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Normothermic Regional Perfusion in Controlled Donation After Circulatory Death: Growing Evidence for Liver Transplantation

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ABSTRACT

Normothermic regional perfusion (NRP) has emerged as a pivotal strategy in controlled donation after circulatory death (cDCD) liver transplantation, mitigating ischemia-reperfusion injury and improving graft outcomes. Compared to super rapid recovery (SRR), NRP significantly reduces rates of early allograft dysfunction, primary nonfunction, and biliary non-anastomotic stricture (NAS), with biliary complications reported in 5%–16% and NAS as low as 0%–2%. Outcomes from cDCD-NRP grafts are increasingly comparable to those of donation after brain death (DBD). Viability assessment during NRP remains variably defined across centers. Nonetheless, stable pump flow, stable or declining lactate levels, controlled transaminase levels, and favorable macroscopic appearance are commonly used parameters. Histological thresholds may guide graft acceptance but are not universally applied. Sequential use of ex situ machine perfusion following NRP offers additional benefits in marginal or prolonged ischemia settings. NRP implementation has improved liver utilization rates from 34% to 63% in the United Kingdom and from 39% to 71% in the United States. This review highlights NRP as a transformative platform that reshapes viability standards, expanding transplant access, and supports sustained growth in liver transplantation.

1 | Introduction

The growing organ shortage has driven the expansion of donation after circulatory death (DCD) to increase the donor pool. However, outcomes following liver transplantation using cDCD grafts have historically lagged behind those of donation after brain death (DBD) grafts. Studies have reported higher incidences of primary nonfunction (PNF; 3% vs. 1%) [1, 2] and biliary non-anastomotic stricture (NAS; 6%–11% vs. 0.6%–3%) [1–3] in cDCD compared to DBD liver transplantation. Additionally, cDCD grafts are associated with elevated post-reperfusion transaminase levels, increased incidence of post-reperfusion syndrome (PRS) [3–6], hyperkalemia [7], greater vasopressor requirements, and higher transfusion needs [8].

Abbreviations: AKI, acute kidney injury; A-NRP, abdominal normothermic regional perfusion; cDCD, controlled donation after circulatory death; CIT, cold ischemic time; EAD, early allograft dysfunction; fWIT, functional warm ischemic time; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; MEAF, model for early allograft function; MELD, model for end-stage liver disease; MRCP, magnetic resonance cholangiopancreatography; NAS, non-anastomotic stricture; NMP, normothermic machine perfusion; PNF, primary non-function; PRS, post-reperfusion syndrome; SCS, standard cold storage; SRR, super rapid recovery; TA-NRP, thoracoabdominal normothermic regional perfusion.

NRP was developed to mitigate ischemia-reperfusion injury and improve outcomes in cDCD liver transplantation. Initially implemented in the early 2000s at the University of Michigan and in Spain [9, 10], NRP saw limited adoption in the United States but gained significant traction across Europe during the 2010s, with widespread implementation in the United Kingdom, Spain, France, and Italy [11–14]. The growing body of evidence supporting NRP has led several European nations to mandate its use in DCD donation, and the American Society of Transplant Surgeons (ASTS) has formally endorsed the technique [15]. NRP encompasses two primary approaches: abdominal NRP (A-NRP), which provides in situ perfusion to abdominal organs only, typically via the infrarenal aorta and inferior vena cava or femoral vessels without reinitiating cardiac activity; and thoracoabdominal NRP (TA-NRP), which involves reinitiation of cardiac activity and perfusion of both thoracic and abdominal organs through cannulation of the aortic arch and right atrium [16].

Despite these advancements, cDCD liver utilization remains suboptimal in the United States. In 2022, only 21.2% of recovered cDCD livers were transplanted, with rates falling to 11.5% in donors aged $\geq$ 50 years [17]. A recent report by the National Academies recommended increasing cDCD liver utilization to approximately 45% of all deceased donors [18]. Achieving this target will require expanded use of extended-criteria grafts—including those from older or steatotic donors—for which NRP may offer critical support.

This review provides a comprehensive summary of the current evidence supporting NRP in cDCD liver transplantation. Key focus areas include clinical outcomes, donor pool expansion, and comparisons with other preservation strategies such as standard rapid recovery (SRR), normothermic machine perfusion (NMP), and hypothermic oxygenated perfusion (HOPE).

2 | Methods

2.1 | Scope of the Review

This narrative review focuses on abdominal and thoracoabdominal NRP in cDCD liver transplantation. Studies limited to technical descriptions without clinical outcomes, animal studies, and case reports were excluded.

2.2 | Search Strategy

A focused literature search was performed in PubMed in March 2025 using the keywords "normothermic regional perfusion," "donation after circulatory death," and "liver transplantation." Additional publications were identified through manual reference screening. Priority was given to recent and larger cohort studies, multicenter analyses, and meta-analyses, with smaller or older studies incorporated for contextual interpretation.

2.3 | Study Selection and Data Handling

Included studies comprised randomized trials, observational cohorts, registry analyses, and major programmatic reports. When multiple reports originated from the same cohort, the most comprehensive or most recent primary study was selected, and secondary reports were used only when they contributed additional outcomes or comparator groups.

2.4 | Outcome Definitions and Terminology Standardization

To ensure consistency across heterogeneous studies, outcome terminology was standardized for synthesis. Non-anastomotic strictures (NAS) and ischemic cholangiopathy were grouped under NAS for consistency. Arterial complications and hepatic artery thrombosis (HAT) were reported separately when distinguished in the original studies and were combined when only global arterial complication rates were available. Early graft injury metrics—including peak ALT, early allograft dysfunction (EAD), and model for early allograft function (MEAF)—as well as kidney outcomes such as creatinine levels and acute kidney injury (AKI), and long-term outcomes including graft survival, patient survival, and retransplantation, were extracted according to each study's definitions but synthesized under standardized categories to facilitate comparison across heterogeneous reports.

2.5 | Data Extraction and Synthesis Strategy

Pre-defined variables included donor characteristics, NRP technical parameters (cannulation strategy, duration, and perfusion settings), viability markers, and post-transplant outcomes. Data were extracted manually by the authors and synthesized qualitatively, given the heterogeneity in study designs and outcome definitions.

2.6 | Quality Assessment

Although this is not a formal systematic review, methodological features—such as study design, cohort size, use of protocol-based imaging, outcome definitions, and completeness of follow-up—were qualitatively evaluated. When applicable, NIH quality assessment criteria for observational studies guided interpretation but were not used to assign numerical scores.

3 | Results

3.1 | NRP Versus SRR in cDCD Liver Transplantation

Two major multicenter retrospective studies have directly compared outcomes between NRP and SRR in cDCD liver transplantation (Table 1). Hessheimer et al. analyzed 545 A-NRP cases and 258 SRR cases across Spain (2012–2019), adjusting for donor, recipient, and procedural factors. NRP was associated with significantly lower rates of EAD, HAT, all biliary complications (12% vs. 29%), NAS (1% vs. 9%), retransplantation, and graft loss [19].

Similarly, Brubaker et al. examined a US cohort of 106 NRP and 136 SRR cases, comprising 79 TA-NRP and 27 A-NRP procedures.

TABLE 1 | Comparison of two major studies comparing NRP versus standard rapid recovery.

Factors	Hessheimer et al. [19]			Brubaker et al. [20]		
	A-NRP ($n = 545$)	SRR ($n = 258$)	p value	NRP ($n = 106$)	SRR ($n = 136$)	p value
Study design, country	Multicenter, retrospective, Spain, 2012–2019 Risk adjusted analysis, A-NRP only			Multicenter, retrospective, USA, 2017–2023, 79 TA-NRP, 27 A-NRP		
Donor age	59 (49–67)	58 (48–67)	0.638	30.5 (22–44)	36 (27–49)	0.040
fWIT (min)	12 (9–16)	14 (11–20)	< 0.001	22 (18–25)	19 (16–23)	0.010
NRP duration (min)	111 (81–126)	—	—	62 (51–89)	—	—
CIT (min)	320 (270-379)	333 (284-388)	0.141	289 (218-355)	298.5 (247-349)	0.700
Recipient age	59 (53–63)	58 (53–63)	0.701	60 (53–66)	58 (51–63)	0.070
MELD score	12 (9–17)	12 (8–16)	0.358	20 (15–24)	20 (15–23)	0.790
HCC	139 (25.5%)	70 (27.1%)	0.617	31 (29.3%)	25 (18.4%)	0.047
Follow-up period (day)	930		—	316 (189-508)	438 (284–631)	—
EAD	81 (15%)	60 (23%)	0.010[a]	77 (36%)	123 (56%)	0.007
HAT	22 (4%)	19 (7%)	0.032[a]	—	—	—
All biliary complications	63 (12%)	75 (29%)	< 0.001[a]	—	—	—
Anastomotic biliary stricture	—	—	—	7/105 (6.7%)	30/134 (22.4%)	0.001
Ischemic cholangiopathy	6 (1%)	24 (9%)	< 0.001[a]	0/104 (0%)	12/133 (9%)	0.002
PNF				0	2 (1.5%)	0.210
Retransplantation	19 (3.5%)	31 (12%)	< 0.001[a]	—	—	—
Graft survival			< 0.001[a]			0.37[b]
1-year graft survival	90%	79%	HR0.37			
3-year graft survival	87%	68%	(0.27–0.52)			

Abbreviations: A-NRP, abdominal normothermic regional perfusion; CIT, cold ischemic time; EAD, early allograft dysfunction; fWIT, functional warm ischemic time; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; PNF, primary non-function; SRR, super rapid recovery; TA-NRP, thoracoabdominal normothermic regional perfusion.

[a]After risk adjustment for several donor, recipient, and other factors.

[b]Kaplan–Meir analysis.

NRP was associated with shorter hospital stays, lower incidence of biliary anastomotic strictures (7% vs. 22%) and NAS (0% vs. 9%), and reduced EAD. PNF occurred only in SRR recipients, although the difference was not statistically significant [20].

Two meta-analyses have further validated these findings. Schurink et al. analyzed 1220 cDCD with NRP cases and reported PNF in 3% (95% CI: 2%–4%) and NAS in 2% (95% CI: 1%–4%). One-year graft survival was 91% (95% CI: 89%–93%), and patient survival was 93% (95% CI: 91%–94%) [21]. De Beule et al. demonstrated in their meta-analysis comparing NRP to SRR in cDCD that NRP significantly reduced the risk of EAD by 56% and all biliary strictures by 79% (NAS by 75% and anastomotic biliary stricture by 65% when analyzing separately), although there was considerable heterogeneity in EAD data. No significant difference was noted for HAT or patient survival, though authors endorsed caution on the interpretation of patient survival data, as estimation methods had to be used [22].

Collectively, these data reinforce NRP as a superior alternative to SRR for improving both short- and long-term outcomes in cDCD liver transplantation.

3.2 | NRP-cDCD Versus DBD

Two of the largest matched cohort studies to date have compared cDCD liver transplantation with NRP to standard DBD liver transplantation, offering valuable insights into the relative efficacy of NRP-supported grafts (Table 2). Savier et al. (France) and Ruiz et al. (Spain) both demonstrated that outcomes with cDCD-NRP grafts are comparable to those of DBD grafts [23, 24].

Savier et al. matched 50 cDCD-NRP cases with 100 DBD transplants [23]. The rates of EAD (18% in NRP vs. 32% in DBD), AKI (26% vs. 33%), arterial complications (4% vs. 12%), and all biliary complications (16% vs. 17%) were comparable. Two-year death, non-censored graft survival (88% vs. 85%), and patient survival (90% vs. 88%) were also equivalent [23].

Ruiz et al. matched 100 cDCD-NRP grafts to 200 DBD livers and reported no significant differences in EAD (19.2% vs. 21%), AKI (19.8% vs. 29.3%), or biliary complications (5.2% vs. 6.3%) [24]. Importantly, no cases of PNF or ischemic-type biliary lesions occurred in the cDCD cohort. One- and three-year graft survival were significantly higher in the cDCD-NRP group (99% and 93%)

TABLE 2 | Comparison of two major studies comparing cDCD with NRP versus DBD.

Factors	Savier et al. [23]			Ruiz et al. [24]		
	cDCD with NRP ($n = 50$)	DBD ($n = 100$)	p value	cDCD with NRP ($n = 100$)	DBD ($n = 200$)	p value
Study design, country	Multicenter, retrospective, France, 2015–2019, matched cohort study			Single center, retrospective, Spain, 2015–2019, matched cohort study		
Donor age	50 (39–56.5)	50 (40–59)	0.49	62 (53–69)	62 (51–72)	0.67
fWIT (min)	22 (20–26.8)			10 (8.5–12.2)	—	—
NRP duration (min)	190 (151–223)	—	—	121 (118–128)	—	—
CIT (min)	348 (300–402)	378 (324–438)	0.03	274 (241–311)	264 (247–349)	0.70
Recipient age	59.9 (54.1-63.9)	58.4 (52.8-62.2)	0.18	59 (54–64)	58 (53–64)	0.79
MELD score	7 (6–12)	10 (6–14)	0.08	12 (9–18)	12 (9–16)	0.63
HCC	35 (70%)	59 (59%)	0.26	39 (39%)	98 (49%)	0.13
Follow-up period, months	34.8 (28.6-39.8)	51.7 (34.1-61.7)	—	36 (20–48.3)		—
EAD	9 (18%)	32 (32%)	0.11	19 (19.2%)	42 (21%)	0.83
AKI	13 (26%)	33 (33%)	0.49	19 (19.8%)	56 (29.3%)	0.11
All arterial complications	2 (4%)	12 (12%)	0.19	5 (5.1%)	12 (6.3%)	0.87
Hepatic artery thrombosis	0	5 (5%)	—	1 (1%)	3 (1.5%)	1.00
All biliary complications	8 (16%)	17 (17%)	0.94	5 (5.2%)	12 (6.3%)	0.90
Anastomotic biliary stricture	2 (4%)	9 (9%)	—	2 (2%)	6 (3%)	—
Ischemic cholangiopathy	1 (2%)	1 (1%)	—	0	0	—
PNF	—	—	—	0	2 (1.5%)	0.21
Graft survival			0.91			0.036
1-year graft survival	—	—	—	99%	92%	—
2-year graft survival	88%	85%	—	—	—	—
3-year graft survival	—	—	—	93%	87%	—

Abbreviations: AKI, acute kidney injury; cDCD, controlled donation after cardiac death; CIT, cold ischemic time; DBD, donation after brain death; EAD, early allograft dysfunction; fWIT, functional warm ischemic time; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NRP, normothermic regional perfusion; PNF, primary non-function.

versus DBD (92% and 87%, $p = 0.04$), although the difference was attenuated when censored for death from non-liver causes, primarily neoplasia in the DBD group [24].

These findings are consistent with the other studies, in which cDCD with NRP documented comparable outcomes in biliary and arterial complications, and patient and graft survival to DBD cases [25, 26]. Collectively, these studies establish NRP as a robust platform not only for improving outcomes but also for narrowing the gap between cDCD and DBD liver transplantation.

3.3 | NRP Versus NMP and HOPE in cDCD

Recent comparative studies have highlighted the expanding role of NRP in cDCD liver transplantation, particularly in contrast to NMP andHOPE (Table 3). In a large single-center study of 233 cDCD liver transplants, both NRP ($n = 69$) and NMP ($n = 67$) improved early graft function compared to static cold storage (SCS; $n = 97$), but only NRP significantly reduced clinically relevant NAS (0% vs. 11% in NMP and 14% in SCS, $p = 0.009$) [27]. Beyond biliary outcomes, the same study demonstrated broader improvements with NRP, including lower MEAF scores compared to SCS (risk-adjusted reduction 1.52 for NRP and 1.19 for NMP), reduced creatinine ratios suggesting lower rates of early AKI (risk-adjusted reduction 0.51 for NRP, $p = 0.02$), and a trend toward decreased 6-month graft failure (HR 0.30, 95% CI 0.08–1.05). Rates of HAT and graft loss due to HAT were similar across groups. Importantly, NRP was associated with significantly lower retransplantation rates (4%) compared with both SCS (18%) and NMP (12%; $p = 0.04$, Table 3).

The same group later reported, using a larger cohort with longer follow-up, favorable outcomes for both NRP and NMP compared with SCS, though only NRP conferred significant benefit in PRS ($p < 0.001$) and 5-year graft survival (HR 2.4, $p = 0.028$) [28]. NRP was also associated with lower peak ALT levels, and absence of PNF (0% vs. 3% in SCS and 1% in NMP, Table 3). These additional outcomes provide a broader context showing that NRP improves not only biliary complications but also early graft injury, PRS, retransplantation rates, and potentially long-term graft survival.

To further assess cDCD outcomes with NMP, two major randomized controlled trials were examined. In the study by Nasralla

TABLE 3 | Key findings of the previous studies comparing NRP to the other machine perfusion systems.

Gaurav et al. [27], UK	**Single center retrospective**			**Risk-adjusted analysis**	
Variables	**SCS ($n = 97$)**	**NRP ($n = 69$)**		**NMP ($n = 67$)**	
			p		***p***
MEAF score	Reference	−1.52	< 0.001	−1.19	< 0.001
Baseline to peak Cr ratio increase	Reference	−0.51	0.02	−0.36	0.09
Non-anastomotic stricture	Reference	OR		OR	
		0.2 (0.06–0.72)	0.01	0.82 (0.82–1.98)	0.19
Graft survival at 6M	Reference	HR		HR	
		0.3 (0.08–1.05)	0.06	1 (0.37–2.7)	0.19

Puttappa et al. [28], UK	**Single center retrospective**				
Variables	**SCS ($n = 59$)**	**NRP ($n = 101$)**		**NMP ($n = 78$)**	***p***
Peak ALT	697 (451–1277)	508 (328–970)		360 (208–621)	< 0.001
MEAF score	5.8 (4.8–7)	4.1 (2.8–5.4)		3.3 (2.1–5.2)	< 0.001
AKI stage ≥ 2	28 (47%)	29 (29%)0.02		22 (28%)	0.033
		OR	*p*	OR	*p*
Reperfusion syndrome	Reference	0.16 (0.06–0.39)	< 0.001	0.38 (0.15–0.91)	0.32
5-year graft survival	69%	85%		84%	
Versus SCS	Reference	HR 2.4 (1.1–5.4) $p = 0.028$		HR 2.0 (0.9–4.4) $p = 0.089$	

Muller et al. [29], France	**Multicenter retrospective**	**Propensity score, matched analysis**	
Variables	**NRP ($n = 132 \rightarrow 32$)**	**HOPE ($n = 93 \rightarrow 32$)**	***p***
Serum Cr, Day7	68 (57–101)	111 (69–214)	0.012
Biliary complications	8 (25%)	11 (34.4%)	0.508
Non-anastomotic stricture	2 (6.3%)	4 (12.5%)	0.688
Arterial complications	3 (9.4%)	2 (6.3%)	1
Overall graft loss	5 (15.6%)	8 (25%)	0.727

Abbreviations: AKI, acute kidney injury; EAD, early allograft dysfunction; HOPE, hypothermic oxygenated machine perfusion; MEAF score, model for early allograft function score; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; SCS, standard cold storage.

et al. using the Metra device, NAS occurred in 11.1% (3/27), but only one case (3.7%) was clinically significant. Importantly, biliary complications were evaluated using 6-month protocol magnetic resonance cholangiopancreatography (MRCP) with subgroup analysis [30]. In the study by Markmann et al., using the OCS device (PROTECT trial), NAS were significantly reduced with NMP (2.6% vs. 9.9%, $p = 0.02$), although no subgroup analysis was conducted and most grafts were from DBD donors. Biliary complications were assessed with MRCP or endoscopic retrograde cholangiopancreatography at clinical discretion, rather than protocol-based imaging [31]. Given these methodological differences, and considering that the PROTECT trial did not perform a subgroup analysis for DCD donors, direct comparison between these two trials or with other studies is challenging.

A multicenter, propensity-matched analysis comparing NRP ($n = 132$) and HOPE ($n = 93$) further showed that both improved outcomes versus SCS, but NRP achieved superior early graft function, lower Day 7 creatinine, and significantly reduced EAD (20% vs. 68%, $p < 0.001$, Table 3) [29]. A recent study compared 298 DCD liver transplants preserved with HOPE/D-HOPE to 136 preserved with NRP followed by HOPE. Five-year death-censored graft survival was comparable between groups (87.5% in HOPE/DHOPE vs. 79.5% in NRP-HOPE, log-rank $p = 0.18$). Post-transplant biliary complications, including the 24-month cumulative incidence of NAS (14.7% vs. 4.6%, $p < 0.001$) and graft loss due to NAS, as well as the incidence of biliary anastomotic strictures, were all significantly lower in the NRP-HOPE group [32].

Overall, while NRP, NMP, and HOPE each offer distinct benefits in cDCD liver transplantation, current evidence suggests that NRP may provide broader improvements across biliary, early graft injury, and long-term outcomes; however, these findings should be interpreted cautiously given heterogeneity in study design, imaging protocols, and donor characteristics.

3.4 | The Role of Ex Situ Machine Perfusion Following NRP in DCD Liver Transplantation

The addition of ex situ machine perfusion (MP) following NRP has emerged as a valuable strategy in select DCD liver transplant scenarios. While NRP alone provides significant improvements in graft viability and early outcomes, sequential use of MP—either NMP or hypothermic oxygenated perfusion (D-HOPE)—may offer added benefit in the setting of prolonged cold ischemia, marginal donor quality, or complex recipient profiles.

In a multicenter retrospective analysis, Croome et al. compared NRP alone ($n = 62$), NRP followed by NMP ($n = 21$), and SCS-preserved cDCD grafts ($n = 297$). Both NRP groups demonstrated significantly lower incidence of EAD, AKI, and NAS, and better 1-year graft outcomes. However, the addition of NMP didn't show any major benefits—except for a slight reduction in FFP usage. Actually, EAD was significantly higher in the NRP + NMP group compared with NRP alone ($p = 0.001$), likely reflecting confounding by indication or more liberal graft selection (e.g., national share grafts, higher terminal lactate at the end of NRP) [33]. Torri et al. reported successful transplantation of 11 grafts from elderly donors (median age 82) treated with sequential NRP + D-HOPE ($n = 6$) or NMP ($n = 5$), with no cases of PNF or NAS and similar graft function between groups [34]. Ghinolfi et al. showed that sequential NRP+MP enabled successful utilization of uncontrolled DCD grafts, with comparable survival and NAS rates to cDCD grafts [35]. De Carlis et al. reported outcomes from 44 cDCD grafts treated with NRP, of which 84% underwent D-HOPE. Compared to a matched static-preserved cohort, NRP+D-HOPE significantly reduced stage 2–3 AKI despite longer donor warm ischemia, while 2-year NAS-free survival was similar (97% vs. 92%, $p = 0.317$) [14].

A meta-analysis by De Beule et al. found that adding ex situ HOPE after NRP did not confer additional benefit compared with NRP alone. Specifically, NRP significantly reduced EAD, NAS, and anastomotic strictures compared to SRR, and these results were essentially unchanged when HOPE following NRP cases were excluded—indicating that the benefit was attributable to NRP itself rather than sequential HOPE [22].

Together, these findings suggest that ex situ machine perfusion following NRP can be particularly useful under certain conditions, such as prolonged ischemia or marginal donors. Additional advantages of machine perfusion after NRP may relate more to surgical logistics, for example, allowing extra time during complex recipient hepatectomy or avoiding nighttime transplantation. NMP may also extend viability assessment for marginal grafts, particularly when terminal lactate levels during NRP remain elevated or increase (Table 4).

3.5 | Definition of Functional Warm Ischemic Time and Its Limit

The definition of functional warm ischemia time (fWIT) varies across centers—reflecting institutional experience and national regulations (Table 5). fWIT is typically defined as the time from a critical decline in systolic blood pressure (SBP) or oxygen saturation to the initiation of NRP or cold flush. Thresholds often include SBP < 50–80 mmHg or oxygen saturation < 70%–80%, with recent U.S. and U.K. studies adopting SBP < 50 mmHg in accordance with ASTS guidelines [15, 28]. The ASTS recommends standardizing key time points—such as drops in SpO_2 and SBP, circulatory arrest, skin incision, cold flush, NRP timing, and organ retrieval—to improve consistency in reporting [15]. Most programs limit fWIT to around 20–30 min, while in countries like Italy, longer fWITs, such as 60 min, are accepted due to mandated 20-min no-touch periods, and favorable outcomes have still been reported [14, 34–36]. For instance, Ghinolfi et al. described a median fWIT of 53 min with an NAS incidence below 5% [36]. ILTS guidance suggests that livers from DCD donors with functional warm ischemia > 30 min recovered with NRP may be considered for transplantation, as long as the evolution of relevant parameters during NRP is adequate [37].

3.6 | Cannulation Strategies and Recovery Technique

The timing of cannulation (antemortem vs. postmortem) must conform to local legislation and institutional policy. ILTS guidance emphasizes that any premortem IR-guided femoral guidewire placement requires explicit consent, although this approach can facilitate rapid initiation of NRP after death declaration [37].

Postmortem cannulation in current US practice most commonly uses direct central cannulation—either via laparotomy (abdominal aorta and IVC) or via thoracotomy (descending aorta and RA)—as these approaches provide reliable high-flow perfusion. Combined procedures—such as A-NRP with rapid thoracic organ recovery or heart retrieval onto an ex situ perfusion device—are technically demanding and should be reserved for centers with substantial experience in standard NRP recovery. When A-NRP is combined with thoracic organ recovery, meticulous hemostasis is essential; the superior vena cava and azygos vein should be ligated, and adequate venous return to the circuit maintained, with at least five units of pRBC immediately available [40].

AST and ASTS recommend mandatory occlusion and venting of the aortic arch vessels during TA-NRP and occlusion and venting of the abdominal aorta during A-NRP to prevent any possibility of cerebral or coronary reperfusion after death declaration. Recent OPTN guidance further specifies that the aorta should be clamped, and the proximal segment transected and allowed to drain to the atmosphere before initiating perfusion; intra-aortic balloons may be used for occlusion, but not as the sole safeguard [41].

4 | Viability Assessment and Perfusion Parameters During NRP in cDCD Liver Transplantation

4.1 | Viability Assessment During NRP

Viability assessment during NRP increasingly follows a multiparametric framework that incorporates lactate kinetics, transaminase levels, and macroscopic and histological evaluation. In most protocols, lactate trends are integrated

TABLE 4 | The role of subsequent ex situ machine perfusion following NRP.

Croome et al. [33], USA	Multicenter retrospective			*p*		
Variables	**SCS (*n* = 297)**	**NRP (*n* = 62)**	**NRP + NMP (*n* = 21)**	**SCS versus NRP**	**SCS versus NRP + NMP**	**NRP versus NRP + NMP**
EAD	187 (64.5%)	7 (11.3%)	9 (42.9%)	< 0.001	0.047	0.001
AKI	90 (30.3%)	9 (14.5%)	2 (9.5%)	0.01	0.04	0.56
RBC during LT, units	7 (4–11)	5 (3–6)	3 (0–6)	< 0.001	0.01	0.26
FFP during LT, units	4 (2–8)	4 (2–6)	2 (0–4)	0.08	0.004	0.057
Ischemic cholangiopathy	50 (16.8%)	0	0	< 0.001 (0.82-1.98)	0.04	NA
Hepatic artery thrombosis	3 (1%)	1 (1.6%)	0	0.68	0.64	0.56
Primary non-function	6 (2%)	0	0	0.26	0.51	NA
3-month graft survival	91.6%	98.3%	100%	SCS versus NRP group		
1-year graft survival	87.5%	96.5%	100%	$p = 0.016$		
2-year graft survival	83.7%	96.5%	NA			

Abbreviations: AKI, acute kidney injury; EAD, early allograft dysfunction; NMP, normothermic machine perfusion; NRP, normothermic regional perfusion; SCS, standard cold storage.

with visual graft inspection and biopsy findings to guide decision-making. Lactate kinetics have emerged as a central component of viability assessment. Ghinolfi et al. reported that a > 23.4% lactate reduction within the first 2 h and a 120-min value < 8.5 mmol/L predicted 90-day graft survival [34]. In most cases, lactate falls by approximately 2 mmol/L or to < 10 mmol/L within the first hour, whereas Watson et al. observed declines ranging from 3 to 14 mmol/L over 2 h [11, 24]. When the initial lactate level was already low, this magnitude of reduction was not always present; however, a clear downward trajectory—however modest—remained a requirement for graft acceptance [16]. Croome et al. recommend 15-min sampling during 60–90-min A-NRP runs, which provides greater temporal resolution than the 30-min intervals used in longer European protocols [16]. As Watson et al. noted, lactate leakage from non-perfused regions may limit the reliability of this biomarker [11], prompting a shift toward thoracic rather than abdominal cannulation in contemporary A-NRP practice.

Transaminase levels, particularly ALT, are also widely used, though thresholds vary across centers. Several European programs apply cutoffs of < 200 IU/L or < 3–4× ULN, whereas the NRP-Milan criteria allow a higher threshold of < 1000 IU/L when interpreted alongside other viability parameters such as fWIT and lactate kinetics [14, 34–36]. ILTS guidance emphasizes that the trajectory of transaminases during NRP—ideally stable or decreasing—is more informative for assessing liver viability than any single absolute value [37].

ASTS A-NRP standards recommend routine lactate monitoring every 15–30 min and emphasize interpretation of absolute values and trends in combination with direct visual assessment. Ongoing research is needed to refine organ viability markers during NRP [41]. Ancillary testing may provide added diagnostic value, particularly for assessment of the biliary tree. Bile studies have been introduced as a potential predictor of NAS risk due to direct measurement of cholangiocyte function. Potential biomarkers include bile volume, bile pH, bile glucose, bicarbonate concentration, and bile lactate dehydrogenase levels [42, 43].

4.2 | Perfusion Parameters and Duration

Perfusion parameters during A-NRP are central to graft physiology because they influence oxygen delivery, microvascular perfusion, and the risk of sinusoidal congestion. Most protocols target flows of ~2–3 L/min (≈2.2–2.4 L/min/m^2), which approximates physiologic cardiac output and supports adequate hepatic arterial and portal venous inflow [11, 19, 20, 39, 38].

Similarly, MAP targets of 50–80 mmHg help balance perfusion pressure and vascular shear stress. Lower pressures risk inadequate microcirculatory oxygenation, while excessive pressures may cause sinusoidal distension and endothelial injury—both recognized contributors to reperfusion injury and biliary ischemia [20].

Adequate oxygen-carrying capacity (hematocrit > 20%–25%) and normothermia (35.5°C–37.5°C) further support mitochondrial metabolism and allow reliable interpretation of viability markers such as lactate trends and transaminase levels. These physiological targets are consistently incorporated into national NRP protocols [39].

Based on current evidence, a minimum NRP duration of approximately 1 h and a maximum of 4 h is generally recommended for organ evaluation [37, 40]. Some Italian centers, however, have extended perfusion to 4–6 h in selected marginal donors to allow additional metabolic recovery, provided that perfusion parameters remain stable throughout [34, 44].

4.3 | Cold Ischemic Time (CIT) After NRP

Nevertheless, CIT after NRP continues to influence graft outcomes. CIT > 6 h is associated with increased risk per the UK

TABLE 5 | Perfusion parameters and viability assessment during NRP in cDCD liver transplantation.

References	Start of fWIT	Viability assessment	Pump settings and cannulation
Hessheimer et al. [19], Spain Multicenter	SBP < 60 mmHg	AST, ALT remained stable and < 200 IU/L Perfusate lactate level down-trended (ideally)	• 2.2–2.4 L/min/m^2 • Postmortem cannulation
Brubaker et al. [20], USA Multicenter	SBP < 80 mmHg or Sat < 80%	N/A	• 2–5 L/min • MAP 50–80 mmHg • Pre- and post-mortem cannulation
Savier et al. [23], France Multicenter	SBP < 45 mmHg fWIT ≤ 30 min	AST, ALT < 200 IU/L macrosteatosis < 20% on frozen biopsy Donor age: 18–65 years CIT < 8 h	• Premortem cannulation • 1–4 h of NRP
Ruiz et al. [24], Spain Single center	SBP< 60 mmHg fWIT ≤ 30 min	AST, ALT < 3 times the normal level ALT and lactate monitored every 30 min < 50% of graft steatosis	• Premortem cannulation by IR 2–3 h prior to withdrawal • 2 h of NRP
Puttappa et al. [28], UK Single center	SBP < 50 mmHg		• Postmortem cannulation • 2 h of NRP
Croome et al. [33], USA Multicenter	SBP < 50 mmHg		• Median 70 (32–263) min of NRP
Muller et al. [29], France Multicenter	meanBP < 45 mmHg fWIT < 45 min no-flow < 25 min	AST, ALT < 4 times the normal level Macrosteatosis < 20% CIT < 8 h	• Postmortem cannulation • Minimum 1 h of NRP
Watson et al. [11], UK	Total WIT only	ALT < 500 Downward trend in lactate	• 2.5–3 L/min for A-NRP • 4–6 L/min for TA-NRP • 2 h of NRP
Croome et al. [16], USA	Total WIT < 75 min SBP < 50, fWIT < 20 min	Downward trend in lactate	• 60–90 min of NRP
Torri et al. [34], Italy De Carlis et al. [14], Italy Ghinolfi et al. [35, 36], Italy NRP-Milan Criteria	SBP < 50 or Sat < 70	At least 2 of the following 1. fWIT ≤ 60 min 2. ALT < 1000 3. Downward in lactate Liver biopsy (mandatory)Decline in case of 1. Macrosteatosis > 30% 2. Fibrosis > 2 per Ishak's score 3. Necrosis > 10% 4. Severe macroangiopathy (arteriolar thickening > 60%)	• NRP flow > 2.0 L/min
Croome et al. [15], ASTS recommendations	SBP < 50	N/A	• 1–4 h of NRP
Hessheimer et al. [37], European Consensus guideline 2025 [38]	Varying	Stable pump flow Stable transaminase levels throughout NRP Stable or declining lactate (at least every 30 min) Good macroscopic appearance	• A-NRP flow > 1.7 L/min = 1 L/min/m^2 BSA

(Continues)

TABLE 5 | (Continued)

References	Start of fWIT	Viability assessment	Pump settings and cannulation
UK protocol [39]	N/A	ALT ≤ 500 at 2 h Downward trend in lactate Routine liver biopsy (before, after, or both)	• 2–3 L/min • 35.5–37.5°C • SvO_2 60%–80% • Arterial pH 7.35–7.45 • Hematocrit > 20% • 2 h of NRP

DCD Risk Score [45], and CIT ≥ 7 h has been identified as an independent risk factor for graft loss in the setting of A-NRP. In a stratified analysis of death-censored graft survival, hazard ratios relative to CIT < 7 h and no retransplantation were CIT ≥ 7 h with no retransplantation (HR 2.732, $p = 0.008$); CIT <7 h with retransplantation (HR 7.604, $p < 0.001$); and CIT ≥ 7 h with retransplantation (HR 27.141, $p < 0.001$) [19].

4.4 | NRP as a Tool to Expand the Donor Pool

NRP not only improves graft outcomes but also enables broader utilization of extended-criteria donors. Countries employing routine NRP report significantly higher liver utilization rates than those using selective approaches (65% vs. 28%), with comparable 5-year graft survival [46]. In the United Kingdom, where > 45% of DCD donors are over 50 years old, NRP has enabled better post-LT outcomes than the United Stataes, despite donor age [47]. Oniscu et al. reported an increase in transplant rates from 34% to 63% with routine NRP use [48]. In the United States, Bekki et al. demonstrated that implementing NRP increased liver utilization from 39% to 71% [49]. These findings highlight NRP's potential not only to improve quality but also to address supply-demand imbalances in liver transplantation.

5 | Limitations

These findings should be interpreted cautiously, as comparisons across studies are limited by substantial heterogeneity in study design, donor selection, procurement techniques, viability criteria, and imaging protocols. Many reports include highly selected donor and recipient populations, and centers vary widely in their thresholds for proceeding with NRP, performing viability assessment, and determining transplant suitability. Differences in local policies—such as the use of protocol-based cholangiography, definitions of NAS, or criteria for reporting arterial complications—further complicate direct comparison. Additionally, several studies originate from high-experience centers with well-developed NRP infrastructures, which may not be generalizable to broader practice. Taken together, these methodological and selection differences underscore the need for cautious interpretation when synthesizing outcomes across heterogeneous cohorts.

6 | Conclusion

NRP has emerged as a transformative strategy in controlled DCD liver transplantation, demonstrating consistent improvements in graft viability, reductions in biliary complications, and enhanced graft survival. Beyond these clinical benefits, NRP expands the donor pool by facilitating safe utilization of extended-criteria and elderly donors. Comparative evidence shows that NRP outperforms traditional cold storage, achieves outcomes comparable to DBD grafts, and offers favorable biliary results—particularly lower NAS rates—relative to other machine perfusion approaches. However, these comparisons should be interpreted with caution given substantial heterogeneity in donor selection, procurement techniques, and outcome assessment across studies. As protocols mature and evidence continues to grow, broader adoption of NRP has the potential to redefine the standard of care in DCD liver transplantation and meaningfully narrow the gap between donor availability and recipient need.

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The authors declare no conflicts of interest.

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