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Original Article

National time trends in mortality and graft survival following liver transplantation from circulatory death or brainstem death donors

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Abstract

Background: Despite high waiting list mortality rates, concern still exists on the appropriateness of using livers donated after circulatory death (DCD). We compared mortality and graft loss in recipients of livers donated after circulatory or brainstem death (DBD) across two successive time periods.

Methods: Observational multinational data from the United Kingdom and Ireland were partitioned into two time periods (2008–2011 and 2012–2016). Cox regression methods were used to estimate hazard ratios (HRs) comparing the impact of periods on post-transplant mortality and graft failure.

Results: A total of 1176 DCD recipients and 3749 DBD recipients were included. Three-year patient mortality rates decreased markedly from 19.6 per cent in time period 1 to 10.4 per cent in time period 2 (adjusted HR 0.43, 95 per cent c.i. 0.30 to 0.62; $P < 0.001$) for DCD recipients but only decreased from 12.8 to 11.3 per cent (adjusted HR 0.96, 95 per cent c.i. 0.78 to 1.19; $P = 0.732$) in DBD recipients (P for interaction $= 0.001$). No time period-specific improvements in 3-year graft failure were observed for DCD (adjusted HR 0.80, 95% c.i. 0.61 to 1.05; $P = 0.116$) or DBD recipients (adjusted HR 0.95, 95% c.i. 0.79 to 1.14; $P = 0.607$). A slight increase in retransplantation rates occurred between time period 1 and 2 in those who received a DCD liver (from 7.3 to 11.8 per cent; $P = 0.042$), but there was no change in those receiving a DBD liver (from 4.9 to 4.5 per cent; $P = 0.365$). In time period 2, no difference in mortality rates between those receiving a DCD liver and those receiving a DBD liver was observed (adjusted HR 0.78, 95% c.i. 0.56 to 1.09; $P = 0.142$).

Conclusion: Mortality rates more than halved in recipients of a DCD liver over a decade and eventually compared similarly to mortality rates in recipients of a DBD liver. Regions with high waiting list mortality may mitigate this by use of DCD livers.

Introduction

Increased numbers of patients who require liver transplantation have contributed to a chronic shortage of donors in many high-income countries[1–4]. As a consequence, livers donated following circulatory death (DCD) have been used increasingly to address the discrepancy between the number of patients waiting to receive a liver transplant and the number of suitable donor organs available[2,4]. Early analyses that compared DCD livers with livers donated following brainstem death (DBD) described inferior post-transplantation outcomes, especially in the early post-transplantation period[2,5–8]. Variable periods of warm ischaemia during the procurement of DCD livers were found to cause irreversible cellular damage and higher rates of postoperative biliary complications, primary non-function (PNF), and hepatic artery thrombosis (HAT)[2,5–8].

These early single-centre reports of poorer graft and patient survival contributed to differences internationally in how DCD donors were utilized[9]. In some countries, there was reluctance to maximize their use due to the risk of postoperative complications and graft failure, whereas in other countries—including the United Kingdom (UK) and Ireland—there was reliance on DCD donors to provide liver transplantation to patients, and especially hepatocellular carcinoma (HCC) patients, before their disease progressed beyond the transplantable criteria[4,10].

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Optimal utilization of grafts from DCD donors is most likely to have been associated with a learning curve[9]. More recent publications from countries outside the UK describe improvements in the use of DCD livers, including improved patient and graft survival and lower rates of biliary complications, PNF, and HAT[11–15]. A recent analysis of the UK liver transplant waiting list indicated that patients fair better by accepting an offer of a DCD liver rather than waiting for a future offer of a better-quality donor liver[16].

Given that, proportionally, the UK continues to be the primary proponent in the utilization of DCD livers, it is important to identify whether temporal improvements in patient and graft survival have been observed. Also, with high rates of graft failure reported previously[9], and retransplantation as the only lifesaving option in this event, it is important to investigate whether the rate of retransplantation has changed over time. Using national data of transplants carried out in the UK and Ireland, we investigated whether there have been changes over time in short- and longer-term post-transplant mortality for patients who received a DCD or DBD liver. In order to understand changes in patient survival, we also investigated changes over time in the rate of graft failure and retransplantation and in the incidence of postoperative complications. Finally, we provide an up-to-date comparison of post-transplant mortality in patients receiving DCD and that in patients who had DBD livers.

Patients and methods

Standard National Liver Transplant Registry

The Standard National Liver Transplant Registry contains detailed information about all liver transplants carried out in all seven liver transplant centres in the UK and Ireland[17]. It is managed by NHS Blood and Transplant[17]. This registry was used to identify recipients of a controlled DCD or DBD liver transplant and to capture information on donor and recipient characteristics, including post-transplantation outcomes (HAT, biliary tract leak, and biliary tract stricture) recorded at 3 months and the date and cause of death and graft failure[17].

Study population

All patients aged 18 years or older who had received a first-time elective liver transplant between 1 January 2008 and 31 December 2016 were eligible for inclusion (*Fig. S1*). Recipients were dichotomized into two groups: those transplanted using a DCD liver; and those transplanted using a DBD liver. To limit heterogeneity of the study cohort, patients who underwent transplantation for types of liver cancer other than HCC and those who underwent multivisceral, superurgent, domino, or living-related liver transplantations were excluded, as well as those who received a liver transplant for acute liver failure (including auxiliary transplantation). We also excluded patients whose survival data were missing. This study complies with the STROBE statement for retrospective studies[18].

Inclusion period and two time periods

Patients were grouped into those who had received a transplant between 1 January 2008 and 31 December 2011 (time period 1) and those between 1 January 2012 and 31 December 2016 (time period 2). The start of time period 1 coincides with the introduction of donor allocation policies that are based on predicted waiting list mortality[19]. We chose the start of time period 2 based on pragmatic considerations, creating as much as possible two time periods of equal duration while using calendar years.

Donor and recipient characteristics

Recipients' functional status at the time of transplantation was assessed using a 5-point scale, ranging from 'able to carry out normal activity without restriction' to 'completely reliant on nursing/medical care'[20]. The United Kingdom Model for End-Stage Liver Disease (UKELD) score, derived from the international normalized ratio (INR), serum bilirubin, sodium, and creatinine, was used to score recipients' severity of liver disease[19], and values for ethnicity were categorized into white and non-white groups. Changes over time in overall donor quality was measured using the UK Donor Liver Index (DLI), derived from donor age, sex, height, type (DCD donor or not), serum bilirubin, smoking history, and whether the liver was split, with larger values representing poorer donor livers[21].

Cold ischaemic time (CIT) was defined as the duration between start of cold perfusion in the donor to start of blood flow through the organ in the recipient[22]. Warm ischaemic time (WIT) was separated into agonal and asystolic time periods[23]. Agonal time was defined as the period between withdrawal of life-sustaining treatment and circulatory arrest, and asystolic time was defined from the time of circulatory death to the time the donor liver was placed in cold storage[23]. A small proportion of donor livers included in time period 2 of this analysis would have been subjected to normothermic machine perfusion, but these patients could not be specifically identified from the Standard National Liver Transplant Registry.

Donor and recipient selection and organ procurement

All DCD donors included in this analysis were procured under controlled circumstances where potentially life-sustaining treatment was withdrawn after further intervention was deemed futile (Maastricht III) or circulatory death occurred in a DBD donor (Maastricht IV)[2]. Criteria for DCD donor selection and post-withdrawal haemodynamic parameters varied among liver transplant centres but broadly followed the experience detailed by Muiesan *et al.*[24] Administration of heparin or prior dissection of femoral vessels is prohibited by UK law[2]. Death was declared at 5 minutes following cardiac arrest and all UK liver procurement centres used a super-rapid recovery technique, although the type of preservation fluid, bag pressure, and use of simultaneous perfusion techniques varied[2].

During the study period, DBD and DCD liver allocation in the UK and Ireland was organized locally and centres selected recipients according to local criteria. In terms of DBD transplantation, patients on local waiting lists were prioritized according to the UKELD scoring system that was designed to predict waiting list mortality[19,25]. In terms of DCD transplantation, local centres could allocate DCD donors outside of the UKELD scoring system if they felt there was a more suitable recipient further down the list. The scoring systems did not award additional points to patients on the waiting list with HCC[19,25].

Statistical analysis

Percentages were used to describe categorical results and the chi-square test was used to compare differences. Biliary complications were stratified into those that required treatment for a biliary tract leak or a biliary tract stricture. Biliary complications were reported as complications in their own right and also as a cause of graft failure. To calculate causes of death and graft failure, the total number of patients in each cohort was used as the denominator. Postoperative renal failure was defined as any

patient requiring renal replacement therapy. Categorical variables were presented as proportions and continuous variables were presented as means with standard deviations.

Kaplan–Meier methods were used to compare patient and graft survival between successive time periods of transplantation. Follow-up was censored at 3 years after transplantation or on the last follow-up visit before 7 April 2017, whichever occurred earlier. Graft failure was defined as either retransplantation or patient death. A 3-year follow-up was chosen to reflect the time period in which most complications associated with DCD transplantation would be expected to occur[2,26].

Multivariable Cox regression models were used to estimate hazard ratios (HRs) that represented the relative differences in post-transplant mortality and graft loss. Models were fitted with adjustment for donor and recipient characteristics, and a categorical variable for transplant centre was also included in each model[27]. Interaction terms were included in the models to investigate whether the effect of time period differed according to whether a DCD or DBD liver had been used if the recipient had been transplanted for HCC or non-HCC indications. The significance of the interaction term was tested using a global Wald test. The outputs of our prediction models are reported in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) statement[28].

Retransplantation rates were calculated, with death considered as a competing risk. Fine and Gray regression was used to estimate adjusted subdistribution HRs to investigate the differences in retransplantation rates between time periods 1 and 2, with adjustment for donor and recipient characteristics[29].

Three sensitivity analyses were performed. First, the post-transplantation period was partitioned into two separate epochs of follow-up time and the impact of time period on short- and longer-term mortality and graft failure was assessed[4,30]. Second, a separate Cox regression model was built to compare mortality with adjustment for WIT, in addition to all other donor and recipient characteristics. Third, another Cox model was built that additionally adjusted for transplant centre volume. In this model, transplant centre annual volumes of DCD and DBD transplants were measured separately.

Missing donor and recipient characteristics were imputed using chained equations, creating ten complete data sets[31,32]. In the imputation procedure, all of the donor and recipient variables used in the case mix adjustment were used to predict missing values, including the outcome variables[33]. The Cox regression results for each of these data sets were pooled using Rubin's rules[31]. Stata V15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses. A *P*-value of < 0.050 was considered statistically significant.

Results

A total of 4925 adult recipients of first elective liver transplants were included (*Fig. S1*). Of these recipients, 1176 (23.9 per cent) received a DCD liver, and 3749 (76.1 per cent) a DBD liver. Use of DCD livers increased markedly (*Fig. 1*).

Comparing donor characteristics, we found that recipients of a DCD liver were more likely to have male donors and to have received a liver with evidence of capsular damage sustained during retrieval, but they were less likely to have received a liver with signs of steatosis, and the average CIT was shorter than in recipients of a DBD liver (*Table 1*). Considering DCD recipients only, there were no time period-related differences in WIT.

Comparing recipient characteristics, recipients of DCD livers were more likely to have HCC as the primary indication for the transplantation and to have blood group O (*Table 1B*). However, they were less likely to be inpatients immediately before the transplantation and to have had previous abdominal surgery. Over time, donor and recipient characteristics remained largely unchanged.

Time period-specific changes in post-transplantation outcomes

Across the two time periods of transplantation, a significant improvement in patient mortality was identified in recipients of a DCD liver, but not in those who received a DBD liver. Three-year patient mortality in DCD liver recipients decreased from 19.6 per cent (95 per cent c.i. 15.9 to 24.1) in time period 1 to 10.4 per cent (95 per cent c.i. 7.9 to 13.8) in time period 2 ($P < 0.001$; *Fig. 2*), whereas DBD recipient mortality decreased only from 12.8 per cent (95 per cent c.i. 10.3 to 13.6) to 11.3 per cent (95 per cent c.i. 9.7 to 13.1) ($P = 0.702$). In recipients of a DCD liver, a non-significant improvement in overall graft failure (defined as failure of graft or death) was observed from 24.6 per cent (95 per cent c.i. 20.5 to 29.4) in time period 1 to 21.2 per cent (95 per cent c.i. 17.9 to 25.1) ($P = 0.171$; *Fig. 3*) in time period 2. No time period-related improvements in graft failure were observed in recipients of a DBD liver.

Following case mix adjustment, the pattern of results remained the same. Comparing time period 2 to time period 1, post-transplant mortality decreased by 57 per cent in those who received a DCD liver, whereas in those who received a DBD liver, no statistically significant improvements in mortality were observed (*Table 2*). For graft failure at 3 years, no statistically significant time period-specific improvements were identified for either DCD or DBD liver recipients (*Table 3*).

The results presented above demonstrate that there was no statistically significant difference in 3-year mortality in time period 2 between recipients of DCD livers and those of DBD livers (adjusted HR 0.78, 95 per cent c.i. 0.56 to 1.09; $P = 0.142$) (*Table S1*), but 3-year graft loss was increased in recipients of DCD livers (adjusted HR 1.71, 95 per cent c.i. 1.33 to 2.18; $P < 0.001$).

Time-period specific changes in retransplantation

Considering death as a competing event, we found an increase in the 3-year retransplantation rate in recipients of a DCD liver (from 7.3 per cent in time period 1 to 11.8 per cent in time period 2; $P = 0.042$), but no corresponding change in recipients of a DBD liver (from 4.9 per cent in time period 1 to 4.5 per cent in time period 2; $P = 0.365$). However, these changes were not statistically significant with adjustment for donor and recipient characteristics in both recipients of a DCD liver (adjusted subdistribution HR 1.47, 95 per cent c.i. 0.91 to 2.36; $P = 0.127$) and those of a DBD liver (adjusted subdistribution HR 0.88, 95 per cent c.i. 0.63 to 1.23; $P = 0.405$). Further, there was no statistically significant evidence that changes in the retransplantation rate over time differed between donation type (P interaction $= 0.056$). We also found that only 2.0 per cent (7 of 348) of all patients who underwent retransplantation received a DCD liver as their second donor graft and all seven patients had received a DCD liver for their first transplant.

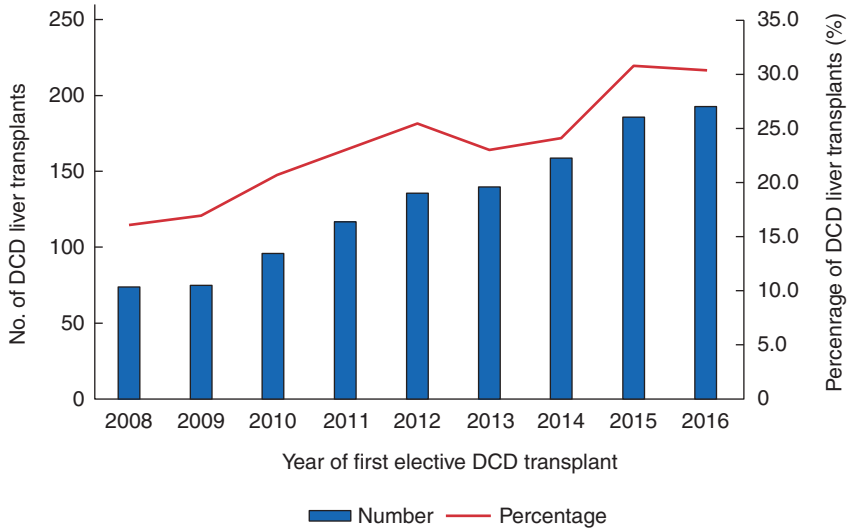

Fig. 1 Time trends in utilization of DCD livers (1176 patients)

Time period-specific changes in postoperative complications

A decrease in the frequency of postoperative renal failure occurred in recipients of a DCD liver, but an increase of this frequency was found in recipients of a DBD liver (*Table 4*). Another remarkable change was an increase in portal thrombosis rate in recipients of a DBD liver from time period 1 to time period 2. Interestingly, no statistically significant change was identified in the era-specific incidence of biliary tract strictures or leaks and this was the same for both recipients of a DCD liver and those of a DBD liver.

Time period-specific changes in causes of death and graft failure

In recipients of a DCD liver, there was a reduction between time period 1 and time period 2 in the proportion of patients dying within 3 years from sepsis-related causes (from 8.5 per cent (31 of 363) to 3.1 per cent (25 of 813); $P < 0.001$) (*Table S2*), cardiac failure (from 2.2 per cent (8 of 363) to 0.2 per cent (2 of 813); $P < 0.001$), and tumour recurrence (from 1.9 per cent (7 of 363) to 0.4 per cent (3 of 813); $P = 0.008$). In recipients of a DBD liver, there were no such reductions in death from these causes and the only significant improvements were in the proportion of patients dying from recurrence of benign disease (from 0.5 per cent (8 of 1520) to 0.0 per cent (0 of 2229); $P < 0.001$) and those whose death was recorded as unknown (from 0.9 per cent (14 of 1520) to 0.2 per cent (5 of 2229); $P = 0.003$).

There was little time period-specific change in causes of graft failure both for recipients of a DCD liver and for those of a DBD liver, except for a decrease in the frequency of recurrent liver disease—including hepatitis C virus (HCV) and cholestatic liver diseases (*Table S3*).

Sensitivity analyses

In a sensitivity analysis exploring time period-related improvements in distinct epochs of follow-up time, statistically significant time period-related improvements in mortality and graft failure from 0 to 1 year were observed for DCD liver recipients (HR 0.32, 95 per cent c.i. 0.21 to 0.51 and HR 0.69, 95 per cent c.i. 0.50 to 0.96, respectively) (*Table S4*), but not for DBD liver recipients (HR 0.91, 95 per cent c.i. 0.73 to 1.13 and HR 0.94, 95 per cent c.i. 0.73 to 1.23, respectively). In the epoch of follow-up time from 1 to 3 years, no time period-related improvements were seen in either cohort (*Table S4*).

In all multivariable models, adjustment for recipient characteristics, and for both recipient and donor characteristics combined, had only a small impact on the time trends observed in post-transplant mortality or graft failure. This is a result of recipient and donor characteristics remaining largely stable over time. Similarly, in the second sensitivity analysis, additional adjustment for donor WIT in DCD liver recipients had very little impact on the pattern of results (*Table S5*).

In the final sensitivity analysis, additional adjustment for transplant centre volume also had little impact of time period on patient mortality (adjusted HR 0.43, 95 per cent c.i. 0.30 to 0.61) or graft failure (adjusted HR 0.95, 95 per cent c.i. 0.77 to 1.18), and transplant centre volume was not found to be an independent risk factor for either outcome (adjusted HR 1.08, 95 per cent c.i. 0.75 to 1.55, $P = 0.664$; adjusted HR 0.97, 95 per cent c.i. 0.75 to 1.24, $P = 0.786$). Global Wald tests found that time period-related differences in post-transplant mortality or graft failure did not differ according to whether patients were transplanted for HCC or non-HCC indications, within either the DCD or DBD cohort (patient mortality: $P = 0.622$ and $P = 0.401$ for DCD and DBD cohorts, respectively; graft failure: $P = 0.096$ and $P = 0.592$ for DCD and DBD cohorts, respectively).

Discussion

In the last decade, the number of liver transplant recipients who received a DCD liver has continually increased and DCD livers have been increasingly more likely to have capsular damage or an appearance documented as abnormal. However, mortality has more than halved for those who received a DCD liver, while remaining unchanged in recipients of a DBD liver. In particular, there have been decreases in DCD recipients who died from septic and cardiac-related causes.

Analysis of the United Network for Organ Sharing (UNOS) database, including 3199 DCD recipients from 2003 to 2014[9], demonstrated era-related reductions in both patient mortality and graft failure, whereas a meta-analysis published in 2014, representing the results from 24 studies and 24 204 patients, identified biliary complications in 26 per cent of

Table 1 Donor and recipient characteristics according to period and stratified by donation type

A. Values are numbers with percentages in parentheses, unless indicated otherwise

			Period of transplantation		
		Overall 2008–2016	Time period 1: 2008–2011	Time period 2: 2012–2016	Missing values, percentage (number)
Number	DCD recipients	1176	363	813	
	DBD recipients	3749	1520	2229	
Donor characteristics					
Female	DCD	474 (40.3%)	153 (42.2%)	321 (39.5%)	0.0% (0)
	DBD	1813 (48.4%)	752 (49.5%)	1061 (47.6%)	0.0% (0)
Age (years), mean (s.d.)	DCD	48.0 (16.3)	45.0 (15.8)	49.3 (16.4)	0.0% (0)
	DBD	49.6 (16.0)	48.3 (15.6)	50.5 (16.2)	0.0% (0)
BMI (kg/m^2), mean (s.d.)	DCD	25.5 (4.6)	25.0 (4.7)	25.6 (4.9)	0.2% (2)
	DBD	26.6 (5.0)	25.3 (3.9)	26.8 (5.1)	0.2% (8)
Trauma as cause of death	DCD	126 (10.7%)	61 (16.8%)	65 (8.0%)	0.0% (0)
	DBD	270 (7.2%)	131 (8.6%)	139 (6.2%)	0.0% (0)
Hepatic steatosis	DCD	446 (38.4%)	128 (35.5%)	318 (39.8%)	1.3% (15)
	DBD	1764 (47.9%)	728 (48.9%)	1036 (47.3%)	1.8% (69)
Presence of capsular damage	DCD	236 (20.3%)	661 (8.3%)	170 (21.3%)	1.3% (15)
	DBD	447 (12.2%)	206 (13.8%)	241 (11.0%)	2.1% (77)
Abnormal donor liver appearance	DCD	296 (30.7%)	93 (35.1%)	203 (29.0%)	17.9% (211)
	DBD	716 (22.5%)	310 (24.7%)	406 (21.1%)	15.2% (570)
Segmental graft type	DCD	1 (0.1%)	1 (0.3%)	0 (0.0%)	0.0% (0)
	DBD	402 (10.7%)	172 (11.3%)	230 (10.3%)	0.0% (0)
	DBD	536.2 (160.7)	548.3 (133.6)	527.5 (163.8)	7.9% (296)
DLI, mean (s.d.)	DCD	1.93 (0.40)	1.89 (0.38)	1.99 (0.40)	3.1% (36)
	DBD	1.16 (0.23)	1.14 (0.23)	1.17 (0.23)	3.7% (139)
WIT (min)—agonal phase, mean (s.d.)	DCD	15.3 (7.6)	15.9 (7.8)	15.0 (7.2)	26.2% (308)
	DBD	N/A	N/A	N/A	N/A
WIT (min)—asystolic, mean (s.d)	DCD	11.0 (40.9)	11.8 (4.0)	10.6 (48.7)	7.7% (91)
	DBD	N/A	N/A	N/A	N/A
ABO match—identical	DCD	1 147 (97.5%)	347 (95.6%)	800 (98.4%)	0.0% (0)
	DBD	283	1 504 (98.9%)	2 199 (98.7%)	0.0% (0)
B. Recipient characteristics					
Female	DCD	383 (32.7%)	113 (31.3%)	270 (33.3%)	0.4% (5)
	DBD	1218 (32.7%)	518 (34.2%)	700 (31.7%)	0.7% (25)
Age (years), mean (s.d.)	DCD	54.6 (9.8)	54.2 (9.5)	54.9 (9.6)	0.0% (0)
	DBD	52.4 (11.8)	52.1 (11.4)	52.6 (12.1)	0.0% (0)
Non-white ethnicity	DCD	153 (13.0%)	59 (16.3%)	94 (11.6%)	0.1% (1)
	DBD	462 (12.3%)	208 (13.7%)	254 (11.4%)	0.03% (1)
Hepatocellular carcinoma indication for transplant	DCD	375 (31.9%)	119 (32.8%)	256 (31.5%)	0.0% (0)
	DBD	830 (22.1%)	359 (23.6%)	471 (21.1%)	0.0% (0)
BMI (kg/m^2), mean (s.d.)	DCD	27.2 (4.9)	26.8 (4.6)	27.4 (5.0)	0.1% (1)
	DBD	27.3 (5.3)	26.9 (5.0)	27.6 (5.4)	0.1% (4)
UKELD, mean (s.d.)	DCD	53.7 (5.1)	54.1 (5.5)	53.5 (4.9)	1.0% (12)
	DBD	55.0 (5.8)	54.9 (5.9)	55.1 (5.7)	0.7% (28)
Waiting list time (days), mean (s.d.)	DCD	133.1 (147.0)	113.6 (114.2)	141.9 (158.9)	0.4% (5)
	DBD	157.7 (199.4)	144.0 (162.6)	161.5 (204.6)	0.6% (24)
Blood group O	DCD	545 (46.5%)	173 (47.9%)	372 (45.9%)	0.4% (5)
	DBD	1469 (39.4%)	595 (39.3%)	874 (39.5%)	0.6% (24)
Functional status: self-care*	DCD	491 (42.4%)	139 (39.3%)	352 (43.7%)	1.4% (17)
	DBD	1699 (45.9%)	693 (46.1%)	1006 (45.8%)	1.9% (46)
Ascites	DCD	608 (52.0%)	180 (49.6%)	428 (53.0%)	0.5% (6)
	DBD	2018 (54.0%)	789 (52.0%)	1229 (55.3%)	0.3% (10)
Previous variceal bleed	DCD	306 (26.4%)	112 (30.9%)	194 (24.3%)	1.3% (15)
	DBD	892 (24.1%)	378 (25.0%)	514 (23.4%)	1.1% (41)
Encephalopathy	DCD	337 (29.1%)	99 (27.4%)	238 (29.8%)	1.4% (16)
	DBD	1629 (27.0%)	435 (28.9%)	706 (32.6%)	0.4% (16)
Presence of HCV antibodies	DCD	254 (22.7%)	87 (25.4%)	167 (21.6%)	5.0% (59)
	DBD	674 (19.1%)	317 (22.9%)	357 (16.7%)	5.9% (223)
Inpatient prior to transplant	DCD	113 (9.6%)	47 (13.0%)	66 (8.1%)	0.2% (2)
	DBD	554 (14.8%)	240 (15.8%)	314 (14.1%)	0.1% (4)
Renal support prior to transplant	DCD	54 (4.6%)	20 (5.5%)	34 (4.2%)	0.2% (3)
	DBD	180 (4.8%)	54 (3.6%)	126 (5.7%)	0.2% (12)
Previous abdominal surgery	DCD	85 (7.3%)	35 (9.7%)	50 (6.2%)	0.3% (4)
	DBD	497 (13.3%)	214 (14.1%)	283 (12.7%)	0.3% (11)

*Third-level of 5-point scale assessing a patient's pretransplantation functional status. DCD, donors of liver donated after circulatory death (DCD); DBD, donors of liver donated after brainstem death. DLI, Donor Liver Index. Donor factors, including DCD, segmental graft, height, age, smoking status, and bilirubin. WIT, warm ischaemic time. UKELD, United Kingdom Model for End-stage Liver Disease; HCV, hepatitis C virus.

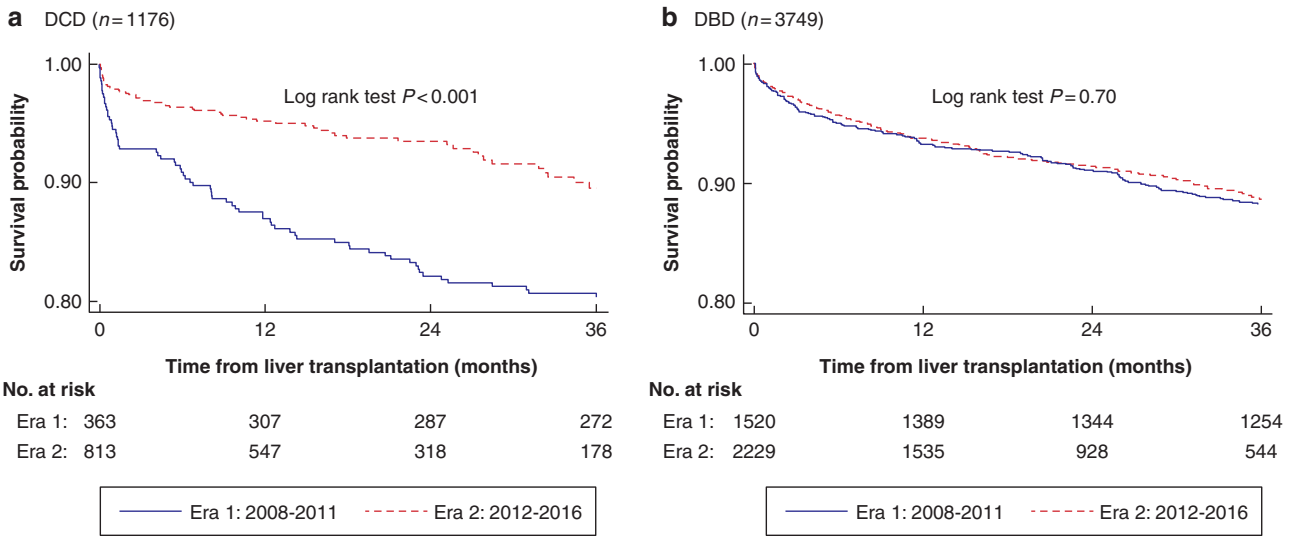

Fig. 2 Three-year patient survival across different periods of transplantation (2008–2011 and 2012–2016) in recipients receiving a DCD or DBD liver (4925 patients)

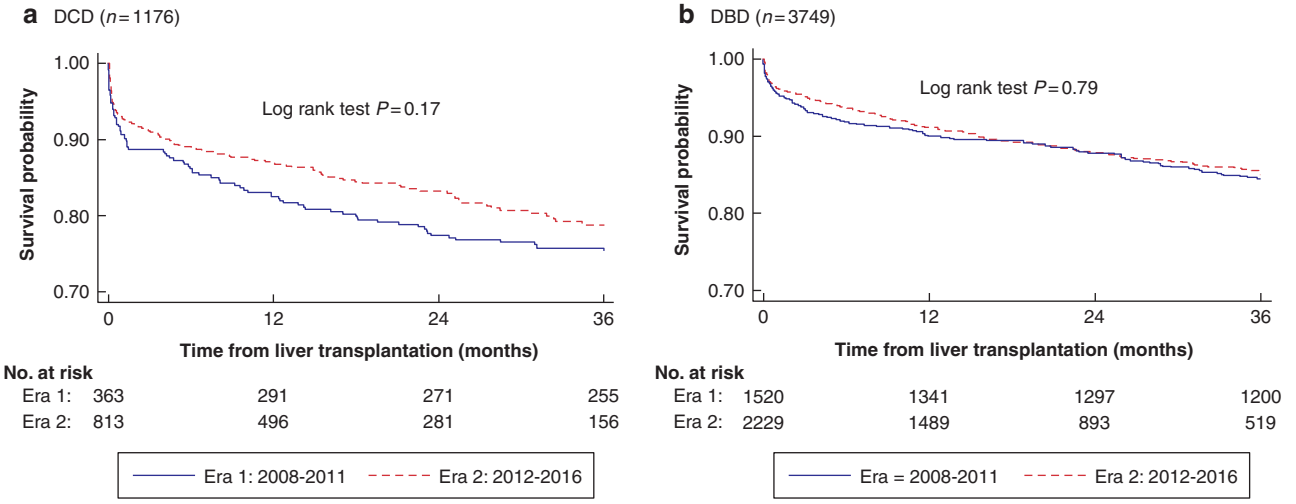

Fig. 3 Three-year graft survival across different periods of transplantation (2008–2011 and 2012–2016) in recipients receiving a DCD or DBD liver (4925 patients)

Table 2 Effect of time period on 3-year post-transplant mortality in patients receiving a DCD or DBD liver

Status of case mix adjustment	Period of transplantation		
	Time period 1:2008–2011	Time period 2:2012–2016	P-value for effect of time period
		Hazard ratio (95% c.i.)	
DCD patients			
Unadjusted	1	0.45 (0.32–0.64)	< 0.001
Adjusted for recipient characteristics only*	1	0.44 (0.31–0.62)	< 0.001
Adjusted for recipient and donor characteristics†	1	0.43 (0.30–0.62)	< 0.001
DBD patients			
Unadjusted	1	0.94 (0.76–1.16)	0.572
Adjusted for recipient characteristics only*	1	0.96 (0.78–1.18)	0.706
Adjusted for recipient and donor characteristics†	1	0.96 (0.78–1.19)	0.732

*Adjusted for recipient characteristics: sex, age, ethnicity, BMI (kg/m^2), functional status, ascites, varices, encephalopathy, hepatitis C virus (HCV) status, United Kingdom Model for End-stage Liver Disease (UKELD), pretransplant inpatient status, pretransplant renal support, previous abdominal surgery, and transplant unit.
†Adjusted for recipient characteristics listed above and for donor characteristics: sex, age, BMI (kg/m^2), cause of death, donor type (donation after circulatory death or donation after brainstem death), steatosis, capsular damage, organ appearance, graft type, and cold ischaemic time.

Table 3 Effect of time period on 3-year graft failure in patients receiving a DCD or DBD liver

Status of case mix adjustment	Period of transplantation		
	Time period 1: 2008–2011	Time period 2: 2012–2016	P-value for effect of time period
	Hazard ratio (95% c.i.)		
DCD patients			
Unadjusted	1	0.83 (0.63–1.09)	0.189
Adjusted for recipient characteristics only*	1	0.82 (0.62–1.08)	0.153
Adjusted for recipient and donor characteristics†	1	0.80 (0.61–1.05)	0.116
DBD patients			
Unadjusted	1	0.93 (0.78–1.11)	0.572
Adjusted for recipient characteristics only*	1	0.95 (0.79–1.14)	0.562
Adjusted for recipient and donor characteristics†	1	0.95 (0.79–1.14)	0.607

*Adjusted for recipient characteristics: sex, age, ethnicity, BMI (kg/m^2), functional status, ascites, varices, encephalopathy, hepatitis C virus (HCV) status, United Kingdom Model for End-stage Liver Disease (UKELD), pretransplant inpatient status, pretransplant renal support, previous abdominal surgery, and transplant unit. †Adjusted for recipient characteristics listed above and for donor characteristics: sex, age, BMI (kg/m^2), cause of death, donor type (donation after circulatory death or donation after brainstem death), steatosis, capsular damage, organ appearance, graft type, and cold ischemic time.

Table 4 Postoperative complications reported at 3 months and stratified by donation type

		Period of transplantation			
		Overall: 2008–2016	Time period 1: 2008–2011	Time period 2: 2012–2016	P-value for effect of time period
Number	DCD recipients	1176	363	813	
	DBD recipients	3749	1520	2229	
Biliary complications					
Biliary tract leak	DCD	68 (5.8%)	17 (4.7%)	51 (6.3%)	0.318
	DBD	199 (5.3%)	75 (4.9%)	124 (5.6%)	0.421
Biliary tract stricture	DCD	74 (6.3%)	18 (5.0%)	56 (6.9%)	0.242
	DBD	163 (4.4%)	57 (3.8%)	106 (4.8%)	0.160
Vascular complications					
Hepatic artery thrombosis	DCD	46 (3.9%)	18 (5.0%)	28 (3.4%)	0.240
	DBD	106 (2.8%)	50 (3.3%)	56 (2.5%)	0.176
Portal vein thrombosis	DCD	38 (3.2%)	12 (3.3%)	26 (3.2%)	0.932
	DBD	116 (3.1%)	22 (1.5%)	94 (4.2%)	< 0.001
IVC occlusion	DCD	14 (1.2%)	4 (1.1%)	10 (1.2%)	0.857
	DBD	37 (1.0%)	19 (1.3%)	18 (0.8%)	0.183
Haemorrhage	DCD	84 (7.1%)	26 (7.2%)	58 (7.1%)	0.991
	DBD	243 (6.5%)	115 (7.6%)	128 (5.7%)	0.046
Infection					
Sepsis*	DCD	436 (37.1%)	122 (33.6%)	314 (38.6%)	0.265
	DBD	1381 (36.8%)	526 (34.6%)	855 (37.4%)	0.112
Renal failure					
Renal failure	DCD	224 (19.1%)	76 (20.9%)	312 (14.0%)	< 0.001
	DBD	487 (13.0%)	175 (11.5%)	148 (18.2%)	< 0.001

*Includes sepsis from bacterial, fungal, and viral infections. Values are numbers with percentages in parentheses. DCD, donation following circulatory death; DBD, donation following brainstem death; IVC, inferior vena cava.

DCD recipients, compared to 16 per cent of DBD recipients[9,34]. However, our results are in line with a European study comparing outcomes in 124 recipients of a DCD liver and 1264 recipients of a DBD liver, published in 2016, that concluded that after DCD liver transplantation, there is increased graft failure, but no difference in patient survival[35].

Increases in the overall donation rates in the UK were almost entirely due to the expansion of DCD programmes[36]. Compared with many other countries, the rate of DBD donation was 'strikingly' low for many years in the UK and attributable to a consistency in the clinical decision-making process that limited or withdrew treatments to patients with non-survivable brain injuries before brainstem death has evolved or can be diagnosed[36]. In fact, in the UK, it was estimated that one-quarter of all patients who fulfilled the preconditions of brainstem death testing did not have tests for brainstem death carried out[36].

By contrast, the proliferation of DCD transplantation in the UK and Ireland is likely to be a reflection of the number of deaths in intensive care that follow a decision to withdraw life-sustaining treatments that are considered to be of no benefit to the critically ill patient[37]. Therefore, increases in DCD liver donation can, at least at an institutional level, be attributed to the resolution of legal and ethical obstacles to this form of donation[37]. In this context, DCD donation at a professional level may also now be viewed as part of the care that a person might wish to receive at the end of their life[37].

We observed substantial improvements in patient mortality over time, but only for DCD recipients and only in the first year a transplantation. Potential explanations for these improvements in early post-transplant mortality are reductions in both the proportion of DCD patients who died as a result of sepsis, cardiac failure, and tumour recurrence and the proportion of patients whose postoperative rehabilitation was complicated by renal failure. This demonstrates that the selection of recipients for DCD transplantation is at least as important as the selection of donors as an explanation for the time period-specific improvements.

The identified improvements in graft survival were again limited to DCD recipients and only found to be significant in the first year after transplantation. These improvements are likely to be attributable to a multitude of factors that may include improvement in surgical and endoscopic techniques (the latter for postoperative treatment of biliary complications), reductions in overall ischaemic times, and a more optimal allocation of DCD livers to patients with primary liver diseases—particularly HCC patients—that do better with this type of donation[5–9].

Failure to demonstrate improved longer-term graft survival in either DCD or DBD recipients is more difficult to explain. It is possible that an overall deterioration in the quality of donors and inability for retrieval of DCD donors to fully mitigate against the deleterious effects of the inevitable WIT—including biliary complications—could have prevented improvements in longer-term graft loss[5–9,11].

A strength of our study is that we described the results of all transplantations carried out in the UK and Ireland and that we had near-complete follow-up. Our results therefore provide a steady benchmark of what post-transplant outcomes can be achieved with both donation types. In addition, several studies have demonstrated the validity of the data available in the Standard National Liver Transplant Registry[4,27].

A first limitation of our study is that the adjustment for donor and recipient characteristics may not have fully captured the time period-related differences in recipient and donor characteristics. However, we adjusted for a wide range of characteristics and therefore, it is unlikely that changes over time in recipient and donor characteristics explain the large reduction in post-transplant outcomes in recipients of DCD livers. Second, the frequency of HAT and biliary complications in the first 3 months following transplantation may be an underestimate of their true frequency, as it is known that they can be difficult to detect[38]. However, we note that the frequency of complications that we found is consistent with other studies[39]. Third, we did not have complete follow-up for some patients transplanted in the second time period of transplantation. In our adjusted analyses, this could have led to an overestimation of the mortality rate in time period 2 and an underestimation of the improvement over time in post-transplantation mortality.

The study has implication for countries with high waiting list mortalities and low rates of DCD utilization[40], especially as mortality following liver transplantation now appears to be comparable for patients receiving DCD and DBD livers[41]. However, we must also acknowledge that, although use of DCD livers has dramatically increased the donor pool, approximately 10 per cent of first-time elective DCD liver recipients still require retransplantation and the graft used for retransplantation typically come from the limited pool of DBD donors. This is likely to be acceptable to both patients and service providers, as it improves the prognosis of the primary liver disease that led to the need for transplantation and helps to reduce waiting list mortalities.

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NIHR statement

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Data statement

The Standard National Liver Transplant Registry is available on request from National Health Service Blood and Transplant.

Supplementary material

Supplementary material is available at *BJS* online.

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