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Original article

Outcomes of transplantation of livers from donation after circulatory death donors in the UK

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Abstract

Background

Outcomes of liver transplantations from donation after circulatory death (DCD) donors may be inferior to those achieved with donation after brain death (DBD) donors. The impact of using DCD donors is likely to depend on specific national practices. We compared risk-adjusted graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK.

Method

Adults who received a first elective liver transplant between January 2005 and December 2010 were identified in the UK National Liver Transplant Database. Multivariable Cox regression and propensity score matching were used to estimate risk-adjusted hazard ratios (HR).

Results

In total, 2572 liver transplants were identified with 352 (14%) from DCD donors. Three-year graft loss (95% CI) was higher with DCD livers (27.3%; 21.8% to 33.9%) than with DBD livers (18.2%; 16.4% to 20.2%). After adjustment with regression, the HR for graft loss was 2.3 (1.7 to 3.0). Similarly, three-year mortality was higher with DCD livers (19.4%; 14.5% - 25.6%) than with DBD livers (14.1%; 12.5% to 16.0%) with an adjusted HR of 2.0 (1.4 to 2.8). Propensity score matching gave similar results. Centre-specific adjusted HRs for graft loss and recipient mortality seemed to differ among transplant centres, although statistical evidence is weak (p-value for interaction 0.08 and 0.24, respectively).

Conclusion

Graft loss and recipient mortality were about twice as high with DCD livers as with DBD livers in the UK. Outcomes after DCD liver transplantation may vary between centres. These results should inform policies for use of DCD livers.

Article Summary

Article focus

- There is increasing disparity between demand and supply of donor livers for transplantation.
- The use of livers from donation after circulatory death (DCD) donors – in addition to those from donation after brain death (DBD) - increases the donor pool.
- We compared graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK.

Key messages

- Recipients of DCD livers, after risk-adjustment, have approximately twice the risk of graft loss and death within 3 years of transplantation than recipients of livers from DBD donors.
- The impact of using DCD livers on graft loss and recipient mortality seemed to differ among the seven UK transplant centres.

Strengths and limitations of this study

- A national database was used with near complete inclusion of all liver transplantations in the UK with high data quality and follow-up, which eliminates the risk or selective reporting.
- Both multivariable regression analysis and propensity score matching were used to adjust for differences risk factors for graft loss and patient mortality between DBD and DCD donors and recipients.
- We were not able to assess the impact that time from withdrawal of life-sustaining treatment to cardiac arrest has on post-transplant outcomes of DCD livers.

Introduction

The increasing disparity between the demand and supply of donor livers is a major challenge. The need to increase the donor pool, and improve organ utilisation, has led to the re-introduction and rapid expansion of the use of livers from donation after circulatory death (DCD) donors. These donors have been classified as either uncontrolled, where cardiac arrest has occurred unexpectedly (Maastricht categories I and II), or controlled, where potential donors have life-sustaining treatment withdrawn after further interventions are deemed futile (Maastricht III), or circulatory death occurs in a donation after brain death (DBD) donor (Maastricht IV) (1).

Unlike DBD donors, livers from DCD donors undergo a variable period of warm ischaemia, during which irreversible cellular damage may occur. Reliably measuring the warm ischaemic period is difficult outside of hospital, which means that the use of livers from uncontrolled DCD donors is limited (2). In contrast, planned withdrawal of life-sustaining treatment in Maastricht III donors enables close cardiorespiratory monitoring, provision of a prepared procurement team, and minimisation of subsequent warm ischaemia. As such, the use of livers from controlled DCD donors has risen dramatically in the US (3) and Europe (4).

US registry analyses have demonstrated that DCD liver transplantation has worse graft and patient survival than DBD liver transplantation (5-9). This is thought to be predominantly due to a higher rate of biliary complications in DCD livers rather than other causes of graft loss (10). Recognition of these issues has perhaps contributed to a recent drop in the number of DCD livers transplanted in the US (3, 11). However, as a result of encouraging early reports (12) and decreasing DBD liver transplantation rates, the use of DCD livers in the UK is now more widespread than the US.

As there are differences between UK and US practice with respect to how DCD livers are being used (13, 14), we report in this paper graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK. Two risk-adjustment techniques were used to control for differences in donor and recipient risk factors.

Materials and methods

Inclusion criteria

Using data submitted to the UK Liver Transplant Audit (15) we identified all adult patients (age >16 years) receiving a first liver transplant in teh 7 UK transplant centres in the UK between 1 January 2005 and 31 December 2010. Follow-up ceased on 31 March 2011. Regular checks show that data are consistently both more than 93% complete and accurate (16-18). Patients receiving living or domino donors were excluded, as were those having an emergency ('super-urgent' (19)) or multi-organ transplant. We are not aware of any uncontrolled DCD liver transplants having been performed in the UK during the study period.

Donor and recipient selection and organ procurement

Criteria for DCD donor selection and acceptable post-withdrawal haemodynamic parameters varied among the liver transplant centres, but were broadly based on the experience of Muiesan et al (12), and in line with US guidelines (19). Administration of heparin or vasodilators, or pre-dissection of femoral vessels before death, is prohibited by law in the UK. Death was declared after cardiorespiratory arrest with a minimum interval of five minutes. All UK liver procurement centres used a super-rapid recovery technique (19), although preservation fluid type, bag pressure, and the use of dual perfusion techniques varied.

Livers from DCD and DBD donors were allocated locally, and centres chose recipients according to local criteria (20). Optimal livers from DBD donors were offered to paediatric centres for splitting and implantation of the left lateral segment, with implantation of the extended right lobe into an adult recipient.

Statistical analyses

Pearson's chi-squared test was used to test differences of categorical variables and Student's t-test or Mann Whitney test for differences of continuous variables. Graft and recipient survival after transplantation were estimated using Kaplan-Meier methods. Graft loss was defined as re-transplantation or death, regardless of perceived graft function at the time of death. Cold ischaemic time was defined as the duration from the start of cold perfusion of the liver in the donor to organ removal from ice immediately prior to implantation.

A multivariable Cox regression model was used to adjust the comparisons of graft loss and recipient mortality between DCD and DBD livers for differences in risk factors at the time of transplantation. The donor, recipient and operative characteristics presented in Table 1 and 2 were included in the model (see Table 1 and 2). United Kingdom End-Stage Liver Disease (UKELD) and Model for End-

Stage Liver Disease (MELD) scores were calculated for recipients (21, 22), but these scores were not incorporated in the multivariable model as the component variables of both were already included.

To test whether the impact of using DCD livers on graft loss and patient mortality varied among UK transplant centre, we included an interaction term of donor type and centre in the Cox model. The likelihood ratio test was used to test the statistical significance of the risk factors. The results of the survival analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI).

An analysis with propensity score matching was also conducted. The propensity score is the probability that a recipient would have received a liver from a DCD (as opposed to a DBD) donor, based on observed donor and recipient characteristics. A logistic regression model was used to generate the propensity score (23). Donor type was regressed on main effects only and donor, recipient and operative characteristics were selected using a stepwise process with conservative removal ($p>0.20$) and entry criteria ($p<0.10$). We considered all two-way interactions of the main effects and explored non-linear relationships by including quadratic terms of continuous model factors. All interactions and quadratic terms with a $p < 0.05$ were selected. We estimated the propensity score based on the logistic regression model as the sum of the products of the model factors and their coefficients. Then, for each recipient in the DCD group we selected an individual from the DBD group by matching on the log of the estimated propensity score, using a nearest-neighbour matching algorithm with callipers (an interval) of maximum width of 0.2 standard deviations. We compared the distribution of all model factors in the DCD and DBD groups to assess the success of the propensity score model. The above processes were repeated for each of the ten imputed data sets (see below for a description of methods to deal with missing data). The balance in the covariates across the treatment groups was considered to be achieved if the standardised differences were less than 10%. (24). Cox regression was then performed on each of the ten sets of matched pairs to estimate the effect of donor type on patient and graft survival. A robust standard error was used to allow for the clustering on the pairs. The estimates were then combined using Rubin's rules to provide adjusted hazard ratios and their 95% CI.

In addition to the donor, recipient and operative characteristics presented in Table 1 and 2, we also considered the following characteristics as candidates for inclusion in the propensity score model (all are yes/no unless otherwise stated): lifestyle activity score on 5-point scale, liver failure grade (acute/not acute), encephalopathy grade on 5-point scale, oesophageal varices, diuretic therapy, pyrexia, sepsis, haemoglobin, white cell count, platelet count, serum urea, anti-CMV status, and anti-HCV status. Types of biliary and hepatic arterial anastomoses were also considered as was the use of anti-fibrinolytic therapy.

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Missing values

All model factors had missing values for less than 5% of patients with the exception of donor history of diabetes (7%), donor organ appearance (19%). Multiple imputation using chained equations was used to fill in missing values for donor diabetes history and donor organ appearance but not the DCD donor post-withdrawal times. The imputation model included the model factors above, type of donor, as well as terms representing the outcome (log of survival time and the censoring indicator) (25). We created 10 imputed data sets and the model parameters based on these datasets were combined using Rubin's rules.

Results

We identified 2572 first elective adult liver transplants. Of these, 352 (14%) had a graft from a DCD donor. Use of livers from DCD donors progressively increased from 6.9% in 2005 to 26.3% in 2010, an almost four-fold rise over that time period. Two centres used DCD donor livers in more than 30% of first elective adult liver transplants in 2010.

Donor, recipient, and operative characteristics

Compared to DBD liver donors, DCD donors were younger, had lower BMIs, lower serum sodium concentrations, and were more likely to be male (Table 1). Although a similar proportion of organs appeared normal in the two groups, DCD donors had a higher proportion of missing values (29%) than DBD donors (18%). The cause of death for DBD donors was predominantly stroke (70%), whereas the corresponding proportion in the DCD group was 49%. Trauma was more common in DCD donors (23%) than in DBD donors (11%). In 352 DCD donors, the median (interquartile range) time from withdrawal of life-support to cardiac arrest was 15 (11 to 20) minutes whereas the median duration from cardiac arrest to cold perfusion was 12 (9 to 14) minutes.

Recipients of a DCD liver were more likely to be older, male, have lower serum bilirubin concentration, and cancer as the primary liver disease (Table 2). Both UKELD and MELD scores were lower in recipients of DCD livers, most probably because a higher proportion of DCD recipients had cancer as their primary disease. DCD livers were more likely to be used as whole rather than partial grafts. Median graft CIT was significantly lower for DCD livers, and there were more ethnicity mismatches in this group.

Graft and patient survival

Graft loss was higher in DCD recipients (Figure 1), with a three-year graft loss (95% CI) of 27.3% (21.8 to 33.9) for DCD recipients and 18.2% (16.4 to 20.2) for DBD recipients with an unadjusted HR of 1.6 (1.2 to 2.0) (Table 3). Recipient mortality was also increased with DCD livers (Figure 1). Three-year mortality was 14.1% (12.5 to 16.0) for DBD recipients and 19.4% (14.5 to 25.6) for DCD recipients with an unadjusted mortality HR of 1.4 (1.1 to 2.0) for use of a DCD donor liver.

After adjustment using the multivariable Cox regression model, we found that the risk of graft loss within three years of transplantation in recipients of a DCD donor liver was more than twice that of those receiving a DBD liver: adjusted HR 2.3 (1.7 to 3.0). Adjusted three-year patient mortality was also significantly higher in recipients of livers from DCD donors: adjusted HR 2.0 (1.4 to 2.8) (Table 3).

After adjustment using the propensity score analysis, use of a liver from a DCD donor was associated with an adjusted HR of 2.3 (1.3 to 4.1) for graft loss. The adjusted HR for recipient mortality was 2.0 (1.0 to 4.2) (Table 3).

Centre-specific estimates of DCD risk

Although the interaction between donor type and centre was not statistically significant for either graft loss (p = 0.08) or recipient mortality (p =0.24), the relative impact of using DCD livers on graft loss and recipient mortality seemed to vary among the seven transplant centres. Centre-specific adjusted HRs for graft loss and recipient mortality varied from being smaller than 1 to larger than 4 (Figure 2).

Causes of graft loss

When causes of graft loss were analysed over three years post-transplantation, the rates of biliary causes of graft loss were higher in livers from DCD donors (4/72 (6%)) than DBD donors (4/330 (1%)) (p = 0.04). Rates of biliary stricture requiring intervention were very similar between the two groups (DCD donors 13/347 (4%) versus DBD donors 81/2193 (4%)) (p = 0.96).

Discussion

Recipients of DCD livers, after risk-adjustment, have approximately twice the risk of graft loss and death within 3 years of transplantation than recipients of livers from DBD donors. This is the first study that has analysed risk-adjusted outcomes in recipients of livers from DCD donors outside of the US. Although US-based studies have reported on larger numbers of DCD liver transplant recipients (6, 7, 9, 13), rates of DCD liver usage in the UK are more than double those of the US (3, 14).

Our results contrast with single-centre reports that demonstrate good short-term results with liver transplantation from DCD donors (12, 26), with graft loss and patient mortality similar to those from DBD donors (27-29). However, it is important to note that we found that the impact of using DCD livers on graft loss and recipient mortality seemed to differ among the seven UK transplant centres, although these differences did not reach statistical significance. This finding indicates that it is important to investigate centre-specific practices that may impact on the outcomes of transplantation of DCD livers, including the selection of DCD grafts, definition of warm ischemic limits, and procurement and implantation techniques.

Risk factors for graft loss and patient mortality are unevenly distributed between DBD and DCD donors and recipients. Risk adjustment or matching techniques (30) are therefore crucial for a valid comparison of outcomes. Because estimates from multivariable models can be less robust when many factors are included, we also used propensity score matching. Reassuringly, both risk-adjustment techniques gave similar HRs for graft loss and recipient death.

In the UK, DCD liver donors are marginally older and have longer times from withdrawal of life-sustaining treatment to cold perfusion than in the US (6, 7, 9, 13, 14, 31). These differences are likely to reflect a wider acceptance of transplantation of DCD livers in the UK and that treatment withdrawal in the UK takes place in the intensive care unit or the anaesthetic room but not in theatre itself. However, cold ischaemic times are shorter for DCD livers in the UK, even taking into account differences in definitions between the two countries (6, 7, 13, 32). This may be due to geographical differences between the two countries (i.e. longer distances between procuring and implanting centres), or an increased willingness on the part of UK surgeons to begin the recipient operation before the organ arrives at the implanting centre.

Transplanted livers from DCD donors appear particularly susceptible to biliary complications, most commonly ischaemic cholangiopathy, which is thought to occur as a result of warm ischaemic damage to the biliary epithelium sustained during the procurement process (10, 33-36). We examined

rates of graft loss from biliary causes and found that this was a relatively rare cause of graft loss in DCD as well as in DBD recipients. In addition, there was no difference in the proportion of DCD and DBD recipients who required an intervention for biliary strictures. Although these findings concur with previous reports suggesting that ischaemic cholangiopathy is not a major problem in UK recipients of livers from DCD donors (26, 27), it should be recognised that analyses of national registry data are prone to under-reporting of post-operative complications.

Unfortunately, data on time from withdrawal of life-sustaining treatment to cardiac arrest were missing in more than 50% of DCD donors, and therefore the impact of this variable on outcome was not assessed. Prolonged time from cardiac arrest to cold perfusion has been shown to be a risk factor for the development of ischaemic cholangiopathy (35), and would therefore be expected to lead to decreased graft survival. We found no significant association (data not shown). This is again likely to be due to lack of power or to most DCD donors having similar times, with an interquartile range of just 5 minutes.

Defining acceptable warm ischaemic limits for livers from DCD donors is hampered by the lack of data on donor cardiorespiratory parameters after treatment withdrawal. Some controlled DCD donors have prolonged periods of cardiorespiratory stability before dying rapidly. It is therefore possible that the duration of hypotension or hypoxia has a greater impact on subsequent graft viability than the duration from treatment withdrawal to cardiac arrest or cold perfusion (8, 37). National prospective data collection of post-withdrawal cardiorespiratory parameters in Maastricht III DCD donors has therefore been initiated in both the UK and the US (8). Further research is also required into the impact of procurement techniques and preservation fluids on graft function (38), and the emerging role of machine perfusion (29).

The allocation of deceased donor livers in the UK is currently on a local basis, with national organ sharing only for those patients with acute liver failure reaching specific criteria (20). Although local allocation reduces cold ischaemic time, which is an important risk factor for graft survival, the current system raises issues of equity of access to a national resource. The ultimate aim of our analyses of national data is to inform discussions on how best to utilise this resource (40). For example, one could use our results as further support for not using livers from DCD donors for patients with a low risk of death on the waiting list as these recipients are able to wait for a graft that is more likely to have a favourable long-term outcome. An exception could be made for patients with HCC. Although, these patients generally have low UKELD scores – indicating a low risk of mortality on the waiting list – they have a high risk of disease progression, which is an additional argument to use livers from DCD donors for this group.

The relative benefit associated with transplantation of a DCD versus a DBD donor liver is expected to be dependent not only on donor and recipient factors, but also on the overall availability of donor livers within each region or country, the rate of deaths on the waiting list, and the impact of DCD transplantation on the subsequent need for re-transplantation (41). Allocation policies also need to determine whether DCD organs are to be distributed on the basis of utility, urgency, or overall survival benefit (42). Although livers transplanted from DCD donors have inferior outcomes to those from DBD donors, they remain a valuable additional source of grafts, especially in countries with relatively low rates of DBD organ donation.

Conflict of interest

None

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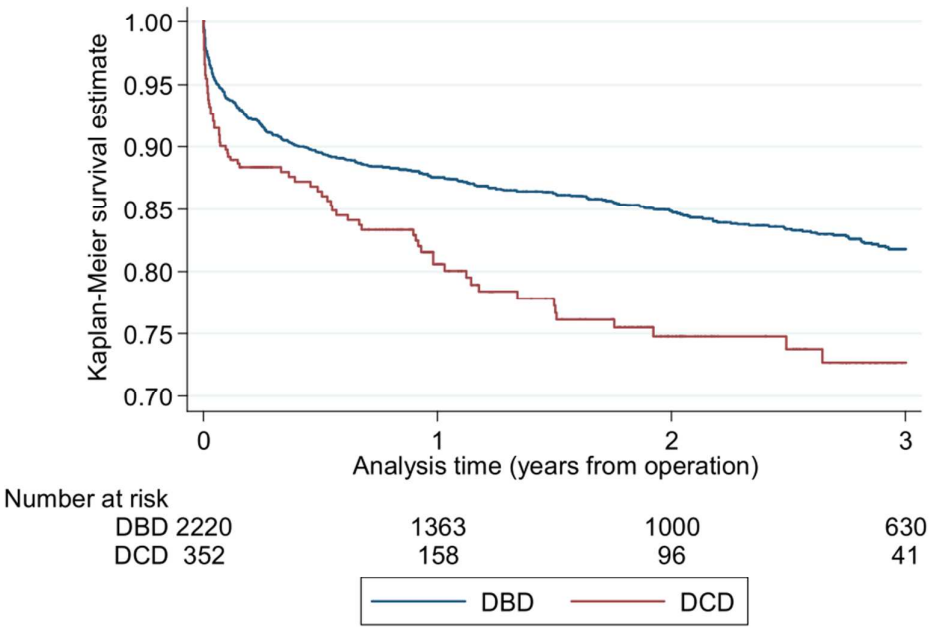
Figure 1 - Graft survival after first elective adult liver transplantation using livers from donation after circulatory death (DCD) donors and donation after brain death (DBD) donors.

Graft failure



Recipient mortality

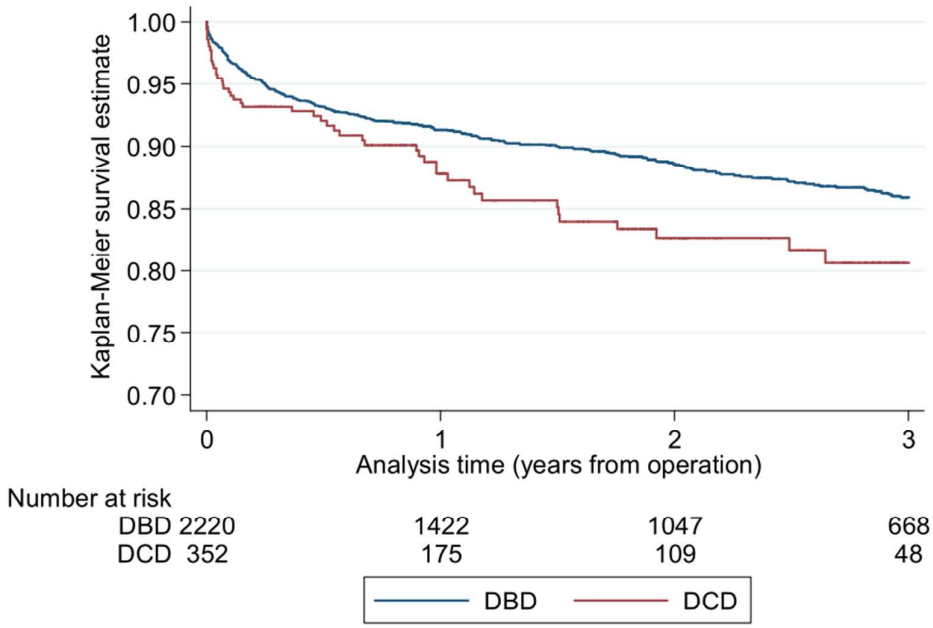
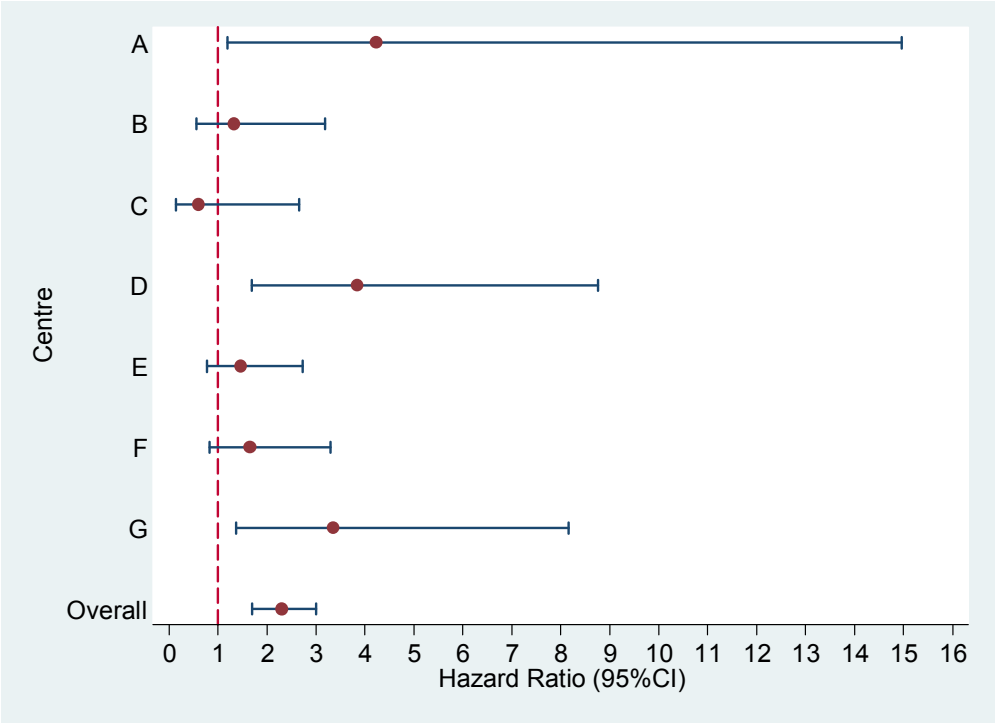


Figure 2 - Centre specific hazard ratios (HR) and 95% CI comparing three-year graft loss (top figure) and recipient mortality (bottom figure). HRs greater than 1 indicate that risks of loss or mortality are greater with DCD than with DBD livers.

Graft failure



Recipient mortality

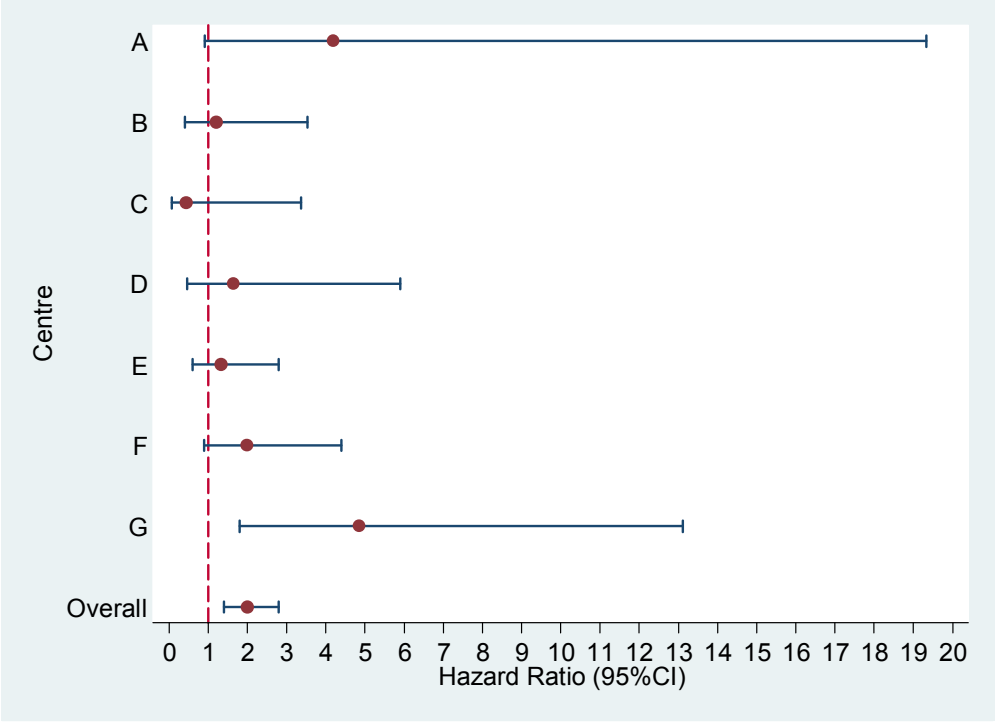


Table 1 - Donor characteristics by donor type.

Liver donor type	DCD (n=352)	DBD (n=2,220)	p-value	Missing (n)
Donor characteristic				
Age, years	42 (16)	46 (15)	<0.01	0
Male sex	206 (59)	1,158 (52)	0.03	0
BMI, kg/m^2	25 (4)	26 (7)	<0.01	20
Serum sodium, mmol/L	144 (140 to 150)	147 (142 to 154)	<0.01	4
Diabetes	14 (5)	111 (5)	0.93	154
Organ appearance				
Healthy	176 (70)	1,384 (76)	0.05	497
Suboptimal	75 (30)	440 (24)		
Cause of death				
Trauma	81 (23)	256 (12)	<0.01	23
Stroke	173 (50)	1,546 (70)		
Anoxia	54 (16)	198 (9)		
Other	37 (11)	204 (9)		

Values are numbers (percentages) for categorical variables and means (standard deviations) or median (interquartile range) otherwise. DBD - donation after brain death; DCD - donation after circulatory death.

Table 2 - Recipient and operative characteristics by donor type.

Liver donor type	DCD (n=352)	DBD (n=2,220)	p-value	Missing (n)
Recipient and operative characteristics				
Age, years	53(9)	52 (11)	0.02	0
Male sex	247 (70)	1,436 (65)	0.04	0
BMI, kg/m^2	27(5)	27 (6)	0.94	12
Serum sodium, mmol/L	137 (134 to 140)	137 (134 to 140)	0.38	7
Serum potassium,mmol/L	4.2 (0.5)	4.2 (0.5)	0.23	52
Serum creatinine , µmol/L	89 (72 to 109)	86(72 to 104)	0.92	4
Serum albumin, g/L	32 (28 to 37)	32 (27 to 36)	0.40	14
Serum bilirubin, mmol/L	41(21 to 79)	47 (24 to 100)	<0.01	8
INR	1.4 (1.2 to 1.6)	1.4 (1.2 to 1.6)	0.90	54
UKELD score	54 (50 to 57)	55 (51 to 59)	<0.01	57
MELD score	15 (11 to 19)	15 (12 to 20)	0.04	57
Primary liver disease				
Cancer	118 (33)	461 (21)	<0.01	0
HCV	47 (13)	265 (12)		
PSC	23 (7)	233 (10)		
HBV	6 (2)	52 (2)		
PBC	34 (10)	238 (11)		
ALD	71 (20)	516 (23)		
AID	22 (6)	193 (9)		
Metabolic	15 (4)	86 (4)		
Other	16 (5)	176 (8)		
Previous abdominal surgery				
No	315 (90)	1,931 (87)	0.15	10
Yes	35 (10)	281 (13)		
Inpatient & ventilatory status				
Outpatient	313 (89)	1,877 (85)	0.10	0
Inpatient, not ventilated	36(10)	322 (14)		
Ventilated	3 (1)	21 (1)		
Days in intensive care	2 (1,4)	2 (1,4)	0.38	15
Pre-operative renal support				
No	333 (95)	2,116 (96)	0.71	7
Yes	18 (5)	98 (4)		

Organ type				
Whole	343 (97)	1,956 (88)	<0.01	1
Partial	9 (3)	263 (12)		
Cold ischaemic time, mins	6.7 (5.6 to 8.0)	9.5 (7.8 to 11.1)	<0.01	93
Anastomosis time, mins	41 (35 to 50)	42 (36 to 51)	0.42	90
Ethnicity mismatch				
No	272 (77)	1,868 (84)	<0.01	10
Yes	79 (22)	343 (15)		

Values are numbers (percentages) for categorical variables and means (standard deviations) or median (interquartile range) otherwise. DBD - donation after brain death; DCD - donation after circulatory death; HCV – hepatitis C virus; PSC – primary sclerosing cholangitis; HBV – hepatitis B virus; PBC – primary biliary cirrhosis; ALD – alcoholic liver disease; AID – autoimmune disease.

Table 3 - Recipient 3-year graft loss and mortality by donor type. Hazard ratios (HR) are unadjusted or adjusted based on either a multivariable Cox regression model or propensity score matching.

Liver donor type		Unadjusted HR (95% CI)	Adjusted HR (95% CI) Multivariable model	Adjusted HR (95% CI) Propensity score analysis
	3-year graft loss % (95% CI)			
Donation after circulatory death	27.3 (21.8 to 33.9)	1.6 (1.2 to 2.0)	2.3 (1.7 to 3.0)	2.3 (1.3 to 4.1)
Donation after brain death	18.2 (16.4 to 20.2)	1	1	1
	3-year mortality % (95% CI)			
Donation after circulatory death	19.4 (14.5 to 25.6)	1.4 (1.1 to 2.0)	2.0 (1.4 to 2.8)	2.0 (1.0 to 4.2)
Donation after brain death	14.1 (12.5.to 16.0)	1	1	1

Outcomes of transplantation of livers from donation after circulatory death donors in the UK

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2, Methods paragraph
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, Results and Conclusion paragraphs
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4, first three paragraphs of Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4, last paragraph of Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5, first paragraph of Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Ibidem
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5, second and third paragraph of Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5 – 7, Statistical analysis section in Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5, first paragraph in Methods
Bias	9	Describe any efforts to address potential sources of bias	Page 5-7 in Methods section describing the multivariable regression analysis and the propensity score matching
Study size	10	Explain how the study size was arrived at	Page 5, first paragraph of Methods
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 5, second paragraph of

			Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 5 – 7, Statistical analysis section in Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Ibidem
		(*c*) Explain how missing data were addressed	Page 7, last paragraph of methods section
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8, first paragraph of Results
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Not used
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8, second and third paragraph of Results
		(b) Indicate number of participants with missing data for each variable of interest	Page 19 and 20, Table 1 and 2
		(c) Summarise follow-up time (eg, average and total amount)	Not done as we have near complete follow-up
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 22, Table 3 and Page 17, Figure 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 22, Table 3
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 9, centre-specific estimates, penultimate paragraph of Results section
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10, first paragraph of Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and	Page 11, second and third

		magnitude of any potential bias	paragraph, Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10, second paragraph and fourth paragraph, Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 10, fourth paragraph
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13, Acknowledgements

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Outcomes of transplantation of livers from donation after circulatory death donors in the UK

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Original article

Outcomes of transplantation of livers from donation after circulatory death donors in the UK

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22 May 2013

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Abstract

Objectives: Outcomes of liver transplantations from donation after circulatory death (DCD) donors may be inferior to those achieved with donation after brain death (DBD) donors. The impact of using DCD donors is likely to depend on specific national practices. We compared risk-adjusted graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK.

Design: Prospective cohort study. Multivariable Cox regression and propensity score matching were used to estimate risk-adjusted hazard ratios (HR).

Setting: Seven liver transplant centres in NHS hospitals in England and Scotland.

Participants: Adults who received a first elective liver transplant between January 2005 and December 2010 who were identified in the UK Liver Transplant Audit.

Interventions: Transplantation of DBD and DBD livers.

Outcomes: Graft loss and recipient mortality.

Results: In total, 2572 liver transplants were identified with 352 (14%) from DCD donors. Three-year graft loss (95% CI) was higher with DCD livers (27.3%; 21.8% to 33.9%) than with DBD livers (18.2%; 16.4% to 20.2%). After adjustment with regression, the HR for graft loss was 2.3 (1.7 to 3.0). Similarly, three-year mortality was higher with DCD livers (19.4%; 14.5% - 25.6%) than with DBD livers (14.1%; 12.5% to 16.0%) with an adjusted HR of 2.0 (1.4 to 2.8). Propensity score matching gave similar results. Centre-specific adjusted HRs for graft loss and recipient mortality seemed to differ among transplant centres, although statistical evidence is weak (p-value for interaction 0.08 and 0.24, respectively).

Conclusions: Graft loss and recipient mortality were about twice as high with DCD livers as with DBD livers in the UK. Outcomes after DCD liver transplantation may vary between centres. These results should inform policies for use of DCD livers.

Article Summary

Article focus

- There is increasing disparity between demand and supply of donor livers for transplantation.
- The use of livers from donation after circulatory death (DCD) donors – in addition to those from donation after brain death (DBD) - increases the donor pool.
- We compared graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK.

Key messages

- Recipients of DCD livers, after risk-adjustment, have approximately twice the risk of graft loss and death within 3 years of transplantation than recipients of livers from DBD donors.
- The impact of using DCD livers on graft loss and recipient mortality seemed to differ among the seven UK transplant centres.

Strengths and limitations of this study

- A national database was used with near complete inclusion of all liver transplantations in the UK with high data quality and follow-up, which eliminates the risk or selective reporting.
- Both multivariable regression analysis and propensity score matching were used to adjust for differences risk factors for graft loss and patient mortality between DBD and DCD donors and recipients.
- We were not able to assess the impact that time from withdrawal of life-sustaining treatment to cardiac arrest has on post-transplant outcomes of DCD livers.

Introduction

The increasing disparity between the demand and supply of donor livers is a major challenge. The need to increase the donor pool, and improve organ utilisation, has led to the re-introduction and rapid expansion of the use of livers from donation after circulatory death (DCD) donors. These donors have been classified as either uncontrolled, where cardiac arrest has occurred unexpectedly (Maastricht categories I and II), or controlled, where potential donors have life-sustaining treatment withdrawn after further interventions are deemed futile (Maastricht III), or circulatory death occurs in a donation after brain death (DBD) donor (Maastricht IV) (1).

Unlike DBD donors, livers from DCD donors undergo a variable period of warm ischaemia, during which irreversible cellular damage may occur. Reliably measuring the warm ischaemic period is difficult outside of hospital, which means that the use of livers from uncontrolled DCD donors is limited (2). In contrast, planned withdrawal of life-sustaining treatment in Maastricht III donors enables close cardiorespiratory monitoring, provision of a prepared procurement team, and minimisation of subsequent warm ischaemia. As such, the use of livers from controlled DCD donors has risen dramatically in the US (3) and Europe (4).

US registry analyses have demonstrated that DCD liver transplantation has worse graft and patient survival than DBD liver transplantation (5-9). This is thought to be predominantly due to a higher rate of biliary complications in DCD livers rather than other causes of graft loss (10). Recognition of these issues has perhaps contributed to a recent drop in the number of DCD livers transplanted in the US (3, 11). However, as a result of encouraging early reports (12) and decreasing DBD liver transplantation rates, the use of DCD livers in the UK is now more widespread than the US.

As there are differences between UK and US practice with respect to how DCD livers are being used (13, 14), we report in this paper graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK. Two risk-adjustment techniques were used to control for differences in donor and recipient risk factors.

Materials and methods

Inclusion criteria

Using data submitted to the UK Liver Transplant Audit (15) we identified all adult patients (age >16 years) receiving a first liver transplant in the seven UK transplant centres in the UK between 1 January 2005 and 31 December 2010. Follow-up ceased on 31 March 2011. Regular checks show that data are consistently both more than 93% complete and accurate (16-18). Patients receiving living or domino donors were excluded, as were those having an emergency ('super-urgent' (19)) or multi-organ transplant. We are not aware of any uncontrolled DCD liver transplants having been performed in the UK during the study period.

Donor and recipient selection and organ procurement

Criteria for DCD donor selection and acceptable post-withdrawal haemodynamic parameters varied among the liver transplant centres, but were broadly based on the experience of Muiesan et al (12), and in line with US guidelines (19). Administration of heparin or vasodilators, or pre-dissection of femoral vessels before death, is prohibited by law in the UK. Death was declared after cardiorespiratory arrest with a minimum interval of five minutes. All UK liver procurement centres used a super-rapid recovery technique (19), although preservation fluid type, bag pressure, and the use of dual perfusion techniques varied.

Livers from DCD and DBD donors were allocated locally, and centres chose recipients according to local criteria (20). Optimal livers from DBD donors were offered to paediatric centres for splitting and implantation of the left lateral segment, with implantation of the extended right lobe into an adult recipient.

Statistical analyses

Pearson's chi-squared test was used to test differences of categorical variables and Student's t-test or Mann Whitney test for differences of continuous variables. Graft and recipient survival after transplantation were estimated using Kaplan-Meier methods. Graft loss was defined as re-transplantation or death, regardless of perceived graft function at the time of death. Cold ischaemic time was defined as the duration from the start of cold perfusion of the liver in the donor to organ removal from ice immediately prior to implantation.

A multivariable Cox regression model was used to adjust the comparisons of graft loss and recipient mortality between DCD and DBD livers for differences in risk factors at the time of transplantation. The donor, recipient and operative characteristics presented in Table 1 and 2 were included in the model (see Table 1 and 2). United Kingdom End-Stage Liver Disease (UKELD) and Model for End-

Stage Liver Disease (MELD) scores were calculated for recipients (21, 22), but these scores were not incorporated in the multivariable model as the component variables of both were already included.

To test whether the impact of using DCD livers on graft loss and patient mortality varied among UK transplant centre, we included an interaction term of donor type and centre in the Cox model. The likelihood ratio test was used to test the statistical significance of the risk factors. The results of the survival analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI).

An analysis with propensity score matching was also conducted. The propensity score is the probability that a recipient would have received a liver from a DCD (as opposed to a DBD) donor, based on observed donor and recipient characteristics. A logistic regression model was used to generate the propensity score (23). Donor type was regressed on main effects only and donor, recipient and operative characteristics were selected using a stepwise process with conservative removal ($p>0.20$) and entry criteria ($p<0.10$). We considered all two-way interactions of the main effects and explored non-linear relationships by including quadratic terms of continuous model factors. All interactions and quadratic terms with a $p < 0.05$ were selected. We estimated the propensity score based on the logistic regression model as the sum of the products of the model factors and their coefficients. Then, for each recipient in the DCD group we selected an individual from the DBD group by matching on the log of the estimated propensity score, using a nearest-neighbour matching algorithm with callipers (an interval) of maximum width of 0.2 standard deviations. We compared the distribution of all model factors in the DCD and DBD groups to assess the success of the propensity score model. The above processes were repeated for each of the ten imputed data sets (see below for a description of methods to deal with missing data). The balance in the covariates across the treatment groups was considered to be achieved if the standardised differences were less than 10%. (24). Cox regression was then performed on each of the ten sets of matched pairs to estimate the effect of donor type on patient and graft survival. A robust standard error was used to allow for the clustering on the pairs. The estimates were then combined using Rubin's rules to provide adjusted hazard ratios and their 95% CI.

In addition to the donor, recipient and operative characteristics presented in Table 1 and 2, we also considered the following characteristics as candidates for inclusion in the propensity score model (all are yes/no unless otherwise stated): lifestyle activity score on 5-point scale, liver failure grade (acute/not acute), encephalopathy grade on 5-point scale, oesophageal varices, diuretic therapy, pyrexia, sepsis, haemoglobin, white cell count, platelet count, serum urea, anti-CMV status, and anti-HCV status. Types of biliary and hepatic arterial anastomoses were also considered as was the use of anti-fibrinolytic therapy.

-

Missing values

All model factors had missing values for less than 5% of patients with the exception of donor history of diabetes (7%), donor organ appearance (19%). Multiple imputation using chained equations was used to fill in missing values for donor diabetes history and donor organ appearance but not the DCD donor post-withdrawal times. The imputation model included the model factors above, type of donor, as well as terms representing the outcome (log of survival time and the censoring indicator) (25). We created 10 imputed data sets and the model parameters based on these datasets were combined using Rubin's rules.

Results

We identified 2572 first elective adult liver transplants. Of these, 352 (14%) had a graft from a DCD donor. Use of livers from DCD donors progressively increased from 6.9% in 2005 to 26.3% in 2010, an almost four-fold rise over that time period. Two centres used DCD donor livers in more than 30% of first elective adult liver transplants in 2010.

Donor, recipient, and operative characteristics

Compared to DBD liver donors, DCD donors were younger, had lower BMIs, lower serum sodium concentrations, and were more likely to be male (Table 1). Although a similar proportion of organs appeared normal in the two groups, DCD donors had a higher proportion of missing values (29%) than DBD donors (18%). The cause of death for DBD donors was predominantly stroke (70%), whereas the corresponding proportion in the DCD group was 49%. Trauma was more common in DCD donors (23%) than in DBD donors (11%). In 352 DCD donors, the median (interquartile range) time from withdrawal of life-support to cardiac arrest was 15 (11 to 20) minutes whereas the median duration from cardiac arrest to cold perfusion was 12 (9 to 14) minutes.

Recipients of a DCD liver were more likely to be older, male, have lower serum bilirubin concentration, and cancer as the primary liver disease (Table 2). Both UKELD and MELD scores were lower in recipients of DCD livers, most probably because a higher proportion of DCD recipients had cancer as their primary disease. DCD livers were more likely to be used as whole rather than partial grafts. Median graft CIT was significantly lower for DCD livers, and there were more ethnicity mismatches in this group.

Graft and patient survival

Graft loss was higher in DCD recipients (Figure 1), with a three-year graft loss (95% CI) of 27.3% (21.8 to 33.9) for DCD recipients and 18.2% (16.4 to 20.2) for DBD recipients with an unadjusted HR of 1.6 (1.2 to 2.0) (Table 3). Recipient mortality was also increased with DCD livers (Figure 1). Three-year mortality was 14.1% (12.5 to 16.0) for DBD recipients and 19.4% (14.5 to 25.6) for DCD recipients with an unadjusted mortality HR of 1.4 (1.1 to 2.0) for use of a DCD donor liver.

After adjustment using the multivariable Cox regression model, we found that the risk of graft loss within three years of transplantation in recipients of a DCD donor liver was more than twice that of those receiving a DBD liver: adjusted HR 2.3 (1.7 to 3.0). Adjusted three-year patient mortality was also significantly higher in recipients of livers from DCD donors: adjusted HR 2.0 (1.4 to 2.8) (Table 3).

After adjustment using the propensity score analysis, use of a liver from a DCD donor was associated with an adjusted HR of 2.3 (1.3 to 4.1) for graft loss. The adjusted HR for recipient mortality was 2.0 (1.0 to 4.2) (Table 3).

Centre-specific estimates of DCD risk

Although the interaction between donor type and centre was not statistically significant for either graft loss (p = 0.08) or recipient mortality (p =0.24), the relative impact of using DCD livers on graft loss and recipient mortality seemed to vary among the seven transplant centres. Centre-specific adjusted HRs for graft loss and recipient mortality varied from being smaller than 1 to larger than 4 (Figure 2).

Causes of graft loss

When causes of graft loss were analysed over three years post-transplantation, the rates of biliary causes of graft loss were higher in livers from DCD donors (4/72 (6%)) than DBD donors (4/330 (1%)) (p = 0.04). Rates of biliary stricture requiring intervention were very similar between the two groups (DCD donors 13/347 (4%) versus DBD donors 81/2193 (4%)) (p = 0.96).

Discussion

Recipients of DCD livers, after risk-adjustment, have approximately twice the risk of graft loss and death within 3 years of transplantation than recipients of livers from DBD donors. This is the first study that has analysed risk-adjusted outcomes in recipients of livers from DCD donors outside of the US. Although US-based studies have reported on larger numbers of DCD liver transplant recipients (6, 7, 9, 13), rates of DCD liver usage in the UK are more than double those of the US (3, 14).

Our results contrast with single-centre reports that demonstrate good short-term results with liver transplantation from DCD donors (12, 26), with graft loss and patient mortality similar to those from DBD donors (27-29). However, it is important to note that we found that the impact of using DCD livers on graft loss and recipient mortality seemed to differ among the seven UK transplant centres, although these differences did not reach statistical significance. This finding indicates that it is important to investigate centre-specific practices that may impact on the outcomes of transplantation of DCD livers, including the selection of DCD grafts, definition of warm ischemic limits, and procurement and implantation techniques.

Risk factors for graft loss and patient mortality are unevenly distributed between DBD and DCD donors and recipients. For example, partial organs were more often used for DBD recipients than for DCD recipients. However, risk adjustment or matching techniques (30) are therefore crucial for a valid comparison of outcomes. Because estimates from multivariable models can be less robust when many factors are included, we also used propensity score matching. Reassuringly, both risk-adjustment techniques gave similar HRs for graft loss and recipient death.

In the UK, DCD liver donors are marginally older and have longer times from withdrawal of life-sustaining treatment to cold perfusion than in the US (6, 7, 9, 13, 14, 31). These differences are likely to reflect a wider acceptance of transplantation of DCD livers in the UK and that treatment withdrawal in the UK takes place in the intensive care unit or the anaesthetic room but not in theatre itself. However, cold ischaemic times are shorter for DCD livers in the UK, even taking into account differences in definitions between the two countries (6, 7, 13, 32). This may be due to geographical differences between the two countries (i.e. longer distances between procuring and implanting centres), or an increased willingness on the part of UK surgeons to begin the recipient operation before the organ arrives at the implanting centre.

Transplanted livers from DCD donors appear particularly susceptible to biliary complications, most commonly ischaemic cholangiopathy, which is thought to occur as a result of warm ischaemic

damage to the biliary epithelium sustained during the procurement process (10, 33-36). We examined rates of graft loss from biliary causes and found that this was a relatively rare cause of graft loss in DCD as well as in DBD recipients. In addition, there was no difference in the proportion of DCD and DBD recipients who required an intervention for biliary strictures. Although these findings concur with previous reports suggesting that ischaemic cholangiopathy is not a major problem in UK recipients of livers from DCD donors (26, 27), it should be recognised that analyses of national registry data are prone to under-reporting of post-operative complications.

Unfortunately, data on time from withdrawal of life-sustaining treatment to cardiac arrest were missing in more than 50% of DCD donors, and therefore the impact of this variable on outcome was not assessed. Prolonged time from cardiac arrest to cold perfusion has been shown to be a risk factor for the development of ischaemic cholangiopathy (35), and would therefore be expected to lead to decreased graft survival. We found no significant association (data not shown). This is again likely to be due to lack of power or to most DCD donors having similar times, with an interquartile range of just 5 hours.

Defining acceptable warm ischaemic limits for livers from DCD donors is hampered by the lack of data on donor cardiorespiratory parameters after treatment withdrawal. Some controlled DCD donors have prolonged periods of cardiorespiratory stability before dying rapidly. It is therefore possible that the duration of hypotension or hypoxia has a greater impact on subsequent graft viability than the duration from treatment withdrawal to cardiac arrest or cold perfusion (8, 37). National prospective data collection of post-withdrawal cardiorespiratory parameters in Maastricht III DCD donors has therefore been initiated in both the UK and the US (8). Further research is also required into the impact of procurement techniques and preservation fluids on graft function (38), and the emerging role of machine perfusion (29).

The allocation of deceased donor livers in the UK is currently on a local basis, with national organ sharing only for those patients with acute liver failure reaching specific criteria (20). Although local allocation reduces cold ischaemic time, which is an important risk factor for graft survival, the current system raises issues of equity of access to a national resource. The ultimate aim of our analyses of national data is to inform discussions on how best to utilise this resource (40). For example, one could use our results as further support for not using livers from DCD donors for patients with a low risk of death on the waiting list as these recipients are able to wait for a graft that is more likely to have a favourable long-term outcome. An exception could be made for patients with HCC. Although, these patients generally have low UKELD scores – indicating a low risk of mortality on the waiting list – they have a high risk of disease progression, which is an additional argument to use livers from DCD donors for this group.

The relative benefit associated with transplantation of a DCD versus a DBD donor liver is expected to be dependent not only on donor and recipient factors, but also on the overall availability of donor livers within each region or country, the rate of deaths on the waiting list, and the impact of DCD transplantation on the subsequent need for re-transplantation (41). Allocation policies also need to determine whether DCD organs are to be distributed on the basis of utility, urgency, or overall survival benefit (42). Although livers transplanted from DCD donors have inferior outcomes to those from DBD donors, they remain a valuable additional source of grafts, especially in countries with relatively low rates of DBD organ donation.

Conflict of interest

None

Contributorship

CJC, AEG, SCC and JvdM designed the study. SCC analysed the data. All authors contributed to the interpretation of the results. CJC wrote the first draft supported by SSC and JvdM;.All authors commented on later drafts. JvdM is guarantor.

Acknowledgements

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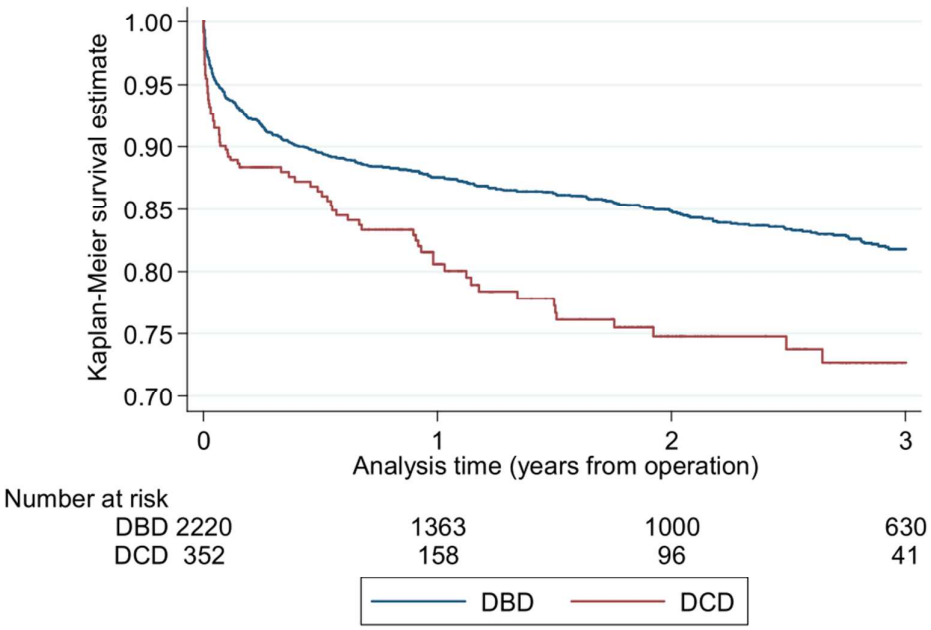
Figure 1 - Graft survival after first elective adult liver transplantation using livers from donation after circulatory death (DCD) donors and donation after brain death (DBD) donors.

Graft failure



Recipient mortality

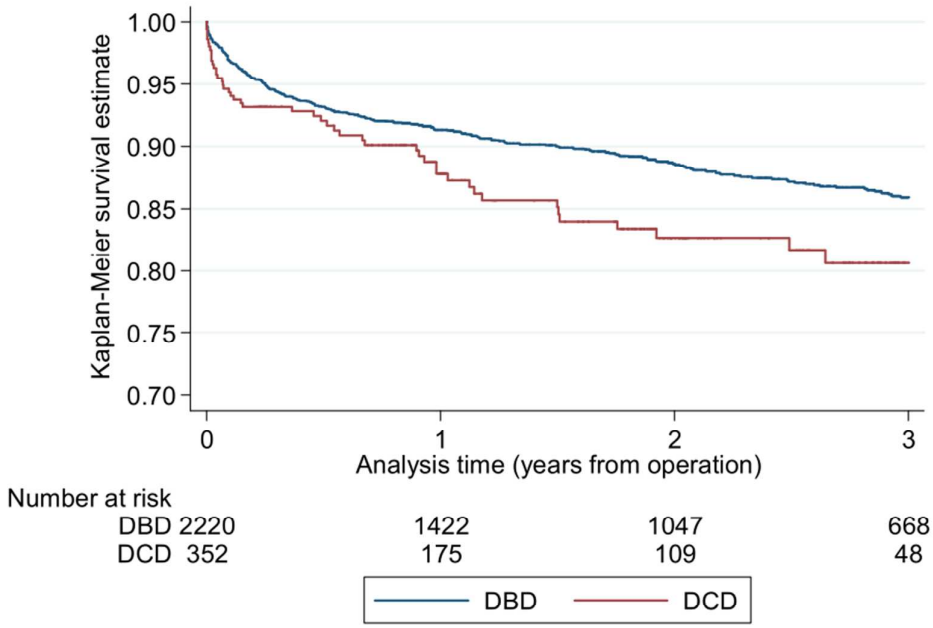
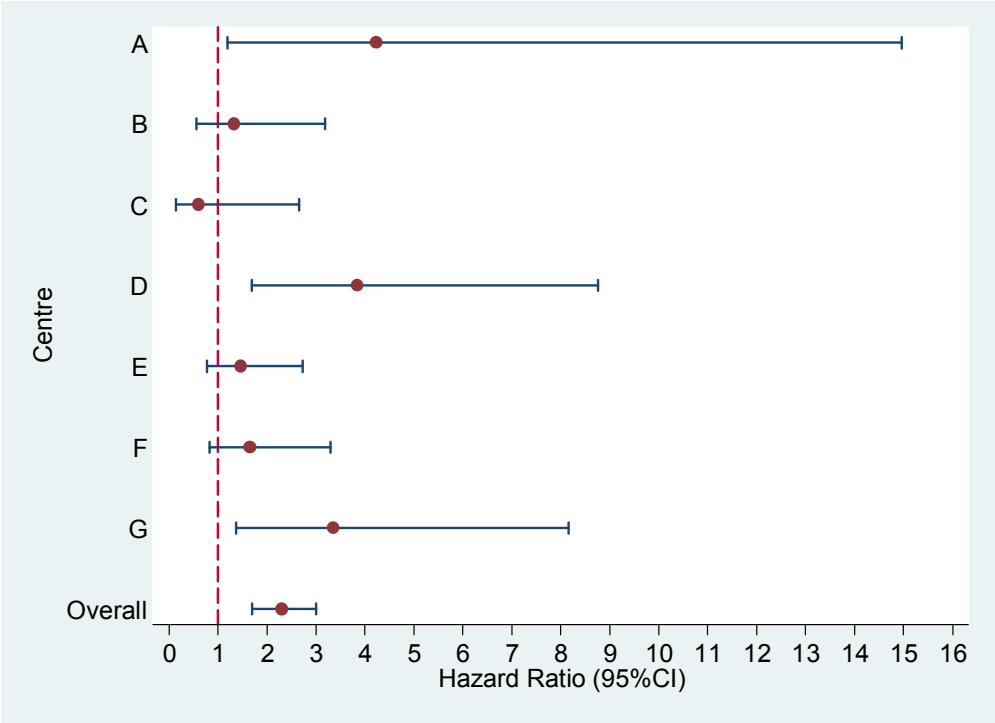


Figure 2 - Centre specific hazard ratios (HR) and 95% CI comparing three-year graft loss (top figure) and recipient mortality (bottom figure). HRs greater than 1 indicate that risks of loss or mortality are greater with DCD than with DBD livers.

Graft failure



Recipient mortality

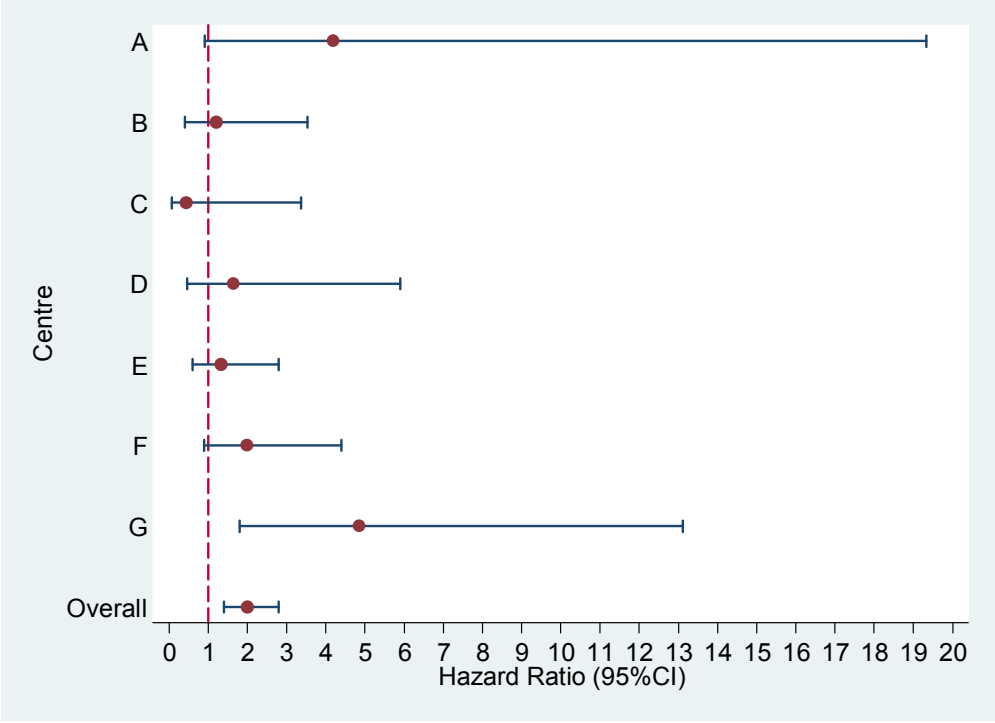


Table 1 - Donor characteristics by donor type.

Liver donor type	DCD (n=352)	DBD (n=2,220)	p-value	Missing (n)
Donor characteristic				
Age, years	42 (16)	46 (15)	<0.01	0
Male sex	206 (59)	1,158 (52)	0.03	0
BMI, kg/m^2	25 (4)	26 (7)	<0.01	20
Serum sodium, mmol/L	144 (140 to 150)	147 (142 to 154)	<0.01	4
Diabetes	14 (5)	111 (5)	0.93	154
Organ appearance				
Healthy	176 (70)	1,384 (76)	0.05	497
Suboptimal	75 (30)	440 (24)		
Cause of death				
Trauma	81 (23)	256 (12)	<0.01	23
Stroke	173 (50)	1,546 (70)		
Anoxia	54 (16)	198 (9)		
Other	37 (11)	204 (9)		

Values are numbers (percentages) for categorical variables and means (standard deviations) or median (interquartile range) otherwise. DBD - donation after brain death; DCD - donation after circulatory death.

Table 2 - Recipient and operative characteristics by donor type.

Liver donor type	DCD (n=352)	DBD (n=2,220)	p-value	Missing (n)
Recipient and operative characteristics				
Age, years	53(9)	52 (11)	0.02	0
Male sex	247 (70)	1,436 (65)	0.04	0
BMI, kg/m^2	27(5)	27 (6)	0.94	12
Serum sodium, mmol/L	137 (134 to 140)	137 (134 to 140)	0.38	7
Serum potassium,mmol/L	4.2 (0.5)	4.2 (0.5)	0.23	52
Serum creatinine , µmol/L	89 (72 to 109)	86(72 to 104)	0.92	4
Serum albumin, g/L	32 (28 to 37)	32 (27 to 36)	0.40	14
Serum bilirubin, mmol/L	41(21 to 79)	47 (24 to 100)	<0.01	8
INR	1.4 (1.2 to 1.6)	1.4 (1.2 to 1.6)	0.90	54
UKELD score	54 (50 to 57)	55 (51 to 59)	<0.01	57
MELD score	15 (11 to 19)	15 (12 to 20)	0.04	57
Primary liver disease				
Cancer	118 (33)	461 (21)	<0.01	0
HCV	47 (13)	265 (12)		
PSC	23 (7)	233 (10)		
HBV	6 (2)	52 (2)		
PBC	34 (10)	238 (11)		
ALD	71 (20)	516 (23)		
AID	22 (6)	193 (9)		
Metabolic	15 (4)	86 (4)		
Other	16 (5)	176 (8)		
Previous abdominal surgery				
No	315 (90)	1,931 (87)	0.15	10
Yes	35 (10)	281 (13)		
Inpatient & ventilatory status				
Outpatient	313 (89)	1,877 (85)	0.10	0
Inpatient, not ventilated	36(10)	322 (14)		
Ventilated	3 (1)	21 (1)		
Days in intensive care	2 (1,4)	2 (1,4)	0.38	15
Pre-operative renal support				
No	333 (95)	2,116 (96)	0.71	7
Yes	18 (5)	98 (4)		

Organ type				
Whole	343 (97)	1,956 (88)	<0.01	1
Partial	9 (3)	263 (12)		
Cold ischaemic time, hours	6.7 (5.6 to 8.0)	9.5 (7.8 to 11.1)	<0.01	93
Anastomosis time, mins	41 (35 to 50)	42 (36 to 51)	0.42	90
Ethnicity mismatch				
No	272 (77)	1,868 (84)	<0.01	10
Yes	79 (22)	343 (15)		

Values are numbers (percentages) for categorical variables and means (standard deviations) or median (interquartile range) otherwise. DBD - donation after brain death; DCD - donation after circulatory death; HCV – hepatitis C virus; PSC – primary sclerosing cholangitis; HBV – hepatitis B virus; PBC – primary biliary cirrhosis; ALD – alcoholic liver disease; AID – autoimmune disease.

Table 3 - Recipient 3-year graft loss and mortality by donor type. Hazard ratios (HR) are unadjusted or adjusted based on either a multivariable Cox regression model or propensity score matching.

Liver donor type		Unadjusted HR (95% CI)	Adjusted HR (95% CI) Multivariable model	Adjusted HR (95% CI) Propensity score analysis
	3-year graft loss % (95% CI)			
Donation after circulatory death	27.3 (21.8 to 33.9)	1.6 (1.2 to 2.0)	2.3 (1.7 to 3.0)	2.3 (1.3 to 4.1)
Donation after brain death	18.2 (16.4 to 20.2)	1	1	1
	3-year mortality % (95% CI)			
Donation after circulatory death	19.4 (14.5 to 25.6)	1.4 (1.1 to 2.0)	2.0 (1.4 to 2.8)	2.0 (1.0 to 4.2)
Donation after brain death	14.1 (12.5.to 16.0)	1	1	1

Outcomes of transplantation of livers from donation after circulatory death donors in the UK

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 2, Methods paragraph
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2, Results and Conclusion paragraphs
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 4, first three paragraphs of Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 4, last paragraph of Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Page 5, first paragraph of Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Ibidem
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 5, second and third paragraph of Methods
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5 – 7, Statistical analysis section in Methods
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 5, first paragraph in Methods
Bias	9	Describe any efforts to address potential sources of bias	Page 5-7 in Methods section describing the multivariable regression analysis and the propensity score matching
Study size	10	Explain how the study size was arrived at	Page 5, first paragraph of Methods
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Page 5, second paragraph of

			Methods
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 5 – 7, Statistical analysis section in Methods
		(*b*) Describe any methods used to examine subgroups and interactions	Ibidem
		(*c*) Explain how missing data were addressed	Page 7, last paragraph of methods section
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Page 8, first paragraph of Results
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	Not used
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Page 8, second and third paragraph of Results
		(b) Indicate number of participants with missing data for each variable of interest	Page 19 and 20, Table 1 and 2
		(c) Summarise follow-up time (eg, average and total amount)	Not done as we have near complete follow-up
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 22, Table 3 and Page 17, Figure 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 22, Table 3
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Page 9, centre-specific estimates, penultimate paragraph of Results section
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 10, first paragraph of Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and	Page 11, second and third

		magnitude of any potential bias	paragraph, Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 10, second paragraph and fourth paragraph, Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 10, fourth paragraph
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 13, Acknowledgements

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Original article

Outcomes of transplantation of livers from donation after circulatory death donors in the UK

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22 May 2013

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Figures: 2

Abstract

Objectives: Outcomes of liver transplantations from donation after circulatory death (DCD) donors may be inferior to those achieved with donation after brain death (DBD) donors. The impact of using DCD donors is likely to depend on specific national practices. We compared risk-adjusted graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK.

Design: Prospective cohort study. Multivariable Cox regression and propensity score matching were used to estimate risk-adjusted hazard ratios (HR).

Setting: Seven liver transplant centres in NHS hospitals in England and Scotland.

Participants: Adults who received a first elective liver transplant between January 2005 and December 2010 who were identified in the UK Liver Transplant Audit.

Interventions: Transplantation of DBD and DBD livers.

Outcomes: Graft loss and recipient mortality.

Results: In total, 2572 liver transplants were identified with 352 (14%) from DCD donors. Three-year graft loss (95% CI) was higher with DCD livers (27.3%; 21.8% to 33.9%) than with DBD livers (18.2%; 16.4% to 20.2%). After adjustment with regression, the HR for graft loss was 2.3 (1.7 to 3.0). Similarly, three-year mortality was higher with DCD livers (19.4%; 14.5% - 25.6%) than with DBD livers (14.1%; 12.5% to 16.0%) with an adjusted HR of 2.0 (1.4 to 2.8). Propensity score matching gave similar results. Centre-specific adjusted HRs for graft loss and recipient mortality seemed to differ among transplant centres, although statistical evidence is weak (p-value for interaction 0.08 and 0.24, respectively).

Conclusions: Graft loss and recipient mortality were about twice as high with DCD livers as with DBD livers in the UK. Outcomes after DCD liver transplantation may vary between centres. These results should inform policies for use of DCD livers.

Article Summary

Article focus

- There is increasing disparity between demand and supply of donor livers for transplantation.
- The use of livers from donation after circulatory death (DCD) donors – in addition to those from donation after brain death (DBD) - increases the donor pool.
- We compared graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK.

Key messages

- Recipients of DCD livers, after risk-adjustment, have approximately twice the risk of graft loss and death within 3 years of transplantation than recipients of livers from DBD donors.
- The impact of using DCD livers on graft loss and recipient mortality seemed to differ among the seven UK transplant centres.

Strengths and limitations of this study

- A national database was used with near complete inclusion of all liver transplantations in the UK with high data quality and follow-up, which eliminates the risk or selective reporting.
- Both multivariable regression analysis and propensity score matching were used to adjust for differences risk factors for graft loss and patient mortality between DBD and DCD donors and recipients.
- We were not able to assess the impact that time from withdrawal of life-sustaining treatment to cardiac arrest has on post-transplant outcomes of DCD livers.

Introduction

The increasing disparity between the demand and supply of donor livers is a major challenge. The need to increase the donor pool, and improve organ utilisation, has led to the re-introduction and rapid expansion of the use of livers from donation after circulatory death (DCD) donors. These donors have been classified as either uncontrolled, where cardiac arrest has occurred unexpectedly (Maastricht categories I and II), or controlled, where potential donors have life-sustaining treatment withdrawn after further interventions are deemed futile (Maastricht III), or circulatory death occurs in a donation after brain death (DBD) donor (Maastricht IV) (1).

Unlike DBD donors, livers from DCD donors undergo a variable period of warm ischaemia, during which irreversible cellular damage may occur. Reliably measuring the warm ischaemic period is difficult outside of hospital, which means that the use of livers from uncontrolled DCD donors is limited (2). In contrast, planned withdrawal of life-sustaining treatment in Maastricht III donors enables close cardiorespiratory monitoring, provision of a prepared procurement team, and minimisation of subsequent warm ischaemia. As such, the use of livers from controlled DCD donors has risen dramatically in the US (3) and Europe (4).

US registry analyses have demonstrated that DCD liver transplantation has worse graft and patient survival than DBD liver transplantation (5-9). This is thought to be predominantly due to a higher rate of biliary complications in DCD livers rather than other causes of graft loss (10). Recognition of these issues has perhaps contributed to a recent drop in the number of DCD livers transplanted in the US (3, 11). However, as a result of encouraging early reports (12) and decreasing DBD liver transplantation rates, the use of DCD livers in the UK is now more widespread than the US.

As there are differences between UK and US practice with respect to how DCD livers are being used (13, 14), we report in this paper graft loss and recipient mortality after transplantation of DCD and DBD livers in the UK. Two risk-adjustment techniques were used to control for differences in donor and recipient risk factors.

Materials and methods

Inclusion criteria

Using data submitted to the UK Liver Transplant Audit (15) we identified all adult patients (age >16 years) receiving a first liver transplant in the seven UK transplant centres in the UK between 1 January 2005 and 31 December 2010. Follow-up ceased on 31 March 2011. Regular checks show that data are consistently both more than 93% complete and accurate (16-18). Patients receiving living or domino donors were excluded, as were those having an emergency ('super-urgent' (19)) or multi-organ transplant. We are not aware of any uncontrolled DCD liver transplants having been performed in the UK during the study period.

Donor and recipient selection and organ procurement

Criteria for DCD donor selection and acceptable post-withdrawal haemodynamic parameters varied among the liver transplant centres, but were broadly based on the experience of Muiesan et al (12), and in line with US guidelines (19). Administration of heparin or vasodilators, or pre-dissection of femoral vessels before death, is prohibited by law in the UK. Death was declared after cardiorespiratory arrest with a minimum interval of five minutes. All UK liver procurement centres used a super-rapid recovery technique (19), although preservation fluid type, bag pressure, and the use of dual perfusion techniques varied.

Livers from DCD and DBD donors were allocated locally, and centres chose recipients according to local criteria (20). Optimal livers from DBD donors were offered to paediatric centres for splitting and implantation of the left lateral segment, with implantation of the extended right lobe into an adult recipient.

Statistical analyses

Pearson's chi-squared test was used to test differences of categorical variables and Student's t-test or Mann Whitney test for differences of continuous variables. Graft and recipient survival after transplantation were estimated using Kaplan-Meier methods. Graft loss was defined as re-transplantation or death, regardless of perceived graft function at the time of death. Cold ischaemic time was defined as the duration from the start of cold perfusion of the liver in the donor to organ removal from ice immediately prior to implantation.

A multivariable Cox regression model was used to adjust the comparisons of graft loss and recipient mortality between DCD and DBD livers for differences in risk factors at the time of transplantation. The donor, recipient and operative characteristics presented in Table 1 and 2 were included in the model (see Table 1 and 2). United Kingdom End-Stage Liver Disease (UKELD) and Model for End-

Stage Liver Disease (MELD) scores were calculated for recipients (21, 22), but these scores were not incorporated in the multivariable model as the component variables of both were already included.

To test whether the impact of using DCD livers on graft loss and patient mortality varied among UK transplant centre, we included an interaction term of donor type and centre in the Cox model. The likelihood ratio test was used to test the statistical significance of the risk factors. The results of the survival analyses are presented as hazard ratios (HR) with 95% confidence intervals (CI).

An analysis with propensity score matching was also conducted. The propensity score is the probability that a recipient would have received a liver from a DCD (as opposed to a DBD) donor, based on observed donor and recipient characteristics. A logistic regression model was used to generate the propensity score (23). Donor type was regressed on main effects only and donor, recipient and operative characteristics were selected using a stepwise process with conservative removal ($p>0.20$) and entry criteria ($p<0.10$). We considered all two-way interactions of the main effects and explored non-linear relationships by including quadratic terms of continuous model factors. All interactions and quadratic terms with a $p < 0.05$ were selected. We estimated the propensity score based on the logistic regression model as the sum of the products of the model factors and their coefficients. Then, for each recipient in the DCD group we selected an individual from the DBD group by matching on the log of the estimated propensity score, using a nearest-neighbour matching algorithm with callipers (an interval) of maximum width of 0.2 standard deviations. We compared the distribution of all model factors in the DCD and DBD groups to assess the success of the propensity score model. The above processes were repeated for each of the ten imputed data sets (see below for a description of methods to deal with missing data). The balance in the covariates across the treatment groups was considered to be achieved if the standardised differences were less than 10%. (24). Cox regression was then performed on each of the ten sets of matched pairs to estimate the effect of donor type on patient and graft survival. A robust standard error was used to allow for the clustering on the pairs. The estimates were then combined using Rubin's rules to provide adjusted hazard ratios and their 95% CI.

In addition to the donor, recipient and operative characteristics presented in Table 1 and 2, we also considered the following characteristics as candidates for inclusion in the propensity score model (all are yes/no unless otherwise stated): lifestyle activity score on 5-point scale, liver failure grade (acute/not acute), encephalopathy grade on 5-point scale, oesophageal varices, diuretic therapy, pyrexia, sepsis, haemoglobin, white cell count, platelet count, serum urea, anti-CMV status, and anti-HCV status. Types of biliary and hepatic arterial anastomoses were also considered as was the use of anti-fibrinolytic therapy.

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Missing values

All model factors had missing values for less than 5% of patients with the exception of donor history of diabetes (7%), donor organ appearance (19%). Multiple imputation using chained equations was used to fill in missing values for donor diabetes history and donor organ appearance but not the DCD donor post-withdrawal times. The imputation model included the model factors above, type of donor, as well as terms representing the outcome (log of survival time and the censoring indicator) (25). We created 10 imputed data sets and the model parameters based on these datasets were combined using Rubin's rules.

Results

We identified 2572 first elective adult liver transplants. Of these, 352 (14%) had a graft from a DCD donor. Use of livers from DCD donors progressively increased from 6.9% in 2005 to 26.3% in 2010, an almost four-fold rise over that time period. Two centres used DCD donor livers in more than 30% of first elective adult liver transplants in 2010.

Donor, recipient, and operative characteristics

Compared to DBD liver donors, DCD donors were younger, had lower BMIs, lower serum sodium concentrations, and were more likely to be male (Table 1). Although a similar proportion of organs appeared normal in the two groups, DCD donors had a higher proportion of missing values (29%) than DBD donors (18%). The cause of death for DBD donors was predominantly stroke (70%), whereas the corresponding proportion in the DCD group was 49%. Trauma was more common in DCD donors (23%) than in DBD donors (11%). In 352 DCD donors, the median (interquartile range) time from withdrawal of life-support to cardiac arrest was 15 (11 to 20) minutes whereas the median duration from cardiac arrest to cold perfusion was 12 (9 to 14) minutes.

Recipients of a DCD liver were more likely to be older, male, have lower serum bilirubin concentration, and cancer as the primary liver disease (Table 2). Both UKELD and MELD scores were lower in recipients of DCD livers, most probably because a higher proportion of DCD recipients had cancer as their primary disease. DCD livers were more likely to be used as whole rather than partial grafts. Median graft CIT was significantly lower for DCD livers, and there were more ethnicity mismatches in this group.

Graft and patient survival

Graft loss was higher in DCD recipients (Figure 1), with a three-year graft loss (95% CI) of 27.3% (21.8 to 33.9) for DCD recipients and 18.2% (16.4 to 20.2) for DBD recipients with an unadjusted HR of 1.6 (1.2 to 2.0) (Table 3). Recipient mortality was also increased with DCD livers (Figure 1). Three-year mortality was 14.1% (12.5 to 16.0) for DBD recipients and 19.4% (14.5 to 25.6) for DCD recipients with an unadjusted mortality HR of 1.4 (1.1 to 2.0) for use of a DCD donor liver.

After adjustment using the multivariable Cox regression model, we found that the risk of graft loss within three years of transplantation in recipients of a DCD donor liver was more than twice that of those receiving a DBD liver: adjusted HR 2.3 (1.7 to 3.0). Adjusted three-year patient mortality was also significantly higher in recipients of livers from DCD donors: adjusted HR 2.0 (1.4 to 2.8) (Table 3).

After adjustment using the propensity score analysis, use of a liver from a DCD donor was associated with an adjusted HR of 2.3 (1.3 to 4.1) for graft loss. The adjusted HR for recipient mortality was 2.0 (1.0 to 4.2) (Table 3).

Centre-specific estimates of DCD risk

Although the interaction between donor type and centre was not statistically significant for either graft loss (p = 0.08) or recipient mortality (p =0.24), the relative impact of using DCD livers on graft loss and recipient mortality seemed to vary among the seven transplant centres. Centre-specific adjusted HRs for graft loss and recipient mortality varied from being smaller than 1 to larger than 4 (Figure 2).

Causes of graft loss

When causes of graft loss were analysed over three years post-transplantation, the rates of biliary causes of graft loss were higher in livers from DCD donors (4/72 (6%)) than DBD donors (4/330 (1%)) (p = 0.04). Rates of biliary stricture requiring intervention were very similar between the two groups (DCD donors 13/347 (4%) versus DBD donors 81/2193 (4%)) (p = 0.96).

Discussion

Recipients of DCD livers, after risk-adjustment, have approximately twice the risk of graft loss and death within 3 years of transplantation than recipients of livers from DBD donors. This is the first study that has analysed risk-adjusted outcomes in recipients of livers from DCD donors outside of the US. Although US-based studies have reported on larger numbers of DCD liver transplant recipients (6, 7, 9, 13), rates of DCD liver usage in the UK are more than double those of the US (3, 14).

Our results contrast with single-centre reports that demonstrate good short-term results with liver transplantation from DCD donors (12, 26), with graft loss and patient mortality similar to those from DBD donors (27-29). However, it is important to note that we found that the impact of using DCD livers on graft loss and recipient mortality seemed to differ among the seven UK transplant centres, although these differences did not reach statistical significance. This finding indicates that it is important to investigate centre-specific practices that may impact on the outcomes of transplantation of DCD livers, including the selection of DCD grafts, definition of warm ischemic limits, and procurement and implantation techniques.

Risk factors for graft loss and patient mortality are unevenly distributed between DBD and DCD donors and recipients. For example, partial organs were more often used for DBD recipients than for DCD recipients. However, risk adjustment or matching techniques (30) are therefore crucial for a valid comparison of outcomes. Because estimates from multivariable models can be less robust when many factors are included, we also used propensity score matching. Reassuringly, both risk-adjustment techniques gave similar HRs for graft loss and recipient death.

In the UK, DCD liver donors are marginally older and have longer times from withdrawal of life-sustaining treatment to cold perfusion than in the US (6, 7, 9, 13, 14, 31). These differences are likely to reflect a wider acceptance of transplantation of DCD livers in the UK and that treatment withdrawal in the UK takes place in the intensive care unit or the anaesthetic room but not in theatre itself. However, cold ischaemic times are shorter for DCD livers in the UK, even taking into account differences in definitions between the two countries (6, 7, 13, 32). This may be due to geographical differences between the two countries (i.e. longer distances between procuring and implanting centres), or an increased willingness on the part of UK surgeons to begin the recipient operation before the organ arrives at the implanting centre.

Transplanted livers from DCD donors appear particularly susceptible to biliary complications, most commonly ischaemic cholangiopathy, which is thought to occur as a result of warm ischaemic

damage to the biliary epithelium sustained during the procurement process (10, 33-36). We examined rates of graft loss from biliary causes and found that this was a relatively rare cause of graft loss in DCD as well as in DBD recipients. In addition, there was no difference in the proportion of DCD and DBD recipients who required an intervention for biliary strictures. Although these findings concur with previous reports suggesting that ischaemic cholangiopathy is not a major problem in UK recipients of livers from DCD donors (26, 27), it should be recognised that analyses of national registry data are prone to under-reporting of post-operative complications.

Unfortunately, data on time from withdrawal of life-sustaining treatment to cardiac arrest were missing in more than 50% of DCD donors, and therefore the impact of this variable on outcome was not assessed. Prolonged time from cardiac arrest to cold perfusion has been shown to be a risk factor for the development of ischaemic cholangiopathy (35), and would therefore be expected to lead to decreased graft survival. We found no significant association (data not shown). This is again likely to be due to lack of power or to most DCD donors having similar times, with an interquartile range of just 5 hours.

Defining acceptable warm ischaemic limits for livers from DCD donors is hampered by the lack of data on donor cardiorespiratory parameters after treatment withdrawal. Some controlled DCD donors have prolonged periods of cardiorespiratory stability before dying rapidly. It is therefore possible that the duration of hypotension or hypoxia has a greater impact on subsequent graft viability than the duration from treatment withdrawal to cardiac arrest or cold perfusion (8, 37). National prospective data collection of post-withdrawal cardiorespiratory parameters in Maastricht III DCD donors has therefore been initiated in both the UK and the US (8). Further research is also required into the impact of procurement techniques and preservation fluids on graft function (38), and the emerging role of machine perfusion (29).

The allocation of deceased donor livers in the UK is currently on a local basis, with national organ sharing only for those patients with acute liver failure reaching specific criteria (20). Although local allocation reduces cold ischaemic time, which is an important risk factor for graft survival, the current system raises issues of equity of access to a national resource. The ultimate aim of our analyses of national data is to inform discussions on how best to utilise this resource (40). For example, one could use our results as further support for not using livers from DCD donors for patients with a low risk of death on the waiting list as these recipients are able to wait for a graft that is more likely to have a favourable long-term outcome. An exception could be made for patients with HCC. Although, these patients generally have low UKELD scores – indicating a low risk of mortality on the waiting list – they have a high risk of disease progression, which is an additional argument to use livers from DCD donors for this group.

The relative benefit associated with transplantation of a DCD versus a DBD donor liver is expected to be dependent not only on donor and recipient factors, but also on the overall availability of donor livers within each region or country, the rate of deaths on the waiting list, and the impact of DCD transplantation on the subsequent need for re-transplantation (41). Allocation policies also need to determine whether DCD organs are to be distributed on the basis of utility, urgency, or overall survival benefit (42). Although livers transplanted from DCD donors have inferior outcomes to those from DBD donors, they remain a valuable additional source of grafts, especially in countries with relatively low rates of DBD organ donation.

Conflict of interest

None

Contributorship

CJC, AEG, SCC and JvdM designed the study. SCC analysed the data. All authors contributed to the interpretation of the results. CJC wrote the first draft supported by SSC and JvdM;.All authors commented on later drafts. JvdM is guarantor.

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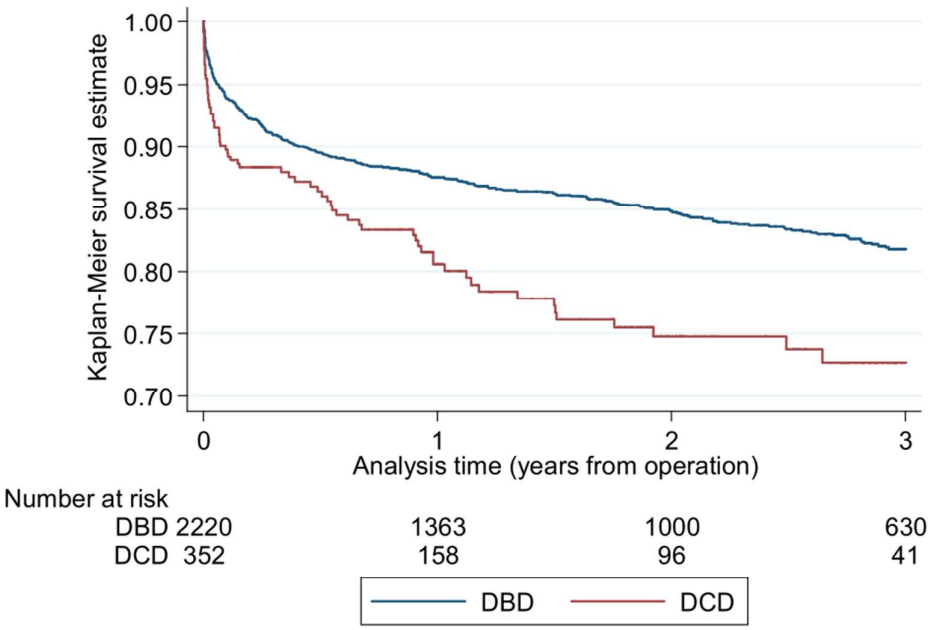
Figure 1 - Graft survival after first elective adult liver transplantation using livers from donation after circulatory death (DCD) donors and donation after brain death (DBD) donors.

Graft failure



Recipient mortality

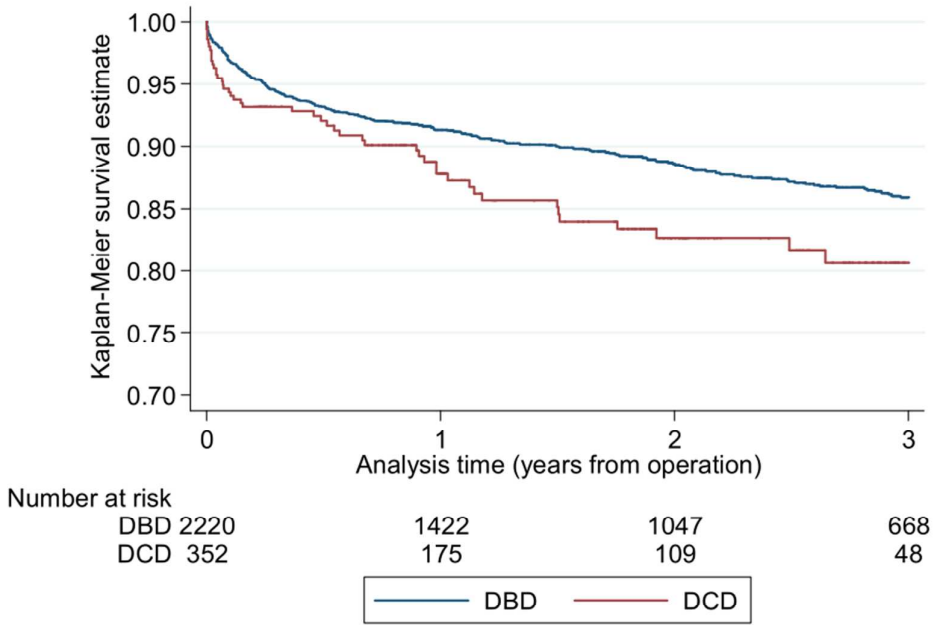
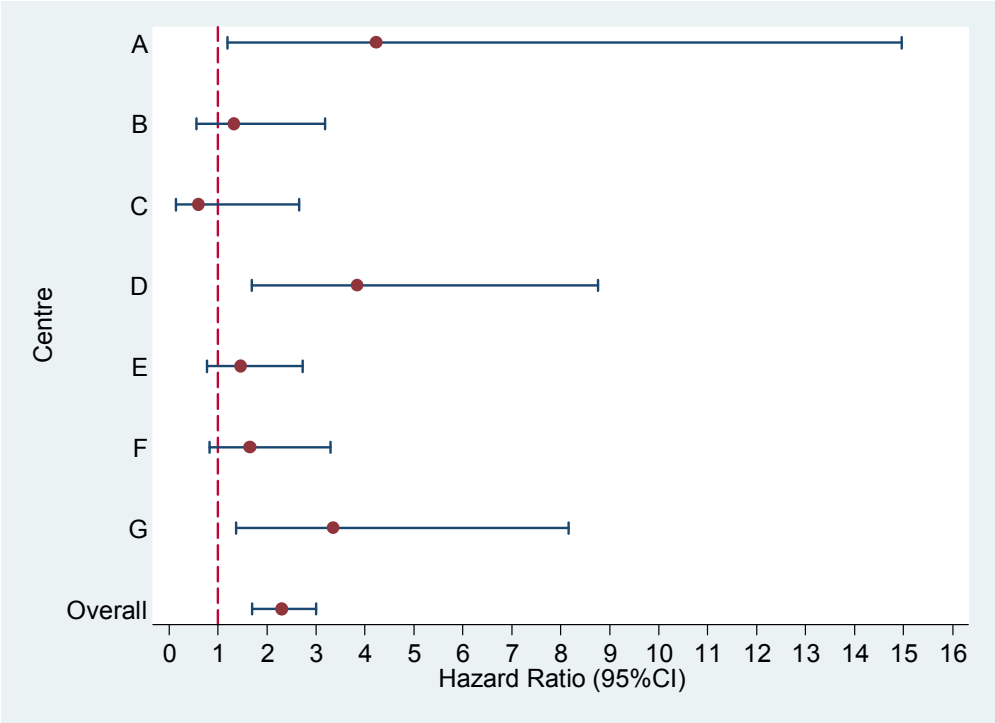


Figure 2 - Centre specific hazard ratios (HR) and 95% CI comparing three-year graft loss (top figure) and recipient mortality (bottom figure). HRs greater than 1 indicate that risks of loss or mortality are greater with DCD than with DBD livers.

Graft failure



Recipient mortality

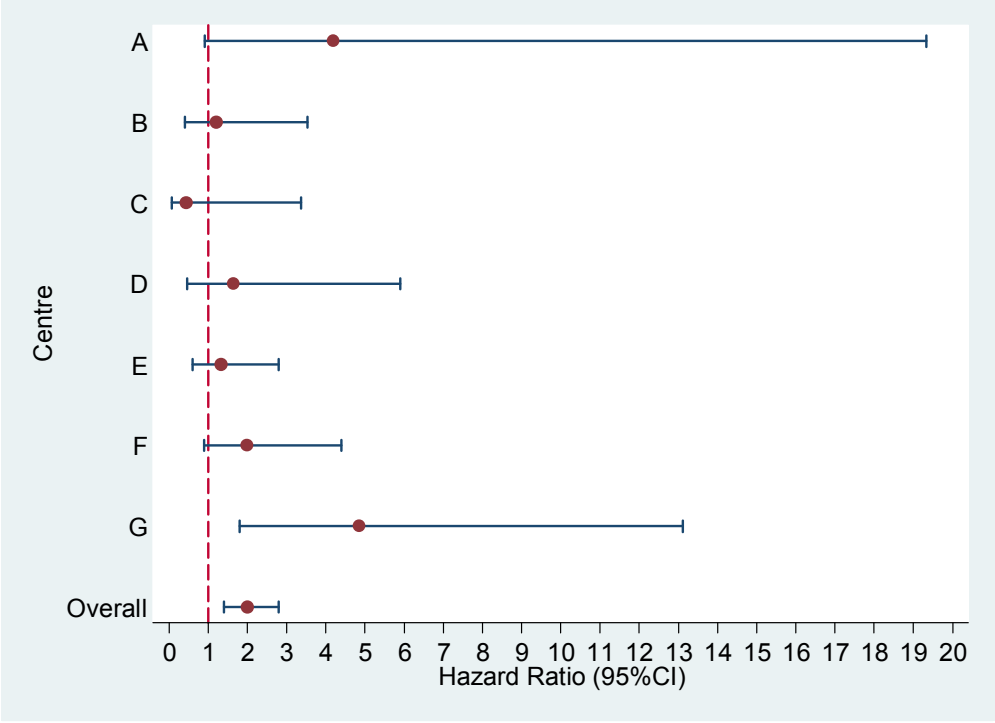


Table 1 - Donor characteristics by donor type.

Liver donor type	DCD (n=352)	DBD (n=2,220)	p-value	Missing (n)
Donor characteristic				
Age, years	42 (16)	46 (15)	<0.01	0
Male sex	206 (59)	1,158 (52)	0.03	0
BMI, kg/m^2	25 (4)	26 (7)	<0.01	20
Serum sodium, mmol/L	144 (140 to 150)	147 (142 to 154)	<0.01	4
Diabetes	14 (5)	111 (5)	0.93	154
Organ appearance				
Healthy	176 (70)	1,384 (76)	0.05	497
Suboptimal	75 (30)	440 (24)		
Cause of death				
Trauma	81 (23)	256 (12)	<0.01	23
Stroke	173 (50)	1,546 (70)		
Anoxia	54 (16)	198 (9)		
Other	37 (11)	204 (9)		

Values are numbers (percentages) for categorical variables and means (standard deviations) or median (interquartile range) otherwise. DBD - donation after brain death; DCD - donation after circulatory death.

Table 2 - Recipient and operative characteristics by donor type.

Liver donor type	DCD (n=352)	DBD (n=2,220)	p-value	Missing (n)
Recipient and operative characteristics				
Age, years	53(9)	52 (11)	0.02	0
Male sex	247 (70)	1,436 (65)	0.04	0
BMI, kg/m^2	27(5)	27 (6)	0.94	12
Serum sodium, mmol/L	137 (134 to 140)	137 (134 to 140)	0.38	7
Serum potassium,mmol/L	4.2 (0.5)	4.2 (0.5)	0.23	52
Serum creatinine , µmol/L	89 (72 to 109)	86(72 to 104)	0.92	4
Serum albumin, g/L	32 (28 to 37)	32 (27 to 36)	0.40	14
Serum bilirubin, mmol/L	41(21 to 79)	47 (24 to 100)	<0.01	8
INR	1.4 (1.2 to 1.6)	1.4 (1.2 to 1.6)	0.90	54
UKELD score	54 (50 to 57)	55 (51 to 59)	<0.01	57
MELD score	15 (11 to 19)	15 (12 to 20)	0.04	57
Primary liver disease				
Cancer	118 (33)	461 (21)	<0.01	0
HCV	47 (13)	265 (12)		
PSC	23 (7)	233 (10)		
HBV	6 (2)	52 (2)		
PBC	34 (10)	238 (11)		
ALD	71 (20)	516 (23)		
AID	22 (6)	193 (9)		
Metabolic	15 (4)	86 (4)		
Other	16 (5)	176 (8)		
Previous abdominal surgery				
No	315 (90)	1,931 (87)	0.15	10
Yes	35 (10)	281 (13)		
Inpatient & ventilatory status				
Outpatient	313 (89)	1,877 (85)	0.10	0
Inpatient, not ventilated	36(10)	322 (14)		
Ventilated	3 (1)	21 (1)		
Days in intensive care	2 (1,4)	2 (1,4)	0.38	15
Pre-operative renal support				
No	333 (95)	2,116 (96)	0.71	7
Yes	18 (5)	98 (4)		

Organ type				
Whole	343 (97)	1,956 (88)	<0.01	1
Partial	9 (3)	263 (12)		
Cold ischaemic time, hours	6.7 (5.6 to 8.0)	9.5 (7.8 to 11.1)	<0.01	93
Anastomosis time, mins	41 (35 to 50)	42 (36 to 51)	0.42	90
Ethnicity mismatch				
No	272 (77)	1,868 (84)	<0.01	10
Yes	79 (22)	343 (15)		

Values are numbers (percentages) for categorical variables and means (standard deviations) or median (interquartile range) otherwise. DBD - donation after brain death; DCD - donation after circulatory death; HCV – hepatitis C virus; PSC – primary sclerosing cholangitis; HBV – hepatitis B virus; PBC – primary biliary cirrhosis; ALD – alcoholic liver disease; AID – autoimmune disease.

Table 3 - Recipient 3-year graft loss and mortality by donor type. Hazard ratios (HR) are unadjusted or adjusted based on either a multivariable Cox regression model or propensity score matching.

Liver donor type		Unadjusted HR (95% CI)	Adjusted HR (95% CI) Multivariable model	Adjusted HR (95% CI) Propensity score analysis
	3-year graft loss % (95% CI)			
Donation after circulatory death	27.3 (21.8 to 33.9)	1.6 (1.2 to 2.0)	2.3 (1.7 to 3.0)	2.3 (1.3 to 4.1)
Donation after brain death	18.2 (16.4 to 20.2)	1	1	1
	3-year mortality % (95% CI)			
Donation after circulatory death	19.4 (14.5 to 25.6)	1.4 (1.1 to 2.0)	2.0 (1.4 to 2.8)	2.0 (1.0 to 4.2)
Donation after brain death	14.1 (12.5.to 16.0)	1	1	1