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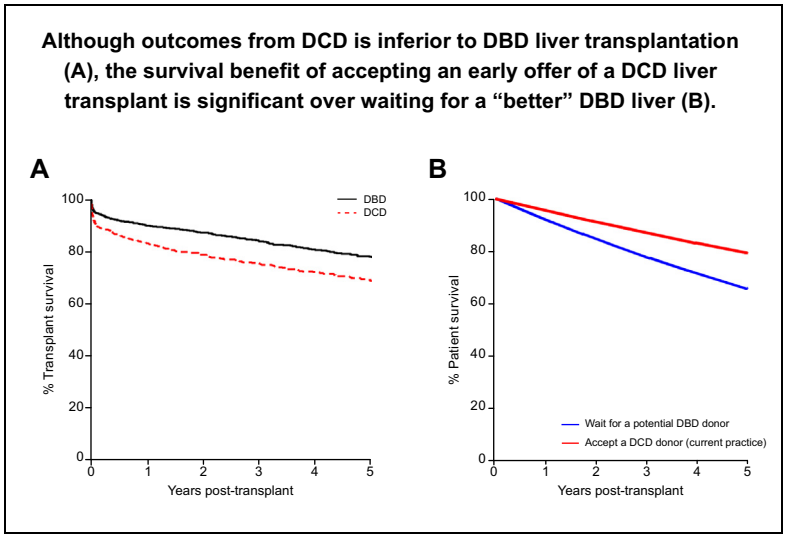
Survival advantage for patients accepting the offer of a circulatory death liver transplant

Graphical abstract



Highlights

- Outcomes for DCD are inferior to DBD liver transplantation in the UK experience.
- There is a survival advantage in accepting a DCD offer rather than waiting for a "better DBD liver.
- This survival advantage is most pronounced in patients with more advanced disease.
- This study provides strong support for the use of DCD livers in all patients.
- This should facilitate discussions with individuals about accepting or declining a DCD liver offer.

Authors

Rhiannon Taylor, Elisa Allen, James A. Richards, ..., James Neuberger, David Collett, Gavin J. Pettigrew

Correspondence

gjp25@cam.ac.uk
(G.J. Pettigrew)

Lay summary

This study looks at patients who require a liver transplant to save their lives; this liver can be donated by a person who has died either after their heart has stopped (donation after cardiac death [DCD]) or after the brain has been injured and can no longer support life (donation after brainstem death [DBD]). We know that livers donated after brainstem death function better than those after cardiac death, but there are not enough of these livers for everyone, so we wished to help patients decide whether it was better for them to accept an early offer of a DCD liver than waiting longer to receive a "better liver from a DBD donor. We found that patients were more likely to survive if they accepted the offer of a liver transplant as soon as possible (DCD or DBD), especially if their liver disease was very severe.

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Survival advantage for patients accepting the offer of a circulatory death liver transplant

Rhiannon Taylor[1], Elisa Allen[1], James A. Richards[2], Mingzheng A. Goh[2], James Neuberger[3], David Collett[1], Gavin J. Pettigrew[2,*], on behalf of members of the Liver Advisory Group to NHS Blood and Transplant

[1]*Statistics and Clinical Studies, NHS Blood and Transplant, Fox Den Road, Stoke Gifford, Bristol BS34 8RR, United Kingdom;* [2]*University Department of Surgery, Addenbrooke's Hospital, Hill Road, Cambridge CB2 0QQ, United Kingdom;* [3]*University Hospital Birmingham NHS Foundation Trust, Mindelsohn Way, Birmingham B15 2TH, United Kingdom*

Background & aims: Donation after circulatory death (DCD) in the UK has tripled in the last decade. However, outcomes following DCD liver transplantation are worse than for donation after brainstem death (DBD) liver transplants. This study examines whether a recipient should accept a "poorer quality" DCD organ or wait longer for a "better" DBD organ.

Methods: Data were collected on 5,825 patients who were registered on the elective waiting list for a first adult liver-only transplant and 3,949 patients who received a liver-only transplant in the UK between 1 January 2008 and 31 December 2015. Survival following deceased donor liver transplantation performed between 2008 and 2015 was compared by Cox regression modelling to assess the impact on patient survival of accepting a DCD liver compared to deferring for a potential DBD transplant.

Results: A total of 953 (23%) of the 3,949 liver transplantations performed utilised DCD donors. Five-year post-transplant survival was worse following DCD than DBD transplantation (69.1% [DCD] *vs.* 78.3% [DBD]; p <0.0001: adjusted hazard ratio [HR] 1.65; 95% CI 1.40–1.94). Of the 5,798 patients registered on the transplant list, 1,325 (23%) died or were removed from the list without receiving a transplant. Patients who received DCD livers had a lower risk-adjusted hazard of death than those who remained on the waiting list for a potential DBD organ (adjusted HR 0.55; 95% CI 0.47–0.65). The greatest survival benefit was in those with the most advanced liver disease (adjusted HR 0.19; 95% CI 0.07–0.50).

Conclusions: Although DCD liver transplantation leads to worse transplant outcomes than DBD transplantation, the individual's survival is enhanced by accepting a DCD offer, particularly for patients with more severe liver disease. DCD liver transplantation improves overall survival for UK listed patients and should be encouraged.

Lay summary: This study looks at patients who require a liver transplant to save their lives; this liver can be donated by a person who has died either after their heart has stopped (donation after cardiac death [DCD]) or after the brain has been injured and can no longer support life (donation after brainstem death [DBD]). We know that livers donated after brainstem death function better than those after cardiac death, but there are not enough of these livers for everyone, so we wished to help patients decide whether it was better for them to accept an early offer of a DCD liver than waiting longer to receive a "better" liver from a DBD donor. We found that patients were more likely to survive if they accepted the offer of a liver transplant as soon as possible (DCD or DBD), especially if their liver disease was very severe.

Introduction

Rates of liver failure are increasing dramatically in the UK[1] and over a million people worldwide die of cirrhosis every year.[2] Liver transplantation is the only effective treatment for end-stage liver disease and provides an average of 17–22 years of additional life.[1,3,4] Access to liver transplantation is limited by donor organ availability, and over the last decade, as the incidence of liver disease has increased,[1] the number of patients on the liver transplant waiting list in the UK has roughly doubled. Consequently, after 2 years, about 13% of listed patients will no longer be eligible for liver transplantation because of death or deterioration in their condition.[5,6] These waiting list pressures have prompted a focus on the use of organs from donation after circulatory death (DCD) donors, with numbers of DCD donors increasing markedly over the last decade, such that they now almost match annual numbers of donation after brain death (DBD) donors in the UK.[5] Worldwide, only the Netherlands achieves similar numbers of DCD donors per million population.[7]

While this increase in DCD donor activity has transformed UK transplant practice, DCD organs are generally regarded as suboptimal, because of the additional warm ischaemic 'hit' they are subject to during retrieval. Published series report higher incidences of primary non-function (PNF) and ischaemic

Keywords: Liver transplantation; Liver failure; Waiting list survival; Donation after circulatory death; Donation after brainstem death.
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* Corresponding author. Address: Department of Surgery, Box 202, Level E9, Addenbrooke's Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge CB2 0QQ, United Kingdom. Tel.: +1 223 336976; fax: +1 223 762523.
E-mail address: gjp25@cam.ac.uk (G.J. Pettigrew).

cholangiopathy following DCD liver transplantation, resulting in inferior short and long-term outcomes.[8–15] These poorer outcomes for DCD transplantation have undoubtedly influenced the decision to select a particular liver for transplantation, and it is notable that in the UK, a much higher proportion of kidneys than livers are transplanted from potential DCD donors.[5] This is emblematic of a wider challenge posed to the transplant community: whether the increasing demand for transplantation merits increased utilisation of less optimal organs that are associated with poorer outcomes. Available evidence suggests that, despite the potential for such organs to increase liver transplant numbers substantially, decline in the quality of available organs often results in decreased utilisation rates.[16] This may reflect that the responsible clinician often finds it difficult to justify, for a particular individual, the use of a 'marginal' liver organ that is associated with higher morbidity and mortality than would be anticipated with a more optimal liver graft. Such a consideration overlooks, however, the potential for excess deaths while waiting for that more optimal organ.

Thus, key to increased utilisation of marginal or DCD liver allografts is whether their use offers a survival advantage *from the point of listing* for the recipient population.

Addressing the important question of whether a recipient should accept a "poorer quality" DCD organ or wait longer for a "better" DBD organ is, however, difficult, and a prospective trial would raise challenging practical and ethical concerns. Here, we perform a cohort analysis of the NHS Blood and Transplant (NHSBT) UK Transplant Registry (UKTR); a prospectively maintained database that records outcomes from listing for liver transplantation for all UK patients, and that includes data on over 1,400 DCD liver transplants that have now been performed in the UK. We show that outcomes following DCD liver transplants are poorer than following DBD liver transplantation, but that the individual's survival prospects are enhanced by accepting, rather than rejecting, a DCD offer.

Materials and methods

Study design and setting

Livers from controlled DCD donors (Maastricht category 3), defined as donors awaiting circulatory arrest after withdrawal of life-supporting treatment (WLST),[17] were included. Since April 2010, organ retrieval was performed by dedicated National Organ Retrieval Service teams, according to a nationally agreed protocol.[18] In brief, WLST occurred in the intensive care unit or anaesthetic room, and vital signs from the time of withdrawal until cardiac arrest, defined as the 'agonal phase', were continuously monitored. Pre-mortem interventions (such as heparin administration) aimed specifically at facilitating organ donation are not permissible in the UK. After cardiorespiratory arrest, a 'stand-off' time of 5 min was observed before death was confirmed by an independent medical practitioner and procurement could begin.[19] Although UK organ retrieval teams wait a minimum of 3 h from WLST before abandoning retrieval,[20] liver donation is typically only pursued for the first hour.

DCD retrieval proceeded using a rapid retrieval technique, via a midline laparotomy, with dual aortic and portal venous perfusion with University of Wisconsin solution (ViaSpanTM, Bristol-Myers Squibb Pharma, Garden City, NY, USA) containing 25,000 units of heparin per litre in the first 2 bags. Topical cooling was achieved with crushed frozen saline. UK National Organ Retrieval Service teams routinely wait 3 h from WLST before abandoning retrieval if cardiorespiratory arrest has not occurred,[20] but the duration of agonal phase for DCD livers implanted was considerably shorter (median (IQR) 15 min (11–20)). During the study period, 50 DCD livers were machine perfused, either by Normothermic Regional Perfusion (NRP) (n = 20) or *ex situ* immediately following retrieval (n = 30); no liver was subject to hypothermic machine perfusion. Information recorded at retrieval included the retrieval surgeon's assessment of the liver appearance: either 'healthy' or 'suboptimal'.

DCD livers were allocated in the UK according to broadly similar principles to DBD livers,[21] but with some slight modifications, in that the DCD liver was first offered to the designated local centre, and then to 2 or 3 regionally linked centres, before offering to all remaining centres via a 'fast-track' scheme. Selection of a specific recipient was at the discretion of the accepting centre, but factors influencing that decision included blood group compatibility, donor and recipient size match, primary liver aetiology, and perceived clinical urgency.

Influence of DCD liver transplantation on post-transplant survival

Data on 3,949 first adult elective NHS group 1 (NHS-entitled) liver-only transplants performed in the UK using livers from deceased donors between 1 January 2008 and 31 December 2015 were analysed. The reported size of the study cohort excludes 415 transplants with missing values in one or more of the recipient, transplant or donor factors or with missing survival information.

The primary outcome was 5-year transplant survival after transplantation, which was defined as the time from transplant to the earlier of patient death or re-transplant. If a patient was alive at the end of the follow-up period or lost to follow-up, then their survival was censored at the last known survival date while patients who survived for longer than 5-years (1,825 days) were censored at 5 years. Unadjusted and adjusted survival were estimated and stratified by donor type. PNF was defined as poor graft function necessitating re-transplantation or culminating in death within 14 days, excluding rejection and vascular thrombosis. Graft failure was defined as death related to graft failure, or re-transplantation. Cold ischaemic time was defined as the time between commencement of cold perfusion in the donor and warm re-perfusion in the recipient.

Impact of accepting a DCD liver compared with waiting for a potential DBD liver

Data on 5,825 UK adult elective NHS-entitled patients who were registered on the elective waiting list for first liver-only transplantation between 1 January 2008 and 31 December 2015 were analysed. Survival status to 10 May 2017 was extracted from the UKTR and the Office for National Statistics. At this date, 81 patients were still active on the transplant list; their outcome was unknown at time of analysis.

To determine how the extant policy allowing DCD liver utilisation affected survival from waiting list entry compared to excluding DCD donors and hypothetically waiting for DBD livers, the analytical technique of sequential stratification was used.[22] This technique uses observational data to emulate data from a hypothetical randomised trial allowing outcome comparisons between patients who receive a particular treatment at a given time and those waiting for a different treatment, akin to the analysis performed by Bonser *et al.*[23]. The time origin was taken to be the waiting list registration date and each DCD

transplant was regarded as an index case. A stratum was then formed from each index case and a control group of all patients on the transplant list for the same length of time (in days) or longer and eligible to receive that same liver (*i.e.* blood group and size compatible). A control patient who received a DBD transplant was followed up until death or last known follow-up post-transplant and was not censored at the time of DBD transplant. However, a control patient who received a DCD transplant was censored at the DCD transplant (as they would no longer have had the opportunity for a DBD liver) and was then another index patient with a separate group of control patients. Although such censoring of control patients constitutes informative censoring, an inverse probability of censoring weighted approach was not adopted, because this would greatly add to the complexity of the analysis. In addition, experience using the UKTR database suggests that adjustments for non-informative censoring have a relatively small impact on subsequent inference.

The survival time of the index case was censored if they were alive at 10 May 2017. The survival times of those in the control group were censored either at the time of removal (from tumour progression or worsening of clinical condition) from the list (if date of death unknown), at the time of transplant from a DCD donor, or at 10 May 2017 if still alive.

Statistical analysis

Donor, recipient, and transplant characteristics were compared, stratified by donor type, using Fisher's exact test, Chi-squared, or the Mann-Whitney *U* test, as appropriate. Unadjusted transplant survival estimates, stratified by donor type, were calculated for different times post-transplant using Kaplan-Meier estimation methods and assessed using the log-rank test as was survival conditional on 90 day and 1-year survival. Cox proportional hazards regression modelling was used to assess whether donor type influenced transplant survival after adjusting for the final set of relevant risk factors. A stepwise procedure was utilised for variable selection.

To account for competing risks, cumulative incidence functions for graft failure (defined as above) and deaths with a functioning graft were compared between DBD and DCD donors using Gray's test/Fine Gray model for competing risks.

A stratified Cox regression model was used to estimate the hazard of mortality from accepting a DCD liver compared to continued waiting for a potential DBD transplant, after adjustment for other relevant recipient risk factors: recipient age; body mass index (body mass index); log (creatinine); log (bilirubin); log(international normalized ratio); serum sodium; blood group; gender; ethnic origin; disease group; grouped registration year; transplant centre; patient location (inpatient, out of

Table 1. Donor and transplant characteristics for first UK adult elective deceased donor liver-only transplants, 1 January 2008 to 31 December 2015, by donor type.

Variable	DBD (n = 3,046)	DCD (n = 903)	*p* value
Donor			
Donor age (yr)	50 (39–61)	49 (35–59)	<0.0001
Donor BMI (kg/m^2)	25.91 (23.31–29.05)	25.08 (22.63–27.69)	<0.0001
Donor blood group			
O	1,206 (39%)	422 (47%)	<0.0001
A	1,361 (45%)	380 (42%)	
B	337 (11%)	91 (10%)	
AB	142 (5%)	10 (1%)	
Donor gender			
Male	1,538 (50%)	542 (60%)	<0.0001
Female	1,508 (50%)	361 (40%)	
Donor grouped cause of death			
CVA	2,092 (69%)	465 (52%)	<0.0001
RTA	124 (4%)	75 (8%)	
Other trauma	129 (4%)	43 (5%)	
Miscellaneous	701 (23%)	320 (35%)	
History of diabetes			
No history of diabetes	2,765 (91%)	845 (94%)	0.03
History of diabetes	199 (6%)	41 (4%)	
Unknown history diabetes	82 (3%)	17 (2%)	
Transplant related			
Blood group match			
Identical	3,009 (99%)	879 (97%)	0.002
Compatible	37 (1%)	24 (3%)	
Liver transplanted			
Whole	2,714 (89%)	902 (100%)	<0.0001
Reduced	5 (0%)	1 (0%)	
Split	327 (11%)	0 (0%)	
Organ appearance			
Healthy	2,117 (69%)	504 (56%)	<0.0001
Suboptimal	598 (20%)	270 (30%)	
Unknown	331 (11%)	129 (14%)	
Cold ischaemia time (h)	8.82 (7.17–10.60)	7.15 (6.08–8.13)	<0.0001

Data are median (IQR) or number (%) as appropriate. Characteristics were compared, stratified by donor type, using Chi-squared, Fisher's exact or Kruskal-Wallis test as appropriate. DBD, donation after brainstem death; DCD, donation after circulatory death.

hospital); ventilation status; renal replacement therapy; ascites; hepatitis C virus and previous abdominal surgery. Stratification produced separate baseline hazards for each of the strata defined by the index cases.

Multiple imputation (MI) was used to impute values for factors with missing values when appropriate. MI was implemented in SAS 9.3, using chained equations. The imputation model considered all variables in the analysis but also the outcome variables; survival time and censoring indicator. Twenty-one imputation datasets were generated, with 50 burn-in iterations preceding each imputation set.[24] Data from the 415 patients that were excluded (see above) were not imputed, because this information was not missing completely at random, and was instead was due to particular centres not submitting the required data.

Public and patient involvement

The draft manuscript has been reviewed by the NHSBT liver patient group and upon confirmation of acceptance for publication, the findings will be disseminated to the major UK liver patient groups.

Patient consent

Consent for use of anonymised data for outcome analysis is obtained from patients at registration onto the national transplant waiting list.

Table 2. Recipient characteristics for first UK adult elective deceased donor liver-only transplants, 1 January 2008 to 31 December 2015, by donor type.

Variable	DBD (n = 3,046)	DCD (n = 903)	*p* value
Age (yr)	55 (46–61)	56 (49–62)	0.00040
Blood group			
O	1,202 (39%)	411 (45%)	0.00018
A	1,332 (44%)	371 (41%)	
B	341 (11%)	97 (11%)	
AB	171 (6%)	24 (3%)	
Gender (Male)	2,019 (66%)	619 (69%)	0.20
Ethnic group			
White	2,675 (88%)	782 (87%)	0.26
Asian	244 (8%)	74 (8%)	
Black	70 (2%)	24 (3%)	
Chinese/South East Asian	23 (1%)	14 (1%)	
Other	34 (1%)	9 (1%)	
Disease aetiology			
Cancer	673 (22%)	289 (32%)	<0.0001
Hepatitis C cirrhosis	334 (11%)	99 (11%)	
Alcohol-related liver disease	731 (24%)	217 (24%)	
Hepatitis B cirrhosis	32 (1%)	11 (1%)	
Primary sclerosing cholangitis	348 (11%)	64 (7%)	
Primary biliary cirrhosis	267 (9%)	100 (11%)	
Autoimmune and cryptogenic disease	219 (7%)	36 (4%)	
Metabolic liver disease	261 (9%)	58 (7%)	
Other liver disease	181 (6%)	29 (3%)	
BMI (kg/m^2)	26.73 (23.49–30.68)	26.5 (23.88–29.67)	0.28
Creatinine (μmol/L)	78 (64–98)	79 (64–98)	0.80
Bilirubin (μmol/L)	49 (25–103)	39 (21–75)	<0.0001
INR	1.4 (1.2–1.7)	1.4 (1.2–1.7)	0.00063
Sodium (mmol/L)	137 (134–140)	138 (135–140)	<0.0001
Albumin (g/L)	31 (26–36)	32 (28–38)	0.0022
Potassium (mmol/L)	4.2 (3.9–4.5)	4.2 (3.9–4.5)	0.14
UKELD	55 (51–59)	53 (50–57)	<0.0001
MELD	16 (12–21)	15 (11–19)	<0.0001
Waiting time (days)	86 (30–196)	77 (31–165)	0.074
Inpatient	469 (15%)	91 (10%)	<0.0001
Ventilated	26 (1%)	5 (1%)	0.37
Renal support	149 (5%)	46 (5%)	0.81
HCV positive	647 (21%)	233 (26%)	0.0038
Prior abdominal surgery	401 (13%)	63 (7%)	<0.0001
Encephalopathy	940 (31%)	261 (29%)	0.26
Clinically detectable ascites	1,669 (55%)	465 (51%)	0.081
Transplant centre			
Newcastle	194 (6%)	23 (3%)	<0.0001
Leeds	475 (16%)	111 (12%)	
Cambridge	359 (12%)	124 (14%)	
Royal Free	371 (12%)	84 (9%)	
Kings College	460 (15%)	183 (20%)	
Birmingham	725 (24%)	297 (33%)	
Edinburgh	462 (15%)	81 (9%)	

Data are median (IQR) or number (%) as appropriate. Characteristics were compared, stratified by donor type, using Chi-squared, Fisher's exact or Kruskal-Wallis test as appropriate. BMI, body mass index; DBD, donation after brainstem death; DCD, donation after circulatory death; INR, international normalized ratio; MELD, model for end-stage liver disease; UKELD, UK model for end-stage liver disease.

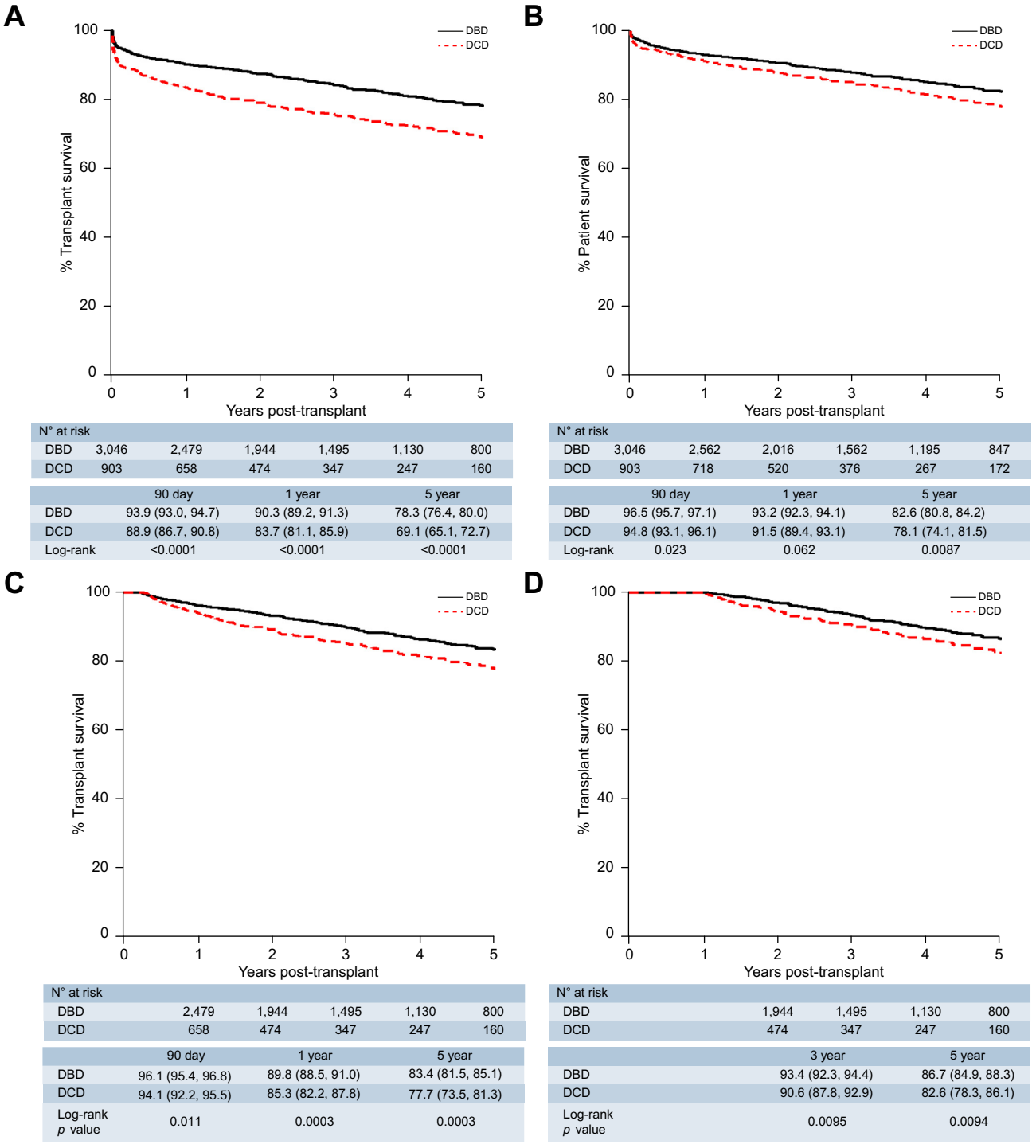
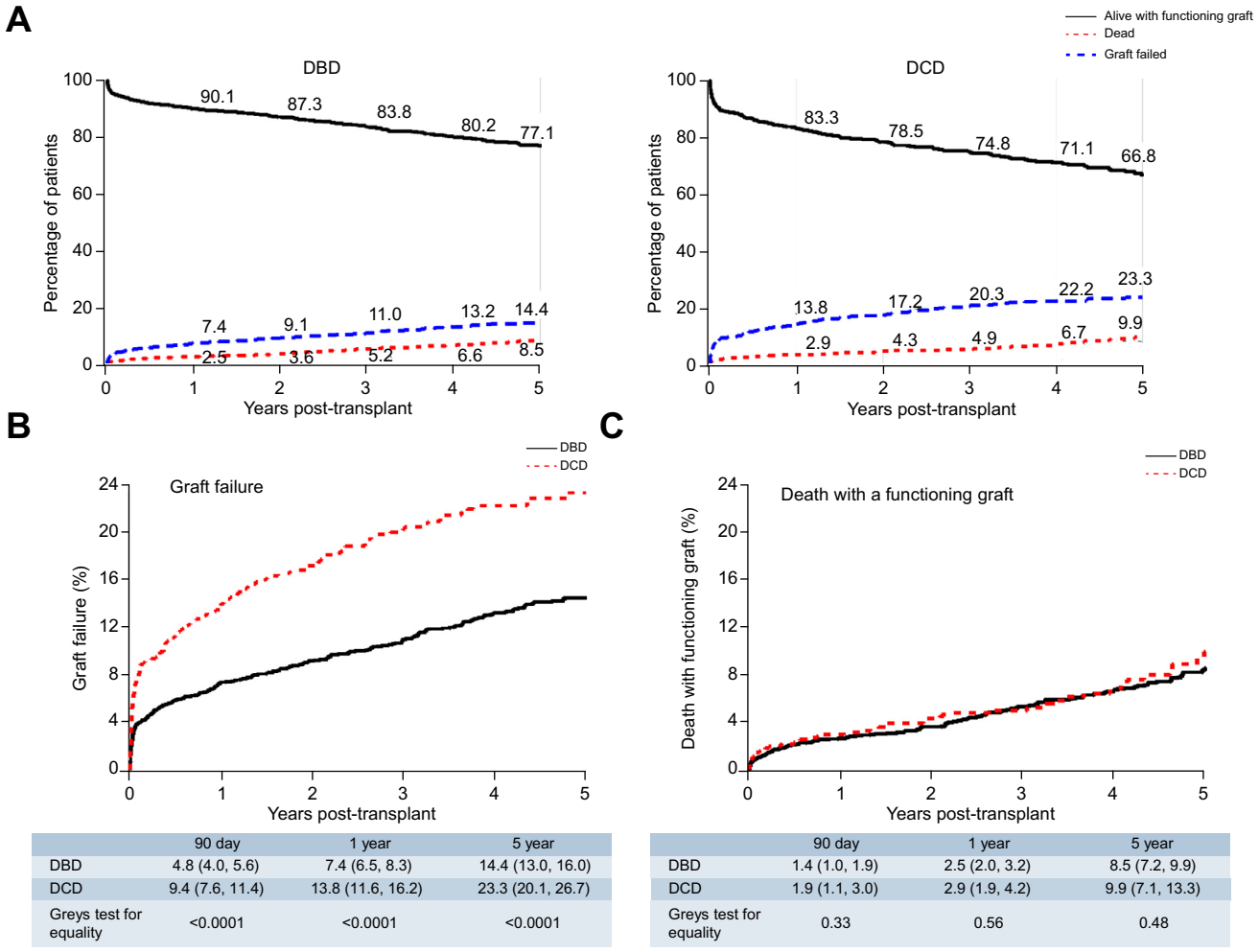


Fig. 1. Survival following DCD and DBD liver transplantation. Kaplan-Meier analysis of: (A) transplant survival, defined as time to patient death or liver re-transplantation, and (B) patient survival, for DCD and DBD liver transplants performed during the study period. The difference in 5-year transplant survival between DCD and DBD liver transplantation, assessed using the log-rank test, was not solely a consequence of early graft failure or patient death because differences were maintained conditional upon transplant survival to 90 days (C) or 1 year (D). DBD, donation after brainstem death; DCD, donation after circulatory death. (This figure appears in colour on the web.)

Results

Comparison of outcomes for DCD and DBD liver transplantation

Of the 3,949 transplants performed during the study period, 903 (23%) utilised livers from DCD donors (Table 1). DCD liver transplant activity increased annually throughout the study period (Fig. S1), although, as previously reported,[8] utilisation rates differed between different UK liver transplant centres (Table 2). Compared to DBD donors, DCD donors were younger, had a lower body mass index and were more likely to have died from trauma than from a cerebrovascular accident (Table 1). DCD liver recipients were more likely to have lower UK model for end-stage liver disease (UKELD)[25] and model for end-stage liver disease (MELD)[26] scores and less likely to have had previous



	90 day	1 year	5 year
DBD	4.8 (4.0, 5.6)	7.4 (6.5, 8.3)	14.4 (13.0, 16.0)
DCD	9.4 (7.6, 11.4)	13.8 (11.6, 16.2)	23.3 (20.1, 26.7)
Greys test for equality	<0.0001	<0.0001	<0.0001

	90 day	1 year	5 year
DBD	1.4 (1.0, 1.9)	2.5 (2.0, 3.2)	8.5 (7.2, 9.9)
DCD	1.9 (1.1, 3.0)	2.9 (1.9, 4.2)	9.9 (7.1, 13.3)
Greys test for equality	0.33	0.56	0.48

Fig. 2. Graft and patient outcomes following DCD and DBD liver transplantation. Competing risk analysis was performed, using Grays test for equality, to compare outcomes following DBD (left panel) and DCD (right panel) liver transplantation with death with functioning graft and graft failure as competing risks (A). Graft failure includes those patients who either underwent re-transplantation or died secondary to graft failure. Rates of graft failure are depicted in greater detail in (B). Rates of death with a functioning graft were similar in the DBD and DCD cohorts (C). DBD, donation after brainstem death; DCD, donation after circulatory death. (This figure appears in colour on the web.)

abdominal surgery or be inpatients at the time of transplantation (Table 2); this suggested a tendency to select lower risk individuals as DCD liver recipients. DCD liver recipients were more likely to have cancer as their primary liver aetiology.

Transplant survival was found to be poorer following DCD liver transplantation, with the difference apparent by 90 days and maintained over 5 years (Fig. 1A; 5-year survival 69.1% DCD *vs.* 78.3% DBD; p <0.0001). Patient survival was also poorer (Fig. 1B). This difference in long-term outcomes is not simply due to differences in early post-transplant graft failure or mortality, because the divergence in transplant survival outcomes was sustained at 5 years, conditional on transplant survival beyond either the initial 90 days (Fig. 1C) or the first year (Fig. 1D) after transplantation.

The Cox regression model analysis considered all pre-transplantation factors shown in Tables 1 and 2. Five risk factors were identified as statistically significant predictors of 5-year survival: donor age, recipient age, primary liver aetiology, inpatient status, and organ appearance (Table S1). The adjusted hazard ratio (HR) for 5-year survival for DCD relative to DBD transplantation was 1.65 (95% CI 1.41–1.95; p <0.0001). There was no statistically significant interaction between donor type and either UKELD (HR 1.61; 95% CI 1.36–1.91 for a particular UKELD value) (p = 0.15) or primary liver aetiology (p = 0.75). Thus, although outcomes for DCD liver transplantation are generally poorer than for DBD liver transplantation, there does not appear to be a specific recipient group for whom DCD liver transplantation is more disadvantageous.

Competing risk analysis (Fig. 2A) demonstrated that the poorer survival for the DCD liver cohort is likely due to the higher failure rates associated with DCD liver transplantation. This reflects an increased incidence of PNF (3.54% (DCD) *vs.* 1.25% (DBD) p <0.0001). However, the rate of graft failure was also higher at later time points, indicating greater ongoing attritional graft loss (Fig. 2B). Consequently, a greater proportion of the DCD liver recipients died from graft failure: in contrast, the proportions of patients dying with a working graft were similar (Fig. 2C).

Is it better to accept a DCD liver or wait for a potential DBD liver?

The above results raise the question of whether it would be better for an individual to accept a DCD liver or to defer for a better 'quality' DBD liver. Fig. 3 depicts outcomes for the registrants on

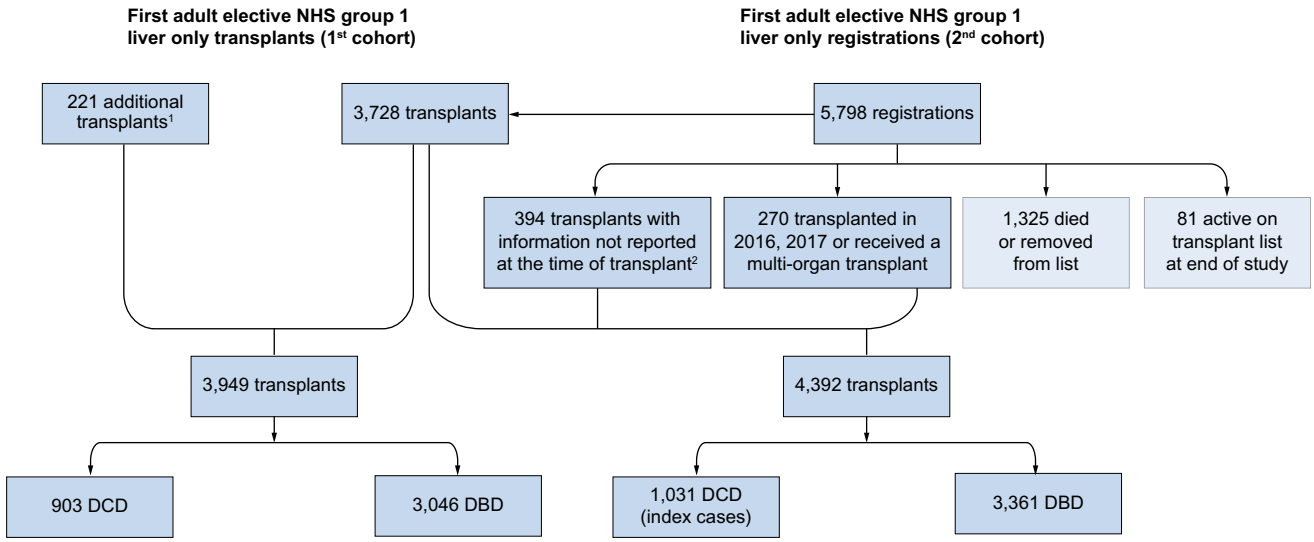


Fig. 3. Outcomes from registration for transplantation from 2008 to 2015. [1]Includes: patients registered on the transplant list prior to 1 January 2008 (n = 153); patients transplanted but not registered for a transplant with NHSBT (n = 27); patients previously registered for a liver transplant (n = 17); multi-organ registration but only received a liver (n = 9); patients classed as paediatric at registration but adult at time of transplant (n = 4); patients only ever suspended on the transplant list and never activated (n = 6); and missing INR at registration (n = 5), [2]Includes patients with: missing cold ischaemia time (n = 332); missing donor height or height <127 cm (n = 8); missing donor weight or weight ≥150 kg (n = 10); INR at transplant not reported (n = 13); serum albumin at transplant not reported (n = 9); potassium at transplant not reported (n = 10); bilirubin at transplant not reported (n = 4); serum sodium at transplant not reported (n = 2); serum creatinine at transplant not reported (n = 1); and post-transplant survival information not reported (n = 5). DBD, donation after brainstem death; DCD, donation after circulatory death; INR, international normalized ratio; NHSBT, NHS Blood and Transplant registry.

Table 3. Unadjusted and risk-adjusted hazard ratio of death for accepting a DCD liver relative to waiting for a potential DBD liver.

	Full time period		2008–2011		2012–2015	
	N	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
Unadjusted	5,798	0.65 (0.55–0.77)	2,640	0.74 (0.60–0.91)	3,158	0.58 (0.43–0.77)
Risk-adjusted	5,798	0.55 (0.47–0.65)	2,640	0.63 (0.51–0.78)	3,158	0.44 (0.32–0.59)

DBD, donation after brainstem death; DCD, donation after circulatory death; HR, hazard ratio.

the liver transplant list during the trial period. Approximately 23% (1,031/4,392) of the patients transplanted received livers from DCD donors, generating 1,031 strata for the sequentially stratified model. Crucially, this model revealed that recipients of DCD livers had a substantially lower *unadjusted* hazard of death post-registration relative to remaining on the list for a potential DBD transplant (Table 3).

A number of recipient factors were identified as statistically significant and these were incorporated into the stratified Cox model (data not presented). Donor type was subsequently added to the model. This approach confirmed that compared to waiting for a potential DBD liver, the *risk-adjusted* HR for post-registration mortality is consistent with the unadjusted analysis (Table 3). The survival advantage of accepting a DCD liver according to the sequential stratification models is illustrated (Fig. 4). The potential survival benefit of using a DCD liver is influenced by a number of principal factors: the rate of de-listing or death while on the waiting list, and the survival differences following transplantation for DCD and DBD organs. It was notable that over the study period there was a marked difference in waiting list outcomes (Fig. 5A,B), with waiting list mortality (censored for transplantation) significantly greater in the earlier (2008–2011) than in the later (2012–2015) era. This difference does not appear to reflect differences in access to transplantation, because the median time to transplant was similar in both eras (140 [95% CI 131–149] and 134 [95% CI 125–143] days for 2008–2011 and 2012–2015, respectively), and may instead be due to either slight differences in the characteristics of the patients listed in the 2 eras (such as UKELD and the requirement for renal support [Table 2]), or to improved management of patients while on the waiting list. In contrast, survival following transplantation was similar in both eras (Fig. 5C). Notably, despite the improved waiting list survival in the later study era, the analysis revealed that the survival benefit associated with DCD liver transplantation was, if anything, greater for the 2012–2015 era (Table 3).

When is the use of a DCD liver most advantageous?

The decision to transplant a liver is made following consideration of the perceived risk-benefit for a particular patient. The results above raise the question of whether there are particular recipient circumstances in which the use of a DCD liver would be particularly advantageous. In this respect, the use of 'suboptimal' liver organs in recipients with particularly advanced liver disease remains controversial. The analysis was therefore adapted to assess the relative benefit of using DCD livers in recipients with different severity of liver disease, by incorporating the patients UKELD score at registration (either as a continuous or categorical variable). UKELD score was designed to predict mortality on the UK liver transplant waiting list,[25] and similar to the US MELD system,[26] a higher score indicates more severe liver disease. As shown (Table 4), the survival benefit

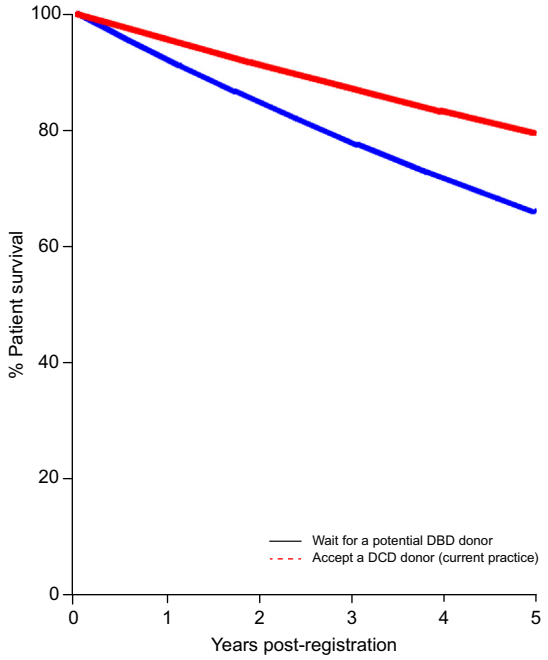


Fig. 4. Graphical depiction of sequential stratification modelling. Actual survival from waiting list registration for liver transplantation during trial period (current practice), and estimated survival if DCD livers were excluded from the donor pool, and patients instead had to wait for DBD liver offers. Time 0 relates to the time of registration/listing for liver transplantation. The curves were calculated by taking median survival time post-transplant from the estimated risk-adjusted survival curve and plotting an illustration of the survival time post-transplant, assuming an exponential distribution. DBD, donation after brainstem death; DCD, donation after circulatory death. (This figure appears in colour on the web.)

associated with accepting DCD livers increases with the recipient's UKELD score, such that for every unit increase of UKELD, the hazard of death after accepting a DCD liver relative to waiting for a potential DBD liver decreases by 0.92 (95% CI 0.89–0.96). This is most strikingly evident when considering UKELD as a categorical variable, with the HR for death associated with DCD liver use in patients with particularly severe liver disease (UKELD >62) approximately one-third of that calculated for patients with mild disease (UKELD–51-53, Table 4). This analysis therefore provides strong support for a policy whereby DCD organs are transplanted preferentially into the sickest patients on the waiting list. Similar results were observed when the modelling was performed using US MELD score as the marker of disease severity (Table S2).

Discussion

In support of the existing literature,[8–14] registry analysis of the UK liver transplant outcomes confirms that survival following DCD liver transplantation is poorer than following DBD liver transplantation. However, the important findings from this study are that accepting a DCD liver conferred a survival advantage over waiting for a more optimal DBD liver, and that the survival advantage was greatest for patients with more advanced liver disease. Thus, our data suggest that the current policy of selecting sicker recipients for "optimal" (DBD) grafts, because of the perception that the use of "suboptimal" (DCD) organs in sicker recipients is associated with particularly poor outcomes, may deny these patients an important chance for survival.

Our findings therefore mirror a recent analysis by Mclean *et al.*, that reported that UK liver recipients with a MELD score >15 have a significant increase in their quality of life from accepting, rather than rejecting, a DCD liver offer.[27] However, the Mclean analysis was performed by using Markov modelling, and the critical difference is that the sequential stratification method adopted in the present study matches a patient who receives a DCD liver with all those who were eligible to receive that liver and who had been registered for the same number of days. This means that the comparison between receiving a DCD liver and waiting for another offer is adjusted for time on the registration list; the sequential stratification approach thus essentially performs a hypothetical randomised trial.

Current UK utilisation patterns of deceased donor organs suggest that concerns relating to outcomes continue to limit utilisation of liver grafts from potential DCD donors. The outcomes for those DCD livers that were unused during the study period, had they been transplanted, is clearly speculative. However, it seems probable, given the marked survival advantage of accepting a DCD liver relative to waiting for a potential DBD liver, that their use would have further improved survival for the listed population, particularly for recipients with more advanced liver disease. We anticipate that our analysis will provide the contextual basis for discussing with individual patients their relative risks of accepting a DCD liver, and that an appreciation of their likely survival benefits from doing so, will change current practices relating to DCD liver utilisation and lead to fewer organ discards. Given the potentially large DCD donor pool, this has the scope to increase liver transplant numbers substantially.

We believe our analysis has important implications for ongoing developments in UK liver transplant practice. Most pertinently, the recently introduced UK liver allocation scheme[28] allocates livers nationally, to the named recipient with the greatest calculated 'transplant benefit score'. This score ranks recipients according to the number of additional years of life they gain from a transplant and will therefore generally prioritise the sickest patients on the waiting list. Only DBD livers are currently allocated through the new allocation scheme, and therefore the very group of patients who, by a similar transplant benefit evaluation, would likely derive most benefit from the potential DCD liver pool, may be denied that opportunity because of the presumption they will soon be allocated a DBD liver. Our analysis therefore highlights the importance of extending the scheme to additionally incorporate national DCD liver offering.

The second aspect of change in UK liver practice concerns the increasing use of *in situ* or *ex vivo* warm perfusion of liver organs for transplantation. Although still under trial evaluation, these approaches offer the potential for improving outcomes by 'resuscitating' DCD liver organs and for providing an additional means of selecting only those livers likely to be associated with favourable transplant outcomes.[29–36] Our analysis suggests that the real benefit of these approaches would be in increasing DCD liver utilisation rates; and further cautions that if warm perfusion technologies were associated with a paradoxical decrease in DCD liver transplant rates, then this would likely reduce survival of the wait-listed UK liver transplant population. Reassuringly, the recent Nasrala study of *ex vivo* normothermic perfusion reports a reduction in DCD liver discard rates.[37]

There are several limitations to our study. We did not consider the potential for living donor livers or the presumed

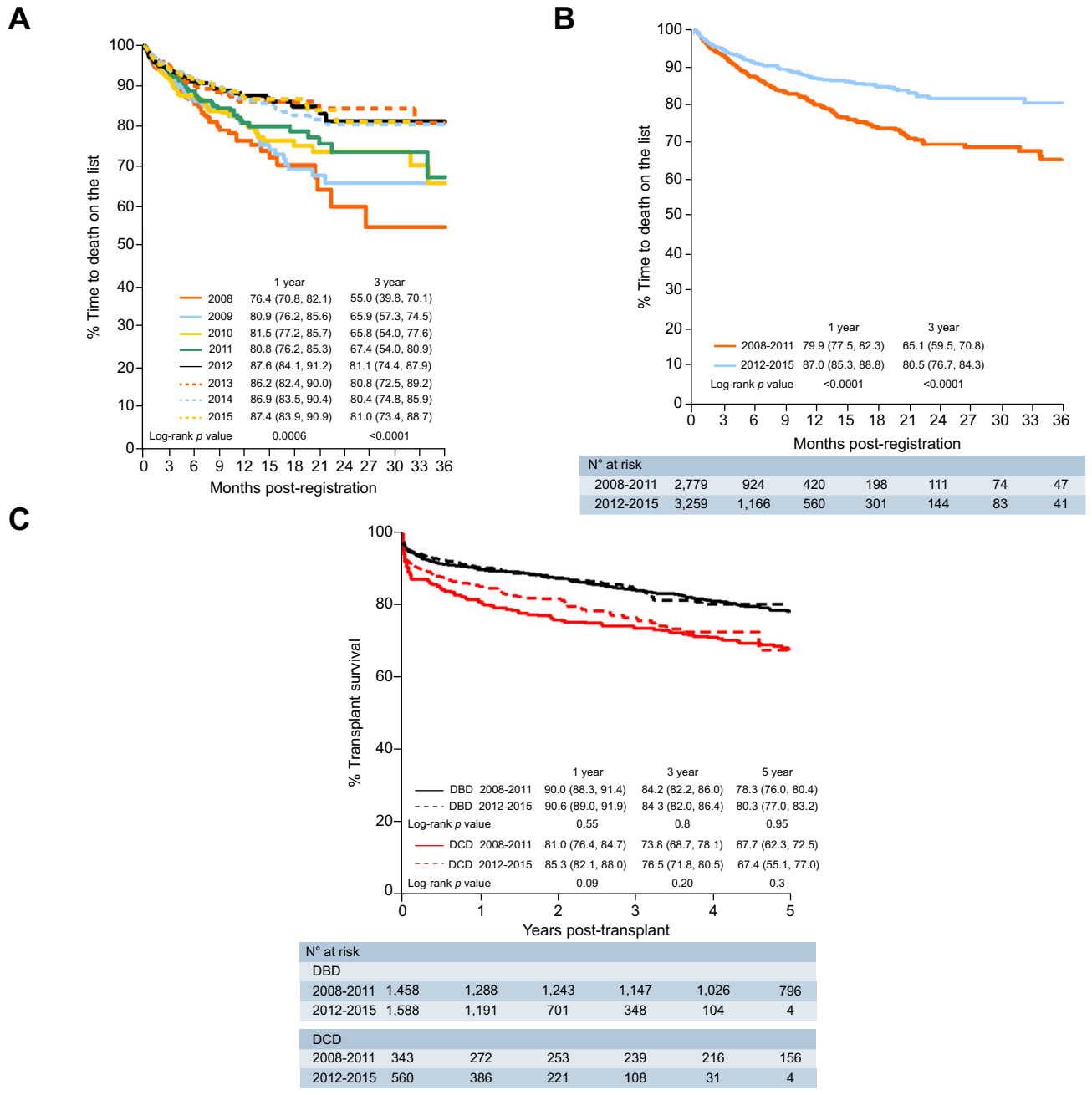


Fig. 5. Registration and transplant outcomes according to listing year. Kaplan-Meier patient survival (censored for transplantation) from point of listing for transplantation; according to year of listing (A). Broadly, survival from listing differs for both eras (2008–2011 and 2012–2015 (B)). In contrast, survival from transplantation (C) was similar in both eras and consistently poorer for DCD liver transplantation. DBD, donation after brainstem death; DCD, donation after circulatory death.

Table 4. Risk-adjusted hazard ratio of death for accepting a DCD liver relative to waiting for a potential DBD liver for UKELD.

	Full time period		2008–2011		2012–2015	
	N	HR (95% CI)	n	HR (95% CI)	n	HR (95% CI)
Linear UKELD	5,798	0.92 (0.89–0.96)	2,640	0.91 (0.87–0.95)	3,158	0.92 (0.87–0.97)
UKELD categories						
51–53	1,288	0.61 (0.42–0.91)	562	0.54 (0.32–0.92)	726	0.79 (0.44–1.43)
54–57	1,607	0.48 (0.34–0.67)	762	0.63 (0.43–0.92)	845	0.23 (0.10–0.51)
≥58	1,584	0.40 (0.27–0.56)	756	0.40 (0.25–0.64)	828	0.34 (0.19–0.62)
Variant syndrome (<49)	739	1.16 (0.81–1.66)	318	1.66 (1.03–2.68)	421	0.81 (0.47–1.40)
Chronic liver disease (49–62)	4,580	0.55 (0.45–0.66)	2,081	0.62 (0.49–0.79)	2,499	0.43 (0.30–0.63)
Top tier (≥63)	479	0.19 (0.07–0.50)	241	0.17 (0.04–0.70)	238	0.16 (0.04–0.64)

DBD, donation after brainstem death; DCD, donation after circulatory death; HR, hazard ratio; UKELD, UK model for end-stage liver disease.

quality of the DBD liver in our analysis, and it is possible, for example, that survival from listing may be better improved by increased use of more 'marginal' DBD organs, rather than DCD organs. Against this, only 214 adult living donor liver transplants were performed in the 7 years of the study, which is unlikely to have impacted on overall UK survival rates for wait-listed patients. Similarly, the definition of an expanded criteria donor for liver transplantation remains vague, and often adopts donor criteria that were established as predictors for kidney allograft survival.[38] In contrast, DCD liver transplants are undoubtedly viewed as a distinct entity from DBD liver transplantation, and hence, the analysis of survival benefit for accepting a DCD liver focuses on a real clinical dilemma. The main limitation of our study is that, as a registry analysis, it may miss confounding factors that are not recorded by the registry. Hence, the use of DCD organs in high-risk recipients may have occurred in highly select occasions, with the recipient generally considered healthier than evident from the UKELD score. Such individual variation would not be captured by the analysis. We think this unlikely, because relatively large numbers of DCD transplants (n = 192) were performed into the sicker (UKELD ≥58) recipients. Similarly, the perceived survival benefit associated with DCD liver transplantation pertains to the particular pressures of UK liver transplant practice during the study period. This advantage is dependent upon 3 main factors: the mortality on the waiting list, and the survival outcomes following DCD and DBD transplantation. Hence alterations in any of these factors would alter the relative survival advantage of using a DCD liver, potentially limiting the applicability of our findings to other countries; the survival advantage would, for example, be more modest or non-existent if waiting list mortality was minimal in a particular country due to high DBD donation rates. Notwithstanding, UK liver waiting list mortality is roughly equivalent to other EU countries, and if anything less than in the US.[39] Reported outcomes for DCD liver transplantation in other countries are also broadly similar to the UK experience. Hence, it is likely that the DCD donor pool will offer similar survival advantages to the waiting list population in these countries.

These limitations notwithstanding, our findings suggest that there needs to be a better evaluation of the risks associated with waiting for liver transplantation, and that an increased awareness of the survival benefit associated with DCD liver transplantation, particularly for those recipients with the more severe disease, would likely lead to wholesale changes in liver transplant practice. Such a change in practice should not be reliant upon the introduction of machine perfusion technologies.

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Conflict of interest
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; and no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions
All authors conceived and designed the study on behalf of the Liver Advisory Group to NHS Blood and Transplant. RT, EA, DC acquired and performed the analysis. All authors provided intellectual input, analysed and interpreted the data, critically revised the manuscript, and approved the final manuscript. GJP is guarantor that all authors satisfy the ICMJE recommendations on authorship.

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Ethical approval
All patients provide consent, at time of listing onto the NHSBT Transplant Registry, for use of their data for analyses of outcomes.

Data sharing
Data are available from the NHSBT.

Transparency
The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Supplementary data
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