Machine Perfusion in Liver Transplantation: A Systematic Review and Meta-Analysis

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Machine perfusion · Liver transplantation · Extended criteria donors · Marginal grafts

Abstract

Background: Liver transplantation (LTx) is the only treatment option for patients with end-stage liver disease. Novel organ preservation techniques such as hypothermic machine perfusion (HMP) or normothermic machine perfusion (NMP) are under investigation in order to improve organ quality from extended criteria donors and donors after circulatory death. The aim of this study was to systematically review the literature reporting LTx outcomes using NMP or HMP compared to static cold storage (SCS).

Methods: The following data were retrieved: graft primary nonfunction rate, early allograft dysfunction (EAD) rate, biliary complication rate, and 12-month graft and patient survival. A total of 15 studies were included (6 NMP and 9 HMP studies), and meta-analysis was performed only for HMP studies because NMP had considerable differences.

Results: The systematic review showed the potential of NMP to reduce graft injury and lower the liver graft discard rate. The performed quantitative analyses showed that the use of HMP reduces the rate of EAD (odds ratio [OR] 0.51; 95% confidence interval [CI] 0.34–0.76; \( p = 0.001 \); \( \chi^2 = 0\% \)) and non-anastomotic biliary strictures (OR 0.34; 95% CI 0.17–0.67; \( p = 0.002 \); \( \chi^2 = 0\% \)) compared to SCS.

Conclusion: Our systematic review and meta-analysis revealed that the use of HMP reduces the rate of EAD and non-anastomotic biliary strictures compared to SCS.

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Introduction

Several decades since the first attempt in 1963, liver transplantation (LTx) remains the only treatment option for patients with end-stage liver disease [1]. Although advances in surgical technique, immunosuppression, and organ preservation led to greatly improved postoperative outcomes, the steadily increasing organ demand is unmet, resulting in organ shortage worldwide [2]. According to the Organ Procurement and Transplantation Network data, in 2019, in the USA, there were 8,896 LTx opposing 13,448 candidates newly added to the waiting list in the same year. Furthermore, 2,415 patients became too sick to be transplanted or died while waiting for LTx. In the Eurotransplant network countries, 1,687 LTx were performed in 2019; however, the waiting list increased by 2,502 new registrations. The discrepancy between the need and availability of liver grafts requires expanding the donor pool with both extended criteria donors (ECDs) and donors after circulatory death (DCD). Therefore, the development of novel organ preservation techniques is mandatory in order to increase the donor organ pool.

For the last few decades, static cold storage (SCS) remained the basically unchanged gold standard in preserving high-quality organs due to its low cost and simplicity [3]. However, its limitations in expanding the donor pool by including ECD organs are well known. Vogel et al. [4]...
outlines 4 major weaknesses of SCS: (I) sustained organ injury is not reversed; (II) further organ injury during storage continues; (III) organ viability cannot be assessed; and (IV) storage time is limited. Some of these shortcomings can be overcome by utilizing machine perfusion (MP). Several modes of MP are possible differing in temperature, perfusion device, perfusion solution, etc. So far, in a clinical setting, the 2 most studied types of MP are hypothermic machine perfusion (HMP) and normothermic machine perfusion (NMP) [5]. HMP relies on the reduced cell metabolism in hypothermic conditions, additionally washing out toxins accumulated during storage [6]. NMP takes a different approach by sustaining the full cell metabolism at body temperature, allowing organ viability assessment before transplantation [7]. However, the high cost and nonconclusive evidence limits its wider use in the LTx setting. The aim of this study was to systematically review the literature reporting LTx outcomes when using NMP or HMP for organ preservation compared to SCS.

### Methods

#### Literature Search Strategy

No ethics approval was required for this type of study. Literature search was performed in PubMed, Web of Science, and EMBASE databases. The following combination of Medical Subject Headings (MeSH) and keywords with the employment of "AND" or "OR" Boolean operators were used: "Liver" OR "Liver Transplantation" AND "Machine perfusion" OR "Hypothermic perfusion" OR "Subnormothermic perfusion" OR "Normothermic perfusion."

The search was restricted to English language only, without a time limitation. The most recent search was performed on May 19, 2021. Database-specific search strategies are provided as online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000519788).

#### Eligibility Criteria

We included studies that compared the use of NMP or HMP with SCS in an LTx setting. According to Karangwa et al. [8] standardized nomenclature proposal cutoff values of >35°C for NMP and <12°C for HMP were used when including studies. Randomized controlled trials (RCTs), cohort studies, case-control studies, and quasi-randomized studies were eligible for inclusion. Case re-

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Fig. 1. PRISMA flowchart of study selection process. MP, machine perfusion.
Table 1. Characteristics and main findings of clinical NMP studies

| Author          | Study design | MP type and comparison | Patients, n | Donor type | Perfusion settings                                                                 | Length of MP, h | Length of SCS, h | Main findings of the study                                                                 |
|-----------------|--------------|------------------------|-------------|------------|-------------------------------------------------------------------------------------|----------------|-----------------|------------------------------------------------------------------------------------------|
| Ravikumar et al. [21] | Case-matched 1:2 study | NMP versus SCS | 20 versus 40 | DBD, DCD | Device: OrganOx metra<sup>®</sup><br>Temperature: 37°C<br>Perfusate: pRBC + colloid solution (Gelofusine<sup>®</sup>) + additives<br>Postperfusion: flushed with 2 L of cold HTK solution | 9.3 (3.5–18.5) | N/A versus 8.9 (4.2–11.4) | 1. Safety and feasibility of clinical NMP use<br>2. Similar 30-day graft and patient survival in both groups<br>3. Significantly lower median peak AST within first 7 days in NMP group |
| Selzner et al. [22] | Case-matched 1:3 study | NMP versus SCS | 10 versus 30 | DBD, DCD | Device: OrganOx metra<sup>®</sup><br>Temperature: 37°C<br>Perfusate: pRBC + albumin and dextran based steen solution + additives<br>Postperfusion: n.r. | 8 (5.7–9.7)<sup>*</sup> | N/A versus 10.5 (8.7–13.1)<sup>*</sup> | 1. Steen solution as a perfusate is safe for NMP<br>2. Similar postoperative graft function, ICU and hospital stay<br>3. No graft loss or patient death in either group |
| Bral et al. [23] | Case-matched 1:3 study | NMP versus SCS | 9 versus 27 ITT (10 vs. 30) | DBD, DCD | Device: OrganOx metra<sup>®</sup><br>Temperature: 37°C<br>Perfusate: pRBC + colloid solution (Gelofusine<sup>®</sup>) + additives<br>Postperfusion: flushed with cold HTK solution | 11.5 (3.3–22.5)<sup>*</sup> | 2.8 (1.6–4.9)<sup>*</sup> versus 3.9 (1.1–14.8)<sup>*</sup> | 1. Similar 30-day and 6-month graft and patient survival<br>2. ICU and hospital stay significantly longer in NMP group<br>3. Similar postoperative graft function |
| Nassalla et al. [24] | Multicenter RCT | NMP versus SCS | 121 versus 101 | DBD, DCD | Device: OrganOx metra<sup>®</sup><br>Temperature: 37°C<br>Perfusate: pRBC + colloid solution (Gelofusine<sup>®</sup>) + additives<br>Postperfusion: n.r. | 9.1 (6.2–11.8) | 2.1 (1.8–2.4) versus 7.8 (6.3–9.6) | 1. Reduced graft injury despite increased preservation time and organ utilization<br>2. No difference in 1-year graft and patient survival<br>3. Significantly lower EAD and post-reperfusion syndrome rate |
| Ghinolfi et al. [25] | Single-center RCT | NMP versus SCS | 10 versus 10 (>70 years) | DBD | Device: LiverAssist<sup>®</sup><br>Temperature: 37°C<br>Perfusate: pRBC + colloid solution (Gelofusine<sup>®</sup>) + human albumin + additives<br>Postperfusion: flushed with 2 L of Celsior<sup>®</sup> solution | 4.2 (3.3–4.7) | 4.1 (3.4–4.5) versus 6.6 (6.1–7.8) | 1. No difference in 6-month graft and patient survival<br>2. Similar complication rate and hospital stay in either group<br>3. Histological evidence of reduced graft injury |
| Liu et al. [26] | Case-matched 1:4 study | NMP versus SCS | 21 versus 84 | DBD, DCD | Device: institutionally developed perfusion machine<br>Temperature: 36°C<br>Perfusate: FFP, pRBC, albumine + additives<br>Postperfusion: flushed with 1 L saline and 2 L of HTK solution | 5.0±1.1 | 3.2±0.8 versus 8.3±1.5 | 1. EAD rate, peak ALT, AST levels significantly lower in the NMP group |

Continuous variables provided as mean ± SD or as median (IQR) if not noted differently. NMP, normothermic machine perfusion; MP, machine perfusion; SCS, static cold storage; DBD, donation after brain death; ECD, e criteria donor; DCD, donation after circulatory death; EAD, early allograft dysfunction; ICU, intensive care unit; RCTs, randomized controlled trials. * Median (range).
### Table 2. Characteristics of clinical HMP studies

| Author et al. | Study design | MP type and comparison | Patients, n | Donor type | Device: | Temperature°C | Perfusate: | Postperfusion: | Length of SCS, h | Main findings of the study |
|---------------|-------------|------------------------|-------------|------------|---------|---------------|-------------|----------------|----------------|--------------------------------|
| Dutkowski et al. [12] | Case-matched | HMP versus 20 versus 20 DCD, DBD | 1:1 study | SCS versus SC versus DBS | Device: Modified Medtronic MPS® device | Temperature 4-8°C | Vasosol® | Flush with 1.5 L Hextend® solution | 4.3±0.9 | 1. Mean hospital stay significantly shorter in the HMP group. 2. SAF and feasibility of clinical HMP use. 3. Peak serum AST, ALT, TBili and SCr levels significantly lower in the HMP group. |
| Dutkowski et al. [13] | 1:2 study | HOPE versus 25 versus 50 DCD, DBD | Device: ECOPS device (OrganAssist®) | Temperature 10°C | UW gluconate solution | Postperfusion: flush with 1 L Hextend® solution | 2.2** | 5.3 (4.7–5.6) | 8.9±2.1 versus 6.6 | 1. Significantly lower ALT levels in the HOPE group. 2. During DHOPE median MP levels were 2.8±1.3 versus 5.8±3.8. 3. ALT and bilirubin levels at 1 week after transplantation were 2 fold lower in the DHOPE group. |
| Guarrera et al. [14] | Case-matched | HMP versus 20 versus 20 DBD Device: Modified Medtronic MPS® device | 1:1 study | SCS versus SC versus DBS | Temperature 4-8°C | Vasosol® | Flush with 1.5 L Hextend® solution | 3.8±0.9 | 9.3±1.6 versus 8.6±2.4 | 1. Mean hospital stay significantly shorter in the HMP group. |
| Dutkowski et al. [15] | Case-matched | HOPE versus 25 versus 50 DCD, DBD | 1:2:2 study | SCS versus SC versus DBS | Device: LiverAssist MPS® | Temperature 4°C | Belzer MPS® UW MP solution | 2.1 (2.1–3.3) | 8.7 (7.9–8.9) | 1. Significantly lower total biliary complication rate in the HOPE group. 2. Significantly lower intrahepatic cholangiopathy and total biliary complication rate in the HOPE group. 3. HOPE-treated livers had a higher 1-year graft survival rate. |
| Rayar et al. [19] | Case-matched | HOPE versus 25 versus 69 ECD, DBD | 1:3 | SCS | Device: LiverAssist MPS® | Temperature 11°C | Belzer MPS® UW MP solution | 2.2 (1–3.5)* | 7.1 (5.4–10)* | 1. Median hospital and ICU stay significantly lower in the HOPE-treated liver transplants. 2. Median hospital and ICU stay significantly lower in the HMP-treated liver transplants. |
| Paterno et al. [18] | Case-matched | HOPE versus 25 versus 50 ECD, DBD | 1:3 | SCS | Device: LiverAssist MPS® | Temperature 10°C | Belzer MPS® UW MP solution | 2.2 (1–3.5)* | 7.1 (5.4–10)* | 1. Median hospital and ICU stay significantly lower in the HOPE-treated liver transplants. 2. Median hospital and ICU stay significantly lower in the HMP-treated liver transplants. |
| Schlegel et al. [17] | Case-matched | HOPE versus 50 versus 50 DCD, DBD | 1:1:1 | SCS versus SC versus DBS | Device: LiverAssist MPS® | Temperature 10°C | Belzer MPS® UW MP solution | 3±0.8 | 6.5±1.2 versus 5.2±0.9 | 1. Stage 2–3 acute kidney injury rate significantly lower in the DHOPE group. 2. Stage 2–3 acute kidney injury rate significantly lower in the DHOPE group. |
| Van Rijn et al. [20] | Multicenter | DHOPE versus 78 versus 78 DCD | RCT | SCS | Device: LiverAssist MPS® | Temperature 10°C | Belzer MPS® UW MP solution | 2.2 (2–2.5) | 6.2±2.6 versus 6.9 | 1. Lower incidence of symptomatic non-anatomic biliary strictures. 2. Lower risk of post-reperfusion syndrome. |

Continuous variables provided as mean ± SD or as median (IQR) if not noted differently. MP, machine perfusion; HOPE, hypothermic oxygenated perfusion; DHOPE, dual hypothermic oxygenated perfusion; HMP, hypothermic machine perfusion; SC, static cold storage; DBD, donation after brain death; ECD, expanded criteria donor; DCD, donation after circulatory death; ICU, intensive care unit.* Median (range). **IQR not available.
ports, case series (sample size less than 10 patients), and studies including children or animals were excluded.

**Study Selection and Data Extraction**

At first, the studies were screened based on their title and abstract. Full text was obtained for potentially eligible studies. The following data were extracted from all included studies: study characteristics, year of publication, sample size, donor type, MP parameters, and organ preservation length. For the outcome assessment, additional data were obtained: graft primary nonfunction (PNF) rate, early allograft dysfunction (EAD) rate, biliary complication rate, and 12-month graft and patient survival.

**Risk of Bias Assessment**

The quality of included nonrandomized studies was evaluated using the ROBINS-I risk of bias assessment tool [9]. Additionally, the quality of included RCTs was evaluated using the RoB 2 risk of bias assessment tool [10].

**Statistical Analysis**

We performed the meta-analyses using the software package RevMan 5.4.1 according to the recommendations of The Cochrane Handbook for Systematic Reviews and Interventions [11]. When analyzing HMP studies, we further subdivided them into 2 groups, ones that used additional oxygen during MP and ones that did not. For dichotomous variables, we calculated odd ratios (ORs) with 95% confidence interval (CI). As we expected a high level of heterogeneity across studies, Mantel-Haenszel (M-H) method and random-effects models were employed. Furthermore, the $F$ test was used to measure statistical heterogeneity. If a study observed no event in either group, it was not included in the quantitative analysis.

**Results**

**Study Selection and Characteristics**

Literature search results and the selection process of the studies are presented in the PRISMA flowchart (Fig. 1.). The initial search retrieved 3,089 potentially relevant studies. After evaluating 22 full-text articles, 15 of them were included in the qualitative synthesis [12–26]. Due to high heterogeneity between studies analyzing NMP ($n = 6$), only studies investigating HMP ($n = 9$) were included in the meta-analysis. Main characteristics of studies examining NMP and HMP are presented in Tables 1 and 2 respectively. In 2 studies, we recognized overlapping patient cohorts; therefore, we mainly extracted outcome data from the lately published study, which has a larger sample size [13, 17]. Unfortunately, this study did not report the EAD rate, and after failure in contacting the authors, we decided to extract the EAD rate from their first study. Additionally, when evaluating these studies as a control group for the meta-analysis, we included untreated DCD liver transplant data.

**Outcome Assessment**

Normothermic Machine Perfusion

A total of 6 studies analyzed the effect of NMP in LTx (Table 1) [21–26]. Nasralla et al. [24] conducted the
largest MP study so far. In this multicenter RCT, a total of 222 patients (121 NMP vs. 101 SCS) successfully underwent LTx [24]. The main finding of the study was that grafts after NMP had 50% lower levels of injury, measured by the peak level of serum AST within 7 days after transplantation. This result was achieved, despite a 50% lower organ discard rate and 54% longer mean preservation time in the NMP group. Furthermore, the authors observed a significantly lower EAD and post-reperfusion syndrome rate in patients who received machine-perfused liver grafts. Although the short-term postoperative outcomes appear to favor NMP over conventional cold storage, long-term results, such as 12-month graft and patient survival, were similar between groups.

Another RCT was conducted in a single center by Ghinolfi et al. [25]. In this study, only donation after brain death (DBD) donors older than 70 years were enrolled. Results demonstrated only histological evidence of reduced graft injury in machine-perfused livers but did not show any clinical benefits of NMP. Complication rate, hospital stay, and 6-month graft and patient survival were similar in both groups.

The other 4 studies were case-matched and included both DBD and DCD donors [21–23, 26]. Ravikumar et al. [21] and Liu et al. [26] found significantly lower peak AST
levels in the NMP group patients. Additionally, Liu et al. [26] reported lower EAD rates in the NMP group. None of these studies showed any graft or patient survival benefits during their follow-up period.

**Hypothermic Machine Perfusion**

**Early Allograft Dysfunction.** The overall EAD rate in the HMP group was 20.1% (47/224) versus 35.2% (122/347) in the SCS group. This difference was similar in both subgroups, and the overall effect was statistically significant (OR 0.51; 95% CI 0.34–0.76; \(p = 0.001; \hat{I}^2 = 0\%\)) (Fig. 2).

**Primary Nonfunction.** The overall effect in the graft PNF rate was not significant between groups (OR 0.75; 95% CI 0.23–2.43; \(p = 0.63; \hat{I}^2 = 0\%\)) (Fig. 3). The overall graft PNF rate in the HMP group was 1.5% (3/194) compared to 3.5% (9/257) in the SCS group. Three studies, included in the meta-analysis, reported no cases of graft PNF [12, 15, 16].

**Biliary Complications.** The overall total biliary complications (biliary strictures, leaks, and casts) rate was 29.3% (73/249) in the HMP group and 33.1% (115/347) in the SCS group, and there was a statistical significance in the overall effect between the groups (OR 0.63; 95% CI 0.43–0.93; \(p = 0.02; \hat{I}^2 = 0\%\)) (Fig. 4). We further analyzed the influence of HMP on the rate of non-anastomotic biliary stricture between the groups. The rates in the HMP and SCS were 6.6% (12/183) and 17.9% (39/218), respectively. This difference was statistically significant (OR 0.34; 95% CI 0.17–0.67; \(p = 0.002; \hat{I}^2 = 0\%\)), there were no differences between subgroups (Fig. 5). Three studies were not included in this analysis [14, 18, 19]. Ravaioli et al. [18] reported the rate of biliary strictures without specifying what type they were. In addition, Guerrera et al. [14] and Rayar et al. [19] observed no non-anastomotic biliary strictures in their study.

**Mortality and Graft Loss within 12 Months.** There was no significant difference in mortality rates between the groups (OR 0.57; 95% CI 0.26–1.26; \(p = 0.16; \hat{I}^2 = 0\%\)), although the overall mortality rate in the SCS group was higher than that in the HMP group – 12.3% (27/219) and 6.8% (10/146), respectively (Fig. 6). Similar results were seen in the graft loss rate analysis. The findings did not reach statistical significance (OR 0.63; 95% CI 0.33–1.22; \(p = 0.17; \hat{I}^2 = 0\%\)), but the graft loss rate was higher in the SCS (17.8% [39/219]) than 11.0% in the HMP group (16/146) (Fig. 7). We did not include 2 studies in this analysis. Patrono et al. [16] did not report these data for the SCS group. Van Rijn et al. [20] report only 6-month patient survival and graft loss; thus, we did not include it in this analysis.

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**Table 1**

| Study or Subgroup | HMP | SCS | Odds Ratio |
|-------------------|-----|-----|------------|
| **4.1.1 Oxygenated** |     |     |            |
| Schlegel [17] 2019 | 0   | 50  | 0.19 [0.01, 4.10] |
| Raviar [18] 2020  | 0   | 10  | 0.54 [0.02, 12.27] |
| Rayar [19] 2020   | 2   | 26  | 2.91 [0.38, 21.86] |
| Van Rijen [20] 2021 | 0 | 76  | 0.33 [0.01, 8.20] |
| Subtotal (95% CI) | 163 | 227 | 0.89 [0.22, 3.30] |
| Total events | 2   | 7   |             |
| Heterogeneity: \(\hat{\tau}^2 = 0.00; \hat{\chi}^2 = 2.81, df = 3 (P = 0.42); \hat{r} = 0\%\) Test for overall effect: \(Z = 0.22 (P = 0.83)\) |

**4.1.2 Non-oxygenated**

| Study or Subgroup | HMP | SCS | Odds Ratio |
|-------------------|-----|-----|------------|
| Guerrera [14] 2015 | 1   | 31  | 0.47 [0.04, 5.44] |
| Subtotal (95% CI) | 31  | 30  | 0.47 [0.04, 5.44] |
| Total events | 3   | 9   |             |
| Heterogeneity: Not applicable Test for overall effect: \(Z = 0.61 (P = 0.54)\) |
| Total (95% CI) | 194 | 257 | 0.75 [0.23, 2.43] |
| Heterogeneity: \(\hat{\tau}^2 = 0.00; \hat{\chi}^2 = 2.98, df = 4 (P = 0.56); \hat{r} = 0\%\) Test for overall effect: \(Z = 0.49 (P = 0.63)\) Test for subarous difference: \(\hat{\chi}^2 = 0.18, df = 1 (P = 0.67); \hat{r} = 0\%\) |

![Fig. 3. Forest plot of studies comparing OR of PNF between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel; PNF, primary non-function.](image-url)
Fig. 4. Forest plot of studies comparing OR of total biliary complications between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel.

Fig. 5. Forest plot of studies comparing OR of non-anastomotic biliary strictures between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel.
Fig. 6. Forest plot of studies comparing OR of graft loss within 12 months between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel.

Fig. 7. Forest plot of studies comparing OR of mortality within 12 months between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage.
Discussion/Conclusion

In this systematic review and meta-analysis, we overviewed the potential effects of MP on liver grafts in a clinical LTx setting. The primary aim was to perform quantitative analysis on both HMP and NMP studies. We included 6 studies that investigated the benefits of NMP, 2 of them were RCTs and the other 4 were observational studies. Due to high heterogeneity in study design and partly to technical variances of perfusion between studies, methodologically, we could not pool all studies into 1 analysis; thus, we decided only to present a qualitative analysis of studies examining NMP. The included studies revealed the potential of NMP to reduce graft injury and lower the liver graft discard rate, which allows broader utilization of liver from DCD [21–26].

From the meta-analysis performed on HMP studies, we concluded that the use of HMP reduces the rate of EAD, total biliary complications, and non-anastomotic biliary strictures compared to SCS. Although the 12-month graft and patient survival had a tendency to favor HMP, these long-term outcomes failed to reach statistical significance.

Currently, there is an ongoing discussion and criticism toward studies evaluating the role of MP in LTx [27, 28]. The main argument is that such studies should focus more on clinically relevant outcomes, for instance, patient survival, graft loss or ischemic cholangiopathy and not on surrogate outcomes, such as peak serum aminotransferase levels. There are studies showing that peak postoperative AST levels may have some value in predicting long-term postoperative outcomes [29]. However, it should be noted that they do not take into account the washout phenomena that occur, when liver is flushed with a large amount of preservation solution or reperfused and oxygenated during MP. Different metabolites, cytokines, and transaminases accumulate in the perfusion system but not in recipient right after the transplantation [30–32]. Thus, such predictive models cannot be used to accurately evaluate the effects of MP on the quality of the liver.

Currently, there is a lack of literature quantitatively analyzing the benefits of MP. Porcine models were a crucial part in bringing MP studies to the clinics; thus, meta-analyses by Bian et al. and Nостедт et al. try to summarize the effects of NMP on porcine liver [33, 34]. Both meta-analyses concluded that NMP is superior to SCS in preserving the liver architecture and function; unfortunately, only short-term outcomes, such as the postoperative levels of ALT and AST or bile production, were available for analysis. The first meta-analysis on human studies was conducted by Zhang et al. [35], and it found that HMP could significantly reduce the incidence of EAD and biliary complications. However, this meta-analysis includes overlapping studies possibly magnifying the true protective effects of HMP. A recent meta-analysis by Jia et al. [36] overcomes this issue and analyzes both HMP and NMP against SCS. They concluded that the incidence of EAD and biliary complications were significantly lower in recipients with MP preservation. Although they performed a subgroup analysis with HMP and NMP, a meta-analysis trying to draw conclusions about the whole clinical MP field is pointless due to enormous heterogeneity of the studies and completely different underlying aims and mechanisms of both MP types [7].

Our study has some limitations, which should be considered. First of all, most of the included studies were nonrandomized; however, they all were case-matched for at least donor age, type (DCD and DBD), and recipient’s MELD score. Furthermore, most of them showed moderate risk of bias when assessed with the ROBINS-I tool. To be noted, studies by Dutkowski et al. [13] and Schlegel et al. [17] were evaluated as having a severe risk of bias, due to differences of immunosuppression therapy between the HMP and SCS groups. In this case, we tested the robustness of our data by conducting a sensitivity analysis, and we did not see significant changes in our results. Second, different perfusion settings were applied in included studies. We tried to partly overcome this limitation by performing a subgroup analysis according to whether additional oxygenation was used or not during MP.

These previously mentioned MP types are technically very different with their own specific advantages and disadvantages. NMP simulates normal liver cell metabolism, which allows for better organ viability assessment [7, 37]. Furthermore, NMP can be utilized for organ repair as different therapeutic agents are currently being investigated [37]. On the other hand, user or device error when using NMP has serious consequences, quite often leading to graft loss. The aforementioned drawback is not that meaningful in the use of HMP as the organ is in a reduced metabolism state. Moreover, the lower initial cost and promising first results make HMP a strong contender to NMP. There is an ongoing trial (NCT04644744) directly evaluating HOPE versus NMP in LTx, which may further highlight the drawbacks and benefits of these MP types.

This research area still lacks high-quality data from randomized trials. Currently, there are only 2 published RCTs, and both of them analyze NMP [24, 25]. The results from several currently ongoing or completed RCTs examining the use of HMP are eagerly awaited (NCT01317342, NCT03484455, NCT03837197, NCT03929523, and NCT03124641).

The current critical liver donation situation prompts the use of ECD or DCD donors with inferior overall re-
sults [38]. The routine use of MP systems could not only increase the quality of these suboptimal liver grafts but also broaden the potential donor pool helping to narrow the gap between organ availability and demand [7].

In conclusion, our systematic review and meta-analysis revealed that the use of HMP reduces the rate of EAD and non-anastomotic biliary strictures compared to SCS. Additionally, the currently available literature shows the potential of NMP to reduce graft injury and lower liver graft discard rate. These findings may provide guidance in choosing the optimal liver preservation method before transplantation.

**Statement of Ethics**

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

**Conflict of Interest Statement**

The authors have no conflicts of interest to declare.

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