11-9-2021

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Survival After Liver Transplantation: An International Comparison Between the United States and the United Kingdom in the Years 2008–2016

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Background. Compared with the United States, risk-adjusted mortality in the United Kingdom has historically been worse in the first 90 d following liver transplantation (LT) and better thereafter. In the last decade, there has been considerable change in the practice of LT internationally, but no contemporary large-scale international comparison of posttransplant outcomes has been conducted. This study aimed to determine disease-specific short- and long-term mortality of LT recipients in the United States and the United Kingdom. **Methods.** This retrospective international multicenter cohort study analyzed adult (≥18 y) first-time LT recipients between January 2, 2008, and December 31, 2016, using the Organ Procurement and Transplantation Network/United Network for Organ Sharing and the UK Transplant Registry databases. Time-dependent Cox regression estimated hazard ratios (HRs) comparing disease-specific risk-adjusted mortality in the first 90 d post-LT, between 90 d and 1 y, and between 1 and 5 y. **Results.** Forty-two thousand eight hundred seventy-four US and 4950 UK LT recipients were included. The main LT indications in the United States and the United Kingdom were hepatocellular carcinoma (25.4% and 24.9%, respectively) and alcohol-related liver disease (20.3% and 27.1%, respectively). There were no differences in mortality during the first 90 d post-LT (reference: United States; HR, 0.96; 95% confidence interval [CI], 0.82–1.12). However, between 90 d and 1 y (HR, 0.71; 95% CI, 0.59–0.85) and 1 and 5 y (HR, 0.71; 95% CI, 0.63–0.81]) the United Kingdom had lower mortality. The mortality differences between 1 and 5 y were most marked in hepatocellular carcinoma (HR, 0.71; 95% CI, 0.58–0.88) and alcohol-related liver disease patients (HR, 0.64; 95% CI, 0.45–0.89). **Conclusions.** Risk-adjusted mortality in the United States and the United Kingdom was similar in the first 90 d post-LT but better in the United Kingdom thereafter. International comparisons of LT may highlight differences in healthcare delivery and help benchmarking by identifying modifiable factors that can facilitate improved global outcomes in LT.

(*Transplantation* 2021;00: 00–00).

Received 21 May 2021. Revision received 23 August 2021.
Accepted 20 September 2021.

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The funder of the study, National Institute for Health Research, had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. D.W., K.W., and J.v.d.M. had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.
The UK Liver Transplant Audit is supported by the National Health Service (NHS) National Specialized Commissioning Group and NHS England.
D.W. is funded by a Doctoral Research Fellowship from the National Institute of Health Research. J.v.d.M. is partly supported by the NHS National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care North Thames at Bart's Health NHS Trust. The other authors declare no conflicts of interest.
T.I., D.W., and J.v.d.M. participated in conception of project, literature review, data analysis, interpretation of results, and write-up of the article. P.A. and M.P.A.W.C. participated in conception of project, literature review, interpretation of results, and write up of the article. C.C. and N.H. participated in interpretation of results and write-up of the article. T.C. and K.W. participated in conception of the project, data analysis, interpretation of results, and write-up of the article. N.M. and G.S. conception of project, interpretation of results, and write-up of article.
This report is independent research arising from a Doctoral Research Fellowship (DRF-2016-09-132) awarded to David Wallace and supported by the National Institute for Health Research. The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the National Institute for Health Research, Health Education England, or the Department of Health.
Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).
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ISSN: 0041-1337/20/00XXX-00

DOI: 10.1097/TP.0000000000003978

<zdoi;10.1097/TP.0000000000003978>

INTRODUCTION

International comparisons of surgical mortality offer insight into the disparities in access to and delivery of surgical treatments.[1–6] Based on such comparisons, reappraising national healthcare practices can afford opportunities for policy and practice change that have, in the past, translated into population-level improvements in postoperative outcomes.[1,2]

Inevitably, many factors drive outcomes following surgery, and many of these are not readily measurable.[1,2,5] This makes benchmarking international variations in surgical outcomes challenging.[4] However, in contrast to other surgical specialties, the standardized nature of liver transplantation (LT) practice makes it well placed for undertaking reliable international comparisons of surgical mortality.[1]

Unfortunately, difficulties in obtaining, combining, and analyzing data sets from different countries mean very few reports describing comparisons of LT outcomes exist.[1] In the only previous comparison between the United States and the United Kingdom, posttransplant mortality in 47 791 LT recipients between 1994 and 2005 was significantly worse in the United Kingdom in the first 90 d after surgery and then better thereafter.[1] However, more than a decade on, further time-dependent analysis by our international collaboration has identified that there have been era-specific improvements in both the short- and long-term outcomes of recipients who received an LT in the United Kingdom.[6] Consequently, a contemporary evaluation is warranted.

Given that international comparisons of healthcare outcomes enable policymakers and clinicians to identify areas of healthcare delivery where countries could learn from each other and that era-specific improvement in posttransplant mortality have been observed,[1–5] we used a uniquely harmonized combined data set to carry out a disease-specific time-dependent comparison of short- and long-term patient mortality following LT in the United Kingdom and the United States between 2008 and 2016.

MATERIALS AND METHODS

Databases

The UK Transplant Registry and the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS) data set were used for this analysis. Descriptions of these databases and evidence of their completeness, accuracy, and reliability have been published elsewhere.[1,5,6]

The study population included all patients aged 18 y or older who received a first-time elective LT in the 2 countries between January 1, 2008, and December 31, 2016 (Figure 1). The study's start date was chosen to coincide with the introduction in the United Kingdom in 2008 of organ offering policies based on predicted waiting list mortality. In the same time period in the United States, the Model for End-Stage Liver Disease (MELD) score-based allocation, the Share 15 and Share 35 scheme, and the MELD-Sodium allocation system were introduced.[7–9] Patients who underwent LT for liver cancer types other than hepatocellular carcinoma (HCC) and those who underwent multivisceral, super-urgent, domino, living-related LTs or were transplanted for acute liver failure were excluded. We also excluded patients whose survival data were missing. This study received ethics approval after review from the National Health Service Health Research Authority (IRAS project ID: 218152; CAG reference 17/CAG/0025).

Data Management

The UK Transplant Registry and OPTN/UNOS data sets were harmonized to ensure that liver disease classification and risk factor definitions were comparable.[1] Patients were grouped according to a liver disease classification system (Table S1, SDC, http://links.lww.com/TP/C303) that was first adopted by Roberts et al.[1,10] In the event of multiple diagnoses, patients were assigned to the diagnosis most likely to have influenced their prognosis at the time of transplantation.[1,10] Disease classification was undertaken in a hierarchical order: cancer, hepatitis C virus (HCV) cirrhosis, primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), alcohol-related liver disease (ALD), autoimmune disease (AID), metabolic, and others.[1,10] For example, patients with a coded diagnosis of HCV cirrhosis and a free text diagnosis of HCC were assigned to the HCC category.[1,10] All patients with Wilson disease and Budd-Chiari syndrome were assigned to the metabolic and other liver diseases categories, respectively, regardless of the mode of their disease presentation.[1,10] Transplant center volume was defined as the average number of first-adult single organ LTs, excluding multivisceral and retransplants, performed during the study period at a given center per year.[1]

For multivariable analyses, creatinine was set to 4.0 mg/dL for those with lower values who received renal replacement therapies immediately before transplantation.[1] Implausible values of body mass index (BMI; <10 or >100 kg/m^2), cold ischemic time (CIT; >40 h), serum bilirubin (<0.1 mg/dL), serum creatinine (<0.1 or >15 mg/dL), and serum albumin (<0.7 or >6.0 g/dL) were considered to be missing.[1] The MELD score (calculated using serum creatinine, total serum bilirubin, and international normalized ratio) was used to score the recipients' severity of the liver disease in both the United States and the United Kingdom.[11] Ascites and encephalopathy were considered as dichotomous variables. Recipients' functional status at the time of transplantation was assessed using a modified 3-point scale ranging from "able to carry out normal activity without restriction—high functional status" to "intermediate functional status" and "completely reliant on care—low functional status."[12–14] Values for ethnicity were categorized into White and non-White groups. Donor quality was measured using the Feng Donor Risk Index (DRI) (derived from donor age, sex, height, type [donation after circulatory death donor (DCD) or not], serum bilirubin, smoking history, and whether the liver was split, with larger values representing poorer donor livers).[15] The DRI was included as a variable as it was developed using UNOS data and has subsequently been validated for the Eurotransplant region, where transplant data from the United Kingdom are included.[16,17] CIT was defined as the duration between the start of cold perfusion in the donor to the start of blood flow through the organ in the recipient.[18] In the United States, UNOS/OPTN collects information on death at 6 and 12 mo intervals and validates their data with information from the Centers for Medicare and Medicaid Services and the National Death Index.[19] UNOS links the OPTN data to the Social Security Death Master File to augment ascertainment of candidate and recipient death, and hence does not solely rely on

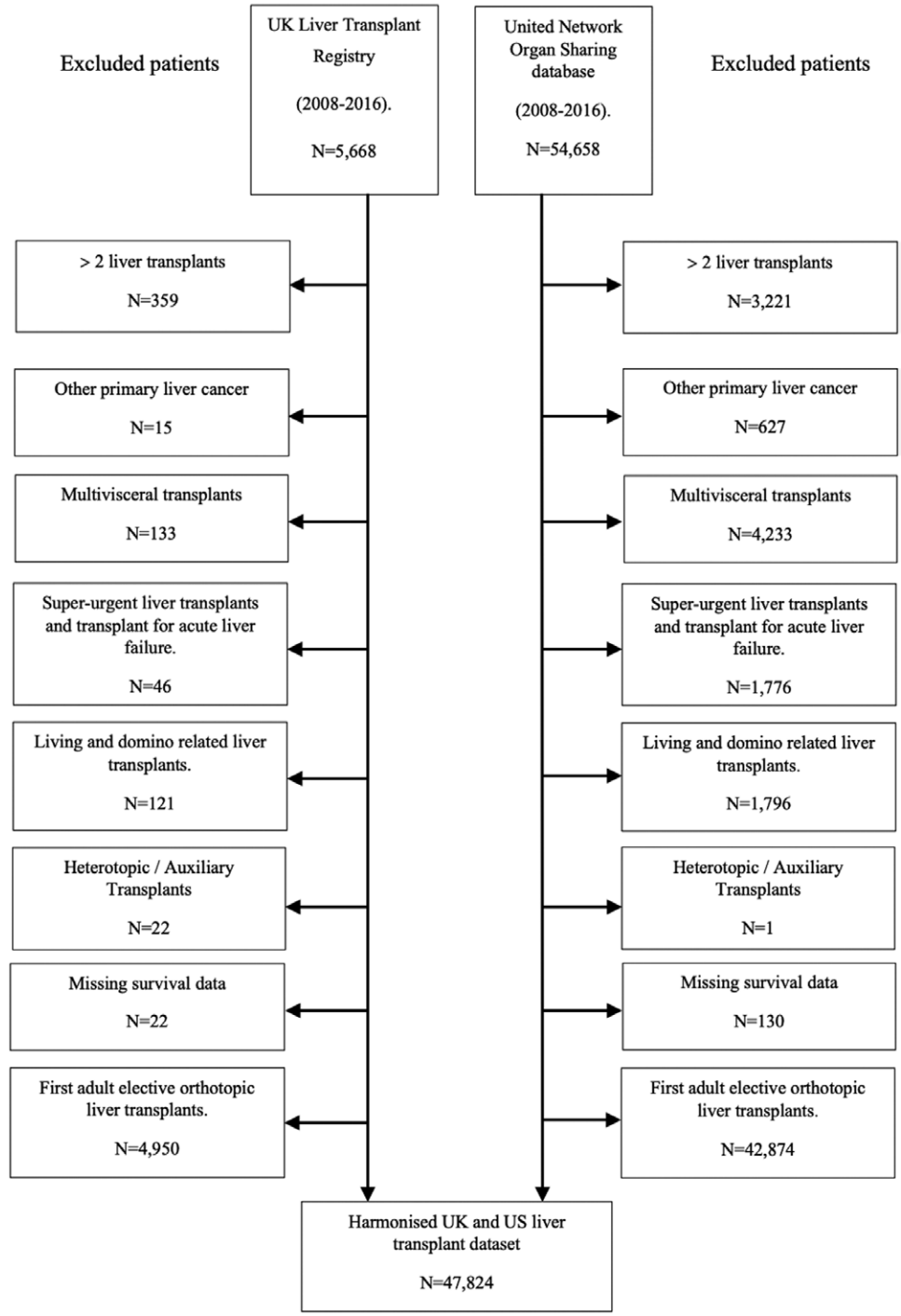

FIGURE 1. Flowchart detailing selection of study population (2008–2016). UK, United Kingdom; US, United States.

individual transplant center reporting as this would lead to inaccuracies if the patients does not continue their follow-up at their original transplant center.[19–21] Death ascertainment in the United Kingdom is closely monitored through center-specific 3-mo follow-up forms submitted centrally to National Health Service Blood and Transplant.

Statistical Analyses

Categorical variables were presented as proportions and compared using chi-square tests, and continuous variables were presented as means with SDs. Patients transplanted for non-HCC indications who were subsequently found to have HCC on explant pathology were analyzed on an intention-to-treat basis and remained in the non-HCC cohorts.

The Kaplan-Meier method was used to compare liver disease-specific patient mortality between the different countries (United Kingdom versus United States). Follow-up data were available until April 7, 2017. The median follow-up time for the United States was 944 d (interquartile range, 346–1820) and for the United Kingdom 1011 d (interquartile range, 370–1796).

Cox regression analysis was used to estimate overall and disease-specific hazard ratios (HRs) indicating the relative

difference in risk of death in the United States versus the United Kingdom in the following periods after LT ("epochs"): the first 90 d, 90 d to 1 y, and beyond the first year. The United States was used as the baseline value with an HR <1, indicating mortality to be higher in the United States compared with the United Kingdom. The analysis was censored at 5 y posttransplantation. Only those clinically plausible recipient and donor risk factors recorded to a comparable degree in both databases with missing values in <10% of the patients were included in the risk-adjusted regression models.[1] These included recipient characteristics: sex, age, ethnicity, BMI (kg/m^2), disease cause, functional status, ascites, encephalopathy, HCV status, MELD, pretransplant renal replacement therapy, previous abdominal surgery, and donor characteristics: sex, age, BMI (kg/m^2), CIT, donor type (DCD/donation after brainstem death), cause of death, ABO match, and graft type. A similar analysis, as for patient survival including risk adjustments for the above-mentioned variables, was performed to investigate risk of graft loss. Adjustment for specific tumor characteristics was not included as comparisons of posttransplantation mortality in HCC patients were made with a cohort of non-HCC patients.[22] Interaction terms were included in the Cox regression models to determine whether the HRs for overall mortality and disease-specific comparison of mortality differed according to the epoch of follow-up time. A sensitivity analysis was performed to assess the impact of the era of transplantation (2008–2011 and 2021–2016). The significance of the interaction term was tested using a global Wald test.

Missing donor and recipient characteristics were imputed using chained equations, creating 10 complete data sets with regression results pooled using Rubin's rules.[23] Stata V15 (StataCorp, College Station, TX) was used for all statistical analyses. A $P < 0.05$ was considered to indicate a statistically significant result.

RESULTS

Clinical Characteristics

Between January 1, 2008, and December 31, 2016, 42 874 adults received a first single organ LT in 134 centers in the United States, whereas 4950 such transplants were performed in 7 centers in the United Kingdom (Table 1).

Compared with recipients in the United Kingdom, LT recipients in the United States were less likely to receive livers from older and from male donors (Table 1). US

TABLE 1.

Donor and recipient characteristics according to country

	Country				
	United States		United Kingdom		
Characteristics	United States (n = 42 874)	Missing, % (n)	United Kingdom (n = 4950)	Missing, % (n)	*P*
Donor					
Female	59.5% (25 529)	0.0% (0)	46.2% (2289)	0.0% (0)	<0.001
Age, mean (SD), y	42.1 (16.6)	0.0% (0)	49.3 (16.0)	0.0% (0)	0.02
BMI, mean (SD), kg/m^2	27.8 (6.4)	0.1% (52)	26.4 (4.9)	0.2% (10)	<0.001
Trauma as cause of death	32.5% (13 654)	2.1% (902)	8.0% (396)	0.0% (0)	<0.001
DCD donors	5.8% (2502)	0.04% (17)	24.0% (1188)	0.0% (0)	<0.001
Segmental graft type	1.3% (555)	0.0% (0)	8.1% (399)	0.0% (0)	<0.001
CIT, mean (SD), min	378 (167)	0.8% (354)	517 (163)	8.0% (400)	<0.001
ABO match—identical	94.5% (40 522)	0.0% (0)	98.5% (4874)	0.0% (0)	<0.001
DRI, mean (SD)	1.44 (0.28)	0.0% (0)	1.72 (0.40)	1.7% (84)	<0.001
Recipient					
Female	31.5% (13 523)	0.002% (1)	32.8% (1622)	0.0% (0)	0.08
Age, mean (SD), y	55.6 (9.6)	0.0% (0)	53.0 (11.2)	0.0% (0)	<0.001
Non-White ethnicity	28.4% (12 158)	0.0% (0)	12.5% (618)	0.04% (2)	<0.001
HCC indication for transplant	29.3% (12 550)	0.0% (0)	25.8% (1276)	0.0% (0)	<0.001
BMI, mean (SD), kg/m^2	28.7 (5.7)	0.02% (9)	27.3 (5.2)	0.1% (5)	<0.001
MELD,[a] mean (SD)	21.7 (10.7)	0.1% (45)	16.5 (6.7)	0.7% (36)	<0.001
Waiting list time (d)	278.8 (515.6)	0.0% (0)	152.3 (189.3)	0.0% (0)	<0.001
Blood group O	44.9% (19 239)	0.0% (0)	41.3% (2045)	0.0% (0)	<0.001
Dependent functional status level 3[b]	21.9% (9270)	1.2% (510)	14.1% (690)	1.3% (64)	<0.001
Ascites	74.4% (31 910)	0.0% (0)	53.6% (2643)	0.3% (17)	<0.001
Encephalopathy	61.5% (26 363)	0.0% (0)	31.0% (1510)	1.7% (83)	<0.001
Presence of anti-HCV antibodies	42.9% (16 974)	2.0% (844)	18.1% (679)	0.4% (21)	<0.001
Renal replacement before LT	9.2% (3947)	0.0% (0)	4.9% (242)	0.3% (13)	<0.001
Previous abdominal surgery	44.2% (18 691)	1.3% (541)	11.8% (582)	0.4% (18)	<0.001
Transplant center volume	62.7 (32.7)	0.0% (0)	92.5 (32.3)	0.0% (0)	<0.001

All data are expressed as percentage (number of patients), unless otherwise specified.

[a]United States Model for End-Stage Liver Disease.

[b]Level 3 of a 3-point modified scale of functional status (including ECOG from United Kingdom and Karnofsky from United States).

BMI, body mass index; CIT, cold ischemia time; DCD, donation after circulatory death; DRI, donor risk index; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; MELD, Model for End-Stage Liver Disease.

recipients were also much less likely to receive livers donated following circulatory death (DCD) but more likely to receive livers donated from those who had died following trauma. CIT in the United States was significantly lower as was the mean DRI.

The differences in age, sex, and BMI distributions of recipients from the 2 countries were small, although the differences in mean age and BMI were statistically significant (Table 1). Patients in the United States waited a markedly longer time to receive their LT and were more often from a non-White ethnic background and more often found to have anti-HCV antibodies. At the time of transplantation, patients in the United States also had more evidence of severe liver disease (mean MELD [SD] United States 21.7 [10.7] versus United Kingdom 16.5 [6.7]) and were more likely to show the clinical sequelae of end-stage liver disease (ascites [%]; United States 74.4% versus United Kingdom 53.6%; encephalopathy [%], United States 61.5% versus United Kingdom 31.0%). They were also more likely to require renal support before their transplant or to have had previous abdominal surgery (Table 1). Mean annual transplant volume was found to be lower in the United States compared with the United Kingdom (62.7 [32.7] versus 92.5 [32.3], respectively, $P < 0.001$).

Indications for Liver Transplant

In the United States and the United Kingdom, the most common indications for LT were HCC and ALD, which together accounted in both countries for approximately one-half of all first-time LTs (Figure 2 and Table S2, SDC, http://links.lww.com/TP/C303). Toward the end of the study period, the rate of transplantation for ALD in both countries was also increasing as it was in those who were transplanted for metabolic liver disease (Figure 2 and Table S2, SDC, http://links.lww.com/TP/C303). In the United States, ALD accounted for a lower proportion of all LTs than it did in the United Kingdom, whereas for metabolic liver disease and HCV, the reverse was true. The frequency of HCV as an indication for transplant was found to decrease markedly in both countries. In contrast, the proportion of patients transplanted for AID, PSC, and PBC remained relatively static in both the United States and the United Kingdom (Figure 2 and Table S2, SDC, http://links.lww.com/TP/C303).

Posttransplant Mortality

Five years after transplantation, overall survival in the United States was poorer than that observed in the United Kingdom (75.6% [95% CI, 75.1%-76.1%] and 81.9% [95% CI, 80.5%-83.3%], $P < 0.001$, respectively; Figure 3) with this pattern of results also reflected in many of the disease-specific comparisons of posttransplantation outcome, including in those patients transplanted for HCC ($P = 0.04$), HCV ($P = 0.001$), PBC ($P = 0.003$), ALD ($P < 0.001$), AID ($P = 0.01$), and metabolic liver disease ($P = 0.01$) (Figure 3 and Figure S1, SDC, http://links.lww.com/TP/C303). In contrast, no statistically significant difference in mortality at 5 y was observed for those transplanted with PSC ($P = 0.48$), HBV ($P = 0.27$), and the heterogeneous set of liver diseases classified as "other" ($P = 0.38$) (Figure S1, SDC, http://links.lww.com/TP/C303).

Risk-adjusted Comparisons

In the first 90 d after transplantation, there was no observed difference in the overall (comparing the United Kingdom with the United States: HR, 0.96; 95% confidence interval [CI], 0.82–1.12; $P = 0.63$; Table 2, Figure 4) or disease-specific risk-adjusted mortality (P always >0.05; Table 2, Figure 4). In contrast, the risk-adjusted overall mortality between 90 d and 1 y was found to be approximately 29% poorer in the United States (comparing the United

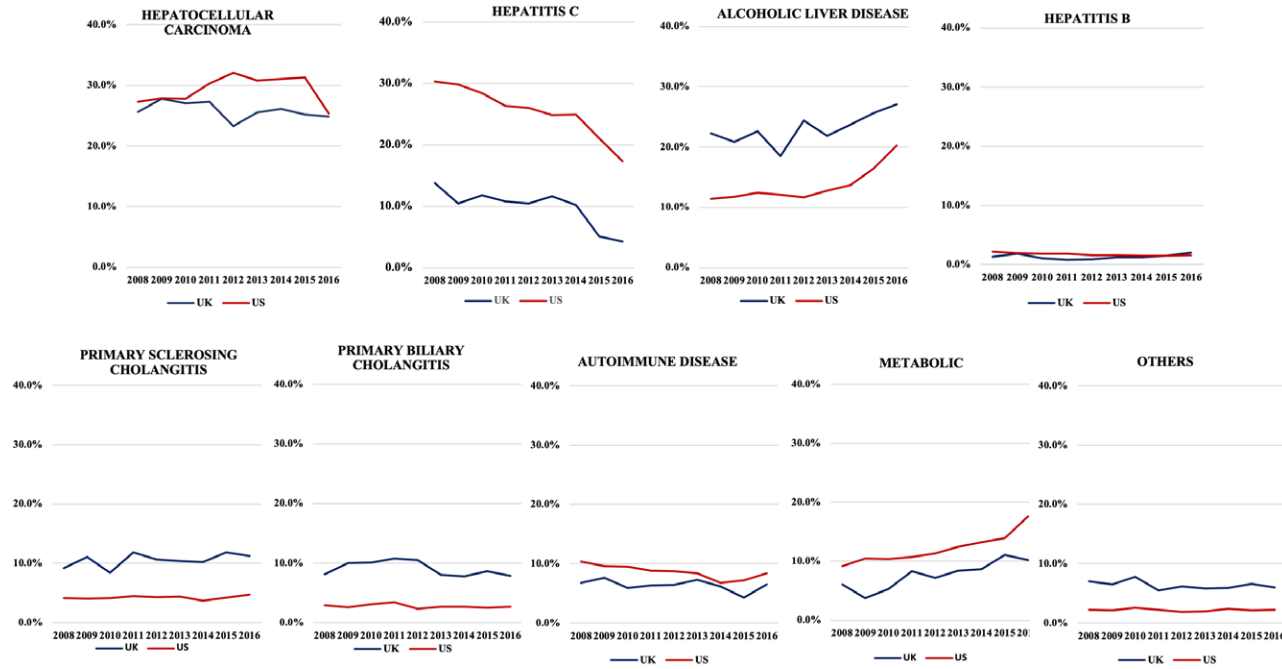

FIGURE 2. Time trends in the indications for liver transplant in the United States and United Kingdom between 2008 and 2016. UK, United Kingdom; US, United States.

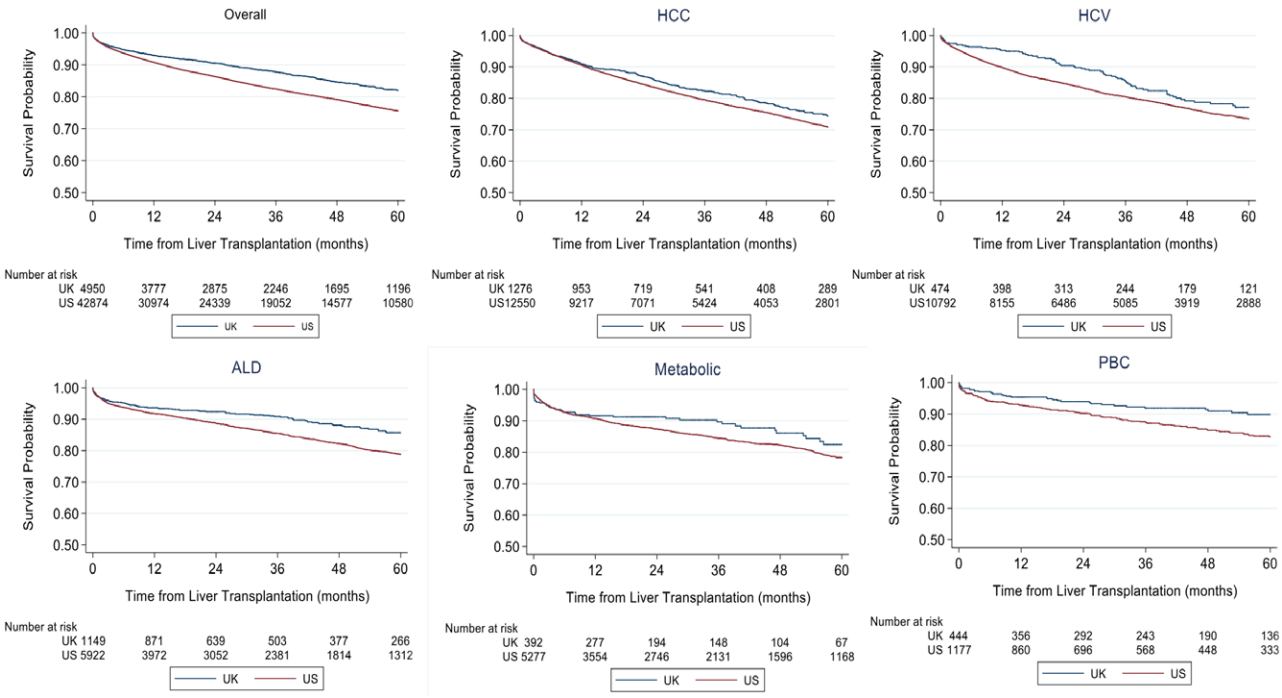

FIGURE 3. Kaplan-Meier survival graphs by liver disease category for liver transplant recipients in the United States and the United Kingdom between 2008 and 2016. ALD, alcohol-related liver disease; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PBC, primary biliary cholangitis; UK, United Kingdom; US, United States.

Kingdom with the United States: HR, 0.71; 95% CI, 0.59–0.85; $P<0.001$; Table 2, Figure 4) with the poorer mortality in the United States in this epoch of follow-up time most clearly in those who underwent LT for HCV (HR, 0.35; 95% CI, 0.19–0.66; $P=0.001$). Between 1 and 5 y after LT, recipients in the United States were again 29% more likely to have died compared with their UK counterparts (comparing the United Kingdom with the United States: HR, 0.71; 95% CI, 0.63–0.81; $P<0.001$). In this epoch of follow-up time, similar results were observed in those transplanted for HCC (HR, 0.71; 95% CI, 0.58–0.88; $P=0.002$), ALD (HR, 0.64; 95% CI, 0.45–0.89; $P<0.001$), and metabolic liver diseases (HR, 0.54; 95% CI, 0.30–0.95; $P=0.03$). The corresponding unadjusted and risk-adjusted graft loss hazards are shown in Figure S2 (SDC, http://links.lww.com/TP/C303) and Table S3 (SDC, http://links.lww.com/TP/C303).

A statistically significant time-dependent country effect was identified in the overall comparisons of mortality ($P=0.004$) and in those who receive a transplant for HCV ($P<0.001$), which indicates that the differences in posttransplant mortality between the United States and United Kingdom varied according to the time period after transplantation. The country-specific impact on risk-adjusted mortality did not differ by era of transplantation ($P=0.38$).

DISCUSSION

Summary of Results

Between 2008 and 2016, we found mortality 5 y after adult first elective LT to be higher in the United States than in the United Kingdom. The risk of graft loss paralleled this observed mortality hazard. This was despite only 1 in 16 recipients in the United States receiving a DCD donor liver compared with 1 in 4 in the United Kingdom. No significant mortality difference between the countries was identified in the first 90 d after transplantation, but it was significantly higher in the United States thereafter.

Comparison With Other Studies

In the only similar study of its kind—and using data from the same data sets between 1994 and 2005—members of this research group identified that mortality in the shorter term (0 and 90 d) was significantly lower in the United States than in the United Kingdom but in the long term significantly worse (1 y onward).[1] It was felt that the most likely explanation for the observed time-dependent differences in mortality was the difference in the provision and quality of care.[1] More specifically, they postulated that the better availability of intensive care beds and superior nurse–patient ratios translated into lower perioperative mortality in the United States and a stronger primary care infrastructure and more equitable access to healthcare into lower long-term mortality in the United Kingdom.[1]

Explanation of Results

The poorer longer-term mortality in the United States may reflect differences in the ability of each country's healthcare system to identify and treat disease recurrence. In the case of HCV, the widespread provision of antivirals in the United Kingdom through their early access programs[24] may have more universally treated early posttransplant HCV recurrence than in the United States and explain superior outcomes from 90 d to 1 y.

With respect to ALD, a healthcare structure more adept at monitoring, managing, preventing, and treating the posttransplant complications[25–29] to be expected in those who have suffered from alcoholism may explain noticeably better survival from 1 to 5 y in the United Kingdom. Observed higher longer-term posttransplant mortality in the United States in HCC recipients may not only be

TABLE 2.

A time-dependent comparison of 5-y patient mortality between the United Kingdom and United States in those receiving a deceased donor liver transplant

Primary liver disease	United Kingdom compared with the United States, hazard ratio (95% CI)			*P* for time dependency
	0–90 d	90 d–1 y	1–5 y	
Overall				
Unadjusted	0.88 (0.76–1.02)	0.65 (0.55–0.77)	0.66 (0.59–0.74)	0.0068
Adjusted[a]	0.96 (0.82–1.12)	0.71 (0.59–0.85)	0.71 (0.63–0.81)	0.004
HCC				
Unadjusted	0.96 (0.71–1.31)	0.96 (0.74–1.24)	0.79 (0.65–0.96)	0.38
Adjusted	0.88 (0.64–1.21)	0.87 (0.66–1.14)	0.71 (0.58–0.88)	0.35
Hepatitis C				
Unadjusted	0.60 (0.34–1.06)	0.36 (0.19–0.66)	1.03 (0.78–1.35)	0.002
Adjusted[a]	0.60 (0.34–1.08)	0.35 (0.19–0.66)	1.01 (0.76–1.35)	0.0006
PSC				
Unadjusted	1.08 (0.62–1.86)	0.61 (0.25–1.44)	0.96 (0.63–1.48)	0.52
Adjusted[a]	1.23 (0.67–2.26)	0.69 (0.28–1.72)	1.06 (0.64–1.76)	0.55
Hepatitis B				
Unadjusted	1.73 (0.60–4.90)	Not enough events (United Kingdom)	Not enough events (United Kingdom)	NA
Adjusted[a]	2.48 (0.72–2.26)	Not enough events (United Kingdom)	Not enough events (United Kingdom)	NA
PBC				
Unadjusted	0.65 (0.35–1.23)	0.60 (0.28–1.30)	0.53 (0.30–0.92)	0.88
Adjusted[a]	0.72 (0.35–1.49)	0.66 (0.28–1.55)	0.57 (0.30–1.10)	0.86
ALD				
Unadjusted	0.82 (0.60–1.12)	0.71 (0.46–1.10)	0.56 (0.41–0.77)	0.23
Adjusted[a]	0.95 (0.68–1.32)	0.82 (0.52–1.29)	0.64 (0.45–0.89)	0.21
AID				
Unadjusted	0.73 (0.43–1.26)	0.96 (0.52–1.78)	0.53 (0.28–1.00)	0.41
Adjusted[a]	0.79 (0.44–1.35)	1.00 (0.53–1.89)	0.54 (0.28–1.03)	0.38
Metabolic				
Unadjusted	1.08 (0.70–1.66)	0.70 (0.37–1.32)	0.57 (0.33–0.99)	0.19
Adjusted[a]	1.07 (0.68–1.69)	0.68 (0.35–1.30)	0.54 (0.30–0.95)	0.14
Others				
Unadjusted	1.05 (0.62–1.77)	1.59 (0.70–3.59)	0.61 (0.32–1.13)	0.16
Adjusted[a]	1.37 (0.75–2.48)	2.12 (0.89–5.07)	0.82 (0.41–1.65)	0.18

[a]Adjusted for recipient characteristics: sex, age, ethnicity, BMI (kg/m^2), disease cause, functional status, ascites, encephalopathy, HCV status, MELD, pretransplant renal replacement therapy, and previous abdominal surgery and for donor characteristics: sex, age, BMI (kg/m^2), CIT, donor type (DCD/DBD), cause of death, ABO match, and graft type.

AID, autoimmune disease; ALD, alcohol-related liver disease; BMI, body mass index; CI, confidence interval; CIT, cold ischemia time; DBD, donation after brainstem death; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; NA, not available; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

because of differences in healthcare structure but also because of differences in tumor characteristics.[30,31]

The mean annual transplant center volume is significantly lower in the United States. Historically, center volume has been proven to be a critical (albeit waning) determinant of outcome.[1,32,33] However, in our model, we felt it unfair to adjust for this parameter as transplant center volume could reflect the health system organization and infrastructure that is used by a country to deliver LT services and therefore help to explain the observed differences in posttransplant mortality. In the United Kingdom, the centralization of surgical specialties has been shown to improve postoperative mortality significantly.[34] Compared with the United Kingdom, the United States is known to have a larger number of transplant centers, most of which perform a relatively low number of LTs annually.[1] However, further analyses (results not shown) that repeat the comparison of post-LT outcomes between the United States and the United Kingdom but leave out the 36 smallest centers (centers performing <100 transplants in the study period)—so that the average volume in the United States is comparable with that in the United Kingdom—did not change the pattern of results.

Differences in the selection of recipients and allocation of donor organs could play a role as well. For example, the MELD score system was introduced in the United States in 2002 as a guide for recipient selection and organs are allocated within geographic regions.[35] In the United Kingdom, the United Kingdom Model for End-Stage Liver Disease score was used for patient selection during the study period and the centers allocate organs offered to them to patients on their own waiting list.[36,37] We included era in the multivariable models as a sensitivity analysis to evaluate for possibly differential impact on the year of transplant. No statistically

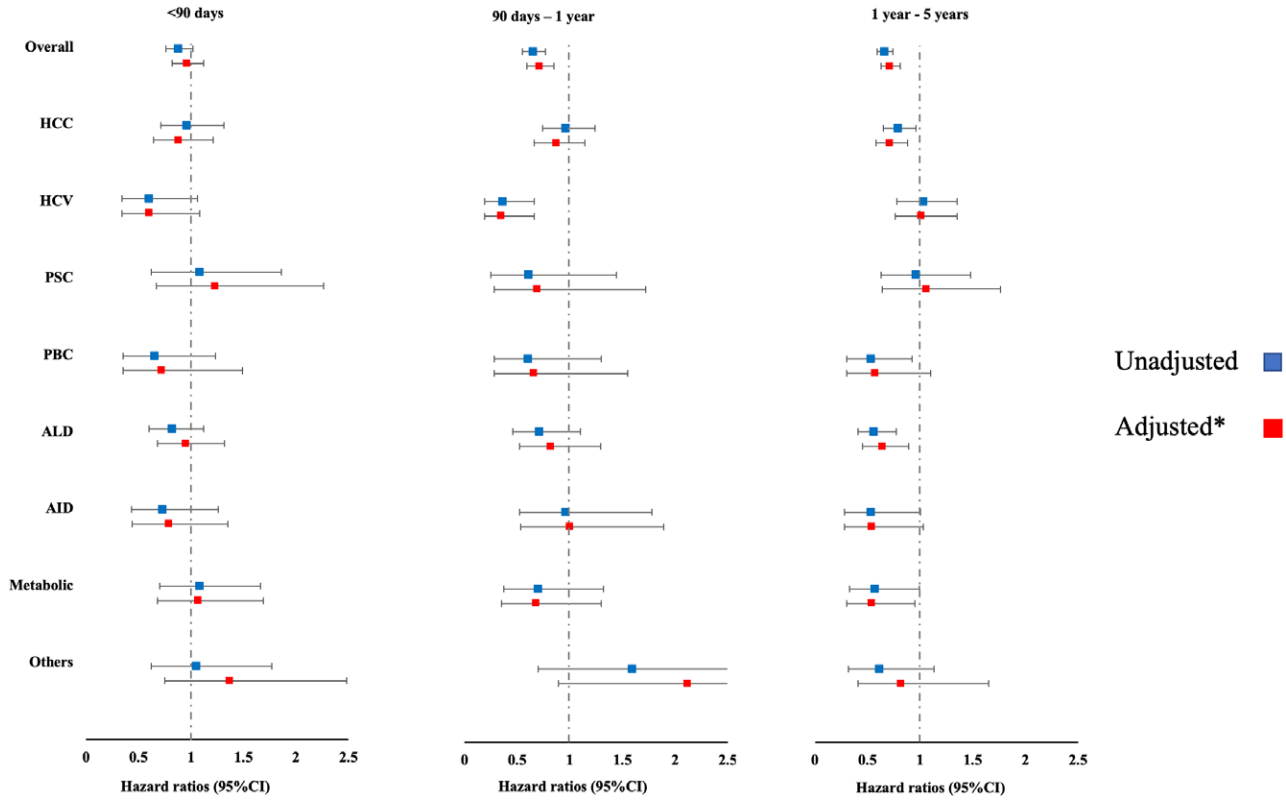

FIGURE 4. Unadjusted and adjusted hazard ratios (and 95% CI) for mortality in the first 90 d, 90 d to 1 y, and beyond the first year in the United States (n = 42 874) compared with the United Kingdom (n = 4950) by liver disease category. *Adjusted for recipient characteristics: sex, age, ethnicity, body mass index (kg/m^2), disease cause, functional status, ascites, encephalopathy, HCV status, model of end-stage liver disease, pretransplant renal replacement therapy, and previous abdominal surgery and for donor characteristics: sex, age, body mass index (kg/m^2), cold ischemic time, donor type (donation after circulatory death/donation after brainstem death), cause of death, ABO match, and graft type. AID, autoimmune disease; ALD, alcohol-related liver disease; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

significant difference in the observed mortality hazard was noted, which was interpreted as the effect of country (United States versus United States) on posttransplantation mortality did not vary according to era of transplant.

It is noteworthy that in the United States, recipients waited considerably longer to receive their LT, but they received a donor liver that was overall of much higher quality than in the United Kingdom. However, given that liver disease severity markers and donor organ quality were included in our risk adjustment, it is unlikely that differences in donor and recipient characteristics fully explain observed differences in mortality. Instead, recently demonstrated improvements in short-term posttransplant term mortality in the United Kingdom may better explain why compared with our previous comparison of posttransplant outcome—almost 15 y ago—the United States no longer has lower 90-d mortality.[6] It remains unclear whether the United States has experienced the same improvements in shorter-term mortality. Our comparison of international outcomes suggests that is not the case.

The higher risk-adjusted mortality among US survivors in the longer term (beyond 90 d) is most likely to be explained by a genuine difference in the organization and quality of care.[1] These differences between countries may be reflected in several factors that predict longer-term posttransplant outcomes, including differences in immunosuppressive strategies and the management of the complications of immunosuppression, disease recurrence, and other comorbidities.[1]

The provision of and adherence to posttransplant immunosuppression is a strong determinant in the LT beyond the initial operation.[25] In the United Kingdom, lifetime state-funded immunosuppressive medications are provided to all transplant recipients, where a lack of a coherent funding policy for transplant recipients in the United States has been postulated as a cause for poorer posttransplantation outcomes.[25,26] For example, the 2016 Commonwealth Fund International Health Policy Survey found that 1 in 3 adults in the United States forgo medical treatment or follow-up due to cost-related barriers compared with <1 in 10 adults in the United Kingdom.[28]

LT recipients are prone to a range of chronic conditions that include hypertension, hyperlipidemia, new-onset diabetes after transplantation, and cardiovascular disease.[29] The better equity of access to "free" healthcare in the United Kingdom and a strong primary care structure—all provided under the umbrella of a universal healthcare system—may be better equipped than the United States to manage the more chronic complications of LT and thus further explain longer-term mortality differences.[38,39]

Methodological Limitations

International comparisons of outcomes come with recognized difficulties.[1] For example, differences between countries in the ascertainment of death could lead to the systematic underreporting of posttransplant mortality and artificial estimates of superior survival.[40] However, in each

of the national data sets, well-established processes for ascertaining death exist.[41,42]

Despite considerable risk adjustment in our comparison, it cannot be excluded that observed short- and longer-term mortality differences can be explained by residual confounding.[1] However, our risk adjustment model includes a wide range of risk factors, so it is unlikely that residual confounding can fully account for the marked differences in mortality.[1] This is in line with conclusions from a related study comparing kidney transplant outcomes between the United States, United Kingdom, and Australasia that specifically aimed to quantify the potential effects of unmeasured confounding.[43]

Despite the risk adjustments for factors that have previously been demonstrated to represent confounders for post-LT outcomes, the databases do not contain detailed information regarding comorbidities, which would require linking other sources of clinical and administrative databases. A previous analysis of UK transplant data carried out by members of our research group found that renal disease, pulmonary disease, and diabetes had no impact on mortality. In contrast, cardiovascular disease was associated with statistically significantly higher mortality in all 3 periods after LT (0–90 d, 90 d to 5 y, beyond 5 y).[29] This suggests that if there are differences between the 2 groups with regards to cardiovascular disease, it may explain some of the differences observed. An evaluation of the impact and possibly varying effects across countries of factors such as cardiovascular disease thus warrants future evaluation. In addition, a number of factors that may be related to the post-LT outcome were not available, including medication coverage, detailed information about comorbidities, geographical distance to a transplantation center, and socioeconomic status.[44] Regarding HCV patients, direct-acting antiviral (DAA) therapy became widely available in 2014 in the United States.[45] In the United Kingdom, the early access program of DAA therapy began in 2014.[46,47] It is conceivable that DAA therapy could be a confounding factor in the analysis, mainly if there were differences in the utilization of such therapy between the countries. Notwithstanding this potential limitation, given that DAA therapy was introduced at similar times in both countries, and the time in which their effects could have been exerted is relatively short in the study period (2014–2016), it is conceivable that any confounding effect, if present, would likely have been small. Linkages with other national data sets may provide these crucial data for further analyses.

Differences in data quality are therefore an unlikely explanation for the observed differences in mortality. In both the United States and the United Kingdom, the collection of data on transplant activity is mandated, which means that they are subject to robust quality assurance procedures that help to ensure the submission of highly complete and accurate data, validation, and ascertainment of posttransplant events. This is well demonstrated by the low rate of missing data and the many high-quality peer-reviewed publications that have originated from data provided by these data sets.

Another limitation of our analysis is that we used predefined posttransplant epochs (up to 90 d, between 90 d and 2 y, and between 2 and 5 y) to investigate the time dependency of the impact of HCC on patient and graft survival. This approach assumes that the prognostic impact of HCC on survival is constant within each of these epochs. The advantage of this approach is that the HRs can be estimated using standard Cox regression methods and, more importantly, that the results are relatively easy to interpret. Its disadvantage is that the partitioning of the survival time in distinct epochs needs to be chosen in advance and that the number of separate epochs as well as their duration is arbitrary.

Implications

There are several implications of this work. First, the difference in long-term outcomes between LT recipients in the United States and the United Kingdom highlights the need for further investigation to clarify factors that may be responsible for driving these differences. It is possible that other factors than those directly related to surgery and immediate perioperative care may contribute to these differences, which may represent actionable targets for future quality improvement. In particular, a reappraisal of the factors related to posttransplant surveillance strategies may be warranted with an emphasis on patients' access to healthcare and immunosuppressive medications.

Second, this study should catalyze future registry development. The reason for this is that, despite the already well-standardized practice of solid organ transplantation, differences may exist that may result from exposures that are not measured, which should be identified to afford continued global improvements in outcome in LT.

Third, this study demonstrates that an increased emphasis on the use of marginal grafts may be necessary in the United States as it carries the potential of reducing the time to transplantation while still maintaining acceptable post-LT outcomes. With respect to this, improvements in short- and longer-term outcomes in the United Kingdom, despite using more marginal grafts, could act as a benchmark, as could the centralization of their LT services.[6,36]

Finally, a range of future analyses are necessary to get a better understanding of the factors that contribute to the observed time-specific differences in post-LT outcomes between the United States and United Kingdom. Additional data may be available through linkage with other national data sets. These future analyses should focus on differences in the impact that donor and recipient characteristics have on outcomes according to time after transplantation. It is also important to investigate to what extent differences in post-LT outcomes between the United States and the United Kingdom can be explained by specific differences in the organization and delivery of transplant services, including recipient selection and organ allocation, the centers' annual transplant volume, and the distance of the recipients' place of residence to their nearest transplant center.

CONCLUSIONS

Despite the use of better-quality donor organs in the United States, long-term post-LT mortality outcomes are worse in comparison with the United Kingdom. Further detailed investigation of differences in the delivery of and management after LT in the United States and United Kingdom may highlight targets for future improvement efforts to maximize outcomes after LT.

ACKNOWLEDGMENTS

The authors would like to thank all liver transplant centers for providing data to the Standard National Liver Transplant Registry. They would also like to thank all those involved in collecting and handling liver transplant data at National Health Service Blood and Transplant.

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