

US Liver Transplant Outcomes After Normothermic Regional Perfusion vs Standard Super Rapid Recovery

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IMPORTANCE Normothermic regional perfusion (NRP) is an emerging recovery modality for transplantable allografts from controlled donation after circulatory death (cDCD) donors. In the US, only 11.4% of liver recipients who are transplanted from a deceased donor receive a cDCD liver. NRP has the potential to safely expand the US donor pool with improved transplant outcomes as compared with standard super rapid recovery (SRR).

OBJECTIVE To assess outcomes of US liver transplants using controlled donation after circulatory death livers recovered with normothermic regional perfusion vs standard super rapid recovery.

DESIGN, SETTING, AND PARTICIPANTS This was a retrospective, observational cohort study comparing liver transplant outcomes from cDCD donors recovered by NRP vs SRR. Outcomes of cDCD liver transplant from January 2017 to May 2023 were collated from 17 US transplant centers and included livers recovered by SRR and NRP (thoracoabdominal NRP [TA-NRP] and abdominal NRP [A-NRP]). Seven transplant centers used NRP, allowing for liver allografts to be transplanted at 17 centers; 10 centers imported livers recovered via NRP from other centers.

EXPOSURES cDCD livers were recovered by either NRP or SRR.

MAIN OUTCOMES AND MEASURES The primary outcome was ischemic cholangiopathy (IC). Secondary end points included primary nonfunction (PNF), early allograft dysfunction (EAD), biliary anastomotic strictures, posttransplant length of stay (LOS), and patient and graft survival.

RESULTS A total of 242 cDCD livers were included in this study: 136 recovered by SRR and 106 recovered by NRP (TA-NRP, 79 and A-NRP, 27). Median (IQR) NRP and SRR donor age was 30.5 (22-44) years and 36 (27-49) years, respectively. Median (IQR) posttransplant LOS was significantly shorter in the NRP cohort (7 [5-11] days vs 10 [7-16] days; $P < .001$). PNF occurred only in the SRR allografts group ($n = 2$). EAD was more common in the SRR cohort (123 of 136 [56.1%] vs 77 of 106 [36.4%]; $P = .007$). Biliary anastomotic strictures were increased 2.8-fold in SRR recipients (7 of 105 [6.7%] vs 30 of 134 [22.4%]; $P = .001$). Only SRR recipients had IC (0 vs 12 of 133 [9.0%]; $P = .002$); IC-free survival by Kaplan-Meier was significantly improved in NRP recipients. Patient and graft survival were comparable between cohorts.

CONCLUSION AND RELEVANCE There was comparable patient and graft survival in liver transplant recipients of cDCD donors recovered by NRP vs SRR, with reduced rates of IC, biliary complications, and EAD in NRP recipients. The feasibility of A-NRP and TA-NRP implementation across multiple US transplant centers supports increasing adoption of NRP to improve organ use, access to transplant, and risk of wait-list mortality.

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Liver wait-list mortality remains unacceptably high. For every 4.1 deceased donor liver transplants in the US in 2022, 1 wait-listed candidate died or was removed from the list because they were too sick to transplant.¹ Organ scarcity is the principal driver that limits organ transplant procedures and contributes to wait-list mortality. In the US, it is evident that controlled donation after circulatory death (cDCD) organ use underperforms, with only 11.4% of liver recipients who are transplanted from a deceased donor receiving a cDCD liver.^{1,2} In 2022, only 1015 of 4777 cDCD livers (21.2%) were transplanted; for cDCD donors 50 years or older, this declines even further, with just 11.5% resulting in a transplant (251 of 2185 livers).¹ The recent National Academies of Science, Engineering, and Medicine report highlights the need to improve cDCD organ use, recommending that cDCD donors constitute approximately 45% of the US deceased donor pool with a parallel increase in organ offer acceptance.³

The most immediate approach to increase access to liver transplant is to improve use of extended-criteria allografts. Historically, extended-criteria liver allografts such as those from older donors, macrosteatotic livers, or cDCD donors have been underutilized given concerns of primary nonfunction (PNF), early allograft dysfunction (EAD), and/or ischemic cholangiopathy (IC).⁴ With cDCD liver allografts, the concern for IC, EAD, PNF, and the need for retransplant stems from the inherent period of prerecovery ischemia.^{5,6} Normothermic regional perfusion (NRP) is an alternative recovery method to standard cDCD super rapid recovery (SRR) that allows for in situ perfusion of potentially transplantable organs with oxygenated blood after the initial period of ischemic tissue injury.⁷⁻¹¹ Preclinical studies have demonstrated that NRP acts to mitigate, if not reverse, tissue injury incurred during the period of functional donor warm ischemia time (f-DWIT).¹²⁻¹⁴ Early experience with livers transplanted from NRP donors in the US is promising, and more mature international data show favorable outcomes for NRP livers compared with those recovered via SRR.^{7-11,15-20}

In the US, recent resurgence in interest around NRP has paralleled the growing field of cDCD heart transplantation but its growth has remained constrained by logistical, operational, and ethical concerns.^{21,22} Although international data are supportive of NRP as a recovery method, the social, legal, and medical climates in respect to organ transplant and use vary in these countries as compared with the US. Understanding the impact of NRP on US recipient and allograft outcomes will better inform the conversation around and guide the national development of NRP. This US multicenter study comparing cDCD liver allograft outcomes after recovery via NRP vs SRR was undertaken to inform these knowledge gaps.

Methods

Study Design and Population

This was a multi-institutional, retrospective, observational cohort study of transplant recipient and graft outcomes of liver allografts transplanted from cDCD donors recovered via NRP or SRR in the US.

Key Points

Question What are the US liver transplant outcomes from controlled donation after circulatory death (DCD) donor livers recovered with normothermic regional perfusion (NRP) vs standard super rapid recovery (SRR)?

Findings In this multicenter cohort study including 136 livers recovered with SRR and 106 livers recovered with NRP, there was comparable patient and graft survival in liver transplant recipients of DCD donors recovered by NRP vs SRR, with reduced rates of ischemic cholangiopathy in NRP recipients.

Meaning Results suggest that NRP improves DCD liver allograft outcomes and has the potential to increase DCD organ use.

All DCD donors were Maastricht category III, or cDCD donors.¹ Seventeen centers were included; institutional review board approval was obtained at each institution with center-specific data use agreements per institutional requirements. Centers provided data on abdominal NRP (A-NRP), thoracoabdominal NRP (TA-NRP), and up to 10 of each center's most recent, contemporaneous SRR cDCD liver allograft recipients from January 1, 2017, to May 10, 2023. Patient written informed consent was not obtained owing to the use of deidentified donor and recipient data collated for analysis. Simultaneous liver-kidney (SLK) recipients were included in both NRP and SRR cohorts. Other multiorgan transplants and recipients of ex situ machine-perfused livers were excluded. Patients self-identified with the following race and ethnicity categories: African American, White, or other race, which included Alaska Native or American Indian, Asian, Native Hawaiian or other Pacific Islander. Race and ethnicity were included as descriptive variables in our study to determine differences or similarities in donor or recipient populations. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Donor Definitions and Data Sources

Donor selection was at the discretion of each transplant center per their standard cDCD practice. There was no study-defined limitation on donor criteria including age or duration of f-DWIT. For study analysis, f-DWIT was defined as sustained systolic blood pressure (SBP) less than 80 mm Hg or oxygen saturation less than 80% until initiation of NRP or aortic flush with cold preservation fluid in the SRR cohort per the Organ Procurement and Transplantation Network (OPTN) agra definition.²³ All allografts were stored in static cold storage (SCS); allografts perfused with ex situ dual-oxygenated hypothermic machine perfusion (D-HOPE) or normothermic machine perfusion (NMP) were excluded. Donor demographics, allograft data, and f-DWIT were abstracted from United Network for Organ Sharing DonorNet. Final liver allograft acceptance was based on transplant center discretion at intraoperative evaluation; biochemical assessment and biopsy were not performed in all cases. As a retrospective study, no specific acceptance criteria were mandated for study inclusion.

Recipient Selection and Study End Points

Recipient selection was at the discretion at each transplant center per their standard cDCD practice. All patients were first-time transplant recipients and greater than 90 days from their index liver transplant at the time of data analysis. Recipient data included demographics, etiology of liver disease, Model of End-Stage Liver Disease (MELD) at the time of transplant, and allocation MELD, which incorporates applicable MELD exception points according to OPTN policy. The primary end point was IC. IC was determined by radiographic imaging (endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography) when prompted by clinical assessment. Secondary end points included PNF, EAD, biliary anastomotic strictures, posttransplant length of stay (LOS), and graft and patient survival.²⁴ Posttransplant LOS was defined as the interval between transplant and hospital discharge. Delayed kidney allograft function (DGF) in SLK recipients was defined as needing dialysis within 7 days of kidney transplant. Immunosuppression was at the discretion of the recipient center and not altered because of recovery technique.

DCD Recovery Methods

Standard cDCD protocols were observed in all cases, including premortem heparin, withdrawal of life-sustaining therapies, and observation of a 2- to 5-minute no-touch period, in accordance with OPTN and organ procurement organization (OPO) and donor hospital guidelines.^{25,26} A-NRP and TA-NRP were conducted as previously described with attention to methods to insure no meaningful cerebral blood flow, including clamping of the aortic arch vessels with cerebral venting of the innominate artery (TA-NRP) or supraceliac aortic occlusion balloon/aortic cross-clamp (A-NRP).^{7,10,15,27} For A-NRP, antemortem or postmortem cannulation was determined by transplant center and OPO practice standards. TA-NRP or A-NRP duration was per center protocol. Temperature was maintained 35 to 37 °C, and targeted pump flow was 2.0 to 5.0

L/min depending on A-NRP or TA-NRP in situ perfusion. Mean arterial pressure was maintained between 50 and 80 mm Hg. Arterial blood gas and lactate levels were trended every 15 to 30 minutes while on NRP. Not all protocols sent laboratory blood samples for liver transaminase levels. Seven centers performed NRP in this study with 1 center performing A-NRP alone, 4 centers performing TA-NRP alone, and 2 centers performing both A-NRP and TA-NRP. Of the 7 centers performing NRP, 2 centers performed antemortem and postmortem sheath/cannula placement, and 5 centers performed postmortem cannulation only. The remaining centers used liver grafts from donors in whom cardiac teams performed TA-NRP.

Statistical Analysis

Categorical variables are described as percentages and continuous variables as median (IQR). Categorical variables were compared using χ^2 test and continuous variables using *t* test or Mann-Whitney *U* test, as appropriate. Survival was analyzed via the Kaplan-Meier method and compared with a log-rank test. A 2-sided *P* value $\leq .05$ was considered significant. Statistical analyses were performed with Stata, version 18.0 (StataCorp).

Results

Across 17 centers, a total of 242 cDCD livers were included in this study: 106 liver allografts were recovered via NRP and 136 were recovered via SRR. Of the 106 NRP liver allografts, 79 were recovered using TA-NRP, and 27 were recovered using A-NRP. Donor demographics are shown in Table 1. Median (IQR) donor age was younger in the NRP cohort, 30.5 (22-44) years, as compared with the SRR cohort, 36 (27-49) years (*P* = .04). Donor race and ethnicity were identified with the following categories: 25 African American (10.3%), 199 White (82.2%), and 18 other (7.4%). When comparing A-NRP donors with the

Table 1. Donor Characteristics in Normothermic Regional Perfusion (NRP) and Standard Super Rapid Recovery (SRR) Cohorts

Characteristic	NRP (n = 106)	SRR (n = 136)	<i>P</i> value
Age, median (IQR), y	30.5 (22-44)	36 (27-49)	.04
A-NRP only vs SRR	48 (41-58)	36 (27-49)	<.001
Race, No. (%)			
African American	11 (10.4)	14 (10.3)	.98
White	84 (79.2)	115 (84.6)	.28
Other ^a	11 (10.4)	7 (5.2)	.12
Sex, No. (%)			
Female	22 (21.2)	41 (30.1)	.12
Male	82 (78.9)	95 (69.9)	
BMI, median (IQR) ^b	29.4 (24.9-32.3)	27.4 (23.4-31.2)	.41
Cause of death, No. (%)			
Anoxia	56 (52.8)	61 (44.9)	.22
Cerebrovascular/stroke	7 (6.6)	24 (17.7)	.01
Head trauma	41 (38.7)	46 (33.8)	.44
Other/NA ^c	2 (1.9)	5 (3.7)	.41
f-DWIT, median (IQR), min	22.0 (18.0-25.0)	19.0 (16.0-23.0)	.01

Abbreviations: BMI, body mass index; f-DWIT, functional donor warm ischemia time; NA, not available.

^a Other race includes Alaska Native or American Indian, Asian, Native Hawaiian or other Pacific Islander.

^b Calculated as weight in kilograms divided by height in meters squared.

^c Other cause of death includes central nervous system tumor and other per Organ Procurement and Transplantation Network criteria and is not specified.

SRR cohort, the median (IQR) age of the A-NRP cohort was significantly older, at 48 (41-58) years vs 36 (27-49) years, respectively ($P < .001$). Median (IQR) f-DWIT was comparable in the NRP (22.0 [18.0-25.0] minutes) and SRR (19.0 [16.0-23.0] minutes) cohorts; interestingly, the longest f-DWIT in the NRP cohort was 53 minutes vs 35 minutes in the SRR group (Table 1). Ten donors in the NRP cohort exceeded the traditional 30 minutes of f-DWIT as compared with 7 donors in the SRR cohort. Median (IQR) duration of NRP was 62 (51-89) minutes.

Recipient demographics are detailed in Table 2. The underlying etiologies of end-stage liver disease were comparable; significantly more patients were transplanted for hepatocellular carcinoma from donors who underwent NRP (31 of 106 [29.3%]) as compared with SRR (25 of 136 [18.4%]; $P = .047$). Laboratory MELD-Na⁺ at transplant was similar across donor recovery modality. SLK recipients accounted for 7 of 106 recipients (6.6%) in the NRP cohort compared with 11

of 136 recipients (8.1%) in the SRR cohort. Median (IQR) length of follow-up was 316 (189-508) days in the NRP group and 438 (284-631) days in the SRR group ($P < .001$).

Table 3 details early recipient outcomes. No intraoperative deaths occurred in either group. There were no cases of PNF from NRP allografts; 2 PNF cases were reported from SRR allografts ($P = .21$). Median (IQR) cold ischemic time was comparable between groups at 298.5 (247-349) minutes in the SRR cohort and 289 (218-355) minutes in the NRP group. There was no significant difference in intraoperative transfusion of packed red blood cells or rates of early reoperation for bleeding. Peak AST and ALT levels in the first 7 days posttransplant were significantly lower in the NRP cohort (NRP vs SRR: AST, 930 [419-1768] U/L vs 1906 [1188-4660] U/L; ALT, 646 [315-1085] vs 1056 [586-1897] U/L; $P < .001$; to convert to microkatal per liter, multiply by 0.0167). EAD was more common in SRRs (123 of 136 [56.1%] vs 77 of 106 [36.4%]; $P = .007$); EAD was not evaluable in 42 recipients (13

Table 2. Recipient Characteristics in Normothermic Regional Perfusion (NRP) and Standard Super Rapid Recovery (SRR) Cohorts

Characteristics	NRP (n = 106)	SRR (n = 136)	P value
Age, median (IQR), y	60 (53-66)	58 (51.5-63)	.07
Race, No. (%)			
African American	2 (1.9)	9 (6.6)	.08
White	82 (77.4)	99 (73.0)	.44
Other ^a	22 (20.8)	28 (20.4)	.95
Sex, No. (%)			
Female	30 (28.3)	42 (30.9)	.66
Male	76 (71.7)	94 (69.1)	
BMI, median (IQR) ^b	29.4 (22.7-32.3)	27.9 (24.8-31.7)	.497
Follow-up, median (IQR), d	316.0 (189.0-508.0)	438.0 (284.0-631.0)	<.001
Etiology of liver disease, No. (%)			
NASH	33 (31.1)	32 (23.5)	.19
HCV	14 (13.2)	22 (16.2)	.52
HBV	1 (0.9)	6 (4.4)	.11
EtOH	42 (39.6)	52 (38.2)	.83
Cholestatic	4 (3.8)	13 (9.6)	.08
Other ^c	15 (14.2)	19 (14.0)	.97
MELD-Na ⁺ at transplant, median (IQR)	20 (15-24)	20 (15-23)	.79
Hepatocellular carcinoma, No. (%)	31 (29.3)	25 (18.4)	.047
SLK, No. (%)	7 (6.6)	11 (8.1)	.66

Abbreviations: BMI, body mass index; EtOH, ethyl alcohol; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD-Na⁺, Model for End-Stage Liver Disease-Sodium; NASH, nonalcoholic steatohepatitis; SLK, simultaneous liver-kidney.

^a Other race includes Alaska Native or American Indian, Asian, Native Hawaiian or other Pacific Islander.

^b Calculated as weight in kilograms divided by height in meters squared.

^c Other liver disease etiology includes autoimmune hepatitis, α -1 antitrypsin deficiency, polycystic liver disease, cryptogenic cirrhosis, liver adenomatosis, cholangiocarcinoma, hemochromatosis, and acute hepatic necrosis/fulminant liver failure.

Table 3. Recipient and Graft Outcomes From Liver Allografts Between Normothermic Regional Perfusion (NRP) and Standard Super Rapid Recovery (SRR) Cohorts

Characteristic	NRP (n = 106)	SRR (n = 136)	P value
Cold ischemic time, median (IQR), min	289 (218-355)	298.5 (247-349)	.70
Intraoperative PRBC transfusion	6 (3-9)	6 (3-10)	.60
Early allograft dysfunction, No. (%)	77 (36.4)	123 (56.1)	.007
Peak AST, median (IQR), U/L	930 (419-1768)	1905.5 (1188-4660)	<.001
Peak ALT, median (IQR), U/L	646 (315-1085)	1055.5 (586-1897)	<.001
Primary nonfunction, No. (%)	0	2 (1.5)	.21
Reoperation for bleeding, No. (%)	7 (6.6)	13 (9.6)	.41
RRT within 7 d, No./total No. (%)	8/82 (9.8)	12/135 (8.9)	.83
Posttransplant length of stay, median (IQR), d	7 (5-11)	10 (7-16)	.001
Readmission, No. (%)	40 (38.0)	65 (47.8)	.18

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PRBC, packed red blood cell; RRT, renal replacement therapy.

SI conversion factor: To convert ALT and AST to microkatal per liter, multiply by 0.0167.

SRR, 29 NRP), all of whom were missing a day-7 international normalized ratio (INR) value, owing to discharge or cessation of INR checks with normalization of the INR. In liver-only recipients, the need for renal replacement therapy after transplant was similar. For SLK recipients, DGF was reported in 2 of 6 recipients (33.3%) receiving an NRP allograft and in 5 of 10 recipients (50.0%) receiving SRR allografts ($P = .52$). Median (IQR) posttransplant LOS was shorter in NRP recipients at 7 (5-11) days as compared with 10 (7-16) days ($P = .001$) for SRR recipients. There was no significant difference in readmissions between the groups. There was 1 recipient in-hospital mortality at posttransplant day 31 in the NRP cohort and 3 in-hospital deaths at posttransplant days 54, 76, and 125 in the SRR cohort.

Excluding graft losses and patient deaths less than 90 days after transplant (NRP, 104; SRR, 133), IC occurred in 12 SRR liver allografts (9.0%) and in 0 NRP allografts ($P = .002$) (Figure 1). Biliary anastomotic strictures were significantly higher and increased 2.8-fold in SRR recipients (SRR, 30 of 134 [22.4%] vs NRP, 7 of 105 [6.7%]; $P = .001$). Overall patient and graft survival were not significantly different between groups (Figure 2). There was 1 NRP graft loss unrelated to death (hepatic artery thrombosis); for SRR livers, graft loss was secondary to IC ($n = 2$), PNF ($n = 2$), chronic rejection ($n = 1$), acute cellular rejection ($n = 1$), and portal vein thrombosis ($n = 1$). IC was associated with graft loss (8 of 12 [66.7%] and 1 of 225 [0.4%]; $P < .001$). IC-free survival was significantly improved in NRP recipients (Figure 2A). Patient and graft survival were comparable between cohorts.

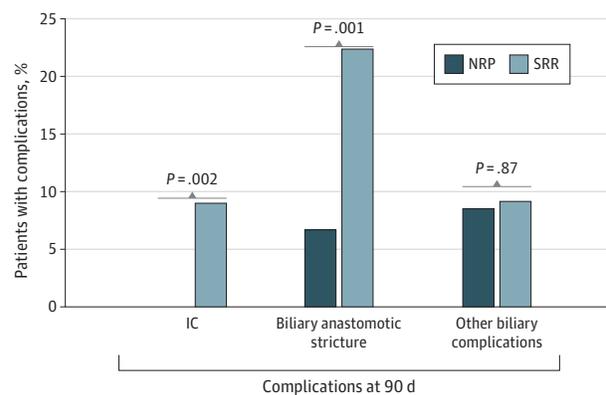
Risk adjustment for donor age between the NRP and SRR cohort demonstrated that donor age was not significantly associated with the primary end point of IC. Unadjusted risk estimates for NRP compared with SRR demonstrate significant association between NRP and reduction in incidence of anastomotic stricture (risk estimate, 0.25; 95% CI, 0.10-0.59; $P = .002$), incidence of EAD (risk estimate, 0.45; 95% CI, 0.25-0.80; $P = .007$), peak AST level (risk estimate, -1826; 95% CI, -2420 to -1232; $P < .001$), peak ALT level (risk estimate, -540; 95% CI, -762 to -319; $P < .001$), and LOS (risk estimate, -6.0; 95% CI, -9.6 to -2.4; $P = .001$). Adjusting for age, NRP was still associated with all of these end points—*anastomotic stricture* (risk estimate, 0.26; 95% CI, 0.11-0.62; $P = 0.003$), *EAD* (risk estimate, 0.45; 95% CI, 0.25-0.80; $P = .007$), *peak AST level* (risk estimate, -1692; 95% CI, -2279 to -1105; $P < .001$), *peak ALT level* (risk estimate, -504; 95% CI, -727 to -282; $P < .001$), and *LOS* (risk estimate, -5.4; 95% CI, 9.0 to -1.9; $P = .003$) (eTable 1 in Supplement 1).

A subgroup analysis of TA-NRP compared with A-NRP was completed to discern differences between the 2 regional perfusion modalities. There were no significant differences between f-DWIT, NRP duration, peak AST level, peak ALT level, EAD, biliary anastomotic stricture, and other biliary complications between groups (eTable 2 in Supplement 1).

Discussion

The findings of this cohort study suggest comparable patient and graft survival in liver transplant recipients of cDCD do-

Figure 1. Ischemic Cholangiopathy and Biliary Complications in Normothermic Regional Perfusion (NRP) Compared With Standard Super Rapid Recovery (SRR) Groups



Percentage of recipients with ischemic cholangiopathy (IC), biliary anastomotic stricture, and other biliary complications in the NRP cohort compared with the SRR cohort.

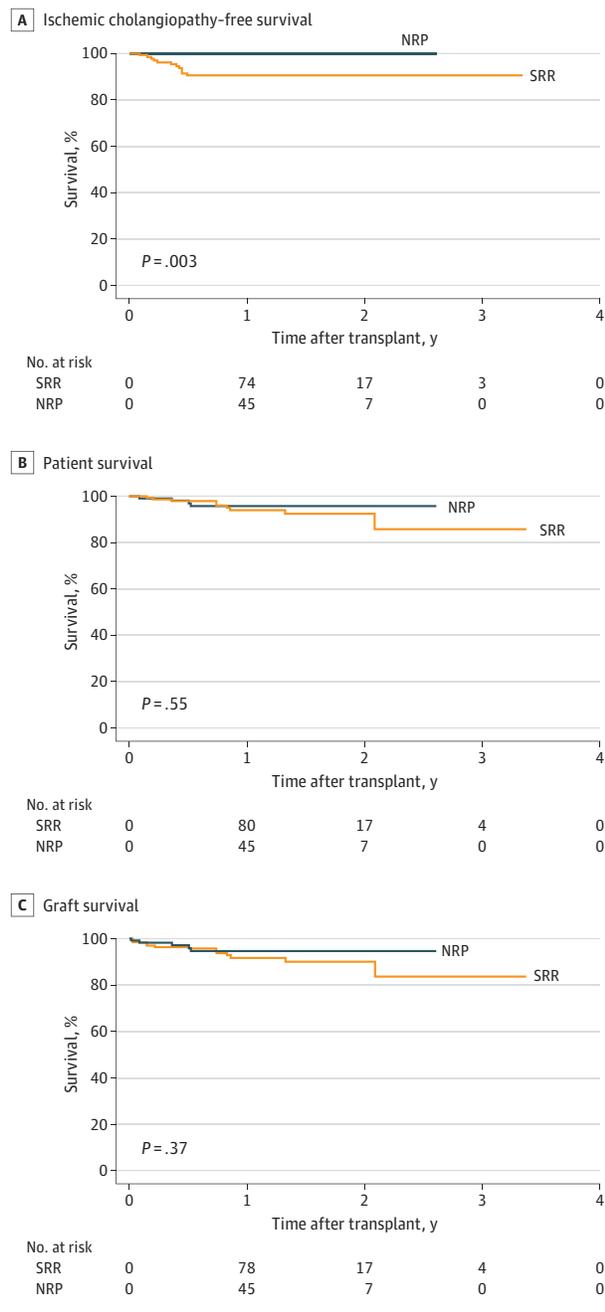
nors recovered by NRP vs SRR, with reduced rates of IC, biliary complications, and EAD in NRP recipients. These data capture the early US experience with NRP and include both cardiothoracic and noncardiothoracic donors. TA-NRP and A-NRP were included in the study as both allow oxygenated perfusion to liver allografts; inclusion of both modalities is reflective of the emerging practice of NRP within the US.

Our findings were similar to those reported in studies from Europe.^{8-10,17-20,28-33} International studies have demonstrated that NRP-cDCD provides similar outcomes as donation after brain death liver allografts, with similar rates of EAD, PNF, and IC, and found significantly better graft survival at 1- and 3-year posttransplant for NRP liver allografts.^{30,33} The largest risk-adjusted study to date demonstrated a reduction in overall biliary complications, ischemic-type biliary lesions, graft loss, and patient death from grafts recovered with A-NRP compared with SRR.¹⁰ Similar smaller studies have supported a reduction in biliary complications and IC; some demonstrated a reduction in EAD after NRP compared with SRR.^{17,34}

Important differences in these studies are related to the practice patterns and use of cDCD donors more broadly in these countries. cDCD livers constitute 11.4% of liver transplants in the US and 22.8% in the UK. In a global study on cDCD use, these 2 countries had the highest rate of cDCD nonuse, between 70% and 80%.² In Spain, Italy, France, Belgium, and Switzerland, there was a near 2-fold reduction in cDCD nonuse to 30% to 40%. This can be explained, in part, by earlier adoption of perfusion technologies, including NRP. For example, in Italy, where the mandatory hands-off period is 20 minutes, NRP has been described as inseparable from DCD.^{35,36} France established their DCD protocol in 2015, mandating NRP as the recovery modality for all DCD donors, resulting in 59% liver allograft use from NRP-DCD donors.³⁷ The outcomes data from Spain has led to an evolution in practice over time, where NRP for DCD donors is not mandatory but is almost universal.¹⁰

Internationally, use of liver allografts from cDCD donors older than 50 years is significantly greater than that in the US.

Figure 2. Kaplan-Meier Survival Curves for Ischemic Cholangiopathy–Free, Patient, and Graft Survival



A, Ischemic cholangiopathy–free survival. B, Patient survival. C, Graft survival. The number at risk in each cohort is detailed out to 3 years for each survival analysis. NRP indicates normothermic regional perfusion; SRR, standard super rapid recovery.

This is driven by concerns of IC and PNF from older DCD donors.^{38,39} International studies comparing SRR and NRP have a median age ranging from 57 to 60 years of age compared with 30 to 48 years of age in our study.^{9,10,30,33} Use of liver allografts from cDCD donors older than 50 years in the US is minimal, accounting for only 4.5% of all cDCD liver allografts transplanted.¹ Many of the TA-NRP cases in our study were younger donors being considered as heart donors. The in-

creased age in the A-NRP cohort demonstrates that there is ample opportunity for safe expansion of NRP to older, abdominal-only donors driven by collaborative efforts of liver transplant centers and OPOs.

There are key differences in definitions. For example, the definition of f-DWIT in international studies is 30 minutes from an SBP of either 50 or 60 mm Hg; the OPTN definition in the US is more conservative, with an f-DWIT trigger at an SBP less than 80 mm Hg or oxygen saturation less than 80%.^{10,19} Moreover, center and surgeon practice around definitions of f-DWIT within the US are variable and changing with the advent of advance recovery and perfusion modalities.^{5,25,40} Together, these international data reflect increased comfort with use of cDCD allografts on a broader scale than seen in the US. These practice differences are imperative when considering implementation of an NRP program. Understanding the nuances of the US and international data is critical to optimally balancing safe recipient and graft outcomes with improving organ utilization, access to transplant, and risk of wait-list mortality.

Rigorous evaluation of NRP outcomes requires discussion of other emerging technologies that offer opportunities to expand cDCD use including NMP and D-HOPE. Studies comparing the relative benefits of these emerging modalities remain limited, and each has demonstrated benefits in the cDCD transplant space. NMP allows for ex situ perfusion of organs after recovery, facilitates metabolic and cellular allograft recovery, offers the ability to monitor graft viability for extended durations, aids in late reallocation of declined organs, and relieves logistical constraints.^{41,42} Two major studies compared outcomes of in situ NRP with ex situ NMP.^{19,31} A single-center retrospective study found that NRP and NMP-cDCD livers had lower mean model for early allograft function scores compared with SCS-cDCD liver allografts. NRP livers also had lower rates of nonanastomotic biliary stricture (0%) compared with the SCS (14%) and NMP (11%) groups, respectively, and NRP livers had a reduced risk of transplant failure compared with SCS cDCD liver allografts.¹⁹ In a multicenter study, the COPE consortium found rates of EAD, nonanastomotic biliary stricture, 30-day graft loss, and 2-year patient survival to be comparable between both perfusion modalities.³¹ The recently published D-HOPE-DCD trial demonstrated a significant reduction in nonanastomotic biliary strictures from 18% in SCS-DCD livers to 6% in recipients of D-HOPE-DCD liver allografts.⁴³ A comparative study of D-HOPE and NRP demonstrated similar posttransplant outcomes, with overall similar rates of nonanastomotic biliary strictures, PNF, and patient and graft survival rates.⁴⁴ A principal limitation of D-HOPE and NMP is that as ex situ devices, they treat 1 organ. NRP can promote metabolic recovery of all perfused organs. In TA-NRP, this can be upward of 8 organs for distinct recipients. Importantly, in situ and ex situ machine perfusion are not mutually exclusive. Their combined benefits can facilitate multiorgan transplant from cDCD donors and provide additional organ metabolic recovery and viability assessment, particularly in the setting of extreme prolonged f-DWIT.^{36,45,46}

The findings of this study highlight the promising allograft and patient outcomes of NRP-cDCD liver allografts and demonstrate the safety and feasibility of implementing TA-NRP and

A-NRP at multiple US transplant centers and across multiple OPOs. In prior publications that detail the early US TA-NRP experience, TA-NRP was performed by 2 mobile TA-NRP programs with the subsequent liver allografts being transplanted at several different centers.^{7,11} In this study, TA-NRP and A-NRP were performed by 7 different centers with liver allografts transplanted at 17 transplant centers. The members of this consortium recommend that implementation of an NRP program, either by a transplant center or OPO, includes infrastructure assessment and development, ethics review, and surgeon and staff training. The accumulating evidence supports continued advancement of NRP as an effective recovery method for DCD donors but recognizes that barriers to widespread adoption exist, including infrastructure development, technical learning curve, and ethical concerns.^{21,22,27} To address some of the barriers, technical and ethical standards need to be established, monitored, and continually re-evaluated to ensure that the transplant community continues to respect legal and ethical principles and honor the gift of donation.

Although this study highlights the changing US NRP transplant landscape, it generates questions that will require much broader and more granular data collection. Pressing specific translational and clinical questions to be addressed are as follows: (1) what duration of NRP results in sufficient metabolic and cellular allograft recovery to result in improved patient outcomes?; (2) what are the most appropriate point-of-care tests to determine organ viability while on NRP?; (3) what is the impact of NRP on organ usage across the US?; (4) what is the impact of NRP on the harm of nondonation (emotional harm to donor families when they have pursued DCD donation, but ultimately no organs are transplanted owing to traditional limitations on DCD organ acceptance?); (5) how to define and implement technical NRP standards?; and (6) what are the ethical and legal implications of NRP?

Strengths and Limitations

This study is strengthened by the broad geographic participation with 17 US sites, as well as the size of the analytic cohort.

Several limitations are noted, including the limitations associated with the retrospective study design and inherent variations in transplant center cDCD acceptance practices. Although a randomized clinical trial comparing cDCD liver transplant outcomes based on recovery modality would allow for a more powerful, definitive conclusion, a study of that nature is improbable in light of international data and data presented herein. Additionally, graft acceptance by centers may have been dependent on the availability of NRP; availability of different perfusion modalities is likely to impact organ acceptance practices moving forward. Granular data around liver viability while on NRP is not currently present in United Network for Organ Sharing DonorNet; future work will be geared toward improved organ viability assessment while on NRP and the relationship with organ transplant outcomes.

Differences in donor age, length of follow-up, and indication for transplant existed between the 2 cohorts. IC was independently associated with SRR irrespective of donor age, and risk adjustment for donor age demonstrated a significant benefit with NRP across several secondary outcomes. As recipient selection was at the discretion of each transplant center, the higher proportion of patients with hepatocellular carcinoma in the NRP cohort likely reflects low native MELD recipients and may have been more represented in the NRP group owing to surgeon comfort with a newer perfusion approach in the US.

Conclusions

Findings of this cohort study suggest that the feasibility of A-NRP and TA-NRP implementation across multiple US transplant centers supports increasing adoption of NRP to improve organ use, access to transplant, and risk of wait-list mortality. In addition, ongoing granular evaluation of NRP-recovered allografts will inform the transplant communities' understanding of how this perfusion technology can redefine traditional limitations on cDCD allografts and impact cDCD liver allograft use.

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Invited Commentary

Normothermic Regional Perfusion to Expand Liver Transplant From Controlled Donation After Circulatory Death

Laura Llado, MD, PhD

Controlled donation after circulatory death (cDCD) donors, who are declared dead following cardiorespiratory arrest, are a growing source of organs. DCD is the best field for donor expansion to help to alleviate the organ shortage. Already in



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2009, the American Society of Transplant Surgeons recommended focusing efforts on increasing the number of organs from cDCD.¹ However, in the US, only 11.4% of liver recipients who undergo transplant from a deceased donor receive a cDCD liver. Other sources of donor expansion, such as living donors, account for less than 10% of liver donation in US² and even less in Europe.

In this issue of *JAMA Surgery*, Brubaker et al³ reflect current practices in the US in the field of cDCD. Although it is a retrospective study, where groups are not comparable, their results deserve consideration. As suggested by the authors, their results may help to solve some of the gaps that limit the improvement of cDCD organ use.

Over the last decade, international data from Europe has demonstrated that the use of abdominal normothermic regional perfusion (A-NRP) overcomes the traditionally worse outcomes of liver transplant after cDCD compared with donation after brain death (DBD).⁴

The study from Brubaker et al³ includes only 27 cases of A-NRP. Thoracoabdominal NRP (TA-NRP) is limited to young

donors and is related to some logistical and ethical concerns. TA-NRP will be also an interesting field of expansion allowing for the recovery of lungs and hearts simultaneously with abdominal organs with similar results.⁵

As shown by Spanish experience, A-NRP has become the standard technique in cases of cDCD, allowing for the expansion of indications without increasing complications.⁶ In the same way, in France, the use of NRP is mandatory and has achieved similar results.

Finally, considering costs, transplant physicians have to keep in mind that NRP is simultaneously used to recover cDCD kidneys, pancreases, and hearts; therefore, the benefits of NRP in terms of posttransplant outcomes extend to these organs. The cost of the cDCD process increases only \$2699.60 to \$5399.10 compared with standard DBD or cDCD with super rapid recovery.

In my opinion, all these aspects should be kept in mind, when other sources of organ expansion are being considered, such as ex situ perfusion or living donor.

This study³ can be considered a first step demonstrating the feasibility of A-NRP and TA-NRP implementation across multiple US transplant centers and supports an increasing adoption of NRP to improve organ use, organ availability, and decrease the risk of wait-list mortality. This is the way to achieve the recommendation of the National Academies of