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Deceased donor liver utilisation and assessment: Consensus guidelines from the European Liver and Intestine Transplant Association

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Summary

Over the past two decades, the application of machine perfusion (MP) in human liver transplantation has moved from the realm of clinical exploration to routine clinical practice. Both *in situ* and *ex situ* perfusion strategies are feasible, safe, and may offer improvements in relevant post-transplant outcomes. An important utility of these strategies is the ability to transplant grafts traditionally considered too risky to transplant using conventional cold storage alone. While dynamic assessment and ultimately transplantation of such livers is an important goal for the international liver transplant community, its clinical application is inconsistent. To this end, ELITA (the European Liver and Intestine Transplant Association) gathered a panel of experts to create consensus guidelines regarding selection, approach, and criteria for deceased donor liver assessment in the MP era. An eight-member steering committee (SC) convened a panel of 44 professionals working in 14 countries in Europe and North America. The SC identified topics related to liver utilisation and assessment for transplantation. For each topic, subtopics were created to answer specific clinical questions. A systematic literature review was performed, and the panel graded relevant evidence. The SC drafted initial statements addressing each clinical question. Statements were presented at the in-person Consensus Meeting on Liver Discard and Viability Assessment during the ELITA Summit held from April 19-20, 2024, in Madrid, Spain. Online voting was held to approve statements according to a modified Delphi method; statements reaching ≥85% agreement were approved. Statements addressing liver utilisation, the definition of high-risk livers, and strategies and criteria for dynamic liver assessment are presented.

Introduction

Since the first pilot studies in the late 2000s and early 2010s,[1–6] the application of machine perfusion (MP) in human liver transplantation has advanced substantially, from the realm of clinical exploration to routine practice. Different international cohort studies and meta-analyses support the use of *in situ* abdominal normothermic regional perfusion (NRP) in donation after circulatory determination of death (DCD) liver transplantation to improve organ utilisation, biliary complications, and graft survival,[7–12] while *ex situ* MP is supported by randomised-clinical trials (RCTs) demonstrating improved early allograft function and reduced rates of relevant post-transplant morbidity, including biliary complications and graft loss in some studies.[13–19]

Recently, there has been increasing focus on use of MP to assess deceased donor livers that would not be transplanted otherwise. While dynamic assessment and ultimately transplantation of such livers is an important goal for the international liver transplant community, clinical application of these strategies

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remains inconsistent. Indications for liver MP are variable, and there are discrepancies regarding the characteristics and nature of liver grafts undergoing functional evaluation.

Given the rise of studies and initiatives using MP to assess livers for transplantation and variability in what is considered a directly transplantable *vs.* initially non-transplantable graft, the European Liver and Intestinal Transplant Association (ELITA) gathered an international panel of experts to create consensus guidelines to guide professionals working in the field. These guidelines are the result of a collaborative effort undertaken by and among liver transplant professionals with significant expertise using high-risk grafts and/or advanced MP strategies, to offer practical advice regarding selection, approach, and criteria for deceased donor liver assessment in the MP era.

Methods

Consensus guideline process and expert panel members

Members of the ELITA Board proposed the consensus process, including its aim, structure, and steering committee (SC) members. The SC then selected the expert panel, chosen based on clinical experience, contributions to the fields of liver transplant and perfusion, and demographic characteristics (Fig. S1).

Selection of topics and clinical questions to be addressed

The SC identified three topics related to liver utilisation and assessment for transplantation: 1) definition of high-risk livers, 2) strategies for dynamic liver assessment, and 3) criteria for dynamic liver assessment. For each topic, subtopics were created answering specific clinical questions, which were formulated according to the PICO methodology (PICO = Population, Intervention, Comparator and Outcome) (Table 1).

Systematic literature review and evidence grading

A systematic literature review was performed by SC members between October and November 2023. Table S1 reflects the search strategy. Prespecified Medical Subject Heading (MeSH) search terms were used and expanded by keywords. Initial search results were filtered according to inclusion and exclusion criteria. Additional references associated with publications retrieved through the search and meeting inclusion criteria were also considered. Medically complex donors in relation to donor-related transmission risk (*e.g.*, infection, malignancy) were not considered.

Studies meeting inclusion criteria were divided among subtopics based on relevance to answering each PICO question. Expert panel members were divided as working group (WG) leaders or members among three WGs corresponding to the three clinical topics. Studies were distributed among WG members to grade according to the Scottish Intercollegiate Guidelines Network methodology (Table S2) (Scottish Intercollegiate Guidelines Network. SIGN 50: A Guideline Developer's Handbook. https://www.sign.ac.uk/media/2038/sign50_2019.pdf). Evidence tables were reviewed by the WG leaders to ensure correct application of the grading system. WG leaders then created considered judgment forms to summarise evidence, quality ratings, and limitations and strengths of studies; draft initial statements and provide strength of recommendations; and identify future areas of research.

Subtopics and the initial statements were summarised by WG leaders and reviewed among SC and expert panel members at the in-person Consensus Meeting on Liver Discard and Viability Assessment held at the ELITA Summit from April 19-20, 2024, in Madrid, Spain. Participants discussed initial statements at the meeting, and the forgoing discussion was considered by the SC when preparing statements for the subsequent Delphi process.

Modified Delphi process

PICO questions, statements, and considered judgment forms were sent out to the entire expert panel for an online stepwise Delphi process, allowing members to agree or disagree with statements and make comments or recommend changes. In each Delphi round, ≥85% agreement among expert panel members was considered sufficient to ensure balance between consensus and voting progress. Statements reaching ≥85% agreement were excluded from further voting, while those with <85% agreement were reviewed by SC and WG leaders and revised accordingly in the next round.

Results

A total of 3,770 publications were screened by the SC; 755 were included for full-text analysis. Ultimately, 289 articles were distributed to expert panel members in WG1 and 201 articles to WG2 and WG3 (Tables S3–10). Participation in the first, second, and third Delphi rounds was 94%, 94%, and 75%, respectively. After three Delphi rounds, achievement of ≥85% agreement was reached for all final statements.

Topic 1: Defining high-risk livers

Recommendations

- The term "discard" should be avoided when describing non-utilisation of a deceased donor liver for transplantation **(LoE 4, strong recommendation).**
- The classification of deceased donor liver non-utilisation into different categories should be considered **(LoE 4, conditional recommendation)**:
  - Type 1: Organ offered, not allocated
  - Type 2: Organ allocated, not recovered
    - 2a: DBD graft
    - 2b: DCD graft, without *in situ* normothermic regional perfusion
    - 2c: DCD graft, not recovered after *in situ* normothermic regional perfusion
  - Type 3: Organ recovered, not transplanted
    - 3a: Without *ex situ* machine perfusion
    - 3b: Not transplanted after *ex situ* machine perfusion

Expert panel comment: Internationally, there have been calls by members of the public and families of organ donors for

Table 1. Topics and clinical PICO questions addressed by consensus guideline process.

PICO	Question	Population	Intervention	Comparator	Outcome
Topic 1: Defining high-risk livers					
1	Which adverse post-transplant outcomes should be used to define whether a deceased donor liver is suitable for transplantation with conventional cold storage alone?	Deceased donor livers	Non-utilisation	Transplantation	To be determined
2	Which donor or graft risk factors should be used to define whether a DBD liver is suitable for transplantation with conventional cold storage alone?	DBD livers			Major adverse post-transplant event
3	Which donor or graft factors should define whether a DCD liver is suitable for transplantation following rapid recovery and conventional cold storage alone?	DCD livers			Wait-list drop-out
4	Should factors related to the intended recipient be used to define whether a particular deceased donor liver is suitable for transplantation or not?	Deceased donor livers Liver recipients	Liver non-utilisation or selection of another recipient		
Topic 2: Strategies for dynamic liver assessment					
5	Can *in situ* normothermic regional perfusion be used to assess DCD livers?	DCD livers	*In situ* NRP	Conventional CS	Liver acceptance *vs.* non-utilisation Graft loss due to ITBL
6	Can *ex situ* HMP be used to assess deceased donor livers?	Deceased donor livers	*Ex situ* HMP		Liver acceptance *vs.* non-utilisation
7	Can *ex situ* NMP be used to assess deceased donor livers?		*Ex situ* NMP		
8	Can combining perfusion modalities (*in situ* and *ex situ* perfusion in DCD, *ex situ* HMP and NMP in general) improve liver assessment relative to individual perfusion modalities performed in isolation?		*In situ* NRP + *ex situ* HMP and/or NMP (DCD only) *Ex situ* HMP + NMP	*In situ* NRP (DCD), *ex situ* HMP, or *ex situ* NMP only	Major adverse post-transplant event
9	What perfusion strategy is recommended for the assessment of DBD livers?	DBD livers	*Ex situ* HMP *Ex situ* NMP *Ex situ* HMP + NMP	Conventional CS	
10	What perfusion strategy is recommended for the assessment of DCD livers?	DCD livers	*In situ* NRP *Ex situ* HMP *Ex situ* NMP *In situ* NRP + *ex situ* HMP and/or NMP		Liver acceptance *vs.* non-utilization Graft loss due to ITBL
Topic 3: Criteria for dynamic liver assessment					
11	What parameters measured during *in situ* normothermic regional perfusion can be used to assess DCD livers?	DCD livers	*In situ* NRP	Conventional CS	Liver acceptance *vs.* non-utilisation Graft loss due to ITBL
12	What parameters measured during *ex situ* HMP can be used to assess deceased donor livers?	Deceased donor livers	*Ex situ* HMP		Liver acceptance *vs.* non-utilisation
13	What parameters measured during *ex situ* NMP can be used to assess deceased donor livers?		*Ex situ* NMP		Major adverse post-transplant event
14	Is there a set of parameters measured during combined perfusion (*in situ* and *ex situ* perfusion in DCD, *ex situ* HMP and NMP in general) that improves liver assessment relative to parameters measured with individual perfusion modalities performed in isolation?		*In situ* NRP + *ex situ* HMP and/or NMP (DCD only) *Ex situ* HMP + NMP	*In situ* NRP (DCD), *ex situ* HMP, or *ex situ* NMP only	
15	Can a best set of parameters be recommended for assessment of hepatocytes during perfusion?		*In situ* NRP (DCD only) *Ex situ* HMP	Conventional CS	
16	Can a best set of parameters be recommended for assessment of the biliary tree during perfusion?		*Ex situ* NMP		Liver acceptance *vs.* non-utilisation Graft loss due to ITBL

CS, cold storage; DBD, donation after brain death; DCD, donation after circulatory determination of death; HMP, hypothermic machine perfusion; ITBL, ischaemic-type biliary lesions; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion.

the transplant community to find alternatives for the term "discard" when discussing donated organs deemed unsuitable for transplantation. While "discard" can be found throughout the medical literature in publications addressing organ evaluation and transplantation, it carries potentially negative connotations that do not reflect the intention for the donated organ to be shared for the benefit of others. As well, "discarded organs" covers a broad range of organs not utilised at different stages of the donation and transplantation process.

Livers that are not suitable for transplantation after conventional storage may undergo alternative, dynamic preservation methods, with or without real-time assessment, and/or be used for research to facilitate future transplantation of similar grafts. The expert panel sought to improve terminology and classification of donated livers that cannot be transplanted. Other authors have described the Critical Pathway of Deceased Organ Donation, a comprehensive system for classifying individuals at different points along the deceased donor process that includes possible, potential, eligible, actual, and utilised deceased donors.[20] While definition and relevance of each of these categories are beyond the scope of this consensus process, they should also be consulted and recorded, as they offer valuable insight into reasons for failure to pursue or utilise deceased donors in different settings.

Q1: Which adverse post-transplant outcomes should be used to define whether a deceased donor liver is suitable for transplantation with conventional cold storage alone?

Recommendations

- Non-utilisation of a liver graft undergoing conventional cold storage alone should be a careful and balanced clinical decision, taking into consideration expected benefits of graft utilisation, waitlist dynamics, potential risks associated with matching the graft to an individual recipient, and techniques to mitigate adverse graft-related outcomes **(LoE 2, strong recommendation).**
- Predicted rates of primary non-function, early allograft dysfunction, acute kidney injury, complication-free survival, overall biliary complications, ischaemic-type biliary lesions, and 3-month and 1-year graft and patient survival should be considered to define a graft as not suitable for transplantation in the designated recipient using conventional cold storage alone **(LoE 2, research recommendation).**
- The European liver transplant community and organ sharing organisations should consistently and uniformly register and analyse liver offers and rates and causes of non-utilisation, primary non-function, early allograft dysfunction, acute kidney injury, complication-free survival, overall biliary complications, ischaemic-type biliary lesions, and 3-month and 1-year graft and patient survival. These are important factors to inform the decision to transplant a patient with a particular graft, as well as to estimate the risk of remaining on the transplant waitlist **(LoE 4, strong recommendation).**

Expert panel comment: Outcome metrics for deceased donor liver transplantation (DDLT) are used to manage risks, patient expectations, and costs. They offer points for comparison among different clinical experiences. In the modern era, DDLT outcome metrics should ideally also include value-based healthcare measures, which focus on optimisation of patient survival and quality of life and minimisation of healthcare costs. They should also aim to avoid missed opportunities for organ utilisation and honour the significance of the donor's gift.[21–23]

Outcome metrics evaluating the suitability of a deceased donor liver typically include early post-transplant measures related to graft quality and its ability to withstand ischaemia-reperfusion injury (IRI). Immediate post-transplant events are also influenced by factors unrelated to graft quality. These include recipient characteristics, such as prior abdominal surgery, previous liver transplantation, portal vein thrombosis, and pre-transplant clinical state; infectious and immunological complications; technical factors; and other intra- and perioperative events.

With the objective of providing a structure that others may follow to determine which grafts and transplants are more-or-less standard and may proceed without advanced (*i.e.*, perfusion) preservation, studies were performed to provide benchmark outcomes for typical cases of primary donation after brain death (DBD), primary controlled DCD (cDCD), and re-do liver transplantation.[24–26] As well, a recent SRTR (Scientific Registry of Transplant Recipients) consensus united various stakeholders to identify priority metrics in transplantation.[22] Taking all this into consideration, as well as the expert opinions of the panel and after reviewing considerable evidence (see Table S3), the following were identified as important outcome metrics in DDLT: graft primary non-function (PNF); parameters of post-transplant recovery, including early allograft dysfunction (EAD), acute kidney injury (AKI), and complication-free survival; overall biliary complications and ischaemic type biliary lesions (ITBL); and 3-month and 1-year graft and patient survival rates.

Definitions for PNF vary among studies but generally include a requirement for immediate re-transplantation or death within 7 days following the index procedure. Pooled data analysis demonstrates that the incidence of PNF has declined to 2.2% (95% CI 0.1-4.3%) and 2.1% (95% CI 0.3-3.9%) for DBD and cDCD grafts, respectively.[27] Among 415 recipients of extended-criteria donor livers, no significant increase was seen in PNF (2.9%) in relation to high-risk graft criteria.[28] While some studies have demonstrated higher PNF among recipients of severely steatotic or DCD grafts,[29,30] the incidence of PNF remains low. The effect size of PNF on its own is suboptimal for classification of deceased donor liver grafts as unsuitable for transplantation with conventional cold storage alone. Biliary complications, AKI, and EAD are other more commonly encountered complications that are influenced by graft quality. Appearance of any these can negatively impact post-transplant hospital stay, costs, and graft and patient survival.[31–37]

Q2: Which donor or graft risk factors should be used to define whether a DBD liver is suitable for transplantation with conventional cold storage alone?

Recommendations

- Graft steatosis, including large- and small-droplet fat, should be considered a major criterion that may define a DBD liver as unsuitable for transplantation with conventional cold storage alone. DBD livers with mild steatosis (≤30%) and no additional risk factors should be considered suitable for transplantation with conventional cold storage alone, while those with mild steatosis and additional relevant risk factors or moderate-to-severe steatosis (>30%) may be considered for transplantation after balancing risks and benefits associated with using grafts with increasing degrees of steatosis, as well as potential additional risk factors and techniques available to mitigate such risks **(LoE 2++, strong recommendation).**
- DBD livers from donors of any age should be considered suitable for transplantation with conventional cold storage, after balancing potential additional risk factors present in the donor, graft, and/or recipient **(LoE 2++, strong recommendation).**
- In order to increase liver utilisation rates and improve outcomes, the complex interplay among different risk factors observed in a particular donor should be defined or summarised in practical algorithms, adopting advanced data analysis techniques such as artificial intelligence and machine learning **(LoE 4, research recommendation).**

Expert panel comment: Extended criteria grafts represent organs with unfavourable characteristics associated with inferior outcomes. Extended criteria for DBD livers described by Eurotransplant include donors >65 years, pre-donation intensive care stay >7 days, BMI >30, serum sodium >165 mEq/L, alanine aminotransferase (ALT) >105 IU/L, aspartate aminotransferase >90 IU/L, bilirubin >3 mg/dl, and graft steatosis >40%.[38] Following these criteria, several observational cohort studies, with high risk for confounding or bias, have demonstrated significant differences in outcomes, including complications, graft loss, and mortality, between recipients of standard *vs.* extended criteria grafts.[39] While these criteria were restated in the EASL (European Association for the Study of the Liver) 2016 Liver Transplantation Clinical Practice Guidelines, recommendations ultimately focused on donor age and graft macrosteatosis as primary risk factors.[40] After reviewing the evidence provided via the systematic review (Table S4), the expert panel has found that there is sufficient evidence supporting graft steatosis as the primary risk factor in DBD liver transplantation. Any other proposed or previously described criteria are supported by minimal and/or low-quality evidence.

Graft steatosis: Traditionally, liver allograft steatosis has been classified as either "macrosteatosis" (single, large vacuole replacing most cell cytoplasm and displacing the nucleus) or "microsteatosis" (smaller lipid vacuoles without nuclear displacement) and as absent (<5%), mild (5-29%), moderate (30-60%), or severe (>60%), based on the percentage of hepatocytes affected by fat droplets. Consistent evidence from high-quality studies suggests DBD livers with mild steatosis and no additional risk factors may be safely transplanted with conventional cold storage alone.[41,42] However, transplantation of livers with moderate or severe macrosteatosis increases the risk of severe IRI, early graft loss, and patient mortality during the first 90 days. Beyond the immediate post-transplant period, there is inconsistent evidence that more remote outcomes are similarly affected by the use of steatotic grafts.[30,41–43] Evidence from retrospective cohort studies and systematic reviews suggests DBD grafts with moderate-to-severe macrosteatosis or those arising from extremely obese donors may offer a viable alternative to help address organ shortages and should not be excluded from judicious use after carefully evaluating potential harms and benefits for the recipient, the presence of other risk factors, and techniques available to mitigate risk.[44]

An issue confusing interpretation of studies evaluating donor liver steatosis is lack of standardized criteria for donor liver biopsy assessment. Recently, the Banff Working Group on Liver Allograft Pathology convened an international group of experts to create consensus recommendations for steatosis assessment in donor livers.[45] Recommendations define large droplet fat as a single droplet distending the cell and displacing the nucleus; small droplet fat as droplets not meeting definitions of either large droplet fat or true microvesicular steatosis; and true microvesicular steatosis as tiny droplets distending hepatocytes, not commonly visible as discrete vacuoles nor seen without a specific fat stain. Future studies should adhere to these recommendations for the evaluation of donor liver large droplet fat and small droplet fat, as the relevance of the latter, in particular, remains an unresolved clinical issue.[46,47]

Donor age: Donor age is consistently included in risk indices as a factor associated with DBD liver graft and recipient survival.[38,48–50] While donor risk indices cannot be validated in all settings, multiple observational cohort studies suggest a synergistic effect of age when other risk factors are present.[50,51] Systematic reviews and meta-analyses of observational cohort studies describe more biliary complications but similar graft and patient survival among recipients of livers from donors >70-80 years *vs.* recipients of livers from younger donors.[52–54] Overall, donor age alone should not exclude judicious use of DBD livers for transplantation using conventional cold storage alone.

Other risk factors: While donor hypernatremia ≥155 mEq/L was historically associated with worse liver-specific functional parameters and increased graft loss,[55,56] more recent reports do not support an association between even severe donor hypernatremia and post-liver transplant outcomes.[57–60]

A large cohort study including >5,000 liver transplant recipients determined that elevated donor transaminases had no impact on post-transplant outcomes.[61] On multivariate analysis, ALT and aspartate aminotransferase levels were not predictive of early or overall graft loss or recipient survival. This observation did not change when subgroups, including steatotic livers, hypoxic brain injury donors, and donors with increasing ALT at the time of donation, were analysed. Even grafts from donors with very high ALT levels >1,000 IU/L displayed good post-transplant outcomes.

An experienced donor surgeon is important to avoid graft injury and minimise donor hepatectomy time (DHT), *i.e.* the time from the start of *in situ* cold preservation to liver recovery during which graft temperature remains mid-thermic (>10 °C),[62] which is associated with greater relative graft injury compared to true

cold storage. In a large study including 12,513 Eurotransplant DBD liver recipients, increasing DHT was independently associated with higher graft loss and patient death; every 10-minute increase in DHT was equivalent to a one-hour increase in cold ischaemia time (CIT).[63] While the effect was greater among recipients of cDCD livers (n = 461), recipients of DBD livers were also at risk. A smaller, single-centre study including 292 DBD liver recipients confirmed the negative impact of increasing DHT on allograft function.[64]

Q3: Which donor or graft factors should define whether a DCD liver is suitable for transplantation following rapid recovery and conventional cold storage alone?

Recommendations

- In the transplantation of controlled DCD livers undergoing rapid recovery and subsequently preserved with conventional cold storage, donor total warm ischaemia time should not exceed 30 minutes **(LoE 2-, strong recommendation).**
- In the transplantation of controlled DCD livers undergoing rapid recovery followed by conventional cold storage, cold ischaemia time should not exceed 6 hours **(LoE 2-, conditional recommendation).**
- In the transplantation of controlled DCD livers, donor hepatectomy should be completed as quickly as possible, ideally within 40 minutes from the start of *in situ* cold preservation **(LoE 2- (range 2- to 2+), strong recommendation).**
- Donor body mass index ≤25 and graft steatosis <30%, including large and small droplet fat, may be considered acceptable cut-offs for the transplantation of controlled DCD livers undergoing rapid recovery and conventional cold storage **(LoE 2- (range 2- to 2+), conditional recommendation).**

Expert panel comment: Transplantation of cDCD livers has been increasing steadily over the past two decades, and cDCD is now an established alternative to DBD in Western countries to meet liver transplant waitlist demands. Nonetheless, the risk of biliary complications, in particular ITBL, persists in relation to the duration of donor warm ischaemia. Donor functional warm ischaemia time (dFWIT), encompassing the period between the onset of donor hypoperfusion and/or hypoxemia following withdrawal of life support therapy (WLST) and the start of *in situ* organ preservation, is a critical determinant of post-transplant outcomes. Definitions for the start of dFWIT vary according to author and setting, and a unifying consensus definition was only published recently.[65] It is reasonable to consider donor total warm ischaemic time (dTWIT), the period between WLST and the onset of *in situ* preservation, as a surrogate for ischaemic injury suffered during the agonal phase of cDCD. Table 2 lists relevant studies analysing the impact of donor warm ischaemia on clinical outcomes in cDCD liver transplantation; if considered, dFWIT definitions are included.

Cold ischaemia is universally recognised as prognostic factor for graft survival among both DBD and DCD liver recipients. Numerous studies have identified prolonged CIT as a risk factor negatively impacting cDCD liver graft and recipient survival.[66–75] Scalea and colleagues analysed >50,000 liver transplants to evaluate 5-year graft survival and identify risk factors for graft loss.[73] Five-year graft survival was higher among recipients of cDCD livers from donors aged <50 years with <6 hours CIT *vs*. DBD livers from donors aged >60 years (p <0.001). Moreover, graft survival was comparable to that observed among recipients of younger DBD livers (p = 0.118). Multivariate analysis confirmed that CIT, both alone and in combination with donor age <50 years, was an independent risk factor for graft loss. CIT was identified as an independent risk factor for ITBL in two other studies.[67,68] A study by Mihaylov and colleagues demonstrated that reducing CIT to <6 hours combined with careful recipient selection (*e.g*., avoiding patients with portal vein thrombosis and/or prior abdominal surgery) improved transplant outcomes, including anastomotic and non-anastomotic biliary strictures and 1-year graft and patient survival rates.[75] Overall, CIT <6 hours appears to be important in protecting cDCD liver recipients from adverse transplant outcomes (Table 3). Every effort should be made to minimise CIT and its impact on grafts, in particular when advanced organ recovery methods, such as *in situ* NRP, are not available.

Donor age is a well-studied risk factor impacting outcomes in cDCD liver transplantation.[66,68–70,72–74,76–87] A primary reason for graft loss using cDCD livers from elderly donors is the development of ITBL, especially when other risk factors are present.[68,77,80,83,88] Based on variability among published experiences, there is no clear donor age cut-off to differentiate standard-*vs.* high-risk cDCD grafts (Table S11). While donor age ≤60 years appears to be a reasonable cut-off for cDCD grafts undergoing rapid recovery followed by conventional cold storage, especially when other non-modifiable risk factors are present, the expert panel was unable to reach sufficient agreement on the issue.

Four studies have demonstrated that prolonged DHT is an independent risk factor for ITBL, graft loss, and death among cDCD liver recipients (Table S12). Farid and colleagues evaluated 1,112 patients undergoing primary cDCD liver transplantation and concluded that DHT >60 minutes was an independent risk factor for PNF and graft loss,[74] while other authors have established shorter cut-offs.[89–91]

Data on donor BMI and graft steatosis and their impact on graft and patient survival in the DCD setting are limited (Table S12). Croome and colleagues evaluated 714 cDCD liver recipients and determined that those receiving livers with moderate macrosteatosis exhibited higher rates of post-reperfusion cardiac arrest, AKI, PNF, and EAD compared to recipients of cDCD livers with less steatosis.[92] Bath and colleagues evaluated the Organ Procurement and Transplantation Network database and observed worse graft and recipient survival for recipients of macro- and microsteatotic cDCD livers.[93] Donor BMI was also identified as a risk factor for cDCD liver graft loss and AKI in four studies, two identifying a BMI cut-off of >25 to differentiate standard-*vs.* high-risk cDCD grafts.[68,80,86,94] Overall, it is appropriate that

livers from cDCD donors with BMI >25 or >30% steatosis, including both large- and small-droplet fat, should be carefully selected and matched with appropriate recipients.

Q4: Should factors related to the intended recipient be used to define whether a particular deceased donor liver is suitable for transplantation or not?

Recommendations

- Recipient MELD score should not be used as a criterion for acceptance *vs.* non-utilisation of a DBD liver undergoing conventional cold storage in that particular recipient **(LoE 2-, strong recommendation).**
- Matching controlled DCD livers undergoing rapid recovery and conventional cold storage to recipients with MELD ≤ 25 is recommended **(LoE 2+, conditional recommendation).**

Expert panel comment: Appropriately balancing characteristics and risk factors of the graft with those of the recipient is crucial to the success of liver transplantation. Several recipient characteristics have been considered relevant in this process.

The model for end-stage liver disease (MELD) score was introduced to prioritise patients based on risk of death awaiting transplantation. In the DBD setting, evidence regarding using MELD to contraindicate use of a particular graft for that recipient is scarce and conflicting (Table 4), and recipient MELD cannot be used reliably in the decision to accept a DBD graft. Using DCD grafts, reperfusion injury may be severe, and DCD liver recipients are more likely to develop severe post-reperfusion syndrome, including cardiac arrest, AKI, and EAD. Use of DCD grafts in sick recipients remains controversial. Evans and colleagues evaluated 44 donor and recipient variables to predict 1-year survival among >5,000 high-acuity recipients undergoing primary liver transplantation registered in the SRTR database and concluded receiving a DCD graft was among the strongest predictors of 1-year mortality in patients with MELD ≥40.[96] Kumar and colleagues, on the other hand, compared outcomes of nearly 8,000 liver recipients undergoing primary transplantation for fulminant hepatic failure using DBD *vs.* DCD livers. One-year graft survival was inferior among DCD liver recipients, while long-term patient survival rates were comparable.[97] Table 4 lists studies evaluating MELD as a risk factor for adverse post-transplant outcomes in both the DBD and DCD settings.

Due to aging of the general population in many settings, liver transplants are being indicated in an increasingly older cohort. Given this is a relatively recent trend, there is no conclusive evidence in the literature supporting exclusion of recipients based solely on age when a DBD graft is available. On the contrary, considering the greater risk associated with DCD grafts, the combination of a DCD graft transplanted into an older recipient could negatively impact both graft and recipient survival. Table S13 lists studies evaluating recipient age as a risk factor impacting graft and/or patient survival. While recipient age ≤60 years appears to be a reasonable cut-off for the transplantation of cDCD livers undergoing rapid recovery and conventional cold storage,

Table 2. Studies evaluating the impact of donor warm ischaemia times on outcomes in cDCD liver transplantation.

Author	Study type	Level	Setting	Period	"N" evaluated	dWIT cut-off(s)	dFWIT start	Results
Coffey[85]	MCC	2+	Belgium, Canada, USA	2007-2014	3,483	dTWIT >25' dFWIT >18'	SpO_2 <60%	Risk factor for graft loss
Kalisvaart[95]	SCC	2+	Netherlands	2008-2016	93	dFWIT >13'	SpO_2 <80%	Risk factor for graft loss
Kalisvaart[94]	MCC	2+	Netherlands, UK	2008-2016	368	dTWIT + rWIT	-	Risk factor for AKI
Kubal[67]	SCC	2+	USA	2003-2016	91	NR	-	Risk factor for ITBL
Mathur[66]	MCC	2++	USA	2001-2009	1,567	dTWIT >35'	-	Risk factor for graft loss
Paterno[69]	MCC	2+	USA	2009-2015	21,017	dTWIT >30'	-	Risk factor for increased LoS
Schlegel[68]	MCC	2+	UK	2000-2015	3,329	dFWIT >30'	SBP <50 mmHg	Risk factor for graft loss

AKI, acute kidney injury; cDCD, controlled donation after circulatory determination of death; dFWIT, donor functional warm ischaemia time; dTWIT, donor total warm ischaemia time; dWIT, donor warm ischaemia time; ITBL, ischaemic-type biliary lesions; LoS, length of stay; MCC, multicentre cohort; NR, none reported; PNF, primary non-function; rWIT, recipient warm ischaemia time; SBP, systolic blood pressure; SCC, single-centre cohort; SpO_2, oxygen saturation.

the expert panel was unable to reach sufficient consensus on the issue.

Finally, mechanical ventilatory support is another factor to consider when managing severely ill liver transplant candidates. Shimada and colleagues classified nearly 30,000 liver transplant recipients into three groups based on donor age: ≥70, 40-69, and <40 years. Among recipients of livers from elderly deceased donors, the need for pre-transplant mechanical ventilation was associated with a higher risk of graft loss during the first year.[98] Croome and colleagues also determined in two studies focused solely on DCD liver transplant recipients that pre-transplant mechanical ventilation was a risk factor for graft failure.[99,100] Based on these experiences, it appears reasonable to exercise caution when transplanting livers from controlled DCD donors undergoing conventional cold storage only into recipients with one or more acute organ failures requiring intensive care support.

Topics 2 & 3: Strategies and criteria for dynamic liver assessment.

The same body of literature was assessed to address strategies and criteria for dynamic liver assessment, and results, statements, and commentary are complementary. For greater ease of reading and understanding, these two topics are presented together.

Recommendations

- Optimisation of pre-recovery donor management and the organ recovery process, including donor surgeon experience and donor hepatectomy time, should be considered an important adjunct to any dynamic liver recovery, preservation, and/or assessment strategy **(LoE 2+, strong recommendation [best clinical practice]).**
- The ultimate decision to accept a liver for transplantation should be based on not only donor- and organ-specific factors but also recipient medical and surgical risk factors; waiting list demands and dynamics; and other local or regional factors, such as technological, financial, and human resources and logistical considerations **(LoE 4, strong recommendation [best clinical practice]).**

Expert panel comment: Prior to implementing liver perfusion in the clinical setting, both pre-recovery care of the potential deceased donor and the organ recovery process should be optimised. In neurocritical patients, including all DBD and most cDCD donors, intracranial hypertension impairs brain perfusion, and consequent catecholamine release provokes varying degrees of inflammation, endothelial dysfunction, and hemodynamic instability. Impaired hypothalamic and pituitary function may reduce circulating cortisol, triiodothyronine, insulin, and antidiuretic hormone.[104] These derangements represent targets for intervention. While donor care research is complicated to perform and deceased donor interventions are not supported by high-level evidence, strategies of donor care management extrapolated from general critical care remain useful. Such strategies include the maintenance of adequate intravascular volume, haemodynamic support, oxygen delivery, and normoglycaemia; correction of electrolyte abnormalities; lung recruitment manoeuvres; prevention of thromboembolic complications and uncontrolled infections; and provision of hormonal support to the donor. These treatments may be standardised and applied prior to organ recovery for both DBD and cDCD transplants, and may help reduce the perceived if not real risk associated with liver grafts at the moment of organ evaluation and recovery.[105]

Q5: Can *in situ* normothermic regional perfusion be used to assess DCD livers?

Recommendations

- *In situ* abdominal NRP can be used to recondition and assess controlled DCD livers for subsequent transplantation **(LoE 2+ (range 2- to 2++), strong recommendation).**
- *In situ* abdominal NRP should be used to recondition and assess uncontrolled DCD livers, though additional *ex situ* machine perfusion preservation should be considered in these grafts prior to their transplantation **(LoE 2-, strong recommendation).**

Q11: What parameters measured during in situ normothermic regional perfusion can be used to assess DCD livers?

Recommendations

- Flow rates, perfusate lactate and transaminases, and macroscopic evaluation should be considered to assess controlled DCD livers during *in situ* abdominal NRP **(LoE 2- (range 2- to 2++), conditional recommendation).**
- Flow rates, perfusate lactate and transaminases, and macroscopic evaluation should be considered to assess uncontrolled DCD livers during *in situ* abdominal NRP **(LoE 2-, conditional recommendation).**
- Abdominal NRP parameter thresholds are not well established, owing to variability among available clinical protocols and studies. Nonetheless, stable pump flow, stable transaminase levels throughout perfusion, stable or declining lactate in samples collected at least every 30 min, and a good macroscopic appearance of the liver during *in situ* evaluation can be considered reasonable requirements **(LoE 2- (range 2- to 2++), conditional recommendation).**
- The optimal timing of abdominal NRP assessment used to guide subsequent clinical decisions is not well established, owing to variability among available clinical protocols and studies. Nonetheless, during *in situ* abdominal NRP, livers can be evaluated for up to 2 hours for controlled DCD and up to 4 hours for uncontrolled DCD, respectively **(LoE 2- (range 2- to 2++), conditional recommendation).**

Expert panel comment: Postmortem abdominal NRP (A-NRP) restores oxygenated perfusion of multiple abdominal organs in DCD, without intervening cold ischaemia. NRP mimics the same warm ischaemia-reperfusion sequence as ischaemic

Table 3. Studies evaluating the impact of cold ischaemia time on outcomes in cDCD liver transplantation.

Author	Study type	Level	Setting	Period	"N" evaluated	CIT	Results
Farid[74]	MCC	2+	USA	2001-2015	1,112	>8 h	Risk factor for PNF, EAD, graft loss
Foley[72]	SCC	2+	USA	1993-2008	1,244	>8 h	Risk factor for ITBL
Jay[70]	MCC	2-	USA	1996-2007	43,367	>12 h	Risk factor for recipient death
Kubal[67]	SCC	2+	USA	2003-2015	91	>6 h	Risk factor for ITBL
Mathur[66]	MCC	2++	USA	2001-2009	1,567	>6 h	Risk factor for graft loss, recipient death
Mihaylov[75]	SCC	2+	USA	2003-2018	208	>6 h	Risk factor for ABS, ITBL, 1-year recipient death
Paterno[69]	MCC	2+	USA	2009-2015	21,017	>6 h	Risk factor for LoS, readmission, 30-day mortality, graft loss
Scalea[73]	MCC	2	USA	2002-2014	52,723	>6 h	Risk factor for graft loss
Schlegel[68]	MCC	2+	UK	2000-2015	3,329	>6 h	Risk factor for graft loss
Yamamoto[71]	SCC	2+	Sweden	1984-2008	40	>7 h	Risk factor for graft loss

ABS, anastomotic biliary stricture; cDCD, controlled donation after circulatory determination of death; CIT, cold ischaemia time; EAD, early allograft dysfunction; ITBL, ischaemic-type biliary lesions; LoS, length of stay; MCC, multicentre cohort; PNF, primary non-function; SCC, single-centre cohort.

preconditioning and similarly mediates its effects, in part, through adenosine.[106] Unlike rapid recovery in DCD, postmortem NRP allows for *in situ* graft observation and dynamic assessment prior to cold preservation.

Use of postmortem A-NRP was originally applied in Maastricht category II uncontrolled DCD (uDCD), where the pre-preservation donor warm ischaemia period is prolonged.[1,107,108] Initially, criteria for assessing uDCD livers during A-NRP included parameters that were rapidly available and provided a reflection of the extent of hepatic ischaemic injury and response to reperfusion. The evolution of perfusate transaminase levels; macroscopic appearance of the reperfused liver, gallbladder, bile duct, and bowel; and ability to maintain a minimum rate of flow through the abdominal aorta were among the original criteria used to assess uDCD livers.[1,108] A stable or downward trend in perfusate lactate was later added to several NRP assessment protocols.[7,9,109] Use of additional parameters, such as perfusate glucose, bile pH, and bile glucose, has been described anecdotally.[110] In one small cohort study, flavin mononucleotide (FMN) measured in NRP perfusate was retrospectively correlated with liver acceptance for transplantation, though the former was not associated with any post-transplant measurement or outcome.[111]

Due to severe donor vasoplegia and/or vascular trauma, inability to maintain minimum A-NRP pump flow >1.7 L/min (approximately 1 L/min/m^2 body surface area) was a primary cause of both liver and kidney non-utilisation in almost 20% of donors in initial uDCD experiences.[108] Subsequent experiences in both uDCD and cDCD have included adequate A-NRP pump flow as a criterion for liver graft utilisation, though this is easily achieved in the cDCD setting. If anything, there is risk for abdominal hyperperfusion and hepatic congestion in cDCD performed with A-NRP when targeting a pump flow of >1.7 L/min/m^2 body surface area as opposed to >1.7 L/min, as was originally described.

Table 5 lists the principle international observational cohort studies on uncontrolled and controlled DCD liver transplant experiences, describing both how livers were assessed during NRP, as well as outcomes achieved with thousands of transplanted grafts. Older or smaller studies describing duplicate or largely overlapping data sets and those in which either NRP assessment parameters or post-transplant outcomes are missing are not listed. Reports in which thoracoabdominal NRP (TA-NRP) was the primary method for cDCD liver recovery are excluded, as TA-NRP donors typically present a younger, more favourable donor profile relative to other cDCD cohorts. Of note, NRP liver assessment parameters include those specifically evaluated during NRP; criteria not specific to NRP (donor age, duration of pre-NRP donor warm ischaemia, graft histology, etc.) are not considered.

Though NRP is standard for liver recovery in the context of uDCD, results using uDCD livers recovered with NRP remain inferior to those achieved with DBD organs.[11,12] Currently, postmortem NRP is more commonly applied in cDCD. While there are no RCTs supporting the use of NRP in cDCD liver transplantation, several observational cohort studies describe significant improvements in liver utilisation rates, biliary complications, ITBL, and patient and graft survival relative to rapid recovery,[7–10] with comparable post-transplant outcomes relative to those achieved with DBD livers of a similar risk profile.[110,112,113] Two meta-analyses of observational cohort studies confirm a significant reduction in overall biliary complications and consistently low rates of ITBL using NRP to recover cDCD livers.[11,12] NRP is typically maintained for 1-2 hours, though progressive benefits in

Table 4. Studies evaluating the impact of recipient MELD on liver transplant outcomes.

Author	Study type	Level	Setting	Period	"N" evaluated	MELD	Results
DBD grafts							
Axelrod[31]	MCC	2+	USA	2002-2005	17,710	>35	Risk factor for higher transplantation costs
Caso-Maestro[101]	SCC	2+	Spain	1986-2016	424	High[1]	Risk factor for graft loss if donor and/or recipient age also increased
Croome[102]	SCC	2+	Canada	2006-2010	310	<15	Risk of EAD if DRI ≥1.7
Croome[47]	SCC	2+	USA	2000-2017	496	High[1]	Risk factor for graft loss if graft microsteatosis ≥30%
cDCD grafts							
Croome[99]	MCC	2++	USA	2003-2014	3,199	High[1]	Risk factor for graft loss
Croome[100]	MCC	2+	USA	2002-2016	471	>30	Risk factor for graft loss
Evans[96]	MCC	2++	USA	2002-2016	5,309	≥40	Risk factor for patient death
Kumar[82]	MCC	2-	USA	2003-2018	7,933	FHF	Risk factor for 1-y graft loss
Mathur[66]	MCC	2++	USA	2001-2009	1,567	>35	Risk factor for graft loss and recipient death
Schlegel[68]	MCC	2+	UK	2000-2015	3,329	>25	Risk factor for graft loss
Sher[103]	MCC	2-	USA	2009-2014	26,919	>20	Risk factor for graft loss

DBD, donation after brain death; cDCD, controlled donation after circulatory determination of death; DRI, donor risk index; EAD, early allograft dysfunction; FHF, fulminant hepatic failure; MCC, multicentre cohort; MELD, model for end-stage liver disease; SCC, single-centre cohort.
[1]No cut-off provided.

injury markers and functional parameters may be achieved with periods lasting up to 4 hours.[114,115] Improved results with DCD livers recovered with NRP are likely related to a combination of both reconditioning effects of NRP itself as well as improved ability to assess and select grafts.

Q6: Can *ex situ* hypothermic machine perfusion be used to assess deceased donor livers?

Recommendation

- Clinical evidence supporting the use of HMP biomarkers to assess livers for transplantation is scarce. Prospective, multicentre trials should be considered to determine how parameters evaluated during *ex situ* HMP may be used on a broader scale to guide clinical decisions regarding liver allograft acceptance *vs.* non-utilisation **(LoE 2- (range 2- to 2+), research recommendation, conditional recommendation restricted to clinical trials).**

Q12: What parameters measured during *ex situ* hypothermic machine perfusion can be used to assess deceased donor livers?

Recommendations

- Perfusion parameters and perfusate flavin mononucleotide and transaminases levels can be prospectively recorded during *ex situ* HMP in deceased donor livers **(LoE 2- (range 2- to 2+), conditional recommendation restricted to clinical trials).**
- HMP parameter thresholds are not well established and should be applied with caution in clinical practice **(LoE 2- (range 2- to 2+), research recommendation, conditional recommendation restricted to clinical trials).**
- The optimal timing of HMP assessment used to guide subsequent clinical decisions is not well established and timings should be applied with caution **(LoE 2- (range 2- to 2+), research recommendation, conditional recommendation restricted to clinical trials).**

Expert panel comment: *Ex situ* hypothermic machine perfusion is performed by pumping acellular perfusate through the liver at 4-10 °C.[126] While the original clinical pilot study published by Guarrera and colleagues in 2010 relied on passive oxygenation of the perfusate via contact with ambient air,[2] current devices typically include continuous, active oxygenation provided by an in-line membrane oxygenator through the portal vein ("HOPE") or dually via both portal vein and hepatic artery circuits ("DHOPE"). Alternatively, the perfusate may be pre-oxygenated according to the "HMPO_2" concept, which has been shown to offer comparable results relative to continuous, active oxygenation in different organs in experimental studies.[127,128] Hereupon, "HMP" (hypothermic machine perfusion) refers to all modern *ex situ* hypothermic perfusion modalities (HOPE, DHOPE, HMPO_2), while individual modalities with particular applications or evidence are listed specifically in the text.

The benefits of *ex situ* HMP are related to improvements induced in graft microvasculature, mitochondria, and energy charge, leading to reduced oxidative injury and inflammation upon normothermic reperfusion.[129,130] Six RCTs have been published to date comparing a period of HMP *vs.* continuous cold storage during *ex situ* preservation. These have demonstrated that use of HMP leads to fewer post-transplant complications and reduced liver-related graft loss, in particular among high-risk DBD liver recipients,[14,17,19,131–133] and lower incidence of ITBL among recipients of cDCD livers.[15] *Ex situ* HOPE and DHOPE have also been shown, in both an international observational cohort study and a single-centre prospective trial, to allow for the extension of *ex situ* preservation for up to 20 hours without adverse clinical effects.[134,135]

Regarding the specific question of whether *ex situ* HMP may be used to assess deceased donor livers, a few single-centre studies have been published evaluating the clinical relevance of parameters measured during *ex situ* HOPE and DHOPE (Table 6). Patrono and colleagues retrospectively evaluated different markers measured in both the perfusate and microdialysate during end-ischaemic DHOPE, associating them with composite outcome measures reflecting the evolution of early post-transplant laboratory values among DBD grafts.[136,137] The Zurich Group has published several

Table 5. Studies evaluating associations between parameters measured during *in situ* normothermic regional perfusion and post-transplant outcomes.

Author	Study type	Level	Setting	Period	"N" evaluated[1]	"N" LTx	% LTx	NRP liver assessment parameters						Early graft loss[4]	ITBL	1-ygraft survival
								Duration	Pump flow	Transaminases[2]	Gross appearance[3]	Lactate	Other			
Uncontrolled DCD																
De Carlis[109]	SCC	2-	Italy	2015-2017	25[5]	20[5]	80%	-	-	<1,000	Good	↓	-	10%[6]	10%[6]	85%[6]
Fondevila[108]	SCC	2-	Spain	2002-2010	290	34	12%	<4 h	>1.7 L/min	<200	Good	-	-	12%	8%	70%
Ghinolfi[116]	MCC	2-	Italy	2018-2019	31[5]	18[5]	58%	-	>2 L/min	<1,000	Good	↓	-	6%[6]	6%[6]	94%[6]
Jiménez-Romero,[117,118] Justo[119]	SCC	2-	Spain	2006-2016	256	75	29%	<5 h	2.5-3.5 L/min	<200 or ↓	Good	-	-	12%	16%	73%
Lazzeri[120]	SCC	2-	Italy	2016-2019	37	10	27%	-	>2 L/min	<1,000	Good	Stable or ↓	-	10%[6]	NR	80%[6]
Savier[121]	MCC	2-	France	2010-2013	183	13	7%	<4 h	2-3 L/min	<200 or ↓	Good	-	-	31%	8%	69%
Controlled DCD																
Camagni[122]	SCC	2+	Italy	2017-2022	34	27[7]	79%	>3 h	-	-	-	↓	-	8%	0	87%
Croome[123]	SCC	2-	USA	2022	14	11	76%	1-1.5 h	2-3 L/min	-	Good	↓	-	0	0	NR
De Carlis[7]	MCC	2-	Italy	2015-2019	78	44	56%	1-4 h	1.7-3 L/min/m^2	<1,000	Good	↓	-	7%[6]	2%[6]	91%[6]
Gaurav[8]	SCC	2+	UK	2013-2020	120	83	69%	2 h	2.5-3 L/min	<500 & stable	Good	↓/-	-	6%[8]	6%	93%
Hessheimer[9]	MCC	2++	Spain	2012-2019	775	545	70%	1-4 h	2.2-2.4 L/min/m^2	<200 or ↓	Good	Stable or ↓	-	8%	1%	90%
Muller[124]	MCC	2+	France	2015-2019	226	159	70%	>1 h	2.6-4.4 L/min	<200 or ↓	Good	-	-	5%	4.5%	93%
Oniscu[10]	MCC	2-	UK	2011-2019	163	94	58%	-	2.5-3 L/min	Stable or ↓	Good	↓/-	-	NR	NR	93%
Schurink[110]	MCC	2+	Netherlands	2018-2021	28	20	71%	>1 h	>1.7 L/min	<200 & stable	-	↓	Perfusate glucose, bile pH & glucose	5%	11%	90%
Steinberg[125]	SCC	2-	Italy	2019-2022	27	20	74%	<4 h	>1.7 L/min/m^2	<1,000	Good	↓	-	5%[6]	5%[6]	NR

DCD, donation after circulatory determination of death; ITBL, ischaemic-type biliary lesions; LTx, liver transplant; MCC, multicentre cohort; NR, not reported; NRP, normothermic regional perfusion; SCC, single-centre cohort.
[1]Cases in which abdominal NRP was initiated.
[2]All values are in IU/L.
[3]Good gross appearance typically includes homogenously well-perfused graft of soft consistency that is neither fibrotic nor cirrhotic nor congested and is fed by a hepatic artery of adequate quality and free of significant atherosclerotic plaques.
[4]Early graft loss captures both graft loss and patient death during the first 90 days.
[5]Includes a minority percentage of cDCD livers.
[6]Additional HMP or NMP applied in all or the majority of cases during the *ex situ* period.
[7]N = 3 livers transplanted with *ex situ* HOPE and excluded from further analyses.
[8]6-month graft loss.

Table 6. Studies evaluating associations between parameters measured during *ex situ* hypothermic oxygenated machine perfusion and post-transplant outcomes.

Author	Study type	Level	Setting	Period	"N" evaluated	(D)HOPE parameters	Parameters used to guide decision to transplant?	Associations between (D)HOPE parameters and post-transplant surrogate markers and outcomes
Eden[141]	SCC	2+	Switzerland	2012-2022	158 DCD	Perfusate FMN and NADH	Y in 48/158 cases	Perfusate FMN associated with graft loss due to PNF, ITBL, and other major complications.
Eden[142]	MCC	2+	International[†]	2019-2022	158 DBD 315 DCD	Perfusate FMN, NADH, purine derivatives, and inflammatory markers	Y in a minority of cases	Perfusate FMN associated with graft loss due to PNF or ITBL, post-transplant AKI, and development of ITBL in general.
Patrono[139]	SCC	2+	Italy	2018-2020	50 DBD	Perfusate ALT, AST, glucose, lactate, LDH, pH	N	Perfusate ALT, AST, LDH, pH associated with transaminase release; LDH associated with L-Graft; all except lactate associated with EAD.
Patrono[137]	SCC	2-	Italy	2019-2020	9 DBD 1 DCD	MD and perfusate FMN, glucose, glutamate, lactate, pyruvate	N	MD glucose and lactate associated with EAD, L-Graft, cumulative complications through 6 months; perfusate FMN associated with L-Graft, cumulative complications through 6 months.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBD, donation after brain death; DCD, donation after circulatory determination of death; EAD, early allograft dysfunction; FMN, flavin mononucleotide; HOPE, hypothermic oxygenated perfusion; LDH, lactate dehydrogenase; MD, microdialysate; NADH, nicotinamide adenine dinucleotide; SCC, single-centre cohort.
[†]10 centres in Italy (n = 3); the Netherlands (n = 2); and Austria, Brazil, Chile, Germany, and Switzerland (n = 1 each).

reports on fluorometric assessment of mitochondrial compounds FMN and nicotinamide adenine dinucleotide (NADH) released during HOPE.[130,137–140] In the most recent update on this centre's experience, 158 cDCD livers had been transplanted following end-ischaemic HOPE, the last 48 of which were transplanted after 30-min FMN and NADH levels were determined to be below pre-defined cut-off values for acceptability.[141] Outcomes for the entire cohort included 4.4% PNF, 6.9% ITBL, and 89% 1-year death-censored graft survival. While outcomes of the subset of livers undergoing prospective assessment were not reported, the authors described a significant increase in liver non-utilisation, from 5% to 20%, following implementation of the HOPE assessment protocol. Some livers that were not utilised following HOPE underwent additional *ex situ* normothermic machine perfusion (NMP) to confirm significant hepato- and cholangiocellular injury among the grafts.

The Zurich experience with FMN and NADH measurement during HOPE was recently expanded to include perfusate samples recovered during HOPE or DHOPE at 10 liver transplant centres in seven Western European and South American countries. Samples taken 60 minutes after the start of (D)HOPE underwent fluorometric spectroscopy to detect FMN and NADH, and the former were retrospectively correlated with cases developing PNF, ITBL, and/or AKI.[142] While the results are promising, there is an ongoing need for prospective, multicentre trials evaluating the ability of these parameters, measured during different *ex situ* HMP, to accurately assess livers for transplant. Initial studies may involve prospectively evaluating parameters in all liver grafts subjected to *ex situ* HMP, assessing not only their correlation with relevant post-transplant outcomes but also user-friendliness, availability, and cost. Subsequently, if and when such parameters are used to guide clinical decisions about liver acceptance *vs.* non-utilisation, initially non-utilised livers may be subjected to *ex situ* NMP assessment as a second perfusion modality to reaffirm the presumed absence of viability.

Q7: Can *ex situ* normothermic machine perfusion be used to assess deceased donor livers?

Recommendations

- *Ex situ* NMP can be used for the assessment of DBD livers that would not be utilised for transplantation otherwise **(LoE 2- (range 3 to 2+), strong recommendation).**
- *Ex situ* NMP can be considered to evaluate DCD livers that would not be utilised for transplantation otherwise **(LoE 2- (range 2- to 2+), conditional recommendation).**
- Prospective, multicentre trials should be considered to validate NMP parameters capable of predicting clinically relevant biliary complications among high-risk grafts, in particular those arising through DCD **(LoE 2- (range 2- to 2+), research recommendation, conditional recommendation restricted to clinical trials).**

Q13: What parameters measured during *ex situ* normothermic machine perfusion can be used to assess deceased donor livers?

Recommendations

- Perfusion parameters (vascular flows, resistive indices), perfusate analytes (pH, lactate, transaminases, glucose), and bile analytes (pH, glucose, bicarbonate) can be used to assess deceased donor livers **(LoE 2- (range 3 to 2+), conditional recommendation).**
- NMP parameter thresholds are not well established, owing to variability among available clinical protocols and studies, and should be applied with caution **(LoE 2- (range 3 to 2+), research recommendation, conditional recommendation restricted to clinical trials).**
- Measuring perfusate lactate levels during the first 2-6 hours of NMP can be used for liver assessment and the prediction of post-transplant outcomes. The timing of the assessment of other NMP parameters is not well established, owing to variability among available clinical protocols and studies **(LoE 2- (range 3 to 2+), research recommendation, conditional recommendation restricted to clinical trials).**

Expert panel comment: *Ex situ* NMP simulates near-physiological perfusion conditions for the liver by providing a solution including an oxygen carrier (typically human packed red blood cells) to the portal vein and hepatic artery at physiological flow rates and temperatures of 35-37 °C. At this temperature range, the liver is fully metabolically active, and a range of substrates are needed to support metabolic activity.[143,144] NMP offers a unique opportunity to assess different liver functions, including lactate clearance, bile production, coagulation factor synthesis, urea production, and other measures of metabolism.[145–148]

To date, four RCTs have been published comparing a period of NMP with continuous cold storage during the *ex situ* preservation phase, either upfront at the donor hospital or after arrival to the recipient hospital. Most have demonstrated that *ex situ* NMP is safe and reduces recipient IRI (decreased post-reperfusion hepatic transaminase release and/or EAD and post-reperfusion syndrome) among the recipients of both DBD and DCD livers, though none has conclusively demonstrated that NMP improves the more clinically relevant outcomes, including overall biliary complications, ITBL, and graft and patient survival.[13,16,149,150] One RCT on "ischaemia-free" liver transplantation, which is particularly complex and involves continuous NMP from organ recovery in the donor to transplantation in the recipient, described fewer biliary and overall complications compared to conventional cold storage among DBD liver recipients.[18]

In a recent retrospective, multicentre study, perfusate lactate levels measured during the first 6 hours after the start of NMP were subsequently associated with early allograft function after transplantation.[151] Other retrospective studies have similarly correlated parameters measured during *ex situ* NMP with surrogate markers and/or post-transplant outcomes.[152–154] Moreover, some groups have prospectively used NMP

Table 7. Studies prospectively evaluating livers for transplantation using *ex situ* NMP.

Author	Study type	Level	Setting	Period	Reason for assessment	"N" "N" eval. Total (DCD)	"N" LTx Total (DCD)	% LTx	NMP liver assessment parameters[1]							Early graft loss[2]	ITBL overall (DCD)	1-y graft survival
									Lactate	pH	Bile prod.	Gluc. met.	Vasc. flows	Macro. aspect	Trans.	Bile biochem.			
Mergental[157]	SCC	2+	UK	2016-2018	Non-utilisation, logistics	31 (14)	22 (10)	71%	+	+	+	+	+	+	-	-	0	18% (30%)	86%
Meszaros[159]	SCC	2-	Austria	2019-2020	Marginal liver, complex recipient and/or logistics	50 (13)	35 (6)	70%	+	+	+	-	+	-	+	-	14%/0	NR	74%
Patrono[160]	MCC	2-	Italy	2019-2022	Moderate/severe macrosteatosis	14 (1)	10 (1)	71%	+	+	+	+	+	+	-	-	20%/20%	0	80%
Quintini[158]	SCC	2-	USA	2020-2021	Non-utilisation, logistics	21 (13)	15 (11)	71%	+	-	+	-	+	+	-	-	0	7% (9%)	NA
Reiling[161]	SCC	2-	Australia	2018-2019	Non-utilisation	10 (5)	10 (5)	100%	+	+	+	+	+	+	-	-	0	0	100%
Watson[155]	SCC	2+	UK	2017-2022	Marginal liver, complex recipient and/or logistics	203 (123)	154 (84)	76%	+	+	+DCD/-DBD	+	+	+	+	+	5%/3%	11% (13%)	91%

DBD, donation after brain death; DCD, donation after circulatory determination of death; ITBL, ischaemic-type biliary lesions; MCC, multicentre cohort; NA, not available; NMP, normothermic machine perfusion; NR, not reported; SCC, single-centre cohort.
[1]NMP liver assessment parameters: "Lactate" refers to perfusate lactate; "pH" to perfusate pH; "Bile prod." to quantitative bile production; "Gluc. met." to glucose metabolism; "Vasc. flow." to macrovascular flows through the portal vein and/or hepatic artery; "Trans." to perfusate hepatic transaminase levels ± LDH; and "Bile biochem." to bile biochemical parameters, including pH and glucose ± bicarbonate.
[2]Early graft loss captures both graft loss and patient death during the first 90 days, followed by death-censored early graft loss rates (when applicable).

parameters to guide the decision to accept a particular liver graft for transplantation. Table 7 reflects protocols that have been used in different settings and the largest or most recent publications describing results achieved to date. Notably, all studies lack the ultimate control (*i.e.* transplantation of livers deemed unsuitable to confirm the development of major adverse outcomes), which would be unethical. Therefore, true positive and negative predictive values cannot be established.

Overall, results are relatively consistent, indicating that assessment during *ex situ* NMP can safely facilitate judgment to proceed with transplantation of "high-risk" livers, while largely avoiding transplantation of grafts developing early graft-specific failure during the first 90 days. However, the capacity of *ex situ* NMP alone to predict the development of clinically relevant biliary complications, including ITBL, is less promising. In the experience of the Cambridge Group, a high-volume liver perfusion and transplant centre in the UK, graft assessment has included serial evaluation of numerous bile parameters (sodium, potassium, glucose, lactate, chloride, bicarbonate, and pH) throughout *ex situ* NMP. In spite of this extensive evaluation of bile biochemistry, cases of clinically relevant post-transplant ITBL have not been avoided entirely.[155,156]

To date, studies prospectively evaluating livers for transplantation using *ex situ* NMP describe variable transplantation rates among evaluated livers, ranging from 63 to 100%. However, these studies have not universally included livers of particularly marginal quality. Rather, recipient factors and/or transplant logistics, including anticipated prolonged cold ischaemia, have factored into decisions to perform *ex situ* NMP preservation with additional liver assessment.[157,158] Given the greater complexities and costs associated with *ex situ* NMP, not to mention the confusion that inclusion of such livers may cause in the interpretation of results from prospective clinical trials, future studies using *ex situ* NMP with the explicit purpose of assessing livers should only include high-risk grafts. Cases with complex recipients and/or logistical concerns but no inherent concerns about the graft itself do not necessarily need *ex situ* NMP preservation but may still benefit from *ex situ* (D)HOPE.[134,135]

Q8: Can combining perfusion modalities (*i.e.*, *in situ* and *ex situ* perfusion in DCD, *ex situ* HMP and NMP in general) improve liver assessment relative to individual perfusion modalities performed in isolation?
Q14: Is there a set of parameters measured during combined perfusion that improves liver assessment relative to parameters measured with individual perfusion modalities performed in isolation?

Recommendation

- Approaches consecutively combining *in situ* and *ex situ* or sequential *ex situ* liver perfusion modalities in the same graft are feasible and safe. The utility of such approaches for the combined, sequential evaluation of DBD and DCD livers should be evaluated in the context of prospective clinical trials **(LoE 2- (range 3 to 2+), research recommendation, conditional recommendation restricted to clinical trials).**

Expert panel comment: Different liver perfusion strategies are not exclusive and can be used in the same grafts prior to transplantation. In several experiences, *in situ* NRP and *ex situ* HOPE, DHOPE, or NMP have been applied consecutively among DCD livers, primarily in Italian centres, some of which are reflected in Table 5.[7,109,116,162,163]

Though most clinical experiences with *ex situ* NMP liver assessment have included grafts recovered and preserved with conventional cold storage prior to NMP, a few have applied a protocol of *ex situ* DHOPE followed by controlled, oxygenated rewarming (COR) and finally NMP assessment (Table 8).[146,164,165] In pre-clinical studies, the combination of *ex situ* hypothermic reoxygenation followed by NMP has been shown to mitigate inflammation and oxidative stress and improve cell viability and metabolic recovery of high-risk grafts *vs.* direct NMP.[166–169] Using sequential DHOPE+COR+NMP and evaluating biliary bicarbonate, glucose, and pH values relative to their perfusate values, the Groningen Group has reported good biliary outcomes and can purportedly avoid development of post-transplant ITBL among DCD livers.[164,170] In a follow-up report including 105 DHOPE-COR-NMP perfused livers (98% cDCD), 69 were ultimately considered viable (66%), with 3-year patient and death-censored graft survival rates of 97% and 91%, respectively.[171] While promising, the experience remains solitary, and results need to be reproduced in other settings to recommend this practice as standard.

As yet, there are no publications describing liver assessment using a true stepwise approach, in which parameters are evaluated during each consecutive perfusion modality applied in the same graft. Nonetheless, liver assessment using a combined, sequential evaluation strategy is an option that may be considered to progressively screen an organ (Fig. 1). A stepwise approach may not only limit liver IRI among high-risk grafts but also prevent unnecessary allograft non-utilisation.

Q9: What perfusion strategy is recommended for the assessment of DBD livers?

Recommendations

- *Ex situ* NMP is recommended to assess DBD livers that would not be transplanted otherwise **(LoE 2- (range 3 to 2+), strong recommendation).**
- Assessment of DBD livers according to a sequential *ex situ* perfusion strategy combining an initial period of (D)HOPE followed by NMP can be considered, ideally in the context of prospective clinical trials **(LoE 2- (range 3 to 2+), research recommendation, conditional recommendation restricted to clinical trials).**

Expert panel comment: *Ex situ* NMP is currently the only strategy that has been prospectively validated for the assessment of DBD liver allograft function prior to transplantation (see Q7: Expert panel comment). There is also evidence to suggest that markers measured during *ex situ* (D)HOPE may be useful in assessing livers. Recently, an

Table 8. Studies prospectively evaluating livers for transplantation using combined *ex situ* normothermic machine perfusion following a brief period of DHOPE+COR.

Author	Study type	Level	Setting	Period	Reason for assessment	"N" eval. Total (DCD)	"N" LTx Total (DCD)	% LTx	NMP liver assessment parameters[1]								Early graft loss[2]	ITBL overall (DCD)	1-year graft survival
									Lactate	pH	Bile prod.	Gluc. met.	Vasc. flows	Macro. aspect	Trans.	Bile biochem.			
Clavien[146]	CR	3	Switzerland	2021	Non-utilisation	1 (0)	1 (0)	100%	+	+	+	+	+	-	+	+	0	0	100%
Liu[165]	SCC	2-	USA	2021	High-risk liver, logistics	17 (12)	13 (9)	76%	+	-	+	-	+	+	-	-	0	15% (22%)	100%
van Leeuwen[164]	SCC	2+	Netherlands	2017-2021	Non-utilization	54 (53)	34 (33)	63%	+	+	+	-	-	-	-	+	3%/3%	3% (3%)	94%

COR, controlled, oxygenated rewarming; CR, case report; DCD, donation after circulatory determination of death; DHOPE, dual hypothermic oxygenated perfusion; ITBL, ischaemic-type biliary lesions, NMP, normothermic machine perfusion; SCC, single-centre cohort.
[1]NMP liver assessment parameters: "Lactate" refers to perfusate lactate; "pH" to perfusate pH; "Bile prod." to quantitative bile production; "Gluc. met." to glucose metabolism; "Vasc. flow." to macrovascular flows through the portal vein and/or hepatic artery; "Trans." to perfusate hepatic transaminase levels ± LDH; and "Bile biochem." to bile biochemical parameters, including pH and glucose ± bicarbonate.
[2]Early graft loss captures both graft loss and patient death during the first 90 days, followed by death-censored early graft loss rates (when applicable).

international, multicentre collaborative study was published retrospectively correlating FMN levels measured after an hour of (D)HOPE with adverse post-transplant events (PNF, AKI, ITBL, and graft loss),[142] though prospective clinical trials validating the predictive value of FMN in clinical decision making are still needed (see Q6: Expert panel comment). As well, while clinical experience among DBD livers remains limited (see Table S13), consideration may be given to combining an initial, brief (*i.e.*, 1-hour) period of *ex situ* (D)HOPE followed by COR and finally NMP assessment, which may not only help improve inflammatory injury, oxidative stress, and metabolic recovery among high-risk DBD grafts[166–169] but also offer an important research opportunity to assess the utility of using (D)HOPE parameters in predicting liver function (Fig. 1).

Q10: What perfusion strategy is recommended for the assessment of DCD livers?

Recommendations

- *In situ* NRP is recommended for the reconditioning and assessment of DCD livers in settings where it is both available and legally regulated **(LoE 2+ (range 2- to 2++), strong recommendation).**
- DCD livers recovered without *in situ* NRP or ones not meeting NRP assessment criteria may undergo *ex situ* NMP, with or without a brief prior period of DHOPE, to further assess them for ultimate transplantation *vs.* non-utilisation **(LoE 2- (range 2- to 2+), conditional recommendation).**

Expert panel comment: Based on the complexity of identifying an appropriate study endpoint for a method that affects multiple organs and has to be applied before any organ has been accepted for transplantation, *in situ* NRP has not been evaluated in the context of an RCT. Nonetheless, in thousands of cases performed over the past two decades, post-mortem NRP has been applied to recondition DCD livers and direct the ultimate decision to transplant them (see Q5: Expert panel comment). *In situ* NRP is unavailable and/or not legally regulated in some settings. Among DCD cases performed without NRP or ones in which liver quality remains questionable even after NRP, 1 hour of (D)HOPE followed by COR and NMP may offer better results than NMP only, in particular with respect to the assessment of irreversible biliary tract injury (see Q8: Expert panel comment). In this regard, an experience published by Gaurav and colleagues compared cDCD liver transplants performed with conventional cold storage (n = 97), *in situ* NRP (n = 69), or *ex situ* NMP only (n = 67). In spite of significantly longer donor warm ischaemia and more "futile" cDCD livers in the NRP group, livers recovered with NRP developed fewer biliary complications, including ITBL, and were associated with better survival rates than both livers recovered with conventional cold storage and those transplanted after *ex situ* NMP only.[8]

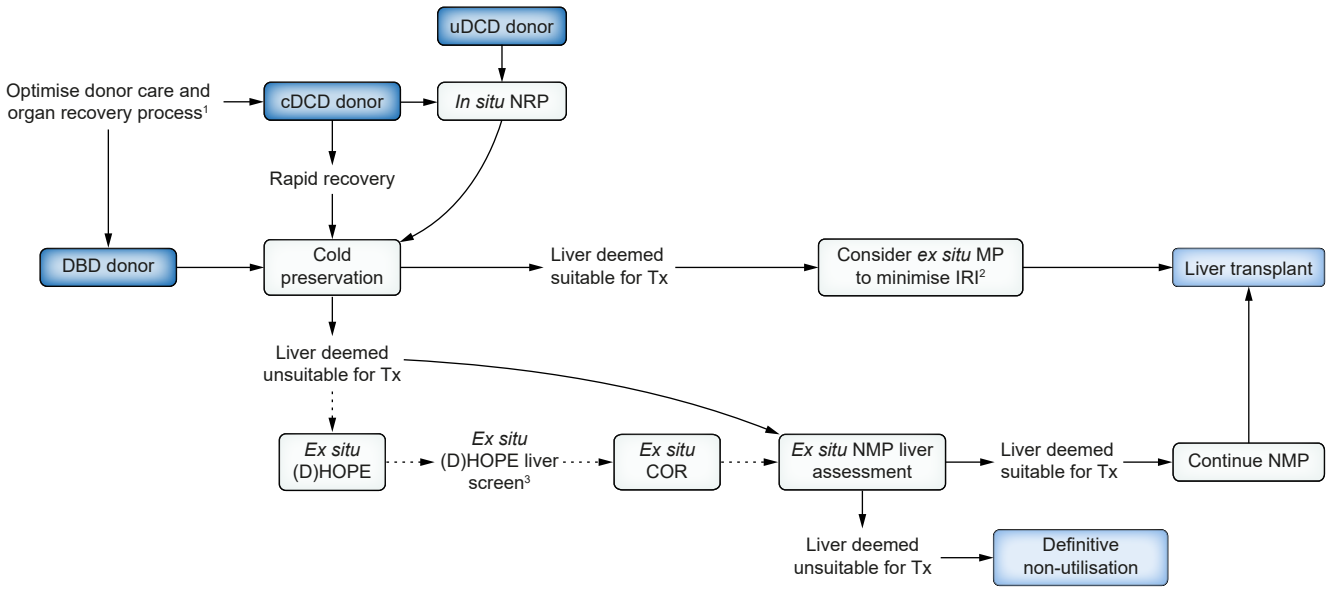

Fig. 1. Stepwise approach to management and assessment of livers arising from deceased donors. [1]Maneuvers in DBD and ventilator-dependent cDCD donors may include correction of hypovolemia, support of tissue perfusion, treatment of diabetes insipidus, neurohormonal support, and lung protective ventilation. See European Directorate for the Quality of Medicines and Healthcare, Ed. Management of the potential donor after brain death. In: Guide to the quality and safety of organs for transplantation. Council of Europe 2018;95-107. [2]*Ex situ* MP, including HMP (HOPE, DHOPE, $HMPO_2$) and NMP, may be used to minimise ischaemia-reperfusion injury, in particular in cases with donor, graft, and/or recipient risk factors. Risk factors include all livers with macrosteatosis >30%; uDCD livers; and cDCD livers with donor total warm ischaemia time >30 minutes, donor hepatectomy time >40 minutes, or cold ischaemia time >6 hours or transplanted into recipients on mechanical ventilation. For cDCD livers, while donor or recipient age >60 years, donor BMI >25, or recipient MELD >25 alone would not necessarily be considered high-risk, the combination of these with other risk factors may prompt application of *ex situ* perfusion preservation to minimise ischaemia-reperfusion injury in these grafts and their recipients. [3]Liver screen performed during an initial post-ischaemic period of (D)HOPE for research purposes but not necessarily used to guide clinical decision-making. cDCD, controlled donation after circulatory determination of death; COR, controlled, oxygenated rewarming; DBD, donation after brain death; DCD, donation after circulatory determination of death; (D)HOPE, hypothermic or dual hypothermic oxygenation perfusion; IRI, ischaemia-reperfusion injury; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; uDCD, uncontrolled donation after circulatory determination of death.

Q15: What set of parameters are recommended for the assessment of hepatocytes during perfusion?

Recommendation

- A combination of parameters for parenchymal cell assessment should be applied cautiously in clinical practice, owing to variability of parameter combinations and thresholds among available clinical protocols and studies **(LoE 2 (range 3 to 2++), research recommendation, conditional recommendation restricted to clinical trials).**

Q16: What set of parameters are recommended for the assessment of the biliary tree during perfusion?

Recommendation

- A combination of parameters for biliary assessment should be applied cautiously in clinical practice, owing to variability of parameter combinations and thresholds among available clinical protocols and studies. The best-described and studied parameters are biliary pH, bicarbonate, and glucose levels measured in relation to perfusate values **(LoE 2 (range 3 to 2++), research recommendation, conditional recommendation restricted to clinical trials).**

Expert panel comment: Though the number of studies on liver MP is growing, defining an optimal set of assessment parameters for the different perfusion techniques remains challenging. This is due to variability in donor, graft, and recipient risk profiles; inconsistent outcome definitions; and reporting differences. Currently, studies cannot accurately define sensitivity, specificity, and positive and negative predictive values for liver assessment parameters, and expectations for a reliable assessment strategy are not well-established. The ideal parameter or parameter combination needs to account for differences in study design and remain robust across diverse perfusion techniques and transplant settings. For liver perfusion, in particular NMP, more data are available regarding the perfusion duration necessary to assess the liver's potential for recovery. Currently used thresholds, such as perfusate lactate levels, may require adjustment as time points and perfusion durations change. Moving forward, interpretation of liver assessment results will also need to take into consideration intraoperative events as well as recipient risk profiles.

Conclusions

This consensus effort combines the expertise of numerous qualified professionals with evidence provided by >15 years of published literature to provide a series of practical considerations and recommendations regarding the evaluation of deceased donor livers for transplantation. While the target audience is the global liver transplant community, guidance provided is largely based on Western European and North

American experiences. Broader application of this guidance will require adjustments that reflect the resources, infrastructure, legislation, and overall needs that are present in different settings. As well, this guidance is provided in a rapidly evolving clinical landscape. While it provides a common foundation, relevant advances in the field of liver machine perfusion in the coming years will undoubtedly prompt refinement of the strategies presented herein.

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Abbreviations

AKI, acute kidney injury; ALT, alanine aminotransferase; A-NRP, abdominal NRP; cDCD, controlled DCD; CIT, cold ischaemia time; COR, controlled, oxygenated rewarming; DCD, donation after circulatory determination of death; DDLT, deceased donor liver transplantation; DHOPE, dual hypothermic oxygenated perfusion; DHT, donor hepatectomy time; EAD, early allograft dysfunction; EASL, European Association for the Study of the Liver; ELITA, European Liver and Intestine Transplant Association; ESOT, European Society for Organ Transplantation; FMN, flavin mononucleotide; HMP, hypothermic machine perfusion; HOPE, hypothermic oxygenated perfusion; IRI, ischaemia-reperfusion injury; ITBL, ischaemic type biliary lesions; MELD, model for end-stage liver disease; MP, machine perfusion; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; PNF, primary non-function; RCT, randomised-clinical trials; SC, steering committee; SRTR, Scientific Registry of Transplant Recipients; TA-NRP, thoracoabdominal NRP; uDCD, uncontrolled DCD; WG, working group; WLST, withdrawal of life support therapy.

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Conflict of interest

AJH and CF have received research funding from Instituto de Salud Carlos III. CW is a consultant for OrganOx Ltd. The remainder of the authors have no conflicts of interest to declare.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

AJH, HH, FM, AS, SS, WP, RJP, and CF contributed to study concept and design. AJH and CF contributed to acquisition of data. All authors contributed to analysis and interpretation of data. AJH, HH, and FM contributed to drafting of the manuscript, while the remainder of authors contributed to critical revision of the manuscript for important intellectual content. All authors give their final approval of the version to be published and agree to be accountable for all aspects of the work.

Data availability statement

All the data presented herein are previously published and, thereby, publicly available.

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Supplementary data

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Author names in bold designate shared co-first authorship

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