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Ischemic Preconditioning for Liver Transplantation: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Keywords
Ischemic preconditioning · Liver transplantation · Extended criteria donors · Marginal grafts

Abstract
Background: In recent decades, liver transplantation (LTx) has increased the survival and quality of life of patients with end-stage organ failure. Unfortunately, LTx is limited due to the shortage of donors. A lot of effort is put into finding new ways to reduce ischemia-reperfusion injury (IRI) in liver grafts to increase the number of suitable organs procured from expanded-criteria donors (ECD). The aim of this study was to systematically review the literature reporting LTx outcomes when using ischemic preconditioning (IPC) or remote ischemic preconditioning (RIPC) to reduce IRI in liver grafts. ***Methods:*** A literature search was performed in the MEDLINE, Web of Science, and EMBASE databases. The following combination was used: "Liver" OR "Liver Transplantation" AND "Ischemic preconditioning" OR "occlusion" OR "clamping" OR "Pringle." The following outcome data were retrieved: the rates of graft primary nonfunction (PNF), retransplantation, graft loss, and mortality; stay in hospital and the intensive care unit; and postoperative serum liver damage parameters. ***Results:*** The initial search retrieved 4,522 potentially relevant studies. After evaluating 17 full-text articles, a total of 9 randomized controlled trials (RCTs) were included (7 IPC and 2 RIPC studies) in the qualitative synthesis; the meta-analysis was only performed on the data from the IPC studies. RIPC studies had considerable methodological differences. The meta-analysis revealed the beneficial effect of IPC when comparing postoperative aspartate aminotransferase (AST) corresponding to a statistically lower mortality rate in the IPC group (odds ratio [OR] 0.51; 95% confidence interval [CI] 0.27–0.98; $p = 0.04$). ***Conclusion:*** IPC lowers postoperative AST levels and reduces the mortality rate; however, data on the benefits of RIPC are lacking.

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Introduction

In recent decades, liver transplantation (LTx) has increased the survival and quality of life of patients with end-stage organ failure by providing a potentially long-term treatment option [1, 2]. Unfortunately, LTx is limited due to the shortage of donors. The organ donor pool can be extended by using expanded-criteria donors (ECD), who are older and have a higher prevalence of fatty liver [3]. Grafts from ECD are particularly susceptible to ischemia-reperfusion injury (IRI), resulting in higher primary nonfunction (PNF) rates that, in turn, lead to inferior transplant outcomes [4, 5]. A lot of effort is put into finding new ways to reduce IRI during LTx to increase the number of suitable organs procured from ECD. Several methods to reduce IRI in LTx are under in-

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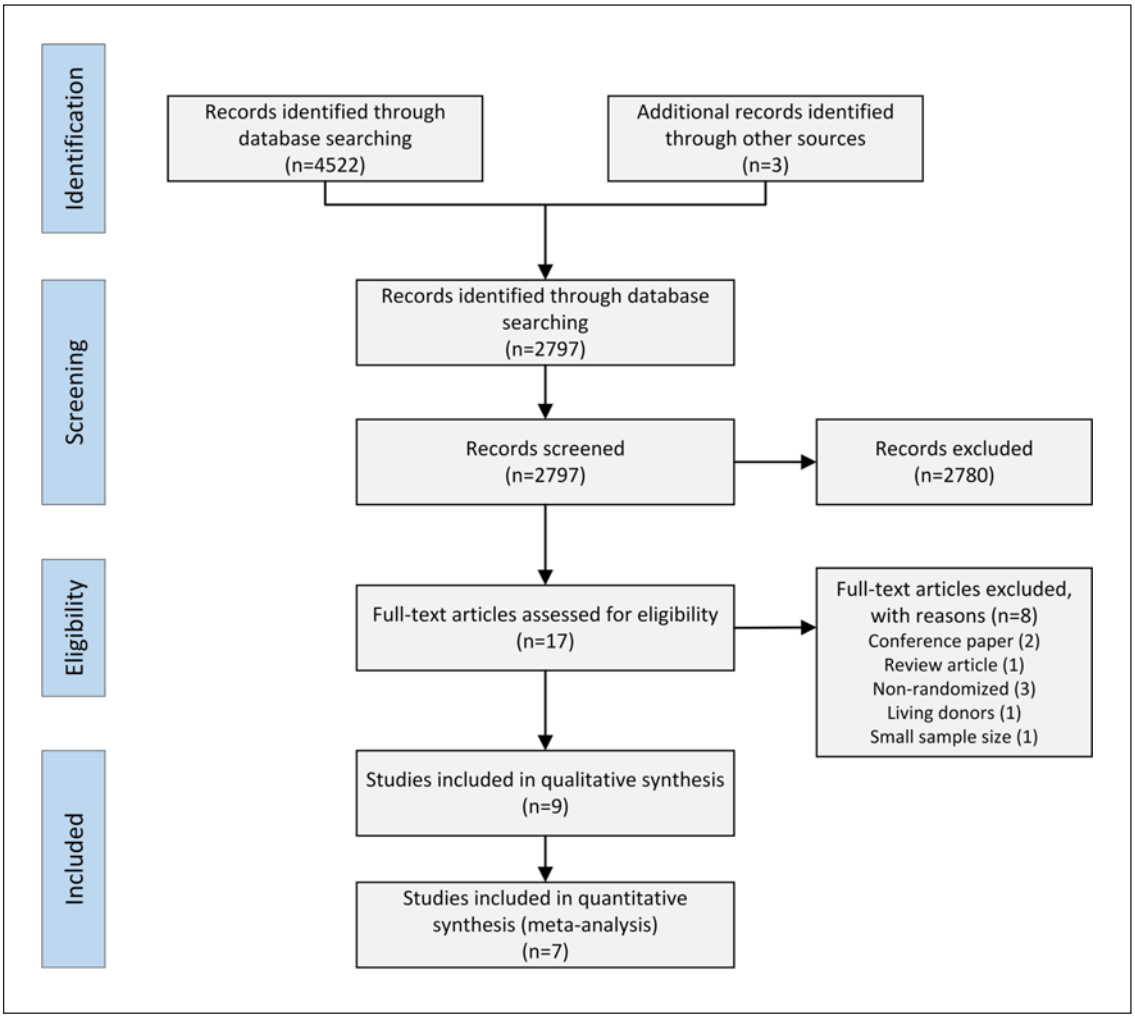

Fig. 1. PRISMA flowchart of study selection process.

vestigation, including new therapeutic agents to reduce IRI, graft perfusion and storage, and different ischemic preconditioning (IPC) strategies [6–9].

IPC describes a surgical method when a short period of ischemia to the target organ is supposed to lessen the harmful effects of IRI. It was first described in 1986 by Murry et al. [10] in a canine cardiac ischemia model and showed a protective effect on the myocardium. Over time, its use was investigated for multiple organs, including the liver [11–13]. The IPC technique for the liver is usually performed during procurement by a short inflow occlusion (the Pringle maneuver) followed by reperfusion. Preliminary data from animal studies showed beneficial effects of IPC in a LTx model, but its application in the clinical setting remains controversial [14]. A simpler procedure, when a short ischemia period is induced, not directly to the target organ but to a remote site (usually limb), causing systemic protection, is called remote (R) IPC. RIPC is a novel technique and its effectiveness in the transplantation setting remains unclear [15].

The aim of this paper was to systematically review the literature reporting LTx outcomes when using IPC or RIPC to reduce IRI in liver grafts.

Methods

Literature Search Strategy

The search was performed in the MEDLINE, Web of Science, and EMBASE databases. The following combination of MeSH terms and keywords (deploying the Boolean operators "AND" or "OR") were used: "Liver" OR "Liver Transplantation" AND "Ischemic preconditioning" OR "occlusion" OR "clamping" OR "Pringle."

The search was restricted to the English language and human studies only, but with no time limitation. The most recent search was performed on 21 September 2020. Database-specific search strategies are provided as online supplementary material (see www.karger.com/doi/10.1159/000516608 for all online suppl. material).

Table 1. Characteristics and main findings of clinical regional IPC studies

First author [ref.], year	IPC group vs. controls, *n*	IPC settings
Koneru [11], 2005	34 vs. 28	IPC time: 5 min early in the donor laparotomy, reperfusion length n.r. Flushed with 2 L of UW® cold storage solution via both the portal vein and the aorta.
Cescon [18], 2006	24 vs. 23	IPC time: 10 min, followed by 15 min of reperfusion before starting cold ischemia. Flushed with 5 L of Celsior® solution through the aorta and 1 L through the portal vein.
Amador [19], 2007	30 vs. 30	IPC time: 10 min, followed by 10 min of reperfusion before starting cold ischemia. Flushed with 2 L of UW solution through the aorta and 3 L through the portal vein.
Koneru [20], 2007	50 vs. 51	IPC time: 10 min early in the donor laparotomy, reperfusion until circulatory arrest. Flushed with 2 L of UW solution via both the portal vein and the aorta.
Cescon [21], 2009	19 vs. 20	IPC time: 10 min, followed by 15 min of reperfusion before starting cold ischemia. Flushed with 5 L of Celsior solution through the aorta and 1 L through the portal vein.
Franchello [22], 2009	30 vs. 45	IPC time: 10 min, followed by 30 min of reperfusion before starting cold ischemia. Preservation solution n.r.
Jassem [23], 2009	19 vs. 16	IPC time: 10 min early in the donor laparotomy, average reperfusion length 30 min. Flushed with UW solution.

n.r., not recorded.

Eligibility Criteria

We included only randomized controlled trials (RCTs) with >10 patients per group, that investigated the use of IPC or RIPC in the LTx setting. Cohort studies, case-control studies, quasi-randomized studies, case reports, case series, and studies including children or animals were excluded.

Study Selection and Data Extraction

At first, the studies were screened based on their title and abstract. The full text was obtained for potentially eligible studies. The following data were extracted from all the included studies: study characteristics, year of publication, sample size, ischemic preconditioning parameters, and preservation solutions used. For the outcome assessment, additional data were obtained: the rates of graft PNF, retransplantation, graft loss, and mortality (for a maximum follow-up of 24 months); stay in hospital and the intensive care unit (ICU); and postoperative serum liver markers (aspartate aminotransferase [AST], alanine aminotransferase [ALT], total bilirubin, and international normalized ratio [INR]). If continuous variables were provided as medians, they were not included in the analysis due to concerns that the data were maybe skewed.

Risk-of-Bias Assessment

The quality of the included RCTs was evaluated using the RoB 2 risk-of-bias assessment tool, which is currently recommended in The Cochrane Handbook for Systematic Reviews and Interventions [16, 17].

Statistical Analysis

We performed the meta-analyses using the software package RevMan v5.3 according to the recommendations of The Cochrane Handbook for Systematic Reviews and Interventions [17]. For dichotomous variables, we calculated the odds ratio (OR) and 95% confidence interval (CI). As we expected a high level of heterogeneity across studies, the Mantel-Haenszel (M-H) method and random-effects models were employed. For continuous variables, we calculated the mean difference using the inverse-variance (IV) method and random-effect models. Furthermore, the I^2 test was used to measure statistical heterogeneity. If a study observed no event in either group, it was not included in the quantitative analysis.

Results

Study Selection and Characteristics

Literature search results and the study selection process are presented in the PRISMA flowchart (Fig. 1). The initial search retrieved 4,522 potentially relevant studies. After evaluating 17 full-text articles, 9 were included in the qualitative synthesis [11, 18–25]. Due to high heterogeneity between studies analyzing remote IPC (n = 2), only studies investigating regional IPC (n = 7) were included in the meta-analysis. Main characteristics of studies examining IPC and RIPC are presented in Tables 1 and 2, respectively. From the study by Jassem et al. [23], we only included AST levels at postoperative day 1 and 3 in the meta-analysis as other variables were not reported.

Table 2. Characteristics and main findings of clinical remote IPC studies

First author [ref.], year	RIPC group vs. controls, *n*	RIPC settings	Main findings
Robertson [24] 2017	20 vs. 20	Donor: deceased Applied to: recipient Place: left middle thigh Applied pressure: 200 mm Hg Time: 3 cycles of 5 min each of ischemia and reperfusion	RIPC is feasible and acceptable in liver transplant recipients No differences in clinical outcomes between RIPC and control groups Lower median IL-6 level in the preconditioned group compared to controls
Jung [25] 2020	75 vs. 73	Donor: living Applied to: donor Place: upper arm Applied pressure: 200 mm Hg Time: 3 cycles of 5 min each of ischemia and reperfusion	No beneficial effect to the donor Significantly lower AST levels on postoperative days 1 and 7 in recipients with preconditioned grafts

Table 3. Risk-of-bias assessment of included RCTs using the RoB 2 tool

First author [ref.], year	Randomization process	Deviations from intended intervention	Missing data on outcomes	Measurement of the outcome	Selection of the reported result	Overall risk-of-bias judgement
IPC studies						
Koneru [11], 2005	low risk	low risk	low risk	low risk	some concerns	some concerns
Cescon [18], 2006	low risk	high risk	some concerns	low risk	some concerns	high risk
Amador [19], 2007	low risk	low risk	low risk	low risk	some concerns	some concerns
Koneru [20], 2007	low risk	low risk	low risk	low risk	some concerns	some concerns
Cescon [21], 2009	some concerns	some concerns	low risk	low risk	some concerns	some concerns
Franchello [22], 2009	some concerns	some concerns	low risk	low risk	some concerns	some concerns
Jassem [23], 2009	low risk	some concerns	low risk	low risk	some concerns	some concerns
RIPC studies						
Robertson [24], 2017	low risk	low risk	low risk	low risk	some concerns	some concerns
Jung [25], 2020	low risk	low risk	low risk	low risk	some concerns	some concerns

Study Quality

All included RCTs, except one, were evaluated as having some concerns in the overall risk-of-bias judgement (Table 3). A study by Cescon et al. [18] was evaluated as having a high risk-of-bias due to the exclusion of some patients from the study, which may have influenced the final results.

Outcome Assessment

IPC

Mortality. The overall mortality rate was 9.7% (18/186) in the IPC group and 16.2% (32/198) in the control group. This difference was statistically significant (OR 0.51; 95% CI 0.27–0.98; p = 0.04; I^2 = 0%) (Fig. 2).

Graft Loss. Four trials reported graft loss rates [11, 18, 20, 21]. Our analysis showed a tendency that favors the IPC group (11.1% [14/126] vs. 18.7 [23/123]), but the difference was not statistically significant (OR 0.54; 95% CI 0.26–1.12; p = 0.10; I^2 = 0%) (Fig. 3). From the data reported by Amador et al. [19], we could not calculate graft loss events, so the study was not included in the quantitative analysis; this did not change the analysis outcome as the reported 24-month graft survival rate was similar between the groups (IPC 86.3% vs. controls 84.9%).

PNF. The overall PNF rate in the IPC and control groups was 0.7% (1/152) and 4.1% (7/170), respectively. The analysis showed no difference between the groups (OR 0.38; 95% CI 0.1–1.53; p = 0.18; I^2 = 0%) (Fig. 4). A trial by Koneru et al. [11] reported no events in either group.

Retransplantation Rate. Similar retransplantation rates were observed when comparing the IPC and control groups (3.8% [4/106] vs. 5.1% [6/117]) with no statistical difference (OR 0.78; 95% CI 0.22–2.75; p = 0.69; I^2 = 0%) (Fig. 5).

Postoperative Serum Liver Markers. Only 3 studies reported mean postoperative AST levels. We did observe statistically significant differences between groups on postoperative days 1 and 3 (Fig. 6, 7). AST level differences equalized on postoperative day 7 (online suppl. Fig.

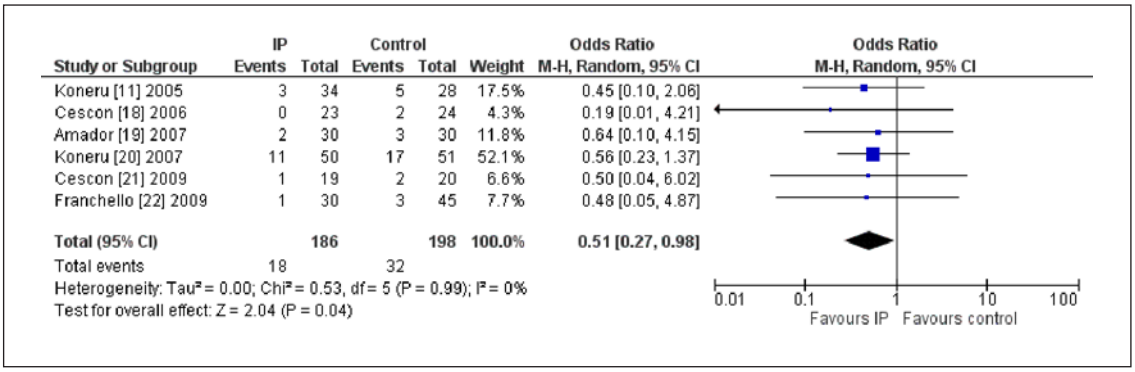

Fig. 2. Forest plot of studies comparing odds ratio of mortality rate between IPC and control groups.

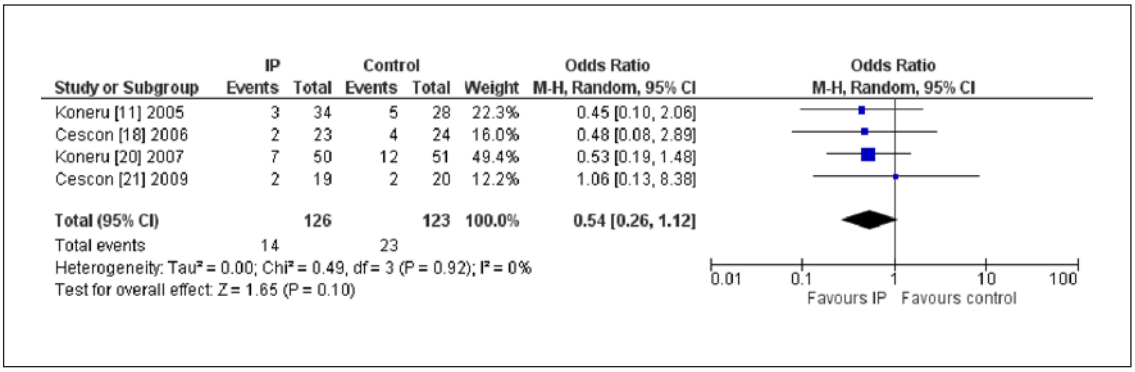

Fig. 3. Forest plot of studies comparing odds ratio of graft loss rate between IPC and control groups.

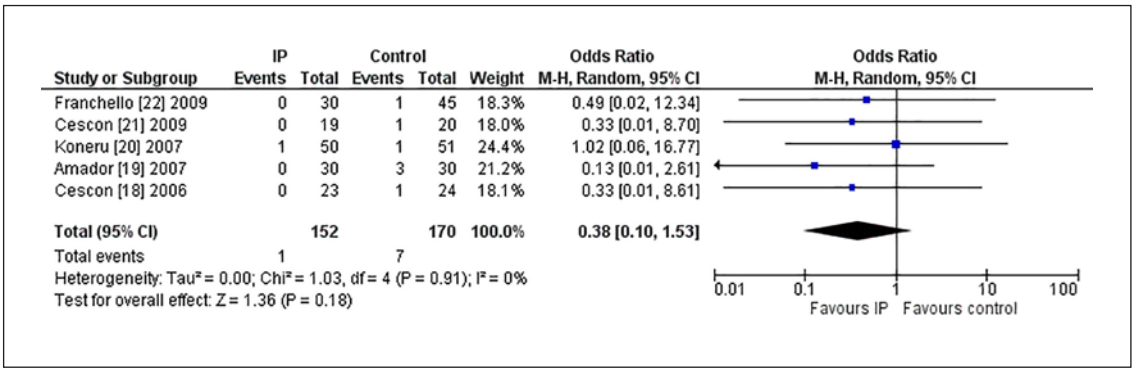

Fig. 4. Forest plot of studies comparing odds ratio of PNF rate between IPC and control groups.

S1). A similar tendency, favoring the IPC group, was observed with the ALT levels, but the differences were not significant (online suppl. Fig. S2, S3). INR and bilirubin levels were similar between groups during the postoperative period (online suppl. Fig. S4–S8).

Hospital and ICU Stay. There were no significant differences in the hospital and ICU stay between the 2 groups (online suppl. Fig. S9, S10).

RIPC

Only 2 studies investigated the use of RIPC in the LTx setting (Table 2) [24, 25]. A pilot, double-blinded RCT was conducted by Robertson et al. [24] with transient ischemia periods in recipients. The primary end point of this study was to investigate whether RIPC is safe and feasible for LTx recipients. The authors concluded that RIPC was indeed safe and acceptable for the LTx recipients, but no clinical outcome differences were observed between

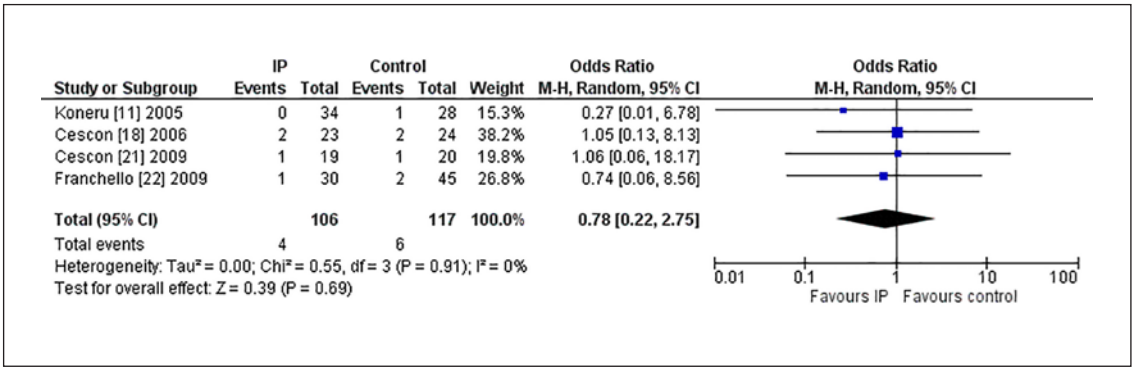

Fig. 5. Forest plot of studies comparing odds ratio of retransplantation rate between IPC and control groups.

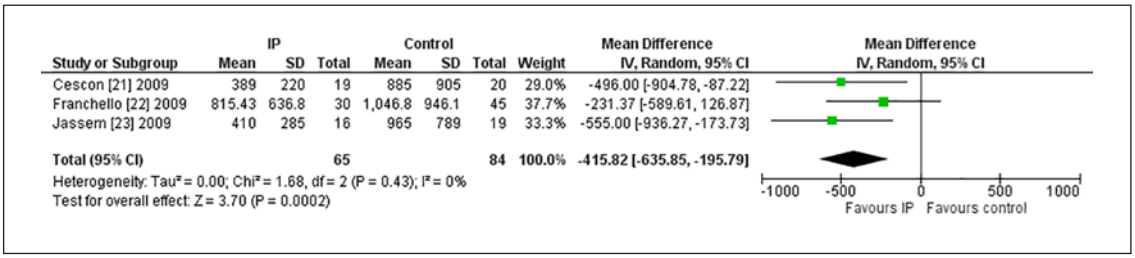

Fig. 6. Forest plot of studies comparing mean difference of AST levels on postoperative day 1 between IPC and control groups.

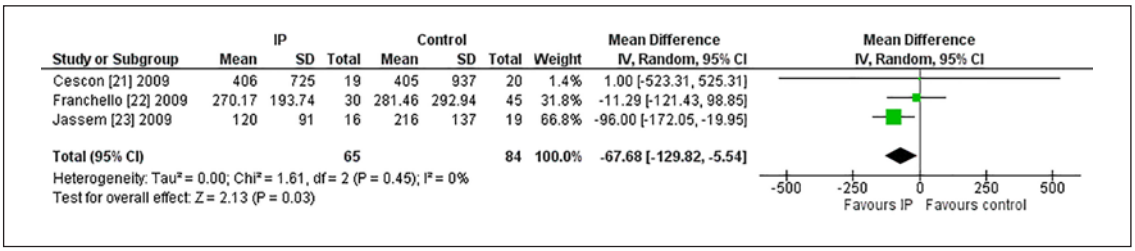

Fig. 7. Forest plot of studies comparing mean difference of AST levels on postoperative day 3 between IPC and control groups.

the groups. A very different RCT was published by Jung et al. [25]. In their trial, RIPC was applied to living donors. They did not find any RIPC benefits for the donors, but postoperative AST levels were significantly lower in recipients who received preconditioned grafts, indicating a beneficial effect of RIPC for the recipient.

Discussion

In this systematic review and meta-analysis, we provide an overview of the potential effects of IPC and RIPC on liver grafts during clinical LTx. The original aim was to perform a quantitative analysis on both IPC and RIPC RCTs, but methodological differences and the lack of RIPC studies limited the meta-analysis to IPC studies.

Our results revealed the beneficial effect of IPC when comparing postoperative AST levels between the groups. Furthermore, this corresponded to a statistically lower mortality rate in the IPC group. In addition, our study showed a tendency towards a lower graft loss rate in the IPC group, although the results were not statistically significant. These data are in line with the findings of Robertson et al. [26], who observed that AST levels on postoperative day 3 were closely related to the survival of the patient and the graft.

The exact mechanism involved in how IPC and RIPC reduce IRI remains unclear. Several studies indicate that there is a bimodal duration of protection [27, 28]. The

early protection period lasts up to 3 h and the later period lasts 12–72 h after preconditioning. Acting through humoral, systemic, and neuronal mechanisms, IPC and RIPC exert liver protection by reducing cell death and inflammatory response and improving the hepatic microcirculation [29]. Robertson et al. [29] provide an in-depth overview of the possible protective mechanisms of IPC and RIPC in liver surgery.

Nowadays, as machine perfusion techniques are becoming more widely available, one could argue that the use of IPC and RIPC has lost its purpose in expanding the possible donor pool. However, the low cost and technical simplicity mean that IPC is still relevant, especially in centers where machine perfusion is not available. Furthermore, the 2 techniques could be combined and, potentially, yield even better results.

Unfortunately, it seems that the research interest in IPC has faded as the last RCT was published in 2009. On the other hand, the research of RIPC is becoming more popular as the 2 included RCTs were published in the last 3 years and we await results from other ongoing studies (NCT03758352 and NCT03855722) with interest.

Currently, there are 2 other meta-analyses on this topic. The first was published by Gurusamy et al. [14] in 2008; they included 5 RCTs and failed to show any benefits of IPC. The other was published by Robertson et al. [30] in 2016 and included both randomized and nonrandomized studies; they found that the IPC group had a significantly lower postoperative day 3 AST level. The main strength of our meta-analysis is that we included only RCTs with a moderate risk of bias when assessed with the RoB 2 tool.

Our analysis has some limitations. First, there is still no consensus about which IPC strategy is best for humans. As Table 1 shows, only 1 study induced transient ischemia for 5 min, while the other RCTs used a 10-min time period. Moreover, there were some differences in the length of reperfusion.

The lack of beneficial IPC effect in the individual studies seems to be associated with graft quality. By performing a subgroup analysis, Franchello et al. [22] determined that IPC is beneficial to marginal grafts and showed no significant effect on the traditional grafts from DBD donors. The upcoming RCTs should focus more on the use of IPC on poor-quality liver grafts.

Statement of Ethics

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, P.Sc., P.St., B.L., and K.S.; methodology, M.J., L.J., P.Sc., and P.St.; software, M.J and L.J.; validation, P.Sc., P.St., and B.L.; formal analysis, M.J. and L.J.; investigation, M.J., L.J., P.Sc., P.St., B.L., and K.S.; resources, P.Sc., P.St., and B.L.; data curation, writing and original draft preparation, M.J. and L.J.; writing, review, and editing, P.Sc., P.St., B.L., and K.S.; visualization, M.J. and L.J.; supervision, P.Sc., P.St., B.L., and K.S.; project administration, P.Sc., P.St., and B.L.

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