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REVIEW ARTICLE

Impact of Prolonged Cold Ischemia on Liver Graft Function in Liver Transplantation: A Systematic Review

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ABSTRACT

Objective: To evaluate and compare the effectiveness of different preservation and preconditioning strategies in reducing the deleterious effects of prolonged cold ischemia in liver transplantation, analyzing their impact on graft dysfunction, post-transplant clinical outcomes, and recipient-associated risk factors. **Methods:** This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Searches were performed in the PubMed, Virtual Health Library, and Cochrane Library databases, last updated in February 2025, resulting in the initial identification of 198 studies. Clinical trials, observational studies, and meta-analyses published in the last 5 years, analyzing the impact of cold ischemia on liver transplantation, were included. After rigorous screening, 10 articles were selected, excluding studies considered irrelevant, with small sample sizes or inadequate methodology. **Results:** Prolonged cold ischemia (PCI) is associated with graft dysfunction, cellular necrosis, inflammation, increased need for clinical support, and higher costs. Strategies such as hypothermic oxygenated perfusion (HOPE), use of the portable Organ Care System (OCS), remote ischemic preconditioning, and N-acetylcysteine (NAC) infusion showed potential to mitigate PCI effects. Factors such as ethnicity, sex, age, and transport time also influence outcomes. The adoption of these strategies may reduce post-transplant complications and improve graft survival. **Conclusion:** The review demonstrated that PCI is a consistent determinant of early graft dysfunction in liver transplantation, influencing ischemia–reperfusion injury, inflammation, and biliary complications. Although only one study evaluated cold ischemia time (CIT) as the primary variable, all included studies confirmed its role as a risk factor or adjusted variable. Technologies such as HOPE, OCS, NAC, and ischemic preconditioning may attenuate its effects but do not fully eliminate them. Thus, reducing CIT, combined with modern preservation strategies and appropriate donor selection, remains essential to improving liver transplant outcomes.

Descriptors: Cold Ischemia; Risk Factors; Liver Graft; Liver Transplantation.

Impacto da Isquemia Fria Prolongada na Função de Enxertos Hepáticos em Transplantes de Fígado: Revisão Sistemática

RESUMO

Objetivos: Avaliar e comparar a eficácia de diferentes estratégias de conservação e pré-condicionamento na redução dos efeitos deletérios da isquemia fria prolongada (IFP) em transplantes hepáticos, analisando seu impacto na disfunção do enxerto, nos desfechos clínicos pós-transplante e nos fatores de risco associados ao receptor. **Métodos:** Esta revisão sistemática foi conduzida de acordo com as diretrizes do Preferred Reporting Items for Systematic Reviews and Meta-Analyses. As buscas foram realizadas nas bases de dados PubMed, Biblioteca Virtual em Saúde e Cochrane Library, com a última atualização em fevereiro de 2025, resultando na identificação inicial de 198 estudos. Foram incluídos ensaios clínicos, estudos observacionais e metanálises publicados nos últimos 5 anos que analisam o impacto da isquemia fria em transplantes hepáticos. Após triagem rigorosa, 10 artigos foram selecionados, excluindo estudos considerados irrelevantes, com amostras reduzidas ou metodologia inadequada. **Resultados:** A IFP está associada à disfunção do enxerto, necrose celular, inflamação, maior necessidade de suporte clínico e aumento de custos. Estratégias como perfusão hipotérmica oxigenada [*hypothermic oxygenated perfusion* (HOPE)], uso do sistema portátil de conservação de órgãos [*Organ Care System* (OCS)], pré-condicionamento isquêmico remoto e infusão de N-acetilcisteína (NAC) demonstraram potencial em mitigar os efeitos da IFP. Fatores como etnia, sexo, idade e tempo de transporte também influenciam os desfechos. A adoção dessas estratégias pode reduzir complicações pós-transplante e melhorar a sobrevida do enxerto. **Conclusão:** A revisão demonstrou que a IFP é um determinante consistente da disfunção inicial do enxerto hepático, influenciando lesão de isquemia-reperfusão, inflamação e complicações biliares. Embora apenas um estudo tenha avaliado o tempo de isquemia fria [*cold ischemia time* (CIT)] como variável principal, todos os trabalhos incluídos confirmaram sua participação como fator de risco ou variável ajustada. Tecnologias como HOPE, OCS, NAC e pré-condicionamento isquêmico podem atenuar seus efeitos, mas não os eliminam completamente. Assim, a redução do CIT, associada a estratégias modernas de preservação e adequada seleção do doador, permanece essencial para melhorar os resultados do transplante hepático.

Descritores: Isquemia Fria; Fatores de Risco; Enxerto Hepático; Transplante de Fígado.

INTRODUCTION

The liver is one of the most important organs in the human body, responsible for functions such as the metabolism of bile, glucose, proteins, coagulation factors, cholesterol, and triglycerides, as well as the detoxification of xenobiotics[1]. Due to its remarkable regenerative capacity, it can be procured from a living donor, enabling living-donor liver transplantation, which can be performed through registration in the National Organ Donation and Transplantation System (*Sistema Nacional de Doação e Transplante de Órgãos*)[2]. The most common indications for this type of procedure are alcoholic cirrhosis or cirrhosis resulting from hepatitis B or C viruses, fulminant hepatitis, and primary liver cancer[1].

Although living-donor liver transplantation is technically feasible, its application in adults has become infrequent since the adoption of the Model for End-Stage Liver Disease score as an allocation criterion, which is based on the international normalized ratio and serum levels of bilirubin, creatinine, and sodium. This system prioritizes patients with greater clinical acuity, optimizing the distribution of organs from deceased donors, resulting in the absence of a clear survival benefit for the adult recipient of a living donor in structured transplant systems[3]. Furthermore, this method poses significant risks to the healthy donor who requires a right hepatectomy and presents higher rates of technical complications in the recipient when compared to pediatric transplantation, in which only segments II and III are used[4]. Currently, this practice is applied more frequently in pediatrics, with 134 pediatric patients registered among the 150 living donor liver transplants performed in Brazil in 2024[5].

In this scenario, organ scarcity remains a critical challenge, and many people die on the waiting list due to a lack of viable grafts. Currently, the priority of the National Transplant System rests on organs from brain-dead donors. Livers donated after circulatory death present a substantially higher risk of primary dysfunction, delayed graft function, and ischemic biliary lesions, which is why they are not routinely used in Brazilian clinical practice[6].

To mitigate these risks and enable the use of livers from circulatory death, the development of machine perfusion techniques is becoming increasingly prevalent. These technologies emerge as a promising solution to combat the underutilization of these organs, allowing for graft rehabilitation before implantation[7]. However, despite the potential to reduce damage from hypoxia and oxidative stress, the implementation of these techniques still faces logistical and economic challenges, remaining far from the operational reality of most transplant centers in Brazil[8].

Furthermore, the time the graft is subjected to cold ischemia also influences the success of liver transplantation, as it directly affects the histological damage caused to the graft. On the one hand, studies demonstrate that prolonged exposure to ischemic stress is independent of histological alterations and the use of vasoactive drugs, compared to grafts with a shorter associated time[9]. On the other hand, research shows that irreparable damage is caused by both cold and warm ischemia, as both are risk factors for the development of primary liver graft dysfunction[10].

Thus, it is essential to analyze the current literature and investigate the impairments caused by prolonged ischemia on the functionality of grafts used in liver transplantation. Despite advances in preservation techniques, disagreement persists about the impact of cold ischemia time (CIT) on clinical outcomes. Therefore, this study aimed to evaluate and compare the efficacy of different preservation and preconditioning strategies in reducing the deleterious effects of prolonged cold ischemia (PCI). Furthermore, it aimed to analyze its impact on graft dysfunction, post-transplant clinical outcomes, recipient-associated risk factors, and the clinical, pharmacological, and technological factors influencing graft function.

METHODS

This systematic review was prepared in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines, rigorously following the steps of identification, screening, eligibility, and inclusion of studies, as recommended by the official flowchart. The review protocol is registered in the International Prospective Register of Systematic Reviews, under number CRD420261287285, with the title *Impact of Prolonged Cold Ischemia on Liver Graft Function in Liver Transplantation: a Systematic Review*.

The guiding question of the research was structured according to the PICO strategy: P (Population) – adult patients undergoing liver transplantation; I (Intervention/Exposure) – prolonged CIT; C (Comparison) – reduced CIT or use of mitigation strategies, such as hypothermic oxygenated perfusion (HOPE), portable organ preservation system (Organ Care System - OCS), N-acetylcysteine (NAC), or remote ischemic preconditioning; O (Outcomes) – early graft dysfunction, post-reperfusion syndrome, biliary complications, need for retransplantation, graft and patient survival. Thus, the aim was to answer the following question: Is PCI time associated with poorer initial liver graft function and unfavorable clinical outcomes after transplantation?

The search was conducted in the PubMed/MEDLINE, Biblioteca Virtual em Saúde (BVS) and Cochrane Library databases. No country-of-origin restrictions were applied to the studies. The search strategy used the descriptors combined by Boolean operators: "Cold Ischemia" AND "Liver Transplantation" AND "Liver Grafting". Filters were applied to articles published in the last 5 years, available in full text, in English, Portuguese or Spanish, involving an adult population (≥ 19 years). Randomized clinical trials, observational studies (cohort and case-control) and meta-analyses that directly or indirectly evaluated the relationship between CIT and liver graft function were included. Initially, 198 articles were identified: 113 from PubMed, 81 from BVS, and 4 from the Cochrane Library. The search was conducted in February 2025. After removing duplicates, titles and abstracts were screened independently by two reviewers. Studies that did not address liver transplantation in adults, that exclusively involved animal models or in vitro experiments, case reports, letters to the editor, narrative reviews without systematic methodology, or that did not analyze the impact of the CIT were excluded. Disagreements between reviewers were resolved by consensus and, when necessary, by evaluation by a third reviewer.

Inclusion criteria

Articles published in the last 5 years (the time restriction was adopted to ensure technological updating of preservation strategies), studies available in full text, in English, Portuguese or Spanish, studies involving adult patients undergoing liver transplantation, studies that directly or indirectly evaluate the relationship between CIT and liver graft function, with outcomes such as primary graft dysfunction, rejection rates, need for retransplantation, post-transplant complications, and patient/organ survival and risk factors, and clinical trials, observational studies (cohort, case-control) and meta-analyses.

Exclusion criteria

Studies published more than 5 years ago, studies that do not specifically address the impact of cold ischemia on liver grafts, case studies, expert opinions, letters to the editor, and review articles without systematic analysis, studies with inadequate methodological quality (absence of a control group; lack of clear description of outcomes), very small samples (≥ 20 patients per group or studies with an adequate comparator group), and studies that do not directly address cold ischemia or that evaluate other liver preservation techniques without considering CIT were excluded. For this review, PCI was defined as exceeding 6-8 hours, as defined in the included studies.

Thirteen articles were selected for full-text reading. Of these, three were excluded for failing to present relevant data on CIT outcomes or for not fully meeting the established eligibility criteria. At the end of the process, 10 studies were included in the

qualitative analysis. For each included study, the following variables were extracted: donor and recipient characteristics, CIT, type of donation (donation after brain death (DBD) or donation after circulatory death (DCD)), type of graft, preservation strategy used, presence of mitigation interventions, outcomes related to initial graft function, postoperative complications, and graft and patient survival.

The risk of bias assessment was conducted according to each study's methodological design. For randomized clinical trials, the Cochrane risk of bias tool[2] was used. For observational studies, the risk of bias in non-randomized intervention studies tool was employed. The analysis was conducted by two independent reviewers, with disagreements resolved by consensus. Due to the methodological heterogeneity among the included studies, especially regarding the definition of PCI (ranging from > 6 hours to > 8 hours), the different outcomes analyzed, and the distinct types of interventions evaluated, it was not possible to perform a quantitative meta-analysis. Therefore, a structured narrative synthesis was chosen, organizing the results according to the role of CIT in each study (main variable, adjusted covariate, or moderating factor).

Due to the small number of included studies and the absence of a meta-analysis, it was not possible to perform a formal assessment of publication bias using funnel plots or statistical tests such as Egger's and Begg's. This limitation was considered in the interpretation of the results. All methodological procedures were conducted in accordance with the updated PRISMA 2020 recommendations, aiming to ensure transparency, reproducibility, and scientific rigor in the selection and analysis of the included studies. The included studies and their main characteristics are described in Table 1, and the study selection process is presented in Fig. 1.

Table 1. Brief description of the articles selected for the literature review.

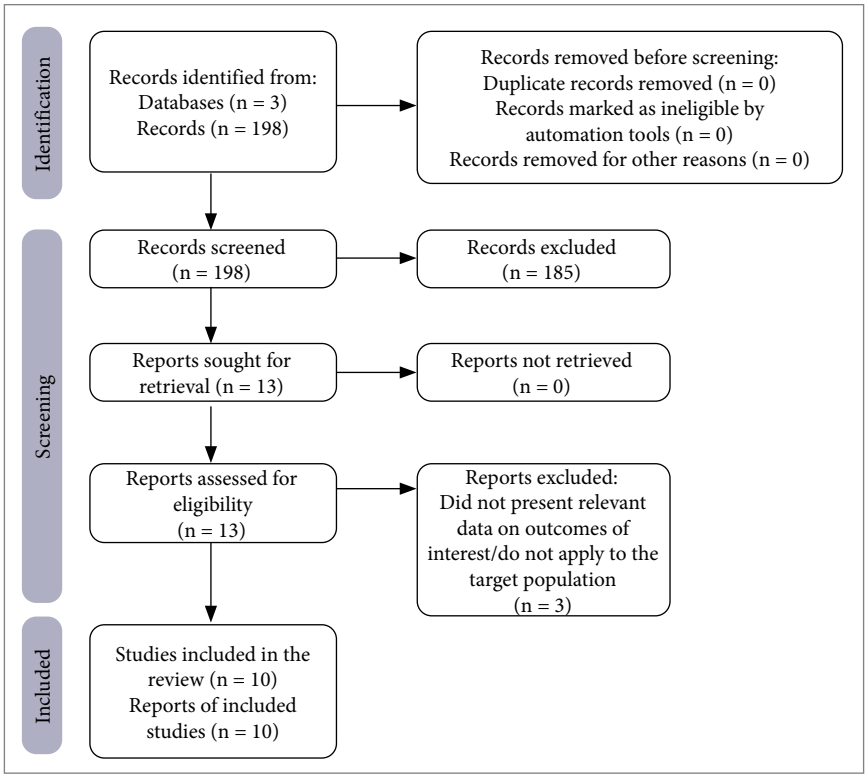
Authors	Sample	Intervention	Results/outcomes
Norén et al.[12]	101 liver transplant recipients with organs from donors ≥ 70 years old, divided into HOPE-LTs (n = 30) and controls (n = 71)	Use of HOPE in livers from elderly donors to reduce IRI injury and impact on AKI.	An increase of 1 hour in CIT raised the risk of postoperative infection by up to 2.6 times. Furthermore, patients with a cold ischemia time exceeding 8 hours had significantly longer hospital stays, averaging 36 days, compared with 20 days for patients with shorter ischemia times. This extended hospital stay and infectious complications resulted in much higher hospital costs, which were associated with lower patient and graft survival rates.
Barbier et al.[13]	Animal model: wild-type and IL-33-deficient mice	Induction of hepatic ischemia/reperfusion to evaluate IL-33 release and its effects on inflammation and tissue injury.	IL-33 was rapidly released after hepatic ischemia without the need for new synthesis and contributed to neutrophil recruitment and tissue injury.
	Clinical study: 40 patients undergoing liver transplantation with serum IL-33 measurements	Measurement of serum IL-33 levels and correlation with clinical outcomes.	IL-33 levels peaked immediately after reperfusion and were associated with post-reperfusion syndrome, post-transplant renal failure, graft dysfunction, and histological ischemia/reperfusion injury. In other words, it is related to early complications following transplantation.
Rodrigues et al.[14]	38 patients who underwent liver transplantation were divided into two groups: Group A: CIT < 8 hours; Group B: CIT > 8 hours.	Evaluation of the impact of CIT on the function of Custodiol-preserved liver grafts in the first 7 days after transplantation.	Group A (CIT < 8 hours) had better outcomes, with fewer transfusions, shorter hospital stays, and lower bilirubin and GGT levels. Group B (CIT > 8 hours) had a greater need for transfusions, longer hospital stays, more time in the ICU, and higher costs.
Carton et al.[15]	790 patients who underwent liver transplantation	Liver transplants performed late at night (between midnight and 5 a.m.) compared with transplants performed at other times (control group).	Nighttime transplants were associated with a greater need for blood transfusions ($p = 0.010$) and a higher chance of serious complications (OR 1.67; 95% CI 1.10-2.54). In the long term, graft and patient survival after 1 year was similar between transplants performed at night and those performed during the day.
Huh and Chae[16]	664 patients aged > 19 years undergoing elective liver transplantation with a living donor, divided into a group with remote ischemic preconditioning (n = 332) and a group without remote ischemic preconditioning (n = 332)	Performing remote ischemic preconditioning and assessing the incidence of post-reperfusion syndrome and the need for rescue epinephrine.	Remote ischemic preconditioning effectively reduces the occurrence of post-reperfusion syndrome (OR: 0.672, 95% CI 0.479-0.953, $p = 0.021$) and the need for rescue epinephrine in patients undergoing elective liver transplantation with a living donor, protecting the graft against ischemia-reperfusion injury.
Markmann et al.[17]	293 recipients of preserved livers using the OCS Liver (n = 151) or refrigerated ischemic storage (CIT Liver) (n = 142)	Use of CIT liver compared to traditional OCS Liver.	Livers preserved with OCS Liver showed a reduction in ischemia-reperfusion injury after reperfusion (6% of affected patients with moderate to severe lobular inflammation, compared to 13% in CIT Liver; $p = 0.004$).

Continue...

Table 1. Continuation.

Authors	Sample	Intervention	Results/outcomes
Eden et al.[18]	1,202 samples were divided substantially into donations after brain death (n = 768) and donations after circulatory death (n = 434).	Use of HOPE perfusion in liver donors for transplantation.	Excellent 5-year post-liver transplant survival in both HOPE-treated groups, featuring low rates of graft loss due to primary non-function or ischemic cholangiopathy, regardless of individual risk profiles
Wallace et al.[19]	Patients aged ≥ 18 years were divided into recipients of DBD (n = 3,749) or DCD (n = 1,176) liver transplants.	Comparison of the outcomes of DCD and DBD liver transplants in two periods (2008 to 2011 and 2012 to 2016).	In DCD liver recipients, mortality rates decreased from 19.6% in the first period to 10.4% in the second period (OR: 0.43; 95% CI 0.30-0.62; $p < 0.001$). In DBD recipients, the reduction was from 12.8% to 11.3% (OR: 0.96; 95% CI 0.78-1.19; $p = 0.732$). Furthermore, there was a slight increase in retransplantation rates among DCD liver recipients between the first and second periods (from 7.3% to 11.8%; $p = 0.042$). Overall, the use of DCD livers is an effective alternative in liver transplantation.
Gómez-Gavara et al.[20]	214 grafts were assigned to either the NAC group (n=113) or the standard protocol without NAC (n=101).	NAC infusion during liver procurement in liver transplant outcomes.	NAC administration impaired ALT levels when CIT exceeded 6 hours (p=0.0125). Graft and patient survival rates at 12 months and 3 years were similar between groups (p=0.54 and p=0.69, respectively). Therefore, the use of NAC during liver procurement does not improve early graft dysfunction. However, NAC is effective in reducing postoperative ALT levels when CIT exceeds 6 hours.
Imaoka et al.[11]	Retrospective data from patients who underwent liver transplantation between 2014 and 2020, registered in the United Network for Organ Sharing database, were analyzed. During the study period, 28,265 patients received DBD grafts and 3,250 received DCD grafts.	The grafts were classified as short-distance or long-distance (> 800 km). Factors related to graft survival and donor and recipient characteristics were analyzed.	The transplantation rate using long-distance grafts was 6.2% for donors with brainstem death and 7.1% for donors with circulatory death. Graft survival at 90 days was lower for long-distance grafts: 94.5% in donors with brainstem death, compared with 95.7% in short-distance donors, and 93.9% in donors with circulatory death, compared with 94.5% in short-distance donors. However, graft survival at 3 years was similar between groups: 85.5% in donors with long-distance brainstem death, 85.1% in short-distance donors, and 81% in donors with long-distance circulatory death, 80.4% in short-distance donors.

Source: Elaborated by the authors.



Source: Elaborated by the authors

Figure 1. Flowchart of the study selection process according to PRISMA 2020 guidelines.

RESULTS

One hundred and ninety-eight (198) articles were selected from searches in the PubMed, BVS, and Cochrane Library databases. Of these, 13 were included for full-text reading, and after evaluating the inclusion, exclusion, and accessibility criteria, 10 remained in this review. The reviewed studies provided a detailed assessment of the direct or indirect influence of PCI (CIT) on liver graft function in liver transplantation, whether as a primary variable, an adjusted covariate, a risk factor, or a moderator of other interventions. The findings are presented below, organized according to the role of cold ischemia in each study.

In a retrospective study, data from patients who underwent liver transplants with deceased donors registered from 2014 to 2020 were analyzed. Donor, recipient, and transplant procedure-related factors were compared between grafts transported over short distances and those transported over long distances (greater than > 800 km). It was observed that the rate of transplants with grafts transported over long distances was 6.2% for DBD and 7.1% for DCD, and the 90-day graft survival was lower in these cases, with 94.5% for DBD versus 95.7% for short-distance DBD, and 93.9% for DCD versus 94.5% for short-distance DCD. However, at 3 years, the rates were similar between the groups: 85.5% versus 85.1% for donors with brainstem death and 81% versus 80.4% for circulatory death. The analysis indicated that the distance the graft traveled did not affect its 3-year survival in a linear manner. Still, younger donor age, lower donor body mass index, and shorter cold ischemia time mitigated the negative impact on 90-day graft survival in long-distance liver grafts. The CIT acted as a moderating factor for the effect of graft distance on initial survival[11].

In this study, cold ischemia was controlled between the HOPE and control groups, allowing for analysis of the effects of ischemia-reperfusion injury (IRI). HOPE has been studied as a strategy to reduce ischemia-reperfusion injury, and liver transplants performed from 2017 to 2022 with donors ≥ 70 years old were analyzed, divided into HOPE-LT (n = 30) and control (n = 71) groups. Acute kidney injury (AKI) was more frequent in the HOPE group (77% vs. 56% in the control group), with no difference in severity or duration. The need for renal therapy (10% vs. 8%) and the use of liver markers were similar. Histology showed greater liver damage in the HOPE group, without any benefit in reducing the injury[12].

Cold ischemia, although not the primary variable in this study, was considered in evaluating reperfusion injury associated with interleukin-33 (IL-33) release. IL-33 has been identified as a potential inflammatory biomarker in IRI injury. To investigate its role in this process, an experimental study used a warm ischemia model in mice, comparing wild-type and IL-33-deficient animals. The results indicated that IL-33 was rapidly released after hepatic ischemia, without requiring resynthesis and contributed to neutrophil recruitment and tissue damage. This contrasted with a study conducted on 40 transplant patients with IL-33 measurements, in which levels peaked immediately after reperfusion and correlated with post-reperfusion syndrome, post-transplant renal failure, graft dysfunction, and histological ischemia/reperfusion lesions. In other words, it is related to early complications in transplantation[13].

To evaluate the influence of CIT on liver graft function, a retrospective study analyzed 38 liver transplants performed at Hospital Leforte Liberdade (São Paulo, 2018). Patients were divided into two groups: Group A: CIT < 8 hours and Group B: CIT > 8 hours. Group A (CIT < 8 hours) had better outcomes, with fewer transfusions, shorter hospital stays, and lower bilirubin and gamma-glutamyl transferase (GGT) levels. Group B (CIT > 8 hours) had a greater need for transfusions, longer hospital stays, longer intensive care unit (ICU) stays, and higher costs. These findings reinforce the correlation between PCI and poorer liver recovery, indicating the need for strategies to mitigate the damage associated with prolonged preservation times[14].

In another study, 790 liver transplants performed from 2012 to 2018 were analyzed, comparing those performed entirely or partially during the late-night/early-morning hours (midnight to 5 a.m.) with those performed at other times. Multivariate analysis, adjusted for Cold Ischemia Time, revealed that nighttime surgeries required a greater need for blood transfusions (p = 0.010) and presented a significantly increased risk of serious complications (Clavien-Dindo ≥ IIIb) in the first 90 days post-transplant [odds ratio (OR) 1.67; 95% confidence interval (95% CI) 1.10-2.54]. However, graft and patient survival at 1 year did not differ significantly between the groups. These findings suggest the need to reassess liver transplant logistics, prioritizing strategies that minimize surgical procedures during the nighttime period. The CIT was included as an adjustment variable and did not, on its own, explain the poorer performance of nighttime transplants, suggesting that operational factors may have a greater impact[15].

A retrospective observational cohort analysis performed remote ischemic preconditioning. It assessed the occurrence of post-reperfusion syndrome, as well as the need for rescue epinephrine, reporting that remote ischemic preconditioning effectively reduces the occurrence of post-reperfusion syndrome (OR: 0.672; 95% CI 0.479-0.953; p = 0.021) and the need for rescue epinephrine in patients undergoing elective liver transplantation with living donors, providing graft protection against ischemia-reperfusion injury. This protection contributes to better postoperative liver function, reducing complications and improving graft and patient survival[16].

In this regard, a multicenter randomized clinical trial compared liver preservation via CIT versus the OCS. Livers preserved using the OCS demonstrated reduced ischemia-reperfusion injury (IRI) after reperfusion, with 6% of patients exhibiting

moderate-to-severe lobular inflammation, compared with 13% in the CIT group (p = 0.004). Furthermore, the OCS led to a significantly higher utilization of livers from donors after circulatory death (DCD), a decrease in early allograft dysfunction (EAD), and a significant reduction in the incidence of ischemic biliary complications at both 6 and 12 months post-transplant. These findings suggest that OCS-mediated liver preservation is associated with improved post-transplant outcomes and enhanced donor liver utilization. Consequently, CIT was compared across preservation systems and influenced the magnitude of ischemia-reperfusion injury[17].

An international, multicenter observational cohort study evaluated the long-term outcomes of liver transplants from donors treated with HOPE, with analyses stratified by DBD and DCD. It showed that the 5-year survival rate after liver transplantation was good in both HOPE-treated groups, with low rates of graft loss due to the incidence of primary non-function or ischemic cholangiopathy, regardless of each patient's individual risk profile. This highlights the clinical importance of HOPE treatment in preventing the impact of PCI on liver graft function, thereby minimizing complications and improving long-term outcomes. Consequently, CIT was analyzed within the HOPE strategy to evaluate its capacity to mitigate PCI-related injuries[18].

A multinational observational analysis of data collected in the United Kingdom and Ireland assessed the evolution of liver transplant outcomes over two distinct periods (2008 to 2011 and 2012 to 2016), separately comparing liver recipient outcomes from donors after DCD and donors after DBD. In DCD liver recipients, a significant reduction in mortality rates was observed, from 19.6% in the first period to 10.4% in the second period (OR: 0.43; 95% CI 0.30-0.62; $p < 0.001$), while in DBD liver recipients the reduction was less pronounced, from 12.8% to 11.3% (OR: 0.96; 95% CI 0.78-1.19; p = 0.732). Furthermore, there was a slight increase in retransplantation rates among DCD liver recipients from the first period to the second period (from 7.3% to 11.8%; p = 0.042). These findings indicate a significant improvement in outcomes of DCD liver transplants in the most recent period, approaching those observed in DBD liver transplants, reinforcing the potential of DCD grafts as a viable alternative in high-mortality scenarios on waiting lists. The study also highlights the importance of using DCD donor livers in liver transplantation, demonstrating that, despite the challenges of PCI, advances in liver preservation strategies offer promising avenues to minimize the negative effects of ischemia. CIT was considered in interpreting the differences between DCD and DBD donors, who present distinct levels of vulnerability to ischemic damage[19].

Finally, a randomized trial compared the impact of NAC infusion during liver procurement on liver transplant outcomes. NAC acts as a sulfhydryl group donor, restoring intracellular glutathione and reducing oxidative stress resulting from ischemia-reperfusion injury. Its benefit was observed only in scenarios with CIT > 6 hours, suggesting an effect dependent on the magnitude of oxidative injury. The use of NAC during liver procurement did not improve early graft dysfunction, as assessed by the Olthoff classification, with similar graft and patient survival rates at 12 months and 3 years between the groups (p = 0.54 and p = 0.69, respectively). However, when the CIT exceeded 6 hours, NAC was effective in reducing postoperative alanine aminotransferase (ALT) levels (p = 0.0125). Therefore, although it does not improve allograft function overall, NAC offers specific benefits by modulating ALT levels under conditions of increased cold ischemia. This modulation during cold ischemia is crucial, as extending ischemia time can negatively impact graft function, compromising long-term graft and patient survival[20].

In conclusion, PCI is associated with poorer initial graft function, greater inflammation, and a higher risk of early dysfunction, and is modulated by factors such as donor age, transport distance, and preservation techniques, including HOPE, OCS, NAC, and remote ischemic preconditioning (RIPC). Of the 10 studies included, only one assessed CIT as a primary variable. In the others, CIT was included as an adjustment variable, covariate, or moderating factor, and was considered in the multivariate analysis of outcomes.

DISCUSSION

Among the included studies, only one directly evaluated Cold Ischemia Time as a primary variable[14]. The focus of this review, which involves CIT, is also a key determinant of transplant success. They observed that patients with CIT greater than 8 hours had a greater need for transfusions, prolonged hospital stays, longer ICU stays, and higher costs than those with CIT less than 8 hours. Thus, this finding highlights the need for strategies that reduce organ preservation time to optimize outcomes. Furthermore, intraoperative factors, such as the time of the procedure, also appear to influence the results, which identified that transplants performed during the late night/early morning (between midnight and 5 a.m.) were associated with a greater need for blood transfusions and a significantly increased risk of serious complications (OR 1.67; 95% CI 1.10-2.54). However, graft and patient survival at 1 year were similar between transplants performed during the day and at night, suggesting that the impact of early complications can be managed over time. The CIT was adjusted in the multivariate analysis and was not responsible for the worse outcome observed in night transplants[15].

From an immunological standpoint, they demonstrated that IL-33 release occurred immediately after hepatic ischemia/reperfusion, contributing to neutrophil recruitment and promoting tissue damage. Although the study investigated ischemia-reperfusion injury and IL-33 as an inflammatory biomarker, CIT was not analyzed as an independent variable, limiting its direct applicability to the present research question[13]. Thus, elevated IL-33 levels were associated with post-reperfusion syndrome, post-transplant renal failure, graft dysfunction, and histological changes consistent with ischemic injury, suggesting that this cytokine may be a relevant marker of early complications. Conversely, strategies to mitigate ischemic injury remain controversial: studies evaluating the use of HOPE in livers from elderly donors (≥ 70 years) observed a higher incidence of AKI in the group undergoing the technique (77% vs. 56% in the control group), without impacting the severity of the injury, the need for renal replacement therapy, or postoperative liver markers. Furthermore, histology revealed greater liver damage in the HOPE group, demonstrating no clear clinical benefit in reducing ischemia-reperfusion injury[12].

Continuing with the context of liver graft preservation, they highlighted the use of HOPE not only for the elderly population, but also for hepatocytes from patients with a prognosis of DBD and DCD[18]. The results obtained showed good survival rates over the 5 years in both groups, with very low graft loss rates, due to less evidence of ischemic cholangiopathy and primary organ dysfunction. Partially contrary to these findings, it suggests that the advantage of HOPE is more evident in heterogeneous groups or in particular clinical settings, thus reinforcing the need to define better the criteria for indicating the technique discussed[12]. These differences suggest that the benefit of HOPE may depend on the donor profile, especially age, type of death (DCD vs. DBD), and baseline risk for ischemic injury.

Regarding livers donated after DCD transplantation, the effectiveness rate of these grafts was compared with that of DBD transplants. In this context, their findings indicated that, although mortality rates are initially higher for DCD liver recipients, long-term survival is comparable to that of DBD transplant recipients. Furthermore, an increase in the retransplantation rate is observed among DCD recipients. However, in general, these results demonstrate that DCD livers are a viable option, especially to increase the number of organs available, given the current donor shortage. Thus, a progressive improvement in the survival of DCD transplant recipients is observed over the years, even considering their greater vulnerability to cold ischemia[19].

From a pharmacological standpoint, several strategies have been evaluated for liver protection, including NAC infusion during graft procurement. NAC was ineffective in reducing early graft dysfunction or improving post-transplant liver function, although it did lower ALT levels in cases of cold ischemia exceeding 6 hours. Thus, the drug is effective in this context, but its isolated use may not protect the graft. In the study by Gómez-Gavara et al.[20], the effect of NAC was directly modulated by the duration of cold ischemia. Although NAC did not reduce early graft dysfunction overall, it showed a significant benefit only when CIT exceeded 6 hours, lowering postoperative ALT levels. This finding reinforces the notion that the effectiveness of pharmacological interventions may depend on the degree of prior ischemic injury[20].

It is also noteworthy that the distance traveled by the graft interacted with the CIT to influence initial outcomes. In this context, transplants performed with short- and long-distance grafts were investigated, where journeys greater than 800 km were associated with a slight worsening of graft survival in the first 90 days (94.5% vs. 95.7% for DBD and 93.9% vs. 94.5% for DCD). However, when considering factors such as donor age and body mass index, distance does not appear to be an independent predictor of lower survival, suggesting that these characteristics are more determinants of transplant success[11].

Additionally, RIPC has been shown to act as a reducing factor in the incidence of post-reperfusion syndrome in elective liver transplant settings with living donors. These findings suggest that RIPC may represent a promising strategy for reducing ischemic injury in liver transplantation. However, only two studies on this topic were identified in the PubMed database, which reinforces the need for further investigation[16].

Furthermore, organ preservation in this context is a determining factor, and liver storage technology with OCS Liver was compared with the CIT Liver method, revealing significant reductions in ischemia-reperfusion injury and a lower incidence of post-transplant complications (13% more in favor of OCS Liver)[17].

Taken together, the studies analyzed indicate that CIT does not act in isolation but interacts with clinical factors (such as diabetes and donor age), logistical factors (distance and surgery time), and technological factors (HOPE, OCS, NAC, RIPC). Thus, the results reinforce that PCI remains a critical determinant of initial graft function, but modern preservation strategies can mitigate its impact.

This review has important limitations. The methodological heterogeneity of the included studies prevented quantitative meta-analysis and formal assessment of publication bias. Furthermore, CIT was not a primary variable in most studies, which frequently analyzed it as an adjusted covariate, and the temporal restriction to the last 5 years may have excluded relevant earlier evidence. Significant heterogeneity is observed among the included studies, both in the definition of PCI (ranging from >6 to >8 hours) and in the outcomes assessed. In most studies, CIT was included only as a control variable, limiting direct causal inference.

CONCLUSION

This systematic review demonstrates that PCI remains one of the most consistent determinants of initial liver graft dysfunction, directly influencing ischemia-reperfusion injury, postoperative inflammation, and the occurrence of biliary and systemic complications. Although only one of the evaluated studies investigated CIT as a primary variable, all others included PCI (CIT) as an adjustment factor, moderator, or risk criterion, reinforcing its central role in post-transplant prognosis. The interventions analyzed, such as HOPE, OCS, NAC, and RIPC, showed that the impact of cold ischemia can be partially mitigated, but not yet completely neutralized. The findings indicate that reducing the CIT, combined with modern preservation technologies and careful donor selection, remains one of the most effective strategies to improve initial graft function. However, there is significant heterogeneity among the studies, with variations in donor type (DBD vs. DCD), transport distance, age, and associated clinical conditions; these factors limit direct comparison between the included studies. Future studies should evaluate, in a standardized manner, the isolated and combined effects of cold ischemia across different scenarios, especially considering emerging technological interventions and higher-risk populations, such as elderly donors and DCD grafts. In summary, despite recent advances, PCI remains a major challenge in modern liver transplantation, and its mitigation should remain a priority in policies, techniques, and clinical decisions.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Rodrigues YMS, Branco LA, Messas GB, Fernandes JG, Vidal LA, Almeida RS, Sá GO; **Conception and design:** Rodrigues YMS, Branco LA, Messas GB, Sá GO; **Data analysis and interpretation:** Rodrigues YMS, Branco LA, Fernandes JG, Vidal LA; **Article writing:** Rodrigues YMS, Branco LA, Fernandes JG, Vidal LA, Almeida RS; **Critical revision:** Branco LA, Messas GB, Fernandes JG, Vidal LA, Almeida RS; Sá GO; **Final approval:** Rodrigues YMS.

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All datasets were generated or analyzed in the current study.

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DECLARATION OF USE OF ARTIFICIAL INTELLIGENCE TOOLS

Artificial intelligence tools were used exclusively to support the writing and organization of the manuscript, not being responsible for the generation or analysis of the data.

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