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Review

Advances in Machine Perfusion for Liver Transplantation: Mechanisms, Clinical Evidence, and Future Directions

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Abstract

Liver transplantation is the definitive treatment for end-stage liver disease, acute liver failure, and selected hepatic malignancies, but its success is limited by a persistent shortage of suitable donor organs. This has driven increased use of extended criteria donors (ECDs), including steatotic and donation after circulatory death (DCD) grafts, which are more susceptible to preservation injury and often inadequately supported by traditional static cold storage (SCS). Machine perfusion (MP) has emerged as a transformative strategy that enables organ preservation, viability assessment, therapeutic intervention, and graft optimization. This narrative review searched PubMed, MEDLINE, and the Cochrane Library up to June 2026, including randomized controlled trials, cohort studies, meta-analyses, registry analyses, and translational studies in English, to evaluate MP modalities-hypothermic oxygenated perfusion

(HOPE), normothermic machine perfusion (NMP), normothermic regional perfusion (NRP), and sequential approaches-integrating mechanistic insights into ischemia-reperfusion injury (IRI) with clinical evidence and critically appraising the limitations and heterogeneity of the supporting data throughout. MP mitigates IRI through improved oxygenation, modulation of mitochondrial function, and reduction of oxidative stress. HOPE reduces biliary complications and graft dysfunction, particularly in DCD grafts, while NMP maintains physiological metabolism, allows real-time functional assessment, and lowers graft discard rates, improving utilization of marginal organs. NRP reverses warm ischemic injury *in situ* with outcomes comparable to brain-death donors, and sequential strategies further enhance graft recovery. Emerging biomarkers, including flavin mononucleotide and syndecan-1, improve viability assessment, while MP also enables therapeutic interventions such as graft defatting and extends preservation time. Overall, MP has transformed liver transplantation into a controlled, data-driven process that expands the donor pool, improves outcomes, and introduces objective viability assessment. However, study heterogeneity, variable viability criteria, and high implementation costs remain as significant challenges. Ongoing advances in multi-omics, regenerative therapies, and artificial intelligence are expected to further refine this approach, address those challenges and establish it as standard care.

Keywords
Liver transplantation; machine perfusion; hypothermic oxygenated perfusion (HOPE); normothermic machine perfusion (NMP); normothermic regional perfusion (NRP); ischemia-reperfusion injury; extended criteria donors (ECD); donation after circulatory death (DCD); viability assessment; organ preservation; graft resuscitation; precision organ preservation

1. Introduction

The field of liver transplantation (LT) stands at a critical juncture. Although LT remains the only definitive therapy for end-stage liver disease, acute liver failure, and selected hepatic malignancies, its overall success continues to be constrained by the persistent shortage of suitable donor organs. This limitation has driven a progressive expansion of donor acceptance criteria, resulting in the increasing utilization of extended criteria donors (ECDs). These grafts-derived from older individuals, steatotic livers, or donors after circulatory death (DCD)-are intrinsically more susceptible to preservation-related injury.

Static cold storage (SCS), historically regarded as the gold standard due to its simplicity and cost-effectiveness, is increasingly recognized as insufficient for preserving these vulnerable grafts. Consequently, machine perfusion (MP) has evolved beyond a mere preservation technique into a dynamic and multifaceted platform that enables viability assessment, targeted therapeutic intervention, and graft reconditioning [1-3].

For nearly five decades, potential ECD liver grafts with SCS were unused due to lack of pre-transplant viability assessment [1]. Upon reperfusion at physiological temperatures during implantation, these metabolically compromised grafts experience a profound “double-hit” phenomenon due to ischemia-reperfusion injury (IRI). While this injury is often reversible in

standard criteria donor (SCD) livers, ECD and DCD grafts are at substantial risk of early allograft dysfunction (EAD), ischemic cholangiopathy (IC), and primary non-function (PNF) [4].

Machine perfusion (MP) has emerged as a dynamic alternative that not only preserves organs at various temperatures more effectively by reducing IRI and improving mitochondrial function, but also enables objective viability assessment prior to implantation [5].

This review provides a structured and critical analysis of the evolving landscape of liver machine perfusion, with particular emphasis mechanistic rationale, key evidence and limitations of different perfusion modalities, emerging viability assessment strategies, economic considerations, and future directions.

2. Methods

This narrative review was conducted through a systematic search of the PubMed, MEDLINE, EMBASE, Google Scholar and Cochrane Library databases for publications up to June 2026. Search terms included combinations of the following: “machine perfusion”, “liver transplantation”, “hypothermic oxygenated machine perfusion”, “dual hypothermic oxygenated perfusion”, “normothermic machine perfusion”, “normothermic regional perfusion”, “ischemia-reperfusion injury”, “viability assessment”, “extended criteria donor”, “donation after circulatory death”, and “ischemia-free liver transplantation”. Reference lists of retrieved articles were hand-searched to identify additional relevant publications. Inclusion criteria encompassed randomized controlled trials, prospective and retrospective cohort studies, meta-analyses, systematic reviews, registry analyses, and translational studies pertaining to machine perfusion in liver transplantation. With a focus on current evidence, methodological quality, and clinical significance, studies were included based on their applicability to the goals of this review. Case reports were considered only where they represented novel information. Studies published in languages other than English were excluded. As this is a narrative rather than systematic review, formal quality appraisal tools like predetermined systematic review protocol, rigorous research quality assessment, or PRISMA-guided screening process were not applied; however, the level of evidence supporting each modality is explicitly characterized throughout, and the limitations of individual trials-including study heterogeneity, potential selection bias, and absence of prospective comparative data-are critically discussed within each section.

3. The Pathophysiology of Ischemia-Reperfusion Injury

A thorough understanding of ischemia-reperfusion injury (IRI) is essential to appreciate the therapeutic advantages of machine perfusion. IRI represents a complex, biphasic process initiated by the interruption of blood flow and paradoxically amplified upon reperfusion.

3.1 The Ischemic Phase: Metabolic Collapse

During organ procurement and SCS, cessation of oxygen delivery arrests mitochondrial oxidative phosphorylation. Hepatocytes shift to anaerobic glycolysis, rapidly depleting intracellular glycogen and adenosine triphosphate (ATP). As ATP declines, the Na^+/K^+-ATPase membrane pump fails, leading to intracellular sodium accumulation, cellular edema, and cytosolic calcium overload [6]. A key biochemical event during the ischemic phase is the supraphysiological accumulation of

succinate within the mitochondria, a metabolic intermediate that remains relatively inert under cold conditions but constitutes a critical liability upon reperfusion [7].

3.2 The Reperfusion Phase: Oxidative Burst

Reperfusion at normothermia triggers rapid oxidation of accumulated succinate via mitochondrial complex II (succinate dehydrogenase). Due to incomplete recovery of electron transport chain components, reverse electron transfer to mitochondrial complex 1 happens, which generates a burst of reactive oxygen species (ROS), predominantly superoxide, at the flavin mononucleotide (FMN) site [5]. This oxidative cascade produces three principal consequences: (i) mitochondrial dysfunction through opening of the permeability transition pore (MPTP), leading to uncoupling of oxidative phosphorylation and necrosis [8]; (ii) sterile inflammation via release of damage-associated molecular patterns (DAMPs-HMGB1 and DNA), Kupffer cell activation, and pro-inflammatory cytokine production (TNF-α, IL-1β, IL-6) [9, 10]; and (iii) microvascular dysfunction through endothelial swelling and "no-reflow," particularly pronounced in DCD grafts [2].

3.3 Vulnerability of the Biliary Tree

The biliary epithelium is uniquely susceptible to IRI due to its exclusive dependence on the peribiliary vascular plexus supplied by the hepatic artery. In DCD grafts, the combined effects of warm ischemia and microvascular thrombosis frequently result in biliary epithelial necrosis. Clinically, this manifests as non-anastomotic biliary strictures (NAS) or ischemic cholangiopathy-both of which are major contributors to graft failure and the need for re-transplantation [9, 11].

4. Machine Perfusion Modalities: Mechanisms and Evidence

The primary objective of machine perfusion is to fundamentally alter the physiological state of the liver outside the human body, thereby mitigating the detrimental effects of IRI. Different perfusion modalities achieve this goal through distinct physiological mechanisms, largely determined by the temperature of the circulating perfusate (Table 1).

Table 1 Overview of Liver Machine Perfusion Modalities: Techniques, Evidence, Outcomes and Limitations.

Modality	Temperature & Strategy	Key Landmark Trials	Primary Outcomes	Level of Evidence	Key Limitations
HOPE/ D-HOPE	4-10°C; portal vein (HOPE) or dual portal + hepatic artery (D-HOPE); oxygenated acellular solution	Zurich RCT (Schlegel 2023); D-HOPE DCD Trial (van Rijn 2021, NEJM)	↓ EAD (20% vs 37%); ↓ ischaemic cholangiopathy (6% vs 18%); ↓ severe graft failure (0% vs 7%); ↓ biliary complications (RR 0.74)	Level 1 (Multiple large RCTs and meta-analyses)	Heterogeneous donor profiles across trials; primary endpoint missed in Zurich RCT; limited long-term follow-up data beyond 1 year
NMP	37°C; continuous RBC-based or HBOC oxygenated perfusate; continuous or end-ischaemic	COPE Trial (Nasralla 2018, Nature); OCS Liver PROTECT Trial (Markmann 2022); VITTAL Trial (Mergental 2020)	↓ AST peak (~50%); ↓ EAD (18% vs 31%); ↓ discard rates (~50%); ↓ biliary complications (2.6% vs 9.9%); ↑ DCD utilization (51% vs 26%)	Level 1 (Multiple large RCTs)	High cost and logistical complexity; variability in perfusion protocols across centres; single-arm design of VITTAL limits generalizability; different viability criteria across institutions
NRP	37°C; *in-situ* VA-ECMO abdominal perfusion before procurement; ~2-hour resuscitation period	UK and US retrospective registry analyses; French and Spanish cohort studies	DCD outcomes approaching DBD; ↓ non-anastomotic strictures; ↓ post-reperfusion syndrome	Level 2 (Large retrospective cohorts)	No prospective RCT data; ethical and legal concerns in some jurisdictions regarding brain-death exclusion; observer bias in registry data; generalizability limited by centre-specific protocols

Sequential (DHOPE-COR-NMP)	10°C → 37°C; hypothermic resuscitation followed by controlled oxygenated rewarming then full NMP	Groningen preclinical and prospective cohort studies (de Vries 2019)	Combines mitochondrial resuscitation (HOPE) with functional viability assessment (NMP); optimal for high-risk ECD-DCD grafts	Level 2-3 (Prospective cohorts)	No RCT evidence; resource-intensive and time-consuming; limited to specialist centres; optimal rewarming rate undefined
IFLT	37°C; continuous *in-situ* → *ex-situ* → *in-vivo* perfusion without any ischaemic phase	He Xiaoshun (2018, proof of concept); Meng et al. (2026, 7-yr cohort); Jia et al. (2025, 5-yr follow-up)	↑ 1-yr patient survival (95.5% vs 86.1%); ↓ EAD; ↓ HCC recurrence; modulation of CXCL10/CXCR3 immune axis	Level 2 (RCTs and prospective cohorts, single centre)	Single-centre experience from China; technically demanding; significant infrastructure required; awaits international multicentre validation

4.1 Hypothermic Oxygenated Perfusion (HOPE): Mechanisms and Clinical Trials

Hypothermic oxygenated perfusion (HOPE) is most commonly applied in the end-ischemic phase at the recipient center. It involves perfusion of the liver with a cold (4-10°C), oxygenated, acellular solution via the portal vein alone (HOPE) or in combination with the hepatic artery (dual-HOPE, D-HOPE) [2, 12].

HOPE promotes controlled mitochondrial recovery under hypothermic, oxygenated conditions by gradually reactivating the electron transport chain, allowing slow metabolism of accumulated succinate and reducing the burst of reactive oxygen species during reperfusion. Controlled oxygen delivery restores intracellular ATP stores before implantation, while continuous perfusion clears damage-associated molecular patterns (DAMPs), cytokines, and metabolic waste, thereby reducing graft immunogenicity and ischemia-reperfusion injury [5, 13].

The Zurich multicenter randomized controlled trial conducted by Schlegel et al. evaluated the impact of HOPE in extended-criteria donation-after-brain-death (DBD) grafts. A total of 170 transplants were randomized to either SCS or HOPE. Although the primary endpoint-Clavien-Dindo grade ≥ III complications within one year-did not differ significantly between groups (54.1% vs. 51.8%; p = 0.76), post hoc analyses revealed a significant reduction in severe liver-related complications in the HOPE group (risk ratio 0.26; p = 0.027). Notably, graft failure due to liver-related causes occurred in 0% of HOPE-treated grafts compared with 7% in the SCS group (p = 0.004) [12]. Post hoc analyses carry an inherent risk of type I error and should be interpreted cautiously.

The benefits of HOPE are most pronounced in DCD grafts. In the D-HOPE DCD trial, a multicenter randomized study published in the New England Journal of Medicine, 156 DCD grafts were randomized to SCS or D-HOPE [2]. The study met its primary endpoint, demonstrating a significant reduction in non-anastomotic biliary strictures (6% vs. 18%; hazard ratio 0.36; p = 0.03). Secondary outcomes included reductions in EAD and post-reperfusion syndrome, with improved graft function and hemodynamic stability. These findings have established D-HOPE as a standard preservation strategy for DCD livers in many European centers.

A 2023 meta-analysis of 11 studies (including 5 RCTs), which demonstrated that HOPE significantly reduced biliary complications (RR 0.74), NAS (RR 0.34), EAD (RR 0.54), and acute rejection (RR 0.54) compared with SCS [14, 15]. A Cochrane review similarly concluded that both HOPE and NMP outperform SCS, with stronger evidence supporting HOPE for improving graft survival and reducing ischemic cholangiopathy in DCD grafts [15].

There are some limitations with the above trials due to considerable difference in study population in donor age, warm ischemic time, center experience and lack of long-term follow up. Additionally, the lack of standardized oxygenation protocols (HOPE vs D-HOPE) introduces technical heterogeneity.

4.2 Normothermic Machine Perfusion (NMP): Physiology and Viability

NMP maintains the liver at 37°C using an oxygenated, nutrient-enriched perfusate-typically red-blood-cell based-to sustain physiological metabolism and allow viability assessment. It can be applied as a transport strategy (upfront NMP) or as an end-ischemic platform [16].

e Consortium for Organ Preservation in Europe (COPE) trial, the first large randomized controlled trial evaluating normothermic machine perfusion (NMP), demonstrated a 50% reduction in graft

injury and donor liver discard rates, while extending preservation time by 54%. These results indicate improved graft utilization of marginal grafts and surgical logistics enabling a shift toward semi-elective transplantation [1].

In the United States, the OCS Liver PROTECT trial evaluated a portable NMP system, showed significantly reduced EAD (18% vs 31%; p = 0.01) and biliary complications at 6 and 12 months (2.6% vs 9.9%), along with increased DCD utilization (51% vs 26%) [17, 18].

The VITTAL trial extended the application of NMP to livers deemed "untransplantable". Using strict viability criteria, 71% of these discarded grafts were successfully transplanted, achieving 100% 90-day patient survival, though this non-randomized single-arm design limits causal inference [19].

Evidence for NMP remains heterogeneous, with differences between major trials in perfusion systems, donor populations, transport strategies, and comparator arms. Lack of standardized viability criteria, high operational costs, and logistical complexity limit widespread adoption. Additionally, the optimal timing of NMP and its comparative benefits versus HOPE in specific donor subgroups remain uncertain and are being investigated in ongoing trials [15].

4.3 Normothermic Regional Perfusion (NRP)

NRP represents a distinct *in situ* preservation strategy specifically applied in donors after circulatory death (DCD), which involves the initiation of Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) to re-establish oxygenated blood flow within the donor's abdominal compartment while excluding cerebral circulation.

NRP resuscitates the liver from the deleterious effects of warm ischemia by restoring physiological perfusion conditions. This resuscitative phase is typically maintained for approximately two hours, during which metabolic recovery occurs and organ function can be assessed using systemic biochemical parameters. Following this period, the liver is flushed with cold preservation solution and retrieved using standard surgical techniques.

NRP has demonstrated remarkable efficacy in preserving the integrity of the peribiliary vascular plexus, thereby significantly reducing the incidence of ischemic cholangiopathy. Large retrospective registry analyses from both the United Kingdom and the United States have shown that outcomes following NRP in DCD donors-including graft survival and biliary complication rates-are comparable to those achieved with donation after brain death (DBD) grafts [15, 20]. Avoiding selection bias and large prospective RCTs would support the evidences of NRP.

4.4 Sequential Perfusion Strategies (DHOPE-COR-NMP)

Sequential perfusion protocols integrate complementary benefits of hypothermic and normothermic modalities. The DHOPE-COR-NMP sequence, developed for high-risk ECD-DCD grafts, begins with end-ischemic dual hypothermic oxygenated perfusion (DHOPE) for mitochondrial recovery with ATP repletion, followed by controlled oxygenated rewarming (COR) from 10°C to 37°C, and concludes with full NMP for viability assessment [21]. This approach leverages mitochondrial protection (HOPE phase), avoids abrupt temperature changes (COR phase) and functional assessment (NMP phase) sequentially. However, this approach is resource intensive and time consuming. There is no defined rewarming rate or COR duration.

4.5 Ischemia-Free Liver Transplantation (IFLT): The New Frontier

While both HOPE and NMP significantly mitigate ischemia-reperfusion injury, they do not completely eliminate ischemic periods during organ procurement and implantation. Ischemia-Free Liver Transplantation (IFLT), pioneered by He Xiaoshun and colleagues, represents a paradigm shift aimed at abolishing ischemia entirely [22].

In IFLT, the liver is cannulated and perfused *in situ* within the donor using normothermic machine perfusion. The organ remains continuously perfused throughout procurement, transport, and implantation, with vascular anastomoses performed while the graft remains connected to the perfusion system. This uninterrupted perfusion effectively eliminates both cold and warm ischemic phases.

Randomized studies showed, improved one-year patient survival (95.5% vs 86.1%), reduced EAD. Long term follow-up studies showed reduced recurrence of hepatocellular carcinoma. IRI promotes tumor recurrence through CXCL10/CXCR3 signaling pathway and IFLT exhibit downregulation of this pathways, providing the biological plausibility for the observed clinical advantages [23-25].

IFLT remains a single-center technique from China, requiring substantial infrastructure and surgical expertise. International multicenter validation is essential before broader adoption can be recommended. Nevertheless, long-term follow-up data from 5- to 7-year cohorts are emerging and support its potential as a transformative strategy for selected grafts [23, 24].

5. Viability Assessment: The Science of Prediction

One of the most clinically valuable aspects of machine perfusion is the ability to evaluate graft viability in real time before transplantation-transforming the decision to implant from a subjective clinical judgement to an objective, data-driven assessment. The parameters used for viability assessment differ according to the temperature and metabolic state of the graft (Table 2).

Table 2 Established Viability Assessment Criteria During Liver Machine Perfusion.

Protocol	Modality	Timeframe	Hepatocellular Criteria	Cholangiocellular Criteria	Limitations
Birmingham Criteria	NMP	Within 4 hours	Lactate ≤2.5 mmol/L AND ≥2 of: pH > 7.30; normal glucose metabolism; HA flow >150 mL/min; PV flow >500 mL/min; homogeneous perfusion	Macroscopic bile production (volume-based)	Does not formally incorporate biliary biochemistry; variable inter-centre application
Cambridge Criteria	NMP	Within 2 hours	Peak lactate fall ≥4.4 mmol/L/kg/h; pH > 7.20; ALT <6,000 IU/L; falling perfusate glucose <10 mmol/L	Biliary pH > 7.5; bile glucose ≤3 mmol/L or ≥10 mmol/L lower than perfusate glucose	Short assessment window may exclude slow-recovering grafts; ALT threshold not externally validated
Groningen Criteria	NMP	Within 2.5 hours	Lactate clearance ≤1.7 mmol/L; perfusate pH 7.35-7.45	Cumulative bile >10 mL; biliary pH > 7.45; Δ bicarbonate >5 mmol/L	Derived from single-centre experience; biliary criteria require standardised collection protocols
FMN Assessment	HOPE/ D-HOPE	~30 minutes	Real-time fluorescence measurement of mitochondrial complex I injury via perfusate FMN release; AUC 0.93 for EAD prediction	Low FMN → predicts biliary integrity; high FMN → associated with NAS and PNF	Requires specialist fluorescence spectroscopy equipment; optimal threshold requires multicentre prospective validation
Syndecan-1/ Glycocalyx	NMP/HOPE	1-6 hours	Perfusate syndecan-1 >4,796 ng/mL predicts severe endothelial injury and EAD	Reflects microvascular injury and peribiliary plexus disruption	Threshold derived from single prospective pilot study; not yet validated in multicentre RCT
Multi-Omics/ Transcriptomics	NMP	Intra-perfusion biopsy	CD274 (PD-L1), LEAP2, IFIT1 expression correlates with graft function; AUC 0.99 in preliminary data	Not separately assessed	Technically complex; not available in routine clinical practice; requires prospective clinical validation

5.1 Normothermic Assessment (NMP)

Under normothermic conditions, the liver is metabolically active, enabling direct measurement of functional performance. Established viability criteria, including those used in the VITTAL trial, incorporate multiple physiological and biochemical parameters. Lactate clearance is the most important marker, with perfusate lactate levels ≤2.5 mmol/L within 4 hours strongly predicting graft viability and failure to achieve this threshold associated with primary non-function. Bile chemistry provides additional information, as a biliary pH > 7.4 reflects active bicarbonate secretion and functional biliary epithelium. Hemodynamic stability, indicated by hepatic artery flow >150 mL/min and portal vein flow >500 mL/min, confirms preserved vascular integrity, while dynamic glucose metabolism, demonstrated by declining perfusate glucose levels after 2 hours or maintenance below 10 mmol/L, reflects ongoing metabolic activity and graft viability [19, 26, 27].

Cholangiocellular viability is critical for preventing late biliary complications. Functional cholangiocytes actively secrete bicarbonate and reabsorb glucose. Accordingly, viability is indicated by a biliary pH > 7.45, elevated bile bicarbonate concentrations (≥18 mmol/L), and bile glucose levels significantly lower than perfusate glucose (<3 mmol/L). These parameters have been incorporated into standardized viability protocols developed by major transplant centers, including the Birmingham, Cambridge, and Groningen criteria [27].

Emerging evidence underscores the importance of endothelial integrity in graft viability. The endothelial glycocalyx plays a critical role in maintaining microvascular function. Elevated levels of syndecan-1-a structural component of the glycocalyx-in the perfusate are indicative of endothelial injury.

High syndecan-1 concentrations (e.g., >4,796.13 ng/mL after six hours of NMP) are strongly associated with early allograft dysfunction, particularly in DCD grafts, and serve as a predictive biomarker of microvascular compromise [28]. A validated consensus protocol through multi-centric study would help for better decision making.

5.2 Hypothermic Assessment: Biomarkers of Mitochondrial Injury

During hypothermic perfusion, metabolic activity is markedly suppressed, precluding the use of functional markers such as bile production. Instead, viability assessment relies on biomarkers of mitochondrial injury. Flavin Mononucleotide (FMN) has emerged as a robust and clinically validated biomarker. During ischemia, FMN dissociates from mitochondrial complex I and is released into the perfusate upon reperfusion [29, 30].

Real-time quantification of FMN using fluorescence spectroscopy enables rapid assessment within 30 minutes. Elevated FMN levels are strongly predictive of graft loss, early allograft dysfunction, and biliary complications, with reported area under the curve (AUC) values of 0.93. This allows for reliable “go/no-go” decisions prior to recipient anesthesia [29, 30].

5.3 Emerging Multi-Omics Approaches

Transcriptomic profiling of perfusate and tissue biopsies during NMP has identified gene expression signatures-including CD274 (PD-L1), LEAP2, and IFIT1-achieving predictive accuracy of AUC 0.99 in preliminary data [31]. While these results are compelling, they are derived from small

exploratory studies and are not yet applicable in routine clinical practice. Prospective validation with standardized methodology is essential before these tools influence transplant decision-making.

6. Expanding the Donor Pool: Steatosis and DCD

Machine perfusion plays a pivotal role in expanding the donor pool by enabling the safe utilization of high-risk grafts.

6.1 Steatotic Livers and Defatting Strategies

Hepatic steatosis exceeding 30% remains a major cause of organ discard due to its association with IRI, EAD, and PNF. NMP enables functional assessment of steatotic grafts by providing real-time metabolic data, allowing transplantation of organs that demonstrate adequate lactate clearance and hemodynamic stability despite donor histology. A recent multicenter cohort study from Mayo Clinic (2022-2025) demonstrated that NMP was associated with reduced post-reperfusion syndrome and improved patient and graft survival in recipients of livers with moderate macrosteatosis (30-60%), providing contemporary real-world evidence for the utility of NMP in this challenging population [32].

Beyond viability assessment, NMP offers a platform for pharmacological "defatting"-the *ex vivo* reduction of hepatocellular lipid content prior to implantation. Preclinical studies incorporating L-carnitine, fenofibrate, and forskolin into the perfusate have demonstrated experimental reductions in macrovesicular steatosis of up to 40% within six hours [33]. More recently, the DeFat Study-a multicentre RCT protocol-has been registered to prospectively evaluate pharmacological defatting with forskolin (NKH477) and L-carnitine combined with lipoprotein apheresis during NMP in discarded steatotic human livers, with transplantation as the primary endpoint. This constitutes the most rigorous ongoing effort to establish defatting as a clinical strategy, and results from this trial are required before defatting can be recommended beyond experimental settings [34]. Proof-of-concept cases have also demonstrated successful transplantation of livers with severe steatosis (>70%) using upfront NMP, further supporting the therapeutic potential of this approach [35].

6.2 DCD Grafts

DCD grafts are particularly susceptible to biliary complications due to warm ischemic injury. HOPE, through controlled mitochondrial recovery without oxidative stress, is ideally suited to these grafts, as demonstrated by the D-HOPE trial [2]. NMP is valuable for functional assessment of DCD grafts with uncertain viability, particularly those with prolonged warm ischemia or borderline hemodynamic parameters [36]. NRP, when available, provides *in situ* resuscitation prior to procurement and has been associated with outcomes approaching DBD grafts in large registry analyses [15, 20]. The choice between these modalities-or their sequential combination-should be guided by institutional expertise, donor characteristics, and the findings of ongoing comparative trials.

7. Operational Logistics and Surgical Education

Machine perfusion has significant implications beyond graft preservation, particularly in improving operational efficiency and surgical training. By extending preservation times, MP

decouples organ procurement from implantation, enabling a transition from emergent nighttime procedures to scheduled daytime operations.

This shift enhances patient safety, optimizes resource utilization, and improves surgical team performance. Additionally, it creates an ideal environment for surgical education, allowing for structured teaching, deliberate practice, and graded autonomy for trainees.

Furthermore, the use of perfusion systems introduces new technical competencies, including device management, cannulation strategies, and interpretation of real-time biochemical data, thereby expanding the educational scope of transplant training programs [37].

8. Economic Analysis and Cost-Effectiveness

Machine perfusion devices carry substantial upfront costs, including equipment acquisition, disposable perfusion circuits, perfusate components, and the staffing required for device management. These costs must be weighed against downstream economic benefits. In the D-HOPE DCD trial, total one-year healthcare costs were significantly lower in the HOPE group versus SCS (€110,794 vs €126,221), primarily driven by reduced intensive care utilization and fewer biliary complications [17]. A prospective cost-effectiveness analysis of FMN-guided viability assessment during NMP similarly demonstrated favorable cost-effectiveness ratios driven by reductions in graft failure and re-transplantation [38]. Comparative economic analyses have further demonstrated that both hypothermic oxygenated perfusion (HOPE) and normothermic machine perfusion (NMP) are economically favorable compared with SCS, particularly for extended criteria donor (ECD) and donation after circulatory death (DCD) grafts, where reductions in graft dysfunction, re-transplantation, and hospital resource utilization offset the higher preservation costs [39].

In a Markov decision-analysis, incorporation of NMP increased liver utilization by approximately 5.8% and yielded an incremental cost-effectiveness ratio of US$33,575 per quality-adjusted life year (QALY), remaining well below commonly accepted willingness-to-pay thresholds [40]. Furthermore, improved graft assessment using viability markers and real-time functional evaluation may reduce unnecessary organ discard while preventing transplantation of nonviable grafts, further enhancing the economic value of machine perfusion [39, 41]. Sequential strategies such as DHOPE-COR-NMP represent the highest-cost approach and currently lack dedicated economic evaluation [21]. Although formal cost-utility analyses incorporating QALYs, national graft utilization data, and real-world implementation costs are needed to guide policy decisions in different healthcare settings, current evidence supports machine perfusion as a clinically effective and economically sustainable preservation strategy. Cost-effectiveness is an explicit endpoint of the Netherlands Sequential Trial, whose results will be informative in this regard [42].

9. Current Ongoing Clinical Trials in Liver Machine Perfusion

To establish definitive, evidence-based clinical guidelines and clarify the optimal use of dynamic perfusion modalities, several large, high-impact randomized controlled trials (RCTs) are currently underway across international centers. A notable shift in trial design has emerged: rather than comparing machine perfusion (MP) with the increasingly outdated standard of static cold storage (SCS), contemporary studies are focusing on direct, head-to-head comparisons between different perfusion strategies. This transition reflects the growing consensus that dynamic preservation

techniques have surpassed SCS and that the key challenge now lies in identifying the most effective modality for specific donor and graft characteristics (Table 3).

Table 3 Key Ongoing Clinical Trials in Liver Machine Perfusion.

Trial/Identifier	Arms	Population	Primary Endpoints	Status
HOPE-NMP Trial NCT04644744 [43]	Arm 1: HOPE (end-ischaemic) Arm 2: NMP (end-ischaemic) Arm 3: SCS (control)	Strict ECD livers from DBD donors	90-day Comprehensive Complication Index (CCI); direct comparison of hypothermic vs normothermic strategies	Recruiting
DCD-Net Trial NCT04744389 [44]	Arm 1: HMP (after *in-situ* NRP) Arm 2: NMP (after *in-situ* NRP)	DCD and extended-criteria DBD grafts	Graft survival; ischaemic-type biliary lesions (ITBL); optimal *ex vivo* strategy following NRP	Active
Netherlands Sequential Trial NCT05327478 [42]	Arm 1: NRP + DHOPE Arm 2: DHOPE alone Arm 3: Sequential COR-NMP	High-risk ECD-DCD livers (donors >50 years)	Organ utilization rates; cost-effectiveness; graft and patient survival	Recruiting
ECD-HOPE Trial NCT03837197 [45]	Arm 1: End-ischaemic HOPE Arm 2: SCS (control)	ECD liver and kidney grafts	Early allograft dysfunction; postoperative outcomes; HOPE in ECD organ preservation	Active
PILOT™ Trial NCT03484455 [46]	Arm 1: Continuous HMP Arm 2: SCS (control)	DCD and broad ECD grafts	Reduction in EAD; safety profiling of continuous portable HMP	Continued Access

9.1 The HOPE-NMP Trial (Arms: HOPE vs. NMP vs. SCS)

The HOPE-NMP Trial is a landmark multicenter RCT designed to address the "cold versus warm perfusion" debate in liver transplantation. In this study, extended criteria donor (ECD) grafts from donation after brain death (DBD) donors are randomized into three groups: end-ischemic hypothermic oxygenated perfusion (HOPE), end-ischemic normothermic machine perfusion (NMP), and a smaller control arm using SCS.

The primary endpoint is the 90-day Comprehensive Complication Index (CCI), a validated composite measure capturing overall postoperative morbidity. This design enables a holistic evaluation of recipient outcomes rather than focusing on isolated complications.

Importantly, this trial directly compares hypothermic and normothermic strategies within a single randomized framework, allowing definitive assessment of whether controlled mitochondrial resuscitation (HOPE) or maintenance of physiological metabolism (NMP) provides superior outcomes in ECD grafts. The findings are expected to significantly influence clinical practice and standardize preservation strategies [43].

9.2 The DCD-Net Trial (Arms: HMP vs. NMP Following NRP)

The DCD-Net Trial investigates the optimal *ex situ* management of donation after circulatory death (DCD) livers following initial *in situ* resuscitation with normothermic regional perfusion (NRP).

In this trial, DCD grafts successfully resuscitated with NRP are randomized 1:1 to either *ex vivo* hypothermic machine perfusion (HMP) or normothermic machine perfusion (NMP). This design isolates the incremental benefit of the subsequent perfusion modality after initial recovery.

Primary endpoints include graft survival and the incidence of ischemic type biliary lesions (ITBL), both critical determinants of long-term outcomes. By comparing hypothermic versus normothermic support post-NRP, the trial aims to determine whether metabolic suppression or sustained physiological activity offers superior protection against biliary injury and graft dysfunction.

With the increasing adoption of NRP, results from this trial are expected to have immediate clinical relevance in refining multi-stage perfusion strategies and improving outcomes in high-risk DCD grafts [44].

9.3 The Netherlands Sequential Trial (Arms: NRP vs. DHOPE vs. COR-NMP)

The Netherlands Sequential Trial is a large, pragmatic, multicenter observational study evaluating real-world, risk-adapted sequential perfusion strategies. Unlike traditional RCTs, this study uses protocol-driven allocation based on donor characteristics, particularly age and graft risk.

Extremely marginal ECD-DCD grafts are assigned to different pathways, including NRP followed by dual hypothermic oxygenated perfusion (DHOPE), standard retrieval followed by DHOPE for intermediate-risk donors (50-60 years), and advanced sequential strategies incorporating controlled oxygenated rewarming followed by normothermic machine perfusion (COR-NMP) for older, high-risk donors (>60 years).

The primary outcomes are organ utilization rates and cost-effectiveness, addressing both clinical and health system considerations. This structured, personalized approach reflects a shift toward tailored organ preservation strategies and is expected to guide optimal allocation of perfusion resources [42].

9.4 Evolving Paradigm in Clinical Trial Design

Collectively, these trials highlight a paradigm shift in liver transplantation. The focus has moved beyond establishing superiority over SCS toward defining the optimal modality, sequence, and timing of perfusion. This evolution underscores the emergence of precision-based organ preservation, integrating donor characteristics, injury profiles, and logistical factors to guide individualized strategies. As these studies mature, they are expected to establish a new generation of evidence-based guidelines for machine perfusion in liver transplantation.

10. Future Directions

Machine perfusion is increasingly recognized as a platform for active organ rehabilitation rather than passive preservation. Several emerging strategies hold transformative potential. Multi-omics integration-combining transcriptomics, proteomics, and metabolomics of perfusate and tissue biopsies during NMP-may enable highly individualized viability prediction and therapeutic targeting [31]. Artificial intelligence-driven analysis of continuous perfusion parameters may identify dynamic graft recovery patterns invisible to static threshold-based criteria. Regenerative therapies, including mesenchymal stem cell delivery and gene editing targeted at inflammatory pathways, represent a further frontier, though all remain preclinical. Pharmacological defatting of steatotic grafts, supported by the ongoing DeFat RCT, may expand the proportion of livers suitable for transplantation [34]. Finally, IFLT-if validated in international multicenter studies-could redefine the technical standard of care for high-risk recipients and oncological transplantation [22-24].

11. Conclusion

Machine perfusion has transformed liver transplantation from a time-critical, preservation-limited procedure into a controlled, physiology-driven, and data-informed practice. By mitigating ischaemia-reperfusion injury, it enables improved preservation, active graft resuscitation, and functional assessment before implantation. HOPE reduces biliary complications with Level 1 evidence, particularly in DCD grafts; NMP supports real-time viability testing and increases utilization of marginal organs; NRP and sequential strategies further optimize outcomes in high-risk donors; and IFLT represents an emerging paradigm shift awaiting international validation.

Critically, a balanced appraisal of the current evidence base must acknowledge its limitations: substantial heterogeneity across trials in donor profiles, perfusion protocols, viability criteria, and comparator arms; absence of head-to-head RCT data comparing HOPE with NMP; reliance on retrospective cohorts for NRP; and high implementation costs that are not uniformly offset by downstream savings across all healthcare systems. Ongoing trials are designed to address these gaps and will define the next generation of evidence-based guidelines.

Future advances integrating AI-assisted perfusion analytics, multi-omics viability assessment, regenerative therapies, and pharmacological defatting will further refine this field and establish machine perfusion as the unequivocal standard of care for liver graft preservation, maximizing both the quantity and quality of donor organs available for transplantation.

Author Contributions

Conception of the work: MP. Drafting the manuscript, Review and editing the manuscript, Critical review of the manuscript: AF, ZT, HM and MP. Final revision and approval for submission: MP.

Competing Interests

The authors have declared that no competing interests exist.

AI-Assisted Technologies Statement

During the preparation of this work the authors used Copilot AI for formatting. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

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