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Ex vivo machine perfusion of extended criteria donor livers: a Bayesian network meta-analysis

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Background: *Ex vivo* liver perfusion offers benefits over static cold storage (SCS) for organ preservation, but specific advantages of different perfusion protocols require further evaluation.

Materials and Methods: Randomized controlled trials and matched studies conducted until December 2024 comparing *ex vivo* machine perfusion and SCS were evaluated. A Bayesian network meta-analysis was conducted to assess the effects of varying temperature settings, cannulation techniques, and perfusion duration in extended criteria donor (ECD) liver grafts. The relative perfusion time within total preservation time was assessed to distinguish between long-term and short-term perfusion.

Results: The meta-analysis included 11 hypothermic oxygenated perfusion (HOPE) studies and 10 normothermic machine perfusion (NMP) studies. Compared to SCS, HOPE reduced the risks of early allograft dysfunction (EAD) [risk ratio 0.46 (95% CI 0.31–0.67)], major complications [0.40 (0.25–0.63)], and acute cellular rejection (ACR) [0.47 (0.27–0.80)] (high-certainty). Compared to NMP, HOPE reduced the risks of EAD, non-anastomotic biliary stricture (NAS), total biliary complications (TBC), and ACR (moderate-certainty). HOPE reduced the risks of NAS in both single [0.18 (0.05–0.51)] and dual [0.32 (0.12–0.77)] cannulation settings compared with SCS (high-certainty). Compared to SCS, short-term and long-term HOPE prevented EAD [long-term: 0.41 (0.22–0.74); short-term: 0.50 (0.29–0.84)], major complications [long-term: 0.48 (0.24–0.92); short-term: 0.32 (0.15–0.64)], and NAS [long-term: 0.14 (0.02–0.56); short-term: 0.30 (0.13–0.66)] (high-certainty). Compared to short-term NMP, long-term NMP reduced the risk of NAS [0.26 (0.07–0.93)] (high-certainty).

Conclusion: HOPE is more effective than NMP in preventing EAD, TBC, NAS, and ACR in ECD grafts. Both single and dual HOPE are effective, and early initiation of NMP may prevent NAS.

Keywords: hypothermic machine perfusion, hypothermic oxygenated machine perfusion, liver grafting, liver transplantation, machine perfusion, network meta-analysis, normothermic machine perfusion, organ preservation, perfusion, postoperative complications, static cold storage

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HIGHLIGHTS

- A network meta-analysis highlighted the advantages of HOPE over NMP in ECD livers.
- In HOPE, no additional benefit was observed from cannulating the hepatic artery.
- In NMP, increasing the proportion of perfusion time prevents NAS in ECD grafts.

Introduction

Organ shortage remains a pressing challenge in modern medicine, with <10% of the global demand for transplants being met[1]. This issue is exacerbated by the limitations of organ preservation techniques, which restrict the viable window for deceased donor transplantation. Although static cold storage (SCS) is the conventional method for preserving organs by lowering cellular metabolism[2], it does not replicate physiological conditions, thereby increasing the risk of ischemia-reperfusion injury (IRI) and limiting preservation times. In liver transplantation, complications such as early allograft dysfunction (EAD) and non-anastomotic biliary strictures (NAS) are frequently observed[3,4]. These challenges are more pronounced when donation after circulatory death (DCD) or extended criteria donor (ECD) organs are used, restricting the available donor pool[5].

Ex vivo liver perfusion is an emerging technology that has several advantages over SCS. By actively circulating fluids, machine perfusion supports metabolism, assesses viability, extends preservation, and reduces IRI. The benefits of machine perfusion are now established following major clinical trials[6,7], with several European countries adopting it as the standard for organ preservation and the US FDA approving perfusion devices in 2021.

Beyond the benefits of machine perfusion, its indications and protocols remain inconclusive with limited evidence. This study aims to address three critical questions:[1] the selection of hypothermic oxygenated perfusion (HOPE) versus normothermic machine perfusion (NMP) for ECD livers[2], whether to cannulate only the portal vein or both the portal vein and hepatic artery in HOPE, and[3] whether to initiate the perfusion at the donor or recipient hospital.

Material and methods

Data sources and search strategy

This meta-analysis followed PRISMA[8] (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and AMSTAR[9] (Assessing the methodological quality of systematic reviews) guidelines for network meta-analysis and was registered in PROSPERO. Although ethical approval was not required, a waiver was granted. Studies were identified by two authors in PubMed, EMBASE, and OVID (Table S1 http://links.lww.com/JS9/E260). Randomized controlled trials (RCTs), matched non-randomized studies (NRSs) comparing HOPE or NMP with SCS in adult liver transplants were included. Non-comparative, non-human, multi-organ transplant studies, and studies with combinatorial perfusion methods were excluded. Other meta-analyses or reviews were also examined. The risk of bias was evaluated by two authors using the RoB2 tool for RCTs[10] and the ROBINS-I tool[11] for NRSs. The GRADE approach was applied to classify the certainty of evidence into high, moderate, low, or very low[12]. Certainty was assessed by examining the risk of bias, inconsistency, indirectness, imprecision, transitivity, and related factors. Publication bias was assessed by Egger's and Begg's tests. Disagreements were resolved through discussion.

Data extraction and analysis

Two authors independently extracted data to minimize potential bias. ECD was defined as per the provided definition[5], with studies[13–15] that included sub-analyses of high donor risk index (DRI) or donor-specific indications also included. Given the inherent risk of bias in NRSs, their inclusion alongside RCTs was justified by a predefined assessment of risk of bias and subgroup consistency. Specifically, eligible outcomes for network meta-analysis were selected based on initial pairwise meta-analysis results, ensuring no significant differences between RCT and NRS subgroups. The outcomes of interest for network meta-analysis were selected based on the results of the initial pairwise meta-analysis of EAD, major complications, total biliary complications (TBC), NAS, hepatic artery thrombosis (HAT), primary non-function (PNF), post-reperfusion syndrome, acute cellular rejection (ACR), retransplantation, acute kidney injury (AKI), renal replacement therapy (RRT), hospital stay, 1-year graft loss, and 1-year patient death. To ensure comparability, outcomes required at least three studies in both HOPE and NMP versus SCS comparisons and no significant publication bias. Biliary complications were addressed by network meta-analysis of single and dual HOPE versus SCS. For outcomes with six or more studies, rankings based on the estimated perfusion-to-preservation time ratio of each studies classified the bottom 50th percentile as short-term (<p50) and the top 50th percentile as long-term (≥p50) for further network meta-analysis and meta-regression. Definitions of outcomes were collected from each study to address inconsistencies in terminology (Table S2 http://links.lww.com/JS9/E260).

Bayesian network meta-analysis was performed using the gemtc package in R Studio (v4.3.3). The deviance information criterion was used to choose between random and fixed effects models, selecting the fixed effects model when the difference in criteria was ≤ 3. Each analysis included network diagrams, and similarity was examined by evaluating patient characteristics. Strategies were ranked and displayed using a rankogram. Additional details including analytical methods are provided in the supplementary materials available at: http://links.lww.com/JS9/E260.

Results

Figure 1 illustrates the study selection process with 27 studies eligible for systematic review and meta-analysis. In HOPE, a total of 826 ECD liver grafts were included (388 from 5 RCTs[15–19] and 438 from 6 NRSs[20–25]), and 1041 grafts were included in NMP (116 from 3 RCTs[7,14,26] and 925 from 7 NRSs[13,27–32]). An overview of the characteristics of the included studies and perfusion settings is presented in Tables S3 and S4 http://links.lww.com/JS9/E260. No study directly compared HOPE and NMP or single and dual HOPE. The time metrics for each study, including perfusion-to-preservation time ratios, are listed in Table S5 http://links.lww.com/JS9/E260. The overall risk of bias is detailed in Tables S6 and S7 http://links.lww.com/JS9/E260. NRSs with a high risk of bias[33–35] and studies of heterogenous populations, where ECD outcomes were not extractable[36,37], were excluded from the meta-analysis.

A pairwise meta-analysis was carried out (Fig. S1, Table S8 http://links.lww.com/JS9/E260) as a preliminary step to the network meta-analysis, selecting EAD, major complications, NAS, TBC, ACR, retransplantation, HAT, PNF, and RRT as outcomes of interest based on the previously stated criteria. The deviance information criterion is in Table S9, and Figure S2 http://links.lww.com/JS9/E260 shows the per-study residual deviance for each analysis. The certainty of evidence was comprehensively evaluated (Table S10 http://links.lww.com/JS9/E260). Concerns regarding transitivity were minimal due to the restriction of the donor population to ECDs, consistent preservation times across control arms, and the preference of transplant centers expertizing a single perfusion technique rather than varying methods for different donor types.

HOPE and NMP vs. SCS

The network plots and rankograms for HOPE and NMP versus SCS are presented in Figure 2 and Figure S3 http://links.lww.com/JS9/E260, with the results summarized in Figure 3. Compared with SCS, high-certainty evidence showed that HOPE reduced the incidence of EAD [eight studies[16,18–24]; risk ratio (RR) 0.46 (95% CI 0.31–0.67)], major complications [seven studies[15,16,18,20,22–24];

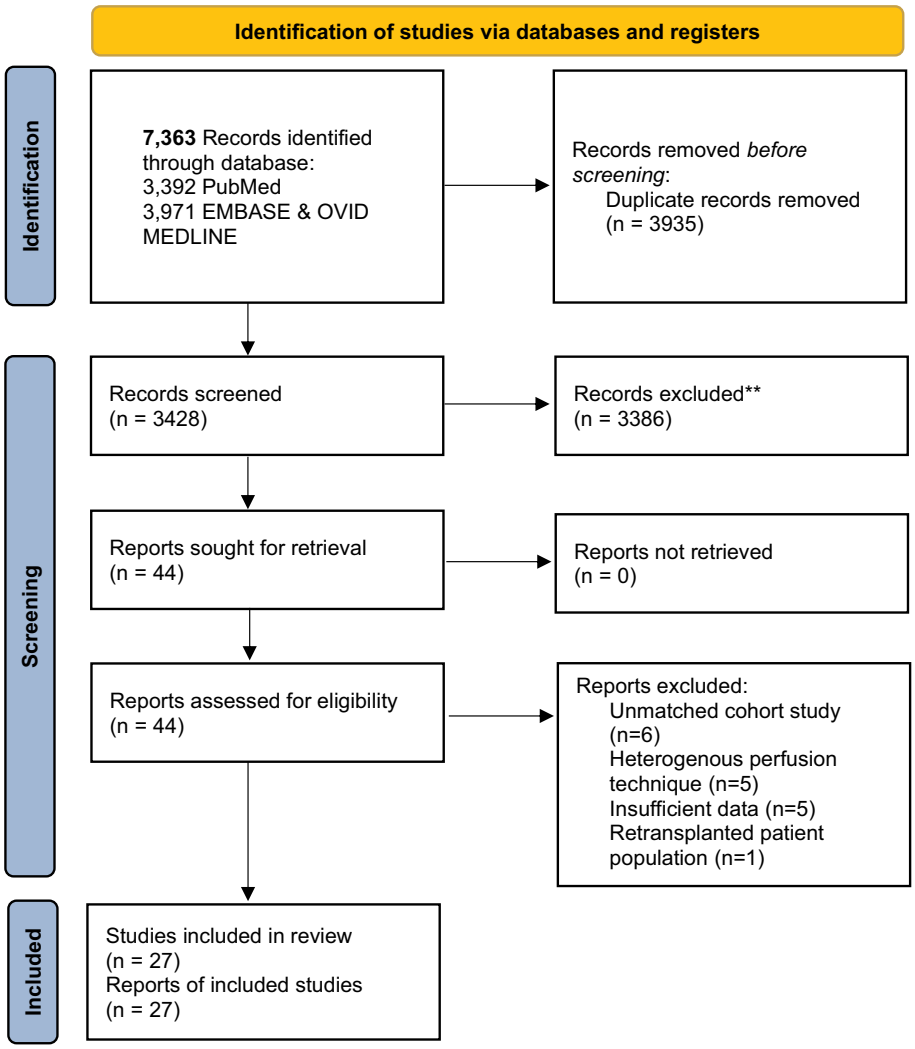

Figure 1. PRISMA flow diagram of the study selection process. A total of 21 studies (8 randomized controlled trials and 13 matched studies) were identified for inclusion in the meta-analysis.

0.40 (0.25–0.63)], and ACR [six studies[16,19,20,22,23,25]; 0.47 (0.27–0.80)]. Moderate-certainty evidence indicated that HOPE reduced the risks of NAS [six studies[17,19,20,22,24,25]; 0.26 (0.12–0.51)], TBC [nine studies[16–20,22–25]; 0.61 (0.43–0.87)], retransplantation [five studies[16,18–20,24]; 0.28 (0.10–0.69)], and HAT [five studies[16,18–20,25]; 0.49 (0.16–1.32)]. The evidence for HOPE in reducing PNF and RRT was low. High-certainty evidence demonstrated that NMP was associated with a lower risk of PNF [five studies[26–29,31]; 0.17 (0.01–1.09)]. Moderate-certainty showed that NMP lowered the risks of retransplantation [four studies[26,28,30,31]; 0.38 (0.15–0.84)] and RRT [three studies[14,28,32]; 0.53 (0.33–0.82)]. Low to very low certainty evidence suggested minimal difference between NMP and SCS in preventing EAD, major complications, NAS, TBC, ACR, and HAT for ECD liver transplantation.

Compared to NMP, HOPE showed moderate-certainty evidence for reducing the risks of EAD [15 studies[13,14,16,18–24,26–29,31]; 0.54 (0.29–0.97)], NAS [14 studies[7,13,17,19,20,22,24–26,28,29,31,32]; 0.30 (0.12–0.71)], TBC [16 studies[13,16–20,22–29,31,32]; 0.61 (0.38–0.99)], and ACR [10 studies[16,19,20,22,23,25,28–30,32]; 0.42 (0.21–0.81)]. The evidence was low to very low for the superiority of HOPE in reducing the risks of retransplantation, HAT, PNF, and RRT.

Single and dual HOPE vs. SCS

Biliary complications, including NAS and TBC, were inspected for single- and dual-cannulated HOPE versus SCS (Fig. 4 and Fig. S3 http://links.lww.com/JS9/E260). Compared to SCS, high-certainty evidence demonstrated that single HOPE prevents NAS [three studies[20,24,25]; 0.18 (0.05–0.51)] and TBC [five studies[16,20,23–25]; 0.59 (0.37–0.95)], and moderate-certainty evidence showed that dual HOPE prevents NAS [three studies[17,19,22]; 0.32 (0.12–0.77)]. The certainty of evidence for dual HOPE reducing TBC risk was low. Evidence with low to very low certainty suggested no advantage of dual HOPE over single HOPE in reducing NAS or TBC. The pairwise subgroup meta-analysis for single and dual HOPE is detailed in Table S9 http://links.lww.com/JS9/E260 for all relevant outcomes.

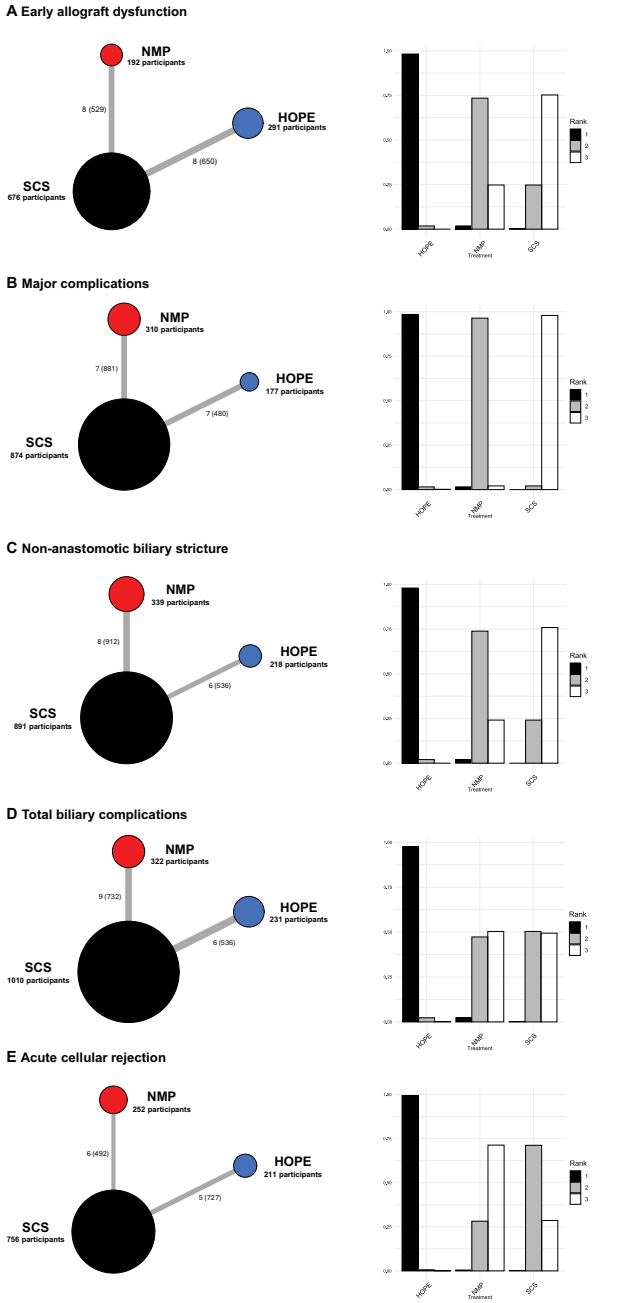

Figure 2. Network maps and rankograms for hypothermic and NMP versus SCS in ECD liver transplantation. The left panel shows the network map, where head-to-head comparisons between liver preservation strategies are depicted by connecting lines. Line thickness reflects the number of studies, and node size represents the number of participants. Numbers on the nodes represent the total number of participants for each strategy, while the numbers on the lines correspond to the number of studies and participants included in each comparison. HOPE, NMP, and SCS are indicated by blue, red, and black nodes, respectively. The right panel displays the rankogram, where the tallest bar for rank 1 indicates the most effective treatment, and the tallest bar for rank 2 suggests the second most effective option. Comparisons between HOPE, NMP, and SCS across various outcomes showed that in ECD liver transplantation, HOPE had the highest likelihood of preventing EAD (A), major complications (B), NAS (C), TBC (D), and ACR (E). HOPE, hypothermic oxygenated perfusion; NMP, normothermic machine perfusion; SCS, static cold storage; EAD, early allograft dysfunction; ACR, acute cellular rejection; NAS, non-anastomotic biliary stricture; TBC, total biliary complications; and ECD, extended criteria donor.

Long-term and short-term HOPE vs. SCS

EAD, major complications, NAS, TBC, PNF, and RRT were assessed for long-term and short-term perfusion of HOPE versus SCS (Fig. 5 and Fig. S3 http://links.lww.com/JS9/E260). Scatter plots present the perfusion-to-preservation time ratio of each study and its corresponding classification into long-term or short-term subgroups for every outcome analyzed (Fig. S4 http://links.lww.com/JS9/E260). Compared with SCS, high-certainty evidence suggested that long-term HOPE is associated with a lower risk of EAD [three studies[18,20,22]; 0.41 (0.22–0.74)], major complications [three studies[18,20,22]; 0.48 (0.24–0.92)], NAS [three studies[17,20,22]; 0.14 (0.02–0.56)], and PNF [four studies[18,20,22,25]; 0.00 (0.00–0.23)]. Similar associations were observed in short-term HOPE with EAD [three studies[16,19,24]; 0.50 (0.29–0.84)], major complications [three studies[15,16,24]; 0.32 (0.15–0.64)], and NAS [three studies[19,24,25]; 0.30 (0.13–0.66)], with PNF being the exception. Moderate-certainty evidence indicated that long-term HOPE is associated with a reduction in TBC [four studies[16,19,24,25]; 0.53 (0.29–0.93)].

Compared to short-term HOPE, long-term HOPE was associated with a reduced risk of PNF [seven studies[16,18–20,22,24,25]; 0.00 (0.00–0.25)], supported by high-certainty evidence. For EAD, MC, NAS, TBC, and RRT, the certainty of evidence was low to very low regarding the superiority of long-term HOPE over short-term HOPE. In meta-regression, the percentage of perfusion-to-preservation time did not show a significant linear association with the prevention of post-transplant complications (Fig. S5 http://links.lww.com/JS9/E260).

Long-term and short-term NMP vs. SCS

Long-term and short-term NMP were compared to SCS for EAD, major complications, NAS, and TBC (Figs 5 and S3 http://links.lww.com/JS9/E260). Scatter plots show the perfusion-to-preservation time ratio and subgroup classification for each outcome (Fig. S4 http://links.lww.com/JS9/E260). The overall certainty of evidence was low to very low for both long-term and short-term NMP in preventing EAD, major complications, NAS, and TBC when compared to SCS. While NMP showed limited effectiveness in ECD liver transplantation, high-certainty evidence demonstrated that long-term NMP is more effective in preventing NAS than short-term NMP [eight studies[7,13,26,28,29,31,32]; 0.26 (0.07–0.93)]. In meta-regression, no significant linear correlation was observed between the percentage of perfusion-to-preservation time and the reduction of EAD, major complications, NAS, and TBC (Fig. S5 http://links.lww.com/JS9/E260).

Discussion

This study expands on previous meta-analyses[38,39] by providing a detailed Bayesian network meta-analysis of ECD liver graft outcomes, incorporating newly available studies and a broader range of clinically relevant outcomes, while ensuring minimal heterogeneity in the donor population. High-certainty evidence demonstrated that compared with SCS, HOPE lowers the risk of EAD, major complications and ACR, whereas NMP only reduces the risk of PNF. Compared with NMP, HOPE showed moderate-certainty benefits in reducing EAD, NAS, TBC, and

Group and comparison	No. of direct comparisons (No. of participants)	Network risk ratio	Certainty of evidence
Early allograft dysfunction			
HOPE vs SCS	8 (650)	0.46 (0.31, 0.67)	High
NMP vs SCS	7 (486)	0.85 (0.54, 1.33)	Low
HOPE vs NMP	-	0.54 (0.29, 0.97)	Moderate
Major complications			
HOPE vs SCS	7 (480)	0.40 (0.25, 0.63)	High
NMP vs SCS	7 (881)	0.73 (0.54, 0.99)	Low
HOPE vs NMP	-	0.54 (0.31, 0.94)	Low
Non-anastomotic biliary stricture			
HOPE vs SCS	6 (536)	0.26 (0.12 to 0.51)	Moderate
NMP vs SCS	8 (912)	0.86 (0.49, 1.45)	Low
HOPE vs NMP	-	0.30 (0.12, 0.71)	Moderate
Total biliary complications			
HOPE vs SCS	9 (732)	0.61 (0.43, 0.87)	Moderate
NMP vs SCS	8 (906)	1.00 (0.72, 1.40)	Low
HOPE vs NMP	-	0.61 (0.38, 0.99)	Moderate
Acute cellular rejection			
HOPE vs SCS	6 (492)	0.47 (0.27, 0.80)	High
NMP vs SCS	5 (727)	1.13 (0.74, 1.70)	Very low
HOPE vs NMP	-	0.42 (0.21, 0.81)	Moderate
Retransplantation			
HOPE vs SCS	5 (481)	0.28 (0.10, 0.69)	Moderate
NMP vs SCS	4 (291)	0.38 (0.15, 0.84)	Moderate
HOPE vs NMP	-	0.75 (0.21, 2.63)	Very low
Hepatic artery thrombosis			
HOPE vs SCS	5 (487)	0.49 (0.16, 1.32)	Moderate
NMP vs SCS	5 (375)	0.68 (0.23, 1.87)	Low
HOPE vs NMP	-	0.72 (0.16, 3.24)	Very low
Primary non-function			
HOPE vs SCS	8 (696)	0.33 (0.07, 1.10)	Moderate
NMP vs SCS	5 (353)	0.17 (0.01, 1.09)	High
HOPE vs NMP	-	1.92 (0.18, 46.7)	Very low
Renal replacement therapy			
HOPE vs SCS	6 (546)	0.97 (0.56, 1.68)	Very low
NMP vs SCS	4 (668)	0.53 (0.33, 0.82)	Moderate
HOPE vs NMP	-	1.85 (0.91, 3.81)	Low

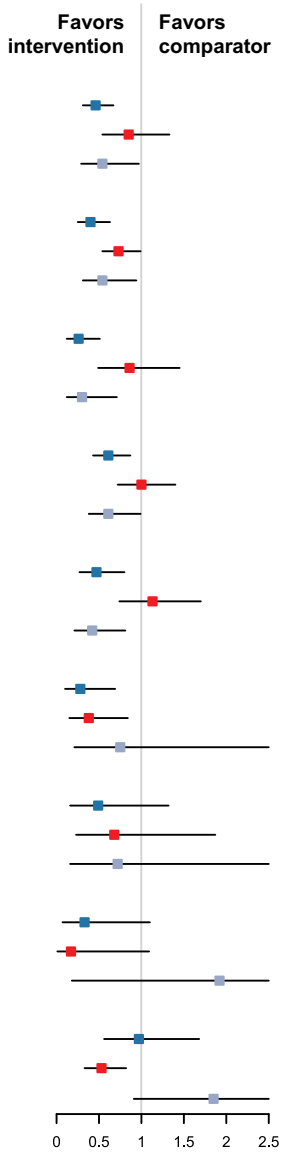

Figure 3. Network meta-analysis comparisons of hypothermic and NMP versus SCS in ECD liver transplantation. The forest plot is scaled from 0 to 2.5, where the box (blue: HOPE, red: NMP, and skyblue: indirect estimate) indicates the risk ratio and the black line represents the 95% CI. HOPE demonstrated high-certainty reductions in EAD, major complications, and ACR compared to SCS, with moderate-certainty benefits for NAS, TBC, retransplantation, and HAT. The evidence for HOPE reducing PNF and RRT was low. Although NMP reduced PNF, retransplantation, and RRT with high to moderate certainty, it showed limited overall benefit compared to SCS for ECD liver transplantation outcomes. Compared to NMP, HOPE demonstrated moderate-certainty advantages in reducing EAD, NAS, TBC, and ACR, while evidence for its superiority in retransplantation, HAT, PNF, and RRT was low to very low. Overall, HOPE showed broad benefits over SCS and advantages over NMP in key outcomes. A random-effects model was applied for retransplantation due to a deviance information criterion difference exceeding 3, while a fixed-effects model was used for all other outcomes. HOPE, hypothermic oxygenated perfusion; NMP, normothermic machine perfusion; SCS, static cold storage; EAD, early allograft dysfunction; ACR, acute cellular rejection; NAS, non-anastomotic biliary stricture; TBC, total biliary complications; HAT, hepatic artery thrombosis; PNF, primary non-function; RRT, renal replacement therapy; and ECD, extended criteria donor.

ACR. Single HOPE demonstrated high-certainty evidence for reducing NAS and TBC compared to SCS, whereas dual HOPE showed moderate-certainty benefits for NAS but lacked significant evidence for TBC. No added benefit of dual HOPE over single HOPE was observed. Long-term HOPE outperformed SCS with high-certainty evidence for reducing EAD, major complications, NAS, and PNF, and with moderate-certainty evidence for TBC, while short-term HOPE showed similar benefits but low to very low certainty for TBC, PNF, and RRT. Long-term NMP reduced NAS compared to short-term NMP with high-certainty evidence, but both had low to very low certainty evidence for other outcomes.

HOPE and NMP vs. SCS

Although studies comparing HOPE and NMP are limited, the existing literature suggests that divergent immune responses play a crucial role. In rodent DCD transplantation models, HOPE demonstrated reduced injury and improved survival compared to NMP, possibly due to the alteration of non-parenchymal cell

Group and comparison	No. of direct comparisons (No. of participants)	Network risk ratio	Certainty of evidence
Non-anastomotic biliary stricture			
Single HOPE vs SCS	3 (269)	0.18 (0.05, 0.51)	High
Dual HOPE vs SCS	3 (267)	0.32 (0.12, 0.77)	High
Single vs Dual HOPE	-	0.54 (0.11, 2.30)	Very low
Total biliary complications			
Single HOPE vs SCS	5 (425)	0.59 (0.37, 0.95)	Moderate
Dual HOPE vs SCS	3 (267)	0.64 (0.38, 1.09)	Low
Single vs Dual HOPE	-	0.93 (0.46, 1.90)	Low

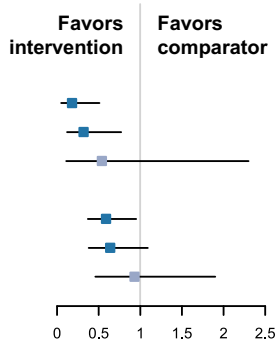

Figure 4. Network meta-analysis comparisons of single and dual cannulated HOPE versus SCS in ECD liver transplantation. The forest plot is scaled from 0 to 2.5, where the box (blue: HOPE, red: NMP, and skyblue: indirect estimate) indicates the risk ratio and the black line represents the 95% CI. Analysis of NAS and TBC for single portal vein HOPE and dual portal vein and hepatic artery HOPE versus SCS revealed high-certainty evidence for single HOPE in reducing NAS and TBC. Moderate-certainty evidence supported dual HOPE for NAS, but evidence for its effect on TBC was low. Dual HOPE showed no significant benefit over single HOPE with low to very low certainty. All outcomes were analyzed using a fixed-effects model. HOPE, hypothermic oxygenated perfusion; NMP, normothermic machine perfusion; SCS, static cold storage; NAS, non-anastomotic biliary stricture; TBC, total biliary complications; and ECD, extended criteria donor.

phenotypes and downstream signaling pathways during normothermic perfusion[40]. Data from an ongoing RCT (NCT04644744) suggest that NMP leads to a significant rise in circulating leukocytes, whereas HOPE perfusate contains fewer granulocytes but a higher proportion of those expressing programmed death-ligand 1[41].

Our study builds on these findings by providing clinical evidence through a network meta-analysis that combines studies with low-to-moderate bias and minimal heterogeneity, further supported by pairwise meta-analysis results. The consistent advantages of HOPE over NMP across various outcomes suggest that HOPE provides superior protection against IRI in ECD livers. However, immunological response during normothermic perfusion differs between donor types and the quality of the grafts, as shown in both rodent[40] and human liver studies[42]. Therefore, it is premature to claim that HOPE is generally superior to NMP outside of ECD grafts without further subgroup analyses of non-ECD grafts (Fig. S6A http://links.lww.com/JS9/E260) or high-DRI and low-DRI grafts, as performed by Grąt *et al*[15].

While HOPE might hold an edge in addressing post-transplant complications of ECD grafts, the distinct proponents for each method should not be overlooked. One of the major strengths of NMP is its capacity to extend preservation time compared to HOPE, as demonstrated in Table S5 http://links.lww.com/JS9/E260. This prolonged preservation window not only facilitates logistical flexibility in organ allocation and transplantation but also provides additional time for viability assessment, potentially reducing the risk of graft discard. This was observed in three major RCTs[7,14,37] on normothermic perfusion, with meta-analysis revealing a significant increase (Fig. S6B http://links.lww.com/JS9/E260). Despite the Zurich group proposing that mitochondrial flavin mononucleotide in the HOPE perfusate can predict liver function and graft outcomes[43], further human trials are needed to confirm its clinical value over NMP. Overall, the current evidence suggests that HOPE should be prioritized for high-risk donors, while NMP may be more suitable in settings where extended preservation is needed due to the geographical distance between donor and recipient.

Single and dual HOPE vs. SCS

The question of whether to perform machine perfusion via the portal vein alone or both the portal vein and hepatic artery remains debatable[44–46]. Anatomically, the intrahepatic biliary tree is supplied by both the portal vein and hepatic artery, whereas the extrahepatic portion is mainly supplied by the peribiliary vascular plexus that arises from the hepatic artery[47]. In normothermic settings where cellular metabolism is active, a dual blood supply is necessary to preserve biliary function[48,49]. In contrast, oxygen demand is reduced in hypothermic perfusion, and several groups have suggested that single-portal vein cannulation is adequate for restoring ATP in liver cells, including extrahepatic cholangiocytes[46,50]. Concerns also arise with the cannulation of the hepatic artery as it can cause mechanical damage to endothelial cells and potentially lead to arterial complications.

A retrospective cohort study, excluded from the current study, demonstrated that compared to single HOPE, dual HOPE reduced biliary complications and the need for surgical revisions[51]. However, the authors acknowledged that selection bias is inevitable, as surgeons are likely to choose livers with more preserved hepatic arteries for dual HOPE. Although the need for RCTs is clear, conducting one may be challenging since many centers have established preferences and randomization to an unaccustomed method could present practical barriers. In this study, the network meta-analysis of SCS, single HOPE, and dual HOPE found no indirect evidence supporting dual HOPE over single HOPE. Overall, our findings suggest that single HOPE is clinically non-inferior to dual HOPE.

Long-term and short-term NMP vs. SCS

The machine perfusion system integrates multiple specialized devices, such as pumps, an oxygenator, a heat exchanger, and a reservoir. Owing to its complexity, transporting the system to and from the donor hospital requires both a technical team and a modified ambulance with an internal power supply. Many centers have adopted a practical approach to HOPE using short-term end-ischemic HOPE followed by SCS. This practice may be explained by rapid mitochondrial reprogramming

Group and comparison	No. of direct comparisons (No. of participants)	Network risk ratio	Certainty of evidence
Early allograft dysfunction			
Long-term HOPE vs SCS	3 (260)	0.41 (0.22, 0.74)	High
Short-term HOPE vs SCS	3 (296)	0.50 (0.29, 0.84)	High
Long-term vs Short-term HOPE	-	0.83 (0.37, 1.81)	Low
Long-term NMP vs SCS	3 (186)	0.94 (0.26, 3.66)	Very low
Short-term NMP vs SCS	3 (250)	1.39 (0.35, 6.8)	Very low
Long-term vs Short-term NMP	-	0.83 (0.37, 1.81)	Very low
Major complications			
Long-term HOPE vs SCS	3 (260)	0.48 (0.24, 0.92)	High
Short-term HOPE vs SCS	3 (180)	0.32 (0.15, 0.64)	High
Long-term vs Short-term HOPE	-	1.51 (0.56, 4.01)	Low
Long-term NMP vs SCS	4 (540)	0.79 (0.52, 1.14)	Very low
Short-term NMP vs SCS	3 (341)	0.68 (0.43, 1.07)	Low
Long-term vs Short-term NMP	-	1.14 (0.62, 2.09)	Very low
Non-anastomotic biliary stricture			
Long-term HOPE vs SCS	3 (186)	0.14 (0.02, 0.56)	High
Short-term HOPE vs SCS	3 (350)	0.30 (0.13, 0.66)	High
Long-term vs Short-term HOPE	-	0.46 (0.06, 2.40)	Low
Long-term NMP vs SCS	4 (361)	0.63 (0.34, 1.16)	Low
Short-term NMP vs SCS	4 (551)	2.46 (0.79, 7.97)	Low
Long- vs Short-term NMP	-	0.26 (0.07, 0.93)	High
Total biliary complications			
Long-term HOPE vs SCS	4 (296)	0.53 (0.29, 0.93)	Moderate
Short-term HOPE vs SCS	4 (396)	0.65 (0.41, 1.02)	Low
Long-term vs Short-term HOPE	-	0.80 (0.39, 1.67)	Low
Long-term NMP vs SCS	4 (355)	0.87 (0.55, 1.39)	Very low
Short-term NMP vs SCS	4 (551)	1.16 (0.71, 1.88)	Low
Long- vs Short-term NMP	-	0.76 (0.39, 1.48)	Very low
Primary non-function			
Long-term HOPE vs SCS	4 (360)	0.00 (0.00, 0.23)	High
Short-term HOPE vs SCS	3 (296)	1.33 (0.23, 6.81)	Very low
Long-term vs Short-term HOPE	-	0.00 (0.00, 0.25)	High
Renal replacement therapy			
Long-term HOPE vs SCS	3 (250)	1.26 (0.58, 2.69)	Very low
Short-term HOPE vs SCS	3 (296)	0.74 (0.32, 1.66)	Low
Long-term vs Short-term HOPE	-	1.69 (0.56, 5.15)	Very low

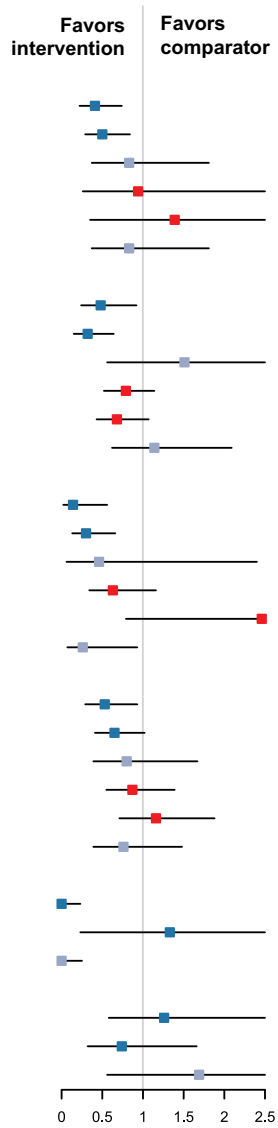

Figure 5. Network meta-analysis comparisons of long-term and short-term machine perfusion versus SCS in ECD liver transplantation. Studies included in each outcome were classified as short-term (lower 50 percentile) or long-term (upper 50 percentile) perfusion based on the perfusion-to-preservation time ratio (Fig. S4, Table S6 http://links.lww.com/JS9/E260). The forest plot is scaled from 0 to 2.5, where the box (blue: HOPE, red: NMP, and skyblue: indirect estimate) indicates the risk ratio and the black line represents the 95% CI. Compared to SCS, long-term HOPE demonstrated high-certainty evidence for reducing EAD, major complications, NAS, and PNF, with moderate-certainty evidence for reducing TBC. The reductions observed with short-term HOPE were similar, but the evidence for TBC and PNF remained low to very low in certainty. High-certainty evidence supported long-term HOPE's superiority over short-term HOPE in reducing PNF, but no significant differences were observed for other outcomes. Compared to SCS, both long-term NMP and short-term NMP showed low to very low certainty evidence for preventing EAD, major complications, NAS, and TBC. Against short-term NMP, long-term NMP demonstrated high-certainty benefits in reducing NAS. A random-effects model was applied for the analysis of NMP in EAD due to a deviance information criterion difference exceeding 3, while a fixed-effects model was used for all other outcomes. HOPE, hypothermic oxygenated perfusion; NMP, normothermic machine perfusion; SCS, static cold storage; EAD, early allograft dysfunction; NAS, non-anastomotic biliary stricture; TBC, total biliary complications; PNF, primary non-function; and ECD, extended criteria donor.

through oxygenation under hypothermic conditions, facilitating ATP recovery and the metabolism of ischemic toxins[52,53]. Similarly, initial clinical studies on NMP readily adopted end-ischemic perfusion to reduce costs. However, growing knowledge about NMP and graft injury has led to critical perspectives on its usage. A mechanistic study of NMP in discarded human livers indicated that prolonging perfusion beyond 6 h is ideal for inactivating proinflammatory neutrophils and increasing anti-inflammatory monocytes and macrophages[42]. Moreover, studies have reported that prolonged hypothermic storage makes tissues more prone to temperature spikes, with warm reperfusion via NMP causing a distinct rewarming injury[54,55]. While the controlled oxygenated rewarming technique may mitigate the latter concern[56], the overall characteristics support the continuous use of NMP from procurement to implantation to maximize its regenerative potential and reduce rewarming injury.

With advancements in machine perfusion technology and complex procedures, clinical trials have introduced portable devices for HOPE[17] and NMP[37,57]. The ischemia-free liver transplantation proposed by Guo *et al*[58,59], though not included in the analysis, could be considered the most radical extension of this concept. Before fully endorsing this trend, an

assessment of the clinical benefits of continuous perfusion and non-inferiority of end-ischemic perfusion is necessary. In this study, high-certainty evidence supports that long-term NMP reduces NAS and long-term HOPE reduces PNF, both compared to their short-term counterparts. Findings related to NMP align with an observational study showing that end-ischemic normothermic perfusion triggers IRI and fails to prevent biliary injury[60]. However, we remain cautious in making conclusions for HOPE, as PNF events were frequently absent in HOPE studies, underscoring that it would be misleading to suggest long-term HOPE is better when short-term HOPE has shown similar success in other outcomes. To establish further guidelines on whether to initiate perfusion at the donor or recipient hospital, we suggest that more studies focus on regression analyses that examine the impact of perfusion-to-preservation time ratios on relevant outcomes.

This study has several limitations. First, the difference between portable and non-portable devices was not addressed due to the limited number of studies, despite differences in machine components, perfusate, flow rate, and oxygenation methods[17]. As portable device adoption increases in HOPE applications, future research would benefit from such comparative analyses, similar to those already attempted in kidney machine perfusion research[61,62]. Second, the analysis of graft loss and patient death was limited, though its necessity is debatable due to their multifactorial etiology and rarity[63]. The 5-year graft survival for HOPE-treated DCD livers has been reported to exceed 80%[64], with a study estimating that over 4000 patients are needed to statistically validate patient survival[65]. Nonetheless, a summary of graft and patient survival from individual studies is provided in Tables S11 and S12 http://links.lww.com/JS9/E260. Third, the perfusion-to-preservation time ratio calculated from median or mean values may not fully represent the studies, although this approach is closely aligned with the timing of perfusion initiation in NMP studies (Table S4 http://links.lww.com/JS9/E260). Finally, our findings are subject to the coherence assumption, which remains weakly verified due to the lack of direct comparisons across HOPE versus NMP, single versus dual HOPE, or long-term versus short-term machine perfusion. Updates on network estimates are required after results are available from the ongoing RCT comparing HOPE and NMP (NCT04644744).

With a focus on ECD grafts, this study employs a Bayesian network meta-analysis to decode critical gaps in machine perfusion research – temperature protocols, indications, cannulation strategies, and timing. This study highlighted three main findings: (1) In ECD liver transplantation, HOPE is more effective than NMP, particularly for preventing EAD, TBC, NAS, and ACR. Recipients of grafts with high DRIs may benefit more from HOPE than NMP. (2) Single portal vein and dual cannulation HOPE show comparable efficacy, and the additional benefit of arterial cannulation is inconclusive. (3) ECD grafts benefit from both long-term and short-term HOPE, while early initiation of NMP at the donor hospital may contribute to reducing the risk of NAS. Well-designed randomized studies are needed to confirm these results and develop standardized clinical protocols.

Ethical approval

The study does not require ethical approval, but a waiver was granted (HYUIRB-202409-012).

Consent

The study does not require patient consent

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Author contributions

Design and conception of the work: MK, BP, and DC; Literature screening: MK and NTHT; Data collection: MK and NTHT; Analysis: MK; Investigation and writing the article: MK and NTHT; Project administration: KSK, BP, and DC; Writing – review and editing: all authors; and Final approval of the version of the manuscript: all authors

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

Research registration unique identifying number

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Data availability statement

Available upon reasonable request.

Assistance with the study

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References

[1] WHO-ONT collaboration. 2021.

[2] Liu WP, Humphries AL Jr, Russell R, Stoddard LD, Moretz WH. 48-hour storage of canine kidneys after brief perfusion with Collins' solution. Ann Surg 1971;173:748–57.

[3] Ito T, Naini BV, Markovic D, *et al*. Ischemia-reperfusion injury and its relationship with early allograft dysfunction in liver transplant patients. Am J Transplant 2021;21:614–25.

[4] Cursio R, Gugenheim J. Ischemia-reperfusion injury and ischemic-type biliary lesions following liver transplantation. J Transplant 2012;2012: 164329.

[5] Vodkin I, Kuo A. Extended criteria donors in liver transplantation. Clin Liver Dis 2017;21:289–301.

[6] Moers C, Smits JM, Maathuis MH, *et al*. Machine perfusion or cold storage in deceased-donor kidney transplantation. N Engl J Med 2009;360:7–19.

[7] Nasralla D, Coussios CC, Mergental H, *et al*. A randomized trial of normothermic preservation in liver transplantation. Nature 2018;557: 50–56.

[8] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Int J Surg 2021;88:105906.

[9] Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008.

[10] Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.

[11] Sterne JA, Hernán MA, Reeves BC, *et al*. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355: i4919.

[12] Izcovich A, Chu DK, Mustafa RA, Guyatt G, Brignardello-Petersen R. A guide and pragmatic considerations for applying GRADE to network meta-analysis. BMJ 2023;381:e074495.

[13] Fodor M, Cardini B, Peter W, *et al*. Static cold storage compared with normothermic machine perfusion of the liver and effect on ischaemic-type biliary lesions after transplantation: a propensity score-matched study. Br J Surg 2021;108:1082–89.

[14] Chapman WC, Barbas AS, D'Alessandro AM, *et al*. Normothermic machine perfusion of donor livers for transplantation in the United States: a randomized controlled trial. Ann Surg 2023;278:e912–e21.

[15] Grąt M, Morawski M, Zhylko A, *et al*. Routine end-ischemic hypothermic oxygenated machine perfusion in liver transplantation from donors after brain death: a randomized controlled trial. Ann Surg 2023;278:662–68.

[16] Czigany Z, Pratschke J, Froněk J, *et al*. Hypothermic oxygenated machine perfusion reduces early allograft injury and improves post-transplant outcomes in extended criteria donation liver transplantation from donation after brain death: results from a multicenter randomized controlled trial (HOPE ECD-DBD). Ann Surg 2021;274:705–12.

[17] Panayotova GG, Lunsford KE, Quillin RCI, *et al*. Portable hypothermic oxygenated machine perfusion for organ preservation in liver transplantation: a randomized, open-label, clinical trial. Hepatology 2024;79:1033–47.

[18] Ravaioli M, Germinario G, Dajti G, *et al*. Hypothermic oxygenated perfusion in extended criteria donor liver transplantation-A randomized clinical trial. Am J Transplant 2022;22:2401–08.

[19] van Rijn R, Schurink IJ, de Vries Y, *et al*. Hypothermic machine perfusion in liver transplantation - a randomized trial. N Engl J Med 2021;384:1391–401.

[20] Dutkowski P, Polak WG, Muiesan P, *et al*. First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: an international-matched case analysis. Ann Surg 2015;262:764–70.

[21] Norén Å, Mölne J, Bennet W, *et al*. End-ischemic hypothermic oxygenated machine perfusion does not improve renal outcome following liver transplantation from aged donors: a single-center retrospective report. Artif Organs 2023;47:1854–64.

[22] Patrono D, Surra A, Catalano G, *et al*. Hypothermic oxygenated machine perfusion of liver grafts from brain-dead donors. Sci Rep 2019;9:9337.

[23] Ravaioli M, De Pace V, Angeletti A, *et al*. Hypothermic oxygenated new machine perfusion system in liver and kidney transplantation of extended criteria donors: first Italian clinical trial. Sci Rep 2020;10:6063.

[24] Rayar M, Beaurepaire JM, Bajeux E, *et al*. Hypothermic oxygenated perfusion improves extended criteria donor liver graft function and reduces duration of hospitalization without extra cost: the PERPHO study. Liver Transpl 2021;27:349–62.

[25] Schlegel A, Muller X, Kalisvaart M, *et al*. Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation. J Hepatol 2019;70:50–57.

[26] Ghinolfi D, Rreka E, De Tata V, *et al*. Pilot, open, randomized, prospective trial for normothermic machine perfusion evaluation in liver transplantation from older donors. Liver Transpl 2019;25: 436–49.

[27] Bral M, Gala-Lopez B, Bigam D, *et al*. Preliminary single-center canadian experience of human normothermic ex vivo liver perfusion: results of a clinical trial. Am J Transplant 2017;17:1071–80.

[28] Gaurav R, Butler AJ, Kosmoliaptsis V, *et al*. Liver transplantation outcomes from controlled circulatory death donors: SCS vs in situ NRP vs ex situ NMP. Ann Surg 2022;275:1156–64.

[29] Hefler J, Leon-Izquierdo D, Marfil-Garza BA, *et al*. Long-term outcomes after normothermic machine perfusion in liver transplantation-experience at a single North American center. Am J Transplant 2023; 23:976–86.

[30] Jassem W, Xystrakis E, Ghnewa YG, *et al*. Normothermic machine perfusion (NMP) inhibits proinflammatory responses in the liver and promotes regeneration. Hepatology 2019;70:682–95.

[31] Mergental H, Laing RW, Kirkham AJ, *et al*. Transplantation of discarded livers following viability testing with normothermic machine perfusion. Nat Commun 2020;11:2939.

[32] Wehrle CJ, Zhang M, Khalil M, *et al*. Impact of back-to-base normothermic machine perfusion on complications and costs: a multicenter, real-world risk-matched analysis. Ann Surg 2024;280:300–10.

[33] Ravikumar R, Jassem W, Mergental H, *et al*. Liver transplantation after ex vivo normothermic machine preservation: a phase 1 (First-in-Man) clinical trial. Am J Transplant 2016;16:1779–87.

[34] Liu Q, Hassan A, Pezzati D, *et al*. Ex situ liver machine perfusion: the impact of fresh frozen plasma. Liver Transpl 2020;26:215–26.

[35] van Rijn R, Karimian N, Matton APM, *et al*. Dual hypothermic oxygenated machine perfusion in liver transplants donated after circulatory death. Br J Surg 2017;104:907–17.

[36] Schlegel A, Mueller M, Muller X, *et al*. A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation. J Hepatol 2023;78: 783–93.

[37] Markmann JF, Abouljoud MS, Ghobrial RM, *et al*. Impact of portable normothermic blood-based machine perfusion on outcomes of liver transplant: the OCS liver PROTECT randomized clinical trial. JAMA Surg 2022;157:189–98.

[38] Parente A, Tirotta F, Pini A, *et al*. Machine perfusion techniques for liver transplantation - A meta-analysis of the first seven randomized-controlled trials. J Hepatol 2023;79:1201–13.

[39] Tingle SJ, Dobbins JJ, Thompson ER, *et al*. Machine perfusion in liver transplantation. Cochrane Database Syst Rev 2023;9:CD014685.

[40] Schlegel A, Kron P, Graf R, Dutkowski P, Clavien PA. Warm vs. cold perfusion techniques to rescue rodent liver grafts. J Hepatol 2014;61: 1267–75.

[41] Lurje I, Uluk D, Hammerich L, Pratschke J, Tacke F, Lurje G. Comparing hypothermic oxygenated and normothermic liver machine perfusion: translation matters. J Hepatol 2024;80:e163–e5.

[42] Hautz T, Salcher S, Fodor M, *et al*. Immune cell dynamics deconvoluted by single-cell RNA sequencing in normothermic machine perfusion of the liver. Nat Commun 2023;14:2285.

[43] Schlegel A, Muller X, Mueller M, *et al*. Hypothermic oxygenated perfusion protects from mitochondrial injury before liver transplantation. EBioMedicine 2020;60:103014.

[44] Schlegel A, Kron P, De Oliveira ML, Clavien PA, Dutkowski P. Is single portal vein approach sufficient for hypothermic machine perfusion of DCD liver grafts? J Hepatol 2016;64:239–41.

[45] Brüggenwirth IMA, Burlage LC, Porte RJ, Martins PN. Is single portal vein perfusion the best approach for machine preservation of liver grafts? J Hepatol 2016;64:1194–95.

[46] Schlegel A, Kron P, de Oliveira Ml, Clavien P-A, Dutkowski P. Reply to 'Is single portal vein perfusion the best approach for machine preservation of liver grafts?' J Hepatol 2016;64:1195–96.

[47] Ramesh Babu CS, Sharma M. Biliary tract anatomy and its relationship with venous drainage. J Clin Exp Hepatol 2014;4:S18–26.

[48] Foley DP, Ricciardi R, Traylor AN, *et al*. Effect of hepatic artery flow on bile secretory function after cold ischemia. Am J Transplant 2003;3:148–55.
[49] Foley DP, Vittimberga FJ, Quarfordt SH, *et al*. Biliary secretion of extracorporeal porcine livers with single and dual vessel perfusion. Transplantation 1999;68:362–68.
[50] de Vries Y, Brüggenwirth IMA, Karangwa IMA, *et al*. Dual versus single oxygenated hypothermic machine perfusion of porcine livers: impact on hepatobiliary and endothelial cell injury. Transplant Direct 2021;7:e741.
[51] Pereyra D, Dingfelder J, Riha M, *et al*. Dual hypothermic oxygenated machine perfusion of the liver reduces post transplant biliary complications - a retrospective cohort study. Int J Surg 2024;110:7909–18.
[52] Schlegel A, Porte RJ, Dutkowski P. Protective mechanisms and current clinical evidence of hypothermic oxygenated machine perfusion (HOPE) in preventing post-transplant cholangiopathy. J Hepatol 2022;76:1330–47.
[53] Martin JL, Costa ASH, Gruszczyk AV, *et al*. Succinate accumulation drives ischaemia-reperfusion injury during organ transplantation. Nat Metab 2019;1:966–74.
[54] Minor T, Efferz P, Fox M, Wohlschlaeger J, Lüer B. Controlled oxygenated rewarming of cold stored liver grafts by thermally graduated machine perfusion prior to reperfusion. Am J Transplant 2013;13:1450–60.
[55] Minor T, von Horn C, Gallinat A, *et al*. First-in-man controlled rewarming and normothermic perfusion with cell-free solution of a kidney prior to transplantation. Am J Transplant 2020;20:1192–95.
[56] Minor T, von Horn C, Zlatev H, *et al*. Controlled oxygenated rewarming as novel end-ischemic therapy for cold stored liver grafts. A randomized controlled trial. Clin Transl Sci 2022;15:2918–27.
[57] Yamamoto T, Atthota S, Agarwal D, *et al*. Impact of portable normothermic machine perfusion for liver transplantation from adult deceased donors. Ann Surg 2023;278:e922–e9.
[58] Guo Z, Zhao Q, Huang S, *et al*. Ischaemia-free liver transplantation in humans: a first-in-human trial. Lancet Reg Health West Pac 2021;16: 100260.
[59] Guo Z, Zhao Q, Jia Z, *et al*. A randomized-controlled trial of ischemia-free liver transplantation for end-stage liver disease. J Hepatol 2023;79: 394–402.
[60] Watson CJE, Kosmoliaptsis V, Pley C, *et al*. Observations on the ex situ perfusion of livers for transplantation. Am J Transplant 2018;18: 2005–20.
[61] Kang M, Kim S, Choi JY, *et al*. Ex vivo kidney machine perfusion: meta-analysis of randomized clinical trials. Br J Surg 2024;111:znae102.
[62] Wszola M, Kwiatkowski A, Diuwe P, *et al*. One-year results of a prospective, randomized trial comparing two machine perfusion devices used for kidney preservation. Transpl Int 2013;26:1088–96.
[63] Blakolmer K, Jain A, Ruppert K, *et al*. Chronic liver allograft rejection in a population treated primarily with tacrolimus as baseline immunosuppression: long-term follow-up and evaluation of features for histopathological staging. Transplantation 2000;69:2330–36.
[64] Eden J, Brüggenwirth IMA, Berlakovich G, *et al*. Long-term outcomes after hypothermic oxygenated machine perfusion and transplantation of 1,202 donor livers in a real-world setting (HOPE-REAL study). J Hepatol 2024;82:97–106.
[65] Richards J, Gimson A, Joh Y, Watson CJE, Neuberger J. Trials & tribulations of liver transplantation- are trials now prohibitive without surrogate endpoints? Liver Transpl 2021;27:747–55.