | RIPC, 30 min<br>pre-HSR                                                   | 0, 2, 6, 12,<br>and 24 h           | ALT, AST<br>TNF- $\alpha$ , IL-1 $\beta$                                                           | (9)     |
| Niu <i>et al</i> , 2020<br>(ex1 and 2)    | China   | M, Sprague<br>Dawley rats | Hindlimb I/R<br>(240)     | Hind limbs,<br>noninvasive                           | Ex1, RIPC,<br>3x5/5 min<br>Ex2, RIPostC,<br>3x1/1 min        | RIPC, 30 min<br>pre-ischemia<br>RIPostC, at<br>reperfusion                | 0 h                                | ALT, AST<br>LDH, TNF- $\alpha$ ,<br>IL-1 $\beta$ , IL-10,<br>apoptosis index                       | (10)    |
| Choi <i>et al</i> , 2020                  | Korea   | M, Sprague<br>Dawley rats | 70% liver I/R<br>(30)     | Unilateral<br>hind limb,<br>non-invasive             | RIPC,<br>3x5 /5 min                                          | RIPC, 30 min<br>pre-ischemia                                              | 2 h                                | ALT, AST, liver<br>histopathology<br>(3-point scale)<br>TNF- $\alpha$                              | (11)    |
| Koh <i>et al</i> , 2019                   | Korea   | M, C57BL/6<br>mice        | 70% liver I/R<br>(30)     | Hind limbs,<br>noninvasive                           | RIPC,<br>4x3 /3 min                                          | RIPC, 24 min<br>pre-ischemia                                              | 6 h                                | ALT, AST, liver<br>histopathology<br>(Suzuki classification)<br>TNF- $\alpha$ , IL-6, IL-10        | (12)    |
| Emontzpohl <i>et al</i> ,<br>2019 (ex1-8) | Germany | M, Lewis rats             | OLT (480)                 | Hind limbs<br>(Infrarenal aorta),<br>invasive        | Ex1-4, RIPC,<br>4x5/5 min<br>Ex5-8,<br>RIPostC,<br>4x5/5 min | RIPC, 40 min<br>pre-ischemia<br>RIPostC,<br>after graft<br>reperfusion    | 1, 3, 24,<br>and 168 h             | ALT, AST, liver<br>histopathology<br>(Suzuki classification)                                       | (13)    |
| Li <i>et al</i> , 2018<br>(ex1-3)         | China   | M, C57BL/6<br>mice        | OLT<br>(235.7 $\pm$ 18.3) | Hind limbs<br>(femoral vascular<br>bundle), invasive | Ex1-3,<br>RIPerC,<br>3x5/5 min                               | RIPerC, during<br>the time from<br>anaesthesia to<br>graft<br>reperfusion | 2, 24, and<br>72 h                 | ALT, AST, liver<br>histopathology<br>(Suzuki classification)<br>TNF- $\alpha$ , apoptosis<br>index | (14)    |

Table I. Continued.

| First author/s,<br>year                    | Country     | Species                                                  | Model (min)                                                                               | Method of RIC                                     | Number and<br>duration of<br>cycles                          | Time of<br>administration                                              | Time of<br>assessment <sup>a</sup> | Interested outcomes                                                                         | (Refs.) |
|--------------------------------------------|-------------|----------------------------------------------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------------------|------------------------------------|---------------------------------------------------------------------------------------------|---------|
| Kambakamba <i>et al</i> ,<br>2018 (ex1-12) | Switzerland | M, C57BL/6<br>mice                                       | Ex1-6,<br>Standard<br>hepatectomy<br>(68%)<br>Ex7-12,<br>Extended<br>hepatectomy<br>(86%) | Right hind limb<br>(femoral vessels),<br>invasive | RIPC,<br>3x5/5 min                                           | RIPC, 30 min<br>pre-ischemia                                           | 0, 24, 48,<br>72, 96,<br>and 168 h | ALT, AST                                                                                    | (15)    |
| Gomes <i>et al</i> , 2018                  | Brazil      | M & F, weaning<br>Wistar rats                            | THI (60)                                                                                  | Right hind limb<br>(femoral vessels),<br>invasive | RIPC,<br>3x5/5 min                                           | RIPC, 30 min<br>pre-THI                                                | 24 h                               | ALT, AST, liver<br>histopathology<br>(Scheuer scores)                                       | (16)    |
| Gao <i>et al</i> , 2018<br>(ex1 and 2)     | China       | Ex1, M, Sprague<br>Dawley rats<br>Ex2, M, Wistar<br>rats | 70% liver I/R<br>(60)                                                                     | Right hind limb<br>(femoral artery),<br>invasive  | RIPostC,<br>1x5/5 min                                        | RIPostC,<br>60 min<br>post-ischemia                                    | 6 h                                | ALT, AST<br>TNF- $\alpha$ , IL-1 $\beta$ ,<br>apoptosis index                               | (17)    |
| Czigany <i>et al</i> ,<br>2018 (ex1-8)     | Germany     | M, Lewis rats                                            | OLT (480)                                                                                 | Hind limbs<br>(Infrarenal aorta),<br>invasive     | Ex1-4, RIPC,<br>4x5/5 min<br>Ex5-8,<br>RIPostC,<br>4x5/5 min | RIPC, 40 min<br>pre-ischemia<br>RIPostC,<br>after graft<br>reperfusion | 1, 3, 24,<br>and 168 h             | ALT, AST, liver<br>histopathology<br>(4-point scale)<br>LDH, IL-10                          | (18)    |
| Liang <i>et al</i> , 2017                  | China       | M, Sprague<br>Dawley rats                                | OLT (45)                                                                                  | Hind limbs,<br>non-invasive                       | RIPerC,<br>3x5/5 min                                         | RIPerC, at<br>the onset of<br>the recipient<br>anhepatic phase         | 3 h                                | ALT, AST, liver<br>histopathology<br>(Suzuki classification)                                | (19)    |
| He <i>et al</i> , 2017                     | China       | M, Sprague<br>Dawley rats                                | OLT (75)                                                                                  | Hind limbs,<br>non-invasive                       | RIPerC,<br>3x5/5 min                                         | RIPerC, at<br>the onset of<br>the recipient<br>anhepatic phase         | 3 h                                | ALT, AST                                                                                    | (20)    |
| Ruan <i>et al</i> , 2016                   | China       | M, Sprague<br>Dawley rats                                | 70% liver I/R<br>(60)                                                                     | Hind limbs,<br>non-invasive                       | RIPC,<br>3x10/10 min                                         | RIPC, 60 min<br>pre-ischemia                                           | 6 h                                | ALT, AST, liver<br>histopathology<br>(Suzuki classification)<br>TNF- $\alpha$ , IL-6, IL-10 | (21)    |

Table I. Continued.

| First author/s,<br>year                      | Country     | Species                   | Model (min)           | Method of RIC                                             | Number and<br>duration of<br>cycles                                                | Time of<br>administration                                    | Time of<br>assessment <sup>a</sup> | Interested outcomes                                                                           | (Refs.) |
|----------------------------------------------|-------------|---------------------------|-----------------------|-----------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------|------------------------------------|-----------------------------------------------------------------------------------------------|---------|
| Park <i>et al</i> , 2016<br>(ex1 and 2)      | Korea       | M, Sprague<br>Dawley rats | 70% liver I/R<br>(30) | Right hind limb<br>(femoral artery),<br>invasive          | Ex1, RIPC,<br>3x5/5 min<br>Ex2, RIPC,<br>3x5/5 min                                 | RIPC, 30 min<br>pre-ischemia<br>RIPC,<br>post-ischemia       | 24 h                               | ALT, AST                                                                                      | (22)    |
| Limani <i>et al</i> , 2016                   | Switzerland | M, C57BL/6<br>mice        | 70% liver I/R<br>(60) | Hind limbs<br>(femoral vascular<br>bundle), invasive      | RIPC,<br>3x5/5 min                                                                 | RIPC, 30 min<br>pre-ischemia                                 | 6 h                                | ALT, AST, liver<br>histopathology (liver<br>necrosis area)                                    | (23)    |
| Li <i>et al</i> , 2016<br>(ex1-3)            | China       | M, C57BL/6<br>mice        | OLT (120)             | Hind limbs<br>(femoral vascular<br>bundle), invasive      | Ex1-3, RIPC,<br>4x6/6 min                                                          | RIPC, 48 min<br>pre-ischemia                                 | 2, 24, and<br>72 h                 | ALT, liver<br>histopathology<br>(Suzuki classification)<br>TNF- $\alpha$ , apoptosis<br>index | (24)    |
| Jia <i>et al</i> , 2015<br>(ex1-3)           | China       | M, Sprague<br>Dawley rats | OLT (75)              | Hind limbs,<br>non-invasive                               | Ex1, RIPC1,<br>3x1/1 min<br>Ex2, RIPC2,<br>3x5/5 min<br>Ex3, RIPC3,<br>3x10/10 min | RIPC, at<br>the onset of<br>the recipient<br>anhepatic phase | 3 h                                | ALT, AST, liver<br>histopathology<br>(Suzuki classification)                                  | (25)    |
| Guimarães <i>et al</i> ,<br>2015 (ex1 and 2) | Brazil      | M, Sprague<br>Dawley rats | 70% liver I/R<br>(45) | Right hind limb<br>(femoral vascular<br>bundle), invasive | Ex1 and 2,<br>RIPC,<br>6x4/4 min                                                   | RIPC, 48 min<br>pre-ischemia                                 | 1 and 3 h                          | ALT, liver<br>histopathology<br>(Suzuki classification)<br>IL-6, IL-10                        | (26)    |
| Czigany <i>et al</i> , 2015                  | Hungary     | M, Wistar rats            | 70% liver I/R<br>(60) | Left hind limb<br>(femoral artery),<br>invasive           | RIPC,<br>4x5/5 min                                                                 | RIPC, 20 min<br>post-ischemia                                | 24 h                               | ALT, AST, liver<br>histopathology (liver<br>necrosis area)                                    | (27)    |
| Wang <i>et al</i> , 2014<br>(ex1-4)          | China       | M, wild-type<br>mice      | 70% liver I/R<br>(45) | Right hind limb<br>(femoral vascular<br>bundle), invasive | Ex1-4, RIPC,<br>6x4/4 min                                                          | RIPC, 48 min<br>pre-ischemia                                 | 2, 6, 12,<br>and 24 h              | ALT, AST, liver<br>histopathology<br>(Suzuki classification)                                  | (28)    |
| Uysal <i>et al</i> , 2014                    | Turkey      | M, Wistar<br>albino rats  | 70% liver I/R<br>(30) | Left hind limb,<br>non-invasive                           | RIPC,<br>3x10/10 min                                                               | RIPC, 60 min<br>pre-ischemia                                 | 4 h                                | ALT, AST, liver<br>histopathology<br>(3-point scale)                                          | (29)    |
| Oberkofler <i>et al</i> ,<br>2014 (ex1-3)    | Switzerland | M & F, C57BL/6<br>mice    | 70% liver I/R<br>(60) | Hind limbs<br>(femoral vascular<br>bundle), invasive      | Ex1-3, RIPC,<br>4x5/5 min                                                          | RIPC, 40 min<br>pre-ischemia                                 | 3, 6,<br>and 24 h                  | ALT, AST, liver<br>histopathology (liver<br>necrosis area)                                    | (30)    |

Table I. Continued.

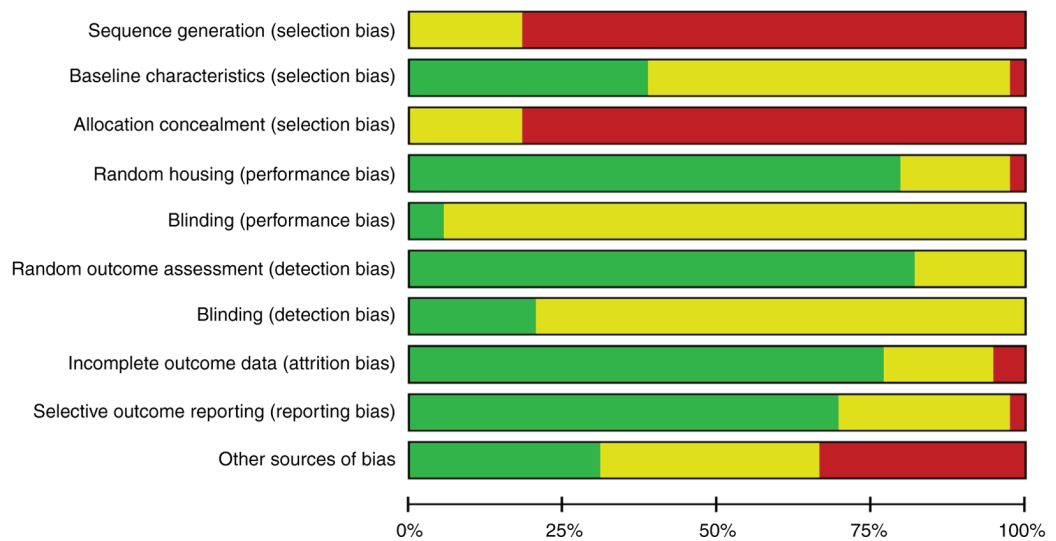
| First author/s,<br>year                  | Country           | Species                         | Model (min)           | Method of RIC                                        | Number and<br>duration of<br>cycles | Time of<br>administration       | Time of<br>assessment <sup>a</sup> | Interested outcomes                                                           | (Refs.) |
|------------------------------------------|-------------------|---------------------------------|-----------------------|------------------------------------------------------|-------------------------------------|---------------------------------|------------------------------------|-------------------------------------------------------------------------------|---------|
| Garab <i>et al</i> , 2014<br>(ex1-3)     | Hungary           | M, Sprague<br>Dawley rats       | 70% liver I/R<br>(60) | Right hind limb<br>(femoral artery),<br>invasive     | Ex1-3, RIPC,<br>2x10/10 min         | RIPC, 40 min<br>pre-ischemia    | 1, 2,<br>and 3 h                   | ALT, AST<br>LDH, TNF- $\alpha$                                                | (31)    |
| Costa <i>et al</i> , 2014                | Brazil            | M, Wistar rats                  | 70% liver I/R<br>(60) | Left hind limb,<br>non-invasive                      | RIPerC,<br>4x5/5 min                | RIPerC, 20 min<br>post-ischemia | 2 h                                | ALT, AST                                                                      | (32)    |
| Wang <i>et al</i> , 2013<br>(ex1-4)      | China             | M, Sprague<br>Dawley rats       | OLT (60)              | Hind limbs,<br>non-invasive                          | Ex1-4, RIPC,<br>4x5/5 min           | RIPC, 40 min<br>pre-ischemia    | 2, 6, 12,<br>and 24 h              | ALT                                                                           | (33)    |
| Czigány <i>et al</i> , 2013<br>(ex1-3)   | Hungary           | M, Wistar rats                  | 70% liver I/R<br>(60) | Hind limbs<br>(Infrarenal aorta),<br>invasive        | Ex1-3,<br>RIPerC,<br>4x5/5 min      | RIPerC, 20 min<br>post-ischemia | 1, 6,<br>and 24 h                  | ALT, AST, liver<br>histopathology<br>(Suzuki classification)<br>TNF- $\alpha$ | (34)    |
| Tapuria <i>et al</i> , 2012              | United<br>Kingdom | M, Sprague<br>Dawley rats       | 70% liver I/R<br>(45) | Unilateral hind<br>limb, non-<br>invasive            | RIPC,<br>4x5/5 min                  | RIPC, 40 min<br>pre-ischemia    | 24 h                               | ALT, AST                                                                      | (35)    |
| Kanoria <i>et al</i> , 2012              | United<br>Kingdom | M, New Zealand<br>white rabbits | THI (25)              | Right hind limb,<br>non-invasive                     | RIPC,<br>3x10/10 min                | RIPC, 65 min<br>pre-THI         | 2 h                                | ALT<br>LDH                                                                    | (36)    |
| Cao <i>et al</i> , 2012<br>(ex1-4)       | China             | M, New Zealand<br>white rabbits | 70% liver I/R<br>(25) | Hind limbs<br>(femoral vascular<br>bundle), invasive | Ex1-4, RIPC,<br>2x5/10 min          | RIPC, 24 h<br>pre-ischemia      | 0.5, 1, 2,<br>and 3 h              | ALT                                                                           | (37)    |
| Björnsson <i>et al</i> ,<br>2012 (ex1-3) | Sweden            | M, Sprague<br>Dawley rats       | 70% liver I/R<br>(60) | Right hind limb,<br>non-invasive                     | Ex1-3, RIPC,<br>1x10/10 min         | RIPC, 20 min<br>pre-ischemia    | 0, 1,<br>and 4 h                   | ALT, AST                                                                      | (38)    |
| Abu-Amara <i>et al</i> ,<br>2011         | United<br>Kingdom | M, C57BL/6<br>mice              | 70% liver I/R<br>(40) | Right hind limb,<br>non-invasive                     | RIPC,<br>6x4/4 min                  | RIPC, 48 min<br>pre-ischemia    | 2 h                                | ALT, AST, liver<br>histopathology<br>(4-point scale)                          | (39)    |
| Wang (1) <i>et al</i> ,<br>2010 (ex1-4)  | Canada            | F, C57BL/6<br>mice              | 70% liver I/R<br>(60) | Right hind limb,<br>non-invasive                     | Ex1-4, RIPC,<br>1x10/10 min         | RIPC, 20 min<br>pre-ischemia    | 0.5, 1, 2,<br>and 3 h              | ALT<br>TNF- $\alpha$                                                          | (40)    |
| Wang (2) <i>et al</i> ,<br>2010          | China             | M, Wistar rats                  | Hindlimb I/R<br>(240) | Hind limbs,<br>non-invasive                          | RIPC,<br>4x5/5 min                  | RIPC, 40 min<br>pre-ischemia    | 4 h                                | ALT, AST                                                                      | (41)    |
| Tapuria <i>et al</i> , 2009              | United<br>Kingdom | M, Sprague<br>Dawley rats       | 70% liver I/R<br>(45) | Right hind limb,<br>non-invasive                     | RIPC,<br>4x5/5 min                  | RIPC, 40 min<br>pre-ischemia    | 3 h                                | ALT, liver<br>histopathology<br>(Suzuki classification)                       | (42)    |

Table I. Continued.

| First author/s,<br>year                       | Country           | Species                         | Model (min)           | Method of RIC                                    | Number and<br>duration of<br>cycles | Time of<br>administration      | Time of<br>assessment <sup>a</sup> | Interested outcomes | (Refs.) |
|-----------------------------------------------|-------------------|---------------------------------|-----------------------|--------------------------------------------------|-------------------------------------|--------------------------------|------------------------------------|---------------------|---------|
| Lai <i>et al</i> , 2006                       | China             | F, Wistar rats                  | 70% liver I/R<br>(45) | Right hind limb<br>(femoral artery),<br>invasive | RIPC,<br>4x10/10 min                | RIPC, before<br>liver ischemia | 4 h                                | ALT                 | (43)    |
| Kanoria <i>et al</i> , 2006<br>(ex1-3)        | United<br>Kingdom | M, New Zealand<br>white rabbits | THI (25)              | Right hind limb,<br>non-invasive                 | Ex1-3, RIPC,<br>3x10/10 min         | RIPC, 65 min<br>pre-THI        | 0.5, 1, and<br>2 h                 | ALT, AST<br>LDH     | (44)    |
| Gustafsson <i>et al</i> ,<br>2006 (ex1 and 2) | Sweden            | F, Wistar rats                  | THI (60)              | Right hind limb<br>(femoral artery),<br>invasive | Ex1 and 2,<br>RIPC,<br>1x10/15 min  | RIPC, 25 min<br>pre-THI        | 0 and 1 h                          | ALT                 | (45)    |

<sup>a</sup>Time of post-reperfusion. RIC, remote ischemic conditioning; RIPC, remote ischemic pre-conditioning; RIPC, remote ischemic per-conditioning; RIPC, remote ischemic post-conditioning; Ex, experiment; OLT, orthotopic liver transplantation; I/R, ischemia-reperfusion; 70% liver I/R, complete ischemia of the median lobe and left lateral lobe (LLL) was achieved by clamping of the portal veins, hepatic arteries, and biliary branches using atraumatic microvascular clip; Hindlimb I/R, liver injury caused by the I/R injury of the hindlimb; HSR-I/R, hemorrhagic shock-resuscitation (HSR) following trauma contributes to organ dysfunction by causing I/R; THI, total hepatic ischemia; F, female; M, male; ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TNF, tumor necrosis factor; IL, interleukin.

A



B

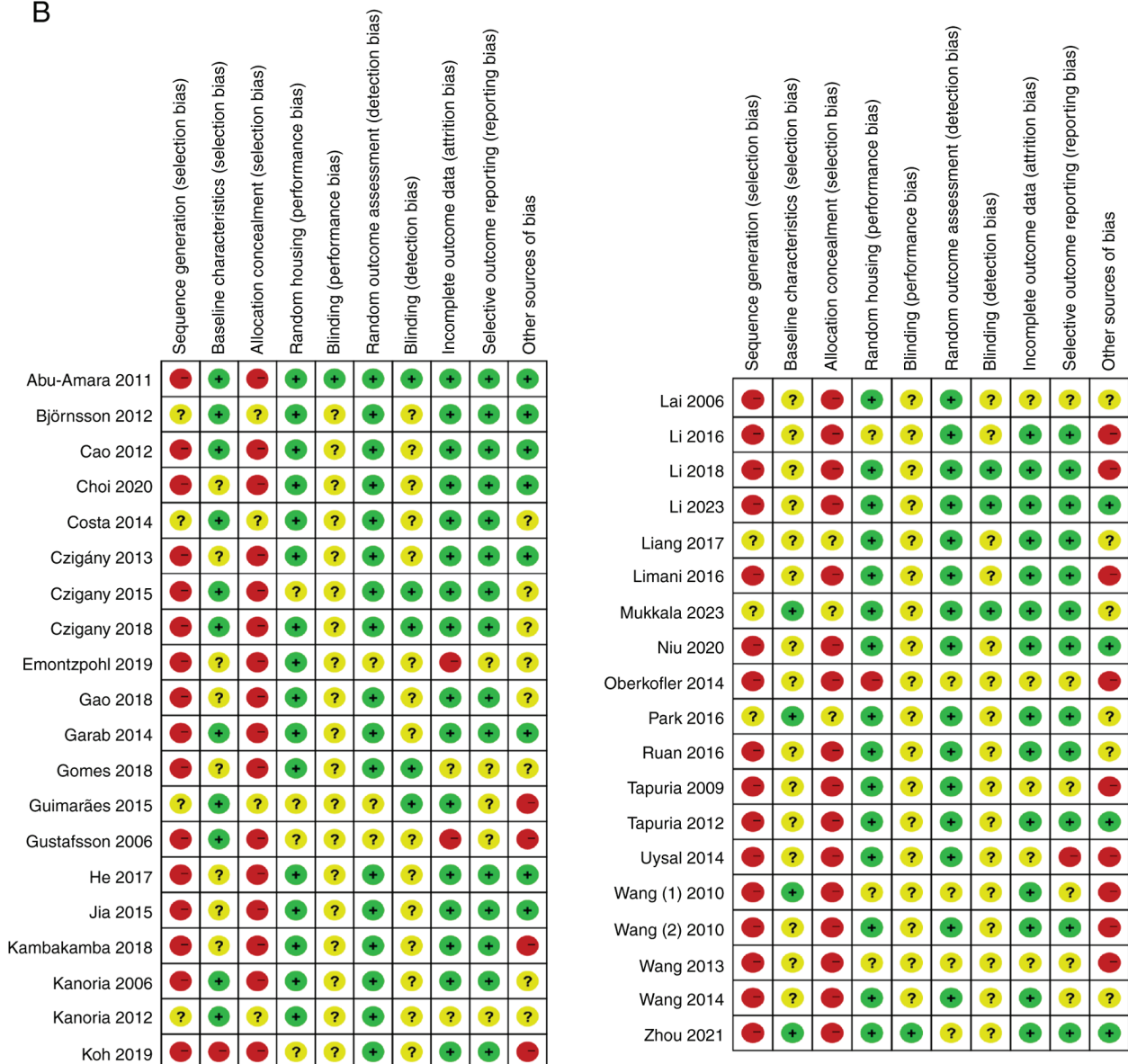


Figure 2. Risk of bias of the included studies. (A) Risk of bias graph. (B) Risk of bias summary.

Table II. Treatment effects of different factors based on primary outcomes.

| Overall effect/factors    | ALT                          |                      |          | AST                          |                      |          | Liver histopathology (scores) |                       |          |
|---------------------------|------------------------------|----------------------|----------|------------------------------|----------------------|----------|-------------------------------|-----------------------|----------|
|                           | No. of experiments (animals) | SMD (95% CI)         | P-value  | No. of experiments (animals) | SMD (95% CI)         | P-value  | No. of experiments (animals)  | SMD (95% CI)          | P-value  |
| Overall effect            | 89 (1,087)                   | -2.15 (-2.54, -1.75) | <0.00001 | 67 (797)                     | -1.66 (-2.06, -1.27) | <0.00001 | 28 (350)                      | -2.10 (-2.69, -1.52)  | <0.00001 |
| Time of administration    |                              |                      |          |                              |                      |          |                               |                       |          |
| RIPC                      | 66 (811)                     | -1.97 (-2.40, -1.55) | <0.00001 | 44 (521)                     | -1.45 (-1.90, -0.99) | <0.00001 | 15 (178)                      | -2.68 (-3.67, -1.69)  | <0.00001 |
| RIPerC and RIPostC        | 23 (276)                     | -2.78 (-3.77, -1.78) | <0.00001 | 23 (276)                     | -2.13 (-2.91, -1.34) | <0.00001 | 13 (172)                      | -1.58 (-2.24, -0.92)  | <0.00001 |
| Species                   |                              |                      |          |                              |                      |          |                               |                       |          |
| All rats                  | 54 (605)                     | -1.99 (-2.51, -1.46) | <0.00001 | 44 (493)                     | -1.44 (-1.92, -0.96) | <0.0001  | 19 (218)                      | -2.23 (-3.06, -1.41)  | <0.00001 |
| Sprague Dawley rats       | 32 (337)                     | -1.82 (-2.51, -1.13) | <0.00001 | 25 (277)                     | -1.34 (-2.08, -0.61) | 0.0003   | 10 (104)                      | -3.02 (-4.86, -1.18)  | 0.001    |
| Wistar rats               | 12 (178)                     | -2.94 (-4.23, -1.65) | <0.00001 | 9 (126)                      | -1.93 (-3.04, -0.81) | 0.0007   | 5 (78)                        | -1.97 (-2.54, -1.39)  | <0.00001 |
| Lewis rats                | 10 (90)                      | -1.48 (-2.37, -0.58) | 0.001    | 10 (90)                      | -1.24 (-1.79, -0.69) | <0.0001  | 4 (36)                        | -1.66 (-2.99, -0.34)  | 0.01     |
| All mice                  | 27 (332)                     | -2.08 (-2.79, -1.36) | <0.00001 | 20 (262)                     | -2.34 (-3.16, -1.52) | <0.0001  | 9 (132)                       | -1.89 (-2.69, -1.09)  | <0.00001 |
| C57BL/6 mice              | 22 (270)                     | -1.85 (-2.56, -1.13) | <0.00001 | 15 (200)                     | -2.24 (-3.17, -1.31) | <0.00001 | 8 (122)                       | -1.77 (-2.59, -0.95)  | <0.0001  |
| Wild-type mice            | 5 (62)                       | -3.21 (-6.00, -0.43) | 0.02     | 5 (62)                       | -2.91 (-4.94, -0.87) | 0.005    | 1 (10)                        | -3.14 (-5.30, -0.98)  | 0.004    |
| New Zealand white rabbits | 8 (150)                      | -3.11 (-3.85, -2.38) | <0.00001 | 3 (42)                       | -1.15 (-2.31, 0.01)  | 0.05     |                               |                       |          |
| HIRI model (min)          |                              |                      |          |                              |                      |          |                               |                       |          |
| All OLT                   | 26 (260)                     | -2.26 (-3.04, -1.47) | <0.00001 | 19 (206)                     | -1.84 (-2.62, -1.05) | <0.00001 | 15 (172)                      | -2.05 (-2.85, -1.24)  | <0.00001 |
| OLT (45)                  | 1 (12)                       | -4.70 (-7.26, -2.14) | 0.0003   | 1 (12)                       | -4.00 (-6.26, -1.74) | 0.0005   | 1 (12)                        | -8.71 (-13.12, -4.31) | 0.0001   |
| OLT (60)                  | 4 (24)                       | -4.06 (-6.21, -1.92) | 0.0002   |                              |                      |          |                               |                       |          |
| OLT (75)                  | 5 (44)                       | -0.84 (-3.11, 1.43)  | 0.47     | 5 (44)                       | -1.02 (-3.58, 1.54)  | 0.43     | 4 (34)                        | -1.78 (-3.66, 0.10)   | 0.06     |
| OLT (120)                 | 3 (30)                       | -3.49 (-4.84, -2.13) | <0.00001 |                              |                      |          | 3 (30)                        | -4.18 (-5.73, -2.63)  | <0.00001 |
| OLT (235.7±18.3)          | 3 (60)                       | -3.46 (-6.52, -0.40) | 0.03     | 3 (60)                       | -3.73 (-5.89, -1.57) | 0.0007   | 3 (60)                        | -0.90 (-1.45, -0.35)  | 0.001    |
| OLT (480)                 | 10 (90)                      | -1.48 (-2.37, -0.58) | 0.001    | 10 (90)                      | -1.24 (-1.79, -0.69) | <0.0001  | 4 (36)                        | -1.66 (-2.99, -0.34)  | 0.01     |
| All 70% liver I/R         | 41 (539)                     | -2.11 (-2.69, -1.54) | <0.00001 | 29 (365)                     | -1.82 (-2.51, -1.13) | <0.00001 | 12 (162)                      | -2.29 (-3.25, -1.32)  | <0.00001 |
| 70% liver I/R (25)        | 4 (96)                       | -2.90 (-3.50, -2.29) | <0.00001 |                              |                      |          |                               |                       |          |
| 70% liver I/R (30)        | 5 (61)                       | -1.71 (-3.53, 0.12)  | 0.07     | 5 (61)                       | -1.51 (-2.94, -0.08) | 0.04     | 3 (44)                        | -2.52 (-3.91, -1.13)  | 0.0004   |
| 70% liver I/R (40)        | 1 (12)                       | -2.40 (-4.02, -0.77) | 0.004    | 1 (12)                       | -2.10 (-3.63, -0.57) | 0.007    | 1 (12)                        | -1.06 (-2.31, 0.18)   | 0.09     |
| 70% liver I/R (45)        | 9 (100)                      | -1.96 (-3.21, -0.71) | 0.002    | 5 (52)                       | -2.02 (-3.85, -0.20) | 0.03     | 4 (45)                        | -2.90 (-6.76, 0.95)   | 0.14     |
| 70% liver I/R (60)        | 22 (270)                     | -2.13 (-2.99, -1.27) | <0.00001 | 18 (240)                     | -1.91 (-2.88, -0.95) | <0.0001  | 4 (60)                        | -2.32 (-3.02, -1.62)  | <0.00001 |
| All THI                   | 7 (110)                      | -2.86 (-3.96, -1.75) | <0.00001 | 4 (58)                       | -1.06 (-1.84, -0.27) | 0.008    | 1 (16)                        | -1.27 (-2.37, -0.16)  | 0.02     |
| THI (25)                  | 4 (54)                       | -3.91 (-5.92, -1.91) | 0.0001   | 3 (42)                       | -1.15 (-2.31, 0.01)  | 0.05     |                               |                       |          |
| THI (60)                  | 3 (56)                       | -2.04 (-3.20, -0.89) | 0.0005   | 1 (16)                       | -0.96 (-2.01, 0.09)  | 0.07     | 1 (16)                        | -1.27 (-2.37, -0.16)  | 0.02     |
| Hindlimb I/R (240)        | 3 (36)                       | -3.49 (-4.69, -2.29) | <0.00001 | 3 (36)                       | -1.99 (-2.89, -1.09) | <0.0001  |                               |                       |          |
| All HSR-I/R               | 6 (72)                       | -1.70 (-3.17, -0.22) | 0.02     | 6 (72)                       | -1.38 (-2.54, -0.21) | 0.02     |                               |                       |          |

Table II. Continued.

| Overall effect/factors          | ALT                          |                      |          | AST                          |                      |          | Liver histopathology (scores) |                      |          |
|---------------------------------|------------------------------|----------------------|----------|------------------------------|----------------------|----------|-------------------------------|----------------------|----------|
|                                 | No. of experiments (animals) | SMD (95% CI)         | P-value  | No. of experiments (animals) | SMD (95% CI)         | P-value  | No. of experiments (animals)  | SMD (95% CI)         | P-value  |
| HSR-I/R (60)                    | 5 (50)                       | -1.00 (-2.02, 0.01)  | 0.05     | 5 (50)                       | -0.99 (-2.08, 0.10)  | 0.08     |                               |                      |          |
| HSR-I/R (150)                   | 1 (22)                       | -5.38 (-7.32, -3.44) | <0.00001 | 1 (22)                       | -2.93 (-4.20, -1.66) | <0.00001 |                               |                      |          |
| Operation of RIC                |                              |                      |          |                              |                      |          |                               |                      |          |
| Non-invasive                    | 33 (382)                     | -2.21 (-2.99, -1.42) | <0.00001 | 23 (294)                     | -1.51 (-2.30, -0.72) | 0.0002   | 11 (126)                      | -2.42 (-3.39, -1.45) | <0.00001 |
| Invasive                        | 56 (705)                     | -2.11 (-2.56, -1.66) | <0.00001 | 44 (503)                     | -1.71 (-2.16, -1.26) | <0.00001 | 17 (224)                      | -1.93 (-2.66, -1.19) | <0.00001 |
| Number of limbs occluded        |                              |                      |          |                              |                      |          |                               |                      |          |
| One limb                        | 47 (567)                     | -1.88 (-2.44, -1.33) | <0.00001 | 36 (427)                     | -1.49 (-2.05, -0.92) | <0.00001 | 8 (98)                        | -2.33 (-3.88, -0.78) | 0.003    |
| Two limbs                       | 42 (520)                     | -2.44 (-2.99, -1.89) | <0.00001 | 31 (370)                     | -1.87 (-2.41, -1.34) | <0.00001 | 20 (252)                      | -2.03 (-2.63, -1.44) | <0.00001 |
| Number of cycles                |                              |                      |          |                              |                      |          |                               |                      |          |
| 1 cycle                         | 11 (152)                     | -1.93 (-3.32, -0.54) | 0.006    | 5 (72)                       | -2.69 (-6.50, 1.11)  | 0.17     |                               |                      |          |
| 2 cycles                        | 7 (132)                      | -2.58 (-3.07, -2.09) | <0.00001 | 3 (36)                       | -1.25 (-2.18, -0.33) | 0.008    |                               |                      |          |
| 3 cycles                        | 33 (385)                     | -1.91 (-2.58, -1.24) | <0.00001 | 32 (373)                     | -1.71 (-2.29, -1.12) | <0.00001 | 12 (158)                      | -1.76 (-2.53, -0.99) | <0.00001 |
| 4 cycles                        | 31 (342)                     | -2.32 (-2.97, -1.67) | <0.00001 | 22 (264)                     | -1.53 (-2.04, -1.02) | <0.00001 | 12 (146)                      | -2.41 (-3.06, -1.76) | <0.00001 |
| 6 cycles                        | 7 (76)                       | -2.73 (-4.54, -0.92) | 0.003    | 5 (52)                       | -2.62 (-4.58, -0.67) | 0.009    | 4 (46)                        | -2.04 (-5.00, 0.93)  | 0.18     |
| Duration of each cycle          |                              |                      |          |                              |                      |          |                               |                      |          |
| 1 min                           | 2 (20)                       | -1.23 (-5.25, 2.79)  | 0.55     | 2 (20)                       | -0.54 (-2.72, 1.64)  | 0.62     | 1 (8)                         | -2.44 (-4.76, -0.12) | 0.04     |
| 3 min                           | 1 (20)                       | -1.48 (-2.50, -0.47) | 0.004    | 1 (20)                       | -1.85 (-2.93, -0.76) | 0.0008   | 1 (20)                        | -2.11 (-3.25, -0.97) | 0.0003   |
| 4 min                           | 7 (76)                       | -2.73 (-4.54, -0.92) | 0.003    | 5 (52)                       | -2.62 (-4.58, -0.67) | 0.009    | 4 (46)                        | -2.04 (-5.00, 0.93)  | 0.18     |
| 5 min                           | 56 (667)                     | -2.30 (-2.80, -1.80) | <0.00001 | 47 (545)                     | -1.95 (-2.42, -1.48) | <0.00001 | 16 (212)                      | -2.01 (-2.65, -1.37) | <0.00001 |
| 6 min                           | 3 (50)                       | -3.49 (-4.84, -2.13) | <0.00001 |                              |                      |          | 3 (30)                        | -4.18 (-5.73, -2.63) | <0.00001 |
| 10 min                          | 20 (264)                     | -1.58 (-2.43, -0.73) | 0.0003   | 12 (160)                     | -0.55 (-1.51, 0.42)  | 0.26     | 3 (34)                        | -1.30 (-2.92, 0.33)  | 0.12     |
| Total duration of limb ischemia |                              |                      |          |                              |                      |          |                               |                      |          |
| ≤5 min                          | 4 (44)                       | -4.31 (-8.39, -0.22) | 0.04     |                              |                      |          | 1 (8)                         | -2.44 (-4.76, -0.12) | 0.04     |
| 10-15 min                       | 38 (521)                     | -1.84 (-2.40, -1.29) | <0.00001 | 28 (345)                     | -1.89 (-2.61, -1.17) | <0.00001 | 9 (136)                       | -1.93 (-2.82, -1.04) | <0.0001  |
| 20-25 min                       | 39 (422)                     | -2.39 (-2.99, -1.78) | <0.00001 | 26 (296)                     | -1.61 (-2.14, -1.09) | <0.00001 | 15 (172)                      | -2.42 (-3.38, -1.46) | <0.00001 |
| 30 min                          | 7 (88)                       | -2.02 (-4.06, 0.01)  | 0.05     | 6 (76)                       | -0.69 (-1.87, 0.48)  | 0.25     | 3 (34)                        | -1.30 (-2.92, 0.33)  | 0.12     |
| 40 min                          | 1 (12)                       | -1.77 (-3.19, -0.35) | 0.01     |                              |                      |          |                               |                      |          |
| Time of assessment <sup>a</sup> |                              |                      |          |                              |                      |          |                               |                      |          |
| 0 h                             | 5 (70)                       | -1.68 (-3.31, -0.04) | 0.04     | 4 (50)                       | -0.58 (-1.71, 0.55)  | 0.32     |                               |                      |          |
| 0.5 h                           | 3 (48)                       | -1.90 (-3.45, -0.34) | 0.02     | 1 (14)                       | -0.32 (-1.38, 0.73)  | 0.55     |                               |                      |          |
| 1 h                             | 10 (142)                     | -2.09 (-3.80, -0.38) | 0.02     | 6 (76)                       | -0.26 (-1.64, 1.13)  | 0.72     | 2 (28)                        | -0.22 (-4.48, 4.04)  | 0.92     |

Table II. Continued.

| Overall effect/factors | ALT                          |                      |          | AST                          |                      |          | Liver histopathology (scores) |                      |          |
|------------------------|------------------------------|----------------------|----------|------------------------------|----------------------|----------|-------------------------------|----------------------|----------|
|                        | No. of experiments (animals) | SMD (95% CI)         | P-value  | No. of experiments (animals) | SMD (95% CI)         | P-value  | No. of experiments (animals)  | SMD (95% CI)         | P-value  |
| 2 h                    | 14 (182)                     | -2.58 (-3.70, -1.45) | <0.00001 | 9 (120)                      | -2.16 (-3.17, -1.15) | <0.0001  | 5 (62)                        | -2.46 (-4.14, -0.78) | 0.004    |
| 3 h                    | 14 (156)                     | -2.00 (-3.03, -0.96) | 0.0002   | 10 (98)                      | -1.27 (-2.47, -0.07) | 0.04     | 7 (70)                        | -3.58 (-5.67, -1.50) | 0.0007   |
| 4 h                    | 4 (54)                       | -1.66 (-3.68, 0.36)  | 0.11     | 3 (42)                       | -1.96 (-4.36, 0.44)  | 0.11     | 1 (14)                        | -1.95 (-3.30, -0.60) | 0.005    |
| 6 h                    | 10 (122)                     | -3.12 (-4.19, -2.06) | <0.00001 | 9 (116)                      | -3.17 (-4.46, -1.89) | <0.00001 | 3 (48)                        | -2.22 (-2.98, -1.46) | <0.00001 |
| 12 h                   | 3 (26)                       | -2.90 (-4.72, -1.08) | 0.002    | 2 (20)                       | -4.70 (-8.21, -1.20) | 0.009    |                               |                      |          |
| 24 h                   | 16 (179)                     | -2.26 (-3.00, -1.53) | <0.00001 | 14 (163)                     | -1.63 (-2.25, -1.02) | <0.00001 | 8 (98)                        | -1.62 (-2.30, -0.94) | <0.00001 |
| 48 h                   | 2 (20)                       | -1.54 (-7.15, 4.06)  | 0.59     | 2 (20)                       | -5.29 (-15.37, 4.79) | 0.30     |                               |                      |          |
| 72 h                   | 4 (50)                       | -2.64 (-5.25, -0.03) | 0.05     | 3 (40)                       | -3.48 (-7.54, 0.58)  | 0.09     | 2 (30)                        | -2.87 (-6.29, 0.56)  | 0.10     |
| 168 h                  | 4 (38)                       | -0.16 (-0.81, 0.50)  | 0.64     | 4 (38)                       | -0.33 (-1.00, 0.35)  | 0.34     |                               | -2.10 (-2.69, -1.52) |          |

<sup>a</sup>Time of post-reperfusion. ALT, alanine transaminase; AST, aspartate aminotransferase; CI, confidence interval; RIPC, remote ischemic pre-conditioning; RPerC, remote ischemic per-conditioning; RIPC, remote ischemic post-conditioning; OLT, orthotopic liver transplantation; I/R, ischemia-reperfusion; 70% liver I/R, complete ischemia of the median lobe and left lateral lobe (LLL) was achieved by clamping of the portal veins, hepatic arteries, and biliary branches using atraumatic microvascular clip; Hindlimb I/R, liver injury caused by the I/R injury of the hindlimb; HSR-I/R, hemorrhagic shock-resuscitation (HSR) following trauma contributes to organ dysfunction by causing I/R; THI, total hepatic ischemia; SMD, standardized mean difference.

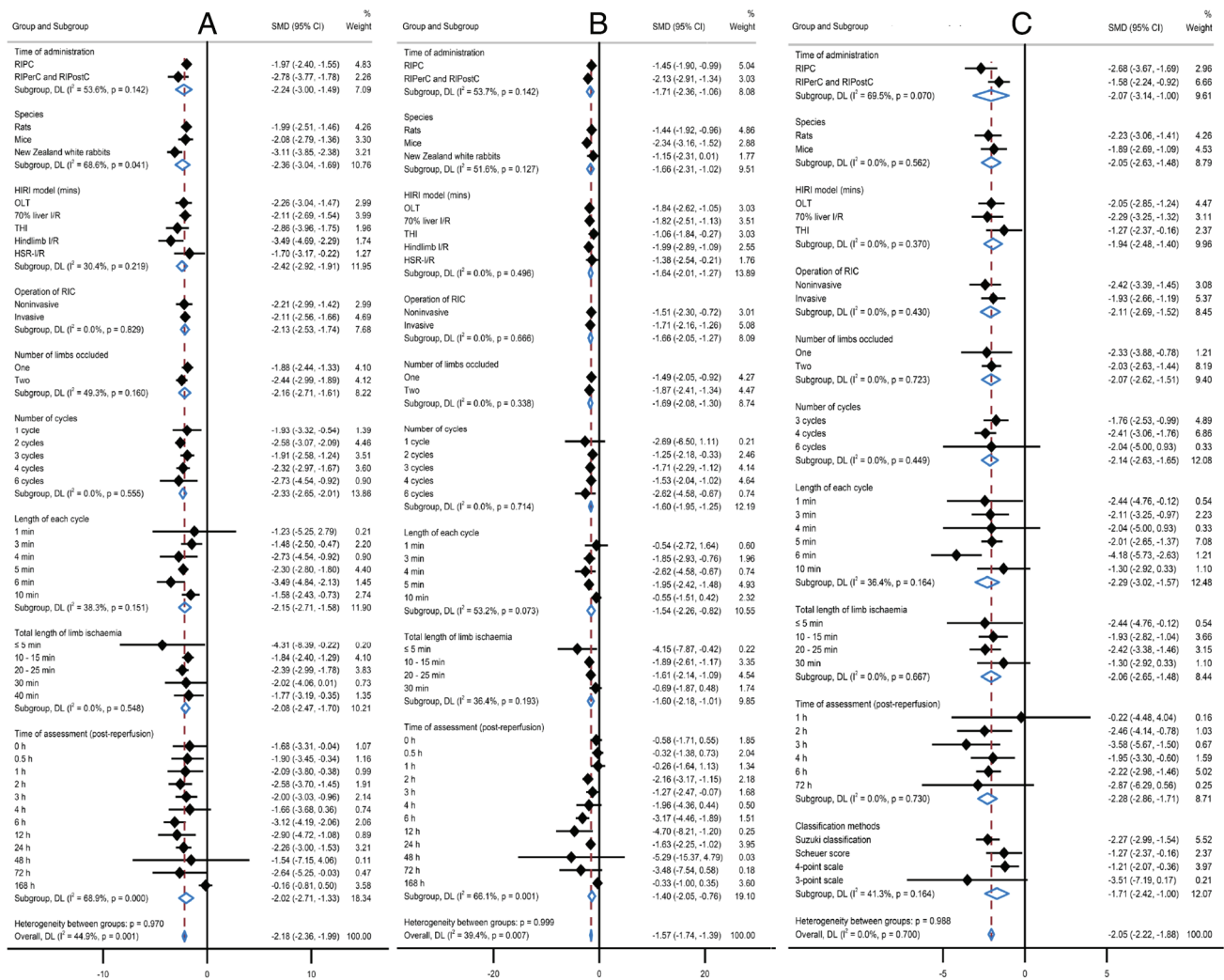


Figure 3. Subgroup analyses of all RIC studies. Changes in (A) ALT, (B) AST and (C) liver histopathology. RIC, remote ischemic conditioning; ALT, alanine transaminase; AST, aspartate transaminase.

**Effects of all RIC studies.** RIC was significantly effective against all the primary outcomes (ALT, AST and liver histopathology; all  $P < 0.00001$ ), although there were significant statistical heterogeneities:  $I^2 = 79\%$  in the ALT change,  $76\%$  in the AST change, and  $71\%$  in the liver histopathology change (Table II; Figs. S1-S3). Notably, RIPerC/RIPostC exhibited greater effects on ALT and AST changes [ALT SMD (95%CI): RIPC -1.97 (-2.40, -1.55) vs. -2.78 (-3.77, -1.78);  $P = 0.142$ ; AST SMD (95%CI): RIPC -1.45 (-1.90, -0.99) vs. -2.13 (-2.91, -1.34);  $P = 0.142$ ], and RIPC exerted a greater effect on liver histopathology change [SMD (95%CI): RIPC -2.68 (-3.67, -1.69) vs. -1.58 (-2.24, -0.92);  $P = 0.070$ ]; however, there was no interactions between the two groups in the meta-regression analysis. RIC was the greatest magnitude effective if the duration of each cycle was 4-6 min or the total duration of limb ischemia was 10-25 min. ALT and AST changes significantly interacted with the assessment times, with two peaks occurring 2-3 or 6-12 h post-reperfusion lasting up to 72 h. The efficacy of RIC on ALT change was greatest in the New Zealand white rabbits model with species interaction ( $P = 0.041$ ), but this animal model was much fewer ( $n = 150$ ). In addition, there were no interactions between liver histopathology and species, the HIRI model, the operation of RIC, the number of limbs

occluded, the number of cycles, the duration of each cycle, the total duration of limb ischemia, or classification methods of liver histopathology score in the meta-regression analysis (all  $P > 0.05$ ). The details are shown in Table II and Fig. 3.

RIC was also significantly effective against several secondary outcomes such as LDH, TNF- $\alpha$  and apoptosis index (all  $P < 0.00001$ ) and there were also significant statistical heterogeneities ( $I^2 = 75\%$ ,  $I^2 = 76\%$ ,  $I^2 = 51\%$ , respectively; Table SII; Fig. S4). Due to the limitations of the sample size and data integrity, only a meta-regression analysis was performed by dividing the groups of RIPC and RIPerC/RIPostC, and there were no interactions between the two groups ( $P = 0.91$ ,  $P = 0.16$ ,  $P = 0.75$ , respectively; Fig. S5). In addition, only four studies (five experiments; 78 animals) (7,12,21,26) evaluated IL-6 change, and five studies (13 experiments; 156 animals) (10,12,18,21,26) evaluated IL-10 change, showing that RIC was ineffective against IL-6 and IL-10 changes [SMD (95%CI): -1.47 (-3.72, 0.79);  $P = 0.20$ ; SMD (95% CI): -0.34 (-1.39, 0.71);  $P = 0.52$ ].

**Effects of RIPC studies.** The effects of RIPC protocol variables were assessed against the primary outcomes changes using meta-regression (Fig. 4). The effects of RIPC on ALT and AST changes were significant if the duration of each cycle was

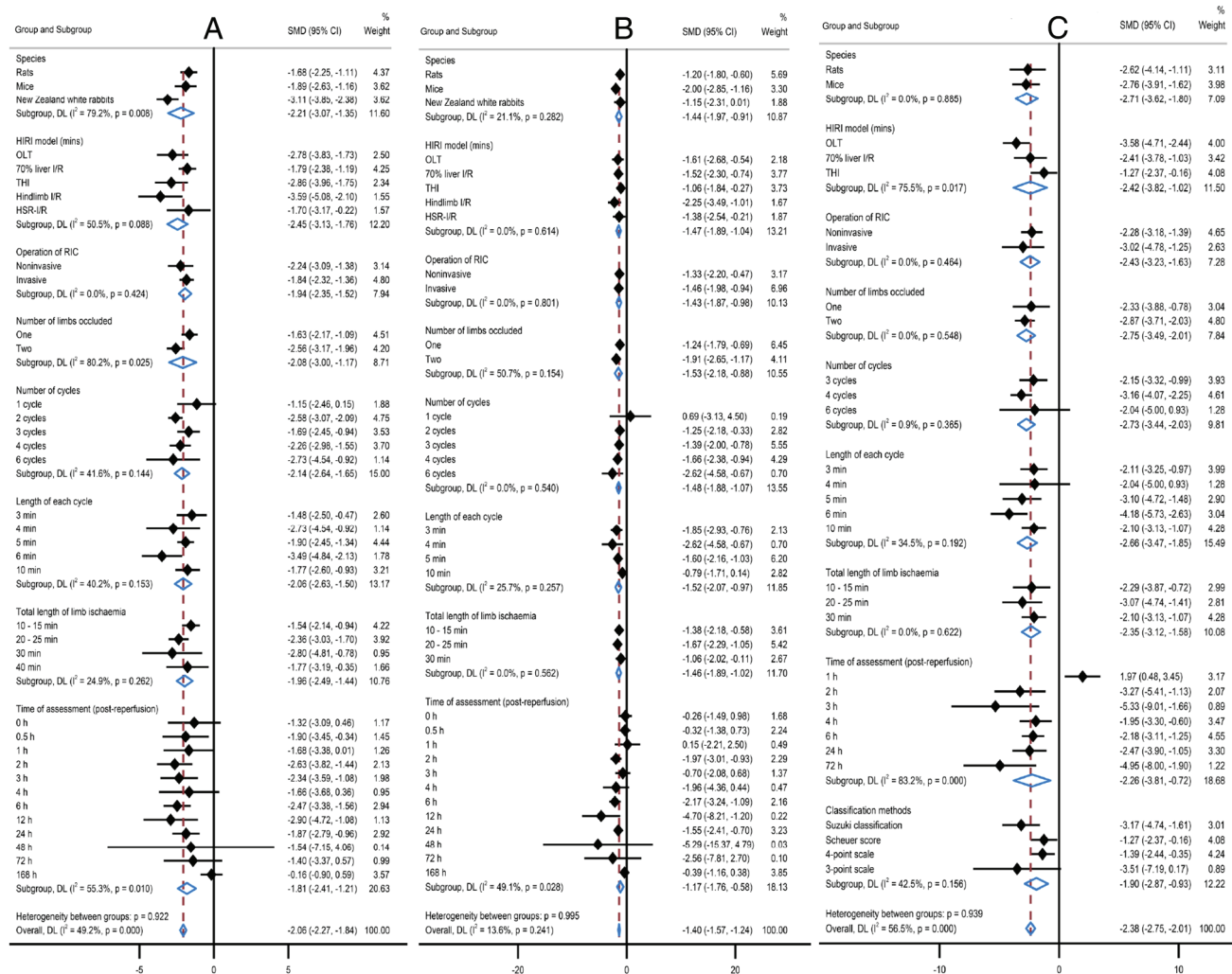


Figure 4. Subgroup analyses of all RIPC studies. Changes in (A) ALT, (B) AST and (C) liver histopathology. RIPC, pre-conditioning; ALT, alanine transaminase; AST, aspartate transaminase.

6 min or the total duration of limb ischemia was 10-25 min, with two peaks occurring at 2-3 or 6-12 h following reperfusion and lasting up to 72 h. RIPC was most effective against ALT change in New Zealand white rabbits and had no interactions in rats or mice ( $P=0.008$ ). Using one or two limbs of RIPC reduced ALT but using two limbs was significantly improved than one limb [SMD (95%CI): -2.56 (-3.17, -1.96) vs. -1.16 (-2.17, -1.09);  $P=0.025$ ]. In addition, the effect of RIPC on the liver histopathological change was improved in the OLT model ( $P=0.017$ ), and there were no interactions between RIPC and the liver histopathological score classification method ( $P=0.156$ ).

**Effects of RIPC/RIPostC studies.** The effects of RIPC/RIPostC protocol variables were assessed against the primary outcomes changes using meta-regression (Fig. 5). Similar to the RIPC protocol, the protective effects against ALT and AST changes revealed two peaks, but the first peak occurred earlier (1-3 h post-reperfusion). The efficacies of RIPC/RIPostC on ALT and AST interacted with the RIC cycles, the most significant at one cycle of RIC ( $P=0.002$ ;  $P<0.001$ ), but this animal model is much fewer ( $n=24$ ). Using one or two limbs of RIPC/RIPostC reduced ALT and AST, but using one limb was a significant improvement on

two limbs [ALT SMD (95%CI): -6.04 (-9.44, -2.65) vs. -2.25 (-3.25, -1.24),  $P=0.036$ ; AST SMD (95%CI): -5.41 (-8.90, -1.93) vs. -1.83 (-2.60, -1.05),  $P=0.049$ ]. Notably, the protection was ineffective if the duration of each cycle was 10 min or the total duration of the limb occlusion was 30 min.

**Publication bias.** Notably, Begg's funnel plot (Fig. 6) shows the asymmetric patterns in included studies, suggesting a possible publication bias in this meta-analysis (All Begg's statistics  $P<0.05$ ). Further analyzing the sources of statistical heterogeneity revealed the presence of interactions with respect to country. The protective effects of RIC on ALT and AST changes were highest in Brazil and the impact on liver histopathology was highest in Korea (Fig. S6).

## Discussion

HIRI is a complex pathophysiological process, which is essentially a series of inflammatory cascade reactions triggered by the release of a large number of inflammatory mediators following the activation of hepatic Kupffer cells, hepatic sinusoidal endothelial cells and hepatic stellate cells, which may lead to the postoperative liver dysfunction and partial

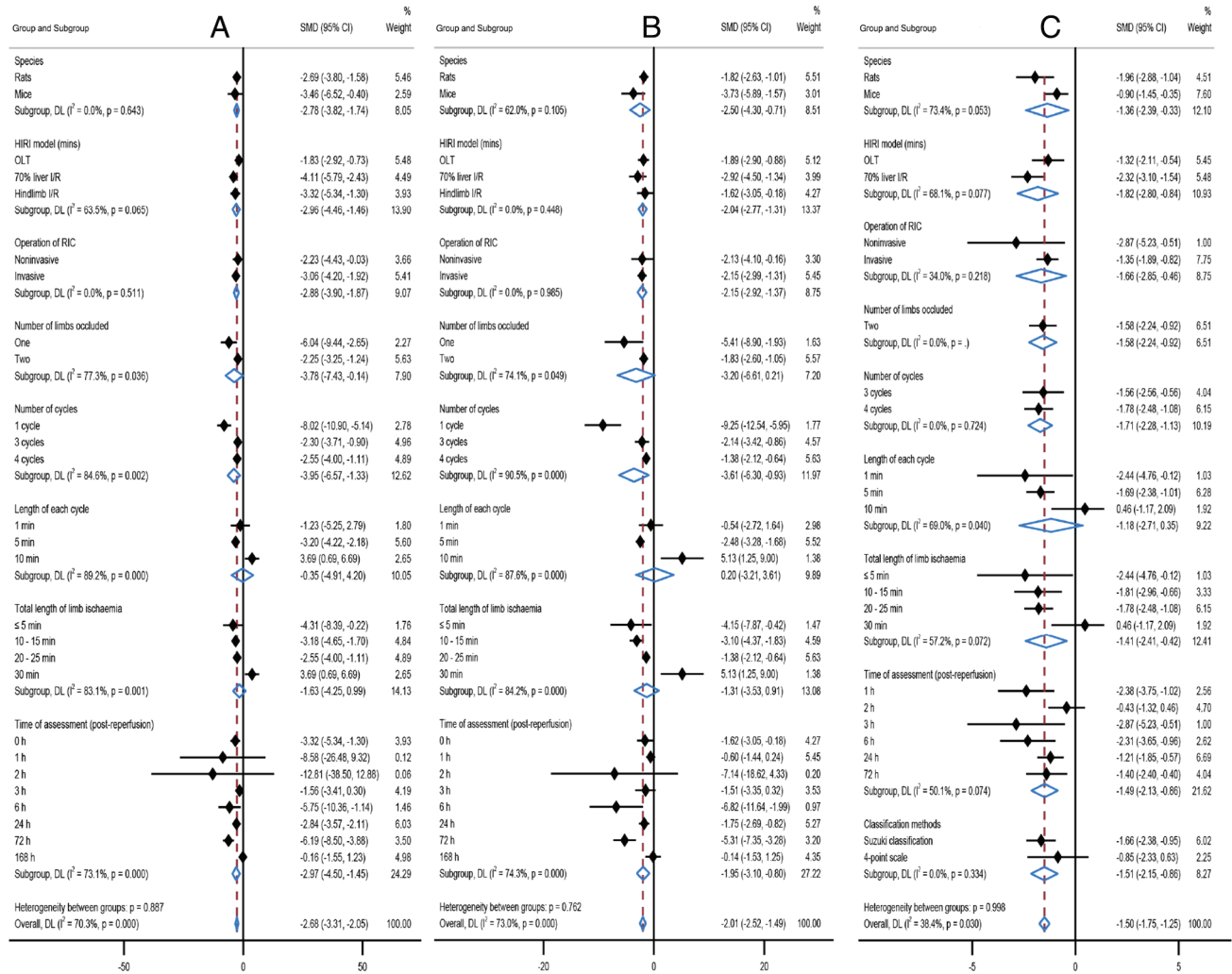


Figure 5. Subgroup analyses of all RIPerC/RIPostC studies. Changes in (A) ALT, (B) AST and (C) liver histopathology. RIPerC, per-conditioning; RIPostC, post-conditioning; ALT, alanine transaminase; AST, aspartate transaminase.

residual liver cell death, or even an increase of perioperative mortality (46,47). Various strategies such as pharmacological modifiers, physiological scavengers and physical processes have been investigated to avoid the adverse effects of HIRI following liver transplantation and liver resection (4,48). RIC is one of these novel strategies, which can induce nonlethal stress to the remote organs through transient ischemia, resulting in local and systemic tolerance to IRI. There is too little clinical evidence; however, the role of RIC in animal HIRI models has been extensively studied. To the best of the authors' knowledge, there have been no systematic reviews and meta-analyses related to this topic.

The reviewers carefully set the primary outcomes to ensure that this systematic review and meta-analysis of preclinical studies can be applied to the clinics. Although there is still a lack of a reliable endpoint that can effectively predict the outcome of patients undergoing surgery, most ongoing HIRI clinical trials focus on the markers of liver injury (ALT and AST) as primary outcomes (2). Considering this clinical setting, the present review briefly analyzed the efficacy of RIC on HIRI in preclinical studies with ALT, AST and liver histopathology as the primary outcomes and LDH, TNF- $\alpha$ , and apoptosis index as secondary outcomes. The present

systematic review and meta-analysis of 39 articles (101 animal experiments, 1,061 animals) confirmed that RIC (RIPC or RIPerC/RIPostC) had a powerful effect on improving ALT, AST and liver histopathology changes in the preclinical liver I/R models. In all RIPerC/RIPostC studies, ALT and AST changes appeared to be more efficacious than RIPC in both rats and mice, in 70% of liver I/R models and using one or two limbs and using invasive or non-invasive operations. However, RIPC appeared to have a more potent effect on liver histopathology change.

Significant statistical heterogeneities were present in both RIPC and RIPerC/RIPostC groups and the meta-regression subgroup analysis helped to explore the effects of these two protocol variables on the changes in primary outcomes. Significant interactions with species in RIC experiments showed that RIPC was most effective in New Zealand white rabbits. However, the RIPerC/RIPostC group lacked the New Zealand white rabbits' trial, and both groups were equally effective in rats and mice. This interspecies difference has raised concerns about treatment failure when moving into clinical trials. A recent study (2) evaluating the beneficial effects and applicability of RIPC in hepatectomy demonstrates that RIPC has some short-term liver protection against

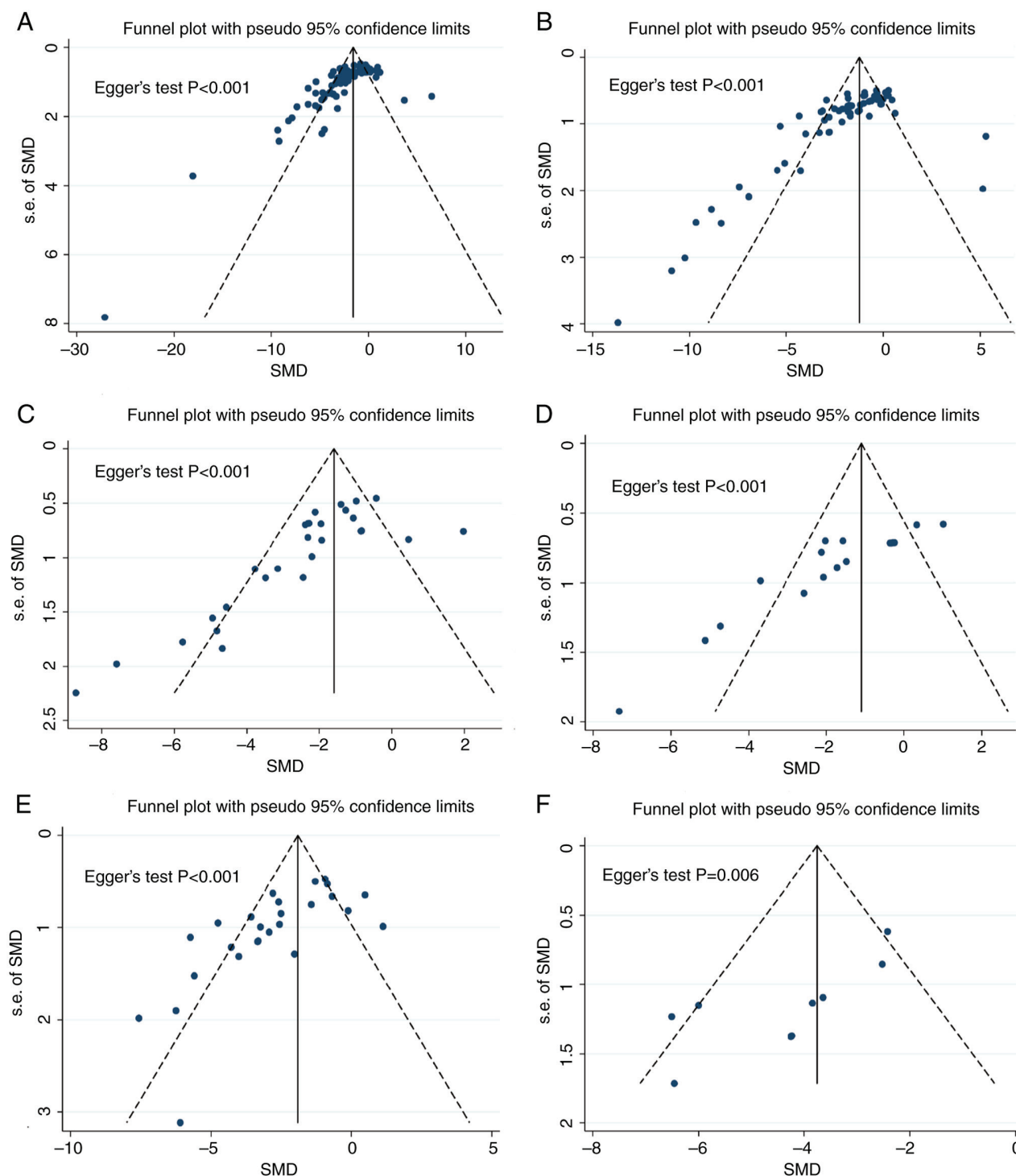


Figure 6. Egger's funnel plots of all RIC studies. Changes in (A) ALT, (B) AST and (C) liver histopathology, (D) LDH changes, (E) TNF- $\alpha$  changes and (F) apoptosis index. RIC, remote ischemic conditioning; ALT, alanine transaminase; AST, aspartate transaminase; LDH, lactate dehydrogenase; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

HIRI during hepatectomy but has limited improvement in clinical outcomes.

RIPerC/RIPostC studies revealed significant interactions with the total duration of limb ischemia (defined as the dose of RIC) and RIC was ineffective when the dose was 30 min. The 40-min dose was not tested in the RIPerC/RIPostC group, but the effect began to wane in the RIPC group. However, RIPC studies showed no significant interactions with doses, suggesting the existence of a dose therapeutic window with an optimal period between

10 and 25 min. The number of limbs used for RIC may somewhat reflect the dose. However, the present review showed that RIPC was a significant improvement, compared with unilateral, regarding ALT change on both sides, whereas RIPerC/RIPostC was the opposite. Frustratingly, the reviewers gained no reasonable explanation and heterogeneity or publication bias could not be ruled out. In addition, none of the included studies involved a repeat dose regimen (RIPC+RIPerC/RIPostC), and whether this provides added benefit warrants further verification.

The mechanisms of RIC are still being explored and may involve various inflammatory mediators, receptors, gene expression and other links. Some studies have demonstrated that RIC has two protective time windows (49-51). The first protective time window (also known as the classical protective window) occurs immediately after RIC and has a strong effect. It lasts for 2-3 h and possibly relates to altering endogenous substances (such as adenosine, bradykinin and nitric oxide) produced during RIC. The second window of protection occurs several hours after RIC, and the effect is weak, lasting 72-96 h. This second window of protection may be related to the cell signaling pathway and gene regulation after releasing endogenous substances. In the present review, the two peak levels of RIC action confirmed the protective time window effect of RIC, and the first peak of RPerC/RIPostC appeared earlier, indicating that it may take effect more quickly.

Although the present meta-analysis provided rigorous information on RIC's efficacy for HIRI, there were still some limitations, suggesting that the results of all outcomes should be interpreted with caution, needing more well-designed preclinical and clinical studies. First, the majority of articles included in this review studied healthy young male rodent models, which may not accurately reflect clinical scenarios involving comorbidities. By contrast, most patients were middle-aged and elderly with one or more comorbidities that may inhibit the effects of RIC, such as hypertension, diabetes, hepatitis B, fatty liver or cirrhosis. Second, anesthesia during RIC implementation is another concern, as propofol or sevoflurane has been reported to have liver protective effects (52,53). All current clinical studies have been conducted under propofol anesthesia or propofol combined with inhalation anesthesia, which may interfere with the effects of RIC and is also a hot topic of debate. Third, for the countries where animal experiments were conducted in this study, the sources of heterogeneity were significant. There was also a substantial risk of publication bias, with a worrying tendency to over-interpret positive results. Fourth, as shown in Table II, the number of experiments on some models and species is small, and some experiments have limited data, so it is difficult to fully consider all animal models and species differences in meta-analysis. Therefore, some species or models were simply merged, such as 'All rats' and 'All OLT' in Table II and Fig. 3. However, from the statistical data of the present review, these will not affect the main results of this study. Fifth, the optimal frequency and repeated dosing effects remain unclear. RIPC combined with RPerC/RIPostC or a daily repetition protocol would be a promising exploration. Overall, the present review demonstrated promising preclinical evidence for RIC in HIRI, but its clinical translation requires addressing these limitations. However, it remains a comprehensive review and probably the most accurate preclinical evidence of the literatures to date.

In summary, RIC significantly alleviated HIRI in the experimental models. RPerC/RIPostC acted more quickly and affected ALT and AST changes, whereas RIPC significantly affected liver histopathology. RIC has a dose therapeutic window and the best period is 10-25 min. However, given the significant statistical heterogeneities and risk of publication bias, future studies using repeated doses in animal models with comorbidities will generate innovative ideas for its therapeutic applications.

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## Availability of data and materials

Not applicable.

## Authors' contributions

CT was responsible for conceptualization, funding acquisition, data curation and writing the original draft. AW was responsible for validation, data curation, software, supervision, writing, reviewing and editing. YK was responsible for conceptualization, validation, writing, reviewing and editing. Data authentication is not applicable

## Ethics approval and consent to participate

The present review was exempted from an ethical opinion by the Ethics Committee of Yongchuan Hospital of Chongqing Medical University as it was a systematic review of the literature.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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