

## **Survival after liver transplantation: an international comparison between the United States and the United Kingdom in the years 2008-2016**

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All other authors declare no competing interests.

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## **ABBREVIATIONS PAGE**

ALD: Alcohol-related liver disease

AID: Autoimmune disease

BMI: Body mass index

CIT: Cold ischaemic time

CI: Confidence interval

DCD: Donation after circulatory death

DBD: Donation after brainstem death

DRI: Donor Risk Index

HAT: Hepatic artery thrombosis

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

HR: Hazard ratio

INR: International Normalised Ratio

LDLT: Living donor liver transplantation

LT: Liver transplantation

MELD: Model of End-stage Liver Disease score

MELD-Na: Model of End-stage Liver Disease Sodium score

NHSBT: National Health Service Blood and Transplant

OPTN: Organ Procurement and Transplantation Network

PBC: Primary biliary cholangitis

PSC: Primary sclerosing cholangitis

SD: Standard deviation

UK: United Kingdom

UNOS: United Network for Organ Sharing

US: United States

## **ABSTRACT**

### **Background**

Compared to the United States (US), risk-adjusted mortality in the United Kingdom (UK) has historically been worse in the first 90-days 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 post-transplant outcomes has been conducted. This study aimed to determine disease-specific short- and long-term mortality of LT recipients in the US and the UK.

### **Methods**

This retrospective international multicentre cohort study analysed adult ( $\geq 18$ -years) first-time LT recipients between 1-January-2008 and 31-December-2016 using the OPTN/UNOS and the UK Transplant Registry databases. Time-dependent Cox-regression estimated hazard ratios (HR) comparing disease-specific risk-adjusted mortality in the first 90-days post-LT, between 90-days and one-year, and between one and five-years.

### **Results**

42,874 US and 4,950 UK LT recipients were included. The main LT indications in the US and the UK were hepatocellular carcinoma (HCC: 25.4% and 24.9%, respectively) and alcohol-related liver disease (ALD) (20.3% and 27.1%). There were no differences in mortality during the first 90-days post-LT (reference: US; HR: 0.96; [95% CI: 0.82-1.12]). However, between 90-days and one-year (HR: 0.71; [95% CI: 0.59-0.85]) and one and five-years (HR: 0.71; [95% CI: 0.63-0.81]) the UK had lower mortality. The mortality differences between one and five-years were most marked in HCC (HR: 0.71; [95% CI: 0.58-0.88]) and ALD patients (HR: 0.64; [95% CI: 0.45-0.89]).

## **Conclusions**

Risk-adjusted mortality in the US and the UK was similar in the first 90-days post-LT but better in the UK thereafter. International comparisons of LT may highlight differences in health care delivery and help benchmarking by identifying modifiable factors that can facilitate improved global outcomes in LT.

## INTRODUCTION

International comparisons of surgical mortality offer insight into the disparities in access to and delivery of surgical treatments.<sup>1-6</sup> 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.<sup>1,2</sup>

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

Unfortunately, difficulties in obtaining, combining, and analyzing datasets from different countries mean very few reports describing comparisons of LT outcomes exist.<sup>1</sup> In the only previous comparison between the US and the UK, post-transplant mortality in 47,791 LT recipients between 1994 and 2005 was significantly worse in the UK in the first 90-days after surgery and then better thereafter.<sup>1</sup> 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 a LT in the UK.<sup>6</sup> Consequently, a contemporary evaluation is warranted.

Given that international comparisons of health care outcomes enable policymakers and clinicians to identify areas of healthcare delivery where countries could learn from each other and that era-specific improvement in post-transplant mortality have been observed,<sup>1-5</sup> we used a uniquely harmonised combined dataset to carry out a disease-specific time-dependent comparison of short- and long-term patient mortality following LT in the UK and the US between 2008 and 2016.



## **MATERIALS AND METHODS**

### Databases

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

The study population included all patients aged 18 years or older who received a first-time elective LT in the two countries between 1<sup>st</sup> January 2008 and 31<sup>st</sup> December 2016 (**Figure 1**). The study's start date was chosen to coincide with the introduction in the UK in 2008 of organ offering policies based on predicted waiting list mortality. In the same time period in the US, the Model for End-Stage Liver Disease (MELD) score-based allocation, the Share 15 and Share 35 scheme, and the MELD-Sodium (MELD-Na) allocation system were introduced.<sup>7-9</sup> Patients who underwent LT for liver cancer types other than 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 datasets were harmonised to ensure that liver disease classification and risk factor definitions were comparable.<sup>1</sup> Patients were grouped according to a liver disease classification system (**Table S1**) that was first adopted by Roberts et al.<sup>1,10</sup> In the event of multiple diagnoses, patients were assigned to the diagnosis most likely to have influenced their prognosis at the time of transplantation.<sup>1,10</sup> Disease classification was undertaken in a hierarchical order: cancer, hepatitis C virus (HCV) cirrhosis, primary sclerosing cholangitis (PSC), biliary cholangitis (PBC), alcohol-related liver disease (ALD), autoimmune disease (AID), metabolic, and others.<sup>1,10</sup> For example, patients with a coded diagnosis of HCV cirrhosis and a free text diagnosis of hepatocellular carcinoma (HCC) were

assigned to the HCC category.<sup>1,10</sup> 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.<sup>1,10</sup> Transplant centre volume was defined as the average number of first-adult single organ LTs, excluding multivisceral and re-transplants, performed during the study period at a given centre per year.<sup>1</sup>

For multivariable analyses, creatinine was set to 4.0 mg/dl for those with lower values who received renal replacement therapies immediately before transplantation.<sup>1</sup> Implausible values of body mass index (BMI <10 or >100 kg/m<sup>2</sup>), cold ischaemic time (CIT >40 hours), 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.<sup>1</sup> The MELD score (calculated using serum creatinine, total serum bilirubin, and international normalised ratio [INR]) was used to score the recipients' severity of the liver disease in both the US and the UK.<sup>11</sup> Ascites and encephalopathy were considered as dichotomous variables. Recipients' functional status at the time of transplantation was assessed using a modified three-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'.<sup>12–14</sup> Values for ethnicity were categorised 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).<sup>15</sup> 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 UK is included.<sup>16,17</sup> 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.<sup>18</sup> In the US, UNOS/OPTN collects information on death at six and twelve months intervals and validates their data with information from the Centers for Medicare and Medicaid Services and the National Death Index.<sup>19</sup> 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 individual transplant center reporting as this would lead to inaccuracies if the patients does not continue their follow-up at their original transplant center.<sup>19-21</sup> Death ascertainment in the UK is closely monitored through centre-specific three monthly follow-up forms submitted centrally to NHSBT.

### Statistical analyses

Categorical variables were presented as proportions and compared using chi-squared tests, and continuous variables were presented as means with standard deviations (SD). 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 (UK vs. US). Follow-up data were available until 7<sup>th</sup> April 2017. The median follow up time for the US was 944 days (interquartile range [IQR] 346-1820) and for the UK 1011 days (IQR 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 US versus the UK in the following periods after LT ('epochs'): the first 90-days, 90-days to one year, and beyond the first year. The US was used as the baseline value with a HR <1, indicating mortality to be higher in the US compared to the UK. The analysis was censored at five years post-transplantation. Only those clinically plausible recipient and donor risk factors recorded to a comparable degree in both databases with missing values in less than 10% of the patients were included in the risk-adjusted regression models.<sup>1</sup> These included recipient characteristics: sex, age, ethnicity, BMI (kg/m<sup>2</sup>), disease aetiology, functional status, ascites, encephalopathy, HCV status, MELD, pre-transplant renal replacement therapy, previous abdominal

surgery, and donor characteristics: sex, age, BMI (kg/m<sup>2</sup>), CIT, donor type (DCD/DBD), cause of death, ABO match, graft type. A similar analysis as for patient survival including risk-adjustments for the abovementioned variables was performed to investigate risk of graft loss. Adjustment for specific tumour characteristics was not included as comparisons of post-transplantation mortality in HCC patients were made with a cohort of non-HCC patients.<sup>22</sup> Interaction terms were included in the Cox regression models to determine whether the hazard ratios 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 to 2011 and 2012 to 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 ten complete datasets with regression results pooled using Rubin's rules.<sup>23</sup> Stata V15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses. A p-value < 0.05 was considered to indicate a statistically significant result.

## RESULTS

### Clinical characteristics

Between 1<sup>st</sup> January 2008 and 31<sup>st</sup> December 2016, 42,874 adults received a first single-organ LT in 134 centres in the US, while 4,950 such transplants were performed in seven centres in the UK (**Table 1**).

Compared to recipients in the UK, LT recipients in the US were less likely to receive livers from older and from male donors (**Table 1**). US 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 US was significantly lower as was the mean DRI.

The differences in age, sex, and BMI distributions of recipients from the two countries were small, although the differences in mean age and BMI were statistically significant (**Table 1**). Patients in the US 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 US also had more evidence of severe liver disease (Mean MELD [SD] US 21.7 [10.7] vs. UK 16.5 [6.7]) and were more likely to show the clinical sequelae of end-stage liver disease (Ascites [%]; US 74.4% vs. UK 53.6%; Encephalopathy [%], US 61.5% vs. UK 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 as found to be lower in the US compared to the UK (62.7 [32.7] vs. 92.5 [32.3], respectively,  $p < 0.001$ ).

#### Indications for liver transplant

In the US and the UK, the most common indications for LT were HCC and alcohol-related liver disease (ALD), which together accounted in both countries for approximately one-half of all first-time LTS (**Figure 2 and Table S2**). 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 and Supplementary Figure 1**). In the US, ALD accounted for a lower proportion of all LTs than it did in the UK, while 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 US and the UK (**Supplementary Figure 2 and Table S2**).

#### Post-transplant mortality

Five years after transplantation, overall survival in the US was poorer than that observed in the UK (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 post-transplantation 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**). In contrast, no statistically significant difference in mortality at five years 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**).

#### Risk-adjusted comparisons

In the first 90 days after transplantation there was no observed difference in the overall (comparing the UK with the US: HR 0.96 [95%CI: 0.82-1.12],  $p=0.63$ , **Table S3**, **Figure 4**) or disease-specific risk-adjusted mortality ( $p$  always  $>0.05$ , **Table S3**, **Figure 4**). In contrast, the risk-adjusted overall mortality between 90-days and one year was found to be approximately 29% poorer in the US (comparing the UK with the US: HR 0.71 [95%CI: 0.59-0.85],  $p<0.001$ , **Table S3**, **Figure 4**) with the poorer mortality in the US 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-years after LT recipients in the US were again 29% more likely to have died compared to their UK counterparts (comparing the UK with the US: 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** and **Table S3**.

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 post-transplant mortality between the US and UK 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 five years after adult first elective LT to be higher in the US than in the UK. The risk of graft loss paralleled this observed mortality hazard. This was despite only 1 in 16 recipients in the US receiving a ~~higher risk~~ DCD donor liver compared to 1 in 4 in the UK. No significant mortality difference between the countries was identified in the first 90-days after transplantation but it was significantly higher in the US thereafter.

### Comparison with other studies

In the only similar study of its kind – and using data from the same datasets between 1994 to 2005 – members of this research group identified that mortality in the shorter-term (0 and 90-days) was significantly lower in the US than in the UK but in the long-term significantly worse (1-year onwards).<sup>1</sup> 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.<sup>1</sup> More specifically, they postulated that the better availability of intensive care beds and superior nurse-patient ratios translated into lower perioperative mortality in the US, and a stronger primary care infrastructure and more equitable access to healthcare into lower long-term mortality in the UK.<sup>1</sup>

### Explanation of results

The poorer longer-term mortality in the US 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 anti-virals in the UK through their early-access programs<sup>24</sup> may have more universally treated early post-transplant HCV recurrence than in the US and explain superior outcomes from 90-days to one-year.

With respect to ALD, a healthcare structure more adept at monitoring, managing, preventing, and treating the post-transplant complications<sup>25-29</sup> to be expected in those who have suffered from alcoholism may explain noticeably better survival from one to five years in the UK. Observed higher longer-term post-transplant mortality in the US in HCC recipients may not only be due to differences in healthcare structure but also in differences in tumour characteristics ~~and selection criteria and bridging therapy practices.~~<sup>30,31</sup>

The mean annual transplant centre volume is significantly lower in the US. Historically, center volume has been proven to be a critical (albeit waning) determinant of outcome.<sup>1,32,33</sup> 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 post-transplant mortality. In the UK, the centralization of surgical specialties, ~~including LT,~~ has been shown to improve postoperative mortality significantly.<sup>34</sup> Compared to the UK, the US is known to have a ~~disproportionately~~ larger number of transplant centers, most of which perform a relatively low number of LTs annually.<sup>1</sup> However, further analyses (results not shown) that repeat the comparison of post-LT outcomes between the US and the UK but leave out the 36 smallest centers (centres performing less than 100 transplants in the study period) - so that the average volume in the US is comparable with that in the UK - 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 US in 2002 as a guide for recipient selection and organs are allocated within geographic regions.<sup>35</sup> In the UK, the UKELD 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.<sup>36,37</sup> We included era in the multivariable models as a sensitivity analysis to evaluate for possibly differential impact on the year of transplant. No difference in the observed results was noted,



which was interpreted as the effect of country (US vs US) on post-transplantation mortality did not vary according to era of transplant.

It is noteworthy that in the US, recipients waited considerably longer to receive their LT, but they received a donor liver that was overall of much higher quality than in the UK. 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 post-transplant term mortality in the UK may better explain why compared to our previous comparison of post-transplant outcome – almost 15 years ago - the US no longer has lower 90-day mortality.<sup>6</sup> It remains unclear whether the US have 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-days) is most likely to be explained by a genuine difference in the organization and quality of care.<sup>1</sup> These differences between countries may be reflected in several factors that predict longer-term post-transplant outcomes, including differences in immunosuppressive strategies and the management of the complications of immunosuppression, disease recurrence, and other comorbidities.<sup>1</sup>

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

LT recipients are prone to a range of chronic conditions that include hypertension, hyperlipidaemia, new-onset diabetes after transplantation (NODAT), and cardiovascular disease.<sup>29</sup> The better equity of access to ‘free’ healthcare in the UK and a strong primary care structure – all provided under the umbrella of a universal healthcare system – may be better equipped than the US to manage the more chronic complications of LT and thus further explain longer-term mortality differences.<sup>38,39</sup>

### Methodological limitations

International comparisons of outcomes come with recognised difficulties.<sup>1</sup> For example, differences between countries in the ascertainment of death could lead to the systematic underreporting of post-transplant mortality and artificial estimates of superior survival.<sup>40</sup> However, in each of the national datasets, well-established processes for ascertaining death exist.<sup>41,42</sup>

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.<sup>1</sup> 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.<sup>1</sup> This is in line with conclusions from a related study comparing kidney transplant outcomes between the US, UK, and Australasia that specifically aimed to quantify the potential effects of unmeasured confounding.<sup>43</sup>

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 three periods after LT (0-90 days, 90-days to 5-years,

beyond 5-years).<sup>29</sup> This suggests that if there are differences between the two 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 socio-economic status.<sup>44</sup> Regarding HCV patients, direct-acting antiviral (DAA) therapy became widely available in 2014 in the US.<sup>45</sup> In the UK, the early access programme of DAA therapy began in 2014.<sup>46,47</sup> 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 effect 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 datasets 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 US and the UK, 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 post-transplant 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 datasets.

Another limitation of our analysis is that we used pre-defined post-transplant epochs (up to 90-days, between 90-days and 2-years, and between 2 and 5-years) 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 hazard ratios 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. Firstly, the difference in long-term outcomes between LT recipients in the US and the UK highlight 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 re-appraisal of the factors related to post-transplant surveillance strategies may be warranted with an emphasis on patients' access to health care and immunosuppressive medications.

Secondly, this study should catalyze future registry development. The reason for this is that, despite the already well-standardised 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.

Thirdly, this study demonstrates that an increased emphasis on the use of marginal grafts may be necessary in the US 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 UK despite using more marginal grafts could act as a benchmark, as could the centralization of their LT services.<sup>6,36</sup>

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 US and UK. Additional data

may be available through linkage with other national datasets. 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 US and the UK can be explained by specific differences in the organization and delivery of transplant services, including recipient selection and organ allocation, the centres' annual transplant volume and the distance of the recipients' place of residence to their nearest transplant center,

### Conclusion

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

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## REFERENCES

1. Dawwas MF, Gimson AE, Lewsey JD, Copley LP, Van Der Meulen JHP. Survival after liver transplantation in the United Kingdom and Ireland compared with the United States. *Gut*. 2007;56(11):1606-1613. doi:10.1136/gut.2006.111369
2. Karthikesalingam A, Holt PJ, Vidal-Diez A, et al. Mortality from ruptured abdominal aortic aneurysms: clinical lessons from a comparison of outcomes in England and the USA. *Lancet (London, England)*. 2014;383(9921):963-969. doi:10.1016/S0140-6736(14)60109-4
3. Kim SJ, Schaubel DE, Fenton SSA, Leichtman AB, Port FK. Mortality after kidney transplantation: a comparison between the United States and Canada. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2006;6(1):109-114. doi:10.1111/j.1600-6143.2005.01141.x
4. Carbone M, Nardi A, Marianelli T, et al. International comparison of liver transplant programmes: differences in indications, donor and recipient selection and outcome between Italy and UK. *Liver Int*. 2016;36(10):1481-1489. doi:10.1111/liv.13132
5. Ibrahim M, Vece G, Mehew J, et al. An international comparison of deceased donor kidney utilization: What can the United States and the United Kingdom learn from each other? *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2020;20(5):1309-1322. doi:10.1111/ajt.15719
6. Wallace D, Cowling TE, Walker K, et al. Short- and long-term mortality after liver transplantation in patients with and without hepatocellular carcinoma in the UK. *Br J Surg*. 2020;107(7):896-905. doi:10.1002/bjs.11451
7. Bittermann T, Makar G, Goldberg D. Exception point applications for 15 points: an unintended consequence of the share 15 policy. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc*. 2012;18(11):1302-1309. doi:10.1002/lt.23537

8. Tschuor C, Ferrarese A, Kuemmerli C, et al. Allocation of liver grafts worldwide – Is there a best system? *J Hepatol.* 2019;71(4):707-718. doi:10.1016/j.jhep.2019.05.025
9. Liver and Intestinal Organ Transplantation Committee - OPTN/UNOS. Clerical changes for implementation of adding serum sodium to the MELD Score. 2015;(804):4-5.
10. Roberts MS, Angus DC, Bryce CL, Valenta Z, Weissfeld L. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc.* 2004;10(7):886-897. doi:10.1002/lt.20137
11. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology.* 2001;33(2):464-470. doi:10.1053/jhep.2001.22172
12. Jacob M, Copley LP, Lewsey JD, Gimson A, Rela M, van der Meulen JHP. Functional status of patients before liver transplantation as a predictor of posttransplant mortality. *Transplantation.* 2005;80(1):52-57. doi:10.1097/01.tp.0000163292.03640.5c
13. Thuluvath PJ, Thuluvath AJ, Savva Y. Karnofsky performance status before and after liver transplantation predicts graft and patient survival. *J Hepatol.* 2018;69(4):818-825. doi:10.1016/j.jhep.2018.05.025
14. Wallace D, Cowling TE, Walker K, et al. The Impact of Performance Status on Length of Hospital Stay and Clinical Complications Following Liver Transplantation. *Transplantation.* October 2020. doi:10.1097/TP.0000000000003484
15. 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. doi:10.1111/j.1600-6143.2006.01242.x
16. Blok JJ, Braat AE, Adam R, et al. Validation of the donor risk index in orthotopic liver transplantation within the Eurotransplant region. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc.* 2012;18(1):112-119. doi:10.1002/lt.22447



17. Braat AE, Blok JJ, Putter H, et al. The Eurotransplant donor risk index in liver transplantation: ET-DRI. *Am J Transplant*. 2012;12(10):2789-2796. doi:10.1111/j.1600-6143.2012.04195.x
18. Furukawa H, Todo S, Imventarza O, et al. Effect of cold ischemia time on the early outcome of human hepatic allografts preserved with UW solution. *Transplantation*. 1991;51(5):1000-1004. doi:10.1097/00007890-199105000-00013
19. Massie AB, Kucirka LM, Segev DL. Big data in organ transplantation: registries and administrative claims. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2014;14(8):1723-1730. doi:10.1111/ajt.12777
20. Dickinson DM, Bryant PC, Williams MC, et al. Transplant data: sources, collection, and caveats. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2004;4 Suppl 9:13-26. doi:10.1111/j.1600-6135.2004.00395.x
21. UNOS. OPTN to implement new process for patient status verification. <https://unos.org/news/optn-to-implement-new-process-for-patient-status-verification/>. Published 2013. Accessed July 20, 2021.
22. Wallace D, Walker K, Charman S, et al. Assessing the Impact of Suboptimal Donor Characteristics on Mortality After Liver Transplantation: A Time-dependent Analysis Comparing HCC With Non-HCC Patients. *Transplantation*. 2019;103(4):e89-e98. doi:10.1097/TP.0000000000002559
23. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi:10.1002/sim.4067
24. Zoulim F, Liang TJ, Gerbes AL, et al. Hepatitis C virus treatment in the real world: optimising treatment and access to therapies. *Gut*. 2015;64(11):1824-1833. doi:10.1136/gutjnl-2015-310421
25. Clavien PA, Muller X, de Oliveira ML, Dutkowski P, Sanchez-Fueyo A. Can immunosuppression

- be stopped after liver transplantation? *Lancet Gastroenterol Hepatol*. 2017;2(7):531-537.  
doi:10.1016/S2468-1253(16)30208-4
26. Gill JS, Tonelli M. Penny wise, pound foolish? Coverage limits on immunosuppression after kidney transplantation. *N Engl J Med*. 2012. doi:10.1056/NEJMp1114394
  27. Yoo HY, Thuluvath PJ. Outcome of liver transplantation in adult recipients: influence of neighborhood income, education, and insurance. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc*. 2004;10(2):235-243. doi:10.1002/lt.20069
  28. The Commonwealth Fund. 2016 Commonwealth Fund International Health Policy Survey of Adults | Commonwealth Fund.  
<https://www.commonwealthfund.org/publications/surveys/2016/nov/2016-commonwealth-fund-international-health-policy-survey-adults>. Accessed December 7, 2020.
  29. Tovikkai C, Charman SC, Praseedom RK, Gimson AE, van der Meulen J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. *BMJ Open*. 2015;5(5):e006971. doi:10.1136/bmjopen-2014-006971
  30. Lingiah VA, Niazi M, Olivo R, Paterno F, Guarrera J V, Pyrsopoulos NT. Liver Transplantation Beyond Milan Criteria. *J Clin Transl Hepatol*. 2020;8(1):69-75. doi:10.14218/JCTH.2019.00050
  31. Brahmania M, Marquez V, Kneteman NM, et al. Canadian liver transplant allocation for hepatocellular carcinoma. *J Hepatol*. 2019;71(5):1058-1060. doi:10.1016/j.jhep.2019.07.016
  32. Ozhathil DK, Li Y, Smith JK, et al. Effect of centre volume and high donor risk index on liver allograft survival. *HPB*. 2011. doi:10.1111/j.1477-2574.2011.00320.x
  33. Beal EW, Black SM, Mumtaz K, et al. High Center Volume Does Not Mitigate Risk Associated with Using High Donor Risk Organs in Liver Transplantation. *Dig Dis Sci*. 2017;62(9):2578-2585.  
doi:10.1007/s10620-017-4639-2

34. Vallance AE, vanderMeulen J, Kuryba A, et al. Impact of hepatobiliary service centralization on treatment and outcomes in patients with colorectal cancer and liver metastases. *Br J Surg*. 2017;104(7):918-925. doi:10.1002/bjs.10501
35. Leventhal TM, Florek E, Chinnakotla S. Changes in liver allocation in United States. *Curr Opin Organ Transplant*. 2020;25(1):52-58. doi:10.1097/MOT.0000000000000726
36. Barber K, Madden S, Allen J, Collett D, Neuberger J, Gimson A. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. *Transplantation*. 2011;92(4):469-476. doi:10.1097/TP.0b013e318225db4d
37. Gimson A. Development of a UK liver transplantation selection and allocation scheme. *Curr Opin Organ Transplant*. 2020;25(2):126-131. doi:10.1097/MOT.0000000000000743
38. Starfield B, Shi L. Policy relevant determinants of health: an international perspective. *Health Policy*. 2002;60(3):201-218. doi:10.1016/s0168-8510(01)00208-1
39. Macinko J, Starfield B, Shi L. The contribution of primary care systems to health outcomes within Organization for Economic Cooperation and Development (OECD) countries, 1970-1998. *Health Serv Res*. 2003;38(3):831-865. doi:10.1111/1475-6773.00149
40. Gallagher AM, Dedman D, Padmanabhan S, Leufkens HGM, de Vries F. 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(5):563-569. doi:10.1002/pds.4747
41. Daily OP, Kauffman HM. Quality control of the OPTN/UNOS Transplant Registry. *Transplantation*. 2004;77(8):1309; author reply 1309-10. doi:10.1097/01.tp.0000120943.94789.e4
42. Karam V, Gunson B, Roggen F, et al. Quality control of the European Liver Transplant Registry: results of audit visits to the contributing centers. *Transplantation*. 2003;75(12):2167-2173.

doi:10.1097/01.TP.0000080271.20145.07

43. Merion RM, Goodrich NP, Johnson RJ, et al. Kidney transplant graft outcomes in 379 257 recipients on 3 continents. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg.* 2018;18(8):1914-1923. doi:10.1111/ajt.14694
44. Leung KK, Kim A, Hansen BE, et al. The impact of primary liver disease and social determinants in a mixed donor liver transplant program - a single centre analysis. *Liver Transplant Off Publ Am Assoc Study Liver Dis Int Liver Transplant Soc.* June 2021. doi:10.1002/lt.26195
45. Flemming JA, Kim WR, Brosgart CL, Terrault NA. Reduction in liver transplant wait-listing in the era of direct-acting antiviral therapy. *Hepatology.* 2017;65(3):804-812. doi:10.1002/hep.28923
46. Vaziri A, Gimson A, Agarwal K, et al. Liver transplant listing for hepatitis C-associated cirrhosis and hepatocellular carcinoma has fallen in the United Kingdom since the introduction of direct-acting antiviral therapy. *J Viral Hepat.* 2019;26(2):231-235. doi:10.1111/jvh.13022
47. Initiative AVH. Access and Uptake of Direct Acting Antiviral Medicines in the UK and selected European countries. [http://www.hcvaction.org.uk/sites/default/files/resources/ABPI PVHI Hep C uptake report FINAL.pdf](http://www.hcvaction.org.uk/sites/default/files/resources/ABPI_PVHI_Hep_C_uptake_report_FINAL.pdf). Published 2017. Accessed July 20, 2021.

**Table 1: Donor and recipient characteristics according to country.**

Characteristics	Country				
	United States		United Kingdom		
	US n=42,874	Missing	UK n=4,950	Missing	P-value
<b>Donor</b>					
Female	59.5% (25,529)	0.0% (0)	46.2% (2,289)	0.0% (0)	<0.001
Age (years) Mean (SD)	42.1 (16.6)	0.0% (0)	49.3 (16.0)	0.0% (0)	0.02
BMI (kg/m <sup>2</sup> ) Mean (SD)	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% (2,502)	0.04% (17)	24.0% (1,188)	0.0% (0)	<0.001
Segmental Graft Type	1.3% (555)	0.0% (0)	8.1% (399)	0.0% (0)	<0.001
CIT (mins) Mean (SD)	378 (167)	0.8% (354)	517 (163)	8.0% (400)	<0.001
ABO match - identical	94.5% (40,522)	0.0% (0)	98.5% (4,874)	0.0% (0)	<0.001
DRI Mean (SD)	1.44 (0.28)	0.0% (0)	1.72 (0.40)	1.7% (84)	<0.001
<b>Recipient</b>					
Female	31.5% (13,523)	0.002% (1)	32.8% (1,622)	0.0% (0)	0.08
Age (Years) Mean (SD)	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% (1,276)	0.0% (0)	<0.001
BMI (kg/m <sup>2</sup> ) Mean (SD)	28.7 (5.7)	0.02% (9)	27.3 (5.2)	0.1% (5)	<0.001
MELD <sup>a</sup> Mean (SD)	21.7 (10.7)	0.1% (45)	16.5 (6.7)	0.7% (36)	<0.001
Waiting list time (days)	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% (2,045)	0.0% (0)	<0.001
Dependent functional status level 3 <sup>b</sup>	21.9% (9,270)	1.2% (510)	14.1% (690)	1.3% (64)	<0.001
Ascites	74.4% (31,910)	0.0% (0)	53.6% (2,643)	0.3% (17)	<0.001
Encephalopathy	61.5% (26,363)	0.0% (0)	31.0% (1,510)	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 prior to LT	9.2% (3,947)	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 Centre Volume	62.7 (32.7)	0.0% (0)	92.5 (32.3)	0.0% (0)	<0.001

*All data is expressed as percentage (number of patients), unless otherwise specified. <sup>a</sup> United States Model for End-stage Liver Disease*

*<sup>b</sup> Level 3 of a 3-point modified scale of functional status (including ECOG from UK and Karnofsky from US)*

**Abbreviations:** ABO: Blood group, BMI: Body mass index, CIT: Cold ischaemia 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, SD: standard deviation, UK: United Kingdom, US: United States,

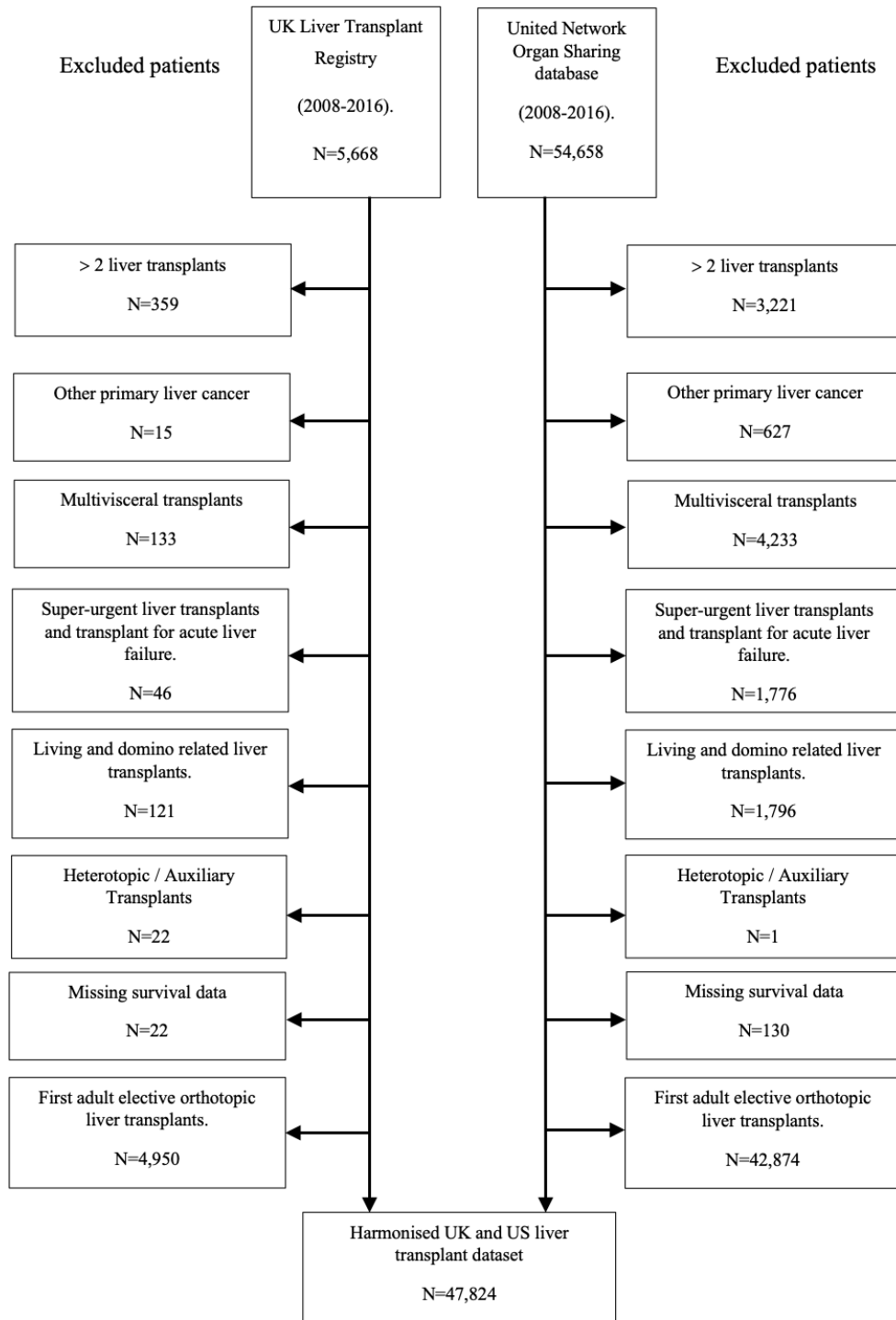
**Table 2: A time-dependent comparison of 5-year patient mortality between the UK and US in those receiving a deceased donor liver transplant.**

UK compared to the US Hazard ratio (95% CI)				P-value for time- dependency
Primary liver disease	0 – 90 days	90 days – 1 year	1 year to 5 years	
<b>Overall</b>				
Unadjusted	0.88 (0.76-1.02)	0.65 (0.55-0.77)	0.66 (0.59-0.74)	0.0068
Adjusted	0.96 (0.82-1.12)	0.71 (0.59-0.85)	0.71 (0.63-0.81)	0.004
<b>HCC</b>				
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
<b>Hepatitis C</b>				
Unadjusted	0.60 (0.34-1.06)	0.36 (0.19-0.66)	1.03 (0.78-1.35)	0.002
Adjusted	0.60 (0.34-1.08)	0.35 (0.19-0.66)	1.01 (0.76-1.35)	0.0006
<b>PSC</b>				
Unadjusted	1.08 (0.62-1.86)	0.61 (0.25-1.44)	0.96 (0.63-1.48)	0.52
Adjusted	1.23 (0.67-2.26)	0.69 (0.28-1.72)	1.06 (0.64-1.76)	0.55
<b>Hepatitis B</b>				
Unadjusted	1.73 (0.60-4.90)	Not enough events (UK)	Not enough events (UK)	N/A
Adjusted	2.48 (0.72-2.26)	Not enough events (UK)	Not enough events (UK)	N/A
<b>PBC</b>				
Unadjusted	0.65 (0.35-1.23)	0.60 (0.28-1.30)	0.53 (0.30-0.92)	0.88
Adjusted	0.72 (0.35-1.49)	0.66 (0.28-1.55)	0.57 (0.30-1.10)	0.86
<b>ALD</b>				
Unadjusted	0.82 (0.60-1.12)	0.71 (0.46-1.10)	0.56 (0.41-0.77)	0.23
Adjusted	0.95 (0.68-1.32)	0.82 (0.52-1.29)	0.64 (0.45-0.89)	0.21
<b>AID</b>				
Unadjusted	0.73 (0.43-1.26)	0.96 (0.52-1.78)	0.53 (0.28-1.00)	0.41
Adjusted	0.79 (0.44-1.35)	1.00 (0.53-1.89)	0.54 (0.28-1.03)	0.38
<b>Metabolic</b>				
Unadjusted	1.08 (0.70-1.66)	0.70 (0.37-1.32)	0.57 (0.33-0.99)	0.19
Adjusted	1.07 (0.68-1.69)	0.68 (0.35-1.30)	0.54 (0.30-0.95)	0.14
<b>Others</b>				
Unadjusted	1.05 (0.62-1.77)	1.59 (0.70-3.59)	0.61 (0.32-1.13)	0.16
Adjusted	1.37 (0.75-2.48)	2.12 (0.89-5.07)	0.82 (0.41-1.65)	0.18
<p><i>* Adjusted for recipient characteristics: sex, age, ethnicity, BMI (kg/m<sup>2</sup>), disease aetiology, functional status, ascites, encephalopathy, HCV status, MELD, pre-transplant renal replacement therapy, previous abdominal surgery, and donor characteristics: sex, age, BMI (kg/m<sup>2</sup>), CIT, donor type (DCD/DBD), cause of death, ABO match, graft type.</i></p> <p><b>Abbreviations:</b> ALD: Alcohol-related liver disease, AID: Autoimmune disease, BMI: Body mass index, CI: Confidence interval, CIT: Cold ischaemia time, DBD: Donation after brainstem death, DCD: Donation after circulatory death, HCC:</p>				

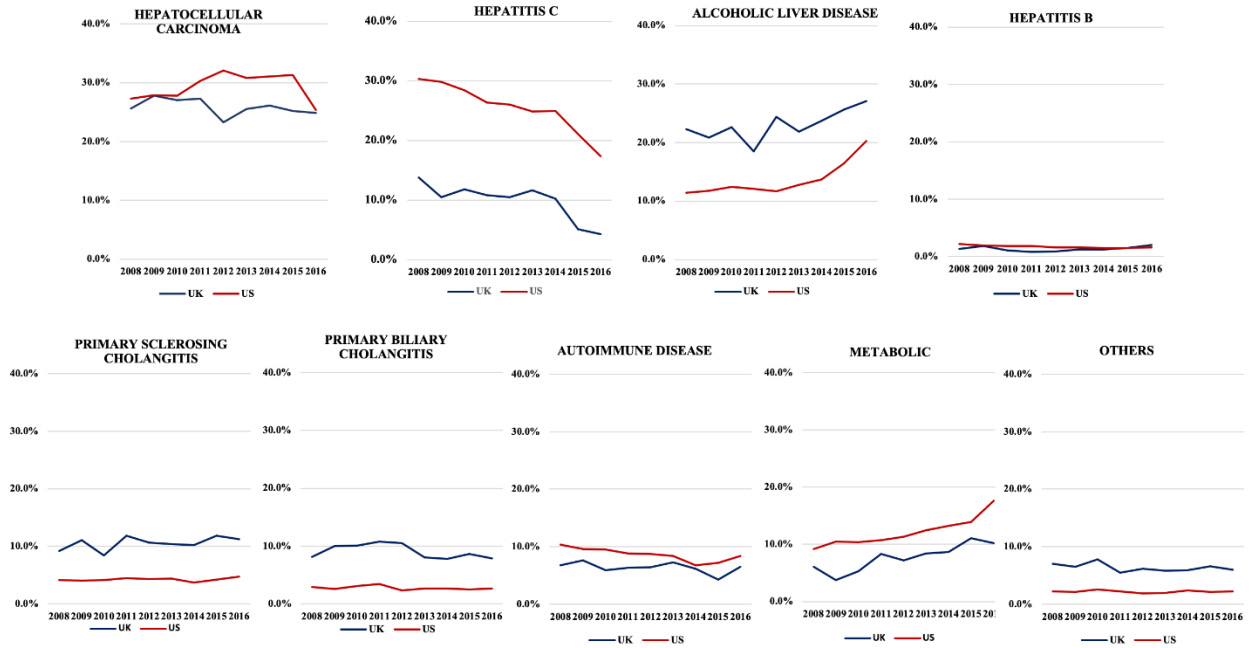
Hepatocellular carcinoma, HCV: Hepatitis C virus, MELD: Model for End-stage liver disease, PBC: Primary biliary cholangitis, PSC: Primary sclerosing cholangitis, UK: United Kingdom, US: United States



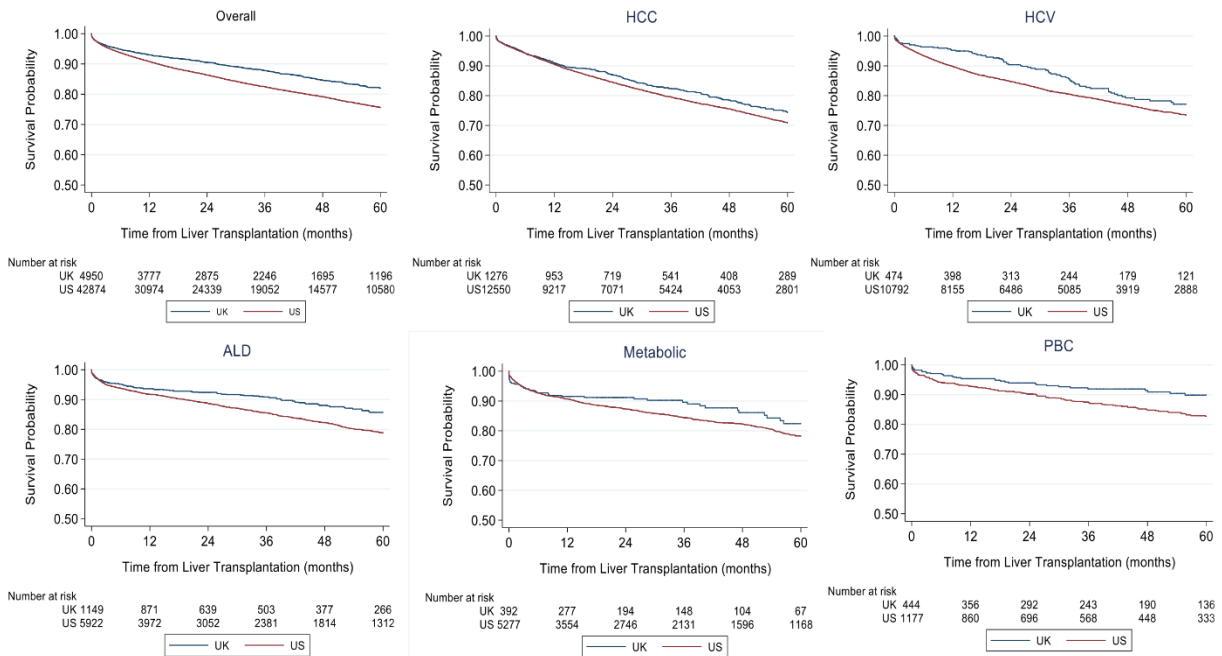
**Figure 1:** Flow chart detailing selection of study population (2008-2016).



**Figure 2:** Time-trends in the indications for liver transplant in the US and UK between 2008 and 2016.



**Figure 3:** Kaplan-Meier survival graphs by liver disease category for liver transplant recipients in the US and the UK between 2008 to 2016.



**Figure 4:** Unadjusted and adjusted HRs (and 95%CI) for mortality in the first 90-days, 90-days to one year and beyond the first year in the US (n=42,874) compared with the UK (n=4,950) by liver disease category. \*Adjusted for recipient characteristics: sex, age, ethnicity, BMI (kg/m<sup>2</sup>), disease aetiology, functional status, ascites, encephalopathy, HCV status, MELD, pre-transplant renal replacement therapy, previous abdominal surgery, and donor characteristics: sex, age, BMI (kg/m<sup>2</sup>), CIT, donor type (DCD/DBD), cause of death, ABO match, graft type.

