Comparative Study of Acute Kidney Injury in Liver Transplantation: Donation after Circulatory Death versus Brain Death

Hilger, Benedikt ; Frick, Katja ; Erlebach, Rolf ; Dutkowski, Philipp ; Andermatt, Rea ; David, Sascha ; Schüpbach, Reto A ; Klinzing, Stephanie

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Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABDEF 1 Benedikt Hilger
B 1 Katja Frick
CD 1 Rolf Erlebach
E 2 Philipp Dutkowski
DEF 1 Rea Andermatt
AE 1 Sascha David
E 1 Reto A. Schüpbach
ADE 1 Stephanie Klinzing

1 Institute of Intensive Care Medicine, University Hospital of Zurich, Zurich, Switzerland
2 Department of Surgery and Transplantation, University Hospital of Zurich, Zurich, Switzerland

Corresponding Author: Benedikt Hilger, e-mail: benedikt.hilger@usz.ch
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Background: Acute kidney injury (AKI) after orthotopic liver transplantation (OLT) contributes to morbidity and mortality. Donation after circulatory death (DCD) has been established to increase the pool of organs. While surgical complications are reported to be comparable in DCD and donation after brain death (DBD) OLT, there is a knowledge gap concerning adverse kidney events in these 2 groups.

Material/Methods: In this retrospective cohort study, 154 patients received a DBD and 68 received a DCD organ (2016-2020). The primary outcome was a major adverse kidney event within 30 days (MAKE-30). The secondary outcome was dynamics of AKI and kidney replacement therapy (KRT) during the first postoperative week and on postoperative day 30. Incidence and resolution from AKI and KRT and patient survival (PS) 30 days after OLT were compared between the DCD and DBD recipients.

Results: MAKE-30 incidence after OLT was comparable in DCD (n=27, 40%) vs DBD (n=41, 27%) recipients (risk ratio 1.49 [95% CI 1.01, 2.21], p=0.073). AKI incidence was comparable in DCD (n=58, 94%) vs DBD (n=95, 82%) recipients (risk ratio 1.14 [95% CI: 1.03, 1.27], *P*=0.057). Overall, 40% (n=88) of patients required KRT, with no difference between DCD (n=27, 40%) vs DBD (n=61, 40%) recipients (risk ratio 1.00 [95% CI 0.71, 1.43], *P*>0.999). Resolution of AKI by day 30 was lower in DCD (n=29, 50%) than in DBD (n=66, 69%) recipients (risk ratio 0.71 [95% CI: 0.53, 0.95], *P*=0.032). Survival after 30 days (DCD: n=64, 94% vs DBD: n=146, 95%, risk ratio 0.99 [95% CI 0.93, 1.06], *P*>0.999) was also comparable.

Conclusions: MAKE-30, short-term renal outcome, and survival did not significantly differ between DBD and DCD-OLT. Resolution of AKI by day 30 was lower in DCD than in DBD recipients.

Keywords: **Acute Kidney Injury • Liver Failure • Liver Transplantation**

Abbreviations: **AKI** – acute kidney injury; **BMI** – body mass index; **DBD** – donation after brain death; **DCD** – donation after cardiac death; **eGFR** – estimated glomerular filtration rate; **HIRI** – hepatic ischemia-reperfusion injury; **HOPE** – hypothermic oxygenated machine perfusion; **ICU** – Intensive Care Unit; **KDIGO** – kidney disease improving global outcomes; **KRT** – kidney replacement therapy; **MAKE** – major adverse kidney events; **MAKE-30** – major adverse kidney events on day 30; **MELD** – model for end-stage liver disease; **OLT** – orthotopic liver transplantation; **POD** – postoperative day; **PS** – patient survival; **SCr** – serum creatinine; **SIRS** – systemic inflammatory response syndrome; **WIT** – warm ischemic time

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Introduction

Acute kidney injury (AKI) is a common complication in the setting of orthotopic liver transplantation (OLT) that substantially contributes to morbidity and mortality [1-4]. Due to the global organ shortage, donor criteria were extended, and in addition to donation after brain death (DBD), donation after circulatory death (DCD) has been established [5-8]. DCD is increasingly used around the world and accounts for approximately 30% of the donations in Switzerland [9]. DCD was initially associated with a high incidence of complications, including ischemic cholangiopathy, primary graft dysfunction, vascular complications, and AKI [3,10-13]. DCD recipients are prone to develop postoperative systemic inflammatory response syndrome (SIRS) due to the additional donor warm ischemic time (WIT). SIRS, in turn, is a well-known trigger for the development of multiple organ dysfunction, including AKI [2,3,14-16]. However, recent studies suggest that survival [17-20] and complication rates in DCD and DBD recipients are comparable [21,22].

The objective of this study was to analyze the short-term renal outcome based on major adverse kidney event within 30 days (MAKE-30) and the incidence and resolution from AKI and kidney replacement therapy (KRT) in DCD and DBD recipients of OLT.

To date, few comparative analyses have been carried out concerning the 2 transplant allocation strategies in relation to renal function [1,23], and none have studied the outcome parameter MAKE. The outcome parameter MAKE-30 consists of the composite of death, newly-started KRT, or persistent worsening of kidney function within 30 days after the intervention [24]. This outcome parameter is valuable in assessing the short-term renal outcome in DCD and DBD recipients.

Material and Methods

Study design

All patients who had undergone deceased-donor liver transplantation at the University Hospital of Zurich from January 1, 2016 to April 30, 2020 (n=231) were eligible for this retrospective study. Only patients who had undergone combined liver-kidney transplantation (n=9) were excluded. In the study cohort (n=222), 154 patients (69%) underwent OLT after DBD and 68 patients (31%) underwent OLT after DCD (**Figure 1**). The study period was chosen due to the availability of comprehensive information on the study cohort over this timeframe, facilitated by a meticulously curated database. The study was approved by the Institutional Ethics Committee of Zurich (BASEC-Nr. 2020-00188). All patients provided written informed consent for data analysis before transplantation.

Data collection and Outcome Parameters

Electronic patient records were screened, and baseline demographic characteristics as well as graft-specific and operative data were recorded. The data extraction was performed manually by a medical staff member and double-checked for accuracy. The data were primarily collected in Microsoft Excel, then secondarily transcribed to R (version 4.1.1), and analyzed using R Studio software for statistical analysis.

We defined the date of transplantation as the baseline and termed it postoperative day (POD) 0. All other days referred to POD 0. Laboratory data were extracted 30 days before transplantation (POD -30), on the day of transplantation (POD 0), daily during the first postoperative week (POD 1-7) and 1 month after transplantation (POD 30±1). Laboratory data on POD -30 were approximated from the blood test temporally closest to POD -30.

Laboratory data included serum creatinine (SCr), serum sodium, international normalized ratio, platelets, and total bilirubin levels. The 2021 CKD-EPI Creatinine equation (without race) was used to calculate the estimated glomerular filtration rate (eGFR) [25]. Additionally, the model for end-stage liver disease (MELD) score [26], Charlson Comorbidity Index [27], and Sequential Organ Failure Assessment score [28] were calculated. At the same time points, the dependency on KRT was analyzed. Patient survival (PS) was registered on day 30 and 1 year after OLT. The WIT was defined as a mean arterial pressure lower than 50 mmHg until the beginning of cold flush of the organ and the cold ischemia time from cross-clamp time in DBD, respectively, and cold flush in DCD until organ reperfusion in the recipient.

The primary outcome for analysis was the incidence of MAKE-30 after OLT with DBD or DCD grafts. Secondary outcomes were incidence and resolution from AKI and KRT, PS 30 days and 1 year after OLT, and length of stay in the Intensive Care Unit (ICU).

Allocation, Operative, and Immunosuppressive Management

DBD livers were obtained using a standard retrieval protocol. DCD livers were harvested using the super-rapid retrieval technique [29], followed by cold storage with the Institute-George-Lopez-1 solution [30,31]. DCD allocation was guided by the UK DCD Risk Score [32]. All DCD and marginal DBD liver grafts received hypothermic oxygenated liver perfusion (HOPE) treatment during recipient hepatectomy according to institutional practice. Organ implantation was performed according to the center's routine approach using the classic cava-replacement technique without venovenous bypass. Reperfusion was

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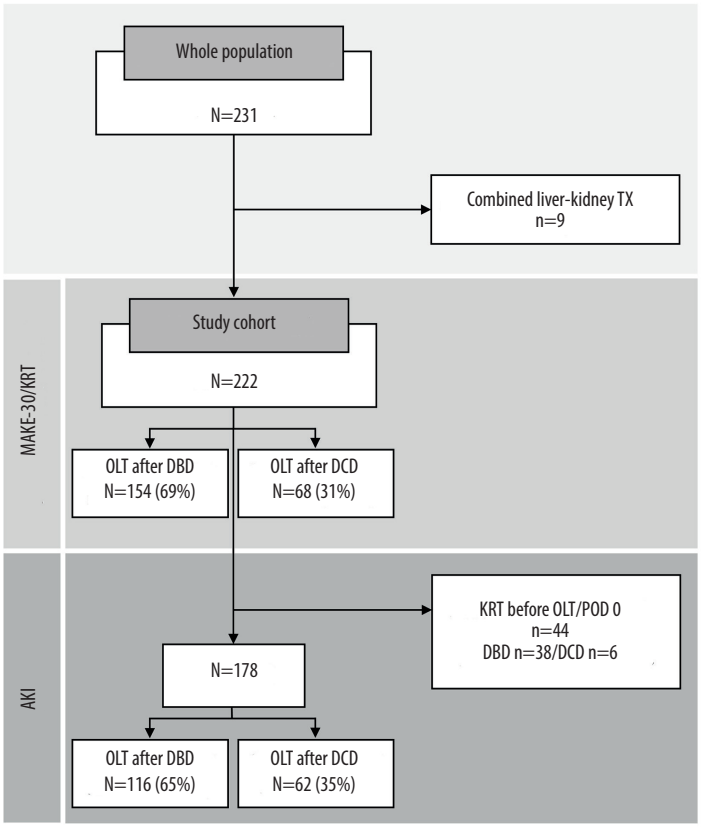

Figure 1. The flow diagram for inclusion and exclusion shows the appropriate study population for the analysis in question. DBD – donation after brain death; DCD – donation after cardiac death; KRT – kidney replacement therapy; OLT – orthotopic liver transplantation; POD – postoperative day; TX – transplantation.

initiated through the portal vein, followed by arterial reperfusion [30]. Immunosuppression was implemented according to the center guidelines, with methylprednisolone (intraoperative: 500 mg, POD 1: 250 mg, POD 2: 165 mg, POD 3: 100 mg, POD 4: 60 mg, POD 5: 40 mg) switched to prednisolone on POD 6 (POD 6-21: 20 mg, POD 22-30: 15 mg), and with tacrolimus started POD 1-5, adjusted for kidney function and induction (starting dose: 0.025 mg/kg body weight twice a day enteral; daily target drug level 4-6 µg/l). All DCD and DBD recipients with an eGFR of <40 ml/min/1.73 m^2 received Basiliximab (20 mg i.v.) induction and repetition on POD 4.

Major Adverse Kidney Events (MAKE)

The incidence of MAKE after AKI as a combined outcome parameter was developed in 2010 [24], and has been used in major landmark trials analyzing the efficacy of interventions [33-36]. Qualities, benefits, and feasibility of the outcome parameter have been demonstrated and recommended several times [33-37]. MAKE-30is defined as the composite of death, newly-started KRT, or persistent worsening of kidney function (defined as persistent SCr value ≥200% of the baseline SCr value) within 30 days after intervention. The baseline was defined as kidney function represented by SCr on the date of OLT before transplantation (POD 0). Patients who had received KRT at baseline did not fulfill the criteria for being counted as new KRT or worsening of kidney function, but could be classified under MAKE-30 if they died within 30 days after OLT.

Acute Kidney Injury (AKI)

AKI was defined according to the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines [38] as an increase in serum creatinine (SCr) ≥26.5 µmol/l within 48 h or an increase in SCr ≥1.5 the baseline value within 7 days [24]. The baseline was defined as kidney function represented by SCr and dependence on KRT on the date of OLT before transplantation (POD 0). Therefore, patients with pre-transplant AKI and acute chronic kidney disease were included in the study. Patients undergoing KRT before OLT were excluded from the AKI analysis. According to KDIGO classification, AKI was subsequently subdivided into Stage 1: rise in SCr of ≥26.5 µmol/l within 48 h or a rise of 1.5-1.9 times baseline; Stage 2: rise in SCr of 2.0-2.9 times baseline; Stage 3: rise in SCr to ≥3.0 times baseline or increase to ≥353.6 µmol/l or need for KRT [38]. Urine output was not available at all collection times and consequently was not used for this study. Resolution of AKI on POD 30 was defined as the absence of AKI criteria and

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survival on POD 30 in patients with AKI on POD 1-7. Patients with KRT on POD 0 met the definition of AKI resolution when they were without KRT on POD 30. No resolution of AKI on POD 30 was defined as persistent KRT; SCr >353.6 µmol/l; SCr POD 30 divided by SCr POD 0 ≥1.5; died.

Kidney Replacement Therapy (KRT)

KRT was performed as continuous KRT, sustained low-efficiency daily dialysis, or intermittent hemodialysis. The choice of dialysis modality was guided by hemodynamic stability and availability. The initiation of KRT and choice of mode followed institutional guidelines based on current scientific knowledge [39,40]. The decision was an individualized assessment of the patient's hemodynamic stability and signs of volume overload by the senior ICU physician in charge.

Bias

The selection process for DCD recipients was meticulously conducted according to internationally published studies designed to mitigate the inherent risks associated with organ donation, and the allocation was guided by the UK DCD Risk Score [32,41].

High-scoring MELD patients and ICU patients were not allocated DCD organs; these were organs in general allocated to low MELD patients (eg, patients with hepatocellular carcinoma). Nevertheless, as pre-operative optimization of marginal grafts has continuously improved, along with an increasingly dramatic organ shortage, selection criteria have been changing and evolving over time. This inevitably resulted in heterogeneity in DCD and DBD recipients, led to a selection bias, and did not allow for true matching of the groups. To account for these conditions, a multivariable logistic regression was performed for KRT and MAKE 30.

Statistical Analysis

Categorical variables are shown as count and percentage, and numeric variables as median with interquartile range (IQR) or mean with 95% confidence interval (CI), as appropriate. Risk ratios with 95% CI are displayed for proportional comparisons. Comparisons between the 2 groups were performed using the Wilcoxon signed-rank test and chi-squared test (with Yate's continuity correction) where appropriate. Statistical significance was defined as a 2-sided *P* value <0.05.

Comparison of eGFR between DBD and DCD recipients was restricted to patients who were alive on POD 365 and who did not receive any KRT before or after liver transplantation. The longitudinal course of eGFR was modelled as a linear mixed-effect model on a natural cubic spline basis (9 degrees of freedom, boundary knots on days 0 and 7), and donation type as an interaction effect, allowing interpolation between day -30 and 30. Individual patients were included as a random effect. *P* values for individual fixed effects were obtained using Satterthwaite's degree of freedom method.

Comparison of KRT between the groups was restricted to patients who were alive until POD 365. A cumulative incidence graph was constructed to determine the resolution of KRT and death. Hazard ratios for KRT discontinuation were calculated using Cox regression analysis.

To identify factors associated with the use of KRT and the occurrence of MAKE-30, recipient characteristics (age, sex, and donor body mass index [BMI]), type of organ donation (DBD vs DCD), and clinically relevant population characteristics (MELD score and baseline eGFR) were entered into a multivariable logistic regression model. The main model assumptions (binary dependent variables, independence of observations, linearity of log-odds, no multicollinearity) were evaluated. Linearity between continuous variables and the log-odds was assessed with Component+Residual-plots and variable transformation was used if necessary. Calculation of the variance inflation factor (VIF) was performed for evaluation of multicollinearity. Estimates as log(OR) with 95% CI and *P* values are reported. We conducted a sensitivity analysis including interaction terms that significantly contributed to the logistic regression model. Due to restrictions on the number of variables, interactions were not included in the main model. Statistical analyses were performed using R (version 4.1.1) and R Studio software.

Results

Baseline Characteristics

The baseline characteristics of the patients are presented in **Table 1**. DCD donors were older (65 vs 57 years, *P*=0.002) and more often male (n=48, 71% vs n=81, 53%, *P*=0.018) compared to DBD donors. DCD recipients had a significantly lower MELD score (12 vs 21, *P*<0.001), were significantly older (60 vs 56 years, *P*=0.006), had more comorbidities (Charlson Comorbidity Index: 5 vs 4, *P*<0.001), and were less frequently female (n=10, 15% vs n=62, 40%, *P*<0.001) than DBD recipients.

Kidney Function

MAKE-30 incidence after OLT was comparable in DCD (n=27, 40%) and DBD (n=41, 27%) recipients (risk ratio 1.49 [95% CI 1.01, 2.21], *P*=0.073 (**Table 2**).

Of the 222 patients included, 124 did not require KRT during the pre- and posttransplant phases (DBD, n=84; DCD, n=40). A temporary drop in eGFR was observed in these patients, as

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Table 1. Baseline characteristics.

	Whole cohort (N=222)	DBD (N=154)	DCD (N=68)	p-value
Donor & graft				
Age (years)	59 (48-71)	57 (39-68)	65 (53-73)	0.002
Female sex	93 (41.9%)	73 (47.4%)	20 (29.4%)	0.018
BMI (kg/m²)	26 (23-28)	25 (23-28)	26 (24-29)	0.025
Cold ischemia time (h)	7.1 (5.85-8.49)	6.79 (5.5-8.41)	7.24 (6.47-8.55)	0.143
Warm ischemia time (min)	34 (30-38)		34 (30-38)	
HOPE	116 (52.3%)	48 (31.2%)	68 (100%)	<0.001
Recipient				
Age (years)	57 (48-63)	56 (46-61)	60 (52-65)	0.006
Female gender	72 (32.4%)	62 (40.3%)	10 (14.7%)	<0.001
Laboratory MELD-score	18 (11-31)	21 (14-33)	12 (9-19)	<0.001
Charlson Comorbidity Index	5 (3-6)	4 (3-5)	5 (4-6)	<0.001
BMI (kg/m²)	27 (23-30)	26 (22-30)	27 (25-30)	0.161
SOFA Score day 1	13 (10-15)	13 (10-16)	12 (10-14)	0.048
Liver cirrhosis (Child-Pugh-Score)				0.001
No cirrhosis	35 (15.8%)	27 (17.5%)	8 (11.9%)	
A	53 (24.0%)	25 (16.2%)	28 (41.8%)	
B	61 (27.6%)	38 (24.7%)	23 (34.3%)	
C	72 (32.6%)	64 (41.6%)	8 (11.9%)	
Liver disease				<0.001
Alcohol-related liver disease	64 (29.8%)	42 (28.4%)	22 (32.8%)	
Non-alcoholic steatohepatitis	20 (9.3%)	14 (9.5%)	6 (9.0%)	
Viral hepatitis	56 (26.0%)	28 (18.9%)	28 (41.8%)	
Biliary liver disease	21 (9.8%)	18 (12.2%)	3 (4.5%)	
Morbus Wilson	2 (0.9%)	1 (0.7%)	1 (1.5%)	
Other	52 (24.2%)	45 (30.4%)	7 (10.4%)	
Acute liver failure	20 (9.0%)	20 (13.0%)	0 (0.0%)	0.004
Carcinoma				<0.001
No	124 (55.9%)	106 (68.8%)	18 (26.5%)	
HCC	96 (43.2%)	47 (30.5%)	49 (72.1%)	
CCC	2 (0.9%)	1 (0.6%)	1 (1.5%)	
Hepatorenal syndrome	62 (28.1%)	52 (33.8%)	10 (14.9%)	0.007
Hepatopulmonal syndrome	5 (2.3%)	4 (2.6%)	1 (1.5%)	0.999

Continuous variables are displayed as median (interquartile range), categorical variables as count (percentage). BMI – body mass index; CCC – cholangiocellular carcinoma; DBD – donation after brain death; DCD – donation after cardiac death; eGFR – estimated Glomerular Filtration Rate; HCC – hepatocellular carcinoma; HOPE – hypothermic oxygenated perfusion; KRT – kidney replacement therapy; MELD – model for end-stage liver disease; SOFA – sequential organ failure assessment. Individual values were missing in less than 5%.

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Table 2. Major adverse kidney events 30 days after transplantation (MAKE-30).

	Overall (N=222)	DBD (N=154)	DCD (N=68)	p-value
MAKE-30	68 (31)	41 (27)	27 (40)	0.073
MAKE-30: Creatinine >200%	17 (11)	8 (7)	9 (17)	0.113
MAKE-30: Death	12 (5)	8 (5)	4 (6)	>0.999
MAKE-30: New KRT	51 (29)	30 (26)	21 (34)	0.341

Categorical variables as count (percentage). MAKE-30 is defined as the composite of death, newly-started KRT, or persistent worsening of kidney function (defined as persistent serum creatinine value ≥200% of the baseline serum creatinine value) within 30 days after intervention. DBD – donor after brain death; DCD – donor after cardiac death; KRT – renal replacement therapy.

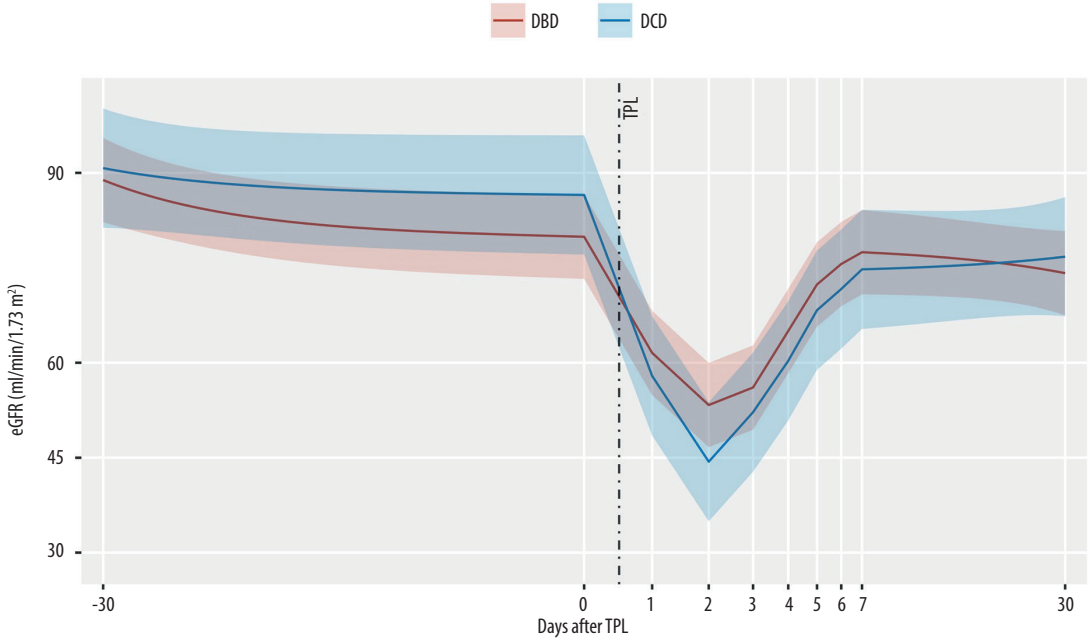

Figure 2. Longitudinal course of eGFR modelled with a linear mixed-effect model on a natural cubic spline basis. The x-axis is displayed on a signed pseudo logarithm scale. P value was obtained using Satterthwaite's degree of freedom method. The effect of group DCD vs DBD on eGFR change over time was not significant (P =0.123). DBD – donation after brain death; DCD – donation after cardiac death; eGFR – estimated Glomerular Filtration Rate; TPL – transplantation. *Statistical analyses were performed using R (version 4.1.1) and R Studio software.*

shown in **Figure 2**. Individual eGFR declined by median 51% (28-68, *P*<0.001) during the first 7 days after transplantation, a nadir was reached after median 2 (2-3) days. Change of eGFR over time did not significantly differ between DBD and DCD recipients in this model (*P*=0.123).

Overall, 86% of patients (n=153) fulfilled the AKI criteria within the first 7 days after OLT. AKI incidence was comparable in DCD (n=58, 94%) vs DBD (n=95, 82%) recipients (risk ratio 1.14 [95% CI: 1.03, 1.27], *P* = 0.057). Patients receiving KRT on POD 0 (DBD n=38; DCD n=6) were not eligible for AKI analysis (**Figure 1**). Resolution of AKI by POD 30 was lower in DCD (n=29, 50%) than in DBD (n=66, 69%) recipients (risk ratio 0.71 [95% CI: 0.53, 0.95], *P*=0.032) (**Table 3, Figure 3**).

Thirty days before transplantation, 5% of patients (n=11) had undergone KRT. On the day of transplantation (POD 0), 20% (n=44) of patients underwent KRT, with significantly more of them DBD than DCD recipients (n=38, 25% vs n=6, 9%, *P*=0.011). During the first 7 days after OLT, 40% (n=88) of patients required initiation or continuation of KRT, with no difference between DCD (n=27, 40%) and DBD (n=61, 40%)

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Table 3. Development of AKI POD 1-7 after OLT.

	Overall (N=178)	DBD (N=116)	DCD (N=62)	p-value
AKI POD 1-7 (%)	153 (86)	95 (82)	58 (94)	0.057
No AKI	25 (14)	21 (18)	4 (7)	
Stage 1 (%)	44 (25)	29 (25)	15 (24)	
Stage 2 (%)	25 (14)	17 (15)	8 (13)	
Stage 3 (%)	84 (47)	49 (42)	35 (56)	
AKI resolution POD 30, N=152	95 (62)	66 (69)	29 (50)	0.032
NA	1 (1)	1 (1)	0 (0)	

Categorical variables as count (percentage); NA – not applicable. Patients on KRT POD 0 were not eligible for AKI analysis. Resolution of AKI: absence of AKI criteria and alive on POD 30 in patients with AKI on POD 1-7. AKI – acute kidney injury; DBD – donor after brain death; DCD – donor after cardiac death; POD – postoperative day.

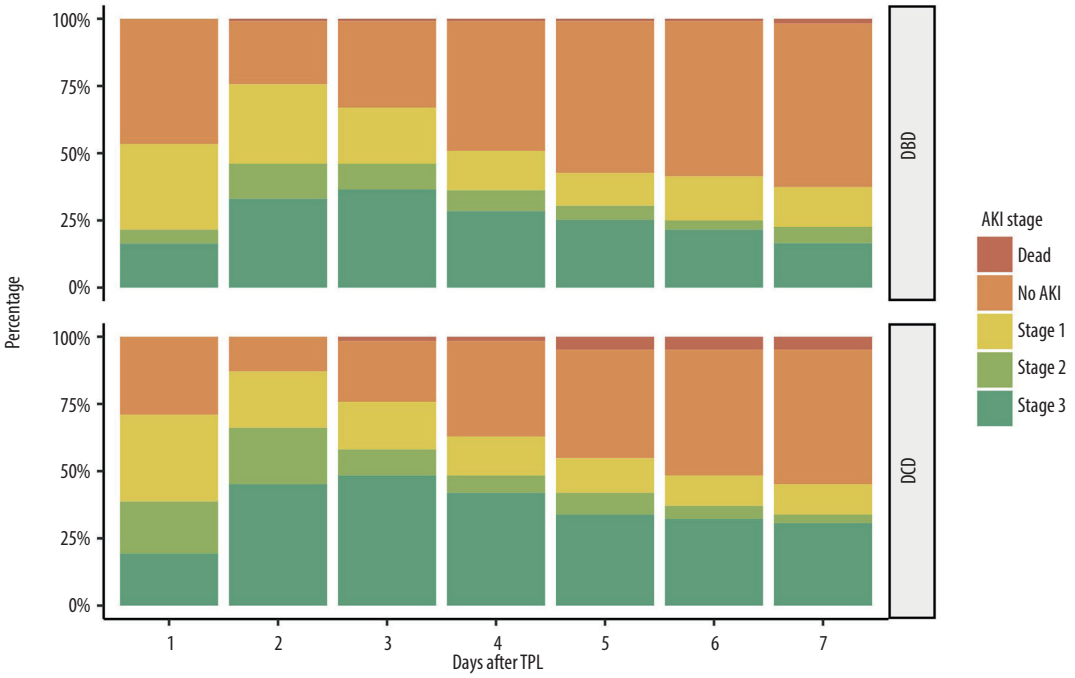

Figure 3. Prevalence of AKI stages in the first posttransplant week in DBD (**upper panel**) and DCD (**lower panel**) recipients. AKI – acute kidney injury; DBD – donation after brain death; DCD – donation after cardiac death; TPL – transplantation. *Statistical analyses were performed using R (version 4.1.1) and R Studio software.*

recipients (risk ratio 1.00 [95% CI 0.71, 1.43], *P*>0.999). The rate of KRT initiation did not differ significantly between DCD (n=21, 34%) and DBD (n=30, 26%) recipients (risk ratio 1.31 [95% CI 0.82, 2.08], *P*=0.341) (**Figure 4**). There was no significant difference concerning the time to discontinuation of postoperatively initiated KRT between groups (Figure 5, Hazard Ratio for discontinuation of KRT in DCD vs DBD: 0.64, 95% CI 0.35-1.18, *P*=0.151). KRT-free days alive up to POD 30 were also comparable between DCD (30 [IQR: 17, 30]) and DBD recipients (30[IQR: 21, 30]), *P*=0.895.

Multivariable Logistic Regression Analysis

Independent risk factors for KRT after OLT were analyzed using a multivariable logistic regression analysis. A quadratic term for baseline eGFR was incorporated in the logistic regression

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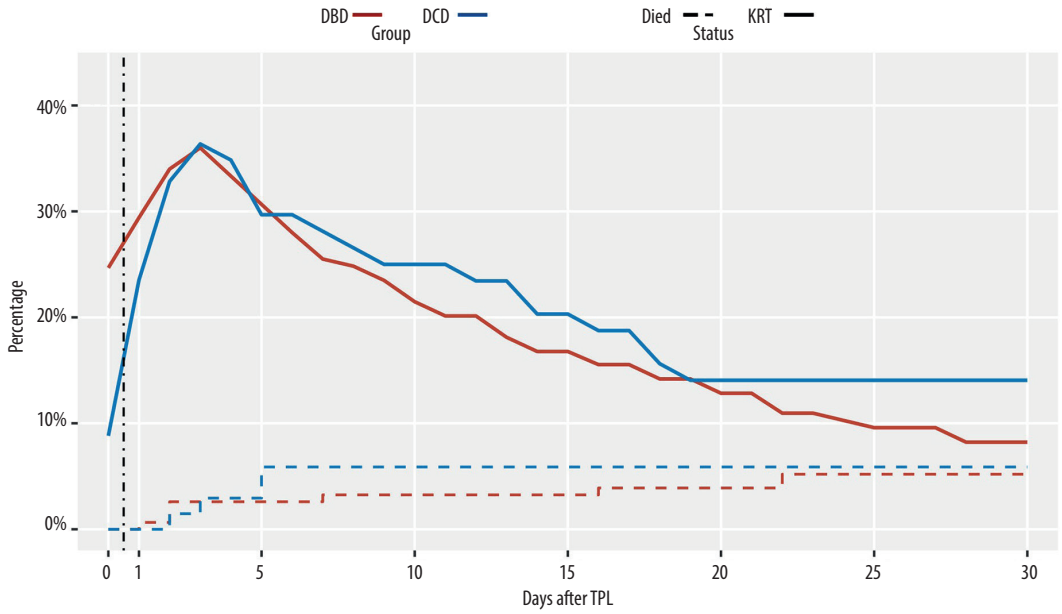

Figure 4. Kaplan-Meier graph for KRT incidence. DBD – donation after brain death; DCD – donation after cardiac death; KRT – renal replacement therapy; TPL – transplantation. *Statistical analyses were performed using R (version 4.1.1) and R Studio software.*

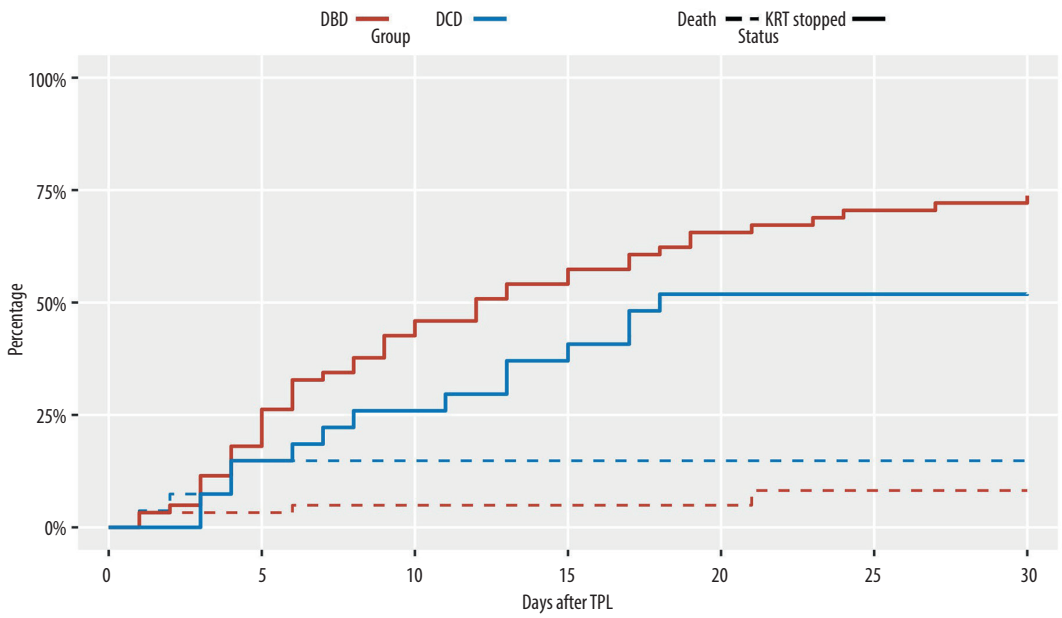

Figure 5. Cumulative incidence graph of KRT resolution and death. DBD – donation after brain death; DCD – donation after cardiac death; KRT – renal replacement therapy; TPL – transplantation. *Statistical analyses were performed using R (version 4.1.1) and the R Studio software.*

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Variable	log (OR) (95% CI)	p-value	
DBD vs DCD	0.92 [0.10, 1.76]	0.300	DCD
Recip. age	0.01 [-0.03, 0.05]	0.665	Years
Sex	0.10 [-0.80, 0.98]	0.820	Female
Recip. BMI	0.09 [0.02, 0.16]	0.017	kg/m^2
MELD score	0.06 [0.01, 0.11]	0.014	
eGFR baseline day -30	-0.09 [-0.18, -0.01]	0.028	ml/min/1.73 m^2
eGFR baseline day-30^2	0.00 [0.00, 0.00]	0.049	ml/min/1.73 m^2

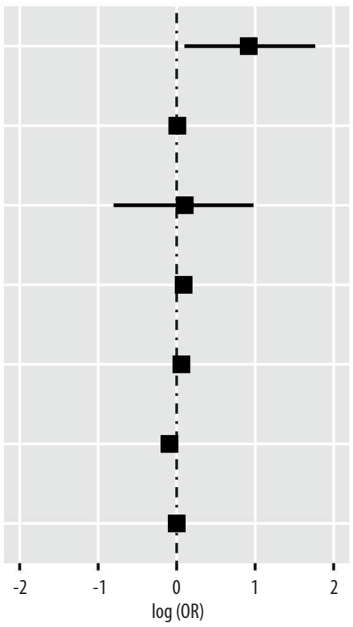

Figure 6. Multivariable logistic regression model of KRT in the first 7 days after OLT. BMI – body mass index; DBD – donation after brain death; DCD – donor after cardiac death; KRT – renal replacement therapy; MELD – model for end-stage liver disease. *Statistical analyses were performed using R (version 4.1.1) and R Studio software.*

Variable	log (OR) (95% CI)	p-value	
DBD vs DCD	0.59 [-0.09, 1.27]	0.090	DCD
Recip. age	0.00 [-0.03, 0.04]	0.784	Years
Sex	0.12 [-0.61, 0.84]	0.746	Female
Recip. BMI	0.06 [0.00, 0.11]	0.049	kg/m^2
MELD score	-0.01 [-0.04, 0.02]	0.566	
eGFR baseline day -30	-0.07 [-0.14, 0.00]	0.040	ml/min/1.73 m^2
eGFR baseline day-30^2	0.00 [0.00, 0.00]	0.063	ml/min/1.73 m^2

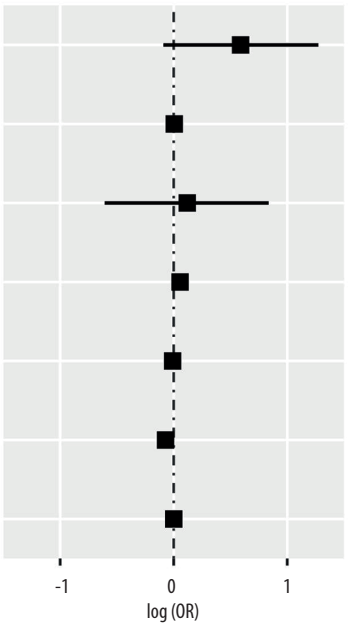

Figure 7. Multivariable logistic regression model of MAKE-30. BMI – body mass index; DBD – donation after brain death; DCD – donor after cardiac death; eGFR – estimated Glomerular Filtration Rate; KRT – renal replacement therapy; MELD – model for end-stage liver disease. *Statistical analyses were performed using R (version 4.1.1) and R Studio software.*

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model to better capture the non-linear relationship observed between eGFR and the logarithm of the outcome variable, ensuring more accurate modelling of the data trends and variability.

In this regression, DCD grafts were independently associated with KRT during the first posttransplant week (log(OR) 0.92 [95% CI 0.10, 1.76], *P*=0.030, **Figure 6**), but not with MAKE-30 (log(OR) 0.59 [-0.09, 1.27], *P*=0.090, **Figure 7**). The independent association of DCD with KRT was lost in a sensitivity analysis including significant interaction terms (log(OR) 0.32 [-7.2, 8.1], *P*=0.933, **Supplementary Table 1**). In summary, the extended analysis did not show a robust independent association between DCD and either KRT or MAKE-30 incidence.

ICU Length of Stay and Survival

ICU length of stay did not differ between the DCD and DBD recipients (2 vs 3 days, *P*=0.711). PS rates after 30 days and 1 year in DCD and DBD were also comparable: 30-day survival in DCD (n=64, 94%) vs DBD (n=146, 95%) recipients (risk ratio 0.99 [95% CI 0.93, 1.06], *P*>0.999) and 1-year survival in DCD (n=60, 88%) vs DBD (n=139, 90%) recipients (risk ratio 0.98 [95% CI 0.88, 1.08], *P*=0.828).

Discussion

In this retrospective single-center study, we characterized the incidence of MAKE-30 and the incidence of and resolution from AKI and KRT after OLT with DBD or DCD grafts. MAKE-30 and AKI incidence in the first week and the need for KRT in the first postoperative month were comparable in DCD and DBD recipients. Meanwhile, DCD (n=29, 50%) had a lower resolution rate of AKI 30 days after OLT than DBD (n=66, 69%) recipients (risk ratio 0.71 [95% CI: 0.53, 0.95], *P*=0.032).

Moreover, in a multivariable logistic regression model including recipient age, sex, BMI, MELD score, and eGFR 30 days before transplantation, the DCD status was an independent risk factor for needing KRT during the first posttransplant week, but not for MAKE-30. As these results lack robustness due to significant intervariable interactions, this analysis should be considered exploratory.

The overall incidence of AKI (86%, n=153) and KRT (40%, n=88) in our study population was notably higher than in previous studies reporting AKI incidences ranging from 40% to 70% after OLT, using standard AKI definitions, and incidences of KRT ranging from 8% to 17% after OLT. [4,15,42,43] This might be associated with the severity of the recipients' underlying medical condition, as reflected by the high MELD scores in our study population in comparison to other international studies. The latter have reported MELD scores of 11-15 in DCD and MELD 11-17 in DBD recipients [3,21-23], in contrast to MELD scores of 9-19 in DCD and MELD 14-33 in DBD recipients in our study cohort. Interestingly, the 1-year survival rate (90% in DBD and 88% in DCD recipients, *P*=0.828) in our cohort did not seem to be affected by MELD, contrary to other data that showed a decline in 1-year survival (from 88% MELD 11-14 patients to 69% in patients with MELD >40) [44,45].

The association between high MELD scores, occurrence of post-OLT AKI, and the need for KRT in the post-OLT period has been demonstrated in several studies [14,46-48]. Multiple risk factors for AKI after OLT have been identified, including high APACHE II scores, hypoalbuminemia, high BMI, chronic kidney disease [15,16,47-49] sepsis, thrombotic microangiopathy, calcineurin inhibitor nephrotoxicity [14,15,50], perioperative vasopressor requirement, blood loss, and cardiopulmonary failure [2,15,49], which are also more prevalent in a sicker cohort. These risk factors are likely independent of the organ allocation strategy, but they might aggravate each other.

In our study population, the incidence of MAKE-30, AKI incidence in the first week, and need for KRT in the first month after OLT was comparable between DCD and DBD recipients. The independent association of DCD organ and need for KRT in the first week after transplantation was lost in sensitivity analysis. Meanwhile, the resolution of AKI by POD 30 was lower in DCD than in DBD recipients. One possible explanation for this is the development of SIRS in the context of concomitant intravascular hypovolaemia and inflammation during OLT. Another causative factor to consider is the corresponding volume therapy, possibly associated with consecutive hypervolemia and the need for fluid removal. Regarding the development of inflammation and SIRS, it is important to take the donor WIT of DCD organs into account. WIT is assumed to be a key mediator for multiple organ dysfunction [2,3,14-16] and for hepatic ischemia-reperfusion injury (HIRI) leading to an inflammatory reaction (SIRS), which is also related to post-OLT AKI [2,3,14-16]. Factors that influence HIRI, such as ischemia time, graft steatosis, and donor age, have also been associated with post-OLT AKI [14,15]. WIT has been associated with primary and early organ dysfunction and inferior graft survival [22,32,51-53]. Machine perfusion, such as HOPE, is a promising method of liver preservation and revitalization to diminish and prevent reperfusion injury [54,55]. In our center, HOPE was applied in all (n=68) DCD and in 31% (n=48) of DBD organs. The impact of HOPE on renal function could not be assessed in our study. Regarding this, one potential approach would be to compare the incidence of AKI and KRT OLT with dates prior to the implementation of HOPE in our transplantation center. Nevertheless, multiple advancements in transplantation medicine since that time have introduced numerous confounders. Ultimately, the impact of HOPE on short-term renal outcomes after OLT must be demonstrated by a prospective, controlled study.

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Our finding of a lower resolution rate of AKI 30 days after OLT in DCD recipients is interesting. However, it remains unclear whether this finding is reproducible in other cohorts. The further development of AKI resolution over a longer time and the incidence of chronic kidney disease in DBD and DCD recipients would be interesting. Regarding this, further studies with longer follow-up periods are needed. In any case, this vulnerable patient group requires careful and close follow-up care with strict avoidance of nephrotoxic substances where possible.

This study has several limitations. Following the international allocation strategy for DCD [41] led to significant differences in baseline characteristics, exemplified by the lower MELD score (DCD 12 vs DBD 21, $P<0.001$) and concerning underlying liver disease and Child-Pugh stadium (**Table 1**).

The heterogeneity of DCD and DBD recipients is inevitable and does not allow true matching of the groups. To account for these conditions, a multivariable logistic regression was performed for KRT and MAKE 30. The overall event rate limits the number of variables in a logistic regression model, which is why residual heterogeneity remains a relevant limitation. The use of continuity correction in frequency comparisons reduces the risk of Type I errors, but can lead to type II errors, which can hinder the detection of significant results. In addition, there may be other factors that affect short-term kidney function after OLT that were not considered in our analysis, like mediators of SIRS and inflammation, WIT, and intravascular hypo- and hypervolemia. A larger cohort in a multicenter study would be desirable. In this context, country-specific rules for DCD, referred to as the 'no-touch' period and WIT [56], must be considered.

A second aspect relates to the uncertainty concerning the optimal timing of KRT initiation in general ICU and in OLT patients. In our center, the decision to initiate KRT follows institutional guidelines based on current scientific knowledge [39,40] and an individualized assessment of the senior physician in charge.

A third limitation concerns our follow-up period of only 1 year, because the PS benefit, in particular, could show a long-term effect [1].

The findings of our study – a similar incidence of MAKE-30 and short-term renal outcome in DBD and DCD recipients – is consistent with more recently published research that includes machine perfusion practice and suggests a lower frequency of postoperative AKI in DBD and DCD recipients [18,21-23]. On the other hand, such results contradict earlier literature, which refers to OLT without machine perfusion practice [2,3,10-13].

We suppose that optimization in the peri-transplant process, wise donor–recipient matching, HOPE, improvements in surgical technique, and strict medication treatment policy are the key elements that lead to comparable short-term renal outcomes in DBD and DCD recipients in our institution. However, scientific studies are necessary to determine the influence of each factor.

However, the analysis in this retrospective study was challenging due to the inherent heterogeneity and limited size of the patient groups. Consequently, the results must be interpreted with caution because of the lack of robustness. To substantiate our hypothesis and provide definitive recommendations for action, larger prospective studies are needed.

Conclusions

In this study we found an overall high incidence of adverse kidney events, but no relevant difference in MAKE-30, AKI, and KRT incidence in DBD or DCD organ recipients after OLT. To preserve kidney function as much as possible, it is essential to prevent any avoidable damage to the kidneys during the entire process of OLT, such as avoidance and close monitoring strategies of nephrotoxic substances, and optimized fluid management to avoid intravasal hypo- and hypervolemia. Comparable short-term renal outcome and PS may encourage counteracting organ shortages with optimized DCD-OLT, while the influence of the inflammatory reaction, WIT, and liver perfusion machines like HOPE on kidney function warrants further clarification.

Ethics Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Cantonal Ethics Committee of Zurich, Switzerland) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Cantonal Ethics Committee of Zurich approved and registered the study (BASEC-Nr. 2020-00188). Informed written consent to participate was obtained from all participants or next of kin prior to study enrolment and/or from the patient after ICU discharge.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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Supplementary Table

Supplementary Table 1. Multivariable logistic regression model of KRT including significant interaction terms. All possible second-order intervariable interactions where tested and only significant interactions were included in the final model.

Variable	log (OR)	95% CI	p-value
DBD vs DCD			
DBD	–	–	
DCD	0.32	-7.2, 8.1	0.933
MELD Score	0.09	0.03, 0.15	0.002
eGFR baseline	-0.16	-0.27, -0.05	0.005
Recip. age (y)	0.01	-0.03, 0.06	0.619
Recip. sex			
Male	–	–	
Female	0.01	-0.97, 0.96	0.978
Recip. BMI (kg/m^2)	0.11	0.03, 0.20	0.007
(eGFR baseline)^2	0.00	0.00, 0.00	0.008
DBD vs DCD * MELD Score			
DCD * MELD Score	-0.25	-0.43, -0.09	0.003
DBD vs DCD * eGFR baseline			
DCD * eGFR baseline	0.17	0.00, 0.35	0.053
DBD vs DCD * (eGFR baseline)^2			
DCD * (eGFR baseline)^2	0.00	0.00, 0.00	0.020

BMI – body mass index; CI – confidence interval; DBD – donation after brain death; DCD – donor after cardiac death; eGFR – estimated Glomerular Filtration Rate; KRT – renal replacement therapy; MELD – model for end-stage liver disease; OR – odds ratio. *Statistical analyses were performed using R (version 4.1.1) and the R Studio software.*

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