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

Matas Jakubauskas[a, b] Lina Jakubauskiene[a, b] Bettina Leber[a]
Kestutis Strupas[b] Philipp Stiegler[a] Peter Schemmer[a]

[a]General, Visceral and Transplant Surgery, Department of Surgery, Medical University of Graz, Graz, Austria;
[b]Faculty of Medicine, Vilnius University, Vilnius, Lithuania

Keywords
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; $p = 0.001$; $I^2 = 0\%$) and non-anastomotic biliary strictures (OR 0.34; 95% CI 0.17–0.67; $p = 0.002$; $I^2 = 0\%$) 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.

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]

Lina Jakubauskiene and Matas Jakubauskas contributed equally to this article.

karger@karger.com
www.karger.com/vis

Correspondence to:
Philipp Stiegler, philipp.stiegler@medunigraz.at

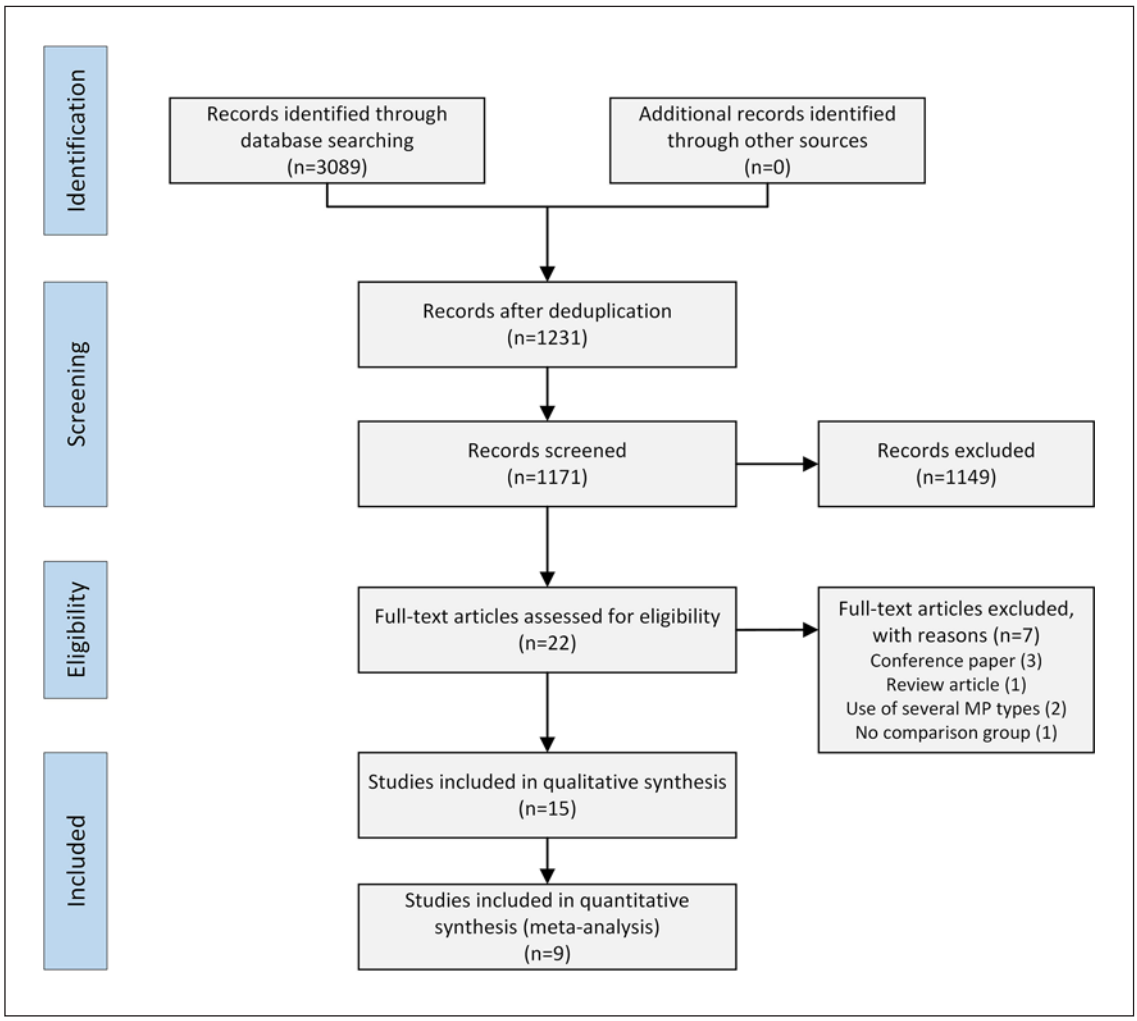

Fig. 1. PRISMA flowchart of study selection process. MP, machine perfusion.

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-

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® Temperature: 37°C Perfusate: pRBC + coloid solution (Gelofusine®) + additives 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 2. Similar 30-day graft and patient survival in both groups 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® Temperature: 37°C Perfusate: pRBC + albumin and dextran based steen solution + additives Postperfusion: n.r.	8 (5.7–9.7)*	N/A versus 10.5 (8.7–13.1)*	1. Steen solution as a perfusate is safe for NMP 2. Similar postoperative graft function, ICU and hospital stay 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® Temperature: 37°C Perfusate: pRBC + coloid solution (Gelofusine®) + additives Postperfusion: flushed with cold HTK solution	11.5 (3.3–22.5)*	2.8 (1.6–4.9)* versus 3.9 (1.1–14.8)*	1. Similar 30-day and 6-month graft and patient survival 2. ICU and hospital stay significantly longer in NMP group 3. Similar postoperative graft function
Nasralla et al. [24]	Multicenter RCT	NMP versus SCS	121 versus 101	DBD, DCD	Device: OrganOx metra® Temperature: 37°C Perfusate: pRBC + coloid solution (Gelofusine®) + additives 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 2. No difference in 1-year graft and patient survival 3. Significantly lower EAD and post-reperfusion syndrome rate
Ghinolfi et al. [25]	Single-center RCT	NMP versus SCS	10 versus 10	DBD (>70 years)	Device: LiverAssist® Temperature: 37°C Perfusate: pRBC + coloid solution (Gelofusine®) + human albumin + additives Postperfusion: flushed with 2 L of Celsior® 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 2. Similar complication rate and hospital stay in either group 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 Temperature: 36°C Perfusate: FFP, pRBC, albumine + additives 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).

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Table 2. Characteristics of clinical HMP 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
Guarrera et al. [12]	Case-matched 1:1 study	HMP versus SCS	20 versus 20	DBD	Device: Modified Medtronic PBS® device Temperature: 4–8°C Perfusate: Vasosol® Postperfusion: flush with 1 L Hextend® solution	4.3±0.9	9.4±2.1 versus 8.9±2.8	1. Safety and feasibility of clinical HMP use 2. Mean hospital stay significantly shorter in the HMP group 3. Peak serum AST, ALT, TBili and SCr levels significantly lower in the HMP group
Dutkowski et al. [13]	Case-matched 1:2:2 study	HOPE versus SCS-DCD versus SCS-DBD	25 versus 50 versus 50	DCD, DBD	Device: ECOPS device (OrganAssist®) Temperature: 10°C Perfusate: UW gluconate solution Postperfusion: n.r.	2.2**	5.3 (4.7–6.5) versus 6.6 (5.8–7.5) versus 5.8 (4.8–7.1)	1. Significantly lower ALT levels 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
Guarrera et al. [14]	Case-matched 1:1 study	HMP versus SCS	31 versus 30	ECD-DBD	Device: Modified Medtronic PBS® device Temperature: 4–8°C Perfusate: Vasosol® Postperfusion: Flush with 1–1.5 L Hextend® solution	3.8±0.9	9.3±1.6 versus 8.6±2.4	1. Significantly lower total biliary complication rate in the HMP group 2. Mean hospital stay significantly shorter in the HMP group
Van Rijn et al. [15]	Case-matched 1:2 study	DHOPE versus SCS	10 versus 20	DCD	Device: LiverAssist® Temperature: 10°C Perfusate: Belzer MPS® UW MP solution supplemented with 3 mmol/L glutathione Postperfusion: in situ flush of 500 mL of recipient's blood	2.1 (2.1–2.3)	8.7 (7.8–9.9) versus 8.4 (7.9–8.8)	1. Safety and feasibility of clinical DHOPE use 2. During DHOPE median ATP levels significantly increased 11 fold 3. ALT and bilirubin levels at 1 week after transplantation were 2 fold lower in the DHOPE group
Patrono et al. [16]	Case-matched 1:2 study	DHOPE versus SCS	25 versus 50	ECD-DBD	Device: LiverAssist® Temperature: ~10°C Perfusate: Belzer MPS® UW MP solution postperfusion: n.r.	3.1±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
Schlegel et al. [17]	Case-matched 1:1:1	HOPE versus SCS-DCD versus SCS-DBD	50 versus 50 versus 50	DCD, DBD	Device: LiverAssist® Temperature: 10–12°C Perfusate: Belzer MPS® UW MP solution Postperfusion: n.r.	2 (1.6–2.4)	4.4 (3.5–5.2) versus 4.7 (4.3–5.3) versus 5 (4–5)	1. HOPE-treated DCD liver grafts had a significantly higher graft survival rate than untreated DCD liver transplants
Ravaioli et al. [18]	Case-matched 1:3	HOPE versus SCS	10 versus 30	ECD, DBD	Device: institutionally developed perfusion machine Temperature: 4°C Perfusate: Belzer MPS® UW MP solution Postperfusion: n.r.	2.2 (1–3.5)*	7.1 (6.1–9.6)* versus 7 (5.4–10)*	1. Median AST levels on postoperative day 7 were significantly lower in the HOPE-treated liver transplants
Rayar et al. [19]	Case-matched 1:3	HOPE versus SCS	25 versus 69	ECD, DBD	Device: LiverAssist® Temperature: 11°C Perfusate: Belzer MPS® UW MP solution postperfusion: Flush with 500 mL of 5% albumin	2.0 (1.3–4.2)*	6.8 (4.2–9.4)* versus 9.3 (3.5–12.0)*	1. Median hospital and ICU stay significantly lower in the HOPE-treated liver transplants
Van Rijn et al. [20]	Multicenter RCT	DHOPE versus SCS	78 versus 78	DCD	Device: LiverAssist® Temperature: 10°C Perfusate: Belzer MPS® UW machine perfusion solution supplemented with 3 mmol/L glutathione	2.2 (2–2.5)	6.2 (5.2–6.9) versus 6.9 (5.9–8.0)	1. Lower incidence of symptomatic non-anastomotic biliary strictures 2. Lower risk of post-reperfusion syndrome and early allograft dysfunction

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; SCS, 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.

Table 3. Risk of bias assessment of included nonrandomized studies using the ROBINS-I tool

	Confounding	Selection of participants	Classification of interventions	Deviation from intended intervention	Missing data	Measurement of outcomes	Selection of the reported results	Overall risk of bias judgment
NMP studies								
Ravikumar et al. [21]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Selzner et al. [22]	Moderate	Serious	Low	Low	Low	Low	Low	Serious
Bral et al. [23]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Liu et al. [26]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
HMP studies								
Guarrera et al. [12]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Dutkowski et al. [13]	Moderate	Low	Low	Serious	Low	Low	Low	Serious
Guarrera et al. [14]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Van Rijn et al. [15]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Patrono et al. [16]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Schlegel et al. [17]	Moderate	Low	Low	Serious	Low	Low	Low	Serious
Ravaioli et al. [18]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Rayar et al. [19]	Moderate	Low	Low	Low	Low	Low	Low	Moderate

NMP, normothermic machine perfusion; HMP, hypothermic machine perfusion.

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 I^2 test was used to measure statistical heterogeneity. If a study observed no event in either group, it was not included in the quantitative analysis.

Results

Study Selection and Characteristics

Literature search results and the 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.

Study Quality

All included nonrandomized studies, except one, showed moderate risk of bias (Table 3). The intervention domain in studies by Dutkowski et al. [13] and Schlegel et al. [17] was evaluated as having serious risk of bias due to differences of immunosuppression therapy between the HMP and SCS groups. These cohorts were included from different transplant centers; immunosuppression differed between the groups, and this may have affected the outcomes. The methodological quality of the 3 included randomized studies is summarized in Table 4.

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

Table 4. Risk of bias assessment of included randomized studies using the ROBINS 2 tool

	Randomization process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall risk of bias judgment
NMP studies						
Nasralla et al. [24]	Low	Some concerns	Low	Low	Low	Some concerns
Ghinolfi et al. [25]	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
HMP studies						
Van Rijn et al. [20]	Low	Some concerns	Low	Low	Low	Some concerns

NMP, normothermic machine perfusion; HMP, hypothermic machine perfusion.

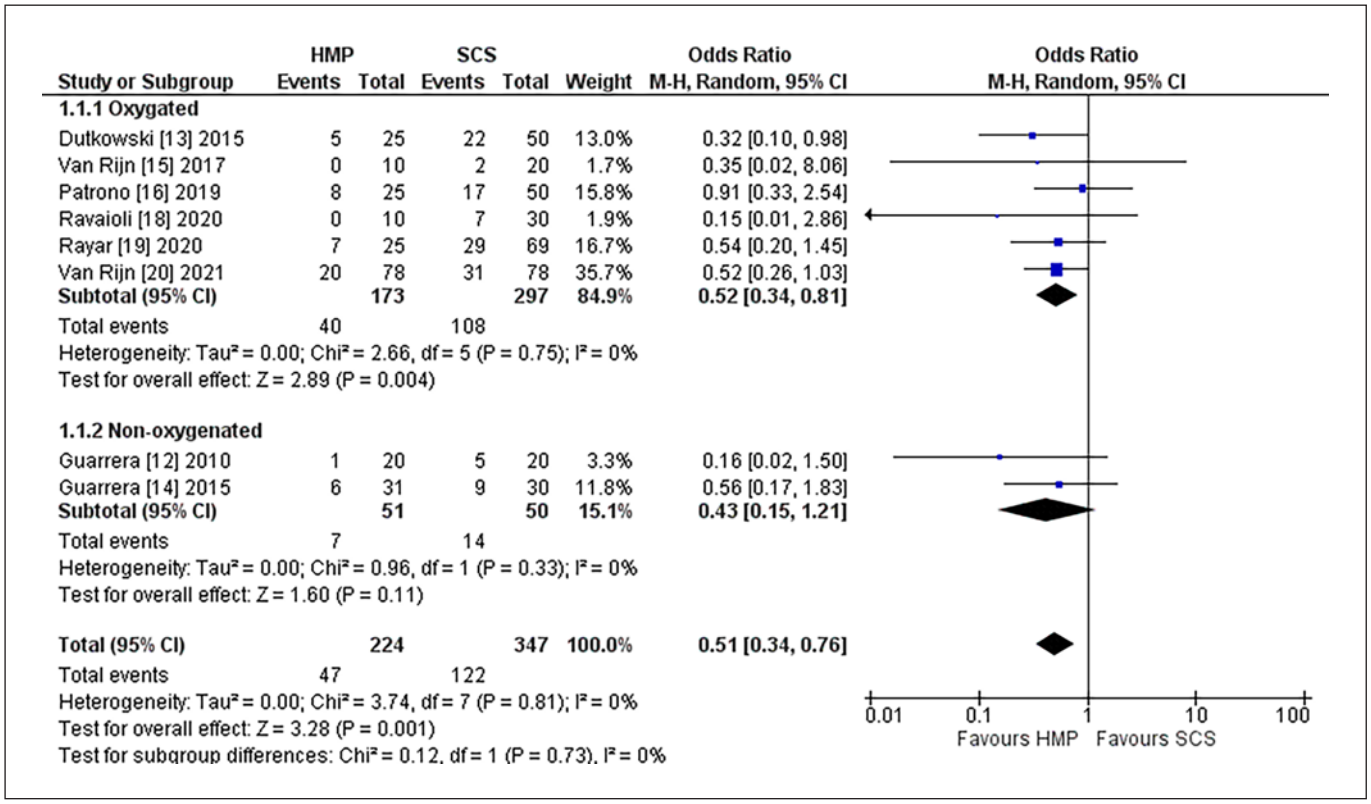

Fig. 2. Forest plot of studies comparing OR of EAD between HMP and SCS groups. OR, odds ratio; EAD, early allograft dysfunction; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel.

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

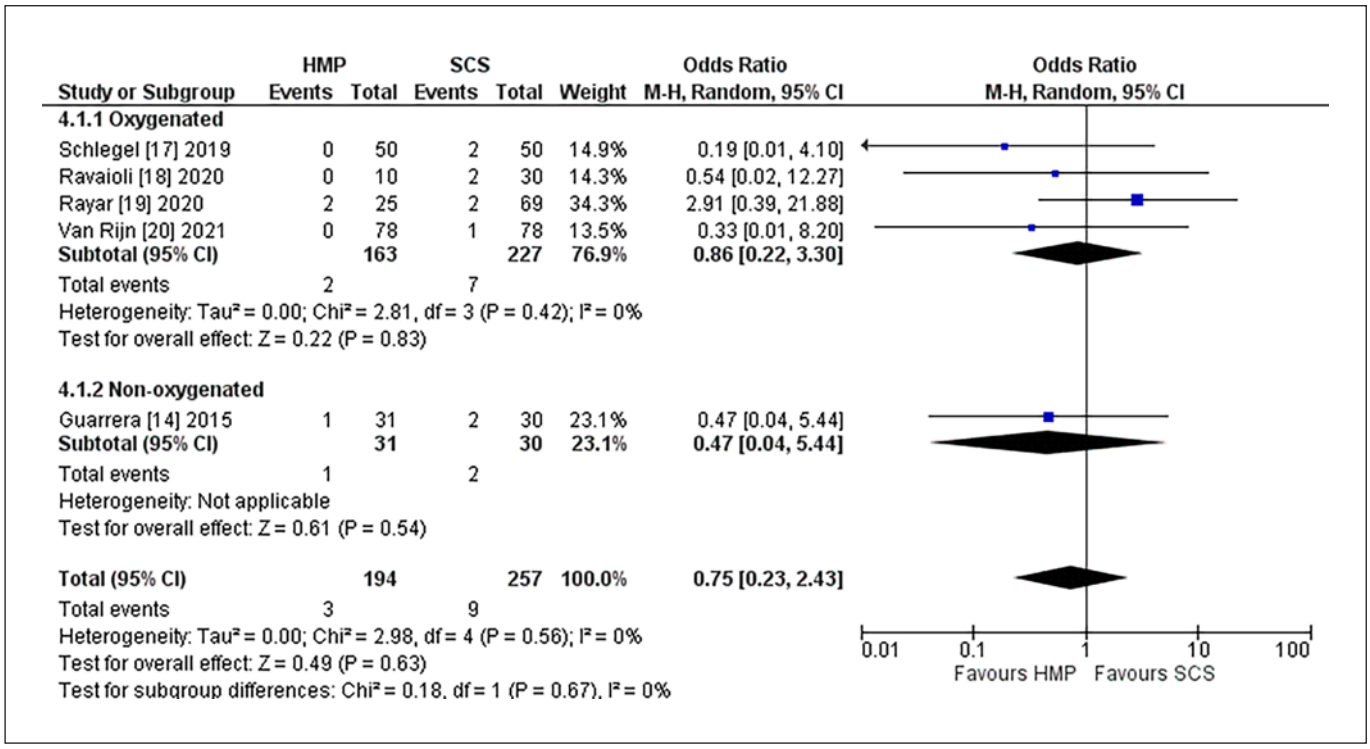

Fig. 3. Forest plot of studies comparing OR of PNF between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel; PNF, primary nonfunction.

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; $p = 0.001$; $I^2 = 0\%$) (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; $p = 0.63$; $I^2 = 0\%$) (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; $p = 0.02$; $I^2 = 0\%$) (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; $p = 0.002$; $I^2 = 0\%$), 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, Guarrera 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; $p = 0.16$; $I^2 = 0\%$), 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; $p = 0.17$; $I^2 = 0\%$), 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.

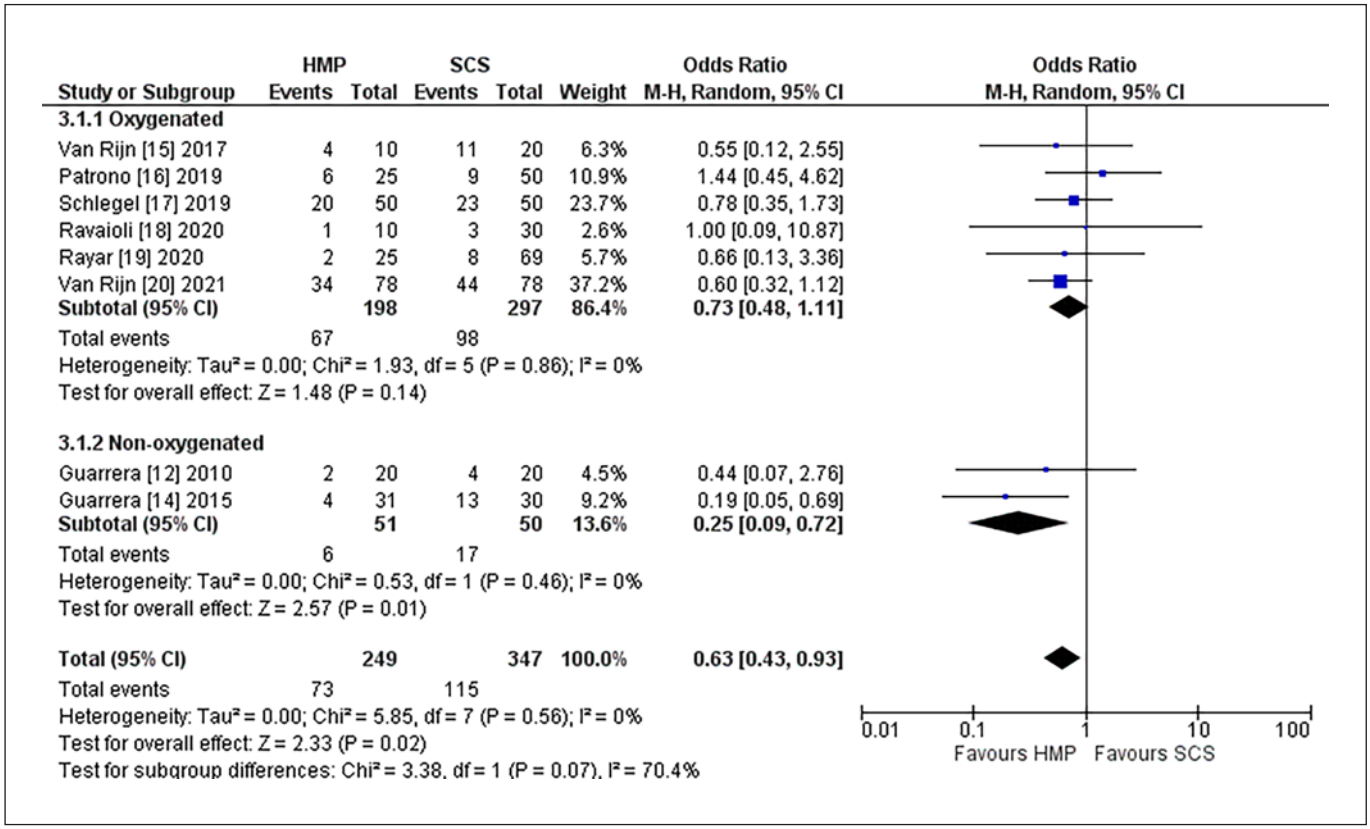

Fig. 4. Forest plot of studies comparing OR of total biliary complications between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel.

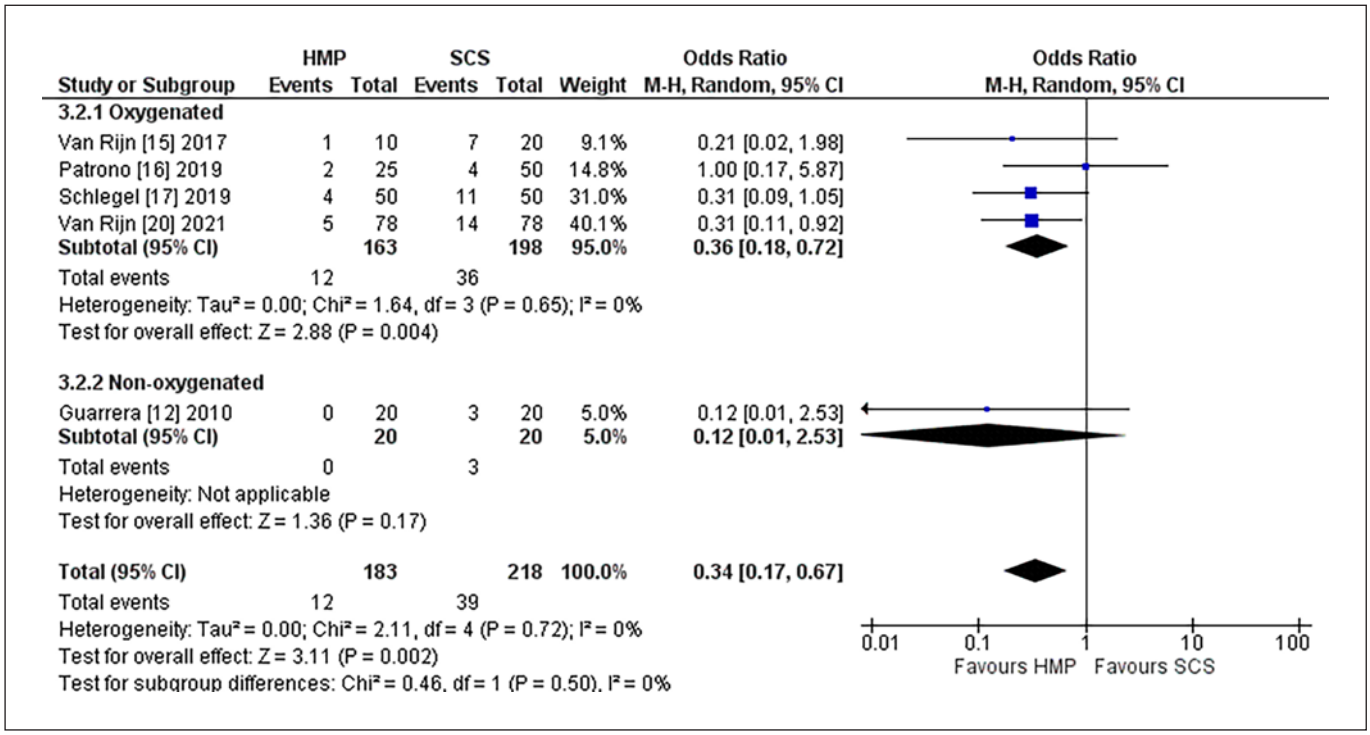

Fig. 5. Forest plot of studies comparing OR of non-anastomotic biliary strictures between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel.

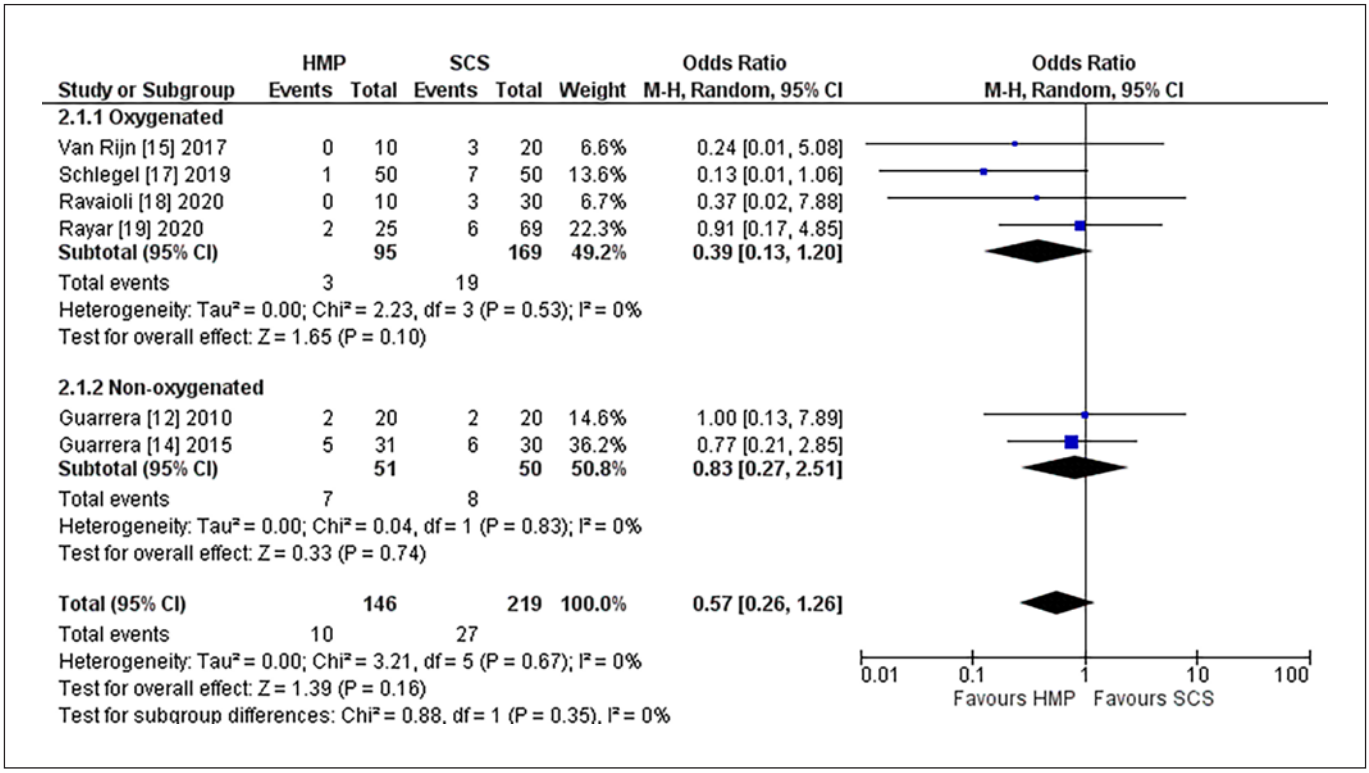

Fig. 6. Forest plot of studies comparing OR of graft loss within 12 months between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage; CI, confidence interval; M-H, Mantel-Haenszel.

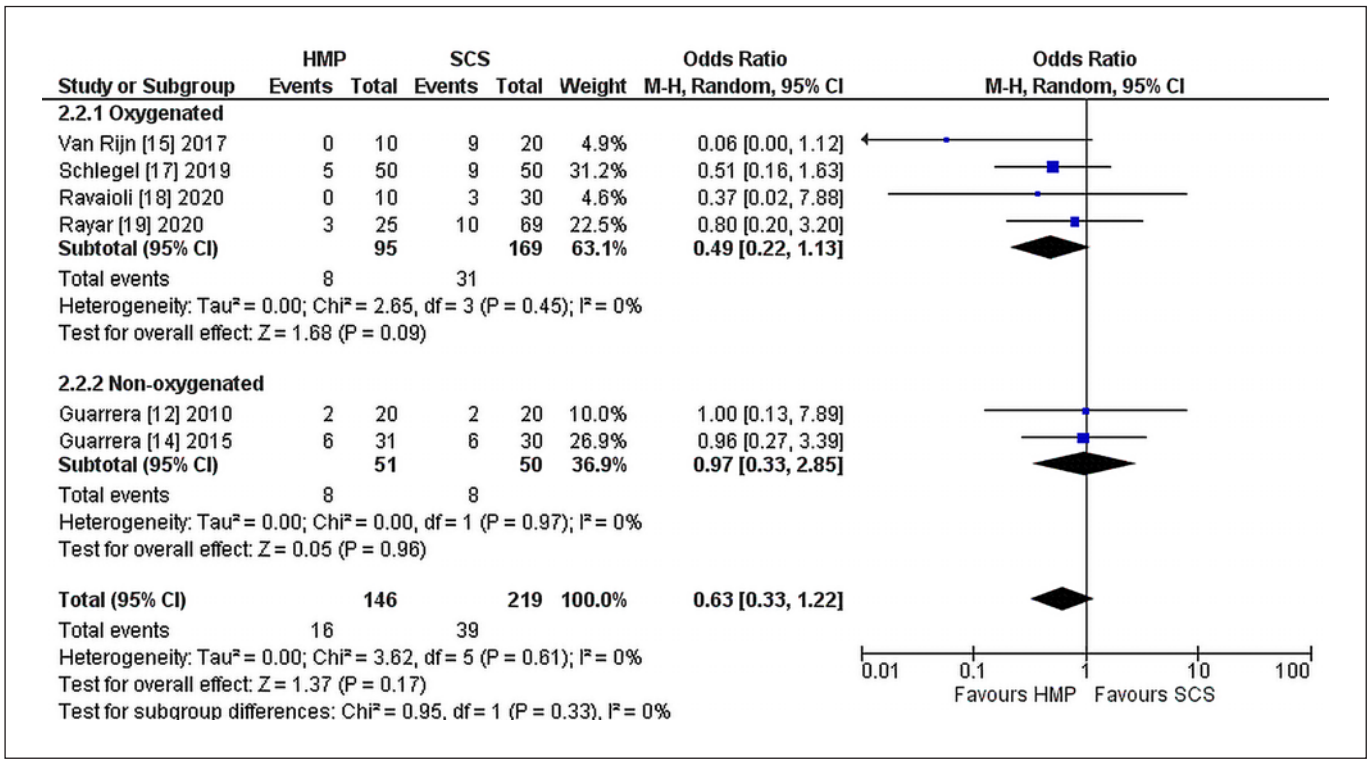

Fig. 7. Forest plot of studies comparing OR of mortality within 12 months between HMP and SCS groups. OR, odds ratio; HMP, hypothermic perfusion; SCS, static cold storage.

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 Nostedt 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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Author Contributions

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

Data Availability Statement

Data are available on reasonable request. All data relevant to the study are included in the article or uploaded as online supplementary information. De-identified data, which underlie the results reported in this article, will be shared with third parties after written request to the corresponding author describing intention of data usage and full affiliation of the requesting organization.

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