The UK DCD Risk Score: A new proposal to define futility in DCD liver transplantation

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SUMMARY

In this study, we provide a new prediction model for graft loss in DCD liver transplantation. Using UK national DCD database, a risk analysis was performed in adult recipients of DCD liver grafts in UK between 2000 and 2015 (n=1153). A new risk score was calculated (UK DCD Risk Score) on the basis of regression analysis, and validated using the UNOS-database (n=1617) and our own DCD liver transplant database (n=315). Finally, the new score was compared with two other available prediction systems, the DCD risk scores from UCLA and Kings-College-Hospital, London. Seven strongest predictors of DCD graft survival were identified: functional donor warm ischemia, cold ischemia, recipient MELD, recipient age, donor age, previous liver transplantation, and donor BMI. A combination of these risk factors (*UK DCD Risk Score*) stratified best recipients in terms of graft survival in the entire UK DCD database as well as in the UNOS and in our own DCD population. Importantly, the *UK DCD Risk Score* significantly predicted graft loss due to PNF or IC in the futile group (>10 score points). The new prediction model demonstrated a better C statistic of 0,79, compared to the two other available systems (0,71 and 0,64; respectively). The *UK DCD Risk Score* is a reliable tool to detect high risk and futile combinations of donor and recipient factors in DCD liver transplantation. It is simple to use and offers a great potential to better decide which DCD graft should be rejected or may benefit from functional assessment and further optimization by machine perfusion.

INTRODUCTION

Driven by organ scarcity and the need to decrease waiting list mortality, liver transplant professionals worldwide have expanded the donor organ pool (1). In this context, livers from DCD donors are increasingly used for transplantation and several countries implemented DCD programs (2–4). However, DCD organs may carry further risk due to the additional donor warm ischemia leading potentially to a higher rate of severe complications, such as PNF and ITBL (5). Specific donor and recipient risk factors are therefore critically evaluated by transplant centres (6–9). For example, graft cold ischemia, donor age and donor BMI or recipient MELD score have all been reported to impact on graft survival (7). Careful selection of grafts and recipients appears therefore decisive for outcome. Data analysis from Kings College Hospital (KCH) underline this fact, showing excellent low rates of ITBL (2.5%), when the overall risk is low and WIT is kept short with an average of functional DWIT of 16 minutes (10,11). Such results stand in contrast to other European centres and to previous analyses of US data (12–14), which report longer donor warm ischemia times with higher incidence of ITBL and graft loss (15). The combination of too dangerous risk originating from three sources, e.g. donor, graft and recipient is however unclear.

The intention of this study was therefore to search for an easily applicable score system, based on a few independent donor and recipient key factors, with the highest possible accuracy in prediction of complications and graft loss after DCD liver transplantation.

METHODS

Study Design and Patients

After approval by the National Health Service (NHS) institutional review board in the UK, records of all adult (≥18 years) DCD recipients transplanted for chronic liver disease were extracted from an NHS Blood and Transplant (NHSBT) Analysis and Research file from January 2000 through December 2015 (national UK cohort) (16). Two other DCD cohorts were used for validation. First, adult DCD cases were extracted from the United Network for UNOS database from December, 1987 through September, 2010, after approval by the University of Washington institutional review board (UNOS cohort). And second, we analysed our own institutional DCD database, which included patients transplanted from January 2005, to December 2015 (Birmingham cohort). To reduce confounding variables, paediatric and partial transplants (split

and living donor liver transplantation), DBD and combined liver transplants, were excluded. Recipients with lost follow up were excluded from the analysis. Patients with exception points (e.g., hepatocellular cancer within Milan criteria) were included in the analysis. Importantly, pretransplant MELD score was calculated without inclusion of those exception points (laboratory MELD). The primary outcome measured for regression analysis was one-year graft survival (least missing entries). The final analysis included 1153 patients. The two validation cohorts, UNOS and Birmingham, consisted of 1861 and 315 DCD transplant cases. 0We defined ITBL in this analysis on the basis of radiological findings, e.g. intrahepatic or hilar biliary strictures and dilatations, occurring in the absence of hepatic artery stenosis (HAS) or thrombosis (HAT), portal vein thrombosis, chronic ductopenic rejection, or recurrent primary sclerosing cholangitis. Overall incidence of biliary complications, extrahepatic strictures, ITBL and bililary leakages for our DCD transplants from Birmingham are described in detail in Suppl. Table 5.

Statistical Analysis

To establish a clinically valid regression model, we choose parameters, which are easily available for surgeons at each DCD transplant centre worldwide. Our aim was, therefore, to combine donor, graft, and recipient factors in one practical score system on post-transplant graft survival. All factors should be easily available prior to transplantation. Accordingly, significant variables with impact on outcome after DCD liver transplantation (with a p-value<0.25) were considered further were selected (6 metric, 1 dichotomous), for example, donor age, functional DWIT, cold ischemia, laboratory MELD score, recipient age and retransplantation (17–20). In an attempt to increase information on graft quality, donor BMI was also included as surrogate marker of steatosis and other metabolic disorders (21). Functional DWIT in UK is defined as time between SBP below 50 mmHg and cold aortic organ flush (22).

For candidate predictors with less than 60% missing values (e.g. recipient lab MELD score pre-transplant (32/1153; 2.8% missing), functional DWIT (464/1153; 40.2%) and cold ischemia of the graft (89/1153; 7.7% missing), we performed multiple imputation (MI) using multivariate normal regression, imputing a total of 20 datasets (n=24213) (23). This method assumes that the data are missing at random MAR, which appears as a less restrictive assumption than that required by complete case analysis and multivariate normal regression has been shown to be valid whether or not all imputed variables follow a normal distribution (24). In each of the imputed datasets we used a backward stepwise approach for the multivariable logistic regression with p-values ranging between <0.001 and >0.05 as inclusion and exclusion thresholds,

respectively. The strongest predictors for one-year graft survival after DCD liver transplantation, that were selected in 75% to 80% of the imputation models were included in the final multivariable model. Backward elimination is generally preferred as an automated predictor selection procedure because it takes correlations among predictors into calculation (23,25–31). The imputed data sets were combined and the point system was developed to enhance clinical applicability according to the Framingham risk scheme (**Table 2**) (32). For each predictor, the median of all values below (Midpoint W_1reference – W_7reference) and above the threshold has been calculated. The Midpoint for the cohort below each threshold (W1-7reference) is subtracted from the midpoint of all values above the threshold. The factor β is multiplied with the difference (Wij-Wireference), separately for each factor (32).

Performance and validation of the new prediction model

The performance of the prediction model in the derivation cohort was evaluated by examining measures of discrimination and calibration. Discrimination is the ability of the risk score to differentiate between patients who do and do not experience an event (in our case, the occurrence of graft loss after DCD liver transplantation). This measure was quantified by calculating the area under the curve (AUC) of the receiver operating characteristic statistic. Calibration reflects the agreement between predicted probabilities from the model and observed outcomes. We used the Hosmer–Lemeshow test to statistically determine the extent of agreement between the predicted and the observed probabilities. We performed an internal validation using a bootstrapping procedure. This approach uses the entire data in order to develop the prediction model and in addition accounts for model overfitting or uncertainty compensating for overoptimism in the final prediction model. The bootstrapping in the current study was performed using 500 bootstrap resamples, each time selecting variables and developing a model within the sample. The new prediction model was compared to available systems from UCLA (DCD risk score UCLA) (17) KCH named as DCD Risk Index (DCD-RI) (Suppl. Table 4) (33). Furthermore, the model was validated externally in the UNOS database and internally, in our own population from Birmingham, where we specifically evaluate the predictive value of our new score, excluding retransplantations. Statistical analysis was performed using IBM SPSS Statistics version 23 (IBM Corporation, Armonk, NY, USA).

RESULTS

Are there differences between the 3 study populations from UK, UNOS and Birmingham?

Following eligibility criteria, 1153 cases were available from the UK database, and 1863 were selected from the UNOS database. Our institutional database included 315 DCD transplants. Median follow-up accumulated to 865 days in the UK, as compared to 600 days in US and 936 days in our population. No differences were found between the three populations in terms of recipient age (median 55 vs. 54 vs. 58 years), recipient BMI (27.0 vs. 27.4 vs. 27.0 kg/m^2), donor BMI (median 25.0 vs. 25.1 vs. 25 kg/m^2) and cold ischemia time (median 7.1 vs. 7.0 vs. 7.0 hours). Major differences (UK data vs. UNOS vs. own data) were noted regarding donor age (median 49 vs. 34 vs. 51 years) and functional DWIT (median 17 vs. 14 vs. 17 min). In the UNOS cohort, centre dependent variations exist on the time of initiation of donor warm ischemia. Most US centres, however, define it also as functional DWIT,

Table 1 - Donor, graft, and recipient characteristics in the 3 DCD cohorts in the UK, UNOS, and in Birmingham.

Donor & graft characteristics	UK (n=1153)	UNOS (n=1861)	Birmingham (n=315)
Age (years)	49 (35–59)	34 (21–47)	51 (36–62)
Body mass index (kg/m2)	25 (23–28)	25.1 (22.0–29.1)	25 (22.7–27.7)
Total donor warm ischaemia time (min)	27 (22–31)	-	27 (22–32)
Functional warm ischaemia time (fDWIT) (min)	17 (14–20)	14 (9–21)	17 (14–21)
No. of donors with fDWIT >20 min	254 (22%)	364 (19.6)	82 (26)
No. of donors with fDWIT >30 min	40 (3.5%)	124 (6.7)	13 (4.1)
Asystolic warm ischaemia time (min)	13 (11–15)	-	12 (10–14)
Cold ischaemia time (h)	7.1 (6–8.2)	7 (5.3–9)	7 (5.7–8.1)
No. of grafts with CIT >6 h	853 (74%)	1145 (61.5%)	222 (70.5%)
Recipient characteristics			
Age (years)	55 (48–61)	54 (49–60)	58 (51–64)
Body-Mass-Index (kg/m2)	27 (24–30)	27.4 (23.8–31.2)	27 (24–30)
lab-MELD score	15 (11–19)	16.4 (10.8–23.5)	13 (9–17)
UKELD score	53 (50–57)	-	53 (49–56)
BAR–Score	5 (3–8)	7 (3–10)	5 (3–7)
Follow-up (days)	865 (364–1704)	600 (160–1355)	936 (426–1602)

Data presented as median and IQR for continuous variables or as number and percent for categorical variables.

BAR, Balance of Risk Score; BMI, Body-Mass-Index; CIT, cold ischaemia time; DCD, donation after circulatory death; fDWIT: IQR, interquartile range; MELD, model of end-stage liver disease; UKELD, United Kingdom model of end-stage liver disease; UNOS, United Network for Organ Sharing.

initiated after a specified period of time during sustained hypotension (systolic blood pressure < 50mmHg)(14). The BAR-score at transplantation was slightly higher in UNOS compared to the other cohorts (median 5 vs. 7 vs. 5 points), corresponding to the slightly higher MELD score in UNOS regions when compared to the European population (median 15 vs. 16.4 vs. 13 points)(18). In addition, the percentage of retransplantations at the time of DCD transplant was comparable in UK and UNOS, while all candidates in our own population were primary transplants (11.3% vs. 11.3% vs. 0%, **Table 1**).

Which are the key prediction factors for graft survival after DCD liver transplantation?

Initial calculations were performed in the large DCD database from UK and tested, in a next step, in the UNOS and our institutional DCD population. We evaluated 43

Table 2. Development of the new prediction score based on multivariate regression analysis.

Parameter	Category	Regression Coefficient ßi	p-value	Reference Value Wi (Midpoint)	ßi x (Wij-Wireference)	Risk Score
Donor age	≤ 60 yr	0.084	*0.001*	46 (W_1reference)	0	0
	> 60 yr			66	1.688	**2**
Donor BMI	£ 25 kg/m^2	0.519	*0.0001*	23 (W_2reference)	0	0
	> 25 kg/m^2			28	2.598	**3**
Functional DWIT	≤ 20 min	0.341	*<0.0001*	15 (W_3reference)	0	0
	21-30 min			24	3.069	**3**
	> 30 min			32	5.797	**6**
Cold ischemia time	no	0.791	*0.001*	5.5 (W_4reference)	0	0
	yes			7.7	1.74	**2**
Recipient age	≤ 6h	0.241	*0.0001*	52 (W_5reference)	0	0
	> 6h			64	2.892	**3**
Recipient lab MELD	≤ 25	0.109	*0.0001*	14 (W_6reference)	0	0
	> 25			30	1.744	**2**
Retransplantation	No	8.571	*<0.001*	0 (W_7reference)	0	0
	Yes			1	8.571	**9**
Total Score Points						**0-27**

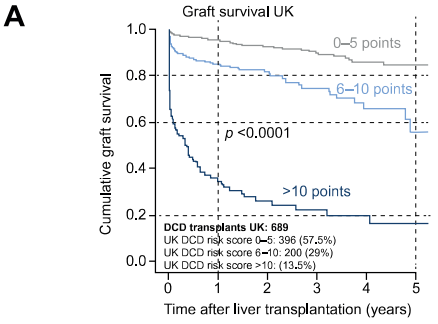
The imputed data sets were combined and the point system was developed according to the Framingham risk scheme. For each predictor, the median of all values (Midpoint W1reference – W7reference) below and above the threshold has been calculated. The Midpoint for the cohort below each threshold (W1-7reference) is subtracted from the midpoint of all values above the threshold. The factor b is multiplied with the difference (Wij-Wireference), separately for each factor to develop the score points.32 BMI, body mass index; CIT, cold ischaemia time; fDWIT: functional donor warm ischaemia time; MELD, model of end-stage liver disease; yr, years; min, minutes; h, hours; b, regression coefficient.

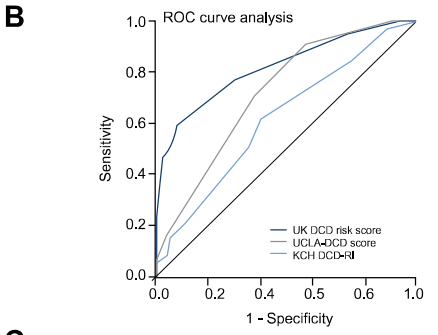
candidate predictors. The median number of missing values per candidate was 6 (IQR 2.5-9.5). Five variables were excluded, due to more than 60% missing values, which involved AST, donor albumin, agonal donor phase, arterial donor pressure and recipient hospital status at transplant. Among the 38 remaining candidate variables 28 had complete data and 10 contained <60% missingness and were subjected to the multiple imputation procedure. The full multivariable prediction model based on the backward stepwise approach and revealed seven parameters as significant predictors for graft loss: donor age and BMI, functional DWIT, cold ischemia time, recipient age, MELD score and previous liver transplantation (**Table 2**).

Recipient BMI was not identified as independent predictor. Using the significant regression coefficients, the UK-DCD-Risk score was calculated with a range from 0 to 27 points reflecting an exponential increase in one-year graft loss. The strongest predictor was retransplantation (0 or 9 points), followed by functional donor warm ischemia (0 or 3 or 6 points), recipient age (0 or 3 points), donor BMI (0 or 3 points), donor age (0 or 2 points), cold ischemia time (0 or 2 points), and lab MELD (0 or 2 points; **Table 2**). Internal validation yielded a c-statistic of 0.79 (95%CI: 0.744-0.839) and the p-value for the Hosmer and Lemeshow goodness of fit test ranged from 0.143 to 0.506 in the 20 imputed data sets, corresponding to a well-calibrated model. Internal validation of the model using bootstrapping procedure revealed minimal optimism of 0.00005 (95%CI: 0.00574 to 0.064).

How does the newly developed risk score compare to other available prediction systems?

In an attempt to compare predictability of outcome, c-statistics of other score systems were assessed in the UK database referred to graft survival. For both available prediction models in DCD liver transplantation, the UCLA-DCDscore (17) and the KCH-DCD-RI from Kings College Hospital(33), the areas under the receiver operator characteristic curves (AUC) were 0.71 and 0.64, respectively (**Figure 1**). These findings were confirmed by a superior AUC for the new DCD model in our own cohort in Birmingham (AUC=0.754), compared to the UCLA-DCD score (AUC=0.639) and the KCH-DCD RI (AUC=0.583) (Suppl. Figure 3). Accordingly, the new UK-DCD-Risk score showed a more significant decrease in graft survival per increasing score cluster (0–5, 6–10, >10; **Figure 1**), when compared to both other models. Of note, the BAR score was also inferior in prediction of graft survival after DCD liver transplantation in this dataset (Suppl. Figure 1). Additional analysis showed that cumulative 1-year graft survival per each single score point followed an exponential increase for the new score model above a certain threshold of approximately 10 points (**Figure 3**). Both





C

Scores	Area	SE	Asymptotic sig.	95% CI
UK DCD risk score	0.79	0.024	<0.0001	0.744–0.839
KCH DCD-RI	0.64	0.027	<0.0001	0.562–0.668
UCLA-DCD score	0.71	0.024	<0.0001	0.663–0.757

Figure 1 - Five-year graft survival according to the UK DCD Risk Score and ROC curve analysis (UK cohort).

(A) Kaplan–Meier survival plots were developed for graft survival according to the three risk classes of the new score model. Comparisons between groups were made using the log-rank test. Discrimination is the ability of the risk score to differentiate between patients who do and do not experience graft loss. This measure was quantified by calculating the AUC statistic. (B) This is displayed in the ROC curve. (C) The table compares the AUC values of the new model with previously described DCD scores from UCLA and KCH. AUC, area under the receiver-operating-characteristic curve; DCD, donation after circulatory death; DCD-RI, donation-after-circulatory-death risk index; KCH, King's College Hospital; ROC, receiver operating characteristic; SE, standard error; UCLA, University of California, Los Angeles.

other DCD scores failed to predict cumulative graft loss at each single score point (**Figure 3**). Of note, UK DCD Score grouping at this threshold (≤10 vs. >10) splitted graft survival best as compared to the two other scores, that is, DCD Score from UCLA (≤4 vs. >4) and DCD-RI from KCH (≤4 vs. >4) (**Figure 3**). The newly developed score showed a very good positive prediction value of 71% and 86.1% in UK and UNOS. The specificity was 0.95.

A

Score	Cohort	Score threshold	n	Positive predictive value*	False omission rate*	Delta	C statistic
UK DCD risk score	UK	≤10	596		13.4%	57.5%	0.79
		>10	93	71.0%			
	UNOS	≤10	1,380		22.7%	63.4%	0.72
		>10	237	86.1%			
KC DCD-RI	UK	≤4	501		17.2%	27.1%	0.64
		>4	97	44.3%			
UCLA-DCD score	UK	≤4	572		19.2%	37.9%	0.71
		>4	42	57.1%			

*: Graft loss above the threshold
*: Graft loss below threshold

B Prediction of one year graft loss by different DCD scores

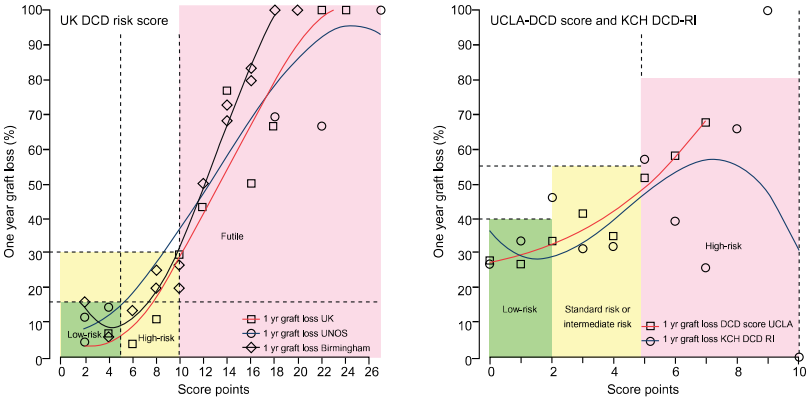
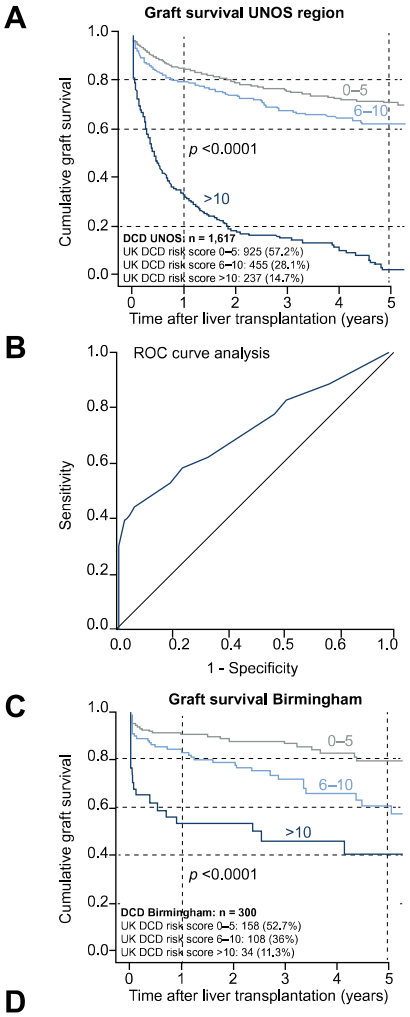


Figure 2 - Prediction of graft loss by the UK DCD Risk Score in all three cohorts, compared to other available DCD risk models.
(A) The positive predictive value and false omission rate are shown together with the specificity of three different score models. (B) Survival plots highlight the percentage of grafts, which are lost with increasing score points, for the new prediction model in three different cohorts (UK, UNOS, and Birmingham) compared to two existing models in the UK. DCD, donation after circulatory death; DCD-RI, donation-after-circulatory-death risk index; KCH, King's College Hospital; UCLA, University of California, Los Angeles; UNOS, United Network for Organ Sharing.

Is the new prediction model valid in other DCD cohorts?

External validation in the UNOS database, confirmed the excellent discrimination between acceptable outcome below the threshold of 10 points and significantly lower graft survival in the futile group with more than 10 UK DCD Score points (**Figure 1&3**). Of note, recipients in the futile group (>10 points) experienced a very high risk for graft loss of more than 60% in one year and > 80% in 5 years. In addition, candidates in the high-risk group (>5 to 10 score points) lost the graft in 18% and 40% in one and five years, compared to the lowest risk group (0-5 points), where 5% and 15% of DCD livers were lost in one and five years, respectively (**Figure 1&2**). Importantly, UK DCD Score ranking was also useful in our own cohort, where the strongest predictor, re-transplantation, was not available ($p<0.0001$; **Figure 2**). Exclusion of cases with a UK DCD risk score of more than 10 points from a DCD liver transplant due to expected poor prognosis would refer to 13.4% of patients in the UK (93/689), to 14.7 % of cases in the US (237/1617) and to 11.4% of cases in our population (34/300) (**Figure 1&2**).



D

Scores	Area	SE	Asymptotic sig.	95% CI
UK DCD risk score UNOS region	0.722	0.015	<0.0001	0.693–0.750

Figure 3 - Validation of the UK DCD Risk Score in the UNOS region and Birmingham. Kaplan–Meier survival plots for graft survival were developed to validate the new model in the UNOS DCD cohort.

Comparisons between groups were made using the log-rank test. (B) In addition, graft survival in our local DCD liver-transplant cohort in Birmingham is displayed. The AUC statistic, obtained from the UNOS cohort, parallels the values we received from the development cohort in the UK. (C) The table demonstrates a similar AUC in the UNOS cohort, when compared to the UK cohort. AUC, area under the receiver-operating-characteristic curve; DCD, donation after circulatory death; ROC, receiver operating characteristic; UNOS, United Network for Organ Sharing.

How does the new score correlate with post-transplant complications and morbidity?

While numerous risk factors have been described previously for DCD liver transplantation, prediction of ischemic cholangiopathy (IC) or also primary non-function (PNF) remains unsolved. We were therefore particularly interested to identify a combination of key factors with significant impact on graft loss due to IC or PNF. Donor-recipient

constellations with more than 10 score points (futile group) experienced significantly more graft loss due to PNFs and IC in both large DCD cohorts in UK and UNOS (*p<0.0001; p=0.0001*; **Table 4**). In addition, recipients in the high risk and futile group developed significantly more often vascular complications, e.g. HAT, leading to graft failure in numerous cases in all cohorts (**Table 4**). In order to evaluate liver function and other important post-transplant complications and general morbidity, we analysed our institutional DCD cohort in accordance with the three clusters of

Table 3. Potential combinations of additional key risk factors providing a UK DCD Risk Score ≤10 or >10 points.

	Potential combinations of risk factors
DCD Risk Score ≤10 points	No retransplantation [0] + recipient MELD ≤25 points [0] + recipient age ≤60 yr [0] + cold ischaemia time >6 h [2] + functional donor warm ischaemia >20 to ≤30 min [3] + donor age ≤60 yr [0] + donor BMI ≤25 [0]
	No retransplantation [0] + recipient MELD >25 points [2] + recipient age ≤60 yr [0] + cold ischaemia time ≤6 h [0] + functional donor warm ischaemia time >30 min [6] + donor age ≤60 yr [0] + donor BMI ≤25 [0]
	No retransplantation [0] + recipient MELD >25 points [2] + recipient age >60 yr [3] + cold ischaemia time >6 h [2] + any functional donor warm ischaemia >20 to ≤30 min [3] + donor age ≤60 yr [0] + donor BMI ≤25 [0]
	No retransplantation [0]+ any functional donor warm ischaemia up to ≤30 min [0–6] + any donor age [0–2] + any recipient MELD [0–2]
	No retransplantation [0]+ functional donor warm ischaemia >20 to ≤30 min [0–3] + any donor age [0–2] + any donor BMI [0–3] + any recipient MELD [0–2]
	Retransplantation [9] + recipient MELD ≤25 points [0] + recipient age ≤60 yr [0] + cold ischaemia time ≤6 h [0] + functional donor warm ischaemia ≤20 min [0] + donor age ≤60 yr [0] + donor BMI ≤25 [0]
DCD Risk Score > 10 points	No retransplantation [0] + recipient MELD >25 points [2] + recipient age >60 yr [3] + cold ischaemia time >6 h [2] + functional donor warm ischaemia >20 to ≤30 min [3] + donor age >60 yr [2] + donor BMI ≤25 [0]
	No retransplantation [0] + recipient MELD >25 points [2] + recipient age ≤60 yr [0] + cold ischaemia time >6 h [2] + functional donor warm ischaemia >30 min [6] + donor age >60 yr [2] + donor BMI ≤25 [0]
	No retransplantation [0] + recipient MELD >25 points [2] + recipient age >60 yr [3] + cold ischaemia time >6 h [2] + functional donor warm ischaemia >30 min [6] + donor age >60 yr [2] + donor BMI ≤25 [0]
	Retransplantation [9] + recipient MELD >25 points [2] + recipient age ≤60 yr [0] + cold ischaemia time ≤6 h [0] + functional donor warm ischaemia ≤20 min [0] + donor age ≤60 yr [0] + donor BMI ≤25 [0]
	Retransplantation [9] + recipient MELD >25 points [2] + recipient age ≤60 yr [0] + cold ischaemia time >6 h [2] + functional donor warm ischaemia >20 to ≤30 min [3] + donor age >60 yr [2] + donor BMI ≤25 [0]

BMI, body mass index; CIT, cold ischaemia time; DCD, donation after circulatory death; fDWIT, functional donor warm ischaemia time; h, hours; MELD, Model of end stage; liver disease; min, minutes; UKELD, United Kingdom model of end-stage liver disease; yr, years.
*Numbers in parenthesis correspond to DCD Risk Score points.

Table 4. Aetiology of graft loss according to the UK DCD Risk Score in the UK, UNOS, and Birmingham DCD cohorts.

Outcome parameter	Overall	Low risk (0-5 points)	High risk (6-10 points)	Futile (>10 points)	p value low vs. high risk	p value high risk vs. futile
UK (n=)	689	396	200	93		
Cause of graft failure						
PNF	29 (4.2%)	2 (0.5%)	2 (1.0%)	25 (26.9%)	0.605	0.001
HAT	14 (2.0%)	1 (0.3%)	4 (2.0%)	9 (9.7%)	0.045	0.005
ITBL	26 (3.8%)	5 (1.3%)	6 (3.0%)	15 (16.2%)	0.194	0.001
One-year graft survival (%)	85%	96%	85%	37%	<0.001	<0.001
UNOS (n=)	1617	925	455	237		
Cause of graft failure						
PNF	87 (5.4%)	21 (2.3%)	12 (2.6%)	54 (22.8%0	0.709	<0.001
HAT	32 (2.0%)	7 (0.7%)	2 (0.4%)	23 (9.7%)	0.726	<0.001
ITBL	58 (3.6%)	9 (1.0%)	4 (0.9%)	45 (19.0%)	1	<0.001
One-year graft survival (%)	75%	85%	80%	33%	<0.001	<0.001
Birmingham (n=)	300	158	108	34		
Cause of graft failure						
PNF	9 (3.0%)	2 (1.3%)	2 (1.9%)	5 (14.7%)	1	0.009
HAT	17 (5.7%)	7 (4.4%)	6 (5.6%)	4 (11.8%)	0.775	0.133
ITBL	19 (6.3%)	5 (3.2%)	7 (6.5%)	7 (20.6%)	0.236	0.041
One-year graft survival (%)	85%	91%	85%	53%	<0.001	<0.001

DCD, donation after circulatory death; HAT, hepatic artery thrombosis; IC, ischaemic cholangiopathy; PNF, primary non-function; UNOS, United Network for Organ Sharing.

the new prediction model. Increasing risk is transmitted by increasing score points resulting in significantly impaired early liver function (INR day one: 1.5 vs. 1.7 vs. 2.0, *p=0.0001*, *p=0.0005*; Suppl. Figure 4) and higher liver enzyme release (median peak ALT during first week after transplant (787 vs. 1116 vs. 1906, *p=0.0004; p=0.0002)*. In addition, ICU and hospital stay after DCD transplantation increased significantly from low risk to futile score group (Suppl. Figure 4). Overall post-transplant morbidity was summarized by the CCI (34), where the new DCD prediction score was associated with a significantly increased median CCI throughout the three risk groups (*p<0.0001*, *p=0.0093;* Suppl. Figure 4).

DISCUSSION

Our search for a new score to optimize justice and utility for DCD liver allocation has led to several new findings. First, by combining a few major donor and recipient parameters, we developed a simple score system which best stratifies recipient graft loss after DCD liver transplantation, as compared to other recent developed prediction concepts. Second, this score proved to be highly discriminatory for PNF and ITBL in both, the national UK (NHSBT) and US (UNOS) databases. Third, our calculations represent the largest analysis of DCD liver transplant recipients. Fourth, the new model correlates well with post-transplant morbidity throughout all three risk clusters.

Risk assessment in liver transplants has been repeatedly addressed by several studies but is usually limited to the main endpoints mortality or graft loss. In addition, it appears arbitrary which thresholds and which combinations of parameters in a critical ill patient predict outcome. Currently, the most convincing calculations of risk prediction in liver transplantation base on a relatively limited number of key parameters leading to varying score points according to their regression coefficients. The sum of such scores expresses the total risk up to a risk threshold (balance principle) (18,19,35). However, while risk scores have been implemented in DBD liver transplantation, their application in DCD liver transplants is limited, as the DCD population is by far smaller in most countries, and parameters depicting higher graft injury are less well defined. Importantly, graft loss due to PNF and ITBL is a major and much more relevant problem in DCD liver transplantation in contrast to DBD liver transplantation, and justifies from our point a new effort to find a formula of their prediction, based on a national analysis.

Minimizing the sum of risk is an old principle in surgery, and many transplant professionals automatically aim to allocate DCD livers to low MELD primary liver transplant candidates (10,22). This established approach has led to a significantly improved early patient survival after DCD grafting (12,22). However, the precise impact of different donor/recipient combinations on graft failure is unclear. Two groups have developed models to predict the likelihood of graft survival after DCD liver transplantation (17,33). In one detailed analysis, Khorsandi et al identified six donor, graft and recipient factors to predict graft failure after transplantation by the DCD-RI, which combines functional DWIT, duration of donor hepatectomy, cold ischemia time, recipient MELD, underlying liver disease and retransplantation (33). DCD transplant cases are not equally distributed to the three risk clusters of this score from KCH. In contrast to the lowest risk group, which includes only a very small number of DCD

transplant cases (11.5%; 69/598), almost 40% are allocated to the highest risk group (235/598) and majority of DCD transplantations are classified into the "standard" risk group (50%; 294/598). Based on the number of score points allocated to each case at parameter cut-offs, the KCH DCD – RI showed inferior prediction in terms of graft loss. For example, one main risk factor in DCD liver transplantation, the functional DWIT, contributes to only 1 score point, when ranging above 25 minutes (53/677 in UK DCD cohort, 7.8%). According to this score, majority of DCD livers receive zero points for an already prolonged functional DWIT of up to 25 minutes (624/677; 92.2% of UK DCD cohort). A similar picture occurs from the parameter cold ischemia time, where the maximum of only 1 parameter point is distributed, when exceeding 10 hours. In UK only, a few DCD grafts experience such long storage times (67/1153; 5.8 %). In contrast, majority of points (three) are allocated to recipients with hepatitis C virus infection, alcohol related liver disease, cryptogenic liver cirrhosis or Budd-Chiari syndrome as indication for liver transplantation. Such parameters, alone may not predict graft loss based on DCD-related complications (PNF and ITBL), but due to recurrence of the underlying disease. In addition, three score points are allocated to DCD liver recipients with an elevated lab MELD of >25 points, which appears only in a limited number of DCD transplantations in UK (59/691; 8.5%). Thus, the DCD-RI from KCH seems less suitable to stratify post-transplant graft survival when compared to the new UK DCD risk score.

Another risk model has been calculated to identify risk combinations, the UCLA-DCD Score, being a combination of 6 variables, e.g. donor HBV-core antibody positivity and functional warm ischemia (MAP <60mmHg to flush), cold storage time, recipient MELD, recipient BMI, retransplantation and underlying liver disease in the recipient (17). The highest predictive factor with 3 points was HCV positivity combined with HCC in this score, which may end up predicting graft loss due to HCV recurrence rather than PNF or ITBL. Secondly, the impact of Hepatitis C positivity will change in the near future due to the direct-acting antiviral medications (36). In addition, important predictors of early graft failure, e.g. functional DWIT contributed only with one score point. An additional score factor, selected by the authors of the UCLA-DCDs core, published in 2011, was donor HBV-core antibody positivity, which is expressed in only very few cases in the UK DCD cohort (14/1153; 1.2%). Thus, the UCLA-DCD score was also inferior in predicting graft survival (Figure 3). To develop a meaningful prediction model, ideally this should base on clinically relevant score parameters, which are of great importance in all countries with DCD liver transplantation (35,37,38).

In contrast to the above-mentioned calculations, our prediction model discriminated best in terms of graft survival below and above a cut-off of 10 (**Table 4; Figure 1-4**). Based on this, donor - recipient combinations with more than 10 points are exposed to a high risk of graft loss due to clinically relevant and DCD related complications, such as PNF or IC (**Table 4**). In addition, the new model significantly correlates with post-transplant morbidity.

Our model has also shortcomings. First, we failed to include graft steatosis in our calculation due to limited donor liver biopsies in the UK. Nevertheless, a correlation of BMI and steatosis has been shown in a recent study (39), and we have been able to demonstrate donor BMI as independent predictor. Second, most DCD recipients in UK have a low MELD score at time of transplantation (median lab MELD 15 points), because DCD liver allocation is excluded from MELD allocation. Third, cut-off definitions for higher risk based on graft survival deterioration with however further impact on complications. For example, candidates in the high-risk group (6 -10 score points) are exposed to significantly higher rate of graft loss due to IC. This high-risk group would therefore, benefit from a graft treatment prior to implantation (40). In this context, machine perfusion approaches such as hypothermic oxygenated perfusion (HOPE) have been previously shown to reduce reperfusion injury and intrahepatic biliary complications after transplantation of human DCD livers (41–43). In addition, ex-situ graft evaluation during normothermic or hypothermic machine liver perfusion might be a useful tool to test liver viability, though better markers of graft function during these approaches are urgently needed (44–46).

One of the advantages of UK DCD risk score is that it derives from objective factors, readily available at the time of an organ offer, with the exception of warm and cold ischemia. However, as the liver retrieval starts and the functional DWIT becomes available, the score can be recalculated with a fairly precise prediction of cold ischemia. At this stage, the score values may suggest a different decision regarding the use of the graft and/or the choice of a different local recipient. In the future, we will calculate the score system at organ offer. When donor/recipient combinations result in more than 10 points, we will either try to find a different recipient to decrease the overall risk and secondly perform graft treatment by machine perfusion prior to implantation. In addition, future models should also consider the amount of graft steatosis and the impact on the score threshold whether to accept a DCD liver for a certain recipient or not (47). Though more reliable methods of fat quantification are urgently needed, analysis of graft biopsies provide additional information on the amount of steatosis and therefore help to decide which DCD liver to accept or

how to adapt the preservation technique for a specific risk combination. Due to the fact that important risk parameters, e.g. WIT, are frequently missing or incomplete in nationwide databases, further multicentre cohort studies are required to refine existing and new scoring systems. More specifically, an outcome study including DCD transplants from multiple centres in Europe and US, has been initiated and will enable us to first provide another validation of our new model and second to demonstrate the effective relation between the number of risk points per DCD case and specific complications in the recipient.

In summary, we believe that the UK DCD Risk Score may be a very practical and new guidance for allocation of a specific organ to a recipient, and helps also to decide which DCD liver requires processing with a new preservation technology, including machine perfusion. This would potentially help to implement such expensive approaches more specifically.

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