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Liver Transplantation Outcomes From Controlled Circulatory Death Donors

SCS vs in situ NRP vs ex situ NMP

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Objective: To compare the outcomes of livers donated after circulatory death (DCD) and undergoing either in situ normothermic regional perfusion (NRP) or ex situ normothermic machine perfusion (NMP) with livers undergoing static cold storage (SCS).

Summary of Background Data: DCD livers are associated with increased risk of primary nonfunction, poor function, and nonanastomotic strictures (NAS), leading to underutilization.

Methods: A single center, retrospective analysis of prospectively collected data on 233 DCD liver transplants performed using SCS, NRP, or NMP between January 2013 and October 2020.

Results: Ninety-seven SCS, 69 NRP, and 67 NMP DCD liver transplants were performed, with 6-month and 3-year transplant survival (graft survival non-censored for death) rates of 87%, 94%, 90%, and 76%, 90%, and 76%, respectively. NRP livers had a lower 6-month risk-adjusted Cox proportional hazard for transplant failure compared to SCS (hazard ratio 0.30, 95% Confidence Interval 0.08–1.05, $P = 0.06$). NRP and NMP livers had a risk-adjusted estimated reduction in the mean model for early allograft function score of 1.52 ($P < 0.0001$) and 1.19 ($P < 0.001$) respectively compared to SCS. Acute kidney injury was more common with SCS (55% vs 39% NRP vs 40% NMP; $P = 0.08$), with a lower risk-adjusted peak-to-baseline creatinine ratio in the NRP ($P = 0.02$). No NRP liver had clinically significant NAS in contrast to SCS (14%) and NMP (11%, $P = 0.009$), with lower risk-adjusted odds of overall NAS development compared to SCS (odds ratio = 0.2, 95%CI 0.06–0.72, $P = 0.01$).

Conclusion: NRP and NMP were associated with better early liver function compared to SCS, whereas NRP was associated with superior preservation of the biliary system.

Keywords: donation after circulatory death, liver transplantation, nonanastomotic biliary stricture, normothermic machine perfusion, normothermic regional perfusion, transplant outcomes

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Liver transplantation is an established treatment for end-stage and acute liver failure, but is restricted by the availability of suitable organs. In the UK, 8% of patients either die or become too sick for liver transplantation within a year postregistration.[1] Donation after circulatory death (DCD) has immense potential to be a source of livers, although traditionally they have been considered suboptimal due to inferior outcomes. When compared to donation after brain death (DBD), DCD livers have a higher risk of primary nonfunction (PNF) (3.5% vs 1.3%), biliary complications [odds ratio (OR) = 2.5], acute kidney injury (AKI) (53% vs 32%), and inferior graft and patient survival [3-year hazard ratio (HR) 2.3].[2–5] DCD status is an independent risk factor for graft loss after liver transplantation.[6–8]

In 2019/20, 40% of deceased organ donors in the UK were DCD donors, but they only translated into 19% of liver transplants.[1] While there was a high utilization rate for DBD livers (78%) from the time an organ is offered, only 27% of the DCD livers were actually transplanted.[1] The situation is similar in the United States, where, in 2019, 23% of donors were DCD, but they accounted for only 9% of liver transplants. The livers recovered from DCD donors were four times more likely to be discarded than those recovered from DBD donors (30% vs 7%, respectively).[9]

The hypotension and catecholamine release during the agonal phase of DCD retrieval combined with a period of asystole results in rapid depletion of ATP stores.[10] This explains the poor tolerance of subsequent cold ischemia and adverse transplant outcomes. In situ normothermic regional perfusion (NRP) and ex situ normothermic machine perfusion (NMP) are two techniques which have

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increasingly gained acceptance in the functional assessment and resuscitation of DCD livers.[11–16]

In this study, we present our experience and compare the impact on clinical outcomes of in situ and ex situ normothermic perfusion to assess and preserve DCD livers compared to standard static cold storage (SCS).

METHODS

Data Collection

This single-center study included retrospective analyses of all consecutive adult patients (aged > 16 years) who underwent orthotopic liver transplantation from controlled (Maastricht category III and IV) DCD donors.[17] The study period was from January 1, 2013 to October 31, 2020 with a minimum of 6-months of follow up. The three arms of the study comprised DCD livers retrieved and undergoing SCS alone, NRP, and NMP. Livers with sequential NRP and NMP (n = 9) were excluded from the analysis.

Donor data available at the time of organ offer enabled calculation of the US-donor risk index[6] and the UK donor liver index (UK-DLI)[7] to provide surrogates of organ quality. The UK-DCD Risk Score, a risk assessment in DCD liver transplantation based on both donor and recipient parameters was also calculated.[18]

Contemporaneously kept recipient records were accessed from the hospital's medical record database (Hyperspace 2014 IU 1, Epic Systems Corporation, Wisconsin, USA). The laboratory model for end-stage liver disease score at admission was calculated as an indication of the severity of liver disease.[19] The UK end-stage liver disease score, which is used in the UK to prioritize graft allocation, was also calculated.[20]

The study endpoints included early graft function as indicated by PNF, early allograft dysfunction (EAD), and model for early allograft function (MEAF); biliary complications [bile leak, anastomotic and nonanastomotic strictures (NAS)]; postoperative AKI, and the incidence of chronic kidney disease (CKD) at 6-month; total length of intensive therapy unit (ITU) and hospital stay; hepatic artery thrombosis (HAT) and postoperative complication rates within 30 days, graded by Clavien-Dindo (CD) classification. Patient, graft (censored for death), and transplant survival (graft survival noncensored for death) were also recorded at 6-month, 1- and 3-year after transplantation.

Definitions and Surgical Techniques

DCD retrieval in the UK is undertaken by dedicated National Organ Retrieval Service teams using rapid sterno-laparotomy.[21] Retrieval commenced after verification of death (no sooner than 5 minutes after circulatory arrest). No intervention, including heparinization and prior cannulation, was permitted before death declaration. University of Wisconsin (UW) preservation solution (Belzer UW, Bridge to Life, London, UK) was used for dual aortic and portal perfusion with concomitant topical cooling with slushed ice. The gall bladder was opened, and the bile duct was divided and flushed with UW after vascular perfusion. Livers undergoing SCS (or with subsequent NMP) were considered if the donor functional warm ischemia time (fWIT), defined as the time interval between systolic pressure <50 mm Hg and start of in situ cold perfusion, was less than 30 minutes. fWIT is a surrogate for warm ischemic damage and was not considered relevant in NRP-DCD livers because function could be assessed on reperfusion in situ. Cold ischemia time (CIT) was defined as the time interval between cold in situ aortic flush with UW and reperfusion in the recipient, or the start of ex situ NMP if it was used. Periods of normothermic perfusion were not included in the calculation of cold ischemic time. Anastomotic WIT was defined as the time interval between the allograft being removed from the ice and the restoration of blood flow by releasing the vascular clamps in the recipient. The liver utilization was defined as usage rate from the point liver had been accepted and proceeding to asystole after treatment withdrawal.

The standard implantation technique included either classical or cava-sparing modified piggyback caval anastomosis. All livers were reperfused on the portal vein. Biliary anastomosis was routinely duct to duct, with Roux-en-Y hepaticojejunostomy forrecipients with primary sclerosing cholangitis, duct size discrepancy, or prior transplant.

EAD was defined using the criteria by Olthoff et al,[22] and the MEAF score by Pareja et al,[23] the latter being a continuous score from 0 to 10 based on bilirubin, international normalized ratio, and alanine transaminase in the first three posttransplant days. MEAF has been validated and correlates with graft loss in DCD liver transplantation.[24] PNF was defined as graft loss or death within 7 days posttransplant excluding HAT, technical issues, or acute rejection. HAT was defined as thrombosis of the hepatic artery diagnosed on imaging.

All posttransplantation data were collected during routine clinical follow-up of the recipients. Those recipients who had persistently raised alkaline phosphatase or as clinically indicated by persistent pruritus, jaundice, or cholangitis underwent magnetic and/or endoscopic resonance cholangiopancreatography (MRCP or ERCP). Six recipients in the NMP group also underwent protocol MRCP at 6 months as part of a clinical trial or service evaluation. MRCP studies were reviewed by two hepatobiliary radiologists, and a consensus was reached. NAS was defined as the presence of any biliary stricture, dilatation, or irregularity of the intra- or extrahepatic bile ducts and/or cast on MRCP away from the biliary anastomosis in the presence of patent arterial vasculature. Clinically significant NAS are defined as those requiring endoscopic and/or surgical intervention. Anastomotic stricture was defined as any stricture at the biliary anastomosis requiring treatment, either endoscopically or surgically. Biliary anastomotic leak was defined as a bile leak confirmed by laparotomy, and no leaks were managed nonoperatively. All biliary strictures were recorded in the livers surviving for 30 days, and anastomotic bile leaks in livers surviving for 7 days.

Posttransplant AKI was defined according to the Risk/Injury/Failure/Loss/End-stage criteria as a peak serum creatinine level within the first 7 days after transplantation ≥2 times the immediate preoperative (baseline) value or the need for renal replacement therapy.[4,25] In addition, we also compared the ratio of peak-to-baseline creatinine between groups. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation at 3 and 6 months. CKD was defined according to the NKF-K/DOQI and the KDIGO CKD guidelines as eGFR <60 mL/min/1.73m^2 for >3months.[26]

Acute cellular rejection was defined as histological evidence of rejection recorded within the first 6-month after transplantation on clinical suspicion.[27] Major postoperative complications in the first 30 days after transplantation were documented using the CD classification.[28] Severe complications were defined as grade ≥IIIa.

This study was supported by an independent patient/public panel review and was approved by the University of Cambridge Human Biology Research Ethics Committee (HBREC.2020.23).

Normothermic Regional Perfusion

NRP was performed on controlled DCD donors as described previously, and was either performed using abdominal perfusion alone or as simultaneous thoraco-abdominal perfusion for recovery of the heart.[14,29] The technique is summarized in the Supplemental Digital Content, http://links.lww.com/SLA/D726.

Normothermic Machine Perfusion

The technique for NMP has been described previously,[11,12] and is summarized in the Supplemental Digital Content, http://links.lww.com/SLA/D726. We previously published our biochemical

criteria favoring transplantation.[11,30] Five livers underwent continuous NMP after establishing machine perfusion at the donor hospital. The rest of the livers were placed on the machine at the recipient center after being flushed with cold UW solution and transported on ice. NMP ceased immediately before recipient hepatectomy to keep the anhepatic phase short. The liver was flushed with cold UW, as it was removed from the NMP machine and stored on ice slush before implantation.

Statistical Analysis

The follow-up ended on April 2021. Discrete variables were reported as absolute numbers and percentages. Continuous variables are presented as mean and standard deviation or as median and interquartile range when data were nonparametric. Comparisons between three groups were performed using χ^2 test test or Fisher exact test for categorical variables and the Kruskal-Wallis test for independent continuous variables. The Kaplan-Meier method was used to assess the time to graft failure (censored and noncensored for death), death, and development of NAS. The log-rank test was used to evaluate differences between survival curves. Multivariate analyses were performed after adjusting for donor/recipient age, UK-DLI, UK end-stage liver disease score, CIT, WIT, and UK-DCD index. A binary logistic regression model was used for NAS; and linear regression model for MEAF score, and peak-to-baseline creatinine ratio. Similarly, a risk-adjusted Cox proportional hazard regression model was used for 6-month transplant survival.

Statistical analyses were performed using IBM SPSS statistics software version 26.0 (IBM Corp., Armonk, NY, USA) and Prism version 9.2.0 (GraphPad Software, La Jolla, CA, USA).

RESULTS

Between January 2013 and October 2020, 120 proceeding DCD donors underwent NRP, leading to 83 liver transplants with 69% utilization rate (Fig. 1). Five NRP livers were transplanted in centers outside of Cambridge and were excluded from the analysis. During this timeframe, 99 DCD livers underwent NMP, and 76 were transplanted (utilization rate 77%). After excluding 9 livers which underwent sequential NRP and NMP, 69 NRP and 67 NMP livers were included in the study. These were compared with 97 SCS liver transplants performed from DCD donors from January 2013 to January 2019, after which no SCS-DCD liver transplants were performed at our institution.

Donor and Recipient Characteristics

The donor and preservation characteristics of the three groups are summarized in Table 1. The most common cause of donor death in SCS (48%) and NRP (42%) groups was cerebrovascular accidents, whereas hypoxic brain damage was the dominant cause in NMP (54%). Trauma as a cause of death was more prevalent in the NRP (SCS 11%, NRP 19%, NMP 9%).

There was no difference in the UK-DLI scores between the three groups ($P = 0.407$). However, the median US-donor risk index, which also considers the CIT and donor hospital location, was lower in the NRP (SCS 2.5, NRP 2.2, NMP 2.5; $P < .001$). A greater proportion of liver transplants in NRP were either high-risk or futile according to the UK-DCD risk score (SCS 43%, NRP 52%, NMP 30%; $P = 0.002$).

The asystolic phase and fWIT was higher in the NRP, as explained by the additional time required to canulate and establish NRP perfusion. The median CIT was 30 minutes longer in the SCS group than in the NRP and NMP groups ($P < 0.001$).

Alcoholic liver disease was the most common cause of chronic liver disease in all groups, with a similar distribution of hepatocellular carcinoma (Table 2). Notably, NRP livers were more likely to be used for recipients with prior transplants (SCS 1%, NRP 12%, NMP 5%; $P = 0.008$). There was no difference in surgeons or surgical techniques used for liver transplantation between the three groups.

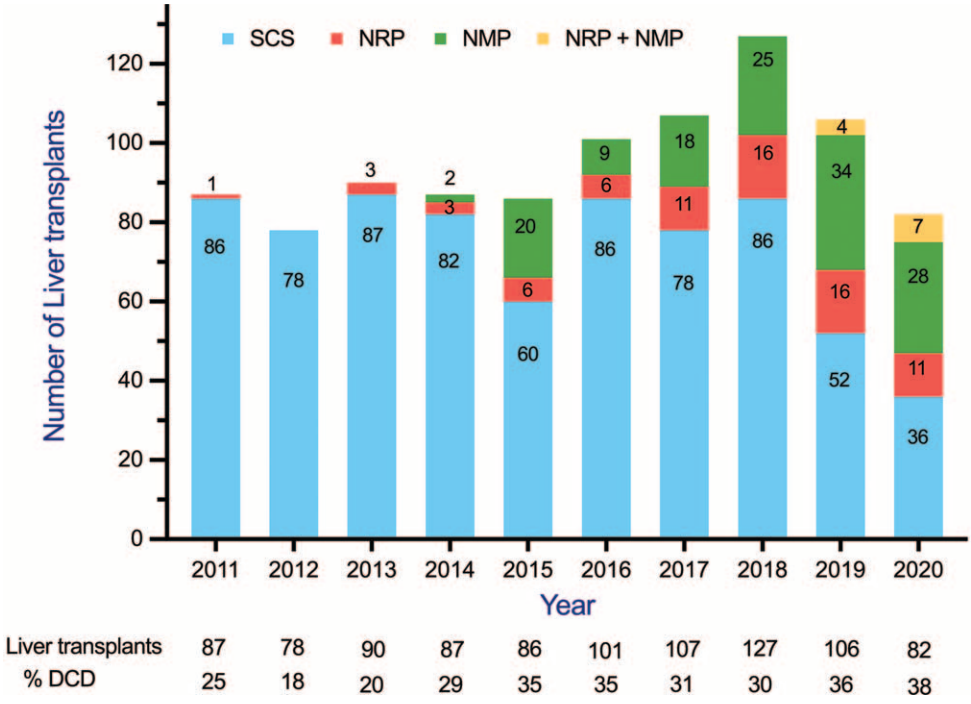

FIGURE 1. Impact of normothermic perfusion devices on liver transplantation in Cambridge (2011-20). SCS and NMP include both DBD and DCD livers.

TABLE 1. Donorand Preservation Parameters

	SCS (n = 97)	NRP (n = 69)	NMP (n = 67)	*P*
Age, years	50 (36–59)	51 (33–58)	52 (29–60)	0.639
Sex, male, n (%)	51 (53)	45 (65)	39 (58)	0.266
BMI, kg/m^2	26 (23–29)	25 (22–28)	25 (22–28)	0.40
US DRI*	2.5 (2.0–3.0)	2.2 (1.8–2.5)	2.5 (2.0–2.9)	<0.001
UK DLI†	2.0 (1.7–2.2)	1.9 (1.7–2.1)	2.0 (1.6–2.3)	0.407
UK DCD risk score, n (%)				
Low-risk	55 (57)	33 (48)	47 (70)	0.002
High-risk	41 (42)	27 (39)	17 (25)	
Futile	1 (1)	9 (13)	3 (5)	
Cause of donor death, n (%)‡				
Hypoxic brain damage	32 (33)	24 (35)	36 (54)	0.08
Cerebrovascular accident	47 (48)	29 (42)	23 (34)	
Trauma	11 (11)	13 (19)	6 (9)	
Others	7 (7)	3 (4)	2 (3)	
Asystolic phase, min§	12 (10–14)	15 (13–18)	12 (10–14)	<0.001
>15 min, n (%)#	12 (12)	29 (42)	7 (10)	<0.0001
Functional WIT (Fwit), min‖	15 (11–18)	19 (15–24)	15 (12–18)	<0.0001
>30 min, n (%)	0	3 (4)	2 (3)	
Total WIT (twit), min¶	26 (22–31)	29 (23–33)	26 (22–31)	0.186
>30 min, n (%)#	24 (25)	26 (38)	19 (28)	0.191
NRP duration, min		133 (121–143)		
NMP duration, min			460 (330–569)	
CIT, min	430 (397–474)	399 (341–471)	396 (346–441)	<0.001
Total preservation time, min	430 (397–474)	534 (456–615)	940 (815–1050)	<0.001
Anastomotic WIT, min	44 (37–51)	41 (32–51)	43 (34–55)	0.399

Continuous data are median (interquartile range) and categorical data are number (percentage).
*Feng et al. *Am J Transplant.* 2006;6:783–790.
†Collett et al. *Transplantation.* 2017;101:786–792.
‡Schlegel et al. *J Hepatol.* 2018;68:456–464.
§Time from mechanical asystole to in situ perfusion of cold UW or start of NRP. Duration includes 5 minutes of ''no touch'' period.
‖fWIT: Time from donor systolic BP below 50 mm Hg to in situ perfusion of cold UW or start of NRP.
¶tWIT: Time from withdrawal of treatment to in situ perfusion of cold UW or start of NRP.
#''High risk donor'' as defined by Schlegel et al. A multicenter outcome analysis to define global benchmarks for donation after circulatory death liver transplantation. *J Hepatol.* October 2021.
BMI indicates body mass index; DRI, donor risk index.

Initial Graft Function

Five (5%) livers in the SCS and one (1.5%) liver in the NMP were lost to PNF compared to none in the NRP (Table 2). Similarly, the SCS livers sustained greater ischemia-reperfusion injury (Table 3) with higher peak alanine transaminase (710, interquartile range 424–1276, $P < 0.001$) posttransplant and with more recipients having EAD (SCS 21%, NRP 14%, NMP 11%; $P = 0.20$). The MEAF score was significantly higher for the SCS ($P < 0.001$) than for both NRP and NMP. In multivariate linear regression, adjusting for donor and recipient risk factors (Table 4), both NRP and NMP interventions led to lower MEAF with a risk-adjusted estimated reduction in the mean MEAF score of 1.52 in the NRP livers and 1.19 in the NMP livers ($P < 0.001$).

Biliary and Arterial Complications

MRCP, performed mainly for clinical indications, was performed in 35% of the NRP (Table 3) as compared to half of the patients with SCS and NMP ($P = 0.021$). The NRP group had lower rates of overall biliary complications (SCS 42%, NRP 22%, NMP 37%; $P = 0.024$); a lower incidence of NAS, both overall (SCS 25%, NRP 6%, NMP 19%; $P = 0.009$) and clinically significant (SCS 14%, NRP 0, NMP 11%; $P = 0.009$). There was no difference in the incidence of bile leak ($P = 0.204$) or anastomotic stricture rate ($P = 0.098$). Biliary strictures in NRP livers, both anastomotic and non-anastomotic, were mostly asymptomatic and diagnosed biochemically, with only five patients (8%) with anastomotic strictures requiring either endoscopic or surgical intervention.

Most of the NAS developed in the first year posttransplant (Fig. 2), and none of the livers in the NRP group were lost to NAS. In the multivariate binary logistic regression model after risk adjustment (Table 4), there were statistically lower odds of having NAS when NRP was used compared to SCS (OR = 0.20, 95%CI 0.06–0.72, $P = 0.01$). The same benefit was not achieved with NMP (OR = 0.80, 95%CI 0.34–1.98, $P = 0.19$).

The incidence of HAT was similar across the three groups, with comparable graft loss due to HAT. Out of seven HAT in the SCS group, 3 (3%) were early (≤30 days) and 4 (4%) late (>30 days); four grafts were lost, one relisted and one salvaged with thrombectomy and revascularization. Similarly, out of five HAT in NMP group, one (2%) had early and 4 (6%) late HAT; out of these, three grafts were lost and one relisted. One graft with late HAT in each SCS and NMP group is still functioning.

AKI and CKD

The SCS recipients sustained a higher rate of AKI (SCS 55%, NRP 39%, NMP 40%; $P = 0.08$), with a higher peak-to-baseline creatinine ratio in the first seven days posttransplant compared to recipients of NRP and NMP livers. The risk-adjusted estimated reduction in mean creatinine ratio between SCS and NRP was significant at 0.51 (standard error 0.2, $P = 0.02$). Between SCS and NMP, there was a reduction of 0.36 (standard error 0.2, $P = 0.09$).

The percent eGFR decrease after 3- and 6-month was similar in the three groups, as was the rate of CKD at 6-month (SCS 33%, NRP 31%, NMP 25%; $P = 0.60$).

TABLE 2. Recipient and Operative Parameters

	SCS (n = 97)	NRP (n = 69)	NMP (n = 67)	*P*
Age, years	56 (50–62)	56 (48–63)	59 (51–63)	0.480
Sex, male, n (%)	56 (58)	48 (70)	45 (67)	0.238
BMI, kg/m^2	26 (24–29)	28 (24–33)	28 (24–33)	0.012
UKELD	55 (53–60)	55 (52–59)	53 (51–56)	0.01
Lab-MELD	16 (13–20)	14 (10–18)	14 (10–16)	0.007
Cause of liver disease, n (%)				
Alcohol	35 (36)	24 (35)	18 (27)	
Nonalcoholic fatty liver disease	12 (12)	14 (20)	15 (22)	
Primary sclerosing cholangitis	12 (12)	6 (9)	4 (6)	
Hepatitis C	14 (15)	9 (13)	12 (18)	
Primary biliary cholangitis	13 (14)	4 (6)	6 (9)	
Hepatic artery thrombosis	0	2 (3)	2 (3)	
Others	11 (11)	10 (14)	10 (15)	
Hepatocellular carcinoma, n (%)	22 (23)	18 (26)	19 (28)	0.703
Prior liver transplant, n (%)	1 (1)	8 (12)	3 (5)	0.008
Biliary reconstruction, n (%)				
Duct to duct	69 (73)	43 (62)	44 (69)	0.351
Roux-en-Y	26 (27)	26 (38)	30 (31)	
Arterial reconstruction, n (%)	25 (26)	20 (29)	14 (21)	0.581
Caval anastomosis, n (%)				
Side to side cavocavostomy	77 (80)	50 (72)	53 (80)	0.472
Classical caval replacement	20 (20)	9 (28)	13 (20)	
Reexploration, n (%)	27 (28)	19 (28)	22 (33)	0.738
Graft loss, 6-month, n (%)	9 (9)	2 (3)	6 (9)	0.246‡
PNF	5	0	1	
HAT	3	1	2	
NAS	0	0	1	
Others*	1	1	2	0.90‡
Death, 6-month, n (%)	4 (4)	2 (3)	4 (6)	
Sepsis	1	0	0	
Malignancy	1	0	0	
Hepatic venous outflow obstruction	0	0	2	
Others†	2	2	2	
Transplant failure, 6-month, n (%)	13 (13)	4 (6)	7 (10)	0.218‡

Continuous data are median (interquartile range) and categorical data are number (percentage).
*Immune mediated graft loss-1; hepatic artery dissection during stenting for stenosis-1; technical issue-2.
†COVID-19-1; graft vs host disease-1; cerebrovascular accident-1; PNF with multiorgan failure-2; unknown reason-1.
‡Log-rank *P* value.
BMI indicates body mass index; UKELD, United Kingdom model for end-stage liver disease; MELD, model for end-stage liver disease.

ITU and Hospital Stay

Severe postoperative complications, as defined by CD classification, were comparable in the three groups with a higher incidence in the SCS (68%, $P = 0.354$). There was no difference in the ITU stay between the groups, with a median stay of 2 days. However, the NRP group had a shorter overall hospital stay (15 days; P = 0.05).

Graft and Patient Survival

There were 17 (7.3%) liver graft failures in the first 6-month posttransplant with PNF (3.4%) as the most common cause, followed by HAT (2.6%). The 6-month death-censored graft survival (SCS 91%, NRP 97%, NMP 92%, long-rank P = 0.246) and patient survival (SCS 96%, NRP 97%, NMP 94%, log-rank P = 0.90) were similar (Table 2). In the NRP group, 6% (95%CI 2–15) patients experienced 6-month transplant failure (graft failure noncensored for death) as compared to 13% (95%CI 8–22) in SCS and 10% (95%CI 5-21) in NMP groups (log-rank $P = 0.218$). Overall, in a Cox proportional hazard regression analysis adjusted for risk factors, the NRP had a lower risk of 6-month transplant failure compared to SCS (HR 0.3, 95%CI 0.08–1.05, P = 0.06; Table 4). No such difference was evident in the NMP recipients. The better transplant survival in NRP was sustained beyond 6-months (Fig. 3A). With a median follow-up of 38 months (SCS 54 months; NRP 28 months; NMP 24 months), the NRP had better transplant actuarial survival at 1-and 3-year, 93% and 90% compared to the SCS 84% and 76%, respectively (HR 0.4, 95%CI 0.2–0.8; log-rank $P = 0.034$). There was no difference in the 1- and 3-year transplant survival rates of NMP (88% and 76%, respectively) compared to SCS recipients. Similarly, there was no difference in 1- and 3-year death-censored graft survival rates (Fig. 3B) of SCS 88% and 86%, NRP 97% and 94%, NMP 91% and 82%, respectively (log-rank $P = 0.154$). The 1-year patient survival was similar (94%) as was the 3-year patient survival (SCS 88%, NRP 94%, NMP 90%; log-rank $P = 0.665$, Fig. 3C). The NRP group had significantly lower rate of retransplantation during the study period (SCS 18%; NRP 4%; NMP 12%; $P = 0.04$).

DISCUSSION

In this study, we report our experience with in situ and ex situ normothermic perfusion in DCD liver transplantation. This is the first direct comparison of SCS with both in situ and ex situ normothermic preservation techniques in DCD liver transplantation from a single center, and one of the largest series of NRP and DCD-NMP to date.

TABLE 3. Transplant Outcomes

	SCS (n = 97)	NRP (n = 69)	NMP (n = 67)	*P*
Initial graft function				
Peak ALT, 1–7 day, U/L	710 (424–1276)	491 (268–755)	360 (216–727)	<0.001
EAD (Olthoff criteria), n (%)*	19 (21)	10 (14)	7 (11)	0.20
MEAF score	5.5 (4.3–7.0)	4.1 (2.5–5.6)	3.7 (2.6–5.7)	<0.001
Biliary complications				
MRCP, n (%)*,‡	50 (57)	23 (35)	33 (52)	0.021
Overall biliary complications, n (%)*,§	38 (42)	15 (22)	23 (37)	0.024
Anastomotic bile leak, n (%)*	10 (11)	6 (9)	2 (3)	0.204
Anastomotic stricture, n (%)†	15 (17)	5 (8)	13 (21)	0.098
Nonanastomotic stricture (NAS), n (%)†				
Overall	22 (25)	4 (6)	12 (19)	0.009
Clinically significant‖	12 (14)	0	7 (11)	0.009
Renal function				
Peak-to-baseline creatinine ratio, 1–7 day	2.1 (1.4–2.9)	1.7 (1.3–2.2)	1.7 (1.4–2.2)	0.08
Acute kidney injury, n (%)	53 (55)	27 (39)	26 (40)	0.08
RRT in 7 days posttransplant, n (%)	18 (20)	11 (16)	9 (14)	0.622
Baseline eGFR, mL/min/1.73 m^2	99 (86–110)	96 (81–112)	100 (84–111)	0.264
% eGFR fall at 3-month from baseline	29 (9–44)	26 (12–38)	24 (8–41)	0.600
% eGFR fall at 6-month from baseline	32 (13–47)	26 (10–39)	23 (13–39)	0.442
Chronic kidney disease, n (%)	28 (33)	20 (31)	15 (25)	0.60
Other outcomes				
HAT, n (%)¶	7 (8)	1 (1)	5 (8)	0.18
ITU stay, days	2 (1–4)	2 (1–4)	2 (2–4)	0.364
Hospital stay, days	18 (15–30)	15 (13–23)	19 (13–29)	0.05
Acute cellular rejection, n (%)	28 (31)	19 (28)	20 (32)	0.844
CD grade for complication, n (%)#				
I-II (mild)	31 (32)	28 (41)	28 (42)	0.354
≥IIIa (severe)	66 (68)	41 (59)	39 (58)	
Retransplant rate, n (%)	17 (18)	3 (4)	8 (12)	0.04

Continuous data are median (interquartile range) and categorical data are number (percentage).

*Grafts surviving 7 days posttransplant, n = 222; SCS 90, NRP 69, NMP 63.

†Grafts surviving 30 days posttransplant, n = 217; SCS 88, NRP 66, NMP 63.

‡MRCPas clinically indicated for persistently raised alkaline phosphatase or symptoms (pruritus, jaundice, cholangitis). Six recipients in NMP group underwent protocol MRCP at 6-month.

§Overall biliary complications include anastomotic bile leaks, anastomotic strictures, and NAS.

‖Clinically significant NAS defined as strictures requiring endoscopic or/and surgical intervention.

¶Grafts with PNF excluded, n = 225; SCS 92, NRP 69, NMP 64.

#Clavien-Dindo classifications: postoperative complications in first 30 days posttransplant.

ALT indicates alanine transaminase; RRT, renal replacement therapy.

Our results show better early allograft function with both NRP and NMP than with SCS. There was no PNF in the NRP group and one in the NMP group. Two grafts were lost in the NMP group due to technical issues, a combination of complicated hepatectomy and implantation of the marginal liver in a hostile surgical field. Better early graft function was also reflected in the incidence of AKI, which was higher in the SCS group, although the difference was not statistically significant. Overall, both NRP and NMP were superior to SCS in terms of early transplant outcomes.

NRP was effective in minimizing biliary complications and abolishing clinically significant NAS, which has been documented in previous studies.[14,16] With an overall NAS rate of 6% in the NRP group, the odds of NAS development were 80% lower than those in the SCS group. NMP livers were used if the bile pH >7.5 and/or biliary glucose was lower than the perfusate, as described previously.[11,31] However, there remained a significant incidence of biliary strictures. The rate of clinically significant NAS after NMP was 11%, higher than the 6% reported in a recent series of hypothermic oxygenated machine perfusion (HOPE), a series with shorter cold times, lower donor risk indices, and a study endpoint at 6-month.[32]

Six month graft and patient survival were similar across the three groups as was 1- and 3-year actuarial survivals with a caveat that this study may not be adequately powered to show differences. NRP livers had superior transplant survival at 1- and 3-year. After adjusting for risk factors, there was relatively better 6-month transplant survival in the NRP group with 70% less risk of transplant failure compared to SCS and NMP. There was a bimodal distribution of graft loss, with most of the early loss due to PNF and HAT. Even though the maximum risk of NAS is in the first year posttransplant, these grafts are lost slowly in the later years. As is evident from Figure 2, 6-months and 1-year are a relatively short times to capture graft loss from NAS.

In both the NMP and NRP groups, there was a greater proportion of transplants classified as futile by the UK-DCD risk score. There was one ''futile'' graft lost in the NRP group due to HAT and one unfortunate 30-day death due to COVID-19. All the others were functioning at the end of the study follow-up period, demonstrating that these techniques facilitate high-risk transplants, including complex retransplants.

NRP was predominantly undertaken in locoregional donors (86%), whereas NMP livers were often from remote hospitals outside our region (78%), after decline by at least one other center. We acknowledge that this selection bias is a limitation, as it favors NRP for locally procured livers and does not favor NMP which has

TABLE 4. Risk-adjusted Analysis of Outcomes Following Liver Transplantation

Preservation	N	Estimate	Standard Error	*P*
MEAF score*				
SCS	97	0	Reference	
NRP	69	−1.52	0.35	<0.0001
NMP	64	−1.19	0.34	0.0007
Peak-to-baseline creatinine ratio*,†				
SCS	97	0	Reference	
NRP	69	−0.51	0.2	0.02
NMP	65	−0.36	0.2	0.09
		NAS		
		Odds Ratio	**95%CI**	
Nonanastomotic biliary stricture (NAS)‡				
SCS	88	1.00	Reference	
NRP	66	0.20	0.06–0.72	0.01
NMP	63	0.82	0.34–1.98	0.19
		Risk of failure		
		HR	**95%CI**	
Transplant survival, 6-month§				
SCS	97	1.00	Reference	
NRP	69	0.30	0.08–1.05	0.06
NMP	67	1.00	0.37–2.70	0.90

Risk-adjusted for UK-DCD risk index, recipient age, donor age, UK DLI, UKELD, CIT, and WIT.
*Generalized linear regression model. The estimate is the difference in mean compared to the reference group (SCS). Negative sign shows reduction in the mean.
†Ratio of peak creatinine from 1 to 7 days posttransplant to baseline creatinine before transplant.
‡Binary logistic regression model.
§Cox proportional hazards model. Transplant survival defined as graft survival, noncensored for death.
UKELD indicates United Kingdom model for end-stage liver disease.

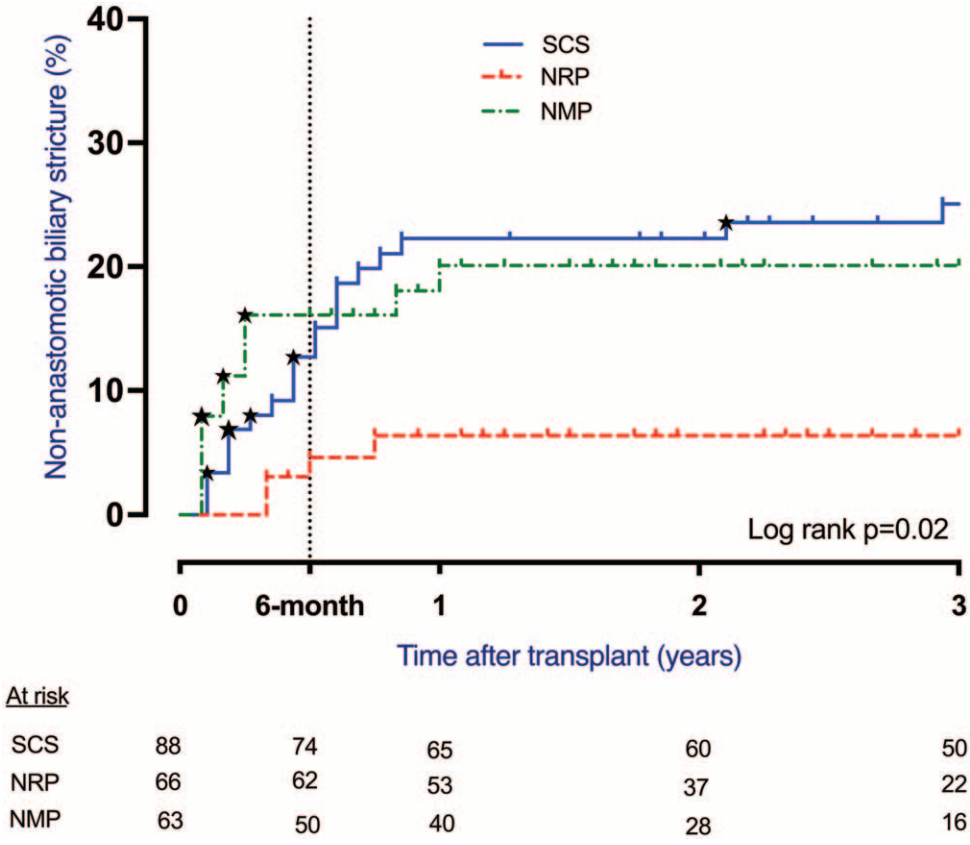

FIGURE 2. Cumulative incidence of nonanastomotic biliary stricture (NAS) with 3-year follow up. NAS as defined by MRCP based on clinical indications. Star indicate the livers which were subsequently lost to NAS (SCS: 6, NRP: 0, NMP 4). *NRP vs SCS: HR 0.3 (95%CI 0.1–0.6), P = 0.005; NMP vs SCS: HR 0.9 (95%%CI 0.4–1.7), P = 0.69; NMP vs NRP: HR 3.5 (95%CI 1.3–9.3), P = 0.02.*

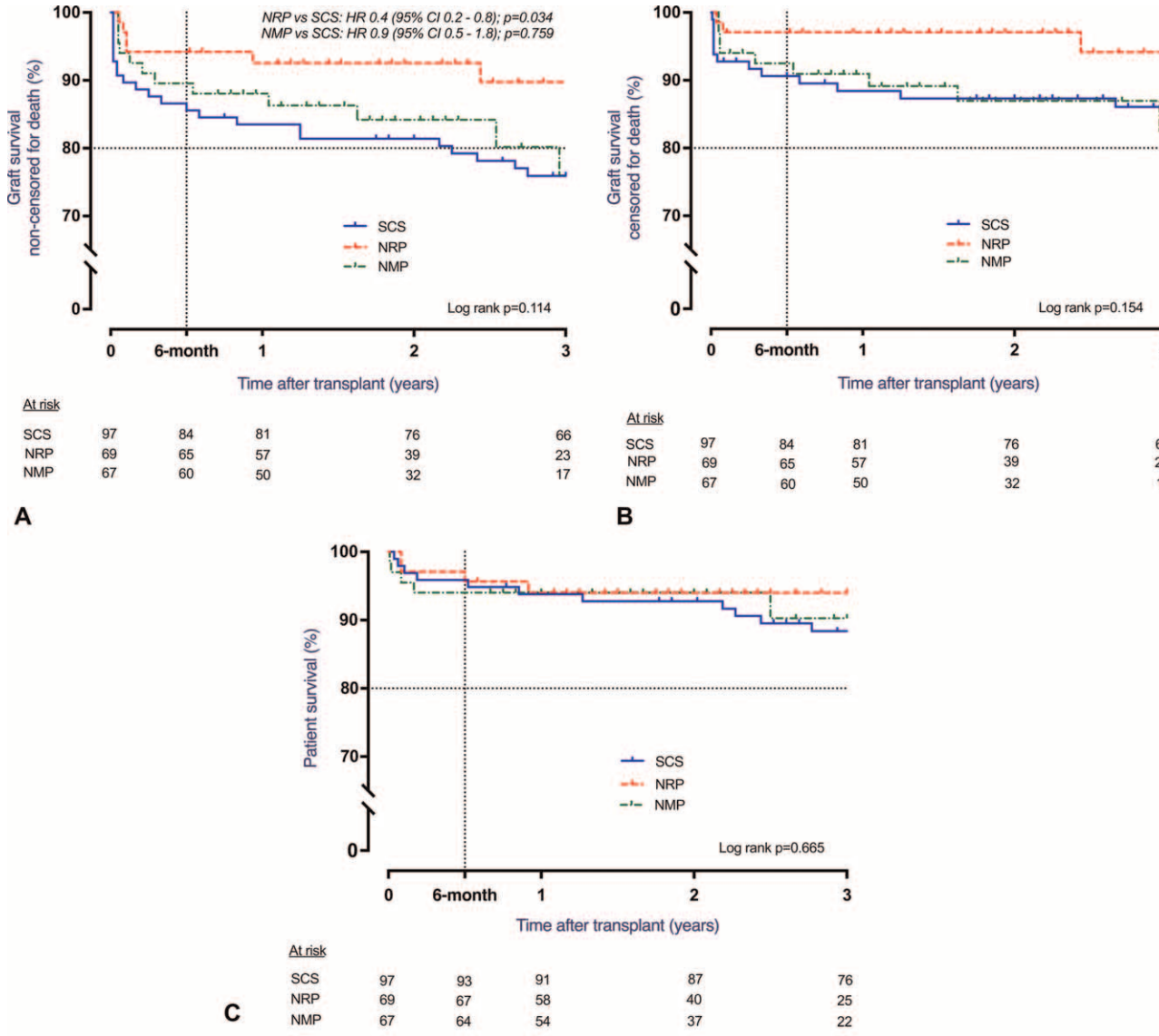

FIGURE 3. Kaplan-Meier survival estimates at 3-year posttransplant by the type of DCD liver preservation. (A) Graft survival, noncensored for death; (B) Graft survival, censored for death; (C) Patient survival.

less than ideal DCDs. Another limitation is the long CIT for all groups in the study, with that for the SCS group being 30 minutes longer than NMP and NRP. To counter this, NRP had significantly longer asystolic and functional warm ischemia than the other two groups, with more of the NRP livers falling in the "high risk" category (SCS 43%, NRP 64%, NMP 37%) as defined in a recent benchmarking paper.[33] It is noteworthy that the superior outcomes of NRP livers were maintained after adjusting for CIT and other risk factors. Another important limitation of the study is its retrospective nature, although the data analyzed were prospectively recorded.

SCS remains the benchmark for organ preservation worldwide, and is both relatively simple and inexpensive. With the increase in the risk profiles of both donor livers and recipients, it is necessary to investigate dynamic preservation techniques, both normothermic (NRP and NMP) and hypothermic (HOPE). Normothermic perfusion techniques have revolutionized liver transplantation in our center, allowing increasingly marginal grafts to be used with acceptable results and efficiently managing operating logistics. Nevertheless, the incidence of cholangiopathy with NMP remains a concern and has prompted us to look at ways to address this issue.[34] Livers which were previously considered marginal can achieve equivalent results, translating to increased utilization.

In conclusion, compared with SCS, both NMP and NRP livers had better early transplant outcomes. NRP had advantage over NMP and SCS after adjusting for donor, recipient, and transplant factors. In addition, NRP was associated with a superior biliary complication profile with lower odds of NAS and subsequent interventions. While the results of this study are noteworthy, the recent data on HOPE highlight the need to compare all new technologies in a randomized manner, and in particular to compare HOPE with NRP and NMP.

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