Renal Dysfunction After Liver Transplantation: Effect of Donor Type

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Recipients of donation after circulatory death (DCD) grafts are reportedly at higher risk of developing renal dysfunction after liver transplantation (LT). We compared the development of acute kidney injury (AKI) and chronic kidney disease (CKD) after LT in recipients of DCD versus donation after brain death (DBD) or living donor liver transplantation (LDLT) livers. Adult recipients of DBD, LDLT, and DCD between 2012 and 2016 at Toronto General Hospital were included. AKI was defined as a post-LT increase of serum creatinine (sCr) ≥26.5 μmol/L within 48 hours or a ≥50% increase from baseline, and CKD was defined as an estimated glomerular filtration rate <60 mL/minute for >3 months. A total of 681 patients (DCD, n = 57; DBD, n = 446; and LDLT, n = 178) with similar baseline comorbidities were included. Perioperative AKI (within the first 7 postoperative days) was observed more frequently in the DCD group (61%; DBD, 40%; and LDLT, 44%; $P = 0.01$) and was associated with significantly higher peak AST levels ($P < 0.001$). Additionally, patients in the DCD group had a significantly higher peak sCr ($P < 0.001$) and a trend toward higher rates of AKI stage 3 (DCD, 33%; DBD, 21%; LDLT, 21%; $P = 0.11$). The proportions of recovery from AKI (DCD, 77%; DBD, 72%; LDLT, 78%; $P = 0.45$) and patients developing CKD (DCD, 33%; DBD, 32%; LDLT, 32%; $P = 0.99$) were similar. Nevertheless, patients who received DCD or DBD LT and required perioperative renal replacement therapy showed significantly lower patient survival in multivariate analysis (hazard ratio, 7.90; 95% confidence interval, 4.51-13.83; $P < 0.001$). In conclusion, recipients of DCD liver grafts experience higher rates of short-term post-LT renal dysfunction compared with DBD or LDLT. Additional risk factors for the development of severe kidney injury, such as high Model for End-Stage Liver Disease score, massive transfusions, or donor age ≥60 years should be avoided.

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Liver transplantation (LT) is the only definitive treatment option for selected patients with end-stage liver disease.[1] With growing numbers of patients on the waiting lists, there is a constantly increasing shortage of available organs. The use of marginal grafts for transplantation, such as grafts from donation after circulatory death (DCD) donors, is a major approach to extend the donor pool and to overcome this organ shortage. According to the United Network for Organ Sharing database, the number of grafts from DCD donors transplanted increased from 12% to 16% between 2012 and 2014 in North America.[2] The disadvantage of DCD grafts is a 10% lower 1-year graft survival rate and a distinct increase of biliary complications after transplantation.[3,4] Furthermore, it was reported previously that patients who received a DCD liver were also under higher risk to develop extrahepatic complications including renal dysfunction. The

Abbreviations: AKI, acute kidney injury; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; CCI, comprehensive complication index; CI, confidence interval; CIT, cold ischemia time; CKD, chronic kidney disease; CMV, cytomegalovirus; CNI, calcineurin inhibitor; DBD, donation after brain death; DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICU, intensive care unit; INR, international normalized ratio; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NSBB, nonselective beta-adrenergic blocker;

mechanisms behind the development of acute kidney injury (AKI) and chronic kidney disease (CKD) after LT are not completely understood yet. However, it has been suggested that besides recipient risk factors, donor quality is an important factor to determine longterm outcomes of kidney injury.[5,6] In 2012, Leithead et al. evaluated risk factors for AKI and CKD in 88 DCD liver recipients and compared the results to a propensity score–matched donation after brain death (DBD) population.[7] The authors reported a significantly higher incidence of AKI in DCD LT compared with DBD LT (DCD versus DBD, 53.4% versus 31.8%; $P = 0.004$). Furthermore, they found AKI to be a risk factor for CKD and mortality in DCD recipients.[7] Peak aspartate aminotransferase (AST) levels in the early posttransplant period were associated with renal dysfunction after LT.[7] During ischemia/reperfusion injury of the liver, a systemic inflammatory response is induced, which can directly lead to renal tubular cell death.[8] Other factors that have been described to increase the risk for the development of post-LT AKI and, later on, de novo CKD include pre-existing renal dysfunction and high Model for End-Stage Liver Disease (MELD) score.[9,10] Since post-LT renal complications have a significant negative impact on overall outcomes after LT, it is important to carefully evaluate the prevalence of AKI and CKD after LT in order to enable a potential necessary adaption of post-LT treatment protocols (eg, immunosuppression).

Using a recent series of a high-volume LT center, we aimed to compare the development of post-LT AKI and CKD in recipients of DBD, DCD, and living donor liver transplantation (LDLT) grafts and to assess its impact on longterm patient outcome.

Patients and Methods

PATIENT COHORT AND STUDY DESIGN

In this retrospective study, all LTs performed from January 2012 to December 2016 at the Multi-Organ Transplant Program, Toronto General Hospital, were included. Patients were grouped into DBD, LDLT, and DCD donors. Pediatric recipients (<18 years) and patients transplanted for fulminant liver failure, patients receiving domino or split LT, and patients with polycystic kidney disease were excluded. Additionally, patients who were in need of pretransplant renal replacement therapy (RRT) were removed from the analysis (total n = 30; DBD n = 23, DCD n = 4, LDLT n = 3). In cases of retransplantation, only the first transplantation was included in the analysis. Data were extracted from our prospectively maintained organ transplant tracking record and complemented by electronic or paper chart review. Data included demographics, renal history, transplantation-related data, donor data, follow-up laboratory values for recipients in terms of graft and kidney functions, and post-LT complications. The study has been approved by the ethics committee of the Toronto General Hospital, University Health Network, Toronto.

LIVER GRAFTS AND LT PROCEDURE

All DCD grafts that were included in this study were recovered from Maastricht category 3 donors. During DCD organ recovery, heparin (1000 IU/kg) was administered before withdrawal of life-sustaining therapies (WLST).[11] The maximal warm ischemia time (WIT) for DCD livers was 30 minutes and was defined from WLST until organ perfusion, without taking pO_2 levels or the mean arterial pressure into account. The WIT was only slightly extended in some exceptional circumstances depending on the surgeons'

OR, odds ratio; pRBC, packed red blood cells; RRT, renal replacement therapy; sCr, serum creatinine; UTI, urinary tract infection; WIT, warm ischemia time; WLST, withdrawal of life-sustaining therapies.

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judgement. In case of a DCD graft with an estimated steatosis of >10%, the organ was declined for transplantation. The recipient allocation of DCD and DBD grafts was based on the MELD score, with patients with hepatocellular carcinoma (HCC) receiving additional exception points. In the case of DCD grafts, the cold ischemia time (CIT) was aimed to stay below 8 hours, and recipients with complicated hepatectomies (need for vascular reconstructions or retransplantation) and/or portal vein thrombosis were therefore not considered for DCD LT. Donors for LDLT were only selected if they were in good health and did not suffer from underlying liver disease, abnormal liver tests, underlying medical conditions and comorbidities, or biliary and vascular anomalies.[12,13] Only donors with an age between 18 and 60 years and donor livers with <10% steatosis were considered for living donation.[14] Graft and donor remnant liver volumes and vascular anatomy were evaluated by triphasic computed tomography. Additionally, magnetic resonance cholangiography was undertaken for assessment of the biliary anatomy. The aim was to achieve a donor residual liver volume of ≥30% and a graft-to-recipient weight ratio of ≥0.8%.

A caval replacement technique was the preferred recipient procedure for DCD and DBD grafts. In all cases, the biliary anastomosis was preferably performed as a duct-to-duct anastomosis. Roux-en-Y hepaticojejunostomy was required in some cases because of underlying liver disease or unfavorable anatomical conditions.

DEFINITION OF AKI, CKD, AND POST-LT COMPLICATIONS

AKI was defined as an increase in serum creatinine (sCr) ≥26.5 μmol/L within 48 hours or a ≥50% increase from a stable baseline sCr (sCr at transplant) within the previous 3 months. The severity of AKI was classified as follows:

Stage 1: an increase in sCr ≥26.5 μmol/L or an increase ≥1.5-2 fold from baseline.
Stage 2: an increase in sCr >2-3× from baseline.
Stage 3: an increase in sCr >3× from baseline, or sCr ≥353.6 μmol/L with an acute increase ≥26.5 μmol/L, or initiation of RRT.

Baseline sCr was defined as stable sCr within 3 months prior to LT. The Cockcroft-Gault formula was used to calculate estimated glomerular filtration rate (eGFR), and CKD was defined as an eGFR <60 mL/minute for >3 months. Patients with AKI were subclassified into full recovery (sCr at 1 month ≤ sCr at LT or within 26.5 μmol/L from sCr at LT), partial recovery (sCr at 1 month < than peak sCr but > than sCr at LT +26.5 μmol/L), and no recovery.[15,16]

Post-LT complications were graded from grades 0-5 using the Clavien-Dindo classification.[17] Examples for the different grades include the following:

Grade 0: no complications.
Grade 1: nausea and vomiting or generalized edema.
Grade 2: urinary tract infection (UTI), pneumonia, or rejection.
Grade 3a: endoscopic or radiological treatment (eg, gastric ulcer bleeding, pneumothorax).
Grade 3b: surgical treatment (eg, bleeding or bile duct revision).
Grade 4a: acute renal failure or respiratory failure.
Grade 4b: multiorgan failure.
Grade 5: patient death.

Additionally, the comprehensive complication index (CCI) was calculated for all complications that were recorded during hospital admission or within the first 30 postoperative days in case of early discharge.[18,19] The CCI integrates all registered complications into a formula, producing a score with a range of 0-100 (CCI of 100 equals death). This validated score is based on the Clavien-Dindo classification.[19-21] Furthermore, the UK DCD risk score, a recently described model to predict graft loss, has been calculated for the DCD cohort.[22]

DATA ANALYSES

Statistical analysis was performed with SPSS, version 24.0 (IBM, Chicago, IL). Statistical differences in categorical variables were determined using chi-square or Fisher's exact test as appropriate. Differences in continuous variables were determined using 1-way analysis of variance or Kruskal-Wallis test as appropriate for the variable and distribution. Graft and patient survival estimates were calculated using the Kaplan-Meier method and compared by log-rank test. Logistic regression and Cox regression models were used to identify the association of variables with outcomes in patients with DBD and DCD LTs. Variables with P <0.200 in univariate analyses were included in multivariate analyses using backward stepwise selection. A P value of <0.05 was considered as statistically significant.

Results

DONOR AND RECIPIENT CHARACTERISTICS

A total of 681 patients (DCD, n = 57; DBD, n = 446; LDLT, n = 178) were included in this study. Detailed donor and recipient characteristics are shown in Table 1. Patients in the LDLT group were significantly younger ($P < 0.001$) and had a significantly lower median (IQR) MELD at the time of transplantation (LDLT, 15 [6-46]; DCD, 18 [6-40]; DBD, 17 [6-56]; $P = 0.03$). Patients in the DCD and DBD group were more often male when compared with the LDLT

TABLE 1. Pretransplant Recipient and Donor Characteristics and Laboratory Data at the Time of LT

	DCD (n = 57)	DBD (n = 446)	LDLT (n = 178)	*P* Value
Recipient characteristics				
Age, years	58 (19-71)	59 (19-73)	55 (18-70)	<0.001
BMI, kg/m^2	27 (18-45)	27 (17-46)	26 (17-41)	0.14
BMI ≥30 kg/m^2	20 (35)	119 (27)	43 (24)	0.27
Sex, male	43 (75)	327 (73)	99 (56)	<0.001
HCC indicated	29 (51)	207 (46)	50 (28)	<0.001
HCV positive	20 (35)	155 (35)	45 (25)	0.07
MELD at listing	16 (6-43)	16 (6-48)	15 (6-40)	0.38
MELD at transplant	18 (6-40)	17 (6-56)	15 (6-46)	0.03
Diabetes	4 (7)	69 (15)	26 (15)	0.23
Hypertension	9 (16)	98 (22)	30 (17)	0.25
NSBB	9 (16)	40 (9)	12 (7)	0.11
Diuretics	8 (14)	69 (15)	23 (13)	0.71
Hepatic encephalopathy	16 (28)	165 (37)	60 (34)	0.36
Ascites	29 (51)	233 (52)	97 (54)	0.84
Refractory ascites	14 (25)	71 (16)	35 (20)	0.19
Bilirubin, μmol/L	60 (9-845)	47 (4-1057)	46 (4-802)	0.73
INR	1.6 (0.9-3.6)	1.5 (0.9-7.5)	1.4 (0.9-4.7)	0.01
Creatinine, μmol/L	94 (44-549)	81 (34-852)	75 (42-438)	<0.001
AKI (within 18 months before LT)	15 (26)	87 (20)	23 (13)	0.04
Donor characteristics				
Age, years	44 (12-64)	53 (9-86)	36 (17-61)	<0.001
Age ≥60 years	6 (10.5)	146 (32.7)	1 (0.6)	<0.001
Sex, male	42 (74)	277 (62)	64 (36)	<0.001
BMI, kg/m^2	26 (17-37)	26 (14-49)	26 (16-40)	0.34
BMI ≥30 kg/m^2	7 (12)	88 (20)	25 (14)	0.13
Reason for death				0.15
Anoxia	16 (28)	99 (22)	—	
Trauma	10 (17)	56 (13)	—	
Cerebrovascular accident	13 (23)	170 (38)	—	
Other/unknown	18 (32)	121 (27)	—	
CIT, hours	6 (0.7-10.7)	7.1 (1.1-18.6)	1.5 (0.4-5.2)	<0.001
WIT–DCD, minutes*	24 (9-32)	—	—	
WIT recipient, minutes†	55 (32-151)	49 (13-749)	44 (15-103)	<0.001
Intraoperative characteristics				
Surgery time, hours	7.7 (4.9-13.1)	7.7 (3-18.8)	8 (3.5-13.9)	0.03
Blood loss, L	2.5 (0-19)	2 (0-44)	2 (0-17.4)	0.01
Transfusion of pRBC, units	4 (0-23)	3 (0-26)	2 (0-20)	0.001
Transfusion of >5 units of pRBC	18 (32)	112 (25)	31 (17)	0.04
Transfusion of platelets, units	3 (0-20)	2 (0-50)	0 (0-54)	0.001

NOTE: Data are given as median (range) or n (%).
*WIT for DCD organs prior to organ removal.
†WIT the organ is exposed to during implantation.

group ($P < 0.001$), with HCC being the main indication ($P < 0.001$). Most comorbidities were equally distributed between the 3 study groups. LDLT recipients displayed lower international normalized ratio (INR) values before transplantation ($P = 0.01$). Notably, median preoperative creatinine levels were significantly higher in the DCD and DBD groups (DCD, 94 [44-549] μmol/L; DBD, 81 [34-852] μmol/L; LDLT, 75 [42-438] μmol/L; $P < 0.001$). In addition, DCD organ recipients had an established pretransplant diagnosis of AKI more often when compared with DBD or LDLT (DCD, 26%; DBD, 20%; LDLT, 13%; $P = 0.04$).

DCD donors were significantly younger compared with DBD donors, and naturally, grafts were exposed to a longer period of WIT. Analysis of intraoperative characteristics revealed a significantly higher blood turnover in DCD recipients, which resulted in more transfusions of packed red blood cells (pRBC) and platelets (Table 1).

LIVER AND KIDNEY FUNCTION AFTER LT

Perioperative AKI within 7 days after transplantation occurred most frequently in the DCD group (61%; DBD, 40%; LDLT, 44%; $P = 0.01$; Table 2) and was associated with significantly higher post-LT peak AST levels (DCD versus DBD versus LDLT, 1960 [37-13,899] versus 937 [68-36,849] versus 498 [20-7998] IU/L; $P < 0.001$). Partitioned scatterplots revealed a good correlation of peak AST and the probability to develop post-LT AKI for all 3 types of donation (Supporting Fig. 1). Particularly in the DCD group, high AST levels show a high probability to develop AKI. In addition to a significantly higher post-LT peak sCr in the DCD group (DCD versus DBD versus LDLT, 136 [58-448] versus 114 [49-933] versus 103 [48-595] μmol/L; $P < 0.001$), there was a trend in the DCD group toward higher proportions of patients with AKI stage 2 (DCD, 23%; DBD, 15%; LDLT, 19%; $P = 0.16$) and stage 3 (DCD, 33%; DBD, 21%; LDLT, 21%; $P = 0.11$; Table 2) . Nevertheless, AKI recovery rates (DCD, 78%; DBD, 72%; LDLT, 79%; $P = 0.45$), and proportions evolving into CKD within the first year after transplantation (DCD, 30%; DBD, 29%; LDLT, 30%; $P = 0.99$) were comparable between the 3 groups. As expected, not all patients who developed CKD suffered from perioperative AKI. However, within the group of patients who developed CKD in the DCD group, a high proportion suffered from AKI stage 1 (18%) and stage 2 (29%; Table 2). The higher total rate of AKI in the DCD group was reflected by a higher proportion of patients with complications graded Clavien Dindo ≥3b (DCD: 44% versus DBD: 24% versus LDLT: 32%; $P = 0.003$) and consequently a higher median CCI score (DCD, 33.7 [0-100]; DBD, 20.9 [0-100]; LDLT, 20.9 [0-100]; $P = 0.01$; Table 2). The median UK DCD risk score was 6 (0-13), and a higher score was not associated with post-LT AKI ($P = 0.41$), post-LT RRT ($P = 0.26$), or development of CKD ($P = 0.14$) in logistic regression analysis in the DCD group. The post-LT length of intensive care unit (ICU) stay was longer in the DCD group compared with the DBD and the LDLT groups (median days [range], DCD, 5 [0-141]; DBD, 2 [0-77]; LDLT, 1 [0-33]; $P = 0.07$; Table 2).

FACTORS ASSOCIATED WITH THE DEVELOPMENT OF AKI IN DBD AND DCD LT

To identify factors associated with post-LT AKI, univariate and multivariate logistic regression models were calculated for DBD and DCD LT recipients (Table 3). High recipient body mass index (BMI), an indication of HCC, high MELD score at the time of transplantation, DCD donor organ, donor age ≥60 years, BMI ≥30 kg/m^2, and high transfusion requirements were identified as significant risk factors for the development of post-LT AKI in the univariate analysis. Interestingly, a history of pretransplant AKI could not predict post-LT AKI. In the multivariate analysis, high recipient BMI, MELD at the time of transplantation, type of transplant (DCD), donor BMI ≥30 kg/m^2, and the need for >5 units of pRBC remained independent risk factors (Table 3).

FACTORS ASSOCIATED WITH POST-LT RRT IN DBD AND DCD LT

Univariate and multivariate analyses were repeated with the need of post-LT RRT as an endpoint. MELD at transplant, donor age ≥60 years, and the requirement of >5 units of pRBC were independent significant risk factors for the need for post-LT RRT (Table 4). However, transplantation of a DCD graft did not show a significant impact on the need for RRT after LT (odds ratio [OR], 2.44; 95% confidence interval [CI], 0.93-6.43; $P = 0.07$; Table 4).

TABLE 2. Perioperative and Postoperative Outcomes

	DCD (n = 57)	DBD (n = 446)	LDLT (n = 178)	*P* Value
Postoperative laboratory values and kidney function				
Peak AST, U/L	1960 (37-13,899)	937 (68-36,849)	498 (20-7998)	<0.001
Peak ALT, U/L	1037 (112-8013)	633 (44-16,210)	425 (108-7509)	<0.001
Peak ALP, U/L	210 (45-558)	160 (41-1059)	122 (45-1791)	<0.001
Peak bilirubin, μmol/L	74 (17-545)	68 (9-703)	104 (10-1006)	<0.001
Peak INR	1.82 (1.21-7.19)	1.74 (1.13-6.42)	2.16 (1.23-8.36)	<0.001
Peak sCr (within 7 days), μmol/L	136 (58-448)	114 (49-933)	103 (48-595)	<0.001
AKI	35 (61)	179 (40)	79 (44)	0.01
Stage 1	3 (5)	19 (4)	7 (4)	0.91
Stage 2	13 (23)	65 (15)	34 (19)	0.16
Stage 3	19 (33)	95 (21)	38 (21)	0.11
AKI patients with full recovery after 1 month	27 (77)	128 (72)	62 (78)	0.45
AKI patients with partial recovery after 1 month	5 (14)	42 (23)	13 (16)	0.27
Creatinine after 1 month	96 (36-382)	89 (39-560)	76 (39-250)	<0.001
Perioperative RRT	7 (12)	25 (6)	10 (6)	0.13
CKD	17 (30)	129 (29)	54 (30)	0.99
CKD and AKI stage 1	3 (18)	5 (4)	3 (6)	0.06
CKD and AKI stage 2	5 (29)	14 (11)	18 (33)	0.001
CKD and AKI stage 3	6 (35)	32 (25)	13 (24)	0.62
Posttransplant ICU stay, days	5 (0-141)	2 (0-77)	1 (0-33)	0.07
Length of hospital stay, days	13 (6-141)	13 (3-174)	12 (6-161)	0.44
Postoperative complications				
Any complication	41 (72)	273 (61)	114 (64)	0.27
More than 1 complication	23 (40)	27 (6)	54 (30)	0.42
Clavien-Dindo				
Grade 3b	13 (23)	41 (9)	30 (17)	0.001
Grade 4a	8 (24)	46 (10)	21 (12)	0.65
Grade 4b	2 (4)	5 (1)	4 (2)	0.30
Grade ≥3b	25 (44)	108 (24)	57 (32)	0.003
CCI	33.7 (0-100)	20.9 (0-100)	20.9 (0-100)	0.01
CCI >60	6 (11)	25 (5.6)	10 (5.6)	0.328
Bacteremia	0	17 (4)	8 (4)	0.28
Lung infection	6 (11)	25 (6)	3 (2)	0.02
UTI	5 (9)	44 (10)	17 (10)	0.96
Peritonitis	2 (4)	12 (3)	10 (6)	0.20
CMV infection	0	15 (3)	4 (2)	0.31
Immunosuppression				
Basiliximab	31 (54)	192 (43)	178 (100)	<0.001
Cyclosporine	14 (25)	78 (17)	28 (16)	0.31
Tacrolimus	48 (84)	405 (91)	160 (90)	0.29
Sirolimus	11 (19)	62 (14)	15 (8)	0.06
Mycophenolate mofetil	27 (47)	149 (33)	43 (24)	0.003
Mycophenolic acid	43 (75)	363 (81)	144 (81)	0.56
Azathioprine	3 (5)	12 (3)	5 (3)	0.55
Survival				
Patient survival, %				0.03
1 year	87	92	96	
3 years	84	85	91	
5 years	64	83	91	

TABLE 2. *Continued*

	DCD (n = 57)	DBD (n = 446)	LDLT (n = 178)	*P* Value
Graft survival, %				0.10
1 year	86	91	94	
3 years	82	84	88	
5 years	62	82	86	

NOTE: Data are given as median (range) or n (%) unless otherwise noted.

TABLE 3. Logistic Regression Analysis of Variables Associated With Perioperative Development of AKI in Patients With DBD or DCD LT

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Recipient				
Age	0.99 (0.98-1.01)	0.56		
Sex, male	1.15 (0.77-1.72)	0.50		
BMI ≥30 kg/m^2	1.98 (1.33-2.93)	0.001	1.68 (1.04-2.70)	0.03
HCC indicated	1.50 (1.05-2.15)	0.02		
HCV positive	1.18 (0.81-1.70)	0.39		
MELD at transplant	1.03 (1.01-1.05)	<0.001	1.02 (1.00-1.05)	0.02
Pre-LT diabetes	1.00 (0.60-1.65)	0.99		
Pre-LT hypertension	0.93 (0.60-1.43)	0.74		
Hepatic encephalopathy	1.28 (0.89-1.85)	0.19		
Pre-LT ascites	1.41 (0.99-2.01)	0.06		
Refractory ascites	1.11 (0.70-1.78)	0.66		
Pre-LT AKI	1.03 (0.66-1.60)	0.89		
Donor, graft, and surgery				
Type of transplant, DCD	2.37 (1.35-4.18)	0.003	2.54 (1.35-4.80)	0.004
CIT	1.02 (0.93-1.11)	0.72		
Donor BMI ≥30 kg/m^2	1.74 (1.11-2.73)	0.02	1.88 (1.11-3.16)	0.02
Donor age ≥60 years	1.52 (1.03-2.52)	0.04		
Recipient WIT	1.01 (1.00-1.02)	0.09		
Transfusion of >5 units of pRBC	1.78 (1.19-2.66)	0.005	1.74 (1.08-2.80)	0.02

GRAFT AND PATIENT SURVIVAL AFTER LT

Graft and patient survival rates of the whole patient cohort are shown in Fig. 1. Patients who received a DCD graft had a slightly impaired longterm survival, which became apparent only after 3 years. The main reasons for death were recurrent HCC (DCD, 27%; DBD, 31%; LDLT, 31%) and sepsis/multiorgan failure (DCD, 46%; DBD, 26%; LDLT, 31%; Supporting Table 1). Kaplan-Meier curves were plotted to depict the impact of AKI and the need for RRT on survival. Overall, perioperative AKI had no effect on patient survival (log-rank *P*, 0.15; Fig. 2A). However, if patients developed AKI stage 3, they had a significantly lower 1-year survival rate (82% versus 95%; $P < 0.001$). The main reason for this was the high impact of post-LT RRT on post-LT survival. In patients who required RRT, survival was significantly impaired with 1-year survival rates of only 48% versus 95% (log-rank *P*, <0.001; Fig. 2B). This strong impact of RRT on patient survival was also seen in the Cox regression models of the DBD and DCD LT cohorts, where RRT was the strongest independent risk factor for post-LT death with a hazard ratio (HR) of 7.90 (95% CI 4.51-13.83; $P < 0.001$; Table 5). Additionally, the requirement of >5 units of pRBC during transplantation showed a significant impact on post-LT survival (HR, 1.86; 95%

TABLE 4. Logistic Regression Analysis of Variables Associated With Need of Perioperative RRT in Patients With DBD or DCD LT

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Recipient				
Age	1.03 (0.99-1.08)	0.16	1.04 (0.99-1.09)	0.10
Sex, male	1.52 (0.71-3.25)	0.28		
BMI ≥30 kg/m^2	1.40 (0.66-2.99)	0.38		
HCC indicated	0.87 (0.42-1.80)	0.71		
HCV positive	0.84 (0.39-1.82)	0.66		
MELD at transplant	1.04 (1.00-1.07)	0.04	1.04 (1.01-1.09)	0.02
Pre-LT diabetes	0.59 (0.18-2.00)	0.40		
Pre-LT hypertension	0.67 (0.25-1.78)	0.42		
Hepatic encephalopathy	0.93 (0.44-1.97)	0.84		
Pre-LT ascites	0.61 (0.29-1.26)	0.18	2.06 (0.94-4.48)	0.07
Pre-LT refractory ascites	0.69 (0.24-2.02)	0.50		
Pre-LT AKI	0.90 (0.36-2.25)	0.82		
Donor, graft, and surgery				
Type of transplant, DCD	2.36 (0.97-5.73)	0.06	2.44 (0.93-6.43)	0.07
CIT	0.93 (0.75-1.16)	0.52		
Donor BMI ≥30 kg/m^2	1.22 (0.51-2.91)	0.66		
Donor age ≥60 years	1.63 (0.78-3.40)	0.19	2.45 (1.08-5.53)	0.03
Recipient WIT	1.00 (1.00-1.01)	0.54		
Transfusion of >5 units of pRBC	3.13 (1.52-6.46)	0.002	2.84 (1.30-6.24)	0.01

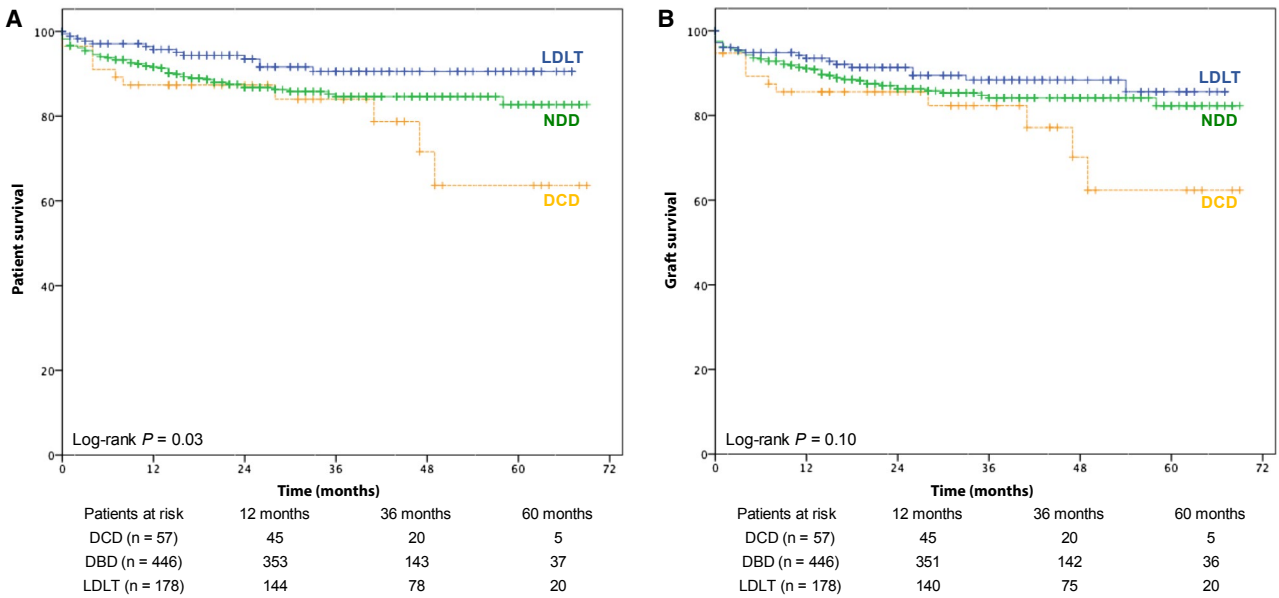

FIG. 1. (A) Patient survival and (B) graft survival are plotted in a Kaplan-Meier curve for recipients of DCD grafts (orange dotted line), DBD grafts (green line), and LDLT grafts (blue line). Number of patients at risk at 12, 36 and 60 months after transplantation are listed in the tables below the graphs.

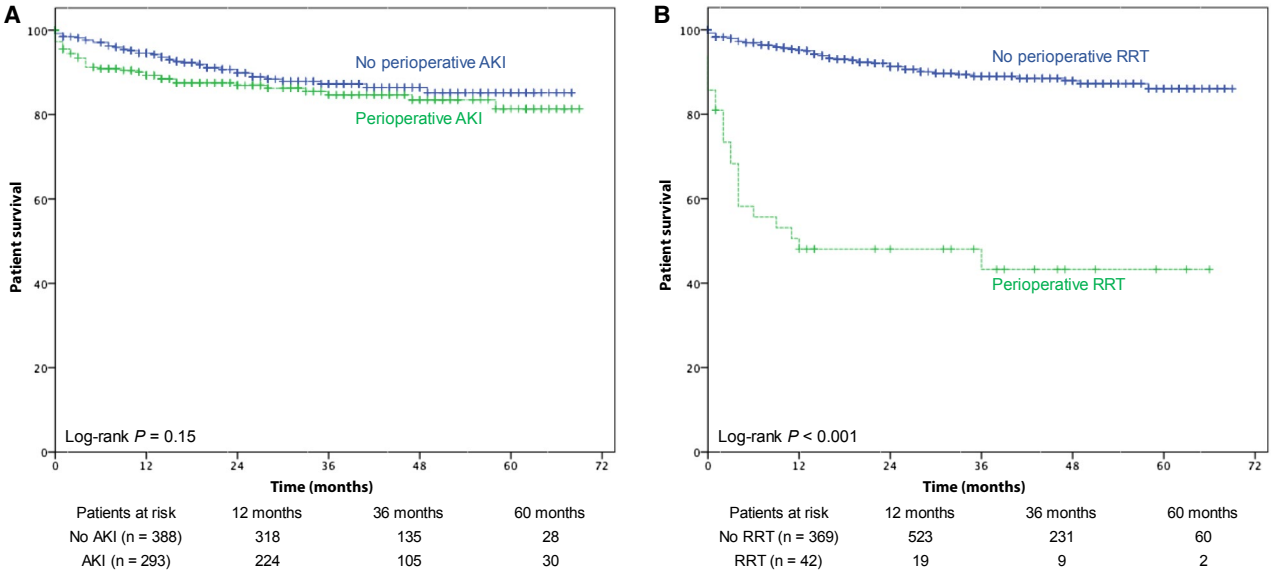

FIG. 2. Post-LT patient survival (A) of recipients developing perioperative AKI (green line) or no AKI (blue line) and (B) of those in need for post-LT RRT versus no RRT. Number of patients at risk at 12, 36, and 60 months after transplantation are listed in the tables below the graphs.

CI, 1.12-3.07; $P = 0.02$; Table 5). In further subanalyses of DCD and DBD recipients, recipient and donor characteristics and postoperative outcome parameters were compared between patients with and without the need for post-LT RRT (Supporting Tables 2 and 3). In DCD recipients, MELD at listing and at transplant and serum bilirubin and creatinine at transplant were significantly higher in patients with post-LT RRT compared with those without. Furthermore, in both DCD and DBD recipients, patients with the need of post-LT RRT showed significantly increased blood loss and need of pRBC. Additionally, peak levels of liver enzymes were significantly higher in patients with the need of post-LT RRT.

Discussion

Within the last years, DCD donation has been adopted by many LT centers to address increasing organ shortage. DCD donation is associated with higher rates of perioperative complications and a slightly reduced overall survival. In addition, there is limited evidence that DCD donation is also associated with a higher risk of perioperative kidney failure. The aim of this study was to revisit the impact of DCD on post-LT kidney function in a contemporary patient cohort from a large-volume center and to compare it with both LDLT and DBD donation.

The most comprehensive study on DCD and AKI has been published by the Birmingham group in 2012.[7] Leithead et al.[7] used the RIFLE (Risk, Injury, Failure, Loss, and End-Stage Kidney Disease) criteria to define perioperative kidney dysfunction, whereas in the current study the KDIGO (Kidney Disease: Improving Global Outcomes) criteria were applied.[15] Nevertheless, in a propensity score–matched analysis, the authors showed that DCD LT led to higher rates of AKI and CKD within the first 3 years of transplantation. In their cohort, AKI resulted in significantly lower 3- and 5-year survival rates.

We found several differences compared with the Birmingham cohort. First, perioperative AKI had no impact on overall survival in our cohort of patients. The reason for this is probably a high rate of full recovery within 1 month after LT (77%) and only a minority of patients with severe AKI after LT and the need for RRT. However, patients who developed AKI stage 3 showed significantly lower survival. Furthermore, the subgroup of patients with need for RRT after LT had a dismal prognosis, with a 48% survival rate within the first year after transplantation. Second, transfusion requirement was an

TABLE 5. Cox Regression Analysis on the Impact of Variables on Posttransplant Patient Mortality in Patients With DBD or DCD LT

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Recipient				
Age	1.01 (0.99-1.04)	0.31		
Sex, male	1.21 (0.68-2.14)	0.52		
BMI ≥30 kg/m^2	1.08 (0.63-1.86)	0.77		
HCC indicated	1.33 (0.82-2.15)	0.25		
HCV positive	1.49 (0.92-2.42)	0.10	1.56 (0.97-2.54)	0.07
MELD at transplant	1.02 (0.99-1.04)	0.21		
Pre-LT diabetes	1.17 (0.62-2.24)	0.63		
Pre-LT hypertension	1.14 (0.65-2.01)	0.64		
Hepatic encephalopathy	1.08 (0.66-1.76)	0.77		
Pre-LT ascites	0.97 (0.60-1.59)	0.93		
Pre-LT AKI	1.16 (0.66-2.02)	0.60		
Donor, graft, and surgery				
Type of transplant, DCD	1.51 (0.79-2.89)	0.21		
CIT	0.99 (0.88-1.12)	0.91		
Donor BMI ≥30 kg/m^2	1.52 (0.86-2.66)	0.15		
Donor age ≥60 years	1.40 (0.86-2.30)	0.18		
Recipient WIT	1.00 (0.99-1.01)	0.82		
Transfusion of >5 units of pRBC	2.24 (1.37-3.65)	0.00	1.86 (1.12-3.07)	0.02
Posttransplant parameters				
Perioperative AKI	1.31 (0.81-2.12)	0.27		
Perioperative RRT	8.76 (5.08-15.12)	<0.001	7.90 (4.51-13.83)	<0.001
CKD	1.16 (0.64-2.09)	0.63		
Bacteremia	2.63 (1.06-6.54)	0.04		
Lung infection	0.83 (0.30-2.28)	0.72		
UTI	0.68 (0.27-1.68)	0.34		
Peritonitis	1.46 (0.46-4.67)	0.52		
CMV infection	1.62 (0.51-5.17)	0.41		

important and independent risk factor for post-LT AKI as well as the need for RRT in our patient cohort but was less relevant in the Birmingham cohort. The amount of pRBC seems to play a critical role since in our cohort transfusion requirements >5 units correlated with an impaired post-LT kidney function. This is well in-line with literature on cardiac[23] and vascular surgical patients[24] as well as non-DCD LT patients.[25]

Recipient selection is a critical factor to reduce post-LT AKI. In our patient cohort, a history of pre-LT AKI as well as higher sCr at the time of transplant had no impact on post-LT kidney function. Patients with the need of pretransplant RRT were excluded from analyses in this study, due to the known impact on posttransplant renal insufficiency and patient survival. Therefore, prerenal azotemia was the origin of pretransplant AKI in the majority of patients. This might explain the lower impact on post-LT outcome compared with other studies. Prerenal azotemia was treated with volume replacement with albumin and the removal of all diuretics.

We could confirm previously published data, showing that peak AST was associated with post-LT AKI.[26] AST is a well-established surrogate marker of hepatic ischemia/reperfusion injury.[27] We could show that after correcting for other confounding factors, levels of peak AST correlated with the probability to develop AKI (Supporting Fig. 1). The development of AKI after transplantation is multifactorial. Besides the hemodynamic instability and renal ischemia during transplantation, severe ischemia/reperfusion

injury triggers an inflammatory cascade that leads to a systemic inflammatory response.[28] The systemic inflammatory response is responsible for multiorgan dysfunction,[29,30] and high-risk organs, such as DCD grafts, are more susceptible to ischemia/reperfusion injury. A DCD LT was an independent risk factor for the development of AKI in this study (OR, 2.54; 95% CI, 1.35-4.80; $P = 0.004$). In case of post-LT AKI, adaption of immunosuppression to a renal-sparing regimen is essential.[31] AKI was not an independent predictor for the development of post-LT CKD or RRT. Even more so, our data show that a high proportion of patients who developed CKD did not suffer from AKI after transplantation. This underlines the still unsolved problem of chronic kidney damage caused by longterm immunosuppression. Although no uniform algorithm is followed in our center, we aim to minimize calcineurin inhibitors (CNIs) by introducing a second agent (proliferation inhibitor) in patients with impaired kidney function. Patients without proteinuria are switched to mTOR inhibitors. Furthermore, delayed introduction of CNI-sparing protocols has been shown to be safe with excellent longterm kidney function.[32,33] Basiliximab as induction therapy with a delayed introduction of CNIs is currently only standard in patients with LDLT at our institution. Additionally, all deceased donor recipients (DCD or DBD) with AKI receive basiliximab in order to delay the introduction of CNIs. In total, 54% of patients received basiliximab as induction therapy in the DCD cohort, and delayed introduction in this group, which is most prone to post-LT kidney injury, should be further investigated.

AKI stage 3 and the need for post-LT RRT had a strong impact on post-LT survival. The development of post-LT AKI was associated with a high MELD at transplant and a high recipient BMI (possibly related to significant inflammation associated with nonalcoholic fatty liver disease).[34] We believe that these factors should alert the transplant team to pre-emptively adapt post-LT therapies, including a delayed introduction of CNIs. Furthermore, in DCD recipients, a high MELD score and high sCr at transplant predisposed to the need of post-LT RRT. Therefore, allocation of DCD organs to patients with these factors should be carefully evaluated. Recipients of DCD organs were more often in need of post-LT RRT compared with recipients of DBD organs (12% versus 6%); however, this did not reach significance. Notably, this impact might be stronger in a larger cohort of DCD recipients. In the Cox regression analysis, DCD was not an independent predictor of post-LT survival. Nevertheless, patients who received a DCD organ showed poorer longterm patient survival when compared with DBD or LDLT recipients. Overall, the accumulation of risk factors should be avoided since this increases the risk for post-LT RRT, finally leading to an increased mortality.

This study has several limitations. First, it is a single-center analysis, and statistical power is thus limited by the sample size. However, this single-center approach facilitates data reporting at a granular level, which cannot be reached in large multicenter studies or registry analyses. In addition, the number of DCD recipients was relatively small in this cohort. Studies with a larger sample size and a multi-institutional approach to study kidney function after LT would be desirable. Notably, hypothermic machine perfusion of liver grafts prior to transplantation has recently been shown to reduce postreperfusion injury as well as instances of stage 2-3 AKI after transplantation.[35] Further studies investigating the impact of the various types of machine perfusion on post-LT kidney injury are needed.

In conclusion, we found that recipients of DCD organs have a higher rate of short-term post-LT renal dysfunction compared with DBD or LDLT liver recipients. However, in most cases, kidney impairment is restricted to mild-to-moderate AKI, which has no impact on post-LT survival. To prevent severe kidney failure, which directly impacts mortality, risk factors including massive transfusions and donor age >60 years should be avoided. Furthermore, allocation of DCD organs to patients with high MELD score and high sCr should be avoided because those factors were associated with the need of post-LT RRT.

REFERENCES

1) Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al.; for all contributing centers; European Liver and Intestine Transplant Association (ELITA). Evolution of indications and results of liver transplantation in Europe. a report from the European Liver Transplant Registry (ELTR). J Hepatol 2012;57:675-688.
2) Scalea JR, Redfield RR, Foley DP. Liver transplant outcomes using ideal donation after circulatory death livers are superior to using older donation after brain death donor livers. Liver Transpl 2016;22:1197-1204.
3) Abt P, Crawford M, Desai N, Markmann J, Olthoff K, Shaked A. Liver transplantation from controlled non-heart-beating donors: an increased incidence of biliary complications. Transplantation 2003;75:1659-1663.

4) Foley DP, Fernandez LA, Leverson G, Anderson M, Mezrich J, Sollinger HW, D'Alessandro A. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. Ann Surg 2011;253:817-825.
5) Doyle MB, Collins K, Vachharajani N, Lowell JA, Shenoy S, Nalbantoglu I, et al. Outcomes using grafts from donors after cardiac death. J Am Coll Surg 2015;221:142-152.
6) Umbro I, Tinti F, Scalera I, Evison F, Gunson B, Sharif A, et al. Acute kidney injury and post-reperfusion syndrome in liver transplantation. World J Gastroenterol 2016;22:9314-9323.
7) Leithead JA, Tariciotti L, Gunson B, Holt A, Isaac J, Mirza DF, et al. Donation after cardiac death liver transplant recipients have an increased frequency of acute kidney injury. Am J Transplant 2012;12:965-975.
8) Bonventre JV, Weinberg JM. Recent advances in the pathophysiology of ischemic acute renal failure. J Am Soc Nephrol 2003;14:2199-2210.
9) Cabezuelo JB, Ramirez P, Rios A, Acosta F, Torres D, Sansano T, et al. Risk factors of acute renal failure after liver transplantation. Kidney Int 2006;69:1073-1080.
10) O'Riordan A, Wong V, McQuillan R, McCormick PA, Hegarty JE, Watson AJ. Acute renal disease, as defined by the RIFLE criteria, post-liver transplantation. Am J Transplant 2007;7:168-176.
11) Kollmann D, Sapisochin G, Goldaracena N, Hansen BE, Rajakumar R, Selzner N, et al. Expanding the donor pool: donation after circulatory death and living liver donation do not compromise the results of liver transplantation. Liver Transpl 2018;24:779-789.
12) Sapisochin G, Goldaracena N, Laurence JM, Levy GA, Grant DR, Cattral MS. Right lobe living-donor hepatectomy-the Toronto approach, tips and tricks. Hepatobiliary Surg Nutr 2016;5:118-126.
13) Kollmann D, Goldaracena N, Sapisochin G, Linares I, Selzner N, Hansen BE, et al. Living donor liver transplantation using selected grafts with 2 bile ducts compared with 1 bile duct does not impact patient outcome. Liver Transpl 2018;24:1512-1522.
14) Goldaracena N, Sapisochin G, Spetzler V, Echeverri J, Kaths M, Cattral MS, et al. Live donor liver transplantation with older (≥50 years) versus younger (<50 years) donors: does age matter? Ann Surg 2016;263:979-985.
15) Wong F. The evolving concept of acute kidney injury in patients with cirrhosis. Nat Rev Gastroenterol Hepatol 2015;12:711-719.
16) Wong F. Acute kidney injury in liver cirrhosis: new definition and application. Clin Mol Hepatol 2016;22:415-422.
17) Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-213.
18) Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1-7.
19) Clavien PA, Vetter D, Staiger RD, Slankamenac K, Mehra T, Graf R, Puhan MA. The comprehensive complication index (CCI): added value and clinical perspectives 3 years "down the line." Ann Surg 2017;265:1045-1050.
20) Kalisvaart M, de Haan JE, Polak WG, Metselaar HJ, Wijnhoven BPL, IJzermans JNM, de Jonge J. Comparison of postoperative outcomes between donation after circulatory death and donation after brain death liver transplantation using the comprehensive complication index. Ann Surg 2017;266:772-778.
21) Yamashita S, Sheth RA, Niekamp AS, Aloia TA, Chun YS, Lee JE, et al. Comprehensive complication index predicts cancer-specific survival after resection of colorectal metastases independent of RAS mutational status. Ann Surg 2017;266:1045-1054.
22) Schlegel A, Kalisvaart M, Scalera I, Laing RW, Mergental H, Mirza DF, et al. The UK DCD risk score: a new proposal to define futility in donation-after-circulatory-death liver transplantation. J Hepatol 2018;68:456-464.
23) Freeland K, Hamidian Jahromi A, Duvall LM, Mancini MC. Postoperative blood transfusion is an independent predictor of acute kidney injury in cardiac surgery patients. J Nephropathol 2015;4:121-126.
24) Nonaka T, Kimura N, Hori D, Sasabuchi Y, Nakano M, Yuri K, et al. Predictors of acute kidney injury following elective open and endovascular aortic repair for abdominal aortic aneurysm. Ann Vasc Dis 2018;11:298-305.
25) Hilmi I, Horton CN, Planinsic RM, Sakai T, Nicolau-Raducu R, Damian D, et al. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. Liver Transpl 2008;14: 504-508.
26) Jochmans I, Meurisse N, Neyrinck A, Verhaegen M, Monbaliu D, Pirenne J. Hepatic ischemia/reperfusion injury associates with acute kidney injury in liver transplantation: prospective cohort study. Liver Transpl 2017;23:634-644.
27) Olthoff KM, Kulik L, Samstein B, Kaminski M, Abecassis M, Emond J, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. Liver Transpl 2010;16:943-949.
28) Dar WA, Sullivan E, Bynon JS, Eltzschig H, Ju C. Ischaemia reperfusion injury in liver transplantation: cellular and molecular mechanisms. Liver Int 2019;39:788-801.
29) Park SW, Kim M, Brown KM, D'Agati VD, Lee HT. Paneth cell-derived interleukin-17A causes multiorgan dysfunction after hepatic ischemia and reperfusion injury. Hepatology 2011;53:1662-1675.
30) Aldrighetti L, Pulitanò C, Arru M, Finazzi R, Catena M, Soldini L, et al. Impact of preoperative steroids administration on ischemia-reperfusion injury and systemic responses in liver surgery: a prospective randomized study. Liver Transpl 2006;12:941-949.
31) Gotthardt DN, Bruns H, Weiss KH, Schemmer P. Current strategies for immunosuppression following liver transplantation. Langenbecks Arch Surg 2014;399:981-988.
32) Mouzaki M, Yap J, Avinashi V, Babu A, Fu A, Deangelis M, et al. Basiliximab with delayed introduction of calcineurin inhibitors as a renal-sparing protocol following liver transplantation in children with renal impairment. Pediatr Transplant 2013;17:751-756.
33) Verna EC, Farrand ED, Elnaggar AS, Pichardo EM, Balducci A, Emond JC, et al. Basiliximab induction and delayed calcineurin inhibitor initiation in liver transplant recipients with renal insufficiency. Transplantation 2011;91:1254-1260.
34) Fricker ZP, Pedley A, Massaro JM, Vasan RS, Hoffmann U, Benjamin EJ, Long MT, et al. Liver fat is associated with markers of inflammation and oxidative stress in analysis of data from the Framingham Heart Study. Clin Gastroenterol Hepatol 2019;17:1157-1164.
35) Patrono D, Surra A, Catalano G, Rizza G, Berchialla P, Martini S, et al. Hypothermic oxygenated machine perfusion of liver grafts from brain-dead donors. Sci Rep 2019;9:9337.