Centre universitaire de santé McGill
McGill University Health Centre

L'Unité d'évaluation des technologies et des modes d'intervention en santé (UETMIS) du Centre Universitaire de Santé McGill (CUSM)
Health Technology Assessment Unit (TAU) of the MUHC

June 11, 2025

Machine Perfusion for Liver Transplantation

Perfusion mécanique pour la transplantation hépatique

Health Technology Assessment Report
Report no. 101

Report prepared for the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC)

by

Eva Suarthana, MD, PhD, Nisha Almeida, PhD, and Thiphavone Oudanonh, MSc

Reviewed by the Policy Committee of the TAU on June 11, 2025

Mission Statement

The MUHC Health Technology Assessment Unit (TAU) advises hospital administrators and clinical teams in difficult resource allocation decisions. Using an approach based on independent, critical evaluations of the available scientific evidence and a transparent, fair decision-making process, novel and existing medical equipment, drugs and procedures used by healthcare professionals are prioritized on a continuous basis ensuring the best care for life with the best use of resources.

TAU Policy Committee

Declaration of Conflicts of Interest

Members of TAU's research staff and policy committee declare no conflicts of interest.

Suggested citation

Suarthana E, Almeida N and Oudanonh T. Machine Perfusion for Liver Transplantation. Montreal (Canada): Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC); 2025 June 11. Report no. 101. 67 pages

Report available from https://muhc.ca/tau

ACKNOWLEDGEMENTS

The expert assistance of the following individuals is gratefully acknowledged for providing background information:

- Dr. Prosanto Chaudhury, Director, Multi-Organ Transplant and Donation Program, McGill University Health Centre (MUHC)

REPORT REQUESTOR

There is province and nation-wide interest in increasing organ utilization rates, particularly in liver transplantation. Dr. Prosanto Chaudhury, Director of the Multi-Organ Transplant and Donation Program at the McGill University Health Centre requested an evaluation by TAU to determine the clinical benefit of these technologies in this population, with the goal of requesting funding from the Ministry.

TYPES OF RECOMMENDATIONS ISSUED BY THE TAU COMMITTEE

Type of recommendation	Explanation
Approved	• Evidence for relevant decision criteria, including efficacy, safety, and cost, as well as context-specific factors such as feasibility, is sufficiently strong to justify a recommendation that the technology be accepted, used and funded through the institutional operating budget
Approved for evaluation	• There is a reasonable *probability* that relevant decision criteria, including efficacy, safety, and cost, as well as context-specific factors such as feasibility, are favorable but the evidence is not yet sufficiently strong to support a recommendation for permanent and routine approval. • The evidence is sufficiently strong to recommend a *temporary* approval in a restricted population for the purposes of evaluation, funded through the institutional operating budget.
Not approved	• There is insufficient evidence for the relevant decision criteria, including efficacy, safety, and cost; • The costs of any use of the technology (e.g. for research purposes) should not normally be covered by the institutional budget.

DISCLAIMER

The Technology Assessment Unit ("TAU") of the McGill University Health Centre ("MUHC") was created in order to prepare accurate and trustworthy evidence to inform decision-making and when necessary to make policy recommendations based on this evidence. The objective of the TAU is to advise the hospitals in difficult resource allocation decisions, using an approach based on sound, scientific technology assessments and a transparent, fair decision-making process. Consistent with its role within a university health centre, it publishes its research when appropriate, and contributes to the training of personnel in the field of health technology assessment.

The information contained in this report may include, but is not limited to, existing public literature, studies, materials, and other information and documentation available to the MUHC at the time it was prepared, and it was guided by expert input and advice throughout its preparation. The information in this report should not be used as a substitute for professional medical advice, assessment and evaluation. While MUHC has taken care in the preparation of this report to ensure that its contents are accurate, complete, and up to-date, MUHC does not make any guarantee to that effect. MUHC is not responsible for any liability whatsoever, errors or omissions or injury, loss, or damage arising from or as a result of the use (or misuse) of any information contained in or implied by the information in this report.

We encourage our readers to seek and consult with qualified health care professionals for answers to their personal medical questions. Usage of any links or websites in the report does not imply recommendations or endorsements of products or services.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
CIT	Cold ischemic time
DBD	Donor after brain death
DCD	Donor after circulatory death
D-HOPE	Dual hypothermic oxygenated machine perfusion
dWIT	Donor warm ischemic time
EAD	Early allograft dysfunction
ECD	Expanded criteria donor
HMP	Hypothermic machine perfusion
HOPE	Hypothermic oxygenated machine perfusion
HR	Hazard Ratio
I^2 statistic	The percentage of variation across studies in a meta-analysis that is due to heterogeneity rather than chance
LOS	Length of stay
MUHC	McGill University Health Center
NAS	Non-anastomotic biliary stricture
NMP	Normothermic machine perfusion
NRP	Normothermic regional perfusion
OR	Odds ratio
PNF	Primary non function
RCT	Randomized clinical trial
rWIT	Recipient warm ischemic time
SCS	Static Cold Storage
TAU	MUHC Technology Assessment Unit

PLAIN LANGUAGE SUMMARY

Can machine perfusion improve the outcomes of liver transplants and increase the number of usable donor livers?

KEY MESSAGES

- Machine perfusion is a new way to preserve donor livers using oxygen-rich fluids rather than storing them on ice (the standard method known as static cold storage, or SCS).
- There are three types of machine perfusion:
    1. Hypothermic oxygenated machine perfusion (**HOPE)**: cold preservation with oxygen
    2. Normothermic machine perfusion (**NMP)**: warm perfusion with oxygen
    3. Normothermic regional perfusion (**NRP)**: warm perfusion done inside the body before organs are removed.
- HOPE and NRP may improve liver transplant outcomes, especially in higher-risk donor livers. NMP may reduce early liver complications, but the evidence for long-term survival outcomes is less clear.
- Machine perfusion might also increase the number of donor livers available for transplant by making it possible to use organs that would normally be discarded.

What is the problem?

Liver transplantation is life-saving but is limited by a shortage of suitable donor livers to meet demand. Some livers, such as those from donors after circulatory death (DCD), are considered higher risk and have not traditionally been used for transplants. Machine perfusion could help preserve these organs better and make them safer to transplant.

What did we want to find out?

We wanted to know if machine perfusion works better than static cold storage (keeping the liver on ice) for high-risk livers, especially in terms of liver and patient survival after transplant.

What did we do?

We conducted a meta-analysis, a statistical method to summarize the results of many different studies to get a more reliable overall estimate. We included recent studies comparing machine perfusion to cold storage, focusing on graft and patient survival, early liver problems (called early allograft dysfunction), and damage to the bile ducts (non-anastomotic biliary strictures). We included studies on both brain death (DBD) and circulatory death (DCD) donors.

What did we find?

Based on 10 clinical trials (n=1513 participants) and 3 non-randomized studies (1038 participants), we found that:

- **HOPE** may reduce the risk of graft failure and early liver complications after transplant, especially in high-risk brain death donor livers, though patient survival impact is unclear.
- **NMP** may help reduce early liver problems (EAD), but the evidence for impact on liver and patient survival is inconclusive.
- **NRP** seems promising for high-risk DCD livers and may lead to better survival and fewer complications, but the evidence comes from non-randomized studies, so we are less confident in the results.
- Machine perfusion, especially NMP, may also help expand the donor pool. In Quebec, up to 42% of livers discarded between 2022 and 2024 were estimated to be very likely or potentially salvageable using machine perfusion, while a large U.S. study projected hundreds more transplants could happen annually if these technologies are used.

How reliable is the evidence?

Most of the evidence was low certainty, meaning we have low to moderate confidence in the results. Therefore, stronger studies are needed before it becomes standard practice.

Bottom line

Machine perfusion shows promise for improving liver transplant outcomes and making more livers available, especially with suboptimal donors. HOPE and NRP appear most beneficial based on current evidence, while more research is needed to confirm the role of NMP. These advances could help reduce wait times and waitlist mortality.

EN BREF

La perfusion mécanique peut-elle améliorer les résultats des transplantations hépatiques et augmenter le nombre de foies utilisables ?

MESSAGES CLÉS

• La perfusion mécanique est une nouvelle méthode de conservation des foies de donneurs utilisant des fluides riches en oxygène plutôt que de les conserver dans de la glace (méthode standard appelée conservation statique au froid (CSF)).

• Il existe trois types de perfusion mécanique :

1. La perfusion mécanique hypothermique oxygénée (**HOPE**) : conservation à froid avec de l'oxygène
2. La perfusion normothermique par machine (**PNM**) : perfusion chaude avec de l'oxygène
3. La perfusion régionale normothermique (**PRN)** : perfusion chaude réalisée à l'intérieur du corps avant le prélèvement des organes.

• La HOPE et la PRN pourraient améliorer les résultats des transplantations hépatiques, en particulier chez les donneurs à haut risque. La PNM pourrait réduire les complications hépatiques précoces, mais les données sur la survie à long terme sont moins claires.

• La perfusion mécanique pourrait également augmenter le nombre de foies de donneurs disponibles pour la transplantation en permettant l'utilisation d'organes qui seraient normalement éliminés.

Quel est le problème ?

La transplantation hépatique permet de sauver des vies, mais elle est limitée par la pénurie de foies de donneurs compatibles pour répondre à la demande. Certains foies, comme ceux issus de donneurs après décès cardiocirculatoire (DDC), sont considérés comme présentant un risque plus élevé et ne sont traditionnellement pas utilisés pour les transplantations. La perfusion mécanique pourrait contribuer à mieux préserver ces organes et à rendre leur transplantation plus sûre.

Que souhaitions-nous découvrir ?

Nous voulions savoir si la perfusion mécanique était plus efficace que la conservation statique au froid (conservation du foie dans la glace) pour les foies à haut risque, notamment en termes de survie du foie et du patient après la transplantation.

Qu'avons-nous fait ?

Nous avons réalisé une méta-analyse, une méthode statistique permettant de synthétiser les résultats de nombreuses études différentes afin d'obtenir une estimation globale plus fiable. Nous avons inclus des études récentes comparant la perfusion mécanique à la conservation statique au froid, en nous concentrant sur la survie du greffon et du patient, les problèmes hépatiques précoces (appelés dysfonctionnement précoce de l'allogreffe ou DPA) et les lésions des voies biliaires (sténoses biliaires non anastomotiques ou SBNA). Nous avons également inclus des études portant sur des donneurs après décès neurologique (DDN) et après décès cardiocirculatoire (DDC).

Qu'avons-nous découvert ?

Sur la base de 10 essais cliniques (n = 1 513 participants) et de 3 études non randomisées (1 038 participants), nous avons constaté que :

- HOPE pourrait réduire le risque d'échec du greffon et de complications hépatiques précoces après la transplantation, en particulier chez les donneurs après décès neurologique, bien que l'impact sur la survie des patients ne soit pas clair.
- La PNM pourrait contribuer à réduire les problèmes hépatiques précoces (DPA), mais les preuves de son impact sur la survie du foie et des patients ne sont pas concluantes.
- La PRN semble prometteuse pour les foies de DDC et pourrait améliorer la survie et réduire les complications. Cependant, les preuves proviennent d'études non randomisées, ce qui nous rend les résultats moins fiables.
- La perfusion mécanique, en particulier la PNM, pourrait également contribuer à élargir le bassin de donneurs. Au Québec, on estime que jusqu'à 42 % des foies refusés entre 2022 et 2024 pourraient très probablement ou potentiellement être récupérés grâce à la perfusion mécanique, tandis qu'une vaste étude américaine prévoit que des centaines de transplantations supplémentaires pourraient avoir lieu chaque année si ces technologies sont utilisées.

Quelle est la fiabilité des données probantes ?

La plupart des données probantes étaient de faible certitude, ce qui signifie que nous avons une confiance faible à modérée dans les résultats. Par conséquent, des études plus approfondies sont nécessaires avant qu'elle ne devienne une pratique standard.

En résumé

La perfusion mécanique est prometteuse pour améliorer les résultats des transplantations hépatiques et rendre plus de foies disponibles, en particulier chez les donneurs sous-optimaux. Les protocoles HOPE et PRN semblent les plus bénéfiques d'après les données actuelles, tandis que des recherches supplémentaires sont nécessaires pour confirmer le rôle du PNM. Ces avancées pourraient contribuer à réduire les temps d'attente et la mortalité.

EXECUTIVE SUMMARY

BACKGROUND

Liver transplantation is a life-saving intervention for patients with end-stage liver disease. While most transplants have traditionally used organs from donors after brain death (DBD), transplantation programs have increasingly turned to donors after circulatory death (DCD), a subset of extended criteria donors (ECD) with higher risk profiles, to expand the donor pool and reduce waitlist mortality.

Successful liver transplantation relies on a well-preserved donor liver. Historically, static cold storage (SCS), also referred to as 'ice-box storage', has been the standard method for preserving liver grafts between procurement and transplantation. Machine perfusion, an organ preservation technique to perfuse the graft with oxygen and thus reduce ischemic time (lack of blood supply), has been proposed as a means to better preserve marginal donor livers and improve organ quality. **Hypothermic oxygenated machine perfusion (HOPE)** preserves the liver at hypothermic conditions of 4–8°C while supplying oxygen, whereas **normothermic machine perfusion (NMP)** maintains perfusion of the portal venous and arterial systems under normothermic conditions of 37°C. In-situ **normothermic regional perfusion (NRP)** incorporates extracorporeal membrane oxygenation (ECMO) to perfuse oxygenated blood to DCD organs at 37°C.

There is province and nation-wide interest in increasing organ utilization rates, particularly in liver transplantation. Dr. Prosanto Chaudhury, Director of the Multi-Organ Transplant and Donation Program at the McGill University Health Centre requested an evaluation by TAU to determine the clinical benefit of using machine perfusion technologies in liver transplantation, with the goal of requesting funding from the Ministry.

POLICY QUESTION

Should machine perfusion be used for liver transplantation at the MUHC?

EVALUATION QUESTIONS (Objectives of this report)

The objectives of this report were to evaluate:

1. The impact of hypothermic oxygenated perfusion on liver transplant clinical outcomes compared to static cold storage.
2. The impact of normothermic machine perfusion on liver transplant clinical outcomes compared to static cold storage.
3. The impact of normothermic regional perfusion on liver transplant clinical outcomes compared to static cold storage for patients receiving circulatory death donor (DCD) livers.

4. The impact of the type of liver donor, i.e. donation after circulatory death donors (DCD) vs donation after brain death donors (DBD) on liver transplant clinical outcomes.

METHODS

We performed a search on PubMed, Medline, Embase, and ClinicalTrials.gov of available studies published 2023 to update the most recent Cochrane review (2023). We conducted a meta-analysis of relevant studies using the inclusion criteria shown below. Two reviewers independently assessed the risk of bias for each outcome for the included studies and rated the overall quality of evidence.

- Population: recipients of livers from DBD, DCD or other extended criteria donors.
- Intervention: three modalities: HMP/HOPE, NMP, and NRP
- Comparator: cold static storage
- Primary outcomes: graft and patient survival
- Secondary outcomes: early allograft dysfunction (EAD) and non-anastomotic biliary strictures (NAS)

RESULTS

Objective 1: HOPE vs Cold Storage

We identified six relevant RCTs for our meta-analysis of HOPE machine perfusion on liver transplant outcomes compared to static cold storage and evaluated the corresponding quality of evidence. All but one study included DBD livers. The certainty of evidence was low for all outcomes except EAD (moderate certainty) due to concerns with randomization and imprecision (low number of events).

Graft survival

- Our meta-analysis (5 RCTs, 62 events in 586 participants) found a 54% decreased risk of graft failure at 12 months in HOPE vs SCS (HR 0.46; 95% CI 0.26 to 0.81).

Patient survival

- Results of our meta-analysis (4 RCTs, 39 patient deaths in 416 participants) were inconclusive for impact of HOPE vs SCS on patient death at 12 months (HR 0.89; 95% CI 0.37 to 2.11).

Early allograft dysfunction (EAD)

- Pooled estimates (6 RCTs, 195 events in 725 participants) showed a 57% decreased risk of EAD in HOPE vs SCS (OR 0.43, 95% CI 0.28, 0.65).

Non-anastomotic biliary strictures (NAS)

- Risk of NAS decreased by 61% in HOPE vs SCS (OR 0.27; 95% CI 0.11 to 0.66) based on our meta-analysis of 4 RCTs (34 events in 569 participants).

Objective 2: NMP vs Cold Storage

We identified four relevant RCTs for our meta-analysis of the impact of NMP machine perfusion on liver transplant outcomes compared to static cold storage. Studies included a mix of DBD and DCD livers. The certainty of evidence was low for all outcomes due to concerns with randomization, deviations from intended interventions or missing outcome data and imprecision (low number of events).

Graft survival

- Our meta-analysis (2 RCTs, 24 graft failures in 486 participants) found no statistically significant difference in risk of graft failure at 12 months for NMP vs SCS (HR 0.90; 95% CI 0.35 to 2.31).

Patient survival

- There was no statistically significant difference in risk of patient death at 12 months in NMP vs SCS (HR 1.72; 95% CI 0.54 to 5.46) based on our meta-analysis (2 RCTs, 17 patient deaths in 486 participants).

Early allograft dysfunction (EAD)

- Risk of EAD was reduced by 48% in NMP vs SCS (OR 0.52; 95% CI 0.27 to 0.98) based on our meta-analysis of 4 RCTs (174 events in 788 participants).

Objective 3: NRP vs Cold Storage

A meta-analysis by Liang evaluated the impact of NRP machine perfusion compared to SCS on EAD and NAS in patients who received controlled DCD from three observational studies. We used the same three studies to evaluate graft and patient survival. The certainty of evidence was low for all outcomes mainly due to a lack of adjustment for confounding factors.

Graft survival:

- Our meta-analysis (3 studies, 192 events in 1038 participants receiving a DCD liver) showed a 58% decreased risk of graft failure at 12 months for NRP compared to SCS (HR 0.42; 95% CI 0.32, 0.55).

Patient survival

- Pooled results from our meta-analysis (2 studies, 101 events in 872 participants) showed that the risk of patient death at 12 months decreased by 52% in NRP vs SCS (HR 0.48; 95% CI 0.35 to 0.67).

Early allograft dysfunction (EAD)

- From Liang et al., three studies (197 events in 1038 participants) showed that NRP decreased EAD by 42% compared to SCS (OR 0.58; 95% CI 0.42 to 0.80).

Non-anastomotic biliary strictures (NAS)

Liang et al.'s meta-analysis of two studies (37 events from 235 participants) showed the likelihood of having NAS declined by 72% in NRP vs SCS (OR 0.28; 95% CI 0.11 to 0.69).

Objective 4: Impact of type of donor

DCD vs. DBD with HOPE

We conducted a subgroup analysis for HOPE vs. SCS by comparing liver transplant patients who received organs from brain death (DBD) versus circulatory death donors (DCD). Only one of the four RCTs by van Rijn et al. was done using DCD livers. The certainty of evidence for all outcomes was low due to deviations from intended interventions and imprecision (low number of events).

Graft survival

- Our subgroup analysis showed that HOPE reduced the risk of graft failure compared to SCS in DBD (HR 0.42; 95% CI 0.22 to 0.80), but not in DCD (HR 0.65; 95% CI 0.18 to 2.32). However, the subgroup difference was not statistically significant (p=0.55).

Patient survival

- Our results indicate that there were no statistically significant differences in patient survival for HOPE vs. SCS in either DBD (HR 0.55; 95% CI 0.23 to 1.30) or DCD (HR 2.45; 95% CI 0.77 to 7.82).

Early allograft dysfunction (EAD)

- Our subgroup analysis showed that HOPE lowered the likelihood of EAD compared to SCS in DBD (OR 0.40; 95% CI 0.24 to 0.69) but not in DCD (OR 0.52; 95% CI 0.26 to 1.03). The subgroup difference was not statistically significant (p=0.65).

Non-anastomotic biliary strictures (NAS)

- HOPE lowered the likelihood of NAS compared to SCS in DBD (OR 0.21; 95% CI 0.05 to 0.97) and in DCD (OR 0.31; 95% CI 0.11 to 0.92). However, the subgroup difference was not statistically significant (p=0.68).

DCD vs. DBD with NMP

We could not perform subgroup analysis by type of donor for NMP vs. SCS because all four RCTs were done in a mixed population including both DBD and DCD livers.

Controlled DCD with NRP vs. DBD with SCS

A meta-analysis of eight observational studies found no significant differences in graft or patient survival, early allograft dysfunction, or biliary complications between controlled DCD livers preserved with NRP and DBD livers with cold storage. However, these findings should be interpreted cautiously, as a formal non-inferiority analysis was not performed.

Impact on donor organ availability

Machine perfusion has shown strong potential to expand the donor liver pool and reduce waitlist mortality. In the UK, the VITTAL trial demonstrated that 71% of previously discarded livers were successfully transplanted using NMP, with excellent long-term outcomes. A U.S. simulation projected that widespread NMP use could lead to 385 additional DCD transplants annually—a 5.8% increase in transplant volume. In Quebec, a recent review estimated that 42% of livers discarded between 2022 and 2024 were very likely or potentially salvageable using this technology, highlighting its promise to improve donor organ availability.

CONCLUSIONS

Hypothermic Oxygenated Perfusion (HOPE):

- Low to moderate certainty evidence indicates that HOPE may improve clinically relevant outcomes when compared to SCS, specifically for graft survival, early allograft dysfunction and non-anastomotic biliary stricture.
- However, results were inconclusive for patient survival at 12 months. Given the small numbers, we do not know the impact of HOPE on mortality as the data to date is compatible with both meaningful increases or decreases in mortality.
- Overall, consistent results from recent RCTs and meta-analyses provide moderate certainty that HOPE improves graft function and survival compared to SCS.

Normothermic Machine Perfusion (NMP):

- Low certainty evidence indicates that NMP was not associated with improved graft or patient survival, but may improve early allograft dysfunction when compared to SCS.
- These findings indicate that while NMP may help mitigate the effects of ischemia-reperfusion injury and improve early graft function, its impact on long-term survival remains unclear; given the small numbers, the data to date are compatible with both meaningful increases or decreases in mortality.
- Overall, the high risk of bias in the individual studies, lack of demonstrated impact on graft or patient survival, and inconsistent results from recent trials, provide low certainty that NMP improves downstream survival outcomes compared to SCS.

Normothermic Regional Perfusion (NRP):

- Low certainty evidence indicates that NRP improves graft and patient survival and decreases early allograft dysfunction and non-anastomotic biliary stricture in DCD livers when compared to SCS.

- NRP is the recommended machine perfusion modality in Europe for DCD livers, likely due to its ability to restore oxygenated blood flow before organ retrieval, thereby mitigating ischemic injury. Therefore, NRP may be especially effective for DCD liver transplantation.
- However, there is low certainty in this evidence because all three studies were observational and at high risk of confounding bias.

- There is emerging evidence that machine perfusion might also increase the number of donor livers available for transplant by making it possible to use organs that would normally be discarded.
- Overall, the findings from this evaluation suggest that machine perfusion techniques, particularly HOPE and NRP, may offer clinical benefits over SCS in certain patient populations. The evidence for NMP on survival outcomes remains inconclusive.
- Given the low to moderate certainty evidence across all modalities, these results should be interpreted with caution and underscore the need for further investigation to better understand the comparative effectiveness of these techniques.

RECOMMENDATIONS

- Given the best available evidence indicating that machine perfusion techniques, particularly hypothermic oxygenated machine perfusion (HOPE) and normothermic regional perfusion (NRP), may improve graft survival in DBD livers (including those with extended criteria) and in DCD livers, respectively, the TAU Policy committee recommends that:
  - There is justification for considering the implementation of machine perfusion technologies within the transplant program in Quebec to improve clinical outcomes and address the critical issue of organ shortage.
  - It would be important to assess the cost-effectiveness of adding these modalities to the provincial transplant program.
  - Any pilot of these techniques should ensure the prospective collection of data on the following variables:
    - Number of liver transplants perfused with each modality;
    - Donor characteristics;
    - Clinical outcomes (graft viability, short and long-term patient survival);
    - Patient-reported outcomes;
    - Associated costs

SOMMAIRE

Perfusion mécanique pour la transplantation hépatique

CONTEXTE

La transplantation hépatique est une intervention qui permet de sauver la vie de patients souffrant d'une maladie du foie en phase terminale. La plupart des transplantations sont généralement réalisées avec des organes provenant de donneurs après décès neurologique (DDN). Cependant, les programmes de transplantation font de plus en plus appel à des donneurs après décès cardiocirculatoire (DDC), un sous-ensemble de personnes répondant à des critères élargis et qui présentent des profils de risque plus élevés. Cette approche visa à accroître le bassin de donneurs et à réduire la mortalité chez les patients en attente d'une transplantation.

La réussite d'une transplantation hépatique repose sur la bonne conservation du foie du donneur. Historiquement, la conservation statique au froid (CSF), également appelée conservation hypothermique, a été la méthode standard pour la conservation des greffons hépatiques entre le moment du prélèvement et celui de la transplantation. La perfusion mécanique, une technique de préservation d'organes consistant à perfuser le greffon avec de l'oxygène et de réduire ainsi le temps d'ischémie (interruption de la circulation sanguine), est aujourd'hui proposée comme solution pour mieux préserver les foies de donneurs marginaux et améliorer la qualité de l'organe. La **perfusion hypothermique oxygénée** (connue sous son acronyme anglais **HOPE**) préserve le foie dans des conditions hypothermiques de 4 à 8 °C tout en lui fournissant de l'oxygène, tandis que la **perfusion normothermique par machine (PNM)** maintient les systèmes porte veineux et artériels dans des conditions normothermiques de 37 °C. La **perfusion régionale normothermique** in situ **(PRN)** fait appel à l'oxygénation par membrane extracorporelle pour perfuser du sang oxygéné aux organes des DDC à 37°°C.

L'augmentation des taux d'utilisation des organes, en particulier pour la transplantation hépatique, suscite l'intérêt des provinces et du pays tout entier. Ainsi, le Dr Prosanto Chaudhury, directeur du programme de transplantation et de don d'organes multiples au Centre universitaire de santé McGill (CUSM), a demandé à l'Unité d'évaluation des technologies de déterminer les avantages cliniques des technologies de perfusion mécanique pour la transplantation hépatique, dans le but de solliciter un financement auprès du ministère.

QUESTION STRATÉGIQUE

Le CUSM devrait-il utiliser la perfusion mécanique pour la transplantation hépatique?

QUESTIONS D'ÉVALUATION

Le présent rapport vise à évaluer les points suivants :

5. Les répercussions de la HOPE sur les résultats cliniques de la transplantation hépatique par rapport à la CSF.
6. Les répercussions de la PNM sur les résultats cliniques de la transplantation hépatique par rapport à la CSF.
7. Les répercussions de la PRN sur les résultats cliniques de la transplantation hépatique par rapport à la CSF pour les patients recevant des greffons hépatiques d'un DDC.
8. Les répercussions du type de donneur de greffon hépatique (DDC par rapport à un DDN) sur les résultats cliniques de la transplantation hépatique.

MÉTHODES

Nous avons recherché les études publiées en 2023 et disponibles sur PubMed, Medline, Embase et ClinicalTrials.gov pour mettre à jour la revue Cochrane la plus récente (2023). Ensuite, nous avons effectué une méta-analyse des études pertinentes en utilisant les critères d'inclusion indiqués ci-dessous. Enfin, deux évaluateurs ont évalué indépendamment le risque de biais pour chaque résultat des études incluses et ont évalué la qualité globale des données probantes.

- Population : receveurs de foies provenant de DDC, de DDN ou d'autres donneurs répondant à des critères élargis.
- Trois méthodes d'intervention : HOPE, PNM et PRN
- Comparateur : CSF
- Résultats primaires : survie du greffon et du patient
- Résultats secondaires : dysfonctionnement précoce de l'allogreffe (DPA) et sténose biliaire non anastomotique (SBNA)

RÉSULTATS

Objectif n °1 : comparaison entre la HOPE et la CSF

Nous avons pris en considération six essais cliniques randomisés (ECR) pertinents dans le cadre de notre méta-analyse de la perfusion mécanique par HOPE sur les résultats de la transplantation hépatique par rapport à la CSF. Nous avons ensuite évalué la qualité des données probantes correspondantes. Tous les essais, sauf un, comprenaient des foies provenant de DDC. Le degré de certitude des données probantes était faible pour tous les

résultats, à l'exception de ceux portant sur le DPA (degré de certitude modéré), en raison de problèmes de randomisation et d'imprécision (faible nombre d'événements).

Survie du greffon

- Les résultats de notre méta-analyse (5 ECR et 62 événements chez 586 personnes) révèlent que le risque d'échec de la greffe après 12 mois diminue de 54 % avec la HOPE par rapport à la CSF (rapport de risque [RR] 0,46; intervalle de confiance [IC] à 95 % de 0,26 à 0,81).

Survie du patient

- Les résultats de notre méta-analyse (4 ECR et 39 décès chez 416 personnes) n'indiquent aucune différence statistiquement significative entre la HOPE et la CSF en ce qui concerne les décès de patients après 12 mois (RR 0,89; IC à 95 % de 0,37 à 2,11).

DPA

- Les estimations regroupées (6 ECR et 195 événements chez 725 personnes) révèlent que le risque de DPA diminue de 57 % avec la HOPE par rapport à la CSF (rapport de cotes [RC] 0,43; IC à 95 % de 0,28 à 0,65).

SBNA

- Les résultats de notre méta-analyse (4 ECR et 34 événements chez 569 personnes) indiquent que le risque de SBNA diminue de 61 % avec la HOPE par rapport à la CSF (RC 0,27; IC à 95 % de 0,11 à 0,66).

Objectif n °2 : Comparaison entre la PNM et la CSF

Nous avons pris en considération quatre ECR pertinents dans le cadre de notre méta-analyse des répercussions de la PNM sur les résultats de la transplantation hépatique par rapport à la CSF. Les essais ont porté sur un mélange de foies provenant de DDN et de DDC. Le degré de certitude des données probantes était faible pour tous les résultats en raison de problèmes de randomisation, d'écarts par rapport aux interventions prévues, de données manquantes sur les résultats et d'imprécision (faible nombre d'événements).

Survie du greffon

- Les résultats de notre méta-analyse (2 ECR et 24 échecs de greffes chez 486 personnes) ne révèlent aucune différence statistiquement significative entre la PNM et la CSF en ce qui concerne le risque d'échec de la greffe après 12 mois (RR 0,90; IC à 95 % de 0,35 à 2,31).

Survie du patient

- Les résultats de notre méta-analyse (2 ECR et 17 décès chez 486 personnes) n'indiquent aucune différence statistiquement significative entre la PNM et la CSF

en ce qui concerne le risque de décès du patient après 12 mois (RR 1,72; IC à 95 % de 0,54 à 5,46).

DPA

- Les résultats de notre méta-analyse (4 ECR et 174 événements chez 788 personnes) révèlent que le risque de DPA diminue de 48 % avec la HOPE par rapport à la CSF (RC 0,52; IC à 95 % de 0,27 à 0,98).

Objectif n °3 : Comparaison entre la PRN et la CSF

Le Dr Liang a réalisé une méta-analyse de trois études d'observation pour évaluer les répercussions de la PRN et de la CSF sur les risques de DPA et de SBNA chez les patients ayant reçu un foie d'un DDC dans un cadre contrôlé. Dans l'une de ces études, les médecins ont eu consécutivement recours à la HOPE pour 25 % des greffons de DDC préservés par PRN, et 40 % des greffons de DDC préservés par CSF. Nous avons utilisé les trois mêmes études pour évaluer la survie des greffons et des patients. Le degré de certitude des données probantes était faible pour tous les résultats, principalement en raison d'un manque d'ajustement pour les facteurs de confusion.

Survie du greffon

- Les résultats de notre méta-analyse (3 études et 192 événements chez 1 038 personnes recevant un foie d'un DDC) indiquent que le risque d'échec de la greffe après 12 mois diminue de 58 % avec la PRN par rapport à la CSF (RR 0,42; IC à 95 % de 0,32 à 0,55).

Survie du patient

- Les résultats de notre méta-analyse (2 études et 101 événements chez 872 personnes) indiquent que le risque de décès après 12 mois diminue de 52 % avec la PRN par rapport à la CSF (RR 0,48; IC à 95 % de 0,35 à 0,67).

DPA

- D'après Liang et coll., trois études (197 événements chez 1 038 personnes) révèlent que le risque de DPA diminue de 42 % avec la PRN par rapport à la CSF (RC 0,58; IC à 95 % de 0,42 à 0,80).

SBNA

- La méta-analyse menée par Liang et coll. portant sur deux études (37 événements chez 235 personnes) indique que le risque de SBNA diminue de 72 % avec la PRN par rapport à la CSF (RC 0,28; IC à 95 % de 0,11 à 0,69).

Objectif n °4 : Incidence du type de donneur

HOPE : comparaison entre les DDC et les DDN

Nous avons effectué une analyse des différents sous-groupes pour les deux techniques (HOPE et CSF) et comparé les résultats des patients ayant subi une transplantation hépatique de greffons de DDN et de DDC. Un seul des quatre ECR menés par la Dr van Rijn et coll. portait sur des foies de DDC. Le degré de certitude des données probantes pour tous les résultats était faible en raison d'écarts par rapport aux interventions prévues et de l'imprécision (faible nombre d'événements).

Survie du greffon

- Les résultats de notre analyse des sous-groupes démontrent que la HOPE diminue le risque d'échec de la greffe chez les patients ayant reçu un foie de DDN par rapport à la CSF (RR 0,42; IC à 95 % de 0,22 à 0,80), mais pas chez les patients ayant reçu un foie de DDC (RR 0,65; IC à 95 % de 0,18 à 2,32). Cependant, la différence entre les sous-groupes n'est pas statistiquement significative (p = 0,55).

Survie du patient

- Nos résultats ne révèlent pas de différences statistiquement significatives entre la HOPE et la CSF en ce qui concerne la survie des patients ayant reçu un foie de DDN (RR 0,55; IC à 95 % de 0,23 à 1,30) ou un foie e DDC (RR 2,45; IC à 95 % de 0,77 à 7,82).

DPA

- Notre analyse des sous-groupes révèle que la HOPE réduit le risque de DPA par rapport à la CSF chez les patients ayant reçu un foie de DDN (RC 0,40; IC à 95 % de 0,24 à 0,69), mais pas chez les patients ayant reçu un foie de DDC (RC 0,52; IC à 95 % de 0,26 à 1,03). La différence entre les sous-groupes n'est pas statistiquement significative (p = 0,65).

SBNA

- Notre analyse indique que la HOPE réduit le risque de SBNA chez les patients ayant reçu un foie de DDN (RC 0,21; IC à 95 % de 0,05 à 0,97) ou un foie de DDC (RC 0,31; IC à 95 % de 0,11 à 0,92). Cependant, la différence entre les sous-groupes n'est pas statistiquement significative (p = 0,68).

PNM : comparaison entre les DDC et les DDN

Nous n'avons pas pu réaliser d'analyse de sous-groupes par type de donneur pour la PNM et la CSF, car les quatre ECR comportaient une population mixte comprenant à la fois des patients ayant reçu un foie de DDN et des patients ayant reçu un foie de DDC.

Foies de DDC préservés par PRN par rapport aux foies de DDN préservés par CSF

Une méta-analyse de huit études observationnelles n'a révélé aucune différence significative en termes de survie du greffon ou du patient, de dysfonctionnement précoce de l'allogreffe ou de complications biliaires les patients ayant reçu un foie de DDC préservé par PRN et les patients ayant reçu un foie de DDN préservé par CSF. Cependant, ces résultats doivent être interprétés avec prudence, car aucune analyse de non-infériorité formelle n'a été réalisée.

Impact sur la disponibilité des organes de donneurs

La perfusion mécanique a démontré un fort potentiel pour élargir le bassin de foies de donneurs et réduire la mortalité sur liste d'attente. Au Royaume-Uni, l'essai VITTAL a démontré que 71 % des foies précédemment éliminés ont été transplantés avec succès grâce à la PNM, avec d'excellents résultats à long terme. Une simulation américaine a projeté que l'utilisation généralisée de la PNM pourrait entraîner 385 transplantations de DDC supplémentaires par an, soit une augmentation de 5,8 % du volume de transplantations. Au Québec, une étude récente a estimé que 42 % des foies éliminés entre 2022 et 2024 étaient très probablement ou potentiellement récupérables grâce à cette technologie, soulignant ainsi son potentiel d'amélioration de la disponibilité des organes de donneurs.

CONCLUSIONS

HOPE :

- Les données probantes, dont le degré de certitude est de faible à modéré, révèlent que la HOPE peut améliorer les résultats cliniques pertinents par rapport à la CSF, en particulier pour la survie du greffon et les risques de DPA et de SBNA.
- Cependant, les résultats ne sont pas concluants pour la survie des patients après 12 mois. Compte tenu du faible nombre d'individus, nous ne connaissons pas l'impact de HOPE sur la mortalité, car les données à ce jour sont compatibles avec des augmentations ou des diminutions cliniquement significatives de la mortalité.
- Des résultats cohérents d'ECR et de méta-analyses récents permettent d'affirmer avec un degré de certitude modéré que la HOPE améliore la fonction et la survie du greffon par rapport à la CSF.

PNM :

- Les données probantes, dont le degré de certitude est faible, indiquent que la PNM n'est pas associée à une amélioration de la survie du greffon ou du patient, mais qu'elle peut toutefois réduire les risques de DPA par rapport à la CSF.
- Ces résultats indiquent que même si la PNM peut aider à atténuer les effets des lésions d'ischémie-reperfusion et à améliorer la fonction précoce du greffon, son impact sur la survie à long terme reste incertain ; compte tenu du faible nombre d'individus, les données à ce jour sont compatibles avec des augmentations ou des diminutions cliniquement significatives de la mortalité.
- Le risque élevé de biais dans les études individuelles, l'absence d'incidence démontrée sur la survie du greffon ou du patient, et les résultats incohérents des essais récents ne permettent pas d'affirmer avec certitude que la PNM améliore les chances de survie en aval par rapport à la CSF.

PRN :

- Les données probantes, dont le degré de certitude est faible, indiquent que la PRN améliore la survie du greffon et du patient et diminue les risques de DPA et de SBNA chez les patients ayant reçu un foie de DDC par rapport à la CSF.
- La PRN est la méthode de perfusion mécanique recommandée en Europe pour les foies de DDC, probablement en raison de sa capacité à restaurer le flux sanguin oxygéné avant le prélèvement de l'organe, atténuant ainsi les lésions ischémiques. Par conséquent, la PRN peut s'avérer particulièrement efficace pour la transplantation hépatique de DDC.
- Cependant, le degré de certitude de ces données probantes est faible, car les trois études sont observationnelles et présentent un risque élevé de facteurs de confusion.

- De nouvelles preuves montrent que la perfusion mécanique pourrait également augmenter le nombre de foies de donneurs disponibles pour la transplantation en permettant d'utiliser des organes qui seraient normalement refusés.
- Dans l'ensemble, les résultats de cette évaluation suggèrent que les techniques de perfusion mécanique, en particulier la HOPE et la PRN, offrent des avantages cliniques par rapport à la CSF chez certaines populations de patients. Les données probantes sur les résultats en matière de survie ne sont pas concluantes pour la PNM.
- Compte tenu de la certitude faible à modérée des données probantes qui s'applique à toutes les méthodes d'intervention, ces résultats doivent être interprétés avec prudence et soulignent la nécessité de mener des recherches plus approfondies pour mieux comprendre l'efficacité comparative de ces techniques.

RECOMMANDATIONS

- Compte tenu des meilleures observations disponibles démontrant l'efficacité des techniques de perfusion mécanique (en particulier la perfusion hypothermique oxygénée [HOPE] et la perfusion régionale normothermique [PRN]) en matière de survie du greffon de foies d'un DDN (y compris ceux répondant à des critères élargis) et de foies d'un DDC, respectivement, le comité consultatif de l'Unité d'évaluation des technologies de la santé émet les recommandations suivantes :
    - Il est justifié d'envisager la mise en œuvre de technologies de perfusion mécanique dans le cadre du programme de transplantation au Québec afin d'améliorer les résultats cliniques et de s'attaquer au problème crucial que constitue la pénurie d'organes.
    - Il convient également d'évaluer le rapport coût-efficacité de l'ajout de ces techniques au programme provincial de transplantation.
    - Tout projet pilote sur ces techniques doit inclure un système prospectif de collecte de données sur les variables suivantes :
        - le nombre de greffons hépatiques perfusés avec chaque technique;
        - les caractéristiques des donneurs;
        - les résultats cliniques (viabilité du greffon, survie du patient à court et à long terme);
        - les résultats rapportés par les patients;
        - les coûts associés à la mise en œuvre de ces techniques.

Machine Perfusion for Liver Transplantation

1. BACKGROUND

1.1 Donor Types in Liver Transplantation

Liver transplantation, in which the damaged liver is replaced with a whole liver from a recently deceased donor or with a portion of a liver from a living donor, is indicated for patients with end-stage liver disease. The number of liver transplants has steadily increased in Canada, with 666 liver transplants in 2023, which comprised 19% of 3,428 organ transplants.(1)

Unfortunately, demand far outstrips the number of available donor livers. 79 patients died while waiting for a liver transplant in Canada, and 509 were still on the waitlist at the end of 2023. In Quebec, 119 patients received a liver graft in 2023, 15 died while on the waitlist, and 186 were still waiting at the end of 2023.(1) To address this donor shortage, transplantation programs have increasingly incorporated livers from marginal donors and therefore, preservation techniques such as machine perfusion have been proposed as a means to improve the quality of such donor livers.

1.1.1 Donors after brain death (DBD)

These comprise the majority of livers for transplantation due to their higher quality and are obtained from donors with a neurological determination of death.

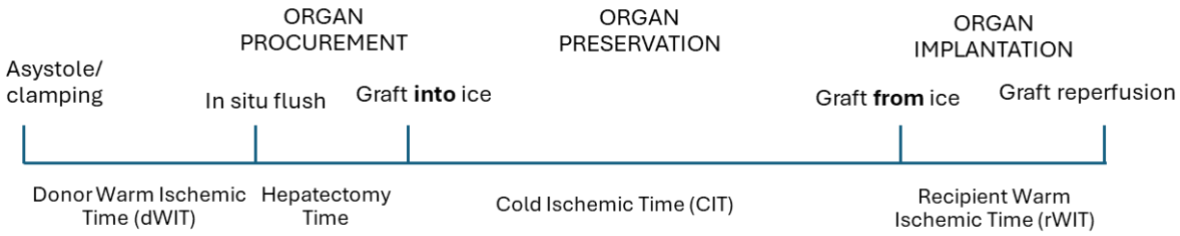
1.1.2 Donors after circulatory death (DCD)

These marginal donors fall within the category of **extended criteria organ donors** because such livers would have been previously discarded due to the presence of known risk factors for poorer outcomes, including older age, steatosis, higher body mass index, cardiovascular disease, and diabetes.(2)

Acccording to the Maastricht classification (3), DCD is further classified into:

- Uncontrolled: includes cardiocirculatory death in the out-of-hospital setting (category I) or after unsuccessful resuscitation (category II);
- Controlled: includes organs from patients awaiting cardiac arrest (category III), cardiac arrest while brain dead (category IV), or euthanasia (category V).

1.2 Modalities for Liver Preservation



Adapted from Lin Y, et al.(4)

Figure 1. Liver transplantation phases and ischemic time

1.2.1 Static cold storage

Static cold storage (SCS), also referred to as 'ice-box storage', traditionally has been the go-to method for preserving liver grafts from the time of procurement until pre-transplantation. With SCS, the donor graft is flushed with preservation solution before being stored under hypothermic conditions at 4–8 °C. However, SCS has its limitations, including the need for quick transplantation, the inability to evaluate organ quality in real-time, and susceptibility to ischemia-reperfusion injury (IRI) leading to post-transplantation complications.(5) "Although SCS slows metabolism by 10- to 12-fold, substantial anaerobic activity continues even at ice temperature."(6) Therefore, the use of SCS in marginal or high-risk livers is sub-optimal.

1.2.2 Machine perfusion modalities

Machine perfusion in liver transplantation is being increasingly incorporated to improve the quality of donor livers and decrease wait time and wait-list mortality. One of the proposed advantages of machine perfusion is to decrease the duration of cold ischemic time of the donor organ as shown in Figure 1 (4). Thus, the risk of IRI is reduced when the organ is re-exposed to oxygenated blood at the time of transplantation.

Machine perfusion techniques circulate a perfusate (a fluid that mimics blood) through the liver to ensure a supply of oxygen and nutrients, thus reducing ischemia-reperfusion injury. They also allow donor organ quality assessment before implantation. Techniques vary according to temperature and timing of use, as shown in Table 1 (5):

- In-situ technique: used before procurement
- Back-to-base technique or end-ischemic technique: used during the pre-implantation phase
- Ischemia-free liver transplantation (IFLT) technique: used from the time of procurement until pre-transplantation.

Table 1. Characteristics of Liver Donor Preservation Modalities

Preservation modalities	Temperature	Pre-procurement	Procurement	Transport	Pre-implantation
SCS	4^{0}C		Cold flush out	Cold storage	Cold storage
HMP LifePort® Liver Transporter	4-12^{0}C		Cold flush out	Cold storage	HMP
HOPE/ D-HOPE Liver Assist PerLife® Perliver® VitaSmart™ Perfusion System	4-12^{0}C		Cold flush out	Cold storage	HOPE/D-HOPE
NMP OrganOx Metra® Transmedics® Organ Care Systems™ Liver Assist PerLife® Perliver®	37^{0}C		Cold flush out	Cold storage	NMP
Continuous NMP OrganOx® Metra	37^{0}C		Cold flush out	NMP	NMP
Ischemic-free LT	37^{0}C		NMP	NMP	NMP
NRP	35-37^{0}C	NRP	Cold flush out	Cold storage	Cold storage

NMP: Normothermic machine perfusion; NRP: normothermic regional perfusion; HOPE: Hypothermic Oxygenated machine Perfusion, D-HOPE: dual HOPE; SCS: static cold storage

Hypothermic machine perfusion (HMP) is done by storing the donor liver under hypothermic conditions at 4–8 °C from procurement until it arrives at the receiving center. The machine will then perfuse the donor liver with cold, oxygenated acellular perfusate for 1-2 hours, or until the recipient hepatectomy is completed and the donor liver is ready to be transplanted. HMP that perfuses through the portal vein (PV) alone is called Hypothermic Oxygenated machine PErfusion (HOPE), while those that use dual perfusion through both the PV and hepatic artery (HA) are called Dual or D-HOPE. HMP is commonly used for DBD.(5)

Normothermic machine perfusion (NMP) delivers oxygenated perfusion of the portal venous and arterial systems under normothermic conditions at 37 °C. NMP can be used for in situ, end-ischemic, or IFLT techniques, for both DBD or DCD.(5) Compared to SCS, advantages of NMP include reduced cold ischemia duration and ability to assess graft viability before transplant.

In-situ normothermic regional perfusion (NRP) was initially developed for DCD after unsuccessful resuscitation (category II) but has now been used for broader DCD

categories. Abdominal NRP incorporates extracorporeal machine oxygenation (ECMO) to perfuse oxygenated blood to the abdominal organs via cannulae in the aorta and the inferior cava vein under normothermic conditions at 37 °C. This modality improves the quality of the preserved organ by warm oxygenated perfusion to avoid prolonged cold ischemia.(5)

1.3 Liver Transplant Outcomes

Clinically important outcomes in machine perfusion techniques for liver transplantation generally focus on **graft viability, post-transplant function, and patient survival**. The key outcomes we studied include:

1.3.1 Measures of graft viability

By reducing IRI and biliary complications, it was hypothesized that machine perfusion would improve graft viability, which are useful indicators of early transplant success.

- Early allograft dysfunction (EAD)(7):
    - EAD is an acute injury marker and validated surrogate for graft survival. According to the Olthoff criteria, EAD is defined as the presence of at least one of the following within the first seven postoperative days: bilirubin level > 10 mg/dL (i.e., 171 µmol/L), international normalized ratio (INR) > 1.6, or serum aspartate transaminase (AST) or alanine transaminase (ALT) level > 2000 IU/L. EAD occurs in 15 to 30% of post-DBD transplantations and can reach 68.4% post-DCD transplantations.
- Primary non-function (PNF)(8):
    - PNF is the very last stage of any EAD defined by a patient's death or the need for re-transplantation within the first seven postoperative days, excluding acute vascular complications. The frequency of PNF ranges from about 2% to over 9%.
- Biliary strictures(9):
    - Some researchers suggest that perfusion may "wash out" liver enzymes, leading to lower postoperative peak levels of AST and ALT, which are vital liver function markers. Consequently, reducing biliary complications was considered a more reliable indicator of liver preservation.
    - Biliary strictures are categorized into anastomotic and non-anastomotic biliary strictures (NAS). **Anastomotic strictures** are usually caused by fibrotic healing, surrounding the biliary anastomosis between the donor and the recipient. **Non-anastomotic strictures** involves biliary strictures and/or dilatations close to the anastomosis. NAS are longer and can involve multiple sites. They occur 3–6 months after liver transplantation, which is earlier than with anastomotic

strictures. NAS is further classified into ischemic biliary lesions (IBLs, caused by thrombosis in the hepatic artery) and ischemic-type biliary lesions (ITBLs, multifactorial causes including IRI, immunologically and bile salt-mediated injury).

1.3.2 Long-term survival outcomes

- 1-year graft survival post-transplantation (10):
  - Graft survival refers to the period during which the transplanted liver functions successfully, meaning it performs the necessary metabolic and detoxification functions of the liver. The event that marks the end of graft survival is either a retransplantation (if the graft fails and a new one is needed) or the death of the recipient due to the failure of the transplanted liver.
- 1-year patient survival(11)
  - Patient survival refers to the period from the transplant date to the patient's death from any cause.

1.4 Context of the Current Report

There is province and nation-wide interest in increasing organ utilization rates, particularly in liver transplantation. Dr. Prosanto Chaudhury, Director of the Multi-Organ Transplant and Donation Program at the McGill University Health Centre requested an evaluation by TAU to determine the clinical benefit of these technologies in this population, with the goal of requesting funding from the Ministry.

In 2023, a meta-analysis by the Cochrane group (Tingle et al. (12)) included seven parallel two-arms clinical trials to compare liver transplantation outcomes between machine perfusion and SCS. Four trials found that HOPE reduced EAD, biliary complications, and graft loss (improved graft survival) compared to SCS. These findings were evident among liver transplants with DBD but inconclusive in DCD. For NMP, three trials reported no impact except for EAD reduction in NMP compared to SCS. There were no trials that evaluated NRP. There were 10 ongoing trials listed by Tingle et al. with the last search done in January 2023. We, therefore, decided to update the search and conduct a meta-analysis by including more recently published clinical trials.

2. POLICY AND EVALUATION QUESTIONS

2.1 Policy Question

Should machine perfusion be used in liver transplant patients at the MUHC?

2.2 Evaluation Questions (Objectives of this report)

The objectives of this report were to evaluate:

1. The impact of hypothermic oxygenated perfusion on liver transplant clinical outcomes compared to static cold storage.
2. The impact of normothermic machine perfusion on liver transplant clinical outcomes compared to static cold storage.
3. The impact of normothermic regional perfusion on liver transplant clinical outcomes compared to static cold storage.
4. The impact of the type of liver donor, i.e. donation after circulatory death donors vs donation after brain death donors on liver transplant clinical outcomes.

3. METHODS

3.1 Literature Search

We conducted a scoping review by searching the PubMed and ClinicalTrials.gov using the following search terms: "machine perfusion" AND "liver transplant*". The last search was done on Jan 13, 2025. We limited the search to clinical trials in humans and adults. We also manually searched relevant studies from the references.

We separately searched for systematic reviews or meta-analysis on NRP in PubMed, Medline, and Embase databases because no controlled clinical trials evaluated this modality. We used the following search terms ("normothermic regional perfusion" or "regional perfusion" or "abdominal normothermic oxygenated recirculation") AND ("liver transplant*"). We limited the search to systematic review and meta-analyses in humans and adults.

3.2 PICO Components

Our inclusion criteria for the population, intervention and outcomes targeted are shown in Table 2.

Table 2. Population, intervention, control and outcomes

	Inclusion Criteria
Population	Recipients of livers from (i) donation after circulatory death (DCD) donors (ii) donation after brain death (DBD) donors (iii) extended criteria donors (ECD) (who are elderly; have hepatic steatosis, malignancies, or viral hepatitis)
Intervention	(i) Hypothermic (oxygenated) perfusion (HMP/HOPE/D-HOPE) (ii) Normothermic machine perfusion (NMP) (iii) Normothermic regional perfusion: thoracic abdominal (TA-NRP) and abdominal (A-NRP) focus on DCD
Comparator	Static cold storage (SCS)
Outcomes	• Primary outcome: ○ Patient survival ○ Graft survival • Secondary outcomes: Liver graft-related complications include: ○ early allograft dysfunction (EAD), and ○ non-anastomotic biliary strictures (NAS)

3.3 Data Extraction

Study selection was done by ES and data extraction were done independently by ES and TO and any discrepancies were resolved by consensus. The following variables were collected:

- Study characteristics: first author, year of publication, country
- Patient characteristics: donor criteria (age)
- Transplantation characteristics: donor and perfusion machine types
- Total number of patients per group (machine types, SCS)
- For graft and patient survival: we first collected the hazard ratio (HR) and 95% confidence interval (CI). When it was not available, we collected the number of events (i.e. graft loss and patient deaths), log-rank p-value, and information from Kaplan-Meier plots.
- For EAD and NAS: we first collected the odds ratio (OR) and 95% CI. When it was not available, we collected the absolute number or the percentage of events.

3.4 Assessment of Bias and Quality of Evidence

3.4.1 Risk of bias

Two reviewers independently assessed the risk of bias for each outcome for the included studies using the Cochrane Risk of Bias Tool for Randomized Trials (RoB 2.0) (11). For the risk of bias for observational studies, we used the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool (12). For all studies, risk of bias was done for each outcome result (11)(12).

- RoB 2.0 tool covers five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. Each domain was graded as high, moderate (some concerns or unclear) or low risk of bias.
- ROBINS-I covers seven domains: bias arising from the confounding, selection of participants, classification of interventions, deviations from intended interventions, missing outcome data, measurement of the outcome, and the selection of the reported result. Each domain was graded as critical, serious, moderate, or low risk of bias.
- A study is considered as having a low overall risk of bias when all domains have a low risk. We considered a high overall risk of bias when at least one domain had a high risk of bias for RCTs or a serious/critical risk of bias for observational studies. Other situations will be considered as moderate risk of bias.
- For bias in the measurement of the outcome domains, the risk of bias is considered low despite a lack of blinding for hard outcomes (i.e. patient and graft survival) and outcomes with objective indicators (e.g. EAD, NAS).

3.4.2 Certainty of the evidence

We rated the overall certainty of evidence as high, moderate or low for each outcome using an in-house decision tree, which was based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) quality assessment (13). Our tool has six domains: overall risk of bias of the included studies, the absence of controlled group, imprecision (i.e. wide confidence intervals, low number of events (<300 for categorical outcomes), and small sample size for continuous outcomes), inconsistency, indirectness, and others (e.g. commercially funded study or improper statistical analytical tests). Low-certainty evidence indicates that our confidence in the overall effect estimate is limited. High certainty evidence is considered for outcomes from studies with a low overall risk of bias and without downgrading from the above domains. Elements of the domains and the decision tree are detailed in Appendix A:.

3.5 Meta-analysis

- Pooled effect sizes of the included studies were estimated as odds ratios (OR) with their 95% confidence intervals (CI) for EAD and NAS, and hazard ratios (HR) and 95% CI for patient and graft survivals. For studies that did not report HR and its 95% CI, we approximated them using the method by Tierney et al. (14).
- A random-effects model (restricted maximum likelihood) was used since the preliminary literature review showed that the populations and interventions were not sufficiently similar across the trials.
- Individual and pooled estimates with their 95% CI were presented in forest plots by outcome. The corresponding traffic light for the risk of bias assessment was added to these forest plots.
- We assessed the heterogeneity in the effect estimates and between-study by calculating I^2 and τ^2 statistics and inspecting the forest plots. Substantial heterogeneity was defined as $I^2 > 50$ and possible sources of heterogeneity were investigated, when plausible as the number of studies was small.
- Subgroup analyses were performed to address the fourth objective about the impact of types of donors (DBD vs. DCD) on liver transplant outcomes.
- Bilateral p-values of 0.05 and confidence intervals were used to assess statistical significance. All analyses were performed with software R v4.4.2.

4. RESULTS

We identified six relevant RCTs for our meta-analysis of HOPE (17-22) and four for NMP (2, 6, 23, 24) compared to static cold storage (Figure 2). The characteristics of the studies are displayed in Table 4. We did not find any clinical trials for NRP. Nonetheless, we found two relevant meta-analyses (25, 26) of observational studies that compared NRP to static cold storage (Figure 3).

4.1 Objective 1: HOPE vs. Cold Storage

The impact of HOPE machine perfusion on liver transplant outcomes compared to static cold storage and the corresponding quality of evidence are summarized in Table 5.

4.1.1 Graft survival

- Our meta-analysis (5 RCTs, 62 events in 586 participants) showed that the hazard (instantaneous risk) of graft failure at 12 months was reduced by 54% in HOPE vs SCS (HR 0.46; 95% CI 0.26 to 0.81) (Figure 4).

- The certainty of evidence was low: it was downgraded due to a high risk of bias arising from a lack of information on concealment in the randomization process and deviations from intended interventions. It was downgraded further for imprecision, i.e. wide confidence intervals, probably due to the small sample size.

4.1.2 Patient survival

- Results of our meta-analysis (4 RCTs, 39 patient deaths in 416 participants) indicate no statistically significant difference in patient survival for HOPE in comparison to SCS (HR 0.89; 95% CI 0.37 to 2.11) (Figure 5).
- The certainty of evidence was low: it was downgraded due to a lack of concealment information in the randomization process. It was downgraded further for imprecision in effect estimates.

4.1.3 Early allograft dysfunction (EAD)

- Our meta-analysis (6 RCTs, 195 events in 725 participants) showed a 57% decreased risk of EAD in HOPE vs SCS (OR 0.43; 95% CI 0.28 to 0.65) (Figure 6).
- The certainty of evidence was moderate: it was downgraded for risk of bias mainly due to deviations from intended interventions.

4.1.4 Non-anastomotic strictures (NAS)

- Summary estimates of our meta-analysis (4 RCTs, 34 events in 569 participants) showed a reduction in NAS of 61% in HOPE vs SCS (OR 0.27; 95% CI 0.11 to 0.66) (Figure 7).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to deviations from intended interventions, and further downgraded for imprecision.

4.2 Objective 2: NMP vs. Cold Storage

The impact of normothermic machine perfusion (NMP) machine perfusion on liver transplant outcomes compared to static cold storage are summarized in Table 6.

4.2.1 Graft survival

- Our meta-analysis (2 RCTs, 24 graft failures in 486 participants) found no statistically significant difference in graft survival at 12 months for NMP vs SCS (HR 0.90; 95% CI 0.35 to 2.31) (Figure 8).

- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of concealment information in the randomization process, deviations from intended interventions, or missing outcome data. It was downgraded further for imprecision for a wide confidence interval, which was probably due to the small sample size.

4.2.2 Patient survival

- Results from our meta-analysis (2 RCTs, 17 patient deaths in 486 participants) indicate no statistically significant difference in patient survival at 12 months for NMP vs SCS (HR 1.72; 95% CI 0.54 to 5.46) (Figure 9).
- The certainty of evidence was low: it was downgraded for lack of concealment information in the randomization process, deviations from intended interventions, or missing outcome data. It was downgraded further for imprecision.

4.2.3 Early allograft dysfunction (EAD)

- Summary estimates from our meta-analysis (4 RCTs, 174 events in 788 participants) showed that risk of EAD decreased by 48% in NMP vs SCS (OR 0.52, 95% CI 0.27, 0.98) (Figure 10).
- The certainty of evidence was low: it was downgraded for high risk of bias mainly due to a lack of concealment information in the randomization process, deviations from intended interventions, or missing outcome data, and imprecision (wide confidence interval due to the low number of events).

4.3 Objective 3: NRP vs. Cold Storage in controlled DCD

A meta-analysis by Liang (25) evaluated the impact of NRP machine perfusion compared to SCS on liver transplant outcomes in patients who received controlled DCD from three observational studies. In one of the studies, HOPE was used consecutively in 25% of the DCD-NRP group and 40% of the DCD-SCS group. Instead of calculating standard hazard ratios, Liang and colleagues calculated the odds ratio of the surviving grafts and patients at 12 months. Moreover, they evaluated the risk of bias per study instead of per outcome. Therefore, we conducted our own meta-analysis to estimate the pooled hazard ratios for graft and patient survival. We also evaluated the risk of bias using the ROBINS and the evidence quality for graft and patient survival, EAD and NAS (Table 7).

4.3.1 Graft survival

- Our meta-analysis (3 studies, 192 events in 1038 participants) showed that the hazard of graft failure at 12 months decreased by almost 60% in NRP compared to SCS (HR 0.42; 95% CI 0.32 to 0.55) (Figure 11).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors.

4.3.2 Patient survival

- Pooled estimated of our meta-analysis (2 studies, 101 events in 872 participants) showed that the hazard of patient death at 12 months decreased by 52% in NRP vs SCS (HR 0.48, 95% CI 0.35, 0.67) (Figure 12).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors.

4.3.3 Early allograft dysfunction (EAD)

- Liang et al.'s meta-analysis of three studies (197 events in 1038 participants) showed that NRP decreased EAD by 42% compared to SCS (OR 0.58; 95% CI 0.42 to 0.80) (Figure 13).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors.

4.3.4 Non-anastomotic strictures (NAS)

- The meta-analysis by Liang et al of two studies (37 events in 235 participants) showed the likelihood of having NAS declined by 72% in NRP vs SCS (OR 0.28; 95% CI 0.11 to 0.69) (Figure 14).
- The certainty of the evidence was low. It was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors. It was further downgraded by the imprecision: a wide confidence interval, possibly due to a low number of events.

4.4 Objective 4: Impact of Donor Type

4.4.1 DCD vs. DBD with HOPE

We performed a subgroup analysis for HOPE vs. SCS by comparing liver transplant patients who received organs from brain death versus circulatory death donors. Only one of the four RCTs by van Rijn et al. (17) was done in DCD.

Graft survival

- Our subgroup analysis showed that HOPE lowered the risk of graft failure compared to SCS in DBD (HR 0.42; 95% CI 0.22 to 0.80) but was inconclusive for DCD (HR 0.65; 95% CI 0.18 to 2.32) (Figure 4). However, the subgroup difference was not statistically significant (p=0.55).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of concealment information in the randomization process or deviations from intended interventions. It was downgraded further for imprecision for a wide confidence interval, especially in the DCD group, which was probably due to the small sample size.

Patient survival

- Our results indicate no statistically significant differences in patient survival for HOPE vs SCS in either DBD (HR 0.55; 95% CI 0.23 to 1.30) or DCD (HR 2.45; 95% CI 0.77 to 7.82)(Figure 5).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of concealment information in the randomization process, imprecision in the summary estimate, especially in the DCD group, which was probably due to the small sample size.

EAD

- Results for the subgroup analysis showed that HOPE lowered the likelihood of EAD compared to SCS in DBD (OR 0.40; 95% CI 0.24 to 0.69) but not in DCD (OR 0.52; 95%I 0.26 to 1.03) (Figure 6). The subgroup difference was not statistically significant (p=0.65).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to deviations from intended interventions and imprecision, especially in the DCD group, which was probably due to the low number of events.

NAS

- The subgroup analysis found that HOPE lowered the likelihood of NAS compared to SCS in DBD (OR 0.21, 95% CI 0.05, 0.97) and in DCD (OR 0.31, 95%CI 0.11, 0.92) (Figure 7). However, the subgroup difference was not statistically significant (p=0.68).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to deviations from intended interventions and imprecision, probably due to the low number of events.

4.4.2 DCD vs. DBD with NMP

We could not perform subgroup analysis by types of donors for NMP vs. SCS because all four RCTs were done in mixed population of DBD and DCD livers.

4.4.3 Controlled DCD with NRP vs. DBD with SCS

The meta-analysis by Mastrovangelis(26) included eight observational studies to evaluate liver transplant outcomes between controlled DCD preserved with NRP versus DBD preserved with SCS. In one of the studies, HOPE was used consecutively in 25% of the DCD-NRP group and 4% of the DBD-SCS group. The Newcastle Ottawa scale (NOS) tool was used to evaluate the risk of bias in the eight included studies. However, the risk of bias was evaluated per study instead of per outcome, and the pooled effect sizes were calculated without adjustment for confounding factors (Table 8).

Graft survival

- Three studies (992 participants) found no difference in graft survival in cDCD with NRP compared to DBD with SCS (HR 0.75; 95% CI 0.47 to 1.20).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors. It was downgraded further by the imprecision.

Patient survival

- Four studies (1037 participants) reported no difference in patient survival in cDCD with NRP compared to DBD with SCS (HR 0.74; 95% CI 0.39 to 1.41).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors and imprecision of the effect estimate.

EAD

- Five studies (168 events in 713 participants) showed no difference in risk of EAD in cDCD with NRP compared to DBD with SCS (RR 0.94; 95% CI 0.64 to 1.39).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors and imprecision.

PNF

- Five studies (10 events of 597 participants) found no difference in PNF with NRP than DBD with SCS (RR 2.0; 95% CI 0.48 to 8.37).

- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors and imprecision, possibly due to a low number of events.

NAS

- Three studies (9 events in 368 participants) reported no difference in NAS for NRP vs DBD with SCS (RR 1.73; 95% CI 0.48 to 6.24).
- The certainty of evidence was low: it was downgraded for risk of bias mainly due to a lack of adjustment for confounding factors and imprecision due to a low number of events.

5. IMPACT ON DONOR ORGAN AVAILABILITY

Machine perfusion has been proposed as a means to expand the donor pool, thereby reducing the waitlist and addressing the increasing shortage of donor organs. A few recent articles evaluated this hypothesis:

- In the UK, the VITTAL single-arm clinical trial found that 71% of livers previously deemed untransplantable were successfully used following viability assessment with NMP, resulting in 100% patient and graft survival at 90 days and 82% and 72% survival at five years, respectively (27).
- A simulation study based on these criteria, comparing NMP with cold storage, projected that implementing NMP across the U.S. could enable approximately 385 additional DCD liver transplants annually i.e. ~20% of discarded livers, which would translated to a 5.8% increase in the yearly yield of liver transplants (28).
- Similarly, a large U.S. registry-based study comparing 15 high-utilization machine perfusion centers to matched controls showed that machine perfusion adoption was associated with a significant increase in the use of higher-risk donor livers, including older DCD donors, steatotic livers, and those with prolonged warm ischemia. The authors concluded that machine perfusion enabled transplant centers to broaden their use of extended-criteria donor livers beyond conventional thresholds, effectively increasing access to liver transplantation (29).
- Within the Quebec context, a recent review of Transplant Quebec data from January 2022 to November 2024 estimated that, among 137 livers deemed ineligible for transplantation, 25 were very likely salvageable (10 DBD, 8 DCD, 7 Medical Asssitance in Dying (MAID)), 61 were potentially salvageable or at least evaluable by machine perfusion (25 DBD, 14 DCD, 22 MAID), while the rest were unlikely salvageable (27 DBD; 12 DCD, 12 MAID). Therefore, 42% of discarded livers

were very likely or potentially salvageable (personal communication with Centre Hospitalier de l'Université de Montréal).

These findings underscore the potential of machine perfusion to address the persistent shortage of organs and improve access to liver transplantation.

6. HEALTH TECHNOLOGY ASSESSMENT AND MEDICAL SOCIETY GUIDANCE

6.1 European Association for the Study of the Liver Guidelines (2024)

- In December 2024, the European Association for the Study of the Liver (EASL) published updated clinical practice guidelines on liver transplantation, with a focus on machine perfusion strategies (30). Key evidence cited included a review by De Beule et al. (2021)(31) for NRP in controlled DCD, RCTs by Nasralla(6) and Markmann(24) for NMP, and RCTs by van Rijn(17) (DCD) and Czigany(18) (DBD) for HOPE/DHOPE.
- They issued strong recommendations for the use of machine perfusion, without specifying the type of machine and donors:
    - "Perfusion preservation strategies should be considered at different points in the donation and transplantation process to reduce adverse post-transplant outcomes, including biliary complications, in particular when using extended criteria and DCD grafts (Level of evidece 2 (based on RCTs or observational studies), strong recommendation, strong consensus).
    - Machine perfusion strategies should be used to increase the donor organ pool and organ utilisation (Level of evidece 1 (based on systematic reviews of RCTs), strong recommendation, strong consensus)."

6.2 National Institute for Health and Care Excellence (NICE) guidelines

- **Initial guidance (January 2019)** (32)**:** Based on a rapid review of the literature up to July 2018, including the RCT by Nasralla et al., NICE concluded that due to limited efficacy evidence, they recommend NMP be used only with special arrangements for clinical governance, consent, and research .
- **Ongoing review (March 2025)**(33)**:** NICE is currently developing updated guidance on machine perfusion. All seven UK specialist liver transplant centers use machine perfusion by special arrangement, with funding provided by charitable sources.

7. COMMERCIAL AVAILABILITY OF MACHINE PERFUSION MODALITIES

- Only two devices (supporting NMP) have been approved by the FDA and Health Canada (OrganOx Metra® and Transmedics® Organ Care Systems™) (Table 3). OrganOx Metra® received FDA approval in 2021; however, recent RCTs on NMP (2018-2023) have only shown benefit for early allograft dysfunction (EAD) and not for downstream outcomes such as patient or graft survival.
- No HOPE devices have received FDA or Health Canada approval yet.

Table 3. Authority approval for machine perfusion devices

Manufacturer	Modality supported	CE certification (Europe)	FDA approved	Health Canada approved
Liver Assist (XVIVO, the Netherlands)	HOPE, DHOPE, NMP	No	Not fully approved; granted Breakthrough Device Designation	No
PerLife® PerLiver® (Aferetica, Italy)	HOPE, DHOPE, NMP	Granted European Union approval	No	No
LifePort® (Liver Transporter, USA)	HMP	Not yet approved for commercial use	Not yet approved for commercial use	No
VitaSmart™ (Bridge to Life, USA)	HOPE, DHOPE	Available in all countries accepting the CE mark	Granted investigational device exemption approval	No
OrganOx Metra® (OrganOx Limited, UK)	NMP	Yes (2016)	Yes (2021)	Yes (2024)
Transmedics® Organ Care Systems™ (Transmedics Inc, USA)	NMP	Yes (2006)	Yes (2021)	Yes (2023)

8. DISCUSSION

The findings from this evaluation build on the meta-analysis published by Tingle in 2023 (12) and provide important insights into the potential clinical benefits of various machine perfusion techniques for liver transplantation when compared to static cold storage (SCS). While the evidence is generally of low quality due to risk of bias arising from concerns with the randomization process and the small study sizes, the results suggest that certain machine perfusion approaches may offer improvements in clinically relevant outcomes.

8.1 Impact on Clinically Relevant Outcomes

Hypothermic Oxygenated Perfusion (HOPE)

- HOPE appears to be associated with a significant reduction in the risk of graft failure, early allograft dysfunction (EAD), and non-anastomotic biliary strictures (NAS) compared to SCS, highlighting its potential as a promising intervention for improving graft function and viability.
- However, results for patient survival at 12 months were inconclusive , indicating that while HOPE may improve graft-related outcomes, it does not necessarily translate to improved overall survival within the time frame assessed.
- While the evaluated studies had moderate to high risk of bias, largely due to some concerns with the randomization process and small study sizes, results from recent RCTs and meta-analyses have been consistent and therefore there is moderate certainty that HOPE improves graft function and survival compared to SCS.
- Our meta-analysis included two additional recent RCTs in comparison to Tingle but our findings are in line with Tingle's conclusions. (Table 9).

Normothermic Machine Perfusion (NMP)

- NMP was associated with a reduction in the risk of EAD but demonstrated no statistically significant impact on graft or patient survival at 12 months.
- These findings indicate that while NMP may help mitigate the effects of ischemia-reperfusion injury and improve early graft function, it may not confer significant long-term survival benefits when compared to SCS.
- The overall low certainty of evidence and inconsistent results from recent trials do not allow us to draw meaningful conclusions for the impact of NMP on important survival outcomes.
- Tingle in 2023 (12) included three RCTs, and we added one recent RCT to our meta-analysis (Table 9); our findings are in line with theirs.

Normothermic Regional Perfusion (NRP)

- NRP is the recommended machine perfusion modality used in Europe for DCD livers (34), likely due to its ability to restore oxygenated blood flow before organ retrieval, thereby mitigating ischemic injury.
- The hypothesis that NRP may be especially effective for DCD liver transplantation was confirmed by our meta-analysis and that of Liang et al. (25), which found a decreased risk of graft failure, a reduction in patient death, and a reduction in EAD compared to SCS. Moreover, the likelihood of NAS was also reduced.

- However, the evidence for NRP remains limited to observational studies, with a high risk of confounding bias. Thefore, the level of certainty provided by these results is low. Further randomized trials are necessary to substantiate these promising results.

8.2 Impact on Logistics

While not the focus of our evaluation, the use of machine perfusion techniques offers the potential advantage of extending donor liver viability beyond what is achievable with standard cold storage (SCS), allowing transplantation to be performed during daytime hours when surgical and medical teams are fully staffed and optimal resources are available. This shift from urgent, overnight procedures to scheduled operations could improve patient safety, surgical outcomes, and overall resource utilization (35). Furthermore, prolonged viability may enhance logistical flexibility, allowing better matching of donor organs to recipients and potentially reducing waitlist mortality.

8.3 Impact on Donor Organ Availability

A few recent studies have evaluated the ability of machine perfusion to expand the donor pool, which could reduce the waitlist and address the increasing shortage of donor organs. These studies found that use of NMP enabled increased acceptance of extended criteria donors, including older DCD donors, steatotic livers, and those with prolonged warm ischemia. These findings underscore the potential of machine perfusion to address the persistent organ shortage and improve access to transplantation.

9. CONCLUSIONS

Hypothermic Oxygenated Perfusion (HOPE):

- Low to moderate certainty evidence indicates that HOPE may improve clinically relevant outcomes when compared to SCS, specifically for graft survival, early allograft dysfunction and non-anastomotic biliary stricture.
- However, results were inconclusive for patient survival at 12 months. Given the small numbers, we do not know the impact of HOPE on mortality as the data to date is compatible with both meaningful increases or decreases in mortality.
- Overall, consistent results from recent RCTs and meta-analyses provide moderate certainty that HOPE improves graft function and survival compared to SCS.

Normothermic Machine Perfusion (NMP):

- Low certainty evidence indicates that NMP was not associated with improved graft or patient survival, but may improve early allograft dysfunction when compared to SCS.
- These findings indicate that while NMP may help mitigate the effects of ischemia-reperfusion injury and improve early graft function, its impact on long-term survival remains unclear; given the small numbers, the data to date are compatible with both meaningful increases or decreases in mortality.
- Overall, the high risk of bias in the individual studies, lack of demonstrated impact on graft or patient survival, and inconsistent results from recent trials, provide low certainty that NMP improves downstream survival outcomes compared to SCS.

Normothermic Regional Perfusion (NRP):

- Low certainty evidence indicates that NRP improves graft and patient survival and decreases early allograft dysfunction and non-anastomotic biliary stricture in DCD livers when compared to SCS.
- NRP is the recommended machine perfusion modality in Europe for DCD livers, likely due to its ability to restore oxygenated blood flow before organ retrieval, thereby mitigating ischemic injury. Therefore, NRP may be especially effective for DCD liver transplantation.
- However, there is low certainty in this evidence because all three studies were observational and at high risk of confounding bias.

- There is emerging evidence that machine perfusion might also increase the number of donor livers available for transplant by making it possible to use organs that would normally be discarded.
- Overall, the findings from this evaluation suggest that machine perfusion techniques, particularly HOPE and NRP, may offer clinical benefits over SCS in certain patient populations. The evidence for NMP on survival outcomes remains inconclusive.
- Given the low to moderate certainty evidence across all modalities, these results should be interpreted with caution and underscore the need for further investigation to better understand the comparative effectiveness of these techniques.

10. RECOMMENDATIONS

- Given the best available evidence indicating that machine perfusion techniques, particularly hypothermic oxygenated machine perfusion (HOPE) and normothermic regional perfusion (NRP), may improve graft survival in DBD livers

(including those with extended criteria) and in DCD livers, respectively, the TAU Policy committee recommends that:

- There is justification for considering the implementation of machine perfusion technologies within the transplant program in Quebec to improve clinical outcomes and address the critical issue of organ shortage.
- It would be important to assess the cost-effectiveness of adding these modalities to the provincial transplant program.
- Any pilot of these techniques should ensure the prospective collection of data on the following variables:
  - Number of liver transplants perfused with each modality;
  - Donor characteristics;
  - Clinical outcomes (graft viability, short and long-term patient survival);
  - Patient-reported outcomes;
  - Associated costs.

FIGURES

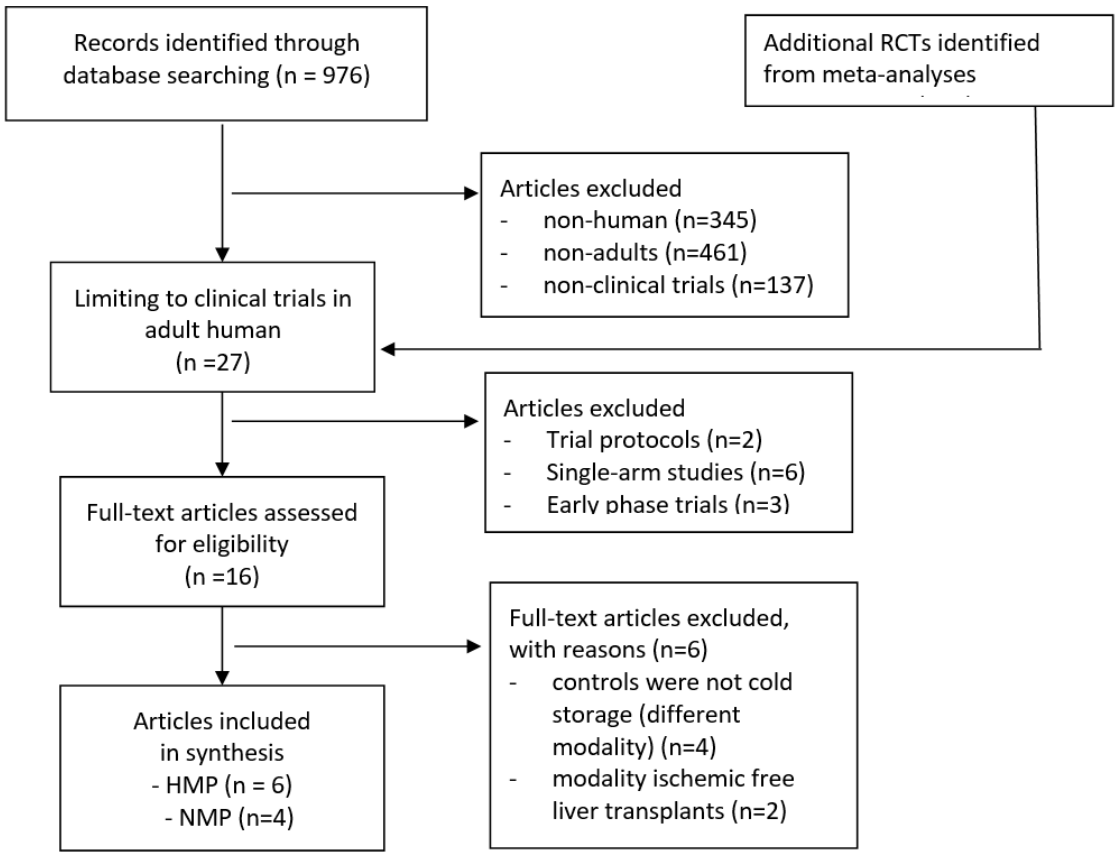


Figure 2. PRISMA Flowchart of the clinical trials evaluating machine perfusions in liver transplantation

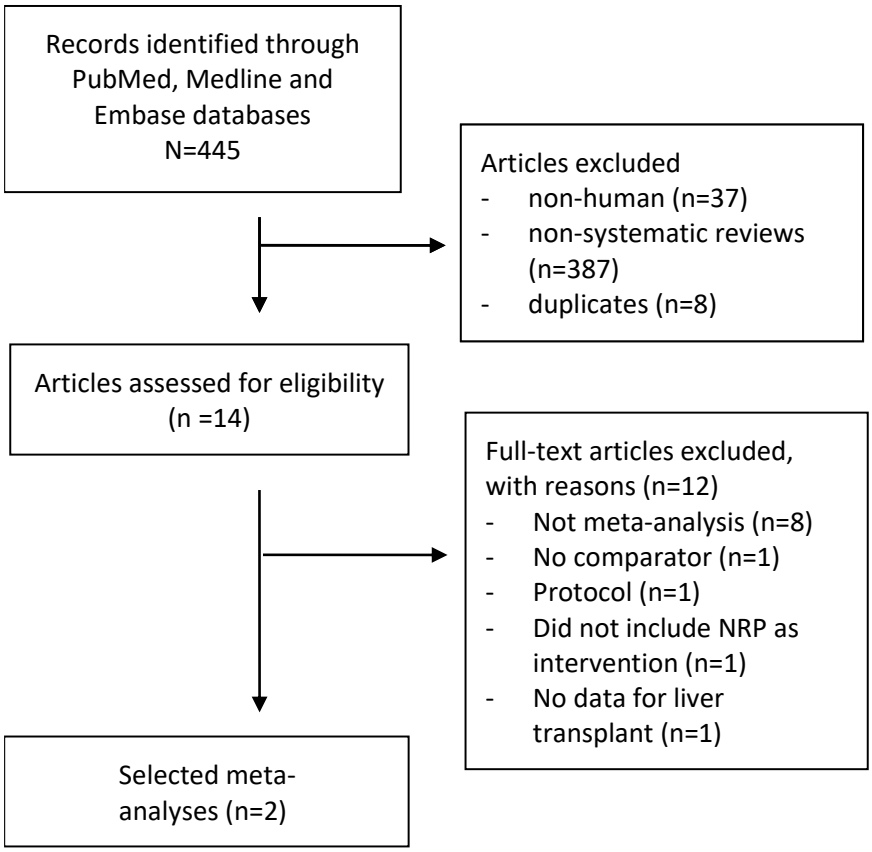


Figure 3. PRISMA Flowchart of the systematic reviews evaluating normothermic regional perfusion in liver transplantation

HYPOTHERMIC MACHINE PERFUSION COMPARED TO STATIC COLD STORAGE

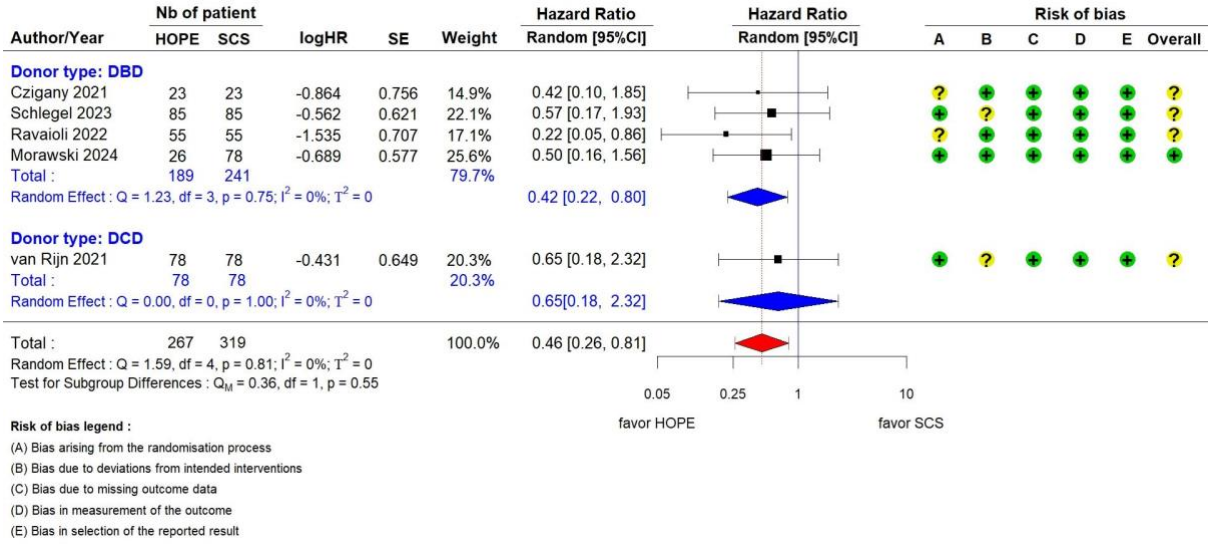


Figure 4. Graft Survival at 12 months: Forest plot of studies assessing graft survival in liver transplant patients using hypothermic machine perfusion compared to static cold storage

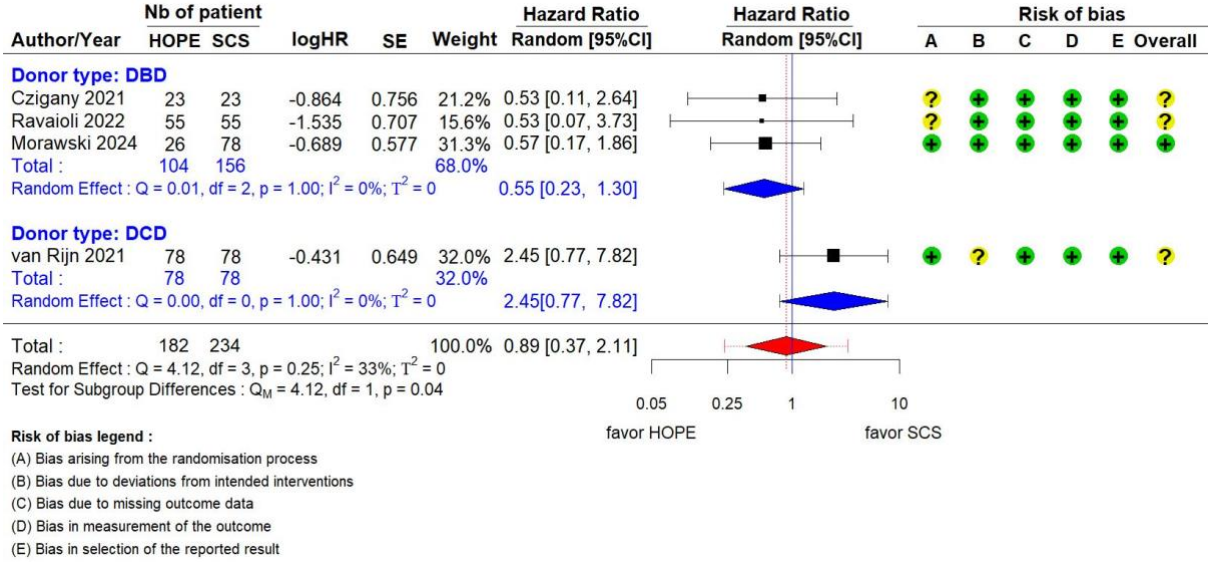


Figure 5. Patient survival at 12 months: Forest plot of studies assessing patient survival in liver transplant patients using hypothermic machine perfusion compared to static cold storage

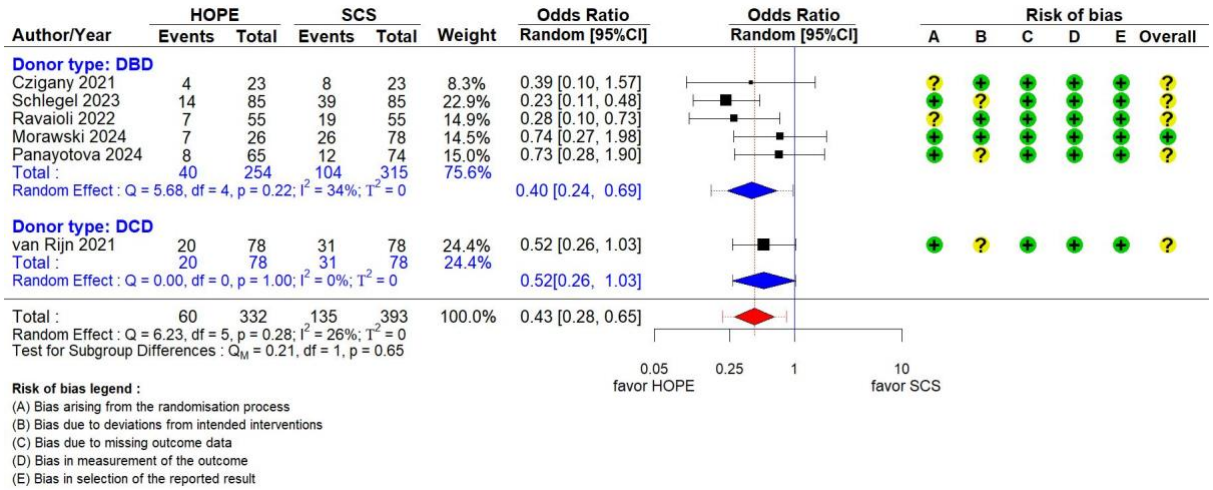


Figure 6. Early allograft dysfunction: Forest plot of studies assessing the risk of early allograft dysfunction in liver transplant patients using hypothermic machine perfusion compared to static cold storage

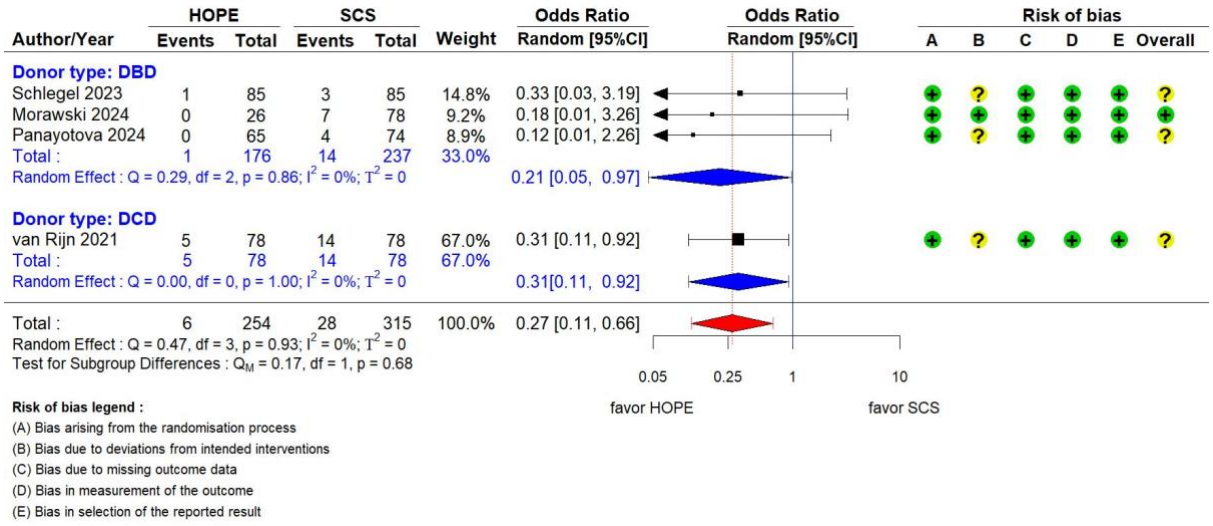


Figure 7. Non-anastomotic biliary stricture: Forest plot of studies assessing the risk of non-anastomotic biliary stricture in liver transplant patients using hypothermic machine perfusion compared to static cold storage

NORMOTHERMIC MACHINE PERFUSION COMPARED TO STATIC COLD STORAGE

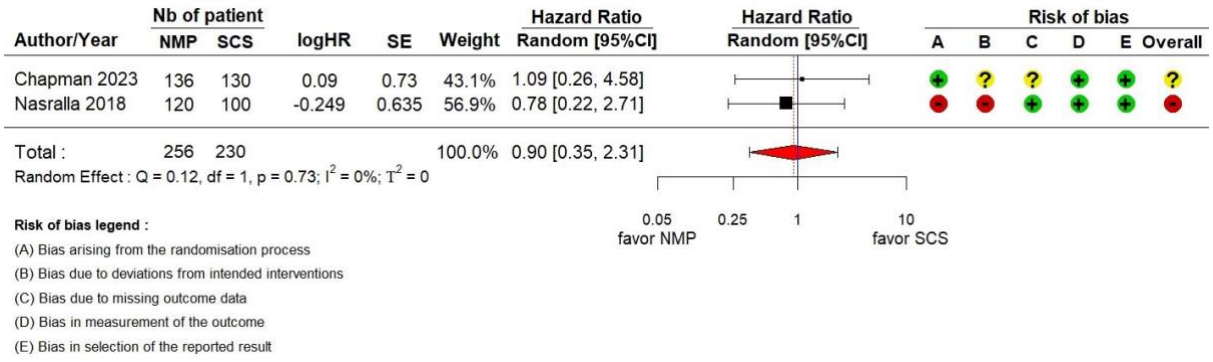


Figure 8. Graft Survival at 12 months: Forest plot of studies assessing graft survival in liver transplant patients using normothermic machine perfusion compared to static cold storage

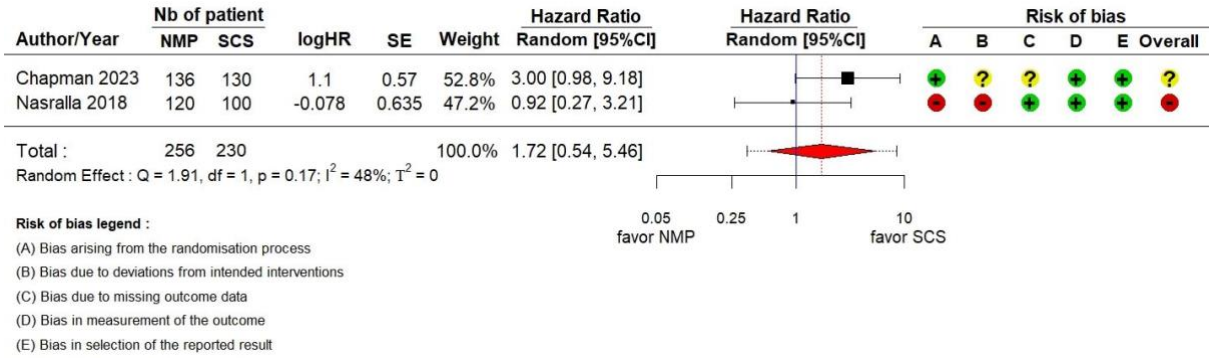


Figure 9. Patient survival at 12 months: Forest plot of studies assessing patient survival in liver transplant patients using normothermic machine perfusion compared to static cold storage

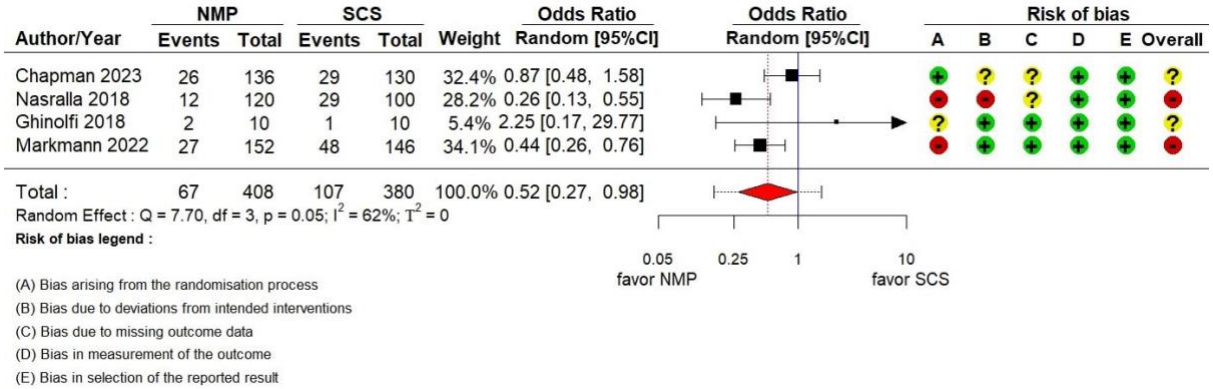


Figure 10. Early allograft dysfunction: Forest plot of studies assessing the risk of early allograft dysfunction in liver transplant patients using normothermic machine perfusion compared to static cold storage

NORMOTHERMIC REGIONAL PERFUSION COMPARED TO STATIC COLD STORAGE

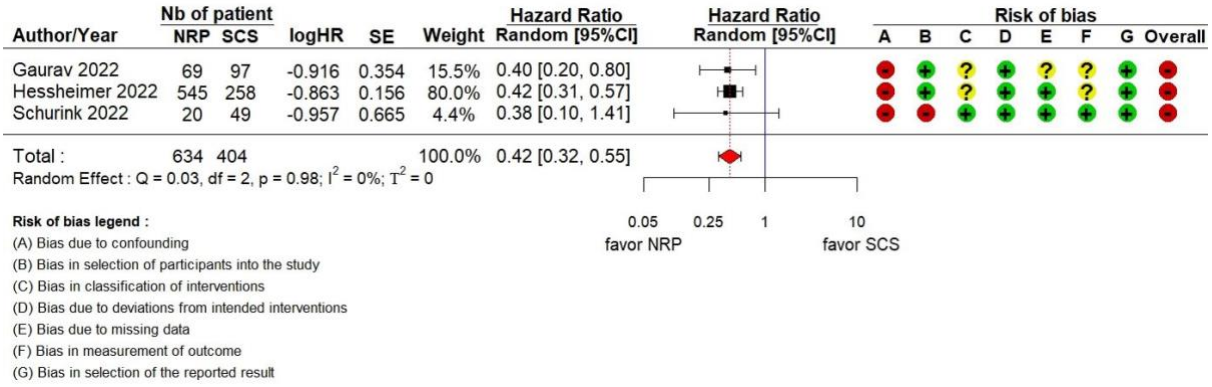


Figure 11. Graft Survival at 12 months: Forest plot of studies assessing graft survival in liver transplant patients using normothermic regional perfusion compared to static cold storage

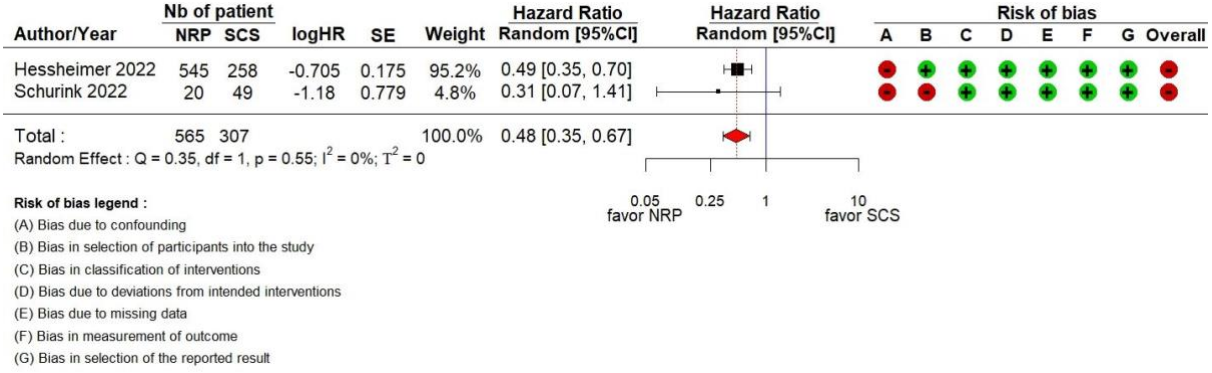


Figure 12. Patient Survival at 12 months: Forest plot of studies assessing graft survival in liver transplant patients using normothermic regional perfusion compared to static cold storage

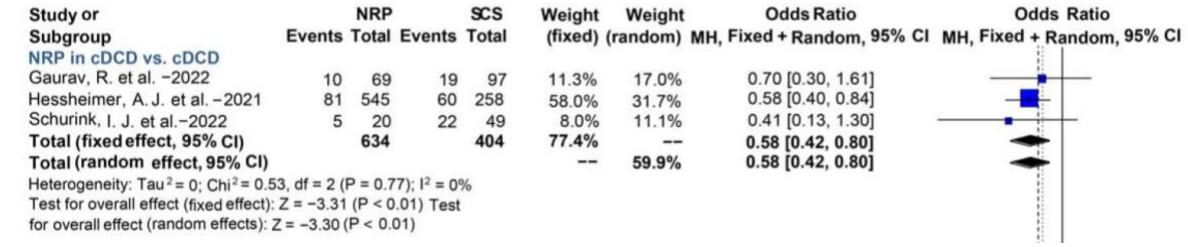


Figure 13. Early allograft dysfunction: Forest plot of studies assessing the risk of early allograft dysfunction in liver transplant patients using normothermic regional perfusion compared to static cold storage (Liang et al)

Figure 14. Non-anastomotic biliary stricture: Forest plot of studies assessing the risk of non-anastomotic biliary stricture in liver transplant patients using normothermic regional perfusion compared to static cold storage (Liang et al)

TABLES

Table 4. Characteristics of the RCTs

Author	Country	Machine Type	Population	Donor criteria	Intervention (n)	Control (n)
van Rijn, R. et al. 2021	Europe, multicenter	D-HOPE [Liver Assist]	Patients ≥18 years of age who were undergoing liver-only transplantation with a DCD graft	DCD. No age restriction (median 49 IQR 37–59). Donor risk index median 2.12	ECD-DCD: 78	ECD-DCD: 78
Czigany, Z. et al.2021	Germany and Czech Republic, 4 centers	HOPE [Liver Assist]	Patients ≥18 years of age, suffering from end stage-liver disease and/or malignant liver tumors, listed for liver transplantation and receiving ECD organs	DBD. ECD criteria: · Donors 65 years of age and older, BMI >30 kg/m2, fatty liver with >40% steatosis, Serum AST or ALT >3 × upper limits of normal. Median age 62 (55–65)	ECD-DBD: 23	ECD-DBD: 23
Ravaioli, M et al. 2022	Italy, single center	HOPE [Vitasmart]	Patients ≥18 years of age undergoing liver-only transplantation with ECD grafts	DBD. Donors met the United Network for Organ Sharing (UNOS) criteria for ECD. Median age 76 (IQR 64–81) in the HOPE arm	ECD-DBD: 55	ECD-DBD: 55
Schlegel, A. et al. 2023	UK, Belgium, Netherlands, France, Switzerland	HOPE [Liver Assist]	Patients ≥18 years of age listed for liver-only transplant with a whole DBD graft	DBD. Median age 60.5 (IQR 47.0–72.0)	DBD 85	DBD 85
Marowski, 2024	Poland, single center	D-HOPE [Liver Assist]	Patients ≥18 years of age who underwent liver transplantation from DBD	DBD. ECD criteria 65 years of age and older, BMI >30 kg/m2, fatty liver with >40% steatosis, Serum AST or ALT >3 × upper limits of normal	DBD 26 (17 ECD)	DBD 78 (39 ECD)
Panayotova , 2024	USA, multicenter	Portable HOPE [LifePort Liver Transporter (LLT)]	Patients ≥18 years of age listed on the United Network of Organ Sharing (UNOS) waitlist for whole liver transplants	DBD. Donor with HIV+ and anticipated cold ischemia time (CIT) <3 hours were excluded. Median age >65.	ECD: DBD: 63	ECD: DBD (age >65): 72
Ghinolfi, D et al. 2019	Italy, single center	Ex-situ NMP [LiverAssist]	Patients ≥18 years of age, potential recipients of a DBD, whole-size, primary, ABO compatible	DBD. A graft was discarded in the presence of any of the following: macrovesicular steatosis >30%; necrosis >5%; fibrosis ≥2 as per Ishak's score; severe microangiopathy (as per arteriolar thickening >60%), and macroangiopathy with impossibility to perform arterial anastomosis. Median age 81 (IQR 77.5-87.2) in the HOPE arm	ECD-DBD 10	ECD-DBD 10

Nasralla, D. et al. 2018	UK, Belgium, Spain, Germany	NMP [OrganOx metra]	Adult patients awaiting a liver-only transplant, excluding those with fulminant liver failure	DBD or DCD donors were eligible for enrolment. Donors median age 55 (IQR 48–62) in both arms	ECD: 87 DBD, 34 DCD (ECD not defined	ECD: 80 DBD, 21 DCD (ECD not defined
Markmann, J. F. et al. 2022	USA, multicenter	Portable NMP [Portable Organ Care System]	Patients ≥18 years of age excluding those with fulminant liver failure	DCD donors and DBD donors at least have 1 of the following characteristics: (1) 40 years of age or older; (2) expected total cross-clamp/cold ischemic time of 6 or more hours; (3) DCD donors if 55 years or younger; or (4) macrosteatotic livers (≤40%). Donors median age 47.5 (range 10.9-83.7) in HOPE arms	ECD:124 DBD, 28 DCD (ECD not defined	ECD: 133 DBD, 13 DCD (ECD not defined
Chapman et al, 2023	USA, multicenter	NMP [OrganOx metra]	Patients ≥18 years of age registered as an active recipient on the UNOS liver transplant waiting list	DBD donors aged ≥40 years. DCD donors aged ≥16 years. Mean (SD) age in the NMP was 53.1 ± 12.9 while in the SCS 52.5 ± 11.5. Mean (SD) BMI was 30.2 ± 7.9 in NMP and 29.4 ± 6.9 in SCS	ECD: DBD 114, DCD 22	ECD: DBD 114, DCD 16

Table 5. Hypothermic machine perfusion compared to cold storage: quality of evidence of studies evaluating liver transplant outcomes

№ of studies	Certainty assessment						Effect			Quality of Evidence
	Risk of bias (RoB)	Controlled study	Imprecision	Inconsistency	Indirectness	Others	№ of events	№ of individuals	Pooled Estimates (95% CI)	
Outcome: Graft survival in all patients										
5	Moderate	RCTs, no downgrading	Small sample size	No downgrading	No downgrading	No downgrading	62*	586	HR 0.46 (0.26; 0.81)	Low
Outcome: Graft survival in patients receiving brain death donors										
4	Moderate	RCTs, no downgrading	Small sample size	No downgrading	No downgrading	No downgrading	42*	430	HR 0.42 (0.22, 0.80)	Low
Outcome: Patient survival in all patients										
4	Moderate	RCTs, no downgrading	Small sample size, wide confident intervals	No downgrading	No downgrading	No downgrading	39*	416	HR 0.89 (0.37, 2.11)	Low
Outcome: Patient survival in patients receiving brain death donors										
3	Moderate	RCTs, no downgrading	Small sample size, wide confident intervals	No downgrading	No downgrading	No downgrading	35*	260	HR 0.55 (0.23, 1.30)	Low
							№ of events HOPE/SCS	№ of individuals HOPE/SCS	Pooled Estimates (95% CI)	
Outcome: Early allograft dysfunction in all patients										
6	Moderate	RCTs, no downgrading	No downgrading	No downgrading	No downgrading	No downgrading	60/332	135/393	RR 0.43 (0.28, 0.65)	Moderate
Outcome: Early allograft dysfunction in patients receiving brain death donors										
5	Moderate	RCTs, no downgrading	Low number of events	No downgrading	No downgrading	No downgrading	40/254	104/315	RR 0.40 (0.24, 0.69)	Low

Outcome: **Non-anastomotic biliary stricture in all patients**										
4	Moderate	RCTs, no downgrading	Low number of events	No downgrading	No downgrading	No downgrading	6/254	28/315	RR 0.29 (0.11, 0.66)	Low
Outcome: **Non-anastomotic biliary stricture in patients receiving brain death donors**										
3	Moderate	RCTs, no downgrading	Low number of events	No downgrading	No downgrading	No downgrading	1/176	14/237	RR 0.21 (0.05, 0.97)	Low

*Number of graft failures or patients who died

Table 6. Normothermic machine perfusion compared to cold storage: quality of evidence of studies evaluating liver transplant outcomes

№ of studies	Certainty assessment						Effect			Certainty of Evidence
	Risk of bias (RoB)	Controlled study	Imprecision	Inconsistency	Indirectness	Others	№ of events	№ of individuals	Effect Estimates (95% CI)	
Outcome: Graft survival at 12 month in all patients										
2	High	RCTs, no downgrading	Small sample size, wide confidence interval	No downgrading	No downgrading	No downgrading	24*	486	HR 0.90 (0.35, 2.31)	Low
Outcome: Patient survival at 12 month in all patients										
2	High	RCTs, no downgrading	Small sample size, wide confidence interval	No downgrading	No downgrading	No downgrading	17*	486	HR 1.72 (0.54, 5.46)	Low
Outcome: Early allograft dysfunction in all patients							**№ of events NPM/SCS**	**№ of individuals NPM/SCS**	**Effect Estimates (95% CI)**	
4	High	RCTs, no downgrading	Wide confidence interval	No downgrading	No downgrading	No downgrading	67/107	408/380	OR 0.52 (0.27, 0.98)	Low

*Number of graft failures or patients who died

Table 7. Normothermic regional perfusion compared to cold storage for controlled donors from circulatory deaths: quality of evidence of studies evaluating liver transplant outcomes

№ of studies	Certainty assessment						Effect			Certainty of Evidence
	Risk of bias (RoB)	Controlled study	Imprecision	Inconsistency	Indirectness	Others	№ of events	№ of individuals	Effect size (95% CI)[a]	
Outcome: Graft survival at 12 month										
3	High	Observational study	No downgrading	No downgrading	No downgrading	No downgrading	192[b]	1038	HR 0.42 (0.32, 0.55)	Low
Outcome: Patient survival at 12 month										
2	High	Observational study	No downgrading	No downgrading	No downgrading	No downgrading	101[b]	872	HR 0.48 (0.35, 0.67)	Low
Outcome: Early allograft dysfunction in all patients							**№ of events NRP/SCS**	**№ of individuals NRP/SCS**		
3	High	Observational study	No downgrading	No downgrading	No downgrading	No downgrading	96/101	634/404	OR 0.58 (0.42, 0.80)	Low
Outcome: Non-anastomotic biliary stricture										
2	High	Observational study	Small sample size, wide confidence interval	No downgrading	No downgrading	No downgrading	6/31	89/146	OR 0.28 (0.11, 0.69)	Low

[a]Effect size were calculated without adjustment for the confounding factors

[b]Number of graft failures or patients who died

Table 8. Normothermic regional perfusion for controlled donors from circulatory deaths compared to cold storage for donors from brain deaths: quality of evidence of studies evaluating liver transplant outcomes

№ of studies	Certainty assessment						Effect			Certainty of Evidence
	Risk of bias (RoB)	Controlled study	Imprecision	Inconsistency	Indirectness	Others	№ of events	№ of individuals	Effect size (95% CI)[a]	
Outcome: Graft survival at 12 months										
3	High	Observational study	Wide confidence interval	No downgrading	No downgrading	No downgrading	NA	992	HR 0.75 (0.47, 1.20	Low
Outcome: Patient survival at 12 months										
4	High	Observational study	Wide confidence interval	No downgrading	No downgrading	No downgrading	NA	1037	HR 0.74 (0.39, 1.41)	Low
Outcome: Early allograft dysfunction							**№ of events NRP/SCS**	**№ of individuals NRP/SCS**		
5	High	Observational study	Wide confidence interval	No downgrading	No downgrading	No downgrading	49/ 119	225/488	RR 0.94 (0.64, 1.39)	Low
Outcome: Primary nonfunction										
5	High	Observational study	Low number of events, wide confidence interval	No downgrading	No downgrading	No downgrading	4/6	188/409	RR 2.00 (0.48, 8.37)	Low
Outcome: Non-anastomotic biliary stricture										
3	High	Observational study	Low number of events, wide confidence interval	No downgrading	No downgrading	No downgrading	3/6	159/209	RR 1.73 (0.48, 6.24)	Low

Table 9. Comparison of the impact of machine perfusion and liver transplant outcomes between Tingle's and our meta-analyses

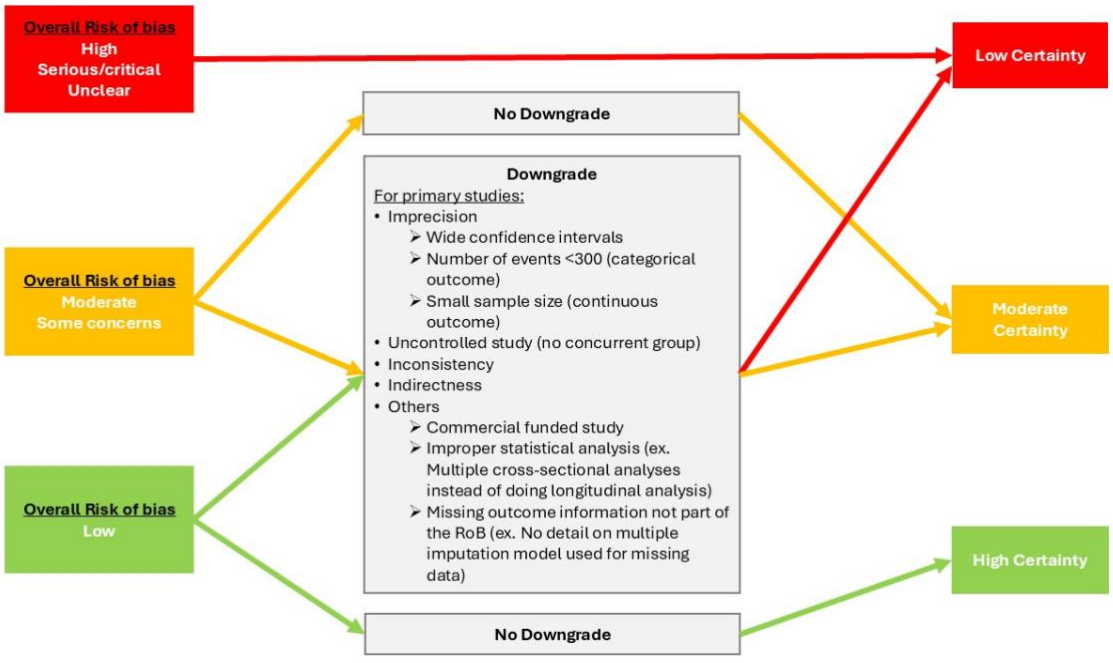
Outcome	Tingle et al		Our meta-analyses	
HMP vs. SCS	**No of participants (studies)**	**Effect size (95% CI)**	**No of participants (studies)**	**Effect size (95% CI)**
Graft survival	482 (4 RCTs) Czigany, Ravaioli, Schlegel, van Rijn	HR 0.45 (0.23 to 0.87)	586 (5 RCTs) Czigany, Ravaioli, Schlegel, van Rijn, Morawski	HR 0.46 (0.26, 0.81)
Patient survival	482 (4 RCTs) Czigany, Ravaioli, **Schlegel**, van Rijn	HR 0.91 (0.42 to 1.98)	416 (4 RCTs) Czigany, Ravaioli, van Rijn, **Morawski**	HR 0.89 (0.37, 2.11)
EAD	482 (4 RCTs) Czigany, Ravaioli, Schlegel, van Rijn	OR 0.35 (0.23 to 0.53)	725 (6 RCTs) Czigany, Ravaioli, Schlegel, van Rijn, Morawski, Panayotova	OR 0.43 (0.28, 0.65)
NAS	326 (2 RCTs) Schlegel, van Rijn	OR 0.32 (0.12 to 0.83)	569 (4RCTs) Schlegel, van Rijn, Morawski, Panayotova	OR 0.29 (0.11, 0.66)
NMP vs. SCS				
Graft survival	522 (2 RCTs) Nasralla, **Markmann**	HR 1.20 (0.44, 3.29)	486 (2 RCTs) Nasralla, **Chapman**	HR 0.90 (0.35, 2.31)
Patient survival	222 (1 RCT) Nasralla	HR 1.08 (0.31, 3.80)	486 (2RCTs) Nasralla, Chapman	HR 1.72 (0.54, 5.46)
EAD	540 (3 RCTs) Ghinolfi, Nasralla, Markmann	OR 0.40 (0.22, 0.74)	788 (4 RCTs) Ghinolfi, Nasralla, Markmann, Chapman	OR 0.52 (0.27, 0.98)

APPENDICES

APPENDIX A: QUALITY ASSESSMENT ALGORITHM

Our in-house tool incorporated the following dimensions to evaluate the certainty of evidence:

i. Overall risk of bias of the included studies (based on controlling bias due to confounding, selection, misclassification, reporting and analytic concerns)
ii. Uncontrolled study (no comparator group)
iii. Imprecision (bias arising from small sample size)
   - Wide confidence intervals
   - Low number of events (<300 for categorical outcomes)
   - Small sample size (for continuous outcomes)
iv. Inconsistency (results vary widely between studies)
v. Indirectness (extrapolating results from indirect comparisons)
vi. Others
   - commercially funded study
   - improper statistical analytical tests (e.g. multiple cross sectional analyses for a longitudinal data)
   - missing outcome information that is not part of RoB (e.g. no details on multiple imputation models used for missing data)



Low certainty evidence:

- This indicates that our confidence in the overall effect estimate is limited.

- Studies with a high overall risk of bias were, by default, considered low certainty evidence.

Moderate certainty evidence:

- Moderate certainty evidence suggests that we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Included studies with a low or moderate overall risk of bias could be downgraded and considered a lower certainty of evidence if one of these domains were met
    - Imprecision (i.e. confidence intervals, low number of events (<300 for categorical outcomes), or small sample size (for continuous outcomes))
    - Uncontrolled study (no comparator group)
    - Inconsistency (i.e. studies have inconsistent effects, or are too heterogenous to compare)
    - Indirectness (i.e. studies reporting outcomes that indirectly answer our research question)
    - Others
        - commercially funded study
        - improper statistical analytical tests (e.g. multiple cross sectional analyses for a longitudinal data)
        - missing outcome information that is not part of RoB (e.g. no details on multiple imputation models used for missing data)

High certainty evidence:

- High certainty evidence indicates that we are very confident that the true effect lies close to that of the estimate of the effect.
- When studies are not downgraded for any of the elements considered above and overall risk of bias is low, this would indicate an overall high certainty evidence.

REFERENCES

1. Canadian Institute for Health Information. Summary statistics on organ transplants, wait-lists and donors 2024 [updated June 6, 2024. Available from: https://www.cihi.ca/en/summary-statistics-on-organ-transplants-wait-lists-and-donors.

2. Chapman WC, Barbas AS, D'Alessandro AM, Vianna R, Kubal CA, Abt P, et al. Normothermic Machine Perfusion of Donor Livers for Transplantation in the United States: A Randomized Controlled Trial. Ann Surg. 2023;278(5):e912-e21.

3. Thuong M, Ruiz A, Evrard P, Kuiper M, Boffa C, Akhtar MZ, et al. New classification of donation after circulatory death donors definitions and terminology. Transpl Int. 2016;29(7):749-59.

4. Lin Y, Huang H, Chen L, Chen R, Liu J, Zheng S, et al. Assessing Donor Liver Quality and Restoring Graft Function in the Era of Extended Criteria Donors. J Clin Transl Hepatol. 2023;11(1):219-30.

5. Banker A, Bhatt N, Rao PS, Agrawal P, Shah M, Nayak M, et al. A Review of Machine Perfusion Strategies in Liver Transplantation. J Clin Exp Hepatol. 2023;13(2):335-49.

6. Nasralla D, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, et al. A randomized trial of normothermic preservation in liver transplantation. Nature. 2018;557(7703):50-6.

7. Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl. 2010;16(8):943-9.

8. Hartog H, Hann A, Perera M. Primary Nonfunction of the Liver Allograft. Transplantation. 2022;106(1):117-28.

9. Michael FA, Friedrich-Rust M, Erasmus HP, Graf C, Ballo O, Knabe M, et al. Treatment of Non-Anastomotic Biliary Strictures after Liver Transplantation: How Effective Is Our Current Treatment Strategy? J Clin Med. 2023;12(10).

10. Canadian Institute for Health Information. Graft Survival Following Organ Transplant 2024 [updated December, 2024. Available from: https://www.cihi.ca/en/indicators/graft-survival-following-organ-transplant.

11. Canadian Institute for Health Information. Patient Survival Following Organ Transplant 2024 [updated December, 2024. Available from: https://www.cihi.ca/en/indicators/patient-survival-following-organ-transplant.

12. Tingle SJ, Dobbins JJ, Thompson ER, Figueiredo RS, Mahendran B, Pandanaboyana S, et al. Machine perfusion in liver transplantation. Cochrane Database Syst Rev. 2023;9(9):Cd014685.

13. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
14. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.
15. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
16. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.
17. van Rijn R, Schurink IJ, de Vries Y, van den Berg AP, Cortes Cerisuelo M, Darwish Murad S, et al. Hypothermic Machine Perfusion in Liver Transplantation - A Randomized Trial. N Engl J Med. 2021;384(15):1391-401.
18. Czigany Z, Pratschke J, Fronek J, Guba M, Schoning W, Raptis DA, et al. Hypothermic Oxygenated Machine Perfusion Reduces Early Allograft Injury and Improves Post-transplant Outcomes in Extended Criteria Donation Liver Transplantation From Donation After Brain Death: Results From a Multicenter Randomized Controlled Trial (HOPE ECD-DBD). Ann Surg. 2021;274(5):705-12.
19. Ravaioli M, Germinario G, Dajti G, Sessa M, Vasuri F, Siniscalchi A, et al. Hypothermic oxygenated perfusion in extended criteria donor liver transplantation-A randomized clinical trial. Am J Transplant. 2022;22(10):2401-8.
20. Schlegel A, Mueller M, Muller X, Eden J, Panconesi R, von Felten S, et al. A multicenter randomized-controlled trial of hypothermic oxygenated perfusion (HOPE) for human liver grafts before transplantation. J Hepatol. 2023;78(4):783-93.
21. Panayotova GG, Lunsford KE, Quillin RC, 3rd, Rana A, Agopian VG, Lee-Riddle GS, et al. Portable hypothermic oxygenated machine perfusion for organ preservation in liver transplantation: A randomized, open-label, clinical trial. Hepatology. 2024;79(5):1033-47.
22. Morawski M, Zhylko A, Rykowski P, Krasnodębski M, Hołówko W, Lewandowski Z, et al. Routine end-ischemic hypothermic machine perfusion in liver transplantation from donors after brain death: results of two-year follow-up of a randomized controlled trial. Int J Surg. 2024;110(11):7003-10.
23. Ghinolfi D, Rreka E, De Tata V, Franzini M, Pezzati D, Fierabracci V, et al. Pilot, Open, Randomized, Prospective Trial for Normothermic Machine Perfusion Evaluation in Liver Transplantation From Older Donors. Liver Transpl. 2019;25(3):436-49.
24. Markmann JF, Abouljoud MS, Ghobrial RM, Bhati CS, Pelletier SJ, Lu AD, et al. Impact of Portable Normothermic Blood-Based Machine Perfusion on Outcomes of Liver Transplant: The OCS Liver PROTECT Randomized Clinical Trial. JAMA Surg. 2022;157(3):189-98.

25. Liang A, Cheng W, Cao P, Cai S, Zhang L, Zhong K, et al. Effects of machine perfusion strategies on different donor types in liver transplantation: a systematic review and meta-analysis. Int J Surg. 2023;109(11):3617-30.
26. Mastrovangelis C, Frost C, Hort A, Laurence J, Pang T, Pleass H. Normothermic Regional Perfusion in Controlled Donation After Circulatory Death Liver Transplantation: A Systematic Review and Meta-Analysis. Transpl Int. 2024;37:13263.
27. Mergental H, Laing RW, Kirkham AJ, Clarke G, Boteon YL, Barton D, et al. Discarded livers tested by normothermic machine perfusion in the VITTAL trial: Secondary end points and 5-year outcomes. Liver Transpl. 2024;30(1):30-45.
28. Handley TJ, Arnow KD, Melcher ML. Despite Increasing Costs, Perfusion Machines Expand the Donor Pool of Livers and Could Save Lives. J Surg Res. 2023;283:42-51.
29. Canizares S, Montalvan A, Chumdermpadetsuk R, Modest A, Eckhoff D, Lee DD. Liver machine perfusion technology: Expanding the donor pool to improve access to liver transplantation. Am J Transplant. 2024;24(9):1664-74.
30. European Association for the Study of the L. EASL Clinical Practice Guidelines on liver transplantation. J Hepatol. 2024;81(6):1040-86.
31. De Beule J, Vandendriessche K, Pengel LHM, Bellini MI, Dark JH, Hessheimer AJ, et al. A systematic review and meta-analyses of regional perfusion in donation after circulatory death solid organ transplantation. Transplant International. 2021;34(11):2046-60.
32. NICE. Interventional procedure overview of ex-situ machine perfusion for extracorporeal preservation of livers for transplantation. 2019.
33. NICE. Ex-situ machine perfusion devices for liver transplants: early value assessment: In development. 2025.
34. Jochmans I, Hessheimer AJ, Neyrinck AP, Paredes D, Bellini MI, Dark JH, et al. Consensus statement on normothermic regional perfusion in donation after circulatory death: Report from the European Society for Organ Transplantation's Transplant Learning Journey. Transpl Int. 2021;34(11):2019-30.
35. Brüggenwirth IMA, Lantinga VA, Lascaris B, Thorne AM, Meerdink M, de Kleine RH, et al. Prolonged hypothermic machine perfusion enables daytime liver transplantation - an IDEAL stage 2 prospective clinical trial. EClinicalMedicine. 2024;68:102411.