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Normothermic Machine Perfusion Is Associated With Improvement in Mortality and Graft Failure in Donation After Cardiac Death Liver Transplant Recipients in the United States

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Background. Use of normothermic machine perfusion (NMP) may help to expand the liver transplantation (LT) donor pool by potentially increasing the utilization of donation after circulatory death (DCD) organs. The aim of this study was to assess the impact of NMP on LT from DCD organs. **Methods.** Data among DCD adult LT recipients in the United Network for Organ Sharing between January 2016 and December 2022 were analyzed. Outcomes were compared between 2 groups: NMP versus non-MP using propensity score matching. **Results.** During the study period, 4217 DCD LT recipients (NMP: 257 and non-MP: 3960) were identified. compared with non-MP, DCD LT recipients in NMP group were older (median recipient age: 61 versus 59 y, $P = 0.013$), had lower model for the end-stage liver disease score, longer wait time (126 versus 107 d, $P = 0.028$), and received organs from older donors (median age: 42 versus 38 y, $P < 0.01$) with longer preservation time (9.9 versus 5.3 h, $P < 0.001$). Two-year overall survival (NMP 94.4% versus non-MP 89.7%, $P = 0.040$) and 2-y graft survival (NMP 91.3% versus non-MP 84.6%, $P = 0.017$) were better in the NMP group. After propensity score matching, 2-y overall survival (NMP 94.2% versus non-MP 88.0%, $P = 0.023$) and graft survival (NMP 91.3% versus non-MP 81.6%, $P = 0.004$) were better in the NMP group. On multivariable cox regression analysis, NMP was an independent factor of protection against mortality (hazard ratio, 0.43; 95% confidence interval: 0.20-0.91; $P = 0.029$) and against graft failure (hazard ratio, 0.26; 95% confidence interval: 0.11-0.61; $P = 0.002$). **Conclusions.** Use of NMP for LT from DCD donors was associated with improved posttransplant patient and graft survival.

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The burden of end-stage liver disease is increasing worldwide, which has led to an increase in the need for organs for liver transplantation (LT).[1] Although the number of LTs is also increasing steadily, mortality on the waiting list for LT still remains high, because of the shortage of available organs.[1] To expand the donor pool, liver grafts from donation after circulatory death (DCD)[2,3] are being increasingly utilized; however, these grafts are associated with increased risk of graft dysfunction and overall worse outcomes when compared with transplantation from donation after brain death (DBD) organs.

Liver allograft preservation has historically relied on static cold storage (SCS),[4–6] which exposes it to ischemic injury and the risk of progressive organ deterioration.[7] The uncertainty of liver allograft condition when using cold preservation leads to a conservative approach while accepting marginal livers, ultimately leading to the underutilization of available donor livers for transplantation. Machine perfusion of liver allograft has been developed to overcome such limitations[8] and to improve LT outcomes, with previous studies showing that liver machine perfusion can help to better utilize liver grafts from DCD donors.[9–15]

A recent randomized trial (the PROTECT trial) showed that normothermic machine perfusion (NMP) utilization has been associated with improved outcomes when using marginal liver allograft for both DBD and DCD transplantation.[6] There was

also a decrease in ischemic biliary complications,[6,16] which are seen more often with use of DCD organs, especially in the setting of prolonged donor warm ischemia time.[17] Although the utilization of NMP in DCD has been expanding in the United Kingdom,[18] the data regarding outcomes of LT using NMP in DCD are limited in the United States.[19] The aim of this study was to assess the outcomes of LT in DCD using NMP and comparing the outcomes of LT in DCD without NMP in a nationwide cohort.

MATERIALS AND METHODS

Study Population

Adult (age >18 y) liver transplant recipients utilizing DCD between January 2016 and December 2022 were analyzed from the de-identified United Network for Organ Sharing (UNOS) database. The standard liver data were merged with deceased donor file based on the key code of DONOR_ID. The variable "LI_MACHINE_PERFUSION: liver machine perfusion" was considered as the use of machine perfusion of the liver in this study. For use of liver machine perfusion, NMP was identified using the variable "LI_MACHINE_PERFUSION_TYPE: machine perfusion." Hypothermic liver machine perfusion and other types of liver machine perfusion were excluded. The adult donors were divided into 2 groups: NMP and non-MP. All the DCD donors were classified into Maastricht Category III (controlled DCD).[20] Multiorgan transplant and retransplant were excluded from the analysis. This study was approved by our local Institutional Review Board. No additional approval was required for secondary analysis of existing data, and confidentiality of patient records was maintained.

Study Endpoints

The primary endpoint of this study was patient mortality and death-censored liver graft failure post-LT. Secondary endpoints were the length of posttransplant hospital stay (LOS) and the discard rate of livers using NMP. The causes of liver allograft failure were also reviewed. Donor warm ischemia time was calculated as the duration between withdrawal time and clamp time.

Definition

Duration of use of NMP is unknown in the UNOS database. Because traditional cold ischemia time as defined as by the time between the organ cross-clamp and first perfusion of warm recipient blood does not reflect appropriately for NMP, in this study, we defined cold ischemia time in database as preservation time. Discard rate of liver was obtained using the variable "LI_DISPOSITION" in the deceased donor file and calculated.[1,21]

Statistical Analysis

Continuous variable was presented as the median (interquartile range [IQR]), unless otherwise specified. The Mann-Whitney U test was used to compare continuous variable between 2 groups. A chi-square or Fisher exact test was performed for categorical variables. The Mann-Kendall trend test was used to analyze the trend. A list of missing values and their frequencies is presented in **Table S1** (**SDC**, http://links.lww.com/TXD/A677). Propensity score (PS) matching was performed using one-to-one matching without replacement between 2 groups with the nearest neighborhood method within a caliper width equal to 0.1 of the SD of the logit of the PSs. The PS was calculated with using recipient's characteristics (age, sex, race, blood type, body mass index, primary diagnosis of liver disease, diabetes status, dialysis at transplant, portal vein thrombosis, history of abdominal surgery, mechanical ventilation at transplant, and model for the end-stage liver disease [MELD] at transplant) and donor's characteristics (age, sex, race, body mass index, and causes of death) (**Figures S1 and S2, SDC**, http://links.lww.com/TXD/A677). The Hosmer-Lemeshow goodness-of-fit test result showed good fit ($P = 0.80$). Variance inflation factor in the model was <2.0. Absolute standard differences were calculated to compare the balance in characteristics between both groups. A threshold of 0.10 was used to indicate a significant imbalance.

The overall survival and graft survival were calculated from the date of transplant to the date of event using the Kaplan-Meier method. The log-rank test was used to compare survival curves. Adjusted posttransplant survival was modeled by using multivariable Cox proportional-hazards regression. Exploratory univariable analysis was performed to determine significance of potential cofounders with a P value of <0.10, and then, a stepwise backward model selection method was used to build the multivariable models for overall and graft survivals. Results were presented as hazard ratios (HRs) and reported with 95% confidence intervals (CIs) and two-sided P values. For all statistical analyses, a P value of <0.05 was considered as significant. Statistical analyses were performed using R-Studio using R Version 4.1.1 (R Studio, Boston, MA).

RESULTS

Study Demographics

A total of 4217 LT recipients (NMP N = 257 and non-MP N = 3960) were identified during the study period (Figure 1). Trends in the number of LTs performed using NMP are shown in Figure 2. The utilization of NMP for LT was highest in 2022 ($P < 0.001$).

compared with recipients of non-MP LTs, the recipients of machine perfused LTs were older (median age NMP 61 versus non-MP 59 y, $P = 0.013$) and had lower MELD score at time of transplant (mean NMP 18 versus non-MP 19, $P = 0.066$) (Table 1).

The most common primary diagnosis was alcohol-related liver disease (NMP 32% versus non-MP 33%) and the NMP group had longer wait time (NMP 126 versus non-MP 109 d, $P = 0.028$). The NMP group had higher median donor age (NMP 42 versus non-MP 38 y, $P < 0.001$). When comparing donor's causes of death, more anoxia (NMP 54% versus non-MP 53%), more cerebral vascular accident (NMP 25% versus non-MP 18%), less trauma (NMP 16% versus non-MP 25%), and higher donor risk index[22] (NMP 2.35 versus non-MP 2.16, $P < 0.001$) were noted. Preservation time was longer in the NMP group (NMP 9.92 versus non-MP 5.30 h, $P < 0.001$). Donor warm ischemia time was longer in the NMP group (NMP 24 versus non-MP 23 min, $P = 0.064$). After PS matching, there was no difference in the covariates between the 2 groups (**Table S2, SDC**, http://links.lww.com/TXD/A677)

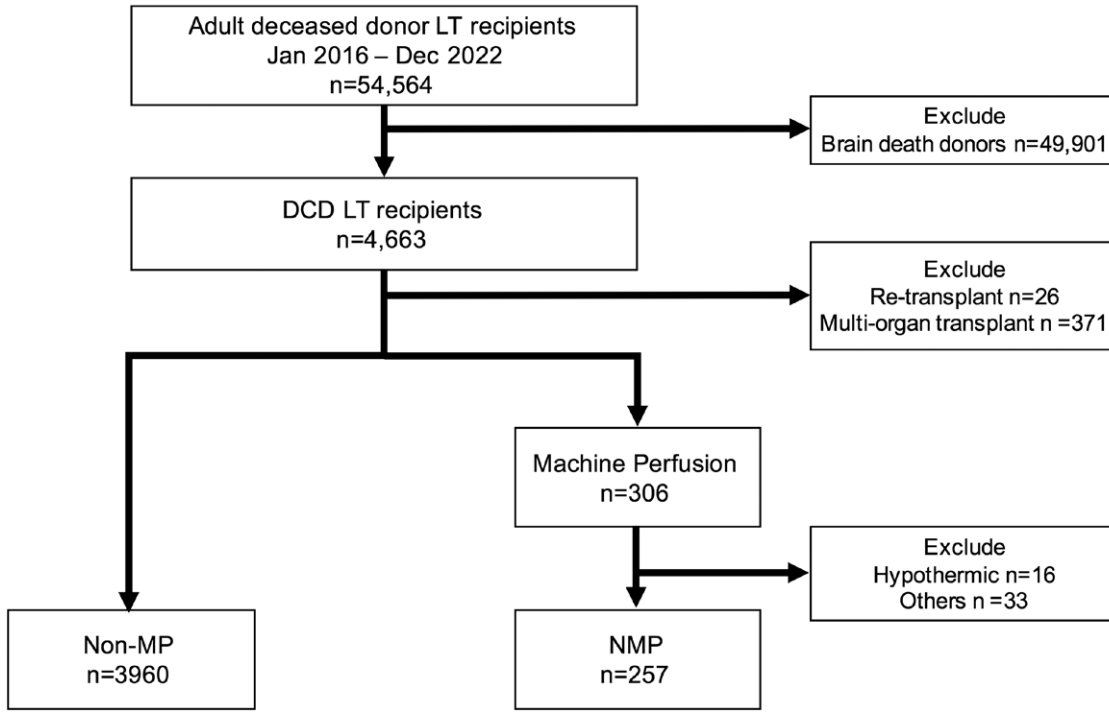

FIGURE 1. Study population.

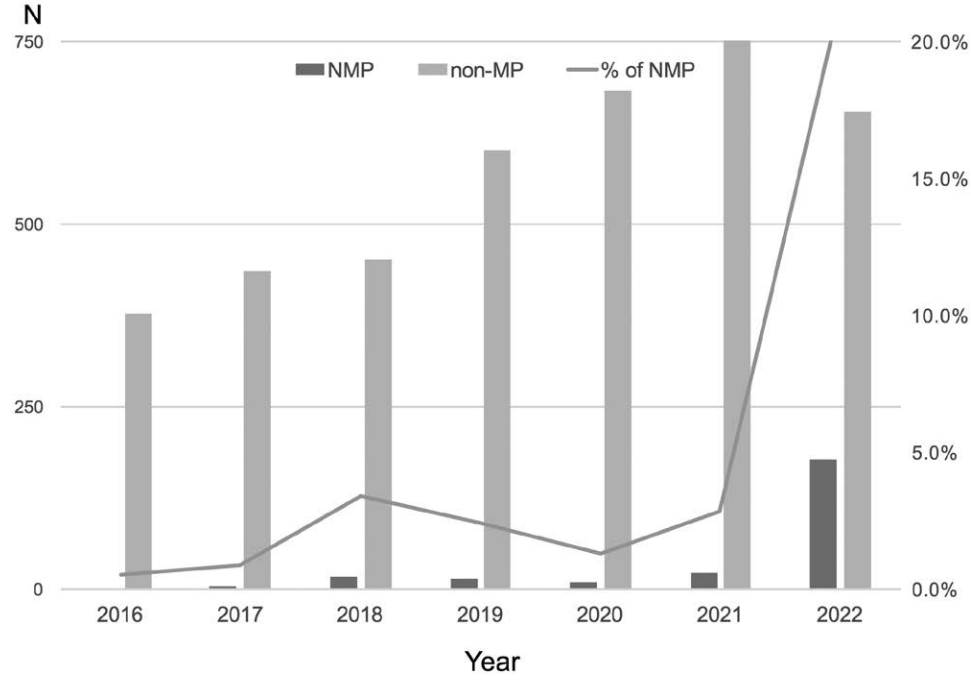

FIGURE 2. Trend of utilization of DCD liver graft. DCD, donation after circulatory death.

Outcomes

The median posttransplant follow-up duration (IQR) was 742 (364–1449) d. The median LOS post-LT was shorter in the NMP group in nonmatched cohort (NMP 7 versus non-MP 8 d, $P = 0.025$) and comparable between the 2 groups in matched cohort (Table 2). The 30-d posttransplant mortality was lower in NMP group in nonmatched (NMP 0.8% versus non-MP 1.9%, $P = 0.24$) and statistically comparable between the 2 groups in matched cohorts (NMP 0.8% versus non-MP 2.8%, $P = 0.18$). The rejection episodes before initial discharge were comparable between the 2 groups in both nonmatched and matched cohorts. The rejection episodes at 6 mo were lower in the NMP group (nonmatched: NMP 4.3% versus non-MP 7.8%, $P = 0.053$; matched: NMP 4.4% versus non-MP 9.3%, $P = 0.051$) and the rejection episodes at 1 y were significantly lower (nonmatched: NMP 3.9% versus

TABLE 1.

Demographics of transplant between NMP and non-MP

	NMP, N = 257	Non-MP, N = 3960	*P*
Recipient			
Age, y, median (IQR)	61.0 (54.0–66.0)	59.0 (52.0–65.0)	0.013
Male, n (%)	173 (67)	2740 (69)	0.53
Race, n (%),			
White	192 (75)	3,043 (77)	0.18
Black	8 (3.1)	192 (4.8)	
Hispanic	46 (18)	538 (14)	
Asian	9 (3.5)	117 (3.0)	
Others	2 (0.8)	70 (1.8)	
Body mass index, kg/m^2, median (IQR)	28.2 (24.9–32.4)	28.7 (25.1–33.1)	0.29
Blood type, n (%)			
O	136 (53)	1,951 (49)	0.59
B	23 (8.9)	359 (9.1)	
A	91 (35)	1,562 (39)	
AB	7 (2.7)	88 (2.2)	
Diabetes, n (%)	89 (35)	1,264 (32)	0.37
Primary diagnosis of liver disease, n (%)			
ALD	83 (32)	1,326 (33)	
MASH	50 (19)	934 (24)	
Hepatitis C virus	17 (6.6)	428 (11)	
Hepatitis B virus	2 (0.8)	72 (1.8)	
Acute liver failure	0 (0)	24 (0.6)	
Hepatocellular carcinoma	14 (5.4)	228 (5.8)	
Others	91 (35)	948 (24)	
HCV-positive status, n (%)	39 (15)	831 (21)	0.026
HCV NAT positive, n (%)	8 (4.2)	117 (7.3)	0.12
Previous abdominal surgery, n (%)	135 (53)	1928 (49)	0.23
Portal vein thrombosis at transplant, n (%)	39 (15)	552 (14)	0.58
Dialysis at transplant, n (%)	4 (1.6)	71 (1.8)	0.99
TIPSS, n (%)	18 (7.0)	368 (9.3)	0.22
MELD at transplant, median (IQR)	18 (11–23)	18 (13–24)	0.066
MELD exception, n (%)	48 (19)	956 (24)	0.056
Mechanical ventilation at transplant, n (%)	1 (0.4)	31 (0.8)	0.72
Waiting days, median (IQR)	126 (33–346)	107 (27–259)	0.028
Donor			
Age, y, median (IQR)	42.0 (32.0–52.0)	38.0 (28.0–49.0)	<0.001
Male, n (%)	182 (71%)	2692 (68)	0.34
Race, n (%)			0.30
White	188 (73)	3018 (76)	
Black	25 (9.7)	422 (11)	
Hispanic	34 (13)	394 (9.9)	
Asian	5 (1.9)	83 (2.1)	
Others	5 (1.9)	43 (1.1)	
Blood type, n (%)			0.33
O	134 (52)	1985 (50)	
B	25 (9.7)	351 (8.9)	
A	93 (36)	1,583 (40)	
AB	5 (1.9)	41 (1.0)	
Body mass index, kg/m^2, median (IQR)	28.2 (24.7–33.2)	26.7 (23.5–30.9)	<0.001
HCV NAT positive, N (%)	8 (3.1)	170 (4.4)	0.32
HCV Ab positive, N (%)	22 (8.6)	285 (7.2)	0.42
Donor causes of death			
Anoxia	140 (54)	2,109 (53)	0.001
Cerebrovascular disease	63 (25)	697 (18)	
Head trauma	41 (16)	1,007 (25)	
Central nervous system tumor	0 (0)	2 (<0.1)	
Others	13 (5.1)	145 (3.7)	
Share type, n (%)			
Local	138 (54)	2,303 (58)	0.005
Regional	63 (25)	1,090 (28)	
National	56 (22)	567 (14)	
Donor WIT, min, median (IQR)	24 (20–27)	23 (19–27)	0.064
Preservation time, h, median (IQR)	9.92 (7.65–13.25)	5.30 (4.40–6.33)	<0.001
DRI, median (IQR)	2.26 (2.00–2.83)	2.16 (1.91–2.49)	<0.001
Distance[a], median (IQR)	95 (12–268)	80 (10–206)	0.011

[a]Distance between donor and recipient hospital.

ALD, alcohol-related liver disease; DBD, donation after brain death; DCD, donation after circulatory death; DRI, donor risk index; HCV, hepatitis C virus; IQR, interquartile range; MASH, metabolic dysfunction-associated steatohepatitis; MELD, model for end-stage liver disease; MP, machine perfusion; NMP, normothermic machine perfusion; TIPSS, transjugular intrahepatic portosystemic shunt; WIT, warm ischemia time.

non-MP 8.5%, $P = 0.012$; matched: NMP 4.0% versus non-MP 11%, $P = 0.006$).

On survival analysis in the nonmatched cohort, both 2-y overall survival (NMP 94.4% versus non-MP 89.7%, $P = 0.040$) and graft survival (NMP 91.3% versus non-MP 84.6%, $P = 0.017$) were better in the NMP group (Figure 3A and B). In the matched cohort, 2-y overall survival (NMP 94.2% versus non-MP 88.0%, $P = 0.023$) and graft survival (NMP 91.3% versus non-MP 81.6%, $P < 0.001$) were better in NMP group (Figure 3C and D). In univariable cox regression analysis, NMP was associated with a factor of protection against mortality (HR, 0.51; 95% CI: 0.26-0.98; $P = 0.044$) and against graft failure (HR, 0.55; 95% CI: 0.33-0.90; $P = 0.018$) (**Table S2, SDC**, http://links.lww.com/TXD/A677). In multivariable cox regression analysis, NMP was associated with an independent factor of protection against mortality (adjusted HR, 0.43; 95% CI: 0.20-0.91; $P = 0.029$) and against graft failure (adjusted HR, 0.41; 95% CI: 0.22-0.74; $P = 0.003$) (Table 3 and **Table S3, SDC**, http://links.lww.com/TXD/A677).

Discard Rate

During the study period, NMP were utilized in 782 adult donors for organ recovery (DCD N = 294 and DBD N = 488). The discard rate using NMP was higher in DCD than that in DBD (5.4% versus 2.9%, $P < 0.001$). However, the discard rate of DCD in the NMP group was significantly lower than that of DCD in non-MP (8.0% versus 29.9%, $P < 0.001$).

TABLE 2.

Outcomes of transplant between liver machine perfusion and nonmachine perfusion

	Nonmatched			Matched		
	NMP, N = 257	Non-MP, N = 3960	*P*	NMP, N = 248	Non-MP, N = 248	*P*
Length of stay, d, median (IQR)	7 (5–12)	8 (6–13)	0.025	7 (5–12)	7 (5–11)	0.25
Primary nonfunction, n (%)	4 (1.6)	65 (1.6)	0.99	3 (1.2)	7 (2.8)	0.34
30-d mortality, n (%)	2 (0.8)	76 (1.9)	0.24	2 (0.8)	7 (2.8)	0.18
Rejection episode before discharge, n (%)	7 (2.7)	128 (3.2)	0.79	7 (2.8)	6 (2.4)	0.99
Rejection episodes at 6 mo, n (%)	11 (4.3)	308 (7.8)	0.053	11 (4.4)	23 (9.3)	0.051
Rejection episodes at 1 y, n (%)	10 (3.9)	338 (8.5)	0.012	10 (4.0)	27 (11)	0.006
Survival rate (%)						
1-y overall survival (%)	95.9	93.5		95.7	91.6	
2-y overall survival (%)	94.4	89.7		94.2	88.0	
1-y graft survival (%)	93.7	89.3		93.8	86.0	
2-y graft survival (%)	91.3	84.6		91.3	81.6	

IQR, interquartile range; MP, machine perfusion; NMP, normothermic machine perfusion.

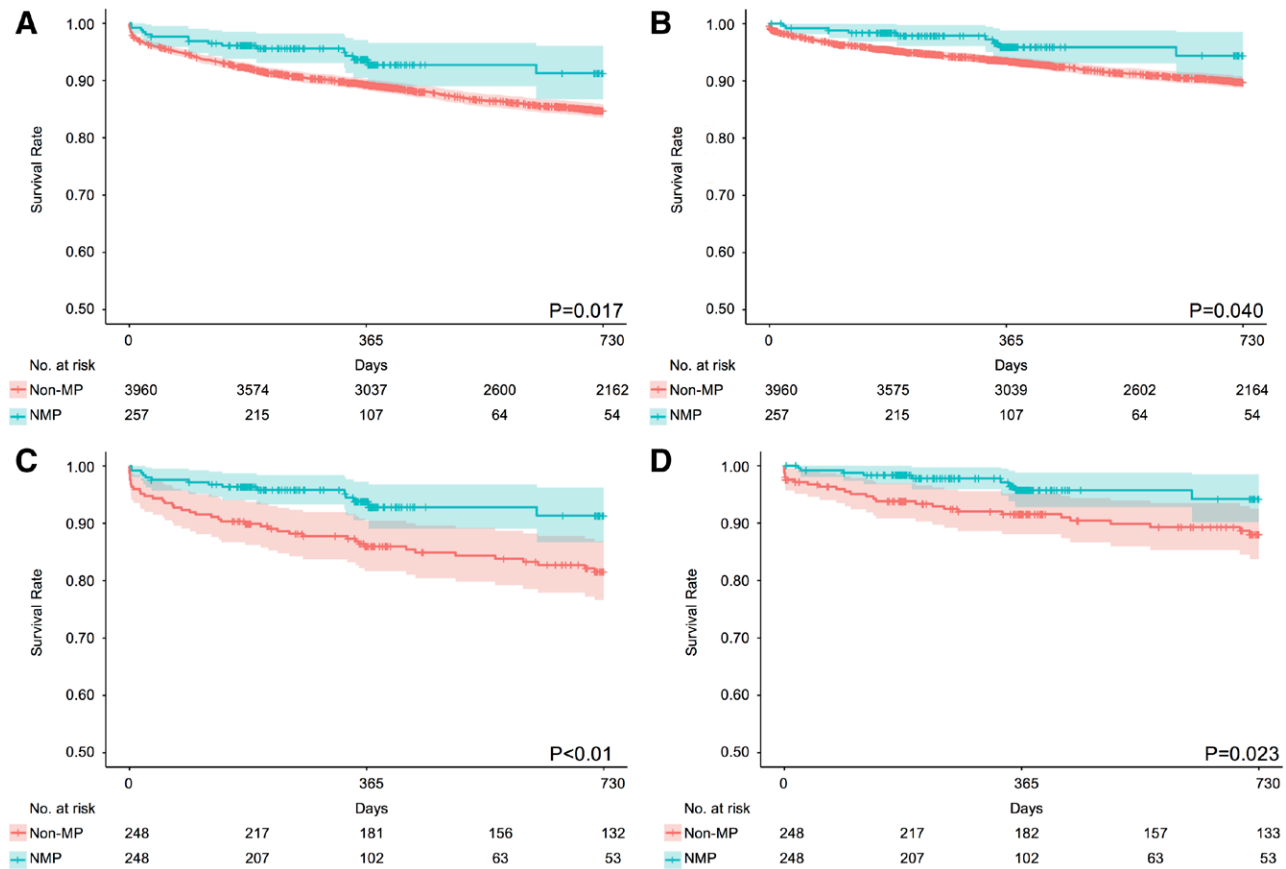

FIGURE 3. Comparisons of overall survival and graft survival between NMP and non-MP. A, Overall survival in the nonmatched cohort. B, Graft survival in the nonmatched cohort. C, Overall survival in the matched cohort. D, Graft survival in matched cohort. MP, machine perfusion; NMP, normothermic machine perfusion.

Causes of Liver Graft Failure

As a cause of graft failure, the incidence of primary nonfunction was comparable between the 2 groups in nonmatched (NMP 1.6% versus non-MP 1.6%, $P = 0.99$) and in matched cohorts (NMP 1.2% versus non-MP 2.8%, $P = 0.34$). The incidence of diffuse cholangiopathy as a cause of graft failure in NMP was lower but not statistically significant in nonmatched (NMP 0.4% versus non-MP 1.6%, $P = 0.10$) and in matched cohorts (NMP 0.4% versus non-MP 0.8%, $P = 0.39$).

DISCUSSION

Our study highlights that the utilization of liver machine perfusion has increased over the years and is associated with improved outcomes and a decrease in discard rate of DCD liver grafts and in the United States.

TABLE 3.

Multivariable Cox-hazard regression analysis of liver transplant recipient for graft failure and mortality in matched cohort

NMP (reference non-MP)	Hazard ratio (95% CI)	*P*
Graft failure[a]	0.41 (0.22-0.74)	0.003
Mortality[b]	0.43 (0.20-0.91)	0.029

[a]Adjusted by recipient portal vein thrombosis, recipient diabetes, donor age, and donor gender.
[b]Adjusted by recipient age, recipient diabetes, and donor age.
CI, confidence interval.

The utilization of liver NMP can help to increase the utilization of marginal organs[8] and therefore safely expand the donor pool. Although utilization of machine perfusion and associated reduction in the ischemic injury leads to better short-term clinical outcomes for all LTs,[6] limited data are available regarding these outcomes for LTs from DCD donors. Previously, we showed that the outcomes of liver machine perfusion were comparable between DCD and DBD in the United States, but the generalization of those results was limited by a small cohort of DCD LT recipients in that study.[19]

The present study highlights the potential of a protective effect on the liver graft by using NMP on DCD organs in the United States. Use of hypothermic machine perfusion for DCD livers was shown to enable prolonging the cold ischemia time and associated decrease in posttransplant allograft dysfunction.[13] However, certain DCD livers which utilized NMP had higher incidence of ischemic biliary complications requiring up to 30% rate of liver retransplant.[23] To the contrary, in our study, NMP use was associated with better overall recipient survival and graft survival when compared with non-MP LTs. These data are especially encouraging as NMP in our study was used for organs from older donors, thus offering a further expansion of the donor pool. NMP also carries the added benefit of being able to assess the liver function and to decreased postreperfusion syndrome.[6,9,24,25] Furthermore, the ability of NMP to assess the liver function before actual transplantation may lead to a significant decrease in the discard rate of the procured livers.

Prolonged cold ischemia time in SCS is associated with worse outcomes including early allograft dysfunction.[22,26] To mitigate these risks, goal of the transplant team is to minimize the preservation time (between donor cross-clamp and recipient reperfusion), including transportation time, optimize the timing of recipient surgery, and better communication between donor and recipient teams in SCS. In the present study, preservation time in the NMP group was longer than that in the non-MP group, which could be because of the current definitions in which cold ischemia time in the UNOS database is defined as the time starting when the organ is cross-clamped and ending with first perfusion of warm recipient blood. The impact of discrepant ways to report cold ischemia time with NMP could be addressed by further standardization of these definitions to account for the duration of NMP utilization. It remains unclear from these data how long NMP was used and the how the duration of NMP impacts transplant outcomes. Similarly, the impact of >8 h on SCS before starting NMP in this study also remains unclear.

With recent advancement, the outcomes of allograft from DCD is comparable to DBD, likely because of careful donor and recipient selection, such as with use in younger donors or in recipients with a lower MELD score.[25–27] Although NMP could clearly help expand the donor pool, DCD LT outcomes using NMP among higher MELD recipient population remain limited. Considering these encouraging early outcomes in NMP, the next challenge would be safe utilization use of marginal grafts assessed with NMP for these populations.

Although the outcomes of LT using NMP are so far good and hold much promise, there are some concerns regarding its use. NMP costs more than SCS because NMP requires transportation arrangement of associated devices and teams. NMP also requires additional time and effort because of back-bench preparation of the liver, cannulation, and connection to the device.[28] The actual costs of utilization of NMP are different between the devices and the studies regarding the cost–benefit analysis of liver NMP have not been performed yet. The other concern as suggested by Kulkarni et al[29] is that NMP utilization might increase the complexity of liver allocation and potentially lead to inequity in the allocation system.

The next steps in the new era of machine perfusion are for the transplant community to standardize the utilization of NMP to help decrease the burden on the transplant programs and to strive for equity in the organ allocation.

LIMITATIONS

This is a retrospective cohort study using UNOS database and missing information. Because of the retrospective nature, direct-casual effects were not able to assess and we only analyzed data of transplanted liver using NMP. Previous studies showed that the utilization of liver has been improved with NMP,[6,8] it is unclear from the data whether the utilization of NMP was in the participation of research or not. The duration and timing of NMP is not available from the dataset and has not been assessed. Currently, 2 types of NMP are available in the United States and are not specified in the current dataset. Duration of follow-up is limited and long-term results remains unknown. The incidence of ischemic cholangiopathy is only available if the recipient has allograft failure and the true incidence of ischemic cholangiopathy is not available in the current dataset.

CONCLUSION

The utilization of NMP is increasing in the United States and is associated with improvement of overall and graft survival in DCD organs.

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