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The Impact of Normothermic Machine Perfusion on Biliary Complications in Donation After Circulatory Death Donor Liver Transplantation

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Background. The incidence of ischemic cholangiopathy (IC) in liver transplant (LT) patients from donation after circulatory death (DCD) has been observed to be higher compared with those from donation after brain death (DBD). It has been reported that the normothermic machine perfusion (NMP) technique was associated with lower rates of IC. However, the effect of NMP on anastomotic biliary complications remains unclear. **Methods.** A total of 450 LTs performed between January 2019 and December 2023 were analyzed in a retrospective study. The primary outcome included biliary complications within 180 d after LT and those classified by type (bile leak, stricture, or IC). Risk factors for biliary complications were compared between the NMP group and the non-NMP group within both the DBD and DCD groups. **Results.** The incidence of IC was higher in the DCD without NMP group at 17.5% (10/57), compared with the DCD with NMP group (0%). DCD was independently associated with the development of biliary complications by all causes after LT (odds ratio, 2.29 [95% confidence interval, 1.29-4.07], $P < 0.01$), whereas NMP did not reduce the risk of biliary complications by all causes (odds ratio, 0.54 [confidence interval, 0.29-1.02], $P = 0.06$). NMP also did not reduce the risk of biliary anastomotic complications, excluding IC in either DBD or DCD groups. **Conclusions.** Although NMP might prevent IC, it did not reduce the risk of biliary complications regardless of donor type. Blood circulation to the biliary system may not be adequate, leading to anastomotic biliary complications.

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INTRODUCTION

Liver transplantation (LT) offers life-saving treatment for patients with end-stage liver disease. The need for organs greatly exceeds the available supply, and there is a significant emphasis on innovations that aim to increase the number of viable deceased donors, as well as exploration of alternative donor sources.[1] Thus, organs from medically complex donors such as those of older age, with multiple comorbidities, or donation after circulatory death (DCD) donors have been used to expand the donor pool.[2] An organ preservation method that has shown great promise is normothermic machine perfusion (NMP). NMP reduces the discard rate of procured livers to 3.5% compared with 13.3% in the standard cold static preservation group.[3] The randomized clinical trial in the United States revealed that NMP preservation of deceased donor livers had a significant reduction of early allograft dysfunction[4] (EAD).[2] As for the graft and patient survival rates, a metanalysis by Mugaanyi et al[5] showed that graft survival was slightly favorable in NMP compared with static cold storage, although not statistically significant.

Posttransplant biliary complications are known as major predisposing factors for morbidity in LT recipients.[6] The ischemic cholangiopathy (IC), which is the most severe form of posttransplant biliary complication, has been reported in approximately 10%–30% of DCD LTs, whereas in 1%–3%

of donation after brain death (DBD) donors.[7] IC typically develops within 1–6 mo after LT, with involvement of both intrahepatic and extrahepatic bile duct, showing progressive cholestasis and cholangitis as the primary clinical manifestations.[8] However, there are the IC cases that occurred >10 y after LT, and the cumulative incidence was reported to be 14% at 3 y, 15% at 5 y, and 16% at 10 y after LT.[9] Donor age and donor weight are known as the risk factors of IC.[8] Chronic rejection, cytomegalovirus infection, recurrent sclerosing cholangitis, and ABO-incompatible transplantation were also known as the risk factors for IC, which may cause injury to the biliary epithelium.[8] For treatments, endoscopic management with repeated stricture dilation and stent placement can reduce the severity of symptoms in 50%–70% of the IC.[10] The only viable treatment for therapy-resistant IC is liver retransplantation.[10] According to the report by Goussous et al,[11] the retransplantation rate for IC was 7.4% among 68 patients who developed IC between 2014 and 2017. Croome et al[12] classified distinct radiologic patterns of IC into 4 categories: diffuse necrosis, multifocal progressive, confluence dominant, and minor form. They found that patients with diffuse necrosis and multifocal progressive patterns experienced recurrent admissions due to cholangitis within the first year after DCD LT and were largely stent dependent.[12]

Earlier studies revealed that machine perfusion (MP) techniques, such as hypothermic MP or NMP, have also been associated with lower rates of IC due to MP inherently having the potential to mitigate ischemic/reperfusion injury.[2,7] Meanwhile, as for other biliary complications, including stricture or leak, the incidence was reported to be comparable between livers with NMP and ischemic cold storage.[2] However, previous clinical studies have included only small pilot studies with a small number of patients, limiting the definite applicability and interpretability of the data collected. Thus, we conducted a retrospective study to evaluate the effect of NMP on biliary complications (anastomotic and nonanastomotic) and assess its utility in different donor groups (DBD group or DCD group).

MATERIALS AND METHODS

Patients and Data Collection

This was a historical cohort study conducted at a single center (Henry Ford Hospital, Detroit, MI). The medical records of LT recipients who underwent deceased donor LT at our hospital between January 2019 and December 2023 were collected. This study was approved by the Institutional Review Board of the Henry Ford Hospital (No. 16745). Informed consent was waived by the Institutional Review Board of the Research Ethics Committee of the Faculty of Henry Ford Hospital. All research procedures were performed in accordance with the Declaration of Helsinki. The exclusion criteria were as follows: (1) patients with transplantations from living donors; (2) patients with primary biliary cholangitis, primary sclerosing cholangitis, or other biliary diseases as the primary liver disease; (3) patients with intraoperative death; and (4) bile duct reconstruction cases involving the use of the gastrointestinal tract. Patient characteristics, operative information, and laboratory data at transplantation were also obtained from medical records.

Outcomes

The primary outcome was biliary complications within 180 d of LT, classified by types; anastomotic biliary complications (bile leak or stricture), and IC. The biliary complications were defined as any leak, stricture, or intrahepatic IC that required stenting based on the findings of endoscopic retrograde cholangiopancreatography. A bile leak was defined as the extravasation of bile outside the biliary system, typically occurring at the anastomotic site. Patients were classified into the DBD and DCD groups to compare the incidence rates of biliary complications. The outcomes were then compared between patients with NMP and those without NMP in each group. The occurrence and date of the first observed cholangiography post-LT were investigated.

The EAD, primary nonfunction (PNF), and 3-y patient and graft survival were also compared between the 4 groups. EAD, which was associated with worse patient and graft survival, was defined as the presence of ≥1 of the following: bilirubin ≥10 mg/dL on day 7, international normalized ratio ≥1.6 on day 7, and alanine or aspartate aminotransferases >2000 IU/L within the first 7 d, according to the definition of Olthoff et al.[13] PNF was identified in organs that have failed to maintain their function, resulting in either death or repeated LT within 7 d of the initial surgery, according to the definition of Ploeg et al.[14]

Selection Criteria for NMP

MP has been used in all cases since 2019. Because we used MP in all DCD LT, there are no clear donor inclusion and exclusion criteria or organ viability criteria. In DBD LT, MP use was considered in the following cases: the donor liver with macrosteatosis of 20%–30%, donor age of 70 y or older, and/or expected cold ischemia time (CIT) of >6 h. Lactate values and bile production were monitored while the liver was on the MP.

Statistical Analysis

All statistical analyses were conducted using software (SPSS, version 27.0.1; IBM Corp, Armonk, NY). Continuous data were expressed as mean ± SD or median (interquartile range). One-way ANOVA or the Kruskal-Wallis test was used to compare continuous variables. The chi-square test or Fisher exact test was used to compare the categorical variables. To reduce selection bias and balance baseline characteristics between the NMP group and the non-NMP group, we performed propensity score matching. Propensity scores were estimated using a logistic regression model, with covariates including donor's age/body mass index, the presence of pretransplant portal vein thrombosis, the operative time, the rate of DCD donors, and the Model for End-Stage Liver Disease score. One-to-one nearest neighbor matching with a caliper of 0.2 SD was applied without replacement. Standardized mean differences were used to assess the balance of covariates before and after matching, with a standardized mean difference of <0.1 indicating adequate balance. Univariable and multivariable logistic regression analyses were performed to analyze significant factors associated with biliary complications after LT. Univariable and multivariable Cox regression analyses were used to investigate significant factors associated with graft survival and patient survival. In logistic or Cox regression analyses, variables significant at a P value of <0.05 on univariate analysis, as well as variables that may have confounding

effects or are of clinical importance, were entered in the initial multivariate model.

The Kaplan-Meier method and log-rank test were used to compare differences in graft survival or patent survival within 3 y posttransplantation between groups with NMP or not in DBD/DCD groups. *P* values of <0.05 were inferred as significant.

RESULTS

Characteristics of Study Participants

In total, 537 LTs were performed in 529 patients from January 2019 to December 2023. Eight patients experienced repeated LTs during the study period. After excluding 87 cases, 450 cases in 442 patients were finally examined as study participants (Figure 1). Table 1 presents the characteristics of 450 cases. The average age of all patients was 56.3 y, of which 65.1% were men. DCD with NMP included the patients with a higher Model for End-Stage Liver Disease score compared with DCD without NMP. Table 2 shows the comparison of intraoperative factors between donor groups. The DCD with NMP group had a longer total operative time and a higher rate of pretransplant portal vein thrombosis compared with the DCD without NMP group.

Outcomes

The DCD without NMP group had a higher rate of EAD compared with the DCD with NMP group (63.2% versus 17.2%, $P < 0.01$; Table 3). There was no statistical difference in the rate of PNF NMP group and non-NMP group within both the DBD and DCD groups (Table 3). Of the 450 LT cases, 107 (23.8%) developed biliary complications by all causes within 180 d post-LT. A total of 12 patients developed IC, and the incidence of IC was significantly higher in the DCD without NMP group at 17.5%, whereas there were no cases in the DBD with NMP or DCD with NMP group (Table 3). There was no difference in the incidence rate of anastomotic biliary complications between the NMP and non-NMP groups within both the DBD and DCD groups, respectively.

To minimize selection bias and ensure comparability of baseline characteristics between the NMP and non-NMP groups, we conducted propensity score matching. Comparisons of patient characteristics in the cohort with propensity score matching are shown in **Tables S1 and S2** (**SDC,** https://links.lww.com/TXD/A772). The rate of EAD and IC were significantly lower in the NMP group in this cohort ($P < 0.01$, $P = 0.03$, respectively; **Table S3, SDC,** https://links.lww.com/TXD/A772). However, no significant difference in biliary complications by all causes or anastomotic biliary complications was observed between the NMP and non-NMP groups.

Logistic regression models were used to evaluate the factors related to the biliary complication after LT. DCD donor was found to be related to the development of all biliary complications after LT (odds ratio, 2.29 [confidence interval, 1.29-4.07], $P < 0.01$; Table 4). Although there was no significant difference, NMP tended to be associated with a lower incidence of all biliary complications (odds ratio, 0.54 [confidence interval, 0.29-1.02]; $P = 0.06$). Factors related to anastomotic biliary complications after LT were also investigated using logistic regression models (Table 5). Regarding anastomotic biliary complications, neither DCD nor NMP demonstrated any association.

The Influence of NMP on Biliary Complications

To investigate the influence of NMP on biliary complications, logistic regression analysis was evaluated separately for the DBD group and the DCD group. In the DBD group, there were no statistically significant factors related to biliary complications by all causes (Table 6) or anastomotic biliary complications (Table 7). Similarly, logistic regression analysis for biliary complications was performed in the DCD groups. It demonstrated that NMP was not related to biliary complications by all causes (Table 6), nor was it related to anastomotic biliary complications (Table 7).

Graft Survival and Patent Survival

The graft and patient survival for 3 y were compared between the DBD without NMP, DBD with NMP, DCD without NMP, and DCD with NMP groups using Kaplan-Meier analysis and log-rank testing (Figure 2A and B). Results showed no significant difference in graft or patient survival

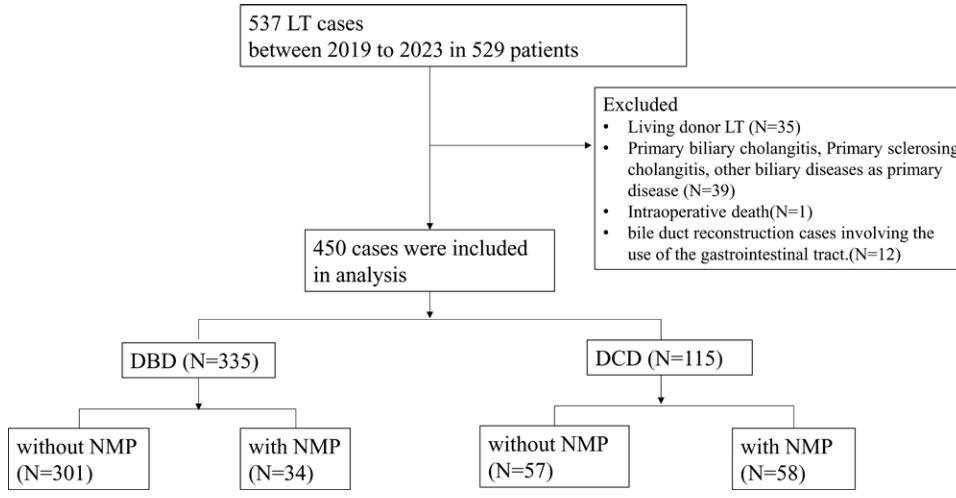

FIGURE 1. Chart showing flow of the study. DBD, donation after brain death; DCD, donation after circulatory death; LT, liver transplant; NMP, normothermic machine perfusion.

TABLE 1.

Comparison of the characteristics between donor groups

	All (N = 450)	DBD			DCD		
		Without NMP (N = 301)	With NMP (N = 34)	*P*	Without NMP (N = 57)	With NMP (N = 58)	*P*
Recipient factors							
Age, y	56.3 ± 10.3	55.32 ± 10.97	57.38 ± 8.38	0.29	58.49 ± 8.86	58.29 ± 8.93	0.91
Male sex, n (%)	293 (65.1)	192 (63.8)	24 (70.6)	0.35	40 (70.2)	37 (63.8)	0.39
Race, n (%)				0.39			0.047
White	379 (84.2)	252 (83.7)	31 (91.2)		52 (91.2)	44 (75.9)	
Black	36 (8.0)	25 (8.3)	2 (5.9)		4 (7.0)	5 (8.6)	
Hispanic	16 (3.6)	11 (3.7)	0 (0.0)		1 (1.8)	4 (6.9)	
Asian	10 (2.2)	7 (2.3)	1 (2.9)		0 (0.0)	2 (3.4)	
Others	9 (2.0)	6 (2.0)	0 (0.0)		0 (0.0)	3 (5.2)	
Body mass index, kg/m^2	28.8 (15.8,47.6)	28.4 (15.8, 47.6)	28.5 (20.2,41.7)	0.92	30.2 (18.7, 40.9)	29.8 (19.2, 44.7)	0.98
Primary liver diseases, n (%)							
Hepatitis C	86 (19.1)	42 (14.0)	2 (5.9)	0.15	6 (10.5)	2 (3.4)	0.13
Alcohol	216 (48.0)	148 (49.2)	13 (38.2)	0.22	29 (50.9)	26 (44.8)	0.52
NASH	132 (29.3)	80 (26.6)	9 (26.5)	0.99	20 (35.1)	23 (39.7)	0.61
AIH	23 (5.1)	13 (4.3)	5 (14.7)	0.03	2 (3.5)	3 (5.2)	0.66
HCC	86 (19.1)	52 (17.3)	5 (14.7)	0.70	18 (31.6)	11 (19.0)	0.12
Final MELD score	25.0 (6.0–61.0)	26.0 (19.0–33.0)	22.0 (18.0–27.0)	0.08	19.0 (14.0–24.0)	24.0 (19.8–26.0)	<0.01
T-Bil, mg/dL	3.20 (0.40–57.6)	3.70 (1.80–10.7)	3.40 (1.90–9.10)	0.83	2.30 (1.40–4.80)	2.55 (1.40–4.73)	0.89
Immunosuppressant, n (%)							
Tacrolimus	375 (83.3)	247 (82.1)	30 (88.2)	0.35	46 (80.7)	52 (89.7)	0.17
Cyclosporine	32 (7.1)	21 (7.0)	3 (8.8)	0.70	4 (7.0)	4 (6.9)	0.98
MMF	417 (92.7)	278 (92.4)	32 (94.1)	0.70	51 (89.5)	56 (96.6)	0.13
Steroid	432 (96.0)	287 (95.4)	33 (97.1)	0.63	56 (98.3)	56 (96.6)	0.57
Donor factors							
Age, y	44.9 ± 13.8	45.7 ± 14.2	48.7 ± 14.1	0.25	40.4 ± 12.0	42.5 ± 11.5	0.33
Male sex, n (%)	269 (60.7)	172 (57.9)	16 (48.5)	0.30	40 (70.2)	41 (73.2)	0.72
Race, n (%)				0.03			0.15
White	324 (72.0)	214 (71.1)	19 (55.9)		43 (75.4)	48 (82.8)	
Black	82 (18.2)	60 (19.9)	10 (29.4)		9 (15.8)	3 (5.2)	
Hispanic	33 (7.3)	21 (7.0)	2 (5.9)		5 (8.8)	5 (8.6)	
Asian	2 (0.4)	2 (0.7)	0 (0.0)		0 (0.0)	0 (0.0)	
Others	9 (2.0)	4 (1.3)	3 (8.8)		0 (0.0)	2 (3.4)	
Body mass index, kg/m^2	28.0 (24.0–33.1)	28.4 (24.1–33.2)	26.5 (23.6–33.1)	0.34	27.1 (23.3–32.3)	27.4 (24.0–32.9)	0.45
Cause of death, n (%)	2			0.52			0.10
Anoxia	4241 (53.6)	158 (52.5)	14 (41.2)				
Cerebrovascular accident	110 (24.4)	79 (26.2)	12 (35.3)		9 (15.8)	10 (17.2)	
Trauma	76 (16.9)	49 (16.3)	7 (20.6)		15 (26.3)	5 (8.6)	

Continuous data are presented as mean ± SD or median (IQR).

AIH, autoimmune hepatitis; DBD, donation after brain death; DCD, donation after circulatory death; IQR, interquartile range; MELD, Model for End-stage Liver Disease; MMF, mycophenolate mofetil; NASH, nonalcoholic steatohepatitis; NMP, normothermic machine perfusion; PNF, primary nonfunction; T-Bil, total bilirubin.

between the 4 groups. In the Cox proportional hazards model for 3-y graft or patient survival, age was detected as a significant predictive factor, whereas NMP and DCD were not identified as significant factors (**Tables S4 and S5, SDC,** https://links.lww.com/TXD/A772).

Clinical Course of Patients Who Developed IC

Table S6 (**SDC,** https://links.lww.com/TXD/A772) shows the clinical course of patients who developed IC. Among 12 IC cases, 8 patients required >3 times a stent replacement within 1 y after the diagnosis. Two patients required repeated LT. Four patients died, 2 of whom succumbed to liver failure attributable to IC.

DISCUSSION

In this study, we investigated the effect of NMP on biliary complications in 450 cases post-LT between the NMP and non-NMP groups in each DBD or DCD group. Of these cases, 23.8% developed biliary complications by all causes within 180 d post-LT, with the highest incidence in the DCD without NMP group. The incidence of IC was significantly higher in the DCD without NMP group at 17.5% and 0% in using NMP cases for both DBD and DCD groups. In logistic regression analysis, it was found that the DCD was independently associated with the development of biliary complications by all causes after LT, whereas the NMP technique did not have an association with lowering the incidence of biliary

TABLE 2.

Comparison of intraoperative factors between donor groups

		DBD			DCD		
	All (N = 450)	Without NMP (N = 301)	With NMP (N = 34)	*P*	Without NMP (N = 57)	With NMP (N = 58)	*P*
EBL, mL	2100 (1450–4000)	2000 (1200–4000)	2000 (200–12000)	0.33	2750 (700–4000)	2500 (1500–5000)	0.36
Cold ischemia time, min	320 (255–383)	334 (290–384)	141 (107–378)	<0.01	320 (273–378)	165 (127–413)	<0.01
Warm ischemia time, min	31 (26–38)	31 (26–28)	32 (27–37)	0.81	30 (25–38)	31 (28–38)	0.26
Total operative time, min	389 (345–452)	382 (337–442)	421 (366–463)	0.051	393 (347–441)	437 (363–495)	0.03
PVT, n (%)	74 (17.5)	39 (13.9)	8 (24.2)	0.14	7 (13.5)	20 (34.5)	<0.01
PVT grade, n (%)				0.11			0.048
0	334 (82.1)	233 (86.3)	24 (75.0)		42 (84.0)	35 (63.6)	
1	46 (11.3)	19 (7.0)	5 (15.6)		7 (14.0)	15 (27.3)	
2	16 (3.9)	10 (3.7)	3 (9.4)		1 (2.0)	2 (3.6)	
3	11 (2.7)	8 (3.0)	0 (0.0)		0 (0.0)	3 (5.5)	

Continuous data are presented as mean ± SD or median (IQR).
DBD, donation after brain death; DCD, donation after circulatory death; EBL, estimated blood loss; IQR, interquartile range; NMP, normothermic machine perfusion; PVT, portal vein thrombosis.

TABLE 3.

Comparison of the rate of EAD, PNF, and biliary complications <180 d post–liver transplantation between donor groups

		DBD			DCD		
	All (N = 450)	Without NMP (N = 301)	With NMP (N = 34)	*P*	Without NMP (N = 57)	With NMP (N = 58)	*P*
EAD, n (%)	104 (23.3)	52 (17.5)	6 (17.7)	0.98	36 (63.2)	10 (17.2)	<0.01
PNF, n (%)	9 (2.1)	4 (1.4)	1 (3.1)	0.50	3 (5.4)	1 (1.8)	0.29
All biliary complications, n (%)	107 (23.8)	64 (21.3)	6 (17.7)	0.61	23 (40.4)	14 (24.1)	0.06
Ischemic-type biliary lesion, n (%)	12 (2.7)	2 (0.7)	0 (0)	0.52	10 (17.5)	0 (0)	<0.01
Anastomotic biliary complication, n (%)	95 (21.1)	62 (20.6)	6 (17.7)	0.68	13 (22.8)	14 (24.1)	0.87
Leak	21 (4.7)	12 (4.0)	1 (2.9)	0.76	5 (8.8)	3 (5.2)	0.45
Stricture	85 (18.9)	55 (18.3)	5 (14.7)	0.60	13 (22.8)	12 (20.7)	0.78
Duration between transplantation and the first ERCP	40 (13–82)	44 (14–89)	14 (9–71)	0.19	23 (12–70)	49 (21–79)	0.16

DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; ERCP, endoscopic retrograde cholangiopancreatography; PNF, primary nonfunction.

complications by all causes. When anastomotic biliary complications excluding IC were set as the outcome, NMP did not significantly reduce the risk of biliary anastomotic complications in both DBD and DCD groups. Although NMP might prevent IC after LT, the risk of biliary complications was not reduced regardless of NMP use.

NMP operates on the principle that organs can be preserved at physiological temperatures outside the body while retaining their metabolic functions.[15] This new technology may provide a strategy to optimize the use of potential donor liver grafts. Indeed, multiple previous studies have demonstrated that the implementation of NMP increases organ utilization.[3,9,16] The occurrence of biliary strictures in allografts after LT is related to the length of preservation time. In animal experiments, bile duct cells produced toxic oxygen species at a rate that was 5 times higher than that of hepatocytes, which suggested that bile duct cells are more vulnerable to reoxygenation injury than to anoxia.[17] Therefore, IC has been described as one of the most feared complications encountered with DCD donors. IC was primarily implicated in the higher risk of graft failure, multiple readmissions, biliary interventions, retransplantation, and mortality after LT.[18-20] It is true that improvements in donor selection, advancements in surgical techniques, and the introduction of thrombolytic protocols can decrease the risk of graft failure and IC in DCD donors, even before the rise of MP.[21] Whether NMP can serve as a preventive and therapeutic modality remains to be determined. However, it is also true that promising results have been emerging. Two randomized controlled trials have shown that NMP lessens ischemia/reperfusion injury in livers classified as low to intermediate risk.[2,22] In our study, there were no occurrences of IC in cases with NMP, regardless of DBD or DCD status, even after adjusting baseline characteristics of donors and recipients, suggesting a favorable effect of NMP on IC. This finding was in line with previous studies.

Biliary complications other than IC also remain a major source of morbidity and mortality in LT patients despite advances in technique, perioperative care, and immunosuppression.[23] Anastomotic biliary complications mainly arise from mechanical and surgical issues that may be related to interfering with the arterial blood flow to the bile duct.[24]

TABLE 4.

Logistic regression model for all biliary complications <180 days post–liver transplantation

Variables	Univariable		Multivariable	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Recipient				
Age	1.00 (0.98-1.02)	0.75	0.99 (0.97-1.02)	0.60
Male	1.28 (0.80-2.03)	0.31	1.21 (0.73-1.99)	0.45
Race (ref: White)		0.29		
Black	1.18 (0.55-2.54)			
Hispanic	0.20 (0.03-1.57)			
Asian	0.77 (0.16-3.67)			
Others	0.38 (0.05-3.10)			
Body mass index	1.02 (0.98-1.06)	0.28	1.02 (0.98-1.06)	0.37
Primary liver diseases				
Hepatitis C	0.84 (0.42-1.70)	0.63		
Alcohol	0.98 (0.63-1.51)	0.98		
NASH	0.88 (0.54-1.42)	0.59		
AIH	1.14 (0.44-2.96)	0.79		
HCC	1.31 (0.77-2.22)	0.32		
Final MELD score	0.98 (0.96-1.00)	0.10	0.98 (0.96-1.01)	0.26
T-Bil	0.98 (0.95-1.00)	0.07		
Immunosuppressant				
Tacrolimus	1.08 (0.60-1.95)	0.80		
Cyclosporine	2.03 (0.96-4.31)	0.06	2.07 (0.94-4.59)	0.07
MMF	0.98 (0.43-2.23)	0.98		
Steroid	1.59 (0.45-5.60)	0.47		
DCD donor	1.79 (1.12-2.87)	0.02	2.29 (1.29-4.07)	<0.01
NMP	0.86 (0.50-1.50)	0.60	0.54 (0.29-1.02)	0.06
Donor				
Age	1.01 (0.995-1.03)	0.18	1.02 (0.998-1.03)	0.08
Male sex	0.76 (0.49-1.19)	0.23	0.65 (0.40-1.06)	0.09
Race (ref: White)		0.99		
Black	1.05 (0.60-1.85)			
Hispanic	1.22 (0.54-2.73)			
Asian	–			
Others	0.93 (0.19-4.56)			
Body mass index	0.996 (0.97-1.03)	0.77	0.99 (0.95-1.02)	0.37
Cause of death (ref; anoxia)		0.21		
Cerebrovascular accident	1.52 (0.91-2.54)			
Trauma	1.42 (0.78-2.55)			
EBL	1.00 (0.99-1.00)	0.77		
Cold ischemia time	1.00 (0.99-1.00)	0.54		
Warm ischemia time	1.00 (0.99-1.01)	0.82	1.00 (0.99-1.01)	0.75
Total operative time	1.00 (0.99-1.00)	0.52		
Portal vein thrombosis	1.04 (0.58-1.87)	0.89		
PVT grade (ref: 0)		0.54		
1	0.99 (0.48-2.05)			
2	0.45 (0.10-2.03)			
3	1.81 (0.52-6.33)			

AIH, autoimmune hepatitis; CI, confidence interval; DCD, donor donation after circulatory death; EBL, estimated blood loss; HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease; MMF, mycophenolate mofetil; NASH, nonalcoholic steatohepatitis; NMP, normothermic machine perfusion; OR, odds ratio; PVT, portal vein thrombosis, T-Bil, total bilirubin.

According to a meta-analysis involving 61 studies with >14 000 LTs, the overall incidence of anastomotic strictures is reported to be approximately 13%.[25] The common risk factors for anastomotic strictures included advanced recipient age, female donor, failure to flush the donor duct, preceding bile leakage, and acute/chronic rejection.[26] As for bile leakage, it has been reported in 2%–25% of the patients after LT, which usually occurs at the anastomotic site.[27] Total operating time and bile duct reconstruction technique (duct-to-duct anastomosis or Roux-en-Y hepaticojejunostomy) were reported as the risk factors for bile leakage.[28] In our analysis, the incidence of anastomotic biliary complications (stricture, leak, or both) was 24.1% in the DCD with NMP group, which was comparable with the other groups. It could not be concluded that NMP was associated with anastomotic biliary complications from the results of the logistic regression analysis; however, possible protective effects of NMP on anastomotic biliary complications, which might be expected to be seen, were not observed in our series.

TABLE 5.

Logistic regression model for anastomotic biliary complications <180 d post–liver transplantation

	Univariable		Multivariable	
Variables	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
Recipient				
Age	0.998 (0.98-1.02)	0.85	1.00 (0.95-1.05)	0.96
Male sex	1.28 (0.79-2.09)	0.32	0.92 (0.35-2.41)	0.87
Race (ref: White)		0.45		
Black	1.21 (0.55-2.67)			
Hispanic	0.24 (0.03-1.86)			
Asian	0.91 (0.19-4.35)			
Others	0.45 (0.06-3.67)			
Body mass index	1.03 (0.99-1.07)	0.14	1.02 (0.94-1.09)	0.75
Primary liver diseases				
Hepatitis C	0.76 (0.36-1.62)	0.48		
Alcohol	0.97 (0.62-1.52)	0.89		
NASH	0.89 (0.53-1.47)	0.64		
AIH	1.34 (0.51-3.50)	0.55		
HCC	1.27 (0.73-2.20)	0.40		
Final MELD score	0.99 (0.96-1.01)	0.31	1.00 (0.95-1.06)	0.96
T-Bil	0.98 (0.95-1.01)	0.13		
Immunosuppressant				
Tacrolimus	1.20 (0.64-2.26)	0.57		
Cyclosporine	2.42 (1.14-5.15)	0.02	–	0.99
MMF	1.54 (0.58-4.11)	0.39		
Steroid	4.73 (0.62-36.0)	0.13		
DCD donor	1.20 (0.73-2.00)	0.47	2.34 (0.78-6.97)	0.13
NMP	1.05 (0.60-1.83)	0.87	0.61 (0.18-2.12)	0.44
Donor				
Age	1.01 (0.99-1.03)	0.28	0.99 (0.97-1.03)	0.96
Male (donor)	0.71 (0.45-1.13)	0.15	0.59 (0.23-1.52)	0.27
Race (ref: White)		0.995		
Black	0.99 (0.54-1.79)			
Hispanic	1.21 (0.52-2.79)			
Asian	–			
Others	1.08 (0.22-5.30)			
Body mass index (donor)	1.01 (0.98-1.04)	0.58	1.02 (0.97-1.08)	0.43
Cause of death (donor) (ref; anoxia)		0.38		
Cerebrovascular accident	1.48 (0.87-2.51)			
Trauma	1.10 (0.58-2.08)			
EBL	1.00 (0.99-1.00)	0.75		
Cold ischemia time	1.00 (0.999-1.00)	0.41		
Warm ischemia time	1.00 (0.99-1.01)	0.78	0.997 (0.97-1.02)	0.79
Total operative time	1.00 (0.99-1.00)	0.56		
Portal vein thrombosis	1.24 (0.68-2.23)	0.48		
PVT grade (ref: 0)		0.50		
1	1.19 (0.57-2.45)			
2	0.54 (0.12-2.42)			
3	2.16 (0.61-7.57)			

AIH, autoimmune hepatitis; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; EBL, estimated blood loss; HCC, hepatocellular carcinoma; MELD, Model for End-stage Liver Disease; MMF, mycophenolate mofetil; NASH, nonalcoholic steatohepatitis; NMP, normothermic machine perfusion; OR, odds ratio; PVT, portal vein thrombosis, T-Bil, total bilirubin.

Although NMP maintains blood circulation throughout the liver parenchyma, including the extrahepatic biliary system, there is a concern with peripheral circulation. When reviewing the patients with anastomotic biliary complications in NMP cases specifically, the cholangiopathy showed long segment extrahepatic anastomotic stricture in some cases. This may be in part due to the lack of adequate perfusion at the bile duct edge. This may be related to the surgical procurement techniques or cannulation technique placed on the NMP pump, which potentially led to similar anastomotic complication rates between the NMP and non-NMP groups. When placing the donor liver on an NMP pump, the cannula might be placed too deep or the size of the cannula might be too big, which could cause significant ischemic damage at the edge of the bile duct. Because of these concerns, we are currently trying to avoid disruption of periductal tissues containing capillaries and transecting the duct as low as possible (ideally intrapancreatic). It is also our practice to avoid oversized cannula for the bile duct and not to advance the cannula too far into the bile duct,

TABLE 6.

Multivariable logistic regression models for all biliary complications <180 days post–liver transplantation

	DBD group		DCD group	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (recipient)	1.01 (0.98-1.04)	0.50	0.95 (0.90-1.00)	0.06
Male (recipient)	1.03 (0.56-1.88)	0.93	1.35 (0.52-3.54)	0.54
BMI (recipient)	1.03 (0.98-1.08)	0.25	1.00 (0.93-1.04)	0.98
Final MELD score	0.99 (0.96-1.03)	0.73	0.97 (0.90-1.04)	0.34
cyclosporine	2.48 (1.01-6.09)	0.048	0.56 (0.07-4.18)	0.57
Age (donor)	1.02 (1.00-1.04)	0.04	1.00 (0.96-1.04)	0.88
Male (donor)	0.77 (0.43-1.38)	0.38	0.61 (0.23-1.62)	0.32
BMI (donor)	0.996 (0.96-1.04)	0.84	0.98 (0.93-1.04)	0.57
Warm ischemia time	0.999 (0.99-1.01)	0.90	1.03 (0.99-1.07)	0.20
NMP	0.68 (0.26-1.76)	0.42	0.48 (0.20-1.16)	0.10

BMI, body mass index; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; HR, hazard ratio; MELD, Model for End-stage Liver Disease; NMP, normothermic machine perfusion.

TABLE 7.

Multivariable logistic regression models for anastomotic biliary complications <180 d post–liver transplantation

	DBD group		DCD group	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age (recipient)	1.01 (0.95-1.08)	0.69	0.97 (0.88-1.07	0.56
Male (recipient)	1.61 (0.44-5.89)	0.47	0.48 (0.09-2.40)	0.37
BMI (recipient)	1.01 (0.92-1.12)	0.78	1.01 (0.89-1.15)	0.88
Final MELD score	0.999 (0.98-1.02)	0.84	0.94 (0.85-1.05)	0.81
Cyclosporine	–	0.99	–	0.99
Age (donor)	1.00 (0.96-1.04)	0.96	0.997 (0.93-1.07)	0.95
Male (donor)	0.32 (0.09-1.16)	0.08	1.71 (0.28-10.5)	0.56
BMI (donor)	1.03 (0.96-1.11)	0.44	1.02 (0.92-1.13)	0.72
Warm ischemia time	0.999 (0.98-1.02)	0.98	0.94 (0.85-1.05)	0.25
NMP	0.64 (0.08-5.34)	0.68	0.57 (0.11-2.85)	0.57

BMI, body mass index; CI, confidence interval; DBD, donation after brain death; DCD, donation after circulatory death; HR, hazard ratio; MELD, Model for End-stage Liver Disease; NMP, normothermic machine perfusion.

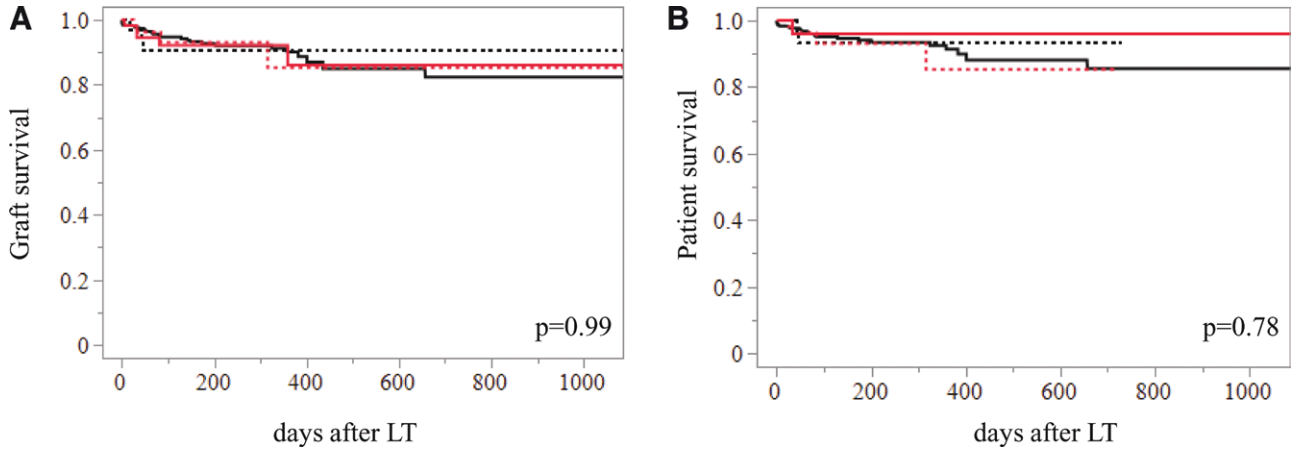

FIGURE 2. Kaplan-Meier analysis for 3-y graft survival (A) and 3-y patient survival (B) after LT. The solid black line represents DBD without NMP, the dashed black line represents DBD with NMP, the solid red line represents DCD without NMP, and the dashed red line represents DCD with NMP. There were no significant differences in both 3-y graft and patient survival between 4 groups. DBD, donation after brain death; DCD, donation after circulatory death; LT, liver transplant; NMP, normothermic machine perfusion.

as well as to avoid torque on the bile duct cannula once the liver is placed on a pump. Before starting the recipient biliary reconstruction, we trim the area of the potentially compromised bile duct to use a healthy cut edge for creation of our anastomosis. The length of bile duct trimming might need to be much longer than in non-NMP cases because it is unclear how well the peripheral circulation was preserved at the edge.

There are limitations in our study. First, this was a retrospective study conducted at a single institution. Second, the impact of CIT was not evaluated in this study as the way we calculated CIT changed during the study period; initially, we included all time after cross-clamp to reperfusion in the recipient surgery as CIT; however, as our understanding of the NMP technique grew, we subtracted the time on pump from our CIT. Another limitation is that our study does not evaluate concomitant hepatic artery pathology in the recipient, which may also contribute to IC. Future studies with longer follow-up periods are needed to understand the benefits and limitations of NMP to continue to verify our findings.

In conclusion, although NMP could prevent IC in DCD LT, it might not be protective against anastomotic biliary complications. Blood circulation to the biliary system, especially the extrahepatic duct, might not be adequate while the liver is placed on an NMP, which could lead to biliary complications. Further investigations would be warranted to confirm these findings, and better surgical techniques and bile duct tissue assessments should be explored.

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