Does machine perfusion improve immediate and short-term outcomes by enhancing graft function and recipient recovery after liver transplantation? - A systematic review of the literature, meta-analysis and expert panel recommendations

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REVIEW ARTICLE

Does machine perfusion improve immediate and short-term outcomes by enhancing graft function and recipient recovery after liver transplantation? A systematic review of the literature, meta-analysis and expert panel recommendations

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Abstract

Background: Recent evidence supports the use of machine perfusion technologies (MP) for marginal liver grafts. Their effect on enhanced recovery, however, remains uncertain.

Objectives: To identify areas in which MP might contribute to an ERAS program and to provide expert panel recommendations.

Data sources: Ovid MEDLINE, Embase, Scopus, Google Scholar, and Cochrane Central.

Methods: Systematic review and meta-analysis following PRISMA guidelines and recommendations using the GRADE approach. CRD42021237713

Results: Both hypothermic (HMP) and normothermic (NMP) machine perfusion demonstrated significant benefits in preventing postreperfusion syndrome (PRS) (HMP OR .33, .15-.75 CI; NMP OR .51, .29-.90 CI) and early allograft dysfunction (EAD) (HMP OR .51, .35-.75 CI; NMP OR .66, .45-.97 CI), while shortening LOS (HMP MD -3.9; NMP MD -12.41). Only NMP showed a significant decrease in the length of ICU stay (L-ICU) (MD -7.07, -8.76; -5.38 CI), while only HMP diminishes the likelihood of major complications. Normothermic regional perfusion (NRP) reduces EAD (OR .52,

.38–.70 CI) and primary nonfunction (PNF) (OR .51, .27-.98 CI) without effect on L-ICU and LOS.

Conclusions: The use of HMP decreases PRS and EAD, specifically for marginal grafts. This is supported by a shorter LOS and a lower rate of major postoperative complications (QOE; moderate | Recommendation; Strong). NMP reduces the incidence of PRS and EAD with associated shortening in L-ICU for both DBD and DCD grafts (QOE; moderate | Recommendation; High) This technology also shortens the length of hospital stay (QOE; low | Recommendation; Strong). NRP decreases the likelihood of EAD (QOE; moderate) and the risk of PNF (QOE; low) when compared to both DBD and SRR-DCD grafts preserved in SCS. (Recommendation; Strong).

KEYWORDS

hypothermic machine perfusion (HMP), hypothermic oxygenated liver perfusion, hypothermic oxygenated perfusion (HOPE), liver transplant, liver transplantation, machine and perfusion, normothermic machine perfusion (NMP), normothermic regional machine perfusion, normothermic regional perfusion (NRP), organ preservation

1 | INTRODUCTION

Liver transplantation is the standard treatment of choice for end-stage liver disease.[1] Recent years have seen increasing organ donation in several countries, although this is still insufficient to meet current demands. For example, approximately 12% of patients in the UK died or had to be removed from the liver transplant list due to their deteriorating condition.[2] In addition, delays in transplantation may compromise surgical outcomes due to deterioration in the condition of patients whilst waiting.

These pressures have led to an increased use of marginal or extended criteria donor organs (ECD), including those from older brainstem death donors (DBD) and those retrieved after circulatory death (DCD). With this, has come an inevitable increase in complications such as EAD, primary nonfunction (PNF) and ischemic cholangiopathy.[3] To mitigate the effects of using ECD organs, clinicians and medical device companies have developed novel technologies that might reduce the damage occurring during the retrieval, preservation and reperfusion process, also allowing us to assess and recondition the organ before its use and prolong the duration for which a liver can be preserved.[4–6]

Recent years have seen fairly rapid development and adoption of these novel preservation techniques by the liver transplant community. This technological boost has led to the publication of a considerable number of both high and low-quality research articles with a degree of contradictory information. Herein we seek to appraise the breadth of evidence in this field to assess the capacity of machine perfusion (MP) to improve immediate and short-term outcomes after liver transplantation.

We performed a systematic review and meta-analysis with the objective of answering such questions according to the current available evidence.

This work was conducted in preparation for the ILTS - ERAS4OLT.org Consensus Conference on Enhanced Recovery for Liver Transplantation, January 2022, Valencia, Spain.

2 | METHODS

2.1 | Protocol and registration

The systematic review protocol was registered at PROSPERO (CRD42021237713).

2.2 | Eligibility criteria

Publications included are those based on adult patients with end-stage liver disease who underwent a cadaveric orthotopic liver transplantation following a MP intervention, including normothermic regional perfusion (NRP) and ex-situ hypothermic and normothermic perfusion. Reports of transplants using livers from both DBD and DCD organ donors were included. Those relating to split-livers and patients undergoing living donor liver transplantation were excluded.

2.3 | Information sources and search

A literature search was conducted in February 2021 through the online Ovid MEDLINE, Embase, Scopus, Google Scholar, Clinical.Trials.gov and the Cochrane Central Register of Controlled Trials. The search algorithm ("normothermic machine perfusion" OR NMP OR Organox OR "hypothermic machine perfusion" OR HMP OR "hypothermic oxygenated liver perfusion" OR "hypothermic oxygenated perfusion" OR HOPE OR (machine AND perfusion) OR "normothermic regional perfusion" OR normothermic regional machine perfusion) AND ((liver OR hepatic) AND (transplant OR transplantation)) was employed. There were no language or publication year limitations. Studies reporting on pediatric populations and/or conference abstracts were excluded.

Titles and abstracts were screened, full-text articles were retrieved and eligibility was assessed by two independent reviewers. Any discrepancies were resolved by consensus. Reference lists of the included

studies were manually searched to extract any potentially relevant studies.

2.4 | Study selection

Studies comparing any of the MP techniques against the current gold standard, static cold storage (SCS), were included in this systematic review. Publications comparing one type of MP with another or those using sequential MP techniques (such as NRP followed by HMP, or HMP followed by NMP) were excluded. This was decided because the main purpose of this study is to assess the effect of MP on the ERAS pathway against the current standard in organ donation and preservation (SCS).

Observational studies and other publications reporting their data in medians and interquartile range were excluded from meta-analysis. The remaining studies were included provided the patient cohorts did not overlap substantially with those used in other publications.

2.5 | Meta-analyses

The meta-analyses were performed using R version 3.3.2 (R Core Team, GNU GPL v2 License, Boston, MA, 2016), R Studio version 1.0.44 (RStudio, Inc. GNU Affero General Public License v3, Boston, MA, 2016) with the graphical user interface (GUI) rBiostatistics.com alpha version (rBiostatistics.com, London, UK, 2017).[7]

2.6 | Quality of studies and recommendations grading

The "Grading of Recommendations Assessment, Development and Evaluation" (GRADE) approach was used for grading quality of evidence (QOE) and strength of recommendations.[8] The GRADE system was designed to provide a comprehensive and structured approach to rating the QOE for systematic reviews, and to grade the strength of recommendations for development of guidelines in health care. We applied the modified GRADE approach for QOE assessment derived from systematic reviews using estimates summarized narratively.[9] The QOE was rated separately for each outcome. The direction and strength of recommendation was assessed individually by all authors and disagreements resolved by consensus.[10,11]

3 | RESULTS

3.1 | Study selection

One thousand eight hundred and forty articles were identified through database searching. Removal of duplicates narrowed the records to 859. From these, 86 articles were assessed for eligibility and 45 initially included. Following the initial consensus meeting between the panel members, seven further articles were excluded because of (i) different MP techniques without including an SCS arm or (ii) sequential use of different perfusion technologies. A total of 38 articles were included in the systematic review. Ten of these were excluded from the meta-analysis due to overlap of cohorts used in different studies and the exclusion of observational studies (Figure 1).

3.2 | Study characteristics

Tables 1–3 report the study characteristics.

3.3 | Results of individual studies

Tables 4–7 lists the results of the individual studies.

3.4 | Quality of evidence

The summary of findings for the main outcomes, including the QOE assessment according to the GRADE approach are summarized in Tables 8–14.

3.5 | Meta-analysis

The use of MP in liver transplantation has shown, across a number of studies of variable quality, to have a positive effect in relation to several events, many of which are relevant to the early postoperative recovery of patients after liver transplantation.

The overall outcome for HMP livers compared to those preserved using SCS (both DBD and DCD) revealed a significant decrease in the incidence of postreperfusion syndrome (PRS) (OR .33, .15–.74 95% CI, $p = .0071$; heterogeneity $p = .44988$; Supplemental Figure S1a), early allograft dysfunction (OR .51, .35–.75 95%CI, $p = .0006$; heterogeneity $p = .9227$; Supplemental Figure S1b) and length of hospital stay (MD -3.9, -5.92; -1.89 95%CI $p = .0001$; heterogeneity $p = .0184$; Supplemental Figure S1c). In addition, HMP was associated with lower peak transaminases after transplantation for ALT (MD -314.19, -492.38; -35.99 95%CI, $p = .0005$; heterogeinity $p = .043$; Supplemental Figure S1d). No difference was found for primary nonfunction (OR .73, .26–2.03 95%CI, $p = .545$; heterogeneity $p = .7514$; Supplemental Figure S1e), the need for postoperative renal replacement therapy (RRT) (.88, .5–1.56 95%CI, $p = .6727$; heterogeneity $p = .9077$; Supplemental Figure S1f) and the length in ICU stay (MD -.21, -1.71; 1.27 95% CI, $p = .772$; heterogeneity $p = .4289$; Supplemental Figure S1g).

In order avoid indirectness, an individual subgroup analysis was carried out, comparing HMP separately against DBD or DCD liver grafts preserved using SCS. This subgroup analysis is best depicted in the forest plot, in which a comparison of HMP against DBD livers revealed a lower postoperative peak in both ALT (MD −238.29, −448.59; −27.99 95%CI $p = .0264$; heterogeneity $p = .0646$; Supplemental Figure S2a)

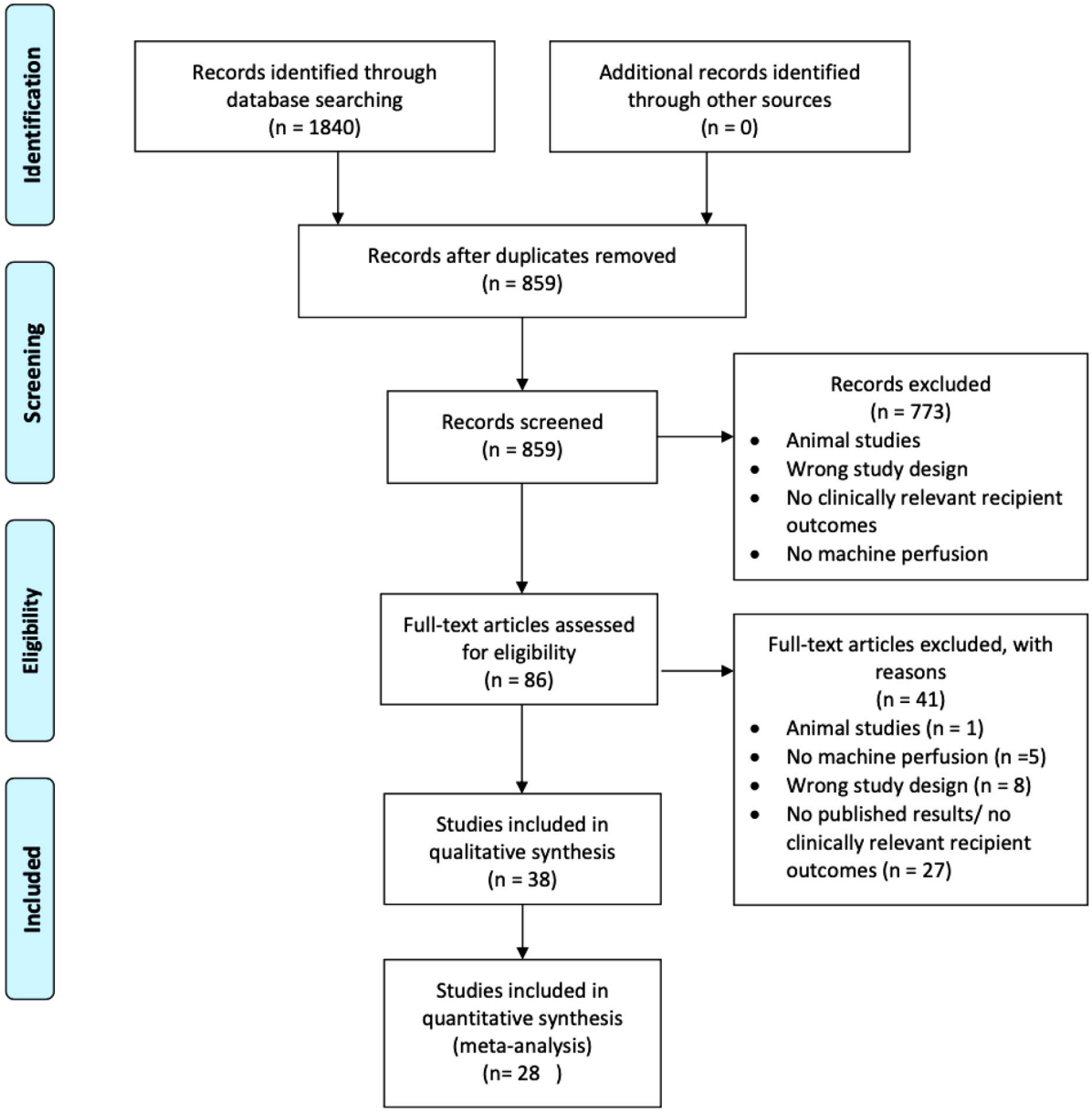

FIGURE 1 Systematic review flow diagram

and AST (MD −389.28, −647.38; −131.17 95% CI $p = .0031$; heterogeneity $p = .0425$; Supplemental Figure S2b). In addition, the use of HMP was associated with a lower likelihood of developing EAD (OR .56, .35–.9 95% CI $p = .0161$; heterogeneity .7171; Supplemental Figure S2c) and shorter length of hospital stay (MD-3.82, -5.95; −1.7 95%CI $p = .0004$; heterogeneity .0052; Supplemental Figure S2d) when compared to DBD grafts preserved by SCS. There was no significant difference for this specific type of graft in PNF (OR .89, .29–2.71 95%CI $p = .8336$; heterogeneity $p = .7230$; Supplemental Figure S2e), RRT (OR 1.03, .48–2.23 95%CI $p = .9336$; heterogeneity $p = .3711$; Supplemental Figure S2f) and length in ICU stay (MD −.02, −1.71–1.65 95%CI $p = .9805$; heterogeneity $p = .1105$; Supplemental Figure S2g).

Similarly, and with a higher degree of effect, HMP prevented EAD (OR .45, .25–.79 95%CI $p = .0059$; heterogeneity $p = .7510$; Supplemental Figure S3a) and revealed a lower postoperative peak in ALT (MD -507.37, −842.88; −171.85 95% CI $p = .0030$; heterogeneity $p = .1071$; Supplemental Figure S3b) specifically when compared in the context of DCD livers. No difference was found in PNF (OR .24, .03–2.21 95%CI $p = .2094$; heterogeneity $p = .8117$; Supplemental Figure S3c), the need for RRT (OR .82, .4–1.67 95%CI $p = .5882$; heterogeneity $p = .8646$; Supplemental Figure S3d) and the length of ICU (MD −.87, −3.97; 2.24 95%CI $p = .5846$; heterogeneity $p = .9762$; Supplemental Figure S3e) and hospital stay (MD -4.63, −11.04; 1.78 95%CI $p = .1570$; heterogeneity $p = .5129$; Supplemental Figure S3f). Moreover, PRS was only reported in the RCT of Van Rijin et al., with a favorable outcome toward HMP (RR .43, .2–.91).[22] The remaining outcome data were reported in medians with IQR and as such an analysis was not possible to perform.

TABLE 1 Study characteristics HMP

Study	Study type	No. of patients	Main outcomes assessed
Guarrera, 2010[6]	Prospective cohort study, historic control matched	20 DBD HMP 20 DBD SCS	• PNF • EAD • Vascular complications • Bile leak and stricture • Hepatic artery stenosis • Length of hospital stay Peak AST, ALT, Bili, Cr, INR
Dutkowski, 2015[12]	Prospective cohort study, historic control Matched 1:2	25 DCD HOPE 50 DCD SCS 50 DBD SCS	• Peak ALT, AST, Bilirubin, Cr • RRT • EAD • PNF • HAT • LOS • L-ICU • 3-months ALP
Guarrera, 2015[13]	Prospective cohort study, historic control Matched 1:1	31 EC-DBD DHOPE30 EC-DBD SCS	• PNF • EAD • HAT and PVT • Bile leak and strictures • Reoperation for bleeding • AKI • LOS • AST, ALT, Bili, INR, Cr post LTx
Van Rijn, 2017[14]	Prospective cohort, clinical pilot study	10 DCD DHOPE 20 DCD SCS	• 6 and 12 months GS and PS • Peak serum ALT, PT, lactate • EAD • Serum bilirubin POD7 • L-ICU • LOS
Patrono, 2019[15]	Retrospective comparative cohort, propensity score matched	25 DBD HOPE 50 DBD SCS	• PRS • Peak ALT & AST • EAD • AKI • RRT
Schlegel, 2019[16]	Retrospective matched cohort	50 DCD HOPE 50 DBD SCS 50 DCD SCS	• Peak ALT • PNF • RRT • L-ICU • LOS • 5-year graft survival • CCI within 1-year post-transplant • Overall complications
Muller, 2019[17]	Single arm, 'futile'	21 DCD HOPE	• Peak ALT & AST • EAD • PNF • RRT • L-ICU • LOS • Complications • 1 year PS & GS

(Continues)

TABLE 1 (Continued)

Study	Study type	No. of patients	Main outcomes assessed
Rayar, 2020[18]	Prospective cohort, propensity score matched control group	25 EC-DBD HOPE 69 EC-DBD SCS	• Peak AST • EAD • PNF • Post op lactate and Cr • L-ICU • LOS • 1 year PS & GS • Cost
Ravaioli, 2020[19]	Prospective cohort historic control, Matched 1:3	10 EC-DBD HOPE 30 EC-DBD SCS	• Peak AST • PNF • EAD • LOS • C-D complications • 1 year GS
Patrono, 2020[20]	Retrospective Observational	50 DBD D-HOPE	• ALT & AST peak • EAD • AKI 2–3 • L-GrAFT • GS
Czigany, 2021[21]	Randomized Controlled Trial	23 DBD HOPE 23 DBD SCS	• Peak ALT & AST • PNF • EAD • RRT • ICU & LOS • Dindo-Clavien Complications • 1 year GS and PS
Van Rijn, 2021[22]	Randomized Controlled Trial	78 DCD DHOPE 78 DCD SCS	• Peak ALT • PRS • EAD • PNF • RRT • LOS • L-ICU • Nonanastomotic biliary strictures • PS & GS

A similar subgroup analysis was not possible for normothermic machine perfusion (NMP) due to the homogeneity across studies, most of which included both DCD and DBD livers in both the intervention and control group. The use of NMP as a way of preservation had positive effects in most of the outcomes, except for PNF (OR 1.3, .16–10.56 95% CI $p = .8030$; heterogeinity $p = .5576$), the need for RRT after surgery (OR 1.16, .61–2.23 95% CI $p = .9151$; heterogeneity $p = .4488$) and the frequency of major complications (Dindo-Clavien ≥ 3) (OR .49, .08–2.81 95% CI $p = .3671$; heterogeinity $p = .6878$). The use of NMP was associated with a decreased likelihood of PRS (OR .51, .29–.9 95% CI $p = .0192$; heterogeneity $p = .227$; Supplemental Figure S4a) and EAD (OR .66, .45–.97 95%CI $p = .0334$; heterogeneity $p = .020$; Supplemental Figure S4b), a shorter length of ICU stay (MD −7.07, −8.76; −5.38 95%CI $p < .0001$; heterogeneity $p < .0001$; Supplemental Figure S4c) and hospital stay (MD −12.41, −17.36; −7.46 95%CI $p < .0001$; heterogeneity $p = .0041$; Supplemental Figure S4d). In addition, NMP was associated with lower peak transaminases after transplantation for both ALT (MD −412.17, −595.38; −228.97 95% CI $p < .0001$; heterogeneity $p = .0044$; Supplemental Figure S4e) and AST (−453.9, −686.78; −221.01 95%CI $p = .0001$; heterogeneity $p = .0006$; Supplemental Figure S4f).

The use of NRP was associated with improvements in both EAD (.52, .38–.7 95%CI $p < .0001$; heterogeneity $p = .5395$; Supplemental Figure S5a) and PNF (.51, .27–.98 95%CI $p = .0424$; heterogeneity $p = .1825$ Supplemental Figure 5b). When sub-analyzed, once more to avoid indirectness, the comparison of NRP against super rapid recovery (SRR) DCD livers revealed an even higher degree of protection against EAD (OR .51, .36–.72 95%CI $p = .0001$; heterogeneity $p = .1815$ Supplemental Figure S6a) and PNF (.42, .21–.84 95%CI $p = .0135$; heterogeneity $p = .4068$ Supplemental Figure S6b). However, when DCD livers

TABLE 2 Study characteristics NMP

Study	Study type	No. of patients	Main outcomes assessed
Angelico, 2016[23]	Prospective cohort study, historic control Matched 1:2	6 NMP 12 SCS (DCD and DBD)	• PRS • RBC, FFP • Inotropes during transplantation
Ravikumar, 2016[4]	Prospective cohort study, historic control Matched 1:2	20 NMP 40 SCS (DCD and DBD)	• AST, ALT, bili, alk Phos, INR 7 days • EAD • PNF • L-ICU • LOS • Vascular complications • 30 day GS & PS
Selzner, 2016[24]	Prospective cohort study, historic control Matched 1:3	10 NMP 30 SCS (DCD and DBD)	• Peak ALT, AST, INR • LOS • L-ICU • Clavien-Dindo Complications • 3 months PS & GS
Bral, 2017[25]	Prospective cohort study, historic control Matched 1:3	10 NMP 30 SCS (DCD and DBD)	• Peak AST • PNF • EAD • LOS • L-ICU • Clavien-Dindo Complications • 30 day GS & PS
Watson, 2017[26]	Retrospective cohort, control Matched 1:2	12 NMP 24 SCS (DCD and DBD)	• Peak ALT • PRS • PNF • 12 months PS & GS • Cholangiopathy
Nasralla, 2018[3]	Randomized controlled trial	120 NMP 100 SCS (DCD and DBD)	• Peak serum AST • EAD • PNF • PRS • 12 months GS and PS • Biliary strictures on MRCP at 6 m • RRT • L-ICU • LOS
Jassem, 2019[27]	Retrospective cohort study, historic control	12 NMP 27 SCS (DBD)	• Peak AST • L-ICU • Gene expression/cell infiltration • GS and PS
Ghinolfi, 2019[28]	Randomized controlled trial	10 NMP 10 SCS (EC-DBD)	• PRS • Peak AST & ALT • EAD • PNF • LOS • Biliary complications • 90 days PS & GS

(Continues)

TABLE 2 (Continued)

Study	Study type	No. of patients	Main outcomes assessed
Reiling, 2020[29]	Prospective pilot study	10 NMP (DCD and DBD)	• Peak AST • EAD • PNF • RRT • L-ICU • LOS • 3, 6, 12 months PS & GS
Cardini, 2020[30]	Prospective Cohort	34 NMP, 25 Transplanted (DCD and DBD)	• Challenges of establishing NMP programs • Logistic and operational challenges • EAD & PNF • Biliary Complications • 20 months PS & GS
Liu, 2020[31]	Prospective Clinical Trial	21 NMP 84 SCS (DCD/DBD)	• Safety and Feasibility of FFP in NMP • Peak AST & ALT • EAD • PNF • NMP parameters
Mergental, 2020[32]	Prospective Clinical Trial, contemporary controls Matched 1:2	22 NMP 44 SCS (DCD & DBD)	• Increased and safe utilization of discarded livers • EAD • PNF • RRT • L-ICU • LOS • Clavien-Dindo Complications • 90 day GS & PS
Fodor, 2021[33]	Retrospective Comparative Cohort	59 NMP 59 SCS (DCD and DBD)	• PRS • EAD • PNF • Clavien-Dindo Complications • Early Biliary Complications • LOS • 30 days, 90 days and 1 year GS & PS

treated with NRP were compared against DBD liver grafts there was an increase in PNF (OR 4.62, 1.12–19.09 95%CI $p = .0347$; heterogeneity $p = .7818$; Supplemental Figure S7).

3.6 | Recommendations

Thirty-eight studies, including four randomized controlled trials on ex-situ liver perfusion, were used to generate the following recommendations.

The use of hypothermic machine perfusion (HMP) may enhance recovery after liver transplantation by significantly decreasing PRS and EAD, alongside a decrease in the likelihood of early complications. This leads to a significantly shorter length in hospital stay and early recovery (Quality of Evidence; Moderate |Grade of recommendation; Strong).

When HMP is compared against DCD grafts preserved in SCS there is an even greater decrease in the likelihood of developing PRS (Quality of Evidence; Moderate) and EAD (Quality of Evidence; High). These improvements, associated with a lower peak in postoperative liver enzymes, suggest an even further advantage (Quality of Evidence; Moderate) (Grade of recommendation; Strong).

TABLE 3 Study characteristics NRP

	Study type	No. of patients	Main outcomes assessed
Oniscu, 2014[5]	Prospective cohort study	21 NRP (11 liver transplants) DCD	• Number of organs recovered • Peak ALT • EAD • PNF • L-ICU • LOS
Minambres, 2017[34]	Retrospective cohort	27 NRP (11 livers transplanted) 11 DBD	• Day 7 ALT & AST • PNF • L-ICU • 6, 12, 18 GS • Biliary complications
De Carlis, 2018[35]	Retrospective cohort	20 NRP 17 ECMO-DBD 52 DBD	• EAD • PNF • RRT • L-ICU • LOS • 6 and 12 months PS & GS • Ischemic cholangiopathy (AS en NAS)
Rodriguez-Sanjuan, 2019[36]	Retrospective cohort	11 NRP 51 DBD	• Peak AST & ALT • PNF • Vascular complications • IC (diffuse intrahepatic stenosis) • AKI
Ruiz, 2019[37]	Single-centre prospective database analysis	46 NRP	• PRS • Peak ALT • EAD PNF • RRT • L-ICU • LOS • 9 months GS & PS
Watson, 2019[38]	Retrospective cohort	43 NRP 187 SCS DCD (historic controls)	• PEak ALT • EAD • PNF • Ischemic Cholangiopathy • Anastomotic strictures • 90 day GS & PS
Hessheimer, 2019[39]	Retrospective registry review, propensity score matching	95 NRP 117 SCS DCD	• EAD • PNF • L-ICU • LOS • ITBL/biliary complications • 1 year GS & PS
Savier, 2020[40]	Retrospective cohort, Control matched 1:2	50 NRP 100 DBD SCS	• Peak AST • EAD • AKI • Arterial & biliary complications • 90 day GS & PS

(Continues)

TABLE 3 (Continued)

	Study type	No. of patients	Main outcomes assessed
Ding, 2020[41]	Prospective Comparative Cohort	7 DBCD NRP 12 DBCD SCS	• Dynamic changes in LFT's, INR, Plt • PNF • 1 year PS
Antoine, 2020[42]	Retrospective registry review	123 NRP	• 90-day and 1-year graft survival • EAD • PNF • L-ICU • LOS • Ischemic Cholangiopathy • 1 year PS & GS
Miñambres, 2020[43]	Retrospective Comparative Cohort	16 DCD NRP 29 SCS DBD	• Peak AST & ALT • EAD • PNF • Ischemic Cholangiopathy • L-ICU • LOS • 3 months, 1- and 2-year PS
Munoz, 2020[44]	Prospective Comparative Cohort	23 NRP 22 DCD	• Peak AST & ALT • PRS • EAD • ITBL
Hessheimer, 2021[45]	Retrospective registry review	545 NRP 258 DCD	• EAD • PNF • HAT • ITBL • 1, 3 years PS & GS

The use of NMP reduces the incidence of PRS (Quality of Evidence; Moderate) and EAD (Quality of Evidence; Moderate) with associated shortening in ICU (Quality of Evidence; Moderate) and in hospital length of stay (Quality of Evidence; Low), favoring enhanced and early recovery after liver transplantation with an additional decrease in peak liver enzymes after surgery (Quality of Evidence; Moderate) (Grade of recommendation; Strong).

NRP decreases the risk of EAD and PNF associated with a lower peak in postoperative liver enzymes when compared with SRR DCD livers. This favors the use of this technique as part of an enhanced recovery after liver transplantation protocol (Quality of Evidence; low|Grade of recommendation; Strong).

The direction and strength of recommendation was rated as *strong for* the use of HMP with regard to PRS, EAD, major complications and length in hospital stay (Table 15).

The direction and strength of recommendation was rated as *strong for* the use of NMP with regard to PRS, EAD, and length in ICU & hospital stay (Table 16).

The direction and strength of recommendation was rated as *strong for* the use of NRP with regard to EAD and PNF (Table 17).

4 | DISCUSSION

The most obvious effect of MP across all technologies is a decrease in early allograft dysfunction, defined according to Olthoff's criteria.[51] The use of both HMP and NMP produce a lower peak in the postoperative liver enzymes (ALT and AST). The absence of a secondary peak in liver enzymes after reperfusion would suggest that this is not an artifact washout effect, but rather a reflection of reduced preservation injury in these organs.[21] Parallel to this, both ex-situ liver perfusion techniques provide a significant degree of protection from PRS whilst shortening the total length of hospital stay. The mechanism behind these effects is likely that of reduced ischemia-reperfusion injury secondary to the restoration of energy through oxygen delivery via ex-situ MP.[3,21,52]

The protective advantages of HMP against PRS and EAD are most apparent when compared with SCS DCD livers.[12,22,53] This effect is mainly seen when HMP is applied for 1–2 h, possibly due to the restoration of mitochondrial function and the reduction in production of radical oxygen species.[46,54] A graft survival advantage is also seen compared with SCS DCD grafts.[12,16] The decrease in length of hospital stay

TABLE 4 Study outcomes for HMP versus DBD - SCS

Study	Donor type	PRS	Biochemical Parameters	EAD	PNF	RRT	ICU Stay	LOS	Early Compli-cations
Guarrera, 2010	HOPE DBD vs. SCS DBD		Peak AST 1154 (79.5[c]) vs. 3339 (755.1[c]) $p = .011$ Peak ALT 560 (79.5[c]) vs. 1358 (270.2[c]) $p = .044$	1(5%) vs. 5(25%) $p = .08$	0 vs. 0			10.9 (±4.7) vs. 15.3 (±4.9) $p = .006$	
Guarrera, 2015	DHOPE EC DBD vs. SCS EC DBD			6(19%) vs. 9(30%) $p = .384$	1(3%) vs. 2(7%) $p = .612$			13.6 (±10.9) vs. 20.1 (±11.1) $p = .001$	
Dutkowski, 2015	HOPE DCD SCS DBD		Peak ALT 1239 (689–2126[a]) vs. 1124(693–2126[a]) $p = ns$ Peak AST 1808 (1133–3547[a]) vs. 1473 (762–3764[a]) $p = ns$	5(20%) vs. 11(22%) $p = ns$	0 vs. 0 $p = ns$	7(28%) vs. 11(22%) $p = ns$	3(1.3–5.7[a]) vs. 3(2–5.7[a]) $p = ns$	20 (14–23[a]) vs. 17.5(13–26[a]) $p = ns$	
Patrono, 2019	HOPE DBD vs. SCS DBD	1 (4%) vs. 10 (20%) $p = .13$	Peak ALT 792 (±773) vs. 817 (±540) $p = .87$ Peak AST 1425 (±1729) vs. 1498 (±1034) $p = .82$	8(32%) vs. 17(34%) $p = 1$		1(4%) vs. 2(4%) $p = 1$	3.9 (±4) vs. 4.2 (±2.6) $p = .74$	15.1 (±9.4) vs. 14.3 (±6.6) $p = .69$	Dindo Clavien ≥ 3 5(20%) vs. 11(22%) $p = 1$

(Continues)

TABLE 4 (Continued)

Study	Donor type	PRS	Biochemical Parameters	EAD	PNF	RRT	ICU Stay	LOS	Early Compli-cations
Schlegel, 2019	HOPE DCD vs. SCS DBD		Peak ALT 1,226 vs. 1425 $p = .38$		0 (0%) vs 1(2%) $p = 1$	8(16%) vs. 4(8%) $p = .35$	3 vs. 3 $p = .25$	18 vs. 9 $p = .0001$	
Rayar, 2020	HOPE EC-DBD vs. SCS EC-DBD	13 (52%)	Day 0 AST 724 vs. 1284 $p = .046$ Day 0 ALT 392 vs. 720 $p = .01$	7(28%) vs. 29(42%) $p = .22$	2(8%) vs. 2(3%) $p = .29$	1(4%) vs. 2(2.9%) $p = 1$	3(1-72[b]) vs. 5(1-43[b]) $p = .01$	15(8-92[b]) vs. 20(9-92[b]) $p = .01$	Dindo Clavien ≥ 3 6 (24%) vs. 31(44.9%) $p = .07$
Ravaioli, 2020	HOPE EC-DBD vs. SCS EC-DBD		Peak AST 344.5 (166-1132[b]) vs. 637 (124-2100[b]) $p = .006$ Peak ALT 330 (122-1350[b]) vs. 601 (114-1837[b]) $p = .14$	0(0%) vs. 7(23.3%) $p = .6135$	0(0%) vs. 2(6.6%) $p = .89$			11.5 (7-29[b]) vs. 12.5 (7-109[b]) $p = .23$	Dindo Clavien ≥ 3 0 (0%) vs. 7(23.3%)
Patrono, 2020	DHOPE DBD		Peak AST 991 (565-1623[a]) Peak ALT 491 (279-945[a])	13 (26%)					
Czigany, 2021	HOPE EC-DBD vs. SCS EC-DBD		Peak ALT 418 (221-828[a]) vs. 796 (477-1195[a]) $p = .03$ Peak AST 652 (415-1322[a]) vs. 1312 (576-2514[a]) $p = .091$	4(17%) vs. 8(35%) $p = .314$	1(4%) vs. 1(4%) $p > .999$	5(22%) vs. 9(39%) $p = .337$	5 (4-8[a]) vs. 8 (5-18[a]) $p = .045$	20(16-27[a]) vs. 36(23-62[a]) $p = .002$	Dindo Clvien > 3 10 (44%) vs. 17 (74%) $p = .036$

Note: SD ±, number of events +.

[a]IQR.

[b]Range.

[c]SEM.

TABLE 5 Study outcomes for HMP - DCD

	Donor type	PRS	Biochemical parameters	EAD	PNF	RRT	ICU stay	LOS	Early complications
Dutkowski, 2015	HOPE DCD vs. SCS DCD		Peak ALT 1239 (689-2126*) vs. 2065 (1331-3596*) $p = .007$ Peak AST 1808(1133-3547*) vs 2848(1485–6724*) P = .005	5(20%) vs. 22(44%) $p = .03$	0 (0%) vs. 3(6%) p = ns	7 (28%) vs. 5 (10%) p = ns	3(1.3-5.7*) vs. 3(2-6*) p = ns	20 (14-23*) vs. 18 (15-29*) p = ns	
Van Rijn, 2017	DHOPE DCD vs. SCS DCD		Peak ALT 966(718-1631*) vs. 1858 (1086-2380*) $p = .006$	0 (0%) vs. 2(10%) $p = 1$	0 vs. 0	1 (10%) vs 2 (10%) $p = 1$	2 (2-6*) vs. 2 (1-5*) $p = .47$	22 (16-33*) vs. 23 (15-32*) $p = .88$	
Schlegel, 2019	HOPE DCD vs. SCS DCD		Peak ALT 1,226 vs. 1,331 $p = .42$		0 (0%) vs. 2 (4%) $p = .49$	8 (16%) vs. 11(22%) $p = .611$	3 vs. 3 $p = .77$	18 vs. 10 $p = .0001$	
Muller, 2019	HOPE DCD		Peak ALT 1239 (710-4183*) Peak AST 2531 (1301-8374*)	14 (66.7%)	0 (0%)	6 (28.6%)	3 (2-5*)	18 (13.5-23.5*)	Dindo Clavien ≥ 3 8 (38.1%)
Van Rijn, 2021	DHOPE DCD vs. SCS DCD	9/72 (12%) vs. 19/70 (27%) RR .43 (.2-.91CI)	Peak ALT 996(838-1184 CI) vs. 1324(1113-1573 CI)	20 (26%) vs. 31 (40%) RR .61 (.39-.96)	0 (0%) vs. 1(1%)	7 (9%) vs. 7(9%) RR .79 (.27-2.34)	2 (2-5*) vs. 2 (1-4*)	15 (12-20*) vs. 15 (12-26*)	Dindo Clavien + 3a: 41 vs. 39 $p = .75$ 3b: 13 vs. 17 $p = .42$ 4a: 16 vs. 16 $p = 1$ 4b: 1 vs. 2 $p = 1.000$

Note: IQR*. Range [a], SD ±, SEM ^, number of events +.

TABLE 6 Study outcomes for NMP versus SCS

	Donor type	PRS	Biochemical parameters	EAD	PNF	RRT	ICU Stay	LOS	Early Complications
Angelico, 2016	NMP (DCD&DBD) vs. SCS (DCD&DBD	0 (0%) vs. 2 (16.7%) $p = .529$							
Ravikumar, 2016	NMP (DBD &DCD) vs. SCS (DBD &DCD)		Peak AST 417 (84-4681[a]) vs. 902 (218–8786[a]) $p = .034$	3 (15%) vs. 9 (22.5%) $p = .734$	0 vs. 0		3 (1-8[a]) vs. 3 (1-41[a]) $p = .459$	12 (6-34[a]) vs. 14 (8-88[a]) $p = .10$	
Selzner, 2016	NMP (DBD &DCD) vs. SCS (DBD &DCD)		Peak ALT 619 (55-2858[a]) vs. 949(233-3073[a]) $p = .55$ Peak AST 1182(167-6700[a]) vs. 1474(521-5156[a]) $p =$ ns				1 (0-8[a]) vs. 2 (0-23[a]) $p = .54$	11 (8-17[a]) vs. 13 (7-89[a]) $p = .23$	Clavien Dindo ≥ 3B 1(10%) vs. 7 (23%) $p = .5$
Bral, 2017	NMP (DBD &DCD) vs. SCS (DBD &DCD)	0% vs. -	Peak AST 1252 (383- > 2,600[a]) vs. 839 (153- > 2600[a]) $p = .52$	5/9 (55.5%) vs. 8/27 (29.6%) $p = .23$	0/9 (0%) vs. 0/27 (0%) $p =$ ns		16 (2-65[a]) vs. 4 (1-29[a]) $p = .004$	45 (13-114[a]) vs. 25 (9-89[a]) $p = .01$	Clavien Dindo ≥ 3 2 /9 (22%) vs. 10/27 (37%) $p = .69$
Watson, 2017	NMP (DBD &DCD) vs. SCS (DBD &DCD)	Hyperoxic NMP 5/6 (83%), Normoxic NMP 0/6 (0%) vs. 5/24 (25%)	Peak ALT 1069 (187-4991[a]) vs. 787 (155-2238[a])		1 (9.1%)				
Nasralla, 2018	NMP (DBD&DCD) vs. SCS (DBD&DCD)	15 (12.4%) vs. 32 (33%) $p = .0002$	Peak AST 488.1 (408.9–582.8[b]) vs. 964.9 (794.5–1,172.0[b]) $p = .0000$	12 (10.1%) vs. 29 (29.9%) $p = .0002$	1 (.8%) vs. 0 (0%)	27 (22.3%) vs. 20 (19.8%) $p = .648$	4 (2-7[b]) vs. 4 (3-7[b]) $p = .339$	15 (10-24[b]) vs. 15 (11-24[b]) $p = .926$	Clavien Dindo + ≥ 3B 21/128 (16.4%) vs. 36/134 (22%)
Jassem, 2019	NMP DBD vs. SCS DBD		Peak AST 371 (162-1,709[a]) vs. 924 (162-8,029[a]) $p < .01$				3 (1-8[a]) vs. 5 (1-28[a]) $p =$ NS		
Ghinolfi, 2019	NMP DBD vs. SCS DBD	3 (30%) vs. 1 (10%) $p = .576$	Peak AST 709 (371-1575[b]) vs. 574 (377-1162[b]) $p = .597$ Peak ALT 332 (263-610[b]) vs. 428 (303-616[b]) $p = .82$	2 (20%) vs. 1 (10%) $p = 1$	0 (0%) vs. 0 (0%) $p = 1$			17 (14-22[b]) vs. 12(11-15[b]) $p = .119$	

(Continues)

TABLE 6 (Continued)

	Donor type	PRS	Biochemical parameters	EAD	PNF	RRT	ICU Stay	LOS	Early Complications
Reiling, 2020	NMP (DBD &DCD)		Peak AST 1690 (572-3463[a])	5 (50%)	0 (0%)	2 (20%)	1.5 (1-2.25[a])	11.5(9.5-19.3[a])	
Cardini, 2020	NMP (DBD &DCD)			5 (20%)	0 (0%)				
Liu, 2020	NMP (DBD&DCD) vs SCS (DBD&DCD)		Peak ALT 363 (±318) vs. 1021 (±999) $p = .001$ Peak AST 1357 (±1492) vs. 2615 (±2541) $p = .00$	19% vs. 46% $p = .02$	0 (0%) vs. 0 (0%)				
Mergental, 2020	NMP (DBD&DCD) vs. control group	10 (45%)		7 (31.8%) vs. 4 (9.1%) $p = .034$	0 (0%) vs. 1(2.3%) $p = 1$	4 (18.2%) vs. 11 (25%) $p = .54$ OR .68 (.19–2.38)	3.5 (3-4[b]) vs. 2 (1-5[b]) $p = .566$	10 (8-17[b]) vs. 9 (8-11[b]) $p = .822$	Clavien Dindo ≥ 3 7 (32%) vs. 17 (38.6%) $p = .89$
Fodor, 2021	NMP (DBD&DCD) vs. SCS (DBD&DCD)	0% vs. 0%		19/59 (32%) vs. 20/58 (34%) $p = .794$	0 (0%) vs. 0 (0%)			17 (12[b]) vs. 23 (21[b]) $p = .006$	Clavien Dindo ≥ 3 37% vs. 34% $p = .086$

Note: SD ±, SEM ^, number of events +

[a]Range.

[b]IQR.

TABLE 7 Study outcomes for NRP

	Donor type	PRS	Biochemical parameters	EAD	PNF	RRT	ICU stay	LOS	Early compli-cations
Oniscu, 2014	NRP DCD		Peak ALT 389(58-2043[b])	4 (36.3%)	1 (9.09%)		1 (0-22)	17 (8-42)	
Minambres, 2017	NRP DCD vs SCS DBD		ALT day 7 77 (57-81[a]) vs 71(42.5-137[a]) $p = .78$ AST day 7 164(139-189[a]) vs 244(145-361[a]) $p = .475$		1 (9.1%) vs 0 (0%)		6.5 (4-9[a]) vs 7 (3-16[a]) $p = .871$		
De Carlis, 2018	NRP DCD vs DBD (ECMO & SCS)			4 (24%) vs 13 (27%) $p > .99$	2 (10%) vs 2 (4%) $p = .58$	5 (25%) vs 3(6%) $p = .04$	4 (3-7[a]) vs 4 (3-4[a]) $p = .2$	17 (14-24[a]) vs 14 (12-20[a]) $p = .62$	
Rodriguez-Sanjuan, 2019	NRP DCD vs SCS DBD		Peak AST within 24 hrs 520 vs 717 Peak ALT within 24 hrs 339 vs 653		1(9.1%) vs 1(2%) $p = .3$				
Ruiz, 2019	NRP DCD	7 (15%)	Peak ALT 1136 (220-6683[b])	11 (23.9%)	0%	1 (2.17%)	4 (1-24)	14 (7-55)	
Watson, 2019	NRP DCD vs SRR DCD		Peak ALT 633 (317-1070[a]) vs 1154 (667-2099[a]) $p < .0001$	5/43 (12%) vs 55/173 (32%) $p = .0076$	0 (0%) vs 13 (7%) $p = .134$				
Hessheimer, 2019	NRP DCD vs SRR DCD			21 (22%) vs 32 (27%) $p = .381$	2 (2%) vs 3 (3%) $p = .135$		4 (3-6[a]) vs 3 (2-6[a]) $p = .135$	15 (12-23[a]) vs 17(11-21[a]) $p = .818$	
Savier, 2020	NRP DCD vs SCS DBD		Peak AST 917 (397-1372[a]) vs 1027 (532-2298[a]) $p = .29$ Peak ALT 702 (267-1012[a]) vs 753 (393-1509[a]) $p = .16$	9 (18%) vs 32(32%) $p = .11$					
Ding, 2020	NRP DBCD vs SRR DBCD				0 vs 0				
Antoine, 2020	NRP DCD			4 (3.25%)	3 (2.4%)		5 (4-7*)	12 (8-18[a])	

(Continues)

TABLE 7 (Continued)

	Donor type	PRS	Biochemical parameters	EAD	PNF	RRT	ICU stay	LOS	Early compli-cations
Miñambres, 2020	DCD NRP vs. SCS DBD		Peak AST 999 (481-1588[a]) vs. 706 (445-1201[a]) $p = .496$ Peak ALT 1287 (642-1436[a]) vs. 813 (525-1511[a]) $p = .48$	3 (18.8%) vs 5 (17.2%) $p = .60$	2 (12.5%) vs 0 (0%) $p = .121$		5 (3-65[a]) vs 5 (3-7[a]) $p = .682$	14 (13-26[a]) vs 21 (14-30[a]) $p = .294$	
Munoz, 2020	NRP DCD vs. SRR DCD	6.3% vs. 27.3% $p = .09$	Peak AST 2,077 vs. 5828 $p = .01$ Peak ALT 1309 vs. 2343 $p = .05$	7 (30.4%) vs. 15 (68.1%) $p = .05$					
Hessheimer, 2021	NRP DCD vs. SRR DCD			81(15%) vs. 60 (23%) $p = .01$	16 (3%) vs. 15 (6%) $p = .18$				

Note: SD ±, SEM ^, number of events +.
[a]IQR. [b]Range

appears to be associated with fewer major complications in the HMP group when compared to the DBD's preserved in SCS. This effect is primarily seen among studies that use extended criteria DBD grafts, suggesting that HMP is beneficial not only for DCD grafts but also for marginal DBD grafts.

NMP appears to provide a significant advantage over SCS by shortening both ICU and hospital length of stay. This meta-analysis overcomes the lack of power seen in individual reports and shows a clear and statistically significant effect with respect to this key outcome in the enhanced recovery pathway. Although there is a trend toward a lower likelihood in major complications, no statistical significance was shown in the NMP group. This is perhaps due to the heterogeneous manner in which results are published, resulting in only two articles being included in this part of the analysis. It is notable that this was not the primary outcome of these studies, which were therefore not powered for this purpose.

The main effect of NRP is a decrease in the risk of EAD and PNF in DCD livers, especially in comparison with organs retrieved using the SRR technique. This benefit translates to an overall increase in graft survival when compared to SCS DCD grafts. On the contrary, when compared to standard DBD grafts, NRP fails to reverse the risk of PNF and the need for RRT. However, these results must be interpreted with caution as these findings are extrapolated from a handful of retrospective low volume studies.

Unfortunately, the degree of major complications according to Dindo-Clavien is not widely reported in NRP research publications. Regardless, a significant reduction in important post-transplant events (such as HAT, biliary complications, graft loss and patient death) is reported in the largest retrospective study.[45]

The development of nonanastomotic biliary strictures after liver transplantation, although highly important, was felt not to be relevant for ERAS given its typical presentation more than three months after transplantation, hence its exclusion from this systematic review and meta-analysis. Likewise, other important outcomes like: long term patient and graft survival, logistics and cost-utility benefit were not considered given the specific scope of this article on ERAS.

However, the use of NMP appears to be a cost-effective strategy, specifically by increasing the utilization of donor allografts and thereby improving the quality-adjusted life years.[48,49] Nevertheless, limited information is available regarding cost-effectiveness for NRP. Yet, this technology provides a benefit for all abdominal organs at a lower cost when compared with NMP.[50] Likewise, limited information is available regarding the cost-effectiveness of HMP where further research is needed to reduce uncertainty.[47]

Looking forwards, future RCTs are needed to compare the different perfusion technologies in order to ascertain the degree of effect they have and determine their individual strengths on specific outcomes (ClinicalTrials.gov Identifier: NCT04644744).[55] Likewise, the advantage of sequential perfusion technologies needs to be explored even further. The use of NRP followed by either HMP or NMP could have additional benefits for marginal grafts. Current trials will shape the future of ex-situ MP as a platform for therapeutic drug delivery, aiming to expand the donor pool to a greater extent. Furthermore, conducting

TABLE 8 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Summary of Findings HMP vs DBD & DCD in SCS									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: PRS									
1	1	1	Lower in intervention group	Not Serious	Not Serious	Serious	Not Serious	Not likely	Moderate ●●●○
Outcome 2: *Biochemical Parameters*									
2	9	2	Lower in intervention group	Not Serious	Not Serious	Serious	Not Serious	Not likely	Moderate ●●●○
Outcome 3: EAD									
2	8	2	Clearly lower in intervention group	Not Serious	Not serious	Serious	Not Serious	Not likely	Moderate ●●●○
Outcome 4: *PNF*									
2	9	1	No difference between groups	Not serious	Not serious	Serious	Serious	Not likely	Low ●●○○
Outcome 5: *RRT*									
2	7	1	No difference between groups	Not serious	Not serious	Serious	Serious	Not likely	Low ●●○○
Outcome 6: *ICU length of stay*									
2	7	1	No difference between groups	Not serious	Not serious	Serious	Serious	Not likely	Low ●●○○
Outcome 7: *Total hospital length of stay*									
2	10	1	Lower in intervention group	Not serious	Serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 8: Early complications									
2	3	1	Lower in intervention group in most studies	Not serious	Serious	Serious	Not serious	Not likely	Low ●●○○

Note: The HMP group is mainly affected in indirectness considering the heterogeneity of the studies. Single or dual hypothermic perfusion was applied to either DBD or marginal grafts (EC-DBD or DCD) and compared to either the same type of graft or against a DBD preserved in SCS.

TABLE 9 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Summary of Findings HMP vs DBD in SCS Livers									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: PRS									
0	1	1	No difference between groups	Serious	Not Serious	Not Serious	Serious	Not likely	Low ●●○○
Outcome 2: *Biochemical Parameters*									
1	6	1	Lower in intervention group	Not Serious	Serious	Not Serious	Not Serious	Not likely	Moderate ●●●○
Outcome 3: EAD									
1	6	1	Lower in intervention group	Not Serious	Not serious	Not Serious	Not Serious	Not likely	High ●●●●
Outcome 4: *PNF*									
1	6	0	No difference between groups	Not serious	Not serious	Not serious	Serious	Not likely	Moderate ●●●○
Outcome 5: *RRT*									
1	4	0	No difference between groups	Not serious	Serious	Not serious	Serious	Not likely	Low ●●○○
Outcome 6: *ICU length of stay*									
1	4	0	Lower in intervention group, with no statistical significance	Not serious	Not serious	Not serious	Serious	Not likely	Moderate ●●●○
Outcome 7: *Total hospital length of stay*									
1	7	0	Lower in intervention group	Not serious	Serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 8: Early complications									
1	3	0	Lower in intervention group in most studies.	Not serious	Serious	Not serious	Not serious	Not likely	Moderate ●●●○

TABLE 10 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Summary of Findings HMP vs DCD in SCS									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: PRS									
1	0	0	Clearly lower in intervention group	Not serious	Not serious	Not serious	Seriou	Not likely	Moderate ●●●○
Outcome 2: *Biochemical Parameters*									
1	3	1	Clearly lower in intervention group.	Not serious	Not serious	Serious	Not serious	Not likely	Moderate ●●●○
Outcome 3: EAD									
1	2	1	Clearly lower in intervention group	Not serious	Not serious	Not serious	Not serious	Not likely	High ●●●●
Outcome 4: *PNF*									
1	3	1	Lower in intervention group, with no statistical difference	Not serious	Serious	Serious	Not serious	Not likely	Low ●●○○
Outcome 5: *RRT*									
1	3	1	No difference between groups	Not serious	Serious	Serious	Not serious	Not likely	Low ●●○○
Outcome 6: *ICU length of stay*									
1	3	1	No difference between groups	Not serious	Not serious	Serious	Not serious	Not likely	Moderate ●●●○
Outcome 7: *Total hospital length of stay*									
1	3	1	No difference between groups	Not serious	Serious	Serious	Not serious	Not likely	Low ●●○○
Outcome 8: Early complications									
1	0	1	No difference between groups	Not serious	Not serious	Serious	Not serious	Not likely	Moderate ●●●○

TABLE 11 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Summary of Findings NMP vs SCS									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: PRS									
2	3	2	Lower in the intervention group	Not serious	Serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 2: *Biochemical Parameters*									
2	6	1	Lower in the intervention group	Not serious	Serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 3: EAD									
2	5	2	Lower in intervention group	Not serious	Serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 4: *PNF*									
2	5	3	No difference between groups	Not serious	Not serious	Not serious	Serious	Not likely	Moderate ●●●○
Outcome 5: *RRT*									
1	1	1	No difference between groups	Not serious	Not serious	Not serious	Not serious	Not likely	High ●●●●
Outcome 6: *ICU length of stay*									
1	5	1	Clearly lower in intervention group	Not serious	Not serious	Not serious	Serious	Not likely	Moderate ●●●○
Outcome 7: *Total hospital length of stay*									
2	5	1	Lower in intervention group	Not serious	Serious	Not serious	Serious	Not likely	Low ●●○○
Outcome 8: Early complications									
1	4	0	No difference between groups	Not serious	Not serious	Not serious	Serious	Not likely	Moderate ●●●○

Note: There is a mild degree of inconsistency in addition to a low number of patients included across some of these studies for a particular outcome affecting imprecision.

TABLE 12 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Summary of Findings NRP vs DCD & DBD									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: PRS									
0	1	1	Lower in intervention group, with no statistical significance	Not serious	Not serious	Not serious	Very serious	Not likely	Low ●●○○
Outcome 2: *Biochemical Parameters*									
0	6	2	No clear difference between groups	Serious	Serious	Serious	Not serious	Not likely	Very low ●○○○
Outcome 3: EAD									
0	7	3	Clearly lower in intervention group	Not serious	Not serious	Serious	Not serious	Not likely	Moderate ●●●○
Outcome 4: *PNF*									
0	8	3	Lower in intervention group	Serious	Not serious	Serious	Not serious	Not likely	Low ●●○○
Outcome 5: *RRT*									
0	1	1	Higher in the intervention group.	Very serious	Not serious	Not serious	Serious	Not likely	Very low ●○○○
Outcome 6: *ICU length of stay*									
0	4	3	No difference between groups	Serious	Not serious	Serious	Not serious	Not likely	Low ●●○○
Outcome 7: *Total hospital length of stay*									
0	3	3	No difference between groups	Serious	Not serious	Serious	Not serious	Not likely	Low ●●○○

Note: Limitations were found to be serious or very serious for the NRP group considering the retrospective nature of the studies for each individual outcome. There are only a few prospective cohorts with matched controls available among the published literature.

TABLE 13 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Summary of Findings NRP vs SRR DCD									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 1: PRS									
0	1	1	Lower in intervention group, with no statistical significance	Not serious	Not serious	Not serious	Very serious	Not likely	Low ●●○○
Outcome 2: *Biochemical Parameters*									
0	2	2	Clearly Lower in intervention group	Serious	Serious	Not serious	Not serious	Not likely	Low ●●○○
Outcome 3: EAD									
0	4	3	Clearly lower in intervention group	Not serious	Not serious	Not serious	Not serious	Not likely	High ●●●●
Outcome 4: *PNF*									
0	4	3	Lower in intervention group	Serious	Not serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 6: *ICU length of stay*									
0	1	3	No difference between groups	Very serious	Not serious	Serious	Not serious	Not likely	Very low ●○○○
Outcome 7: *Total hospital length of stay*									
0	1	3	No difference between groups	Very serious	Not serious	Serious	Not serious	Not likely	Very low ●○○○

TABLE 14 Summary of findings leading to the quality of evidence assessment according to the GRADE approach

Summary of findings NRP vs DBD SCS									
Number of studies									
RCT	Observational comparative	Observational non-comparative	Effect from comparative studies	Limitations	Inconsistency	Indirectness	Imprecision	Publication Bias	Quality of Evidence (GRADE)
Outcome 2: *Biochemical Parameters*									
0	4	o	No difference between groups	Serious	Not serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 3: EAD									
0	3	0	Lower in intervention group with no statistical significance.	Serious	Not serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 4: *PNF*									
0	4	0	Higher in intervention group	Serious	Not serious	Not serious	Serious	Not likely	Low ●●○○
Outcome 5: *RRT*									
0	1	1	Higher in the intervention group.	Very serious	Not serious	Not serious	Serious	Not likely	Very low ●○○○
Outcome 6: *ICU length of stay*									
0	3	0	No difference between groups	Serious	Not serious	Not serious	Not serious	Not likely	Moderate ●●●○
Outcome 7: *Total hospital length of stay*									
0	2	0	No difference between groups	Serious	Not serious	Not serious	Not serious	Not likely	Moderate ●●●○

TABLE 15 HMP-Evidence to recommendation framework according to the GRADE approach

Question: Does hypothermic machine perfusion improve immediate and short-term outcomes by enhancing graft function and recipient recovery after liver transplantation?			
	Judgement		
Decision domain	**Yes**	**No**	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	✓		No evident harm was identified with the use of HMP. Only one study identified an increase in LOS which reflected different discharge policies with no difference in complications.[46]
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*	✓		High quality evidence with both RCT and prospective matched cohorts.
Confidence in Values and Preference, and their Variability *Are you confident about the typical values and preferences and are they similar across the target population?*	✓		Recommendations were based on our meta-analysis.
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*	✓		Limited information is available regarding cost-effectiveness. Further research is needed to reduce uncertainty.[47]
Overall Quality of Evidence: Moderate			
Recommendation: Strong for the intervention			

TABLE 16 NMP-Evidence to recommendation framework according to the GRADE approach

Question: Does normothermic machine perfusion improve immediate and short-term outcomes by enhancing graft function and recipient recovery after liver transplantation?			
	Judgement		
Decision domain	**Yes**	**No**	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	✓		No evident harm was identified with the use of NMP. Isolated reports of machine disfunction have not led to a poor outcome.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*	✓		High quality evidence with both RCT and prospective matched cohorts.
Confidence in Values and Preference, and their Variability *Are you confident about the typical values and preferences and are they similar across the target population?*	✓		Recommendations were based on our meta-analysis.
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*	✓		The use of NMP is a cost-effective strategy, specifically by increasing the utilization of donor allografts and improving quality-adjusted life years.[48,49]
Overall Quality of Evidence: Moderate			
Recommendation: Strong for the intervention			

TABLE 17 NRP-Evidence to recommendation framework according to the GRADE approach

Question: Does normothermic regional perfusion improve immediate and short-term outcomes by enhancing graft function and recipient recovery after liver transplantation?			
	Judgement		
Decision domain	**Yes**	**No**	**Reason for Judgement**
Balance between desirable and undesirable outcomes (estimated effects), with consideration of values and preferences (estimated typical) *Given the best estimate of typical values and preferences, are you confident that the benefits outweigh the harms and burden or vice versa?*	✓		No evident harm was identified with the use of NRP.
Confidence in the magnitude of estimates of effect of the interventions on important outcomes (overall quality of evidence for outcomes) *Is there high, moderate or low-quality evidence?*		✓	Only 2, out of 13 studies, are prospective comparative cohorts. The rest are retrospective studies.
Confidence in Values and Preference, and their Variability *Are you confident about the typical values and preferences and are they similar across the target population?*	✓		Recommendations were based on our meta-analysis
Resource implications *Are the resources worth the expected net benefit from following the recommendation?*	✓		Limited information is available regarding cost-effectiveness. Yet, NRP provides a benefit for all abdominal organs at a lower cost when compared with NMP.[50]
Overall Quality of Evidence: Low			
Recommendation: Strong for the intervention			

randomized trials on NRP is highly encouraged even though it is now considered standard practice for DCDs in France, Spain and parts of Italy.

4.1 | Limitations

This meta-analysis is limited by some of the studies' data reported in medians and IQR, which precluded its analysis. In addition, the analysis of certain outcomes was limited by the nature of how these were reported. The development of major complications, for example, was reported in myriad ways. Likewise, graft and patient survivals were reported in different time ranges, making a 3-month survival analysis unfeasible. Lastly, most of the studies included in this systematic review were not powered and/or designed to reach a conclusion for most of the outcomes we assessed in this manuscript, making a meta-analysis necessary for conclusive recommendations. Moreover, most of the analyzed outcomes for the NRP studies are retrospective while some of them have overlapping cohorts.

5 | CONCLUSION

High-quality evidence for ex-situ MP, accompanied by many other prospective and retrospective studies, provides sufficient support for the use of these technologies to achieve the specific outcomes associated with an enhanced recovery program.

Both HMP and NMP technologies diminish the risk of PRS and EAD accompanied by a shorter length in hospital stay.

Whilst the overall QOE for NRP is lower than that for ex-situ MP techniques, the findings from large retrospective studies are consistent in demonstrating a clear benefit associated with the use of this technology and support its use to improve certain outcomes like EAD and PNF associated with an enhanced recovery program.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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