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Disparities in the Use of Older Donation After Circulatory Death Liver Allografts in the United States Versus the United Kingdom

Emmanouil Giorgakis

Tommy Ivanics
Henry Ford Health, tivanic1@hfhs.org

Shirin E. Khorsandi

David Wallace

Lyle Burdine

See next page for additional authors

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Disparities in the Use of Older Donation After Circulatory Death Liver Allografts in the United States Versus the United Kingdom

Emmanouil Giorgakis, MD, MSc,[1,2,3] Tommy Ivanics, MD, MPH,[4,5,6] Shirin E. Khorsandi, MD, PhD,[3,7] David Wallace, MD, PhD, MSc, MA, BSc,[3,7,8] Lyle Burdine, MD, PhD,[1,2] Wayel Jassem, MD, PhD,[3] Amit K. Mathur, MD, MS,[9] and Nigel Heaton, MD[3]

Background. This study aimed to assess the differences between the United States and the United Kingdom in the characteristics and posttransplant survival of patients who received donation after circulatory death (DCD) liver allografts from donors aged >60 y. **Methods.** Data were collected from the UK Transplant Registry and the United Network for Organ Sharing databases. Cohorts were dichotomized into donor age subgroups (donor >60 y [D >60]; donor ≤60 y [D ≤60]). Study period: January 1, 2001, to December 31, 2015. **Results.** A total of 1157 DCD LTs were performed in the United Kingdom versus 3394 in the United States. Only 13.8% of US DCD donors were aged >50 y, contrary to 44.3% in the United Kingdom. D >60 were 22.6% in the United Kingdom versus 2.4% in the United States. In the United Kingdom, 64.2% of D >60 clustered in 2 metropolitan centers. In the United States, there was marked inter-regional variation. A total of 78.3% of the US DCD allografts were used locally. One- and 5-y unadjusted DCD graft survival was higher in the United Kingdom versus the United States (87.3% versus 81.4%, and 78.0% versus 71.3%, respectively; $P < 0.001$). One- and 5-y D >60 graft survival was higher in the United Kingdom (87.3% versus 68.1%, and 77.9% versus 51.4%, United Kingdom versus United States, respectively; $P < 0.001$). In both groups, grafts from donors ≤30 y had the best survival. Survival was similar for donors aged 41 to 50 versus 51 to 60 in both cohorts. **Conclusions.** Compared with the United Kingdom, older DCD LT utilization remained low in the United States, with worse D >60 survival. Nonetheless, present data indicate similar survivals for older donors aged ≤60, supporting an extension to the current US DCD age cutoff.

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[1] *Division of Transplantation, Department of Surgery, University of Arkansas for Medical Sciences, Little Rock, AR.*
[2] *Hepatopancreatobiliary Surgery, Department of Surgical Oncology, Rockefeller Cancer Institute, University of Arkansas for Medical Sciences, Little Rock, AR.*
[3] *Liver Transplant, Institute of Liver Studies, Kings College Hospital, London, United Kingdom.*
[4] *Multi-Organ Transplant Program, Division of General Surgery, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Canada.*
[5] *Department of Surgery, Henry Ford Hospital, Detroit, MI.*
[6] *Department of Surgical Sciences, Akademiska Sjukhuset, Uppsala University, Uppsala, Sweden.*
[7] *Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom.*
[8] *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*
[9] *Division of Transplantation, Department of Surgery, Mayo Clinic, Phoenix, AZ.*

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Correspondence: Emmanouil Giorgakis, MD, MSc, Division of Transplantation, Department of Surgery, University of Arkansas for Medical Sciences, 4301 W Markham St, Little Rock, AR 72205. (EGiorgakis@uams.edu).

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INTRODUCTION

Each year, >1 in 10 patients die on the liver transplant (LT) waiting list.[1] The discrepancy between the number of patients waiting to receive a LT and the number of available donor organs has driven the exploration of alternative avenues to expand the donor pool.[2]

One such method has been the use of livers from donation after circulatory death (DCD).[3,4] Although early analyses described inferior results compared with those who received a liver from brain stem death donors, more recent studies have observed marked era-specific improvements in the use of DCD livers.[5-9] Over recent years, both single-center and international comparative studies have reported equivalent patient survival between those who receive a DCD liver and those who receive a donation after brain stem death liver.[8,9]

By 2030, 15% of the US population is expected to be older than 70 y of age.[10] Consequently, the proportion of potential older DCD donors will increase.[2,11] Livers donated from DCD donors are known to be more susceptible to ischemic insult, biliary complications, and higher rates of early and late allograft dysfunction.[12-16] For these reasons, most US transplant surgeons are apprehensive about using older DCD allografts: the majority of US transplant centers would currently decline organs from DCD donors older than 60 or even 50 y of age.[2,13,14,17,18]

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This relative conservatism comes in stark contrast to transplant programs in other countries.[19-21] For example, in Spain, Cascales-Campos et al[19] report noninferior survival using controlled older DCD allografts up to an age of 70 y. In the United Kingdom, DCD donors account for almost 30% of the donor pool.[11,20,21] Studies from this country have shown that LTs from DCD donors over 60 y of age can yield acceptable posttransplant outcomes, albeit in the absence of other risk factors.[22,23] A nationwide UK long-term analysis reported acceptable outcomes in using DCD donors older than 70 in highly selected cohorts at experienced centers.[11] A more recent study provides an international comparison of disease-specific short- and long-term mortality of LT recipients among the United States and the United Kingdom.[24] However, we could not find any international comparative analysis of posttransplantation outcomes in the use of older DCD donors.

In the context of low rates of DCD utilization and high waiting list mortalities in the United States and the ever-expanding DCD donor age criteria in many European countries and the United Kingdom, we felt it time to challenge the conventional 50-y age limit commonly practised in most US DCD centers. Between 2001 and 2015, we used the UK Transplant Registry and the United Network for Organ Sharing (UNOS) database from the United States to compare the outcomes of those receiving a LT from DCD donors aged 60 y and above.

MATERIALS AND METHODS

Data Sources

UK Transplant Registry

UK cohort data were extracted from the UK Transplant Registry, following application to National Health Service Blood and Transplant.[25] The UK Transplant Registry captures donor and recipient characteristics and posttransplant outcomes from all transplants performed at all 7 LT units.

UNOS Database

Observations were collected from transplant centers in accordance with UNOS practices in administering the Organ Procurement and Transplantation Network (OPTN) contract.[26] OPTN data are transmitted and compiled by the Scientific Registry of Transplant Recipients.[27] Scientific Registry of Transplant Recipients is responsible for creating and disseminating reports on national transport activity and center performance in the United States. Our study cohort was derived from a retrospective analysis of DCD LT from 2001 to 2015.

Study Population

We included all adult (≥18) LT recipients transplanted from January 1, 2001, to December 31, 2015. The cohort study included patients transplanted until the end of 2015 to ensure adequate long-term follow-ups for all subjects. To keep our study cohort as homogenous as possible, we excluded pediatric recipients and recipients of split, reduced, living donor grafts, combined liver-kidney, or multivisceral LT. The UK Transplant Registry and the UNOS databases were partitioned into 5 donor age groups (≤30, 31–40, 41–50, 51–60, and ≥61 y of age).[1,22,24] Transplant centers were ranked based on their annual DCD LT volume ranking and then divided into volume tertiles, designated as high-, middle-, and low-volume centers. The center rank volume-based designation was annually recalculated to reflect migration of center volume ranking between years.

Donor and Recipient Characteristics

In the United Kingdom, the donor factors included age, sex, race, body mass index (BMI), UK donor risk index (UKDRI)[28]; total donor warm ischemia time in minutes (WIT), defined as the time from donor extubation to aortic flush; cold ischemia time in hours (CIT), defined as the time from donor aortic flush to allograft reperfusion[29,30]; donor cause of death (cerebrovascular accident, anoxia, head trauma, central nervous system tumor, or other); graft import status, defined as local if the allograft has been procured by the implanting center's own National Organ Retrieval Service (NORS) team versus imported, if it has been procured by a different NORS team. Donor factors included in the UKDRI included donor age, DCD status, smoking history, height, sex, split liver, and donor bilirubin.[28] The recipient factors included were age at transplant, BMI (kg/m^2), sex, race; primary indication for transplant: alcohol-induced, nonalcohol related fatty liver disease, hepatitis C cirrhosis, hepatitis B cirrhosis, cryptogenic cirrhosis, primary hepatic malignancy, autoimmune (primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune hepatitis), polycystic liver disease, or other. Primary hepatic malignancy was subclassified into cirrhotic-hepatocellular carcinoma, noncirrhotic-hepatocellular carcinoma or other, native Model for End-Stage Liver Disease (MELD) score, UK Model for End-Stage Liver Disease score,[31] transplantation urgency status (elective versus super urgent), inpatient status at the time of transplant, hemodialysis need before transplant, waitlist time, transplant center DCD volume tertile (high, medium, or low), and transplant region.

In the United States, the donor demographics obtained were age, liver DRI,[32] sex, race, BMI, cause of death, graft import status (local versus imported), CIT (defined as the time from donor aortic flush to allograft reperfusion),[29] and WIT (referring to the total donor warm ischemia time, defined as the time from donor extubation to aortic flush).[29] Center characteristics obtained were the total number of LTs per year and the OPTN region. The recipient characteristics studied included age, sex, BMI, race, primary indication for transplant, native MELD, urgency status (status 1A versus no), medical condition at the time of transplant, time on the waitlist, and hemodialysis in the week before transplant.

Statistical Analysis

The donor and recipient continuous demographic characteristics were assumed to have nonparametric distribution and were represented as medians (interquartile range [IQR]) and compared with Kruskal-Wallis nonparametric testing.[33,34] Differences between age groups within each national cohort were compared using independent *t* tests for continuous and χ^2 for categorical variables. Yates-correction was supplied on χ^2 analysis to prevent overestimation of statistical significance on small data.[35]

The 2 national data sets were harmonized to allow comparisons of graft survival between the United Kingdom and the United States. Survival curves were generated using the

Kaplan-Meier method and compared by log-rank testing. Graft failure was defined as the event of graft loss in a living (retransplant) or deceased recipient.

In the first stage of the analysis, the impact of the different age groups on graft survival was compared separately for the United Kingdom and the United States. Next, graft survival in each country was compared between those who received a DCD donor aged 60 or above (D >60) and those who received a DCD donor aged ≤60 y (D ≤60). We selected 60 y as the donor age cutoff because donor age over 60 has been previously described as an independent DCD outcome risk factor and is included in the UK DCD risk score).[22,36]

In the second stage of the analysis, graft survival was compared between the United Kingdom and the United States. First, the overall graft survival following DCD transplantation was compared between the 2 countries, then an international comparison of DCD graft survival in D >60 donors was conducted to assess whether the effect of donor age >60 on posttransplant outcomes varies between the United Kingdom and the United States. Lastly, we evaluated the country impact on the outcome, using a multivariable cox proportional hazard model adjusting for the clinically relevant confounders of donor age >60, CIT, and WIT (causal analysis).[37]

In the United States, registry studies with publicly available, deidentified data are not considered human subjects research, and therefore, the study was exempt from Institutional Review Board approval.[38] All statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistic v25 (IBM Corp, Armonk, NY). All statistical tests were 2 sided. The level of significance was set at $P < 0.05$.

RESULTS

UK Cohort

During our study period, a total of 1157 DCD LTs were performed in the United Kingdom. The donors in D >60 accounted for 22.6% of the UK cohort (n = 261). Those in D ≤60 accounted for 77.4% (n = 896).

UK DCD Donor Characteristics

The UK DCD donor characteristics for both age groups are shown in Table 1. D >60 donors had a median age of 65 (IQR, 62–70) y versus a median of 43 (IQR, 28–51) y for D ≤60, $P < 0.001$. The median BMI for the overall UK cohort was 25.0 kg/m^2 (22.6–27.7). The median UKDRI was higher in D >60. For the entire UK cohort, the median WIT was 26 (22–31) min, similar between the 2 groups ($P = 0.060$). The median CIT was 7.2 (6.1–8.2) h, similar between the groups ($P = 0.256$). Cerebrovascular accidents had been the dominant cause of death among the D >60 donors (67.5% versus 47.1%, $P < 0.001$).

UK DCD Recipient Characteristics

The UK DCD recipient characteristics are shown in Table 2. There was no difference in native MELD ($P = 0.422$), inpatient status ($P = 0.867$), or need for pretransplant hemodialysis ($P = 0.320$) at the time of transplant. No D >60 allograft was used for a super-urgent LT (the UK equivalent of US UNOS status 1A). Waitlist time was 86 (33–185) d, longer for the D >60 recipients (median of 100 versus 83 d, $P = 0.051$). More D >60 allografts were used in the high-volume tertile centers versus all other centers combined (77.2% versus 22.7%, respectively; $P = 0.005$).

UK DCD Transplant Activity Distribution

In the United Kingdom, two-thirds of DCD LTs were performed in London (37.1%) and West Midlands (27.1%). Although most of the D >60 recipients were transplanted in London and Birmingham (West Midlands), D >60 allografts had been recovered in all UK transplant regions. In the entire United Kingdom, 74.3% of all DCD allografts and 88.1% ($P = 0.001$) of D >60 allografts were imported, that is, had not been procured locally, Table 1. Donor grafts procured in regions with no transplant institutions were transferred to the accepting transplant center while keeping CIT short.

US Cohort

From 2001 to 2015, a total of 3394 DCD LTs were performed in the United States. D >60 included 83 patients (2.4%). D ≤60 included 3311 (97.6%).

US DCD Donor Characteristics

The US DCD donor characteristics for both age groups are shown in Table 1. D >60 donors had a median age of 64 (61–67) y versus a median of 33 (22–45) y in D ≤60 ($P < 0.001$). The median BMI for the entire US cohort was 25.6 kg/m^2 (22.4–29.5), similar for both donor age groups ($P = 0.134$). As expected, the median DRI[32] was higher in D >60 (2.66 versus 1.77; $P < 0.001$). For the United States, the median WIT was 15 min (10–22), similar between the 2 groups ($P = 0.906$). CIT was 6 h (4.9–7.9) ($P = 0.606$). Cerebrovascular accidents were the dominant cause of death among D >60 (42.2% versus 17.5%, $P < 0.001$). Most of the DCD allografts that were used had been procured locally (68.5% versus 31.5%, $P = 0.010$).

US DCD Recipient Characteristics

The US DCD recipient characteristics are shown in Table 2. The median recipient age at the time of transplant was 56 (50.8–62) y, similar across donor age groups ($P = 0.633$) as was the BMI. The median MELD score was lower in D >60 patients ($P = 0.042$). There was no difference in patient hospitalization status at the time of transplant. A total of 2.2% of DCD allografts were used in status 1A (UK equivalent of super urgent) patients, which was similar between the 2 age groups ($P = 0.869$). A total of 13.6% of US DCD recipients had an underlying primary hepatic malignancy. Compared to D ≤60 recipients, the waitlist time was markedly shorter in D >60 recipients (56 versus 102 d; $P = 0.056$).

US DCD Transplant Activity Distribution

D >60 donor grafts were more likely to be used at the high-volume centers (88.0%) versus middle-volume centers (12.0%). No D >60 grafts were used in the low DCD volume centers. There was marked variation in the use of DCD livers across the United States. Contrary to the United Kingdom, there was no correlation of population density and DCD volumes in the United States. Similarly, analysis showed marked variation in the use of older DCD livers across the US OPTN regions (0%–42.2%, $P < 0.001$).

TABLE 1.

Donor characteristics NHSBT/UK and SRTR/US

	NHSBT/UK				SRTR/US			
		Donor age, y				Donor age, y		
	Total	>60 N = 261 (D >60)	≤60 N = 896 (D ≤60)	*P*	Total	>60 N = 83 (D >60)	≤60 N = 3311 (D ≤60)	*P*
Age, y	48 (34–58)	65 (62–70)	43 (28–51)	<0.001	33 (22–46)	64 (61–67)	33 (22–45)	<0.001
BMI, kg/m^2	25 (22.6–27.7)	25.6 (23.4–28)	24.7 (22.3–27.7)	0.002	25.6 (22.4–29.5)	26.6 (23.3–30.86)	25.53 (22.4–29.5)	0.134
UKDRI	2.19 (1.9–2.5)	2.6 (2.4–2.9)	2.059 (1.8–2.3)	<0.001				
DRI					1.77 (1.55–2.08)	2.660 (2.51–2.98)	1.77 (1.54–2.06)	<0.001
WIT,min	26 (22–31)	27 (22–32)	26 (21–31)	0.060	15 (10–22)	10 (16–22)	15 (10–22)	0.906
Missing data, %	33.1	17.6	37.6		9.5	12.0	9.5	
CIT, h	7.2 (6.1–8.2)	7.2 (6.3–7.2)	7.1 (6–8)	0.256	6 (4.9–7.9)	6 (4.35–8.02)	6 (4.9–7.9)	0.606
Missing data, %	0.9	1.9	0.6		3.8	3.6	3.8	
Male sex, %	59.7	51.1	62.2	0.001	67.6	54.2	67.9	0.009
Race, %				0.529				<0.001
White	95.9	96.6	95.6		89.5	90.4	89.5	
Black	0.9	0.4	1.1		8.6	4.8	8.7	
Other	3.2	3	3.2		1.9	4.8	1.8	
Cause of death, %				<0.001				<0.001
CVA	51.8	67.5	47		18.1	42.2	17.5	<0.001
Anoxia	24.2	20.5	25.4		37.7	34.9	37.8	
Head trauma	14.6	4.1	17.8		39.3	14.5	39.9	
CNS tumor	0.7	0.4	0.8		0.4	1.2	0.4	
Other	8.7	7.5	9.1		4.4	7.2	4.3	
Imported, %	74.3	88.1	70.2	<0.001	31.5	21.7	31.7	0.010

BMI, body mass index; CIT, cold ischemia time; CNS, central nervous system; CVA, cerebrovascular accident; D, donor; DRI, donor risk index; NHSBT, National Health Service Blood and Transplant; SRTR, Scientific Registry of Transplant Recipients; UKDRI, United Kingdom donor risk index; WIT, warm ischemia time.

TABLE 2.

Recipient characteristics NHSBT/UK and SRTR/US

	NHSBT/UK				SRTR/US			
		Recipient age, y				Recipient age, y		
	Total	>60 N = 261 (D >60)	≤60 N = 896 (D ≤60)	*P*	Total	>60 N = 83 (D >60)	≤60 N = 3311 (D ≤60)	*P*
Age at Tx, y[a]		57 (50–63)	55 (48–61)		56 (50.8–62)	56 (50–64)	56 (51–62)	0.633
BMI, kg/m^2		26.8 (24–29.4)	26.4 (23.7–29.9)		27.7 (24.3–41.5)	27.32 (24.6–31.7)	17.72 (24.3–31.4)	0.756
Male sex, %	68	63.8	69.3	0.092	70.0	29.8	70.2	0.085
Race, %				0.228				
White	83.2	86.2	82.3		86.9	89.2	86.9	0.807
Black	3.2	1.9	3.6		8.6	9.6	8.5	
Other	13.6	11.9	14.1					
Primary indication for Tx, %				0.092	4.5	1.2	3.8	0.001
Alcohol	27.9	32.8	26.4		16.4	20.5	16.2	
NAFLD	5.5	4.5	5.8		6.6	3.6	6.7	
HCV	18.9	13.4	20.6		29.7	18.1	30	
HBV	5	4.9	5		2.2	2.4	2.2	
Cryptogenic	3	3.7	2.8		4.7	2.5	4.7	
PBC/PSC/AIH	14.8	12	15.6		8.2	18	8	
Primary hepatic malignancy	10.5	15	9.1		13.6	7.2	13.7	
HCC cirrhotic	10	14.6	8.6		8.1	6.0	8.1	
HCC noncirrhotic	0.3	0.4	0.3		4.6	0	4.6	
Other	0.2	0	0.2		0.9	1.2	1	
UKELD	55 (48–61)	52 (50–56)	54 (50–57)	0.005				
Missing data, %	4	1	3					
MELD	15 (11–19)	14 (11–18)	15 (11–19)	0.422	17 (12–23)	11 (16–20)	17 (12–23)	0.042
Missing data, %	4	1	3		0.5	4.8	0.8	
Urgency status, %				0.120				0.869
Super urgent (US status 1A)		0	0.9		2.2	2.4	2.1	
Inpatient at time of Tx, %	10.8	10.5	10.9	0.867	20.2	13.2	20.4	0.244
In ICU					7.4	3.6	7.5	
Hospitalized, non-ICU					12.8	9.6	12.9	
Not hospitalized	89.2	89.5	89.1		79.8	86.7	79.6	
Hemodialysis before Tx, %	4	3	4.4	0.320	4.9	1.2	5	<0.001
DCD volume tertile, %				<0.001				0.005
HV	56.7	77.2	50.6		73.0	88.0	72.6	
MV	33.7	19	38.1		22.3	12.0	22.6	
LV	9.5	3.7	11.3		4.7	0.0	4.8	
Tx region				<0.001				<0.001
Waiting time, d	85.5 (33–184.8)	100 (35–222)	83 (32–177.8)	0.051	101 (29–296.3)	56 (20–200)	102 (29–298)	0.056

[a]Continuous variables were represented as median (IQR).

AIH, autoimmune hepatitis; BMI, body mass index; D, donor; DCD, donation after cardiac death; HBV, hepatitis B; HCC, hepatocellular carcinoma; HCV, hepatitis C; HV, high volume; ICU, intensive care unit; IQR, interquartile range; LV, low volume; MELD, Model for End-Stage Liver Disease; MV, medium volume; NAFLD, nonalcoholic fatty liver disease; NHSBT, National Health Service Blood and Transplant; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SRTR, Scientific Registry of Transplant Recipients; Tx, transplant; UKELD, United Kingdom End-Stage Liver Disease

The Donor Age Group Effect on the UK and the US DCD LT Data Sets

In the United Kingdom, DCD donors were almost uniformly distributed across the age groups: 22.1% of the UK DCD donors aged ≤30. In the United States, DCD donation decreased with advancing age groups (Table 3). Almost half (44.3%) of the US DCD donors were 30 y or younger (Table 3). Only 15.1% of US DCD donors were >50 y, contrary to 45.8% in the United Kingdom. Only about 1 in 40 US DCD donors were above 60 y (D >60) compared with >1 in 5 in the United Kingdom (Table 3). Figure 1 illustrates the Kaplan-Meier graft survival curves for the different donor age groups for the respective national DCD cohorts. In the United Kingdom (Figure 1A), LTs from donors ≤30 y had better graft survival compared with all other donor age groups (reference: donors aged >60, graft loss hazard ratio [HR] 0.528, $P = 0.002$; Table 3). In the US cohort (Figure 1B), donor age ≤30 or ≤40 y were associated with better graft survival (reference donors aged >60, HR, 0.574, $P < 0.001$, and HR, 0.693, $P = 0.027$, respectively; Table 3). In the United States, there was no significant difference in the graft survival between donors aged 41 to 50 and 50 to 60 (reference donors aged >60, HR, 0.908, $P = 0.566$; Table 3).

UK Versus US DCD Donor Graft Survival

Although US DCD graft survival has been improving, for the 15-y period studied, DCD graft survival in the United Kingdom has been overall higher (log-rank, $P < 0.001$, respectively, Figure 2). This DCD graft survival difference has diminished over the most recent years (unpublished data). Kaplan-Meier comparison of D >60 versus D ≤60 graft survivals for each national cohort are illustrated in Figure 3. In the UK cohort (Figure 3A), graft survival was similar in 1 (87.3% versus 87.3%), 5 (78.2% versus 80.5%), and 10 y (76.2% versus 78.6%; $P = 0.312$). In the United States (Figure 3B), graft survival was worse in D >60 at 1, 5, and 10 y (69.9%, 51.8%, 42.2% versus 81.7%, 68.6%, and 63.0% for D >60 versus D ≤60, respectively; $P = 0.005$). Kaplan-Meier comparison of the D >60 graft survival between the 2 countries is shown in Figure 4. Overall D >60 UK graft survival has been higher at each follow-up period (1-, 5-, and 10-y survival was 87.3%, 77.9%, and 75.8% in the United Kingdom versus 68.1%, 51.4%, and 43.1% in the United States, respectively; $P < 0.001$).

Univariable Cox-regression analysis of the harmonized CD cohort identified donor CIT and country (United Kingdom versus United States) as significant DCD LT graft loss risk factors. The United Kingdom was associated with a decreased hazard of graft loss (HR, 0.572, $P = 0.000$), adjusted to the pertinent to this study confounder of donor age >60, and the clinically relevant CIT and WIT (Table 4).

TABLE 3.

Graft loss univariable Cox-regression analysis on US and UK DCD donor age groups

	Frequency (%)	Hazard ratio	95% CI	*P*
UK DCD donor age groups				
Donor age group,[a] y				
≤30	256 (22.1)	0.528	0.350-0.799	0.002
31–40	153 (13.2)	0.869	0.571-1.324	0.514
41–50	236 (20.4)	1.022	0.712-1.427	0.907
51–60	268 (23.2)	0.987	0.694-1.405	0.944
>60	261 (22.6[b])	Reference		
US DCD donor age groups				
Donor age group,[a] y				
≤30	1505 (44.3)	0.574	0.419-0.784	<0.001
31–40	652 (19.2)	0.693	0.500-0.960	0.027
41–50	736 (21.7)	0.768	0.558-1.058	0.106
51–60	429 (12.7)	0.908	0.652-1.263	0.566
>60	83 (2.4[b])	Reference		

[a]Unadjusted.
CI, confidence interval; DCD, donation after circulatory death.

DISCUSSION

This present report is a large-scale retrospective analysis of DCD LTs performed in the United Kingdom and United States over a 15-y period. In the United States, DCD donors accounted for 4.9% of deceased donor LTs (data not shown), while in the United Kingdom, the DCD rate approximated 30% of LTs performed.[20,21] Transplant systems continue to challenge the established upper donor age limits, pushing the age cutoff beyond the US conventional 50 y.[11,17,19,21] Contrary to the United Kingdom, US transplant centers, perhaps in response to highly publicized previous predictive models,[5,32,39] have erred away from the use of older DCD donors, with sharp decline in the DCD donor usage over the age of 50 (Table 3), despite the ever-increasing need for more grafts and recent reports of improved DCD outcomes in the United States.[2,8]

In both systems, higher DCD volume centers were more proactive in using elderly grafts. In the United Kingdom, irrespective of the donor location, the organs were transferred in a timely fashion to transplant centers, thus maximizing graft utilization while achieving similar survival, despite using a an extended criteria graft, therefore, optimizing donation beneficence.[11]

Comparing the UK and US DCD practice has highlighted a few key points. In the United States, DCD rates showed remarkable inter-regional variation. This may be attributed to a myriad of reasons, starting with logistic limitations inherent to US geography, often necessitating long and expensive flights for pursuing a higher risk graft that might not even progress. It is common US practice for the accepting center to perform the DCD donor operation. However, this increases the mileage and time expenditure for each successful DCD recovery, and as a result, the costs, logistic complexity, and travel-related hazards. What is more, current reimbursement policies reflect poorly these increased costs associated with DCD utilization.[40] The accepting center performing its own DCD liver recoveries also potentially limits surgeon exposure to DCD procurements, which may negatively impact the DCD procurement team's learning curve, especially if the receiving center has a low DCD volume practice.[41] In contrast, UK DCD procurements are performed by the on-call procurement NORS team, that is organized centrally according to the geography of the donor in the United Kingdom, rather than associated with the implanting unit.[42] This facilitates

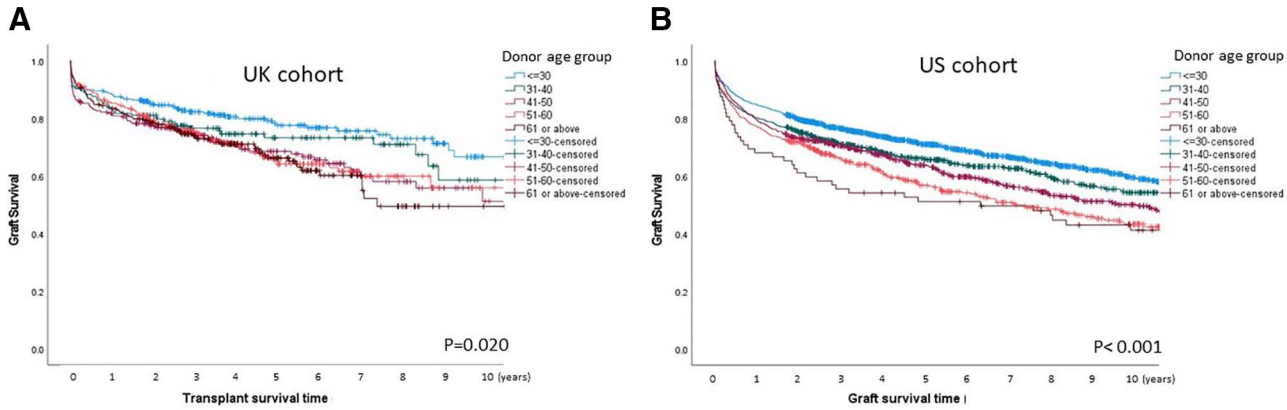

FIGURE 1. Kaplan-Meier liver graft survival curves for the different donor age groups in the United Kingdom (UK) and the United States (US). A, UK cohort; B, US cohort. In the UK cohort, donors ≤30 y had better graft survival compared with all other donor age groups. In the US cohort, donor age ≤30 or ≤40 y was associated with better graft survival. In the US, there was no significant difference in the graft survival between donors aged 41–50 and 50–60 y (reference donors aged >60, hazard ratio [HR], 0.908, $P = 0.566$; Table 4).

a more uniform, standardized DCD procurement practice (standard surgeon-lead accompanied by the trainee(s), the team perfusionist(s), own operating and cannulation instrument equipment, own scrub technicians, even the same pilot/driver).[42] This practice facilitates replicable DCD donor outcomes, optimizes efficiency and transferability of the DCD procurement skills while reducing the costs of logistics and long-travel related risks for the surgical team. This success of this UK DCD recovery model perhaps underlines the need for reaching a consensus in US DCD recovery practices, a notion supported by recent national surveys undertaken by US transplant surgeons and the Organ Procurement Organization leadership.[43] Organization of the donor service may explain, at least partially, the country risk factor identified in our multivariable analysis. Furthermore, DCD organs in the United Kingdom are generally allocated in a center-based fashion, which allows for more flexibility in donor-recipient matching. UK LT centers typically maintain DCD candidate waitlists, i.e. list with patients eligible for DCD organs, therefore, optimizing an expedient allocation to the appropriate candidate minimizing graft waste and ischemic time.

The current US DCD procurement practice, perhaps in conjunction with limitations of MELD-allocation driven systems and of the recently implemented acuity circles policy (allocation sequence based on a series of concentric

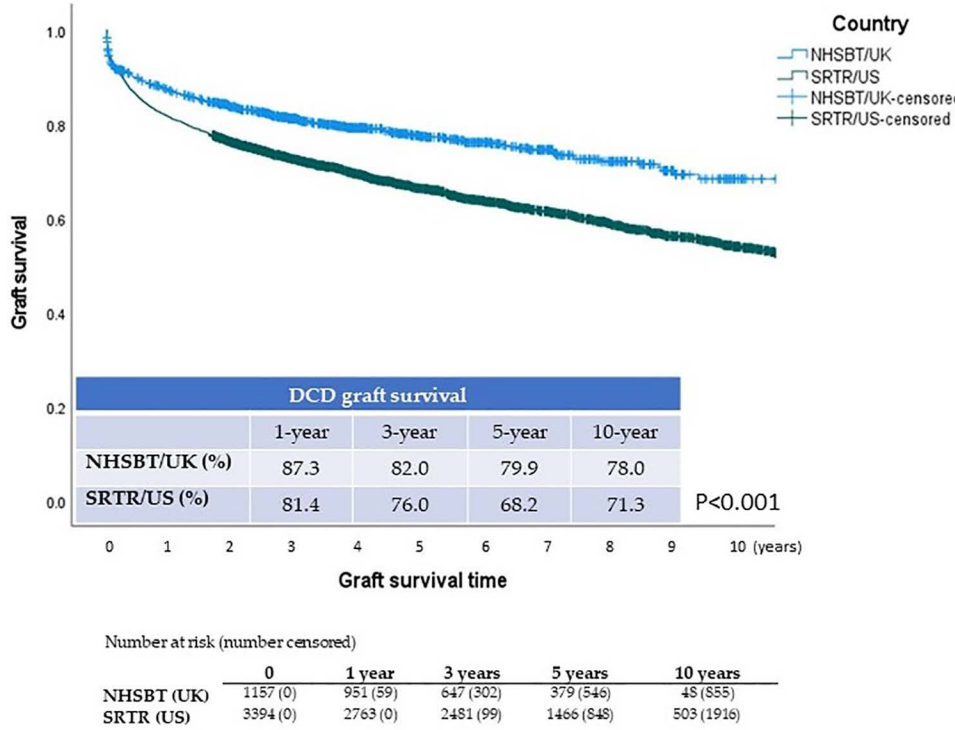

FIGURE 2. Kaplan-Meier liver graft survival curves in the United Kingdom (UK) vs the United States (US) 2001–2015. During the period studied (2010–2015), overall 1-, 3-, 5-, and 10-y donation after circulatory death (DCD) graft survival was higher in the UK ($P < 0.001$). DCD graft survival difference across the 2 countries diminished over the most recent years (data not shown). NHSBT, National Health Service Blood and Transplant; SRTR, Scientific Registry of Transplant Recipients.

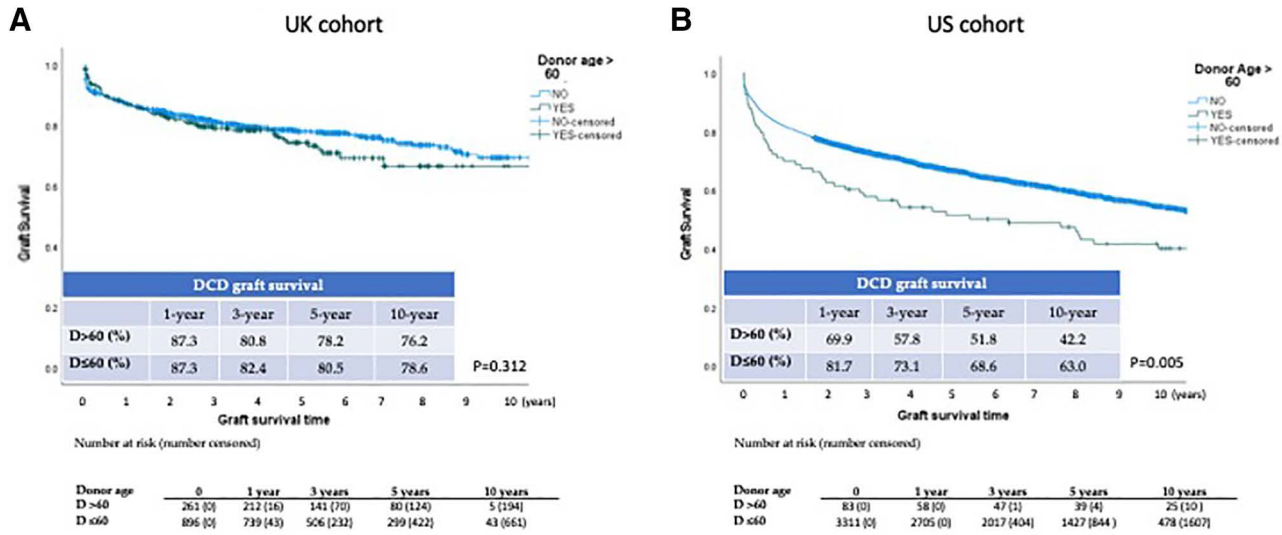

FIGURE 3. Kaplan-Meier donor (D) >60 y vs D ≤60 y donation after circulatory death (DCD) liver graft survival curves in the United Kingdom (UK) and the United States (US). A, UK D >60 y. D ≤60 y 1-, 3-, 5-, and 10-y survival was similar ($P = 0.312$). B, US graft survival of the respective follow-up periods was worse in D >60 y vs D ≤60 y ($P = 0.005$).

circles originating from the donor hospital),[44-48] has contributed to a greater likelihood of nonpursuing or maintaining a lower threshold to discard DCD opportunities, particularly at higher median MELD zones, even for local donors. These effects are likely to be exaggerated with higher risk DCDs, that is, the older DCD donor.

Our study has shown better overall DCD LT outcomes in the United Kingdom versus the United States, a finding supported by recently published large international comparative analyses.[9,24] Contrary to the United Kingdom, US DCD utilization drastically drops after the age of 50 (Table 3). US D >60 donors have worse outcomes compared with the United Kingdom (Figure 4). Nonetheless, the US 5-y survival using D >60 DCD grafts has been >50%, which makes it arguably preferential to use such grafts as opposed to transplant candidates dying on the waiting list. Lastly, given the similar outcomes on donors aged 41 to 50 versus 51 to 60 seen in both national cohorts and the growing need for organs, our findings are supportive for an extension of the upper US DCD donor age cutoff from 50 to 60 y on otherwise suitable donors and after proper donor-recipient matching.

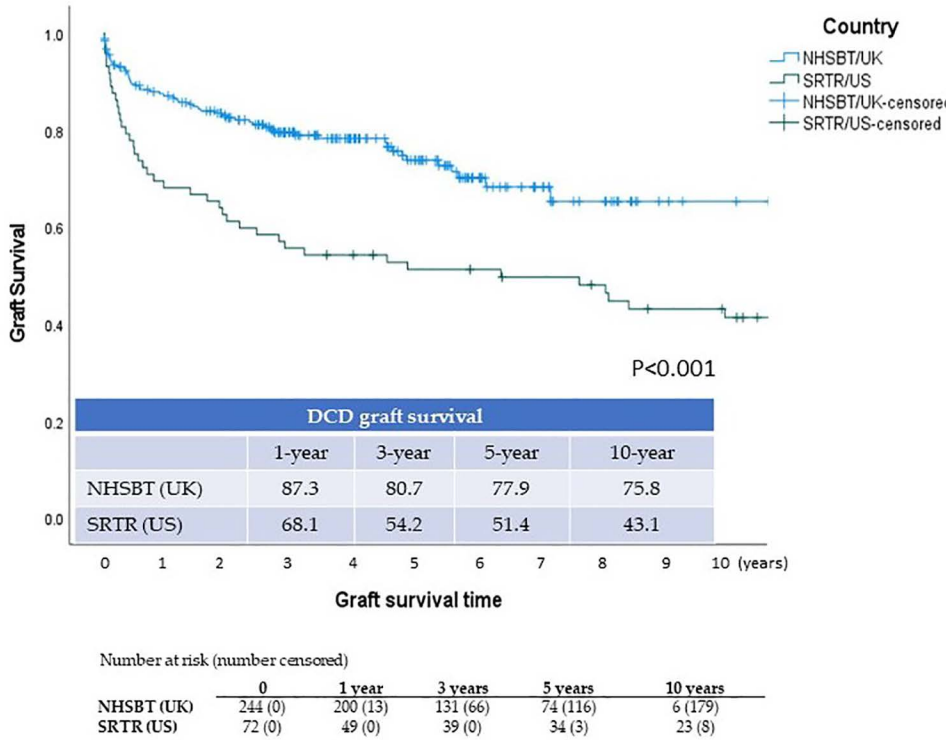

FIGURE 4. Kaplan-Meier liver graft survival curves from donors >60 y in the United Kingdom (UK) vs the United States (US). One-, 3-, 5-, and 10-y donation after circulatory death (DCD) graft survival from donors >60 y was higher in the UK ($P < 0.001$). NHSBT, National Health Service Blood and Transplant; SRTR, Scientific Registry of Transplant Recipients.

TABLE 4.

Causal Cox-regression graft survival analysis of harmonized UK and US cohorts

	Univariable Cox-regression			Multivariable cox-regression		
	HR	95% CI	*P*	HR	95% CI	*P*
UK vs US	0.637	0.556-0.728	<0.001	0.572	0.473-0.691	<0.001
Donor age >60 y	0.987	0.808-1.207	0.903	0.723	0.570-0.918	0.008
Cold ischemia time	1.051	1.037-1.065	<0.001	1.050	1.036-1.064	<0.001
Warm ischemia time	0.998	0.992-1.003	0.409	1.003	0.998-1.009	0.240

CI, confidence interval; DCD, donation after circulatory death; HR, hazard ratio.

Our study has several limitations inherent to its retrospective nature: selection bias, unaccounted confounders, and the potential for misclassification due to the differences in DCD definitions used in the United States and the United Kingdom. For example, the total donor hepatectomy time, which is now an established DCD outcome predictor,[49-52] was not universally retrievable over the time period of the analysis and, therefore, not included. Similarly, ischemic cholangiopathy risk has not been studied because of insufficient data and variation in defining and monitoring standards across the transplant programs and systems. International comparisons come with difficulties, such as bias in the ascertainment of death or graft loss, resulting in systematic under-reporting of posttransplant events and, therefore, artificial estimates of survival.[53,54] Another methodological limitation is differences in data quality; however, in both systems, transplant data collection is mandatory and subject to robust quality controls to ensure the data validity and ascertainment of events.[24]

Our analysis spanned a 15-y period, over which period DCD and LT practice have continually evolved.[8,55] Machine perfusion (MP) technologies undeniably hold promise for safer and improved utilization of expanded criteria donors, such as the older DCD livers.[56-59] However, for the period studied, the impact of MP implementation was minimal, since the first normothermic MP randomized control trial started in the United Kingdom in the final year of the present retrospective analysis, and MP use in the United States started after 2015.[60]

CONCLUSIONS

Present data demonstrate lower use and poorer outcomes of DCD LT donors aged >60 in the United States versus the United Kingdom. Nonetheless, data also indicate similar survival using older donors aged ≤60, supporting an extension to the current US DCD age cutoff. Pushing the donor age limits after appropriate donor and recipient selection and in experienced centers should be encouraged.

REFERENCES

1. Kim WR, Lake JR, Smith JM, et al. OPTN/SRTR 2017 Annual Data Report: Liver. *Am J Transplant*. 2019;19 (Suppl 2):184–283.
2. Haugen CE, Holscher CM, Luo X, et al. Assessment of trends in transplantation of liver grafts from older donors and outcomes in recipients of liver grafts from older donors, 2003-2016. *JAMA Surg*. 2019;154:441–449.
3. Washburn K, Pomfret E, Roberts J. Liver allocation and distribution: possible next steps. *Liver Transpl*. 2011;17:1005–1012.
4. Halazun KJ, Quillin RC, Rosenblatt R, et al. Expanding the margins: high volume utilization of marginal liver grafts among >2000 liver transplants at a single institution. Ann Surg. 2017;266:441–449.
5. Foley DP, Fernandez LA, Leverson G, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. *Ann Surg.* 2005;242:724–731.
6. Mateo R, Cho Y, Singh G, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. *Am J Transplant*. 2006;6:791–796.
7. de Vera ME, Lopez-Solis R, Dvorchik I, et al. Liver transplantation using donation after cardiac death donors: long-term follow-up from a single center. *Am J Transplant*. 2009;9:773–781.
8. Croome KP, Lee DD, Keaveny AP, et al. Improving national results in liver transplantation using grafts from donation after cardiac death donors. *Transplantation*. 2016;100:2640–2647.
9. Wallace D, Cowling TE, Suddle A, et al. National time trends in mortality and graft survival following liver transplantation from circulatory death or brainstem death donors. *Br J Surg*. 2021;109:79–88.
10. University of California Berkeley. *Statistical Abstract of the United States*: 2010. Available at: https://www.census.gov/library/publications/2009/compendia/statab/129ed.html.
11. Giorgakis E, Khorsandi SE, Mathur AK, et al. Comparable graft survival is achievable with the usage of donation after circulatory death liver grafts from donors at or above 70 years of age: a long-term UK national analysis. *Am J Transplant*. 2021;21:2200–2210.
12. Dasari BVM, Schlegel A, Mergental H, et al. The use of old donors in liver transplantation. *Best Pract Res Clin Gastroenterol*. 2017;31:211–217.
13. Durand F, Levitsky J, Cauchy F, et al. Age and liver transplantation. *J Hepatol*. 2019;70:745–758.
14. Croome KP, Muiesan P, Taner CB. *Donation After Circulatory Death (DCD) Liver Transplantation*. 1st ed. Springer Nature Switzerland; 2020.
15. Schlegel A, Dutkowski P. Impact of machine perfusion on biliary complications after liver transplantation. *Int J Mol Sci*. 2018;19:E3567.
16. Schlegel A, Kalisvaart M, Isaac J, et al. Reply to: "DCD consensus and futility in liver transplantation". *J Hepatol*. 2018;69:257–258.
17. Croome KP, Mathur AK, Lee DD, et al. Outcomes of donation after circulatory death liver grafts from donors 50 years or older: a multicenter analysis. *Transplantation*. 2018;102:1108–1114.
18. Foley DP, Fernandez LA, Leverson G, et al. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. *Ann Surg*. 2011;253:817–825.
19. Cascales-Campos PA, Ferreras D, Alconchel F, et al. Controlled donation after circulatory death up to 80 years for liver transplantation: pushing the limit again. *Am J Transplant*. 2020;20:204–212.
20. Laing RW, Scalera I, Isaac J, et al. Liver transplantation using grafts from donors after circulatory death: a propensity score-matched study from a single center. *Am J Transplant*. 2016;16:1795–1804.
21. Schlegel A, Scalera I, Perera MTPR, et al. Impact of donor age in donation after circulatory death liver transplantation: Is the cutoff "60" still of relevance? *Liver Transpl*. 2018;24:352–362.
22. Schlegel A, Kalisvaart M, Scalera I, et al. The UK DCD risk score: a new proposal to define futility in donation-after-circulatory-death liver transplantation. *J Hepatol*. 2018;68:456–464.
23. Schlegel A, Kalisvaart M, Isaac J, et al. Reply to: "Redefining futility in DCD liver transplantation in the era of novel perfusion technologies". *J Hepatol*. 2018;68:1328–1330.
24. Ivanics T, Wallace D, Abreu P, et al. Survival after liver transplantation: an international comparison between the United States and the United Kingdom in the years 2008–2016 [Epub ahead of print. November 9, 2021]. Transplantation. doi:10.1097/TP.0000000000003978
25. NHS Blood and Transplant *Organ Specific Reports: 2018-2019*. Available at: https://www.odt.nhs.uk/statistics-and-reports/organ-specific-reports/. Accessed on February 11, 2020.

26. Available at: Organ Procurement and Transplantation Network. About the OPTN. Available at: https://optn.transplant.hrsa.gov/governance/about-the-optn/. Accessed April 16, 2019.
27. The Scientific Registry of Transplant Recipients. *Health Resources and Services Administration.* Available at: https://srtr.transplant.hrsa.gov.Accessed April 16, 2019.
28. Collett D, Friend PJ, Watson CJ. Factors Associated with short- and long-term liver graft survival in the United Kingdom: development of a UK donor liver index. *Transplantation*. 2017;101:786–792.
29. Thuong M, Ruiz A, Evrard P, et al. New classification of donation after circulatory death donors definitions and terminology. *Transpl Int*. 2016;29:749–759.
30. Giorgakis E, Khorsandi SE, Jassem W, et al. DCD consensus and futility in liver transplantation. *J Hepatol*. 2018;69:255–256.
31. Neuberger J, Gimson A, Davies M, et al; Liver Advisory Group; UK Blood and Transplant. Selection of patients for liver transplantation and allocation of donated livers in the UK. *Gut*. 2008;57:252–257.
32. Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant*. 2006;6:783–790.
33. Kruskal W, Wallis A. Use of ranks in one-criterion variance analysis. *J Am Stat Assoc*. 2012;47:583–621.
34. Siegel C. *Nonparametric Statistics for the Behavioral Sciences. 2nd ed.* McGraw–Hill; 1988.
35. Dodge Y. *The Concise Encyclopedia of Statistics*. 1st ed. Springer; 2009.
36. Melcher M. UK DCD risk calculator.
37. Schooling CM, Jones HE. Clarifying questions about "risk factors": predictors versus explanation. *Emerg Themes Epidemiol*. 2018;15:10.
38. Office for Human Research Protections. *Human Subject Regulations Decision Charts*. Available at: https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts/index.html. Accessed November 10, 2021.
39. Mathur AK, Heimbach J, Steffick DE, et al. Donation after cardiac death liver transplantation: predictors of outcome. *Am J Transplant*. 2010;10:2512–2519.
40. Montgomery JR, Highet A, Hobeika MJ, et al. Going the distance for procurement of donation after circulatory death livers for transplantation—Does reimbursement reflect reality? *Clin Transplant*. 2020;34:e13780.
41. Giorgakis E, Burdine L, Khorsandi S, et al. Impact of center volume on donation after circulatory death liver transplant outcomes. A retrospective scientific registry of transplant recipients analysis. Conference abstract. *Transplantation*. 2019;103:30–30.
42. NHS Blood and Transplant. *National Protocols, Policies and Reports.* Available at: https://www.odt.nhs.uk/retrieval/policies-and-nors-reports/.Accessed April 13, 2022.
43. Hobeika MJ, Glazner R, Foley DP, et al. A step toward standardization: results of two national surveys of best practices in donation after circulatory death liver recovery and recommendations from The American Society of Transplant Surgeons and Association of Organ Procurement Organizations. *Clin Transplant*. 2020;34:e14035.
44. Vagefi PA, Bertsimas D, Hirose R, et al. The rise and fall of the model for end-stage liver disease score and the need for an optimized machine learning approach for liver allocation. *Curr Opin Organ Transplant*. 2020;25:122–125.
45. Halazun KJ, Mathur AK, Rana AA, et al. One size does not fit all–regional variation in the impact of the share 35 liver allocation policy. *Am J Transplant*. 2016;16:137–142.
46. Haugen CE, Ishaque T, Sapirstein A, et al. Geographic disparities in liver supply/demand ratio within fixed-distance and fixed-population circles. *Am J Transplant*. 2019;19:2044–2052.
47. Ivanics T, Vianna R, Kubal CA, et al. Impact of the acuity circle model for liver allocation on multivisceral transplant candidates. *Am J Transplant*. 2022;22:464–473.
48. Organ Procurement and Transplantation Network. *Acuity Circles Frequently Asked Questions.* Available at: https://optn.transplant.hrsa.gov/media/3612/acuity-circles-faq.pdf. Accessed November 14, 2021.
49. Khorsandi SE, Giorgakis E, Vilca-Melendez H, et al. Developing a donation after cardiac death risk index for adult and pediatric liver transplantation. *World J Transplant*. 2017;7:203–212.
50. Farid SG, Attia MS, Vijayanand D, et al. Impact of donor hepatectomy time during orgn procurement in donation after circulatory death liver transplantation: the United Kingdom experience. *Transplantation*. 2019;103:e79–e88.
51. Jochmans I, Fieuws S, Tieken I, et al. The impact of hepatectomy time of the liver graft on post-transplant outcome: a eurotransplant cohort study. *Ann Surg*. 2019;269:712–717.
52. Boteon APCS, Schlegel A, Kalisvaart M, et al. Retrieval practice or overall donor and recipient risk: what impacts on outcomes after donation after circulatory death liver transplantation in the United Kingdom? *Liver Transpl*. 2019;25:545–558.
53. Dawwas MF, Gimson AE, Lewsey JD, et al. Survival after liver transplantation in the United Kingdom and Ireland compared with the United States. *Gut*. 2007;56:1606–1613.
54. Gallagher AM, Dedman D, Padmanabhan S, et al. The accuracy of date of death recording in the Clinical Practice Research Datalink GOLD database in England compared with the Office for National Statistics death registrations. *Pharmacoepidemiol Drug Saf*. 2019;28:563–569.
55. Monbaliu D, Pirenne J, Talbot D. Liver transplantation using donation after cardiac death donors. *J Hepatol*. 2012;56:474–485.
56. Dutkowski P, Polak WG, Muiesan P, et al. First comparison of hypothermic oxygenated perfusion versus static cold storage of human donation after cardiac death liver transplants: an international-matched case analysis. *Ann Surg*. 2015;262:764–770.
57. Schlegel A, Muller X, Kalisvaart M, et al. Outcomes of DCD liver transplantation using organs treated by hypothermic oxygenated perfusion before implantation. *J Hepatol*. 2019;70:50–57.
58. Sutherland AI, Oniscu GC. Challenges and advances in optimizing liver allografts from donation after circulatory death donors. *J Nat Sci Biol Med*. 2016;7:10–15.
59. Weissenbacher A, Vrakas G, Nasralla D, et al. The future of organ perfusion and re-conditioning. *Transpl Int*. 2019;32:586–597.
60. Nasralla D, Coussios CC, Mergental H, et al; Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature*. 2018;557:50–56.