ORIGINAL ARTICLE

Conditional probability of graft survival in liver transplantation using donation after circulatory death grafts – a retrospective study

Kazunari Sasaki[1], Amit Nair[1], Daniel J. Firl[2], John C. McVey[1], Amika Moro[1], Teresa Diago Uso[1], Masato Fujiki[1], Federico N. Aucejo[1], Cristiano Quintini[1], Choon-Hyuck D. Kwon[1], Bijan Eghtesad[1], Charles M. Miller[1] & Koji Hashimoto[1]

1 Department of General Surgery, Digestive Disease Institute, Cleveland Clinic Lerner College of Medicine, Cleveland Clinic, Cleveland, OH, USA
2 Department of Surgery, Duke University Hospital, Durham, NC, USA

Correspondence
Kazunari Sasaki MD, General Surgery, Digestive Disease and Surgery Institute, Cleveland Clinic 9500 Euclid Avenue Cleveland, OH 44195, USA.
Tel 216-445-7159;
fax: 216-444-9375;
e-mail: sasakik@ccf.org

SUMMARY

The use of livers from donation after circulatory death (DCD) is historically characterized by increased rates of biliary complications and inferior short-term graft survival (GS) compared to donation after brain death (DBD) allografts. This study aimed to evaluate the dynamic prognostic impact of DCD livers to reveal whether they remain an adverse factor even after patients survive a certain period following liver transplant (LT). This study used 74 961 LT patients including 4065 DCD LT in the scientific registry of transplant recipients from 2002–2017. The actual, 1 and 3-year conditional hazard ratio (HR) of 1-year GS in DCD LT were calculated using a conditional version of Cox regression model. The actual 1-, 3-, and 5-year GS of DCD LT recipients were 83.3%, 73.3%, and 66.3%, which were significantly worse than those of DBD (all $P < 0.01$). Actual, 1-, and 3-year conditional HR of 1-year GS in DCD compared to DBD livers were 1.87, 1.49, and 1.39, respectively. Graft loss analyses showed that those lost to biliary related complications were significantly higher in the DCD group even 3 years after LT. National registry data demonstrate the protracted higher risks inherent to DCD liver grafts in comparison to their DBD counterparts, despite survival through the early period after LT. These findings underscore the importance of judicious DCD graft selection at individual center level to minimize the risk of long-term biliary complications.

Transplant International 2021; 34: 1433–1443

Key words
conditional survival analysis, DCD, donation after circulatory death, liver transplant, long-term survival, SRTR

Received: 4 November 2020; Revision requested: 14 December 2020; Accepted: 15 February 2021; Published online: 13 July 2021

Introduction

The use of livers from donation after circulatory death (DCD) is historically characterized by increased rates of biliary complications and inferior graft survival (GS) compared to those from donation after brain death (DBD) [1–3]. DCD grafts were reported as one of the strongest adverse risk factors in two well-known liver donor risk indices from the United States (US) and Europe [4,5]. These grafts are still not well utilized compared with DBD livers, accounting for less than 10% of LT in the US [6,7]. This is primarily attributed

doi:10.1111/tri.13846

to the inherent risks associated with these organs, especially in the early post-transplant period [8]. However, the reported GS and rate of biliary complications, especially ischemic cholangiopathy (IC), has been decreasing due to the gradual optimization of donor and recipient selection [9–11]. With steady improvements in outcomes, DCD grafts are expected to provide a viable approach to decrease the disparity between demand and supply of liver grafts.

While numerous studies on DCD graft outcomes have been conducted, most of the previous work focused on short-term outcomes after LT because of the increased risk of related adverse events in this time frame, such as primary non-function (PNF) and IC [11–13]. To date, only a few reports have focused on the long-term outcomes of DCD LT [14,15]. One report by Croome et al. showed comparable long-term GS between DCD and DBD grafts after propensity score matching [14]. On the other hand, a European multi-institutional study showed significantly worse 5-year GS in DCD compared with DBD grafts (54% vs. 66%, log-rank test $P = 0.038$ in overall GS) [15]. Therefore, long-term prognostic influences of DCD graft are still controversial and not fully elucidated. Notably, the conclusions in many previous studies were based on Kaplan-Meier estimates of survival rates. These analyses therefore did not take into account other confounding factors such as donor age, recipient age, recipient morbidity etc.

Conditional survival (CS) estimates, which account for years that a patient has already survived after treatment, have been proposed as better predictors of long-term prognosis and hazard at any defined time period following an intervention [16–19]. For example, CS analysis for long-term outcomes in LT using DCD organs may demonstrate that surviving patients experience a consistent decrease in the probability of future graft loss, as more time elapses. In this context, CS analysis can answer the clinical question of whether DCD organs can be considered equivalent to DBD organs if patients survive the early period after LT (Fig. 1). The aim of this study was to evaluate the dynamic prognostic impact of DCD grafts using CS analysis, to reveal whether DCD liver grafts are still an adverse factor if patients survive a defined period after LT.

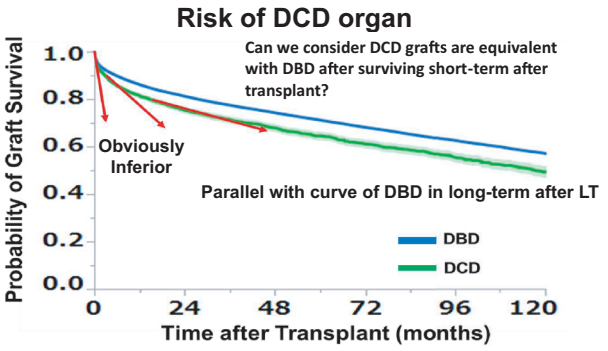

Figure 1 Can Kaplan Meier survival curve estimate long-term prognostic implication of DCD grafts?

Methods

Study population

This study was conducted using the data provided in Scientific Registry of Transplant Recipients database between March 2002 and December 2017. Only adult recipients (age > 17y.o) who underwent primary deceased donor LTs were included, whereas patients who received multiple organ transplants were excluded. All patients with incomplete basic recipient/donor characteristics for: donor age, donor sex, height, race, cause of death, DCD or not, organ sharing status (local/regional/national), cold ischemic time, recipient age, recipient sex, Model for End stage Liver Disease (MELD) score, and pre-transplant medical condition, etiology of liver disease were excluded, leaving 74 961 patients (Table 1). With respect to warm ischemic time (WIT), of 4065 DCD grafts in the cohort, 1290 (31.7%) patients had missing data. Therefore, multiple imputation was done using chained equations [20]. The cause of death was detected by the following text terms: "grf_fail_cause_ostxt, cod, cod_ostxt", and considered variables "pri_grf_fail, vasc_thromb, biliary, hep_denovo, hep_recur, recur_disease, rej_acute, infect". A sensitivity analysis was conducted to assess the influence of era as many studies reported improvement of outcomes of DCD grafts after accumulation of case numbers and experience 9–11. The study period was divided into 2 eras: March 2002 to November 2009, and after October 2009, which were periods before and after the publishing of the American Society of Transplant Surgeons practice guidelines for controlled cardiac death organ procurement and transplantation, respectively [1]. The major recommendations towards mitigating biliary complications were as follows; (i) Limit the use of DCD livers with longer ischemia, (ii) Perform an expeditious, in situ biliary flush to minimize bile-induced epithelial damage during organ recovery, and (iii) Consider arterial revascularization before or simultaneously with portal revascularization of DCD livers. This study was approved by the institutional review board of Cleveland Clinic (IRB No. 19-537).

Transplant International 2021; 34: 1433–1443

Table 1. Patient characteristics

	DCD liver graft (n = 4065)	DBD liver graft (n = 70 896)	P
Donor characteristics			
Age, years	34.0 [23.0–46.0]	43.0 [27.0–55.0]	<0.01
Sex, % female	1317 (32.4)	28 876 (40.7)	<0.01
Height, cm	173.0 [165.1–181.3]	172.7 [165.0–180.0]	<0.01
Weight, kg	78.0 [66.5–90.7]	78.9 [67.1–92.0]	<0.01
Body mass index, kg/m^2	25.8 [22.5–29.8]	26.4 [23.1–30.5]	<0.01
Race/Ethnicity			<0.01
White, %	3320 (81.7)	46 715 (65.9)	
African American, %	357 (8.8)	12 358 (17.4)	
Others, %	388 (9.5)	11 823 (16.7)	
Cause of death			<0.01
Head trauma, %	1504 (37.0)	24 114 (34.0)	
Anoxia, %	1665 (41.0)	28 389 (40.0)	
CVD, %	710 (17.5)	16 678 (23.5)	
Others, %	186 (4.6)	1715 (2.4)	
Share			<0.01
Local, %	2740 (67.4)	50 306 (71.0)	
Regional, %	1018 (25.0)	17 081 (24.1)	
National, %	307 (7.6)	3509 (4.9)	
Cold ischemic time, hours	6.0 [4.7–7.4]	6.3 [5.0–8.1]	<0.01
Recipient characteristics			
Age, years	57.0 [51.0–62.0]	56.0 [49.0–61.0]	<0.01
Sex, % female	1206 (29.7)	23 185 (32.7)	<0.01
Height, cm	172.7 [165.1–180.3]	172.7 [165.1–180.3]	<0.01
Weight, kg	83.5 [72.1–96.7]	83.0 [71.0–97.1]	0.19
Body mass index, kg/m^2	27.9 [24.4–32.1]	27.9 [24.5–31.8]	0.82
Cause of cirrhosis			
Viral Hepatitis	1562 (38.4)	26 621 (37.5)	0.27
PBC/PSC/AIH	307 (7.6)	6674 (9.4)	<0.01
EtOH	997 (24.5)	15 625 (22.0)	<0.01
Exception for HCC	1177 (29.0)	17 389 (23.2)	<0.01
Medical condition			<0.01
ICU	254 (6.2)	8827 (12.5)	
Hospitalized	497 (12.2)	12 376 (17.5)	
Home	3314 (81.5)	49 693 (70.1)	
Previous abdominal surgery	1715 (42.2)	29 219 (41.2)	0.01
Portal vein thrombosis	414 (5.8)	6739 (9.5)	<0.01
Laboratory MELD, points	17.0 [12.0–23.5]	20.0 [13.0–29.0]	<0.01
Waiting time, days	103.0 [29.0–290.5]	88.0 [17.0–289.0]	<0.01

Continuous variables: median [IQR]; Categorical variable: number (%).

CVD, cardiovascular disease; DBD, donor after brain dead; DCD, donor after circulation death; HCC, hepatocellular carcinoma; ICU, intensive care unit; MELD, model for end stage liver disease.

Statistical analyses

Summary statistics were reported as frequencies with percentages or median values using interquartile ranges (IQR). Differences between categorical values were estimated using the chi-squared test, while differences between continuous values were assessed with the Mann-Whitney U test or the Kruskal-Wallis test, as appropriate. The Kaplan-Meier method was used to assess prognostic outcomes and tested using the Log-rank test. A multivariable stepwise Cox regression analysis (backward elimination method) was performed to identify independent predictors of decreased 1- year GS. The following variables were used in the multivariate analysis model to adjust the hazard ratio (HR) and 95 % confidence interval (95 % CI) of DCD; donor age, donor sex, race, height, cause of death, recipient age, recipient sex, history of previous abdominal surgery,

presence of portal vein thrombosis at the time LT, pre-transplant medical condition, MELD score at the time of LT, presence of pathologically proven HCC or not, viral hepatitis or not, split/reduced graft or not, cold ischemic time, and organ sharing status. Conditional graft survival (CGS) can be expressed as CGS (y|x), where y is the probability of surviving for additional y years given that the person has already survived for x years. It can be calculated by traditional Kaplan-Meier analysis or from actual survival data. CGS(1|x) can be calculated as: CGS(1|x) = S(x + 1)/S(x), where S indicates the number of years survived from the date of surgery. This study also employed a conditional version of Cox regression analysis for the prediction time points S = 0, 1, 3, 6, 12, 18, 24, 36, 48, and 60 months by restricting to all patients who are alive at S = 0, 1, 3, 6, 12, 18, 24, 36, 48, and 60 months, respectively, to estimate CGS probabilities [17]. In 1-year cGS, survival was censored at one year after the landmark time point. The HRs of graft loss due to biliary related complication were estimated using Fine-Gray model competing risk regression. All testing was two-sided and used a 5% level of significance. All analyses were done using JMP pro 14 and STATA 16.

Results

Baseline characteristics

The characteristics of donors and recipients of DBD and DCD in this series are reported in Table 1. Of 74 961 patients, 4065 patients received DCD livers (5.4%). Compared with DBD donors, DCD donors were significantly younger (34yo vs. 43yo), male dominant (67.6% vs. 59.3%), of lower body mass index (BMI), and with higher rates of head trauma/anoxia, lower rates of cardiovascular disease, and frequently shared nationally (7.6% vs. 4.9%) (all $P < 0.01$). The median cold ischemic time was significantly shorter in the DCD group compared with the DBD group (6.0hours vs. 6.3hours). The recipient age of the DCD group was slightly higher than those of the DBD group (57.0 vs. 56.0, $P < 0.01$), and the percentage of male recipients was higher in the DCD group (70.3% vs. 67.3%, $P < 0.01$). The proportion of patients who had HCC exception points was significantly higher in the DCD group (29.0% vs. 23.2%, $P < 0.01$). The pre-transplantation medical condition was better in DCD patients than DBD patients (ICU patients; 6.2% vs. 12.5%, $P < 0.01$, hospitalized patients; 12.2% vs. 17.5%, $P < 0.01$). The presence of portal vein thrombosis at the time of LT was significantly lower in the DCD group (5.8% vs. 9.5%, $P < 0.01$). The chemical MELD score at the time of LT was also significantly lower in DCD patients (17 vs. 20, $P < 0.01$). The median days on waiting list were significantly longer in the DCD group (103.0 vs. 88.0days).

Actual and conditional survival

At median follow-up of 47.5 months, 23 229 grafts were lost (31.0%), which was significantly more frequent in patients with DCD liver grafts (33.8% vs. 30.8%). The actual 1-, 3-, and 5-year GS of DCD patients were 83.3%, 73.3%, and 66.3%, respectively, which were also significantly worse than figures in the DBD group (87.8%, 79.4%, and 73.2%, respectively) (all $P < 0.01$, Fig. 2a). The factors associated with actual 1-year GS are shown in Table 2. DCD graft was a significant poor predictor of 1-year GS as HR 1.87 (95% CI; 1.72–2.03).

The Kaplan-Meier estimations of overall GS comparison between DBD and DCD group in patients who survived 1, 3-, and 5-year after LT are shown in Fig. 2b–d. Although the overall GS differences between DBD and DCD grafts decreased over time, DCD patients had significantly worse overall GS up to 3 years from LT ($P < 0.01$ in 1- and 3-year survivors, and $P = 0.10$ in 5-year survivors). The 1-year actual and conditional GS are plotted in Fig. 3a. Conditional 1-year GS of DCD recipients gradually improved and reached that of DBD grafts when patients survived 3 years from LT (CGS (1|3) was 95.2% for DCDvs. 96% for DBD; $P = 0.08$).

The conditional version of Cox regression analysis for 1-year GS was performed to investigate adjusted prognostic influences on DCD grafts. The factors associated with conditional 1-year GS in 1-, 3-, and 5-year survivors are shown in Table 2. Most of the significant predictive factors in actual1-year GS lost their predictive power after patients survived one year from LT. Only three factors viz. "transplant year," "donor age," and "DCD organ" were consistently significant at all-time points. HRs of transplant year and donor age were almost the same at all-time points. The HR of pathological proven HCC was significant in actual analysis, but was higher after patients survived 1-year from LT (HR = 1.06 vs. 1.50), then decreased to 1.24 in 3 years survivors and 1.26 in 5 years survivors. The HR of DCD grafts was highest in actual (HR = 1.87) and gradually decreased according to the patient surviving years; 1.49 in 1-year survivors, 1.39 in 3-year survivors, and 1.33 in 5-year survivors respectively. To understand the

Transplant International 2021; 34: 1433–1443

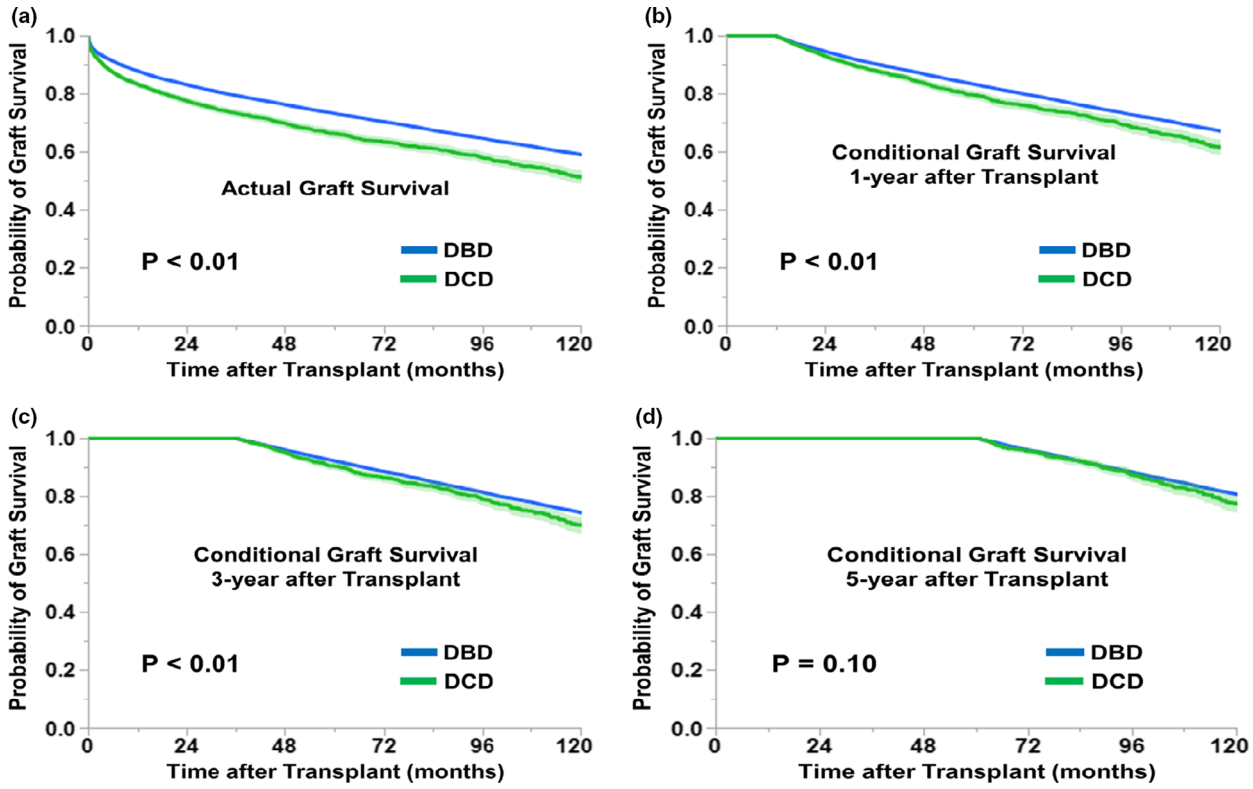

Figure 2 Actual and conditional graft survival curves comparison between DBD and DCD grafts. (a) Actual graft survival. (b) 1-year conditional survival. (c) 3-year conditional survival. (d) 5-year conditional survival.

trends of HRs of DCD graft in more detail according to survival time from LT, adjusted HRs were plotted as shown in Fig. 3b. The curve of conditional HRs in DCD graft decreased gradually until patients survived 2 years after LT. Although the conditional HR curve of DCD graft reached a plateau, the HR was still significantly high even in patients who survived 5 years from LT (HR = 1.33 95% CI; 1.01–1.75, $P = 0.04$).

Cause of graft loss/patient death in long-term after LT

The details of graft loss/patient death cause were recorded in most patients (19 046/23 229 patients, 82.0%). The percentage of 15 most common causes of graft loss/patient death according to graft types in actual and 3-year survivor after LT are shown in Table 3. Of the known actual causes of graft loss/patient death, only biliary complications and primary non-function were significantly higher in the DCD group compared to those of the DBD group (both $P < 0.01$). The percentage of graft loss due to biliary complication was nearly 4 times higher in the DCD group compared with the DBD group (12.3% vs. 3.2%, $P < 0.01$). Even after patients survived 3-years from LT, biliary complication rates in patients who received DCD grafts were still high compared to those receiving DBD grafts (3-year; 5.3% vs. 1.2%, $P < 0.01$). A competing risk model to predict graft loss due to biliary complication was therefore performed (Table 4). A younger donor age (HR = 0.98 per year) and shorter cold ischemic time (HR = 0.95 per hour) were found to be significant factors to reduce graft loss related to biliary complication.

The influence of Era

A comparison of baseline recipient and donor characteristics within the DCD group was also performed between Era 1 (3/2002-9/2009) and Era 2 (10/2009-12/2017) (Tables S1–S3). Additionally, the actual, 1-, 3-year conditional Kaplan-Meier GS estimations, and 1-year GS probability plots were conducted, and results are shown in Figure S1 and S2. The GS curves of DCD graft improved in Era 2. The GS differences between curves of DBD and DCD became smaller in Era 2 comparing with Era 1. The conditional HR plots were depicted in each Era and are shown in Fig. 4. The actual HR of DCD grafts decreased from 2.01 (Era 1) to 1.74 (Era 2). However, 3-year conditional HRs were

Table 2. Factors associated with 1-year graft survival after liver transplantation

Factors	Actual HR (95% CI)	1-year survivor HR (95% CI)	3-year survivor HR (95% CI)	5-year survivor HR (95% CI)
Transplant year (per year)	0.94 (0.94–0.95)	0.95 (0.95–0.96)	0.98 (0.97–0.99)	0.96 (0.94–0.98)
Recipient age (per year)	1.02 (1.01–1.02)	-	-	1.01 (1.01–1.02)
Recipient gender (Ref female)	-	-	1.20 (1.07–1.34)	
Medical condition (Ref home)			-	-
Hospital	1.25 (1.18–1.33)	1.22 (1.11–1.35)		
ICU	1.99 (1.85–2.14)	1.33 (1.18–1.50)		
Portal vein thrombosis	1.46 (1.37–1.56)	-	-	-
MELD (per point)	1.01 (1.01–1.02)	-	-	-
Viral Hepatitis	1.09 (1.04–1.14)	1.36 (1.27–1.47)	1.13 (1.02–1.25)	-
Pathological proven HCC	1.06 (1.01–1.12)	1.50 (1.39–1.63)	1.24 (1.12–1.38)	1.26 (1.11–1.42)
Donor age (per year)	1.01 (1.01–1.01)	1.01 (1.01–1.01)	1.01 (1.01–1.02)	1.01 (1.01–1.02)
Donor Gender	1.11 (1.05–1.17)	-	-	-
Cause of death (Ref head trauma)		-	-	-
Anoxia	1.02 (0.96–1.09)			
CVD	1.14 (1.08–1.21)			
Others	1.11 (0.97–1.26)			
Donor Race (Ref White)		-	-	
African American	1.16 (1.09–1.22)			1.18 (1.01–1.38)
Others	1.09 (1.03–1.15)			1.19 (1.01–1.39)
Share (Ref local)		-	-	-
Regional	1.04 (0.99–1.09)			
National	1.14 (1.04–1.24)			
Cold Ischemic time (per hour)	1.03 (1.02–1.04)	-	-	-
Donor height (per 10cm)	1.01 (1.01–1.01)	-	1.01 (1.00–1.02)	-
Split/Reduced graft	1.51 (1.27–1.80)	-	-	-
DCD graft	1.87 (1.72–2.03)	1.49 (1.28–1.72)	1.39 (1.12–1.73)	1.33 (1.01–1.74)

CI, confidence index; HR, hazard ratio Note: Multivariate Cox regression was applied with stepwise backward selection, with $P = 0.10$ as the critical value for entering and excluding variables in the model.

CVD, cardiovascular disease; DCD, donor after circulation death; HCC, hepatocellular carcinoma; ICU, intensive care unit; MELD, model for end stage liver disease.

similar in the two Eras as 1.40 (Era 1) and 1.38 (Era 2). Conditional HR of DCD graft stayed significantly high after 3 years after LT, even in Era 2 (Tables S4 and S5).

The survival benefits of young donor age for young recipient

To investigate the survival benefits of young donor age in young recipients, additional analyses were done. The young recipient age was defined as 45 years old or younger, young donor age was defined as 40 years old or younger. The analyses were limited to patients whose MELD score was 25 or lower for the purpose of limiting patients who do not need urgent life-saving transplant. The Kaplan-Meier survival curves were compared between young donors and old donor in young recipients (Fig. 5a,b). The 1-, 5-, and 10-year survival rates of young donor group were significantly better than those of old donor group: 88.0%, 79.5%, and 64.3% vs. 78.5%, 50.4% and 43.9% (all $P < 0.05$). The conditional survival curves comparison in patients who survived 3 years after LT were also shown in Fig. 5c,d. The survival curve of old donors was significantly worse than that of young donors in both groups, and the difference was bigger in the young recipient group.

Discussion

This study aimed to assess the long-term risk of DCD liver allografts using conditional survival analyses with US national registry data. Statistical analyses showed that adverse effects of DCD grafts on GS persisted even in patients who survived 5 years after LT. The analyses of the cause of graft loss also showed those lost due to biliary related complications remained higher in DCD LT recipients who survived even long-term after

Transplant International 2021; 34: 1433–1443

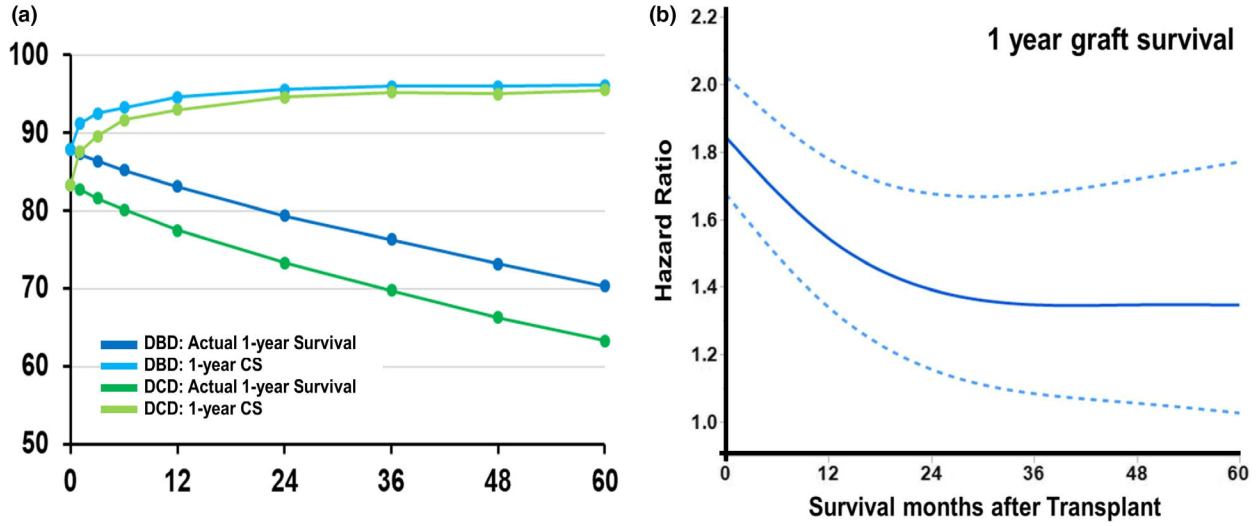

Figure 3 (a) 1-year conditional survival relative to actuarial survival in DBD and DCD grafts. (b) Hazard ratio plots of 1-year graft survival in DCD grafts according to the time from transplant.

Table 3. Cause of graft loss/patient death after liver transplant

		Actual			3-year survivor		
Cause of death	Median time	DBD	DCD	P	DBD	DCD	P
1. Malignancy (recurrence/de novo)	34.6	3305 (15.1)	175 (12.7)	0.02	1609 (19.1)	73 (18.4)	0.79
2. Infection	10.6	2441 (11.2)	119 (8.7)	<0.01	705 (8.4)	29 (7.3)	0.52
3. Cardio-vascular disease	9.7	2191 (10.0)	138 (10.0)	1.00	780 (9.3)	32 (8.1)	0.48
4. Recurrence of original liver disease	23.8	1942 (8.9)	77 (5.6)	<0.01	724 (8.6)	22 (5.6)	0.03
5. Multiple organ failure	15.6	1526 (7.0)	77 (5.6)	0.05	509 (6.0)	18 (4.5)	0.28
6. Vascular-related complications	1.1	958 (4.4)	51 (3.7)	0.25	86 (1.0)	2 (0.5)	0.44
7. Respiratory failure	23.6	886 (4.1)	49 (3.6)	0.40	372 (4.4)	19 (4.8)	0.71
8. Biliary related complications	9.1	700 (3.2)	169 (12.3)	<0.01	100 (1.2)	21 (5.3)	<0.01
9. Primary non-function	0.2	775 (3.5)	74 (5.4)	<0.01	0 (0)	0 (0)	-
10. End-stage renal disease	56.5	386 (1.8)	17 (1.2)	0.17	243 (2.9)	9 (2.3)	0.64
11. Cerebrovascular disease	12.2	341 (1.6)	10 (0.7)	0.01	100 (1.2)	1 (0.3)	0.09
12. Rejection	15.7	316 (1.4)	15 (1.1)	0.35	87 (1.0)	5 (1.3)	0.61
13. Intraoperative death/bleeding	0.0	128 (0.6)	14 (1.0)	0.07	0 (0)	0 (0)	-
14. GVHD	2.1	104 (0.5)	9 (0.7)	0.32	0 (0)	0 (0)	-
15. PTLD	29.1	105 (0.5)	6 (0.4)	1.00	47 (0.6)	4 (1.0)	0.29
Miscellaneous	22.1	1843 (8.4)	99 (7.2)	0.12	658 (7.8)	32 (8.1)	0.85
Unspecified	48.1	3907 (17.9)	276 (20.1)	0.04	2328 (27.6)	127 (32.1)	0.06
Total		21 854 (100)	1375 (100)	-	8422 (100)	396 (100)	-

DBD: donor after brain dead, DCD: donor after circulation death; GVHD, graft versus host disease; PTLD, post-transplant lymphoproliferative disease.

transplant. Liver transplantation is an established treatment for end-stage liver disease and an increasing demand for this procedure has generated a continuing organ shortage [8]. As a result, interest in DCD grafts has grown as evidenced by an increase in case numbers of DCD LTs [8]. Although utilizing DCD grafts is an attractive approach for candidates who would otherwise accrue a longer time on the waiting list, LT using DCD grafts can be a double-edged sword. Numerous reports showed that the overall GS of DCD is inferior to those of DBD, which are mainly derived from PNF and IC [1–3]. These well-known complications of DCD mainly occur in the early period after LT [11,12]. The definition of PNF is graft failure within seven days. According to a previously reported meta-analysis, the prevalence of PNF in DCD is 1.7 times higher than DBD grafts [21]. Another meta-analysis reported biliary complications and IC in DCD grafts are 2.4 times and 10.8 times

Table 4. Factors associated with biliary-related graft loss after liver transplantation using DCD grafts

Factors	*P*	HR (95% CI)
Transplant year (per year)	<0.01	0.90 (0.87–0.94)
Recipient age (per year)	<0.01	0.97 (0.96–0.99)
Medical condition (Ref home)		
Hospital	0.51	0.80 (0.38–1.72)
ICU	<0.01	0.21 (0.08–0.51)
Donor age (per year)	<0.01	1.02 (1.01–1.03)
Warm ischemic time, per min	0.11	1.01 (0.99–1.03)
Cold Ischemic time, per hour	<0.01	1.05 (1.03–1.07)

The A competing risk model was generated using the Fine and Gray model. Warm ischemic time was used as special interest variable.

CI, confidence interval: DCD, donation after circulation death: HR, hazard ration.

higher than DBD grafts [3]. Moreover, a previous study determined that most instances of IC happen within 120 days after LT [10]. In this context, the inferiority of DCD graft to DBD graft in the early post-transplant period is well established. On the other hand, it is still unclear whether DCD grafts attain equivalence to DBD grafts if patients survive the early post-transplant period. This clinical question is similar to the situation in cancer patients. Most cancers recur within 2–3 years of treatment, and the probability of recurrence/life expectancy varies based on the time from intervention. Conditional survival analysis is a well-known statistical approach in the oncology field, which is commonly used to answer clinical questions about practical life expectancy of cancer survivors [14–17]. This study is the first study that employed conditional survival analysis to reveal the prognostic influences of DCD grafts on long-term graft survival.

The statistical analyses showed that the unadjusted conditional Kaplan-Meier curves and the plotted conditional 1-year GS probability of DCD livers reached a similar level to those of DBD after surviving 3 years from LT, whereas in the early period after LT, those of DCD grafts were significantly inferior to DBD. These findings are not novel since previous studies have shown that the Kaplan-Meier curve of DCD grafts significantly drops in the early period after LT and become parallel with those of DBD grafts later on [15,22]. As a result, prior studies have concluded that DCD grafts are statistically comparable to DBD grafts if patients survive the early postoperative period. However, these studies did not perform an adequate risk adjustment using multivariate analysis because of the limitation of case numbers [3,15]. As shown in Table 1, LT using DCD grafts had some well-known favorable prognostic factors such as young donor age, Pre-LT medical condition, shorter cold ischemic time, and lower MELD score [4,23,24]. Moreover the DCD group had higher proportion of HCC patients, which should favorably influence the short-term GS and adversely influence the long-term GS due to cancer recurrence. As such, the true prognostic influence of DCD grafts in patients surviving

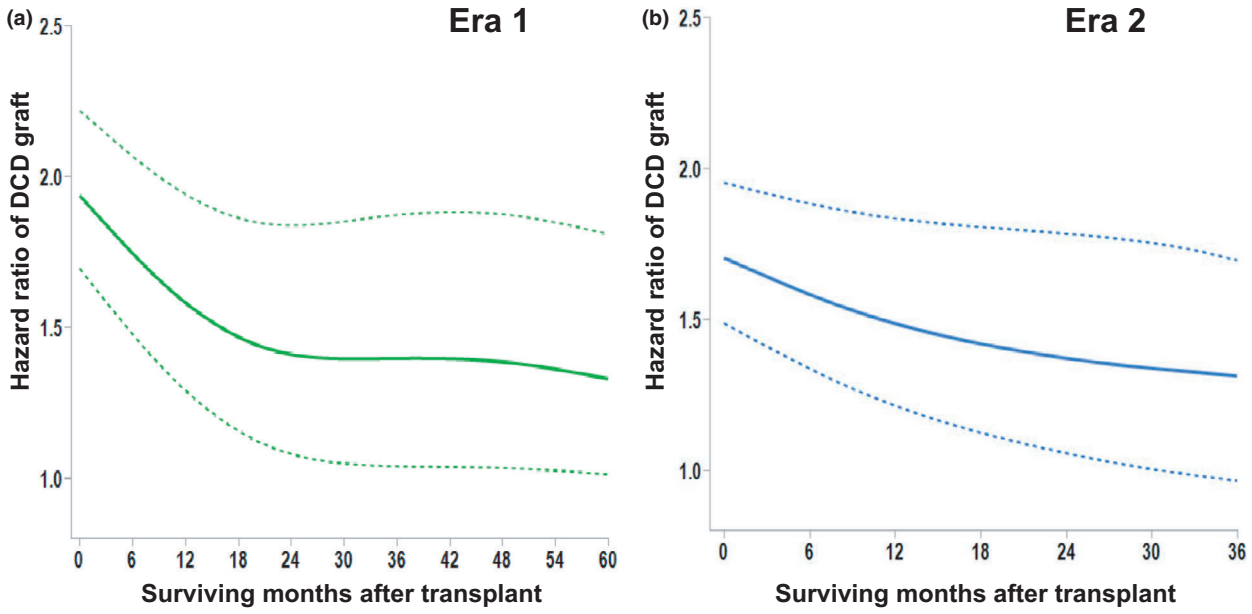

Figure 4 The era influences on conditional hazard ratio of 1-year graft survival in DCD grafts. (a) Era 1 (3/2002–9/2009). (b) Era 2 (10/2009-12/2017).

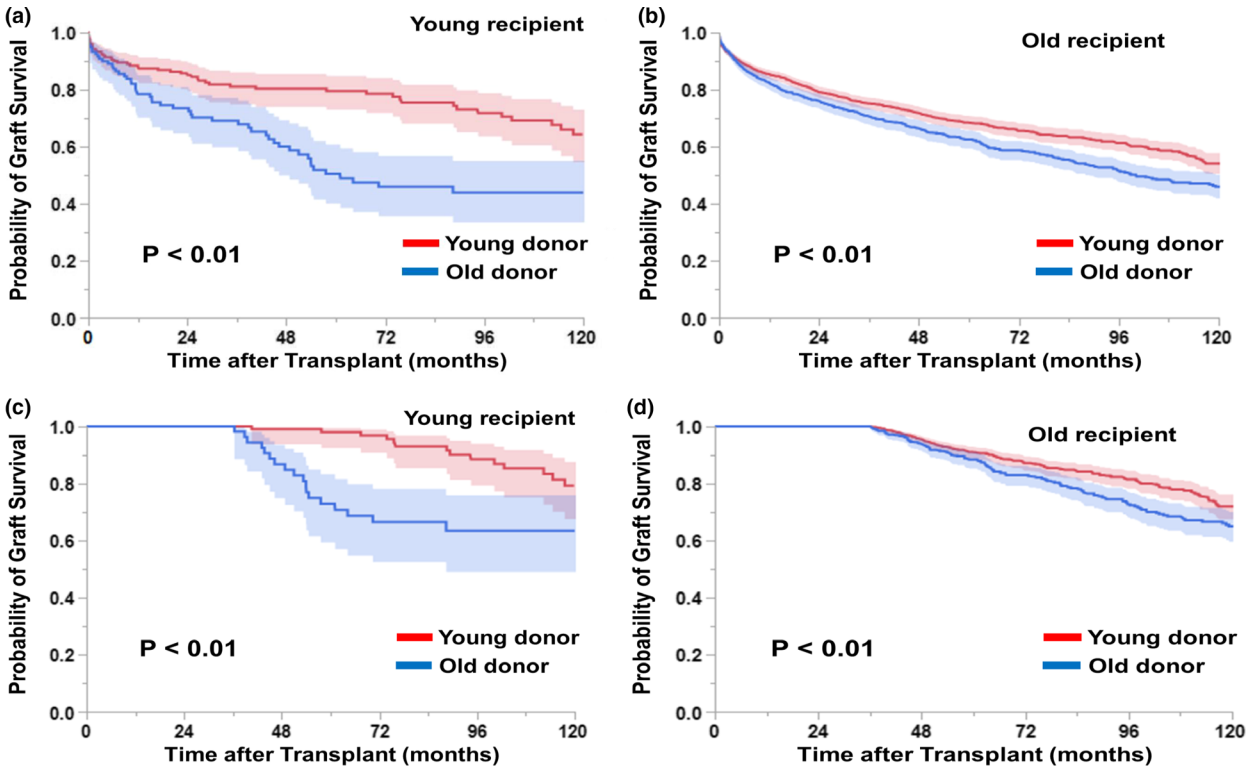

Figure 5 Actual and conditional graft survival curves comparison between young and old donor grafts in young recipients. (a) Actual graft survival in young recipients. (b) Actual graft survival in old recipients. (c) 3-year conditional survival in young recipients. (d) 3-year conditional survival in old recipients.

a certain period from LT should be ideally assessed using the conditional version of Cox regression analysis in a large study population.

The conditional version of Cox regression model revealed that the adverse prognostic effect of DCD grafts decreased as patients survived longer, although still significantly higher even after surviving 5 years from LT. These results suggest that DCD grafts cannot be considered equivalent to DBD grafts even when patients survive the early period after LT. Earlier publications have shown that GS in DCD livers improves over time with accumulation of cases and knowledge [25]. Therefore, a sensitivity analysis regarding the time period was conducted. Not surprisingly, the HR of DCD graft in the short-term after LT decreased in the second era. On the other hand, the HR of DCD organ in the long-term after LT was around 1.3 in both eras (Fig. 4). These findings suggest that the HR associated with long-term survival is the nature of the DCD organ regardless of era. These findings are important when deciding on the use of DCD grafts. DCD grafts are usually utilized for patients who do not need urgent life-saving transplant but also require avoidance of the long waiting time to decrease their waiting-list mortality. DCD grafts maintain their inferiority in GS compared with DBD grafts even in the long-term after LT. Given that, we would recommend surgeons carefully consider using a DCD graft in recipients who are able to safely wait for DBD grafts or a living donor. Specifically, young donor age organs should be applied for young recipients since younger donor age has potential to mitigate the adverse influences of DCD grafts in long-term GS (Fig. 5). Although the conditional version of Cox regression analysis revealed the long-term adverse prognostic influences of DCD, the exact causes of this adverse effect were still unclear. To elucidate the background cause of the adverse prognostic influence of DCD grafts in long-term survivors, we conducted an analysis to investigate the cause of graft loss/patient death.

In the analysis of the cause of graft loss, the proportion of graft loss due to biliary related complications was continuously higher in DCD grafts than DBD even in patients who survived 3 years from LT (1.2% vs. 5.3%, $P < 0.01$). Biliary complications, including non-anastomotic biliary stricture, (ischemic cholangiopathy), comprise the most critical drawbacks of DCD grafts [1–3]. The graft loss rate due to biliary related complications in this study also showed that DCD grafts are significantly worse than DBD grafts (12.3% vs. 3.2%, $P < 0.01$). As mentioned above, it

is reported that almost all IC happened in the early post-transplant period [3,10]. Statistical analysis revealed that the adverse influence of biliary related complications in DCD grafts affects not only short-term but also lasts long-term after LT. These results indicate that biliary related complications in DCD can eventually be critical, although they can usually be temporized through interventional radiological approaches in the early period after LT. In this respect, prevention of biliary related complications is important for short term outcomes as well as for long-term outcomes. Recently, various machine perfusion (MP) protocols have been published and some of them reported to reduce IC rate by MP [26–29]. Especially, two reports using postmortem normothermic regional perfusion (NRP) from European countries showed substantial decreasing of IC by MP at the time of organ procurement. A nationwide study from Spain showed that NRP improved IC occurrence (odds ratio 0.14 by using NRP comparing standard super-rapid recovery) and similar results were seen from UK (0% IC in 43 DCD using NRP) [26,27]. On the other hand, although many studies showed normothermic ex-vivo MP (NMP) can provide information to predict future IC in DCD graft, there is no solid evidence that NMP itself can reduce IC occurrence thus far [28,29]. In liver transplant using DCD organs, further optimization of interventions targeting biliary complications are warranted and would impact more than just the short-term outcomes of PNF and IC that most investigators are interested in.

We acknowledge that our study has some inherent limitations, including its retrospective study design. National registry datasets comprise information collected from hundreds of institutions and are subject to some degree of heterogeneity or variability in reporting by different centers, which does not necessarily mean that the same holds true for individual centers. Center and regional bias must also be considered when interpreting the results of this work. Additionally, finer details of circumstances that led to DCD graft usage were not clear from our analysis, which have to be answered by future non-registry based studies. Moreover the influences of changes in intensive care and other clinical practices occurring over the study period were not completely assessed by dividing time-era or adjusting transplant year in this type of retrospective registry-based study design. In this study, we analyzed up to 5-year survivors in conditional survival analysis and 3-year survivors in the analysis of graft loss cause. A criticism can be leveled that DCD grafts may become comparable to DBD grafts after surviving longer than 5 years, especially when the prognostic influence of biliary complications potentially disappears in the long-term. Unfortunately, our cohort did not have enough event numbers to perform a firm statistical analysis to reveal the very long-term prognosis of DCD grafts. Future study, after accumulation of cases, will reveal whether DCD is still an adverse risk factor after a very long-term following LT.

In conclusion, national registry data analysis reveals that DCD grafts cannot be considered equivalent to DBD grafts despite survival through the early period after LT. The prolonged adverse influences of DCD grafts would likely be derived from biliary related complications. At an individual center level, careful risk adjustment is thus important in the use of DCD organs, not only for short-term prognosis but also towards improving their long-term outcomes.

Authorship

KS, DJ, JM, KH: Participated in research design. KS, AN, DJ, JM, AM: Participated in the writing of the paper. AN, DJ, JM, KH: Participated in the critical review. KS, DJ, JM: Participated in data analysis.

Funding

The authors have declared no funding.

Conflicts of Interests

The authors declare no conflicts or competing interests as described by T*ransplant International*.

Acknowledgements

The authors thank Dr. Daisuke Morioka for his comments and suggestions, which were of inestimable value for our study.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. The actual, 1-, 3-year conditional Kaplan-Meier GS estimations, and 1-year GS probability plots between DBD and DCD in Era 1 (3/2002-9/2009).

Figure S2. The actual, 1-, 3-year conditional Kaplan-Meier GS estimations, and 1-year GS probability plots between DBD and DCD in Era 2 (10/2009-12/2017).

Figure S3. The actual, 1-, 3-year conditional Kaplan-Meier GS estimations, and 1-year GS probability plots between Era 1 and Era 2.

Table S1. Patient characteristics comparison between era 1 and era 2.

Table S2. Patient characteristics in era 1.

Table S3. Patient characteristics in era 2.

Table S4. Factors associated with 1-year graft survival after liver transplantation in era 1.

Table S5. Factors associated with 1-year graft survival after liver transplantation in era 2.

REFERENCES

1. Reich DJ, Mulligan DC, Abt PL, *et al*. ASTS recommended practice guidelines for controlled donation after cardiac death organ procurement and transplantation. *Am J Transplant* 2009; **9**: 2004.
2. Foley DP, Fernandez LA, Leverson G, *et al*. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. *Ann Surg* 2005; **242**: 724.
3. Jay CL, Lyuksemburg V, Ladner DP, *et al*. Ischemic cholangiopathy after controlled donation after cardiac death liver transplantation: a meta-analysis. *Ann Surg* 2011; **253**: 259.
4. Feng S, Goodrich NP, Bragg-Gresham JL, *et al*. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant* 2006; **6**: 783.
5. Braat AE, Blok JJ, Putter H, *et al*. European Liver and Intestine Transplant Association (ELITA) and Eurotransplant Liver Intestine Advisory Committee (ELIAC). The Eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant* 2012; **12**: 2789.
6. Haque O, Yuan Q, Uygun K, Markmann JF. Evolving utilization of donation after circulatory death livers in liver transplantation: the day of DCD has come. *Clin Transplant.* 2020: e14211.
7. Croome KP, Taner CB. The changing landscapes in DCD liver transplantation. *Curr Transplant Rep* 2020; **7**: 194.
8. Kim WR, Lake JR, Smith JM, *et al*. OPTN/SRTR 2017 annual data report: liver. *Am J Transplant* 2019; **19**(Suppl 2): 184.
9. Kubal C, Mangus R, Fridell J, *et al*. Optimization of perioperative conditions to prevent ischemic cholangiopathy in donation after circulatory death donor liver transplantation. *Transplantation* 2016; **100**: 1699.
10. Bohorquez H, Seal JB, Cohen AJ, *et al*. Safety and outcomes in 100 consecutive donation after circulatory death liver transplants using a protocol that includes thrombolytic therapy. *Am J Transplant* 2017; **17**: 2155.
11. Foley DP, Fernandez LA, Leverson G, *et al*. 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.
12. Chan EY, Olson LC, Kisthard JA, *et al*. Ischemic cholangiopathy following liver transplantation from donation after cardiac death donors. *Liver Transpl* 2008; **14**: 604.
13. Mourad MM, Algarni A, Liossis C, Bramhall SR. Aetiology and risk factors of ischaemic cholangiopathy after liver transplantation. *World J Gastroenterol* 2014; **20**: 6159.
14. Croome KP, Lee DD, Perry DK, *et al*. Comparison of longterm outcomes and quality of life in recipients of donation after cardiac death liver grafts with a propensity-matched cohort. *Liver Transpl* 2017; **23**: 342.
15. Blok JJ, Detry O, Putter H, *et al*. Longterm results of liver transplantation from donation after circulatory death. *Liver Transpl* 2016; **22**: 1107.
16. Merrill RM, Hunter BD. Conditional survival among cancer patients in the United States. *Oncologist.* 2010; **15**: 873.
17. Margonis GA, Buettner S, Andreatos N, *et al*. Prognostic factors change over time after hepatectomy for colorectal liver metastases: a multi-institutional, international analysis of 1099 patients. *Ann Surg* 2019; **269**: 1129.
18. Kim Y, Ejaz A, Spolverato G, *et al*. Conditional survival after surgical resection of gastric cancer: a multi-institutional analysis of the us gastric cancer collaborative. *Ann Surg Oncol* 2015; **22**: 557.
19. Sahara K, Merath K, Tsilimigras DI, *et al*. Conditional disease-free survival after curative-intent liver resection for neuroendocrine liver metastasis. *J Surg Oncol.* 2019; **120**: 1087.
20. Stuart EA, Azur M, Frangakis C, *et al*. Multiple imputation with large data sets: a case study of the Children's Mental Health Initiative. *Am J Epidemiol* 2009; **169**: 1133.
21. Tang JX, Na N, Li JJ, Fan L, Weng RH, Jiang N. Outcomes of controlled donation after cardiac death compared with donation after brain death in liver transplantation: a systematic review and meta-analysis. *Transplant Proc* 2018; **50**: 33–41.
22. Firl DJ, Hashimoto K, O'Rourke C, Diago-Uso T, Fujiki M. Aucejo FN Role of donor hemodynamic trajectory in determining graft survival in liver transplantation from donation after circulatory death donors. *Liver Transpl* 2016; **22**: 1469.
23. Rana A, Hardy MA, Halazun KJ, *et al*. Survival outcomes following liver transplantation (SOFT) score: a novel method to predict patient survival following liver transplantation. *Am J Transplant* 2008; **8**: 2537.
24. Dutkowski P, Oberkofler CE, Slankamenac K, *et al*. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann Surg.* 2011; **254**: 745; discussion 753.
25. Croome KP, Lee DD, Keaveny AP, Taner CB. Improving national results in liver transplantation using grafts from donation after cardiac death donors. *Transplantation* 2016; **100**: 2640.
26. Hessheimer AJ, Coll E, Torres F, *et al*. Normothermic regional perfusion vs. super-rapid recovery in controlled donation after circulatory death liver transplantation. *J Hepatol* 2019; **70**: 658.
27. Watson CJE, Hunt F, Messer S, *et al*. In situ normothermic perfusion of livers in controlled circulatory death donation may prevent ischemic cholangiopathy and improve graft survival. *Am J Transplant* 2019; **19**: 1745.
28. Nasralla D, Coussios CC, Mergental H, *et al*. Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557**: 50.
29. Watson CJE, Kosmoliaptsis V, Pley C, *et al*. Observations on the ex situ perfusion of livers for transplantation. *Am J Transplant* 2018; **18**: 2005.