LIVER

Survival after liver transplantation in the United Kingdom and Ireland compared with the United States

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Background and objective: Surgical mortality in the US is widely perceived to be superior to that in the UK. However, previous comparisons of surgical outcome in the two countries have often failed to take sufficient account of case-mix or examine long-term outcome. The standardised nature of liver transplantation practice makes it uniquely placed for undertaking reliable international comparisons of surgical outcome. The objective of this study is to undertake a risk-adjusted disease-specific comparison of both short- and long-term survival of liver transplant recipients in the UK and Ireland with that in the US.

Methods: A multicentre cohort study using two high quality national databases including all adults who underwent a first single organ liver transplant in the UK and Ireland (n = 5925) and the US (n = 41 866) between March 1994 and March 2005. The main outcome measures were post-transplant mortality during the first 90 days, 90 days to 1 year and beyond the first year, adjusted for recipient and donor characteristics.

Results: Risk-adjusted mortality in the UK and Ireland was generally higher than in the US during the first 90 days (HR 1.17; 95% CI 1.07 to 1.29), both for patients transplanted for acute liver failure (HR 1.27; 95% CI 1.01 to 1.60) and those transplanted for chronic liver disease (HR 1.18; 95% CI 1.07 to 1.31). Between 90 days and 1 year post-transplantation, no statistically significant differences in overall risk-adjusted mortality were noted between the two cohorts. Survivors of the first post-transplant year in the UK and Ireland had lower overall risk-adjusted mortality than those transplanted in the US (HR 0.88; 95% CI 0.81 to 0.96). This difference was observed among patients transplanted for chronic liver disease (HR 0.88; 95% CI 0.81 to 0.96), but not those transplanted for acute liver failure (HR 1.02; 95% CI 0.70 to 1.50).

Conclusions: Whilst risk-adjusted mortality is higher in the UK and Ireland during the first 90 days following liver transplantation, it is higher in the US among those liver transplant recipients who survived the first post-transplant year. Our results are consistent with the notion that the US has superior acute perioperative care whereas the UK appears to provide better quality chronic care following liver transplantation surgery.

International comparisons of health care outcomes and practices provide a unique opportunity for benchmarking and allow policymakers and clinicians to identify areas of health care delivery where countries could learn from each other.[1] Surgical mortality in the US is widely perceived to be superior to that in the UK. Previous transatlantic comparisons of surgical outcome have reported that, compared with the US, the UK has a fourfold higher risk-adjusted inpatient mortality rate following major non-cardiac surgery,[2] higher unadjusted 1-year mortality among heart transplant recipients (23% vs 14%)[3] and similar unadjusted 1-year mortality among elective adult first liver transplant recipients in the year 2000 (13.5% vs 12%) in the face of some evidence of less severe liver disease.[4] Those comparisons have, however, failed to take sufficient account of case-mix or examine long-term outcome.

Given the standardised nature of liver transplantation practice, which makes it uniquely placed for undertaking reliable international comparisons of surgical outcome, and the fact that risk-adjusted post-transplant survival is a function of the underlying liver disease,[5] we carried out a disease-specific risk-adjusted comparison of both short- and long-term patient survival following liver transplantation in the UK and Ireland and the US between 1 March 1994 and 31 March 2005.

MATERIALS AND METHODS

Databases

We used the databases of the UK and Ireland Liver Transplant Audit and the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS). Detailed descriptions of these databases and evidence of their completeness, accuracy and reliability have been published elsewhere.[6–8] The study population included all adults (aged 16 years or older) who received a first liver transplant in the three countries between 1 March 1994 and 31 March 2005. Patients who underwent multiorgan transplantation, those who had received a previous liver transplant and those with missing survival data (three in the UK and Ireland and two in the US) were excluded.

Data management

The two databases were harmonised to ensure that liver disease classification and risk factor definitions were comparable.

We adopted a 10-category liver disease classification system (table 1) similar to that used by Roberts *et al*.[5]

Patients were classified according to both diagnostic code and, if present, free text diagnosis. In line with previous studies,[9–11] we assigned patients to the acute liver failure category only if their diagnostic details were consistent with this designation and were also transplanted at the highest listing urgency status (ie, ''super-urgent'' status in the UK and Ireland and UNOS status 1 in the US). In order to ensure that, in the event of multiple diagnoses, patients were assigned to

Abbreviations: HR, hazard ratio; INR, international normalised ratio; MELD, model for end-stage liver disease; OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing

Table 1 Liver disease classification scheme

Category	Diseases
Primary biliary cirrhosis (PBC)	Primary biliary cirrhosis
Primary sclerosing cholangitis (PSC)	Primary sclerosing cholangitis (with Crohn's disease; ulcerative colitis; no bowel disease; other)
Alcoholic liver disease (ALD)	Alcoholic cirrhosis; acute alcoholic hepatitis
Autoimmune and cryptogenic disease (AID)	Cirrhosis (autoimmune; cryptogenic; drug/industrial exposure; chronic active hepatitis—aetiology unknown; type non-A, non-B; uncertain or unknown aetiology); giant cell hepatitis
Hepatitis C cirrhosis (HCV)	Cirrhosis (type C; type B and C); alcoholic cirrhosis with hepatitis C
Hepatitis B cirrhosis (HBV)	Cirrhosis (type B—HBsAg+; type B and D; type D)
Acute liver failure (ALF)	Fulminant hepatic failure; acute hepatic necrosis (type A; type B—HBsAg+; type non-A- non-B; type C; type D, type B and C; type B and D; drug induced—paracetamol; drug (not paracetamol)/toxin induced; aetiology unknown; trauma; ischaemic; postoperative; other)
Cancer	Primary liver malignancy (hepatocellular carcinoma (HCC)—non-cirrhotic; HCC and cirrhosis; fibrolamellar; cholangiocarcinoma; hepatoblastoma; haemangioendothelioma–haemangiosarcoma; other); bile duct cancer; secondary hepatic malignancy
Metabolic liver disease	Alpha-1-antitrypsin deficiency; Wilson disease (acute; chronic); haemochromatosis–haemosiderosis; cirrhosis (non-alcoholic steatohepatitis (NASH); fatty liver disease); TPN/hyperalimentation-induced liver disease; glycogen storage disease type I; glycogen storage disease type II; hyperlipidaemia type II—homozygous hypercholesterolaemia; tyrosinaemia; primary oxalosis/oxaluria–hyperoxaluria; maple syrup urine disease; amyloidosis; sarcoidosis; haemophilia; von Willebrand disease; Crigler–Najjar syndrome; urea cycle disorder; other metabolic disease
Other liver diseases	Cirrhosis (type A; non-specified viral hepatitis; other); secondary biliary cirrhosis (Caroli disease; choledochal cyst; other); familial cholestasis (Byler disease; other); cholestatic liver disease—other; neonatal cholestatic liver disease; biliary atresia or hypoplasia (extrahepatic; biliary hypoplasia—non-syndromic paucity; biliary hypoplasia—Alagille syndrome; other); idiopathic adulthood ductopaenia; cystic fibrosis; congenital hepatic fibrosis; Budd–Chiari syndrome (acute; chronic); portal vein thrombosis; benign tumour (hepatic adenoma; polycystic liver disease; other); graft versus host disease; trauma; nodular regenerative hyperplasia; other, not already noted above; not reported

the diagnosis which is deemed most likely to influence their prognosis, disease classification was undertaken in a hierarchical order: cancer, hepatitis C cirrhosis and primary sclerosing cholangitis. For example, patients with a coded diagnosis of hepatitis C cirrhosis and a free text diagnosis of hepatocellular carcinoma were assigned to the ''Cancer'' category, as were patients with incidental malignant tumours found in the explanted liver. 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.

For the purposes of multivariable analyses, creatinine was set to 4.0 mg/dl for those with lower values who received renal support immediately prior to transplantation.

Implausible values of body mass index (BMI; <10 or >100 kg/m^2), cold ischaemic time (>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.

The model for end-stage liver disease (MELD) score, an objective widely used method of predicting liver disease mortality without transplantation, was calculated using serum creatinine, serum total bilirubin and international normalised ratio (INR) of prothrombin time values obtained immediately before transplantation as described by UNOS,[12] with the exceptions that no upper or lower limits were applied to the score, and hepatocellular carcinoma recipients and other special cases were not awarded extra points. A high MELD score corresponds to a poorer prognosis.

Statistical analyses

We used survival analysis to analyse mortality after liver transplantation. Patients lost to follow-up were censored at the date of last follow-up. Patients requiring a second graft were not censored at the time of re-transplantation. Unadjusted mortality estimates were calculated using the Kaplan–Meier method. Piecewise proportional hazard regression[13] was used to generate overall and disease-specific hazard ratios (HRs) indicating the relative risk of death in the UK and Ireland versus the US in the following time periods after liver transplantation: the first 90 days, 90 days to 1 year and beyond the first year. Thus, HRs >1 indicate that the mortality in the UK and Ireland is higher than in the US. The analysis was censored at 10 years post-transplantation. Only those clinically plausible recipient and donor risk factors that were well recorded to a comparable degree in both databases with non-missing values of $>80\%$ were included in the regression models. Those risk factors were: liver disease category, recipient age, race, BMI, serum albumin, serum bilirubin, serum creatinine, requirement for preoperative renal support, requirement for preoperative ventilation and history of previous upper abdominal surgery, graft type, organ cold ischaemic time, donor age, type, cause of death and BMI, donor–recipient gender match, donor–recipient blood group match, donor–recipient cytomegalovirus serology match and year of transplantation. We categorised BMI according to the World Health Organization guidelines as follows: non-obese (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese ($\geq$30.0 kg/m^2) or underweight (<18.5 kg/m^2). All other numerical data were used as continuous variables in the multivariable analyses.

Information on every variable included in the risk models was available for 30 493 patients (63.8%). Variables with the highest percentage of missing values included donor–recipient cytomegalovirus serology match (15.0%), organ cold ischaemic time (12.2%), donor BMI (7.7%) and recipient history of previous upper abdominal surgery (5.6%). All other variables used had rates of missing values between 0% and 4%.

To ensure that patients with missing values were not excluded from the analysis, we used the technique of multiple imputation as described by Royston.[14 15] Missing values were imputed 10 times using switching regression to create 10 complete data sets which were each independently analysed. Analyses were then pooled to give final estimates.

We also carried out two sets of additional analyses. The first was restricted to patients with acute liver failure and included aetiology (paracetamol- vs non-paracetamol-induced) in the risk model in addition to the above-described risk factors. The second entailed repeating all the analyses having included transplant centre volume in the risk models. In line with previous studies,[16 17] transplant centre volume (defined as the

average number of adult single organ liver transplants, including re-transplants, performed during the study period at a given centre per year) was used as a dichotomous variable with a cut-off of 20 transplants per year. For the purposes of all analyses incorporating transplant centre volume, the standard errors of the estimates were adjusted in order to account for the possibility of transplant centre clustering.[18]

All analyses were performed using Stata version 9 (StataCorp, College Station, TX, US).

RESULTS

Clinical characteristics

Between 1 March 1994 and 31 March 2005, 5925 adults received a first single organ liver transplant at eight centres in the UK and Ireland, while 41 866 such transplants were performed at 137 centres in the US. The mean annual transplant centre volume in the UK and Ireland was significantly larger than in the US (table 2).

The age, gender and racial distributions of the two cohorts were similar. The most common indications for liver transplantation were primary biliary cirrhosis and alcoholic liver disease in the UK and Ireland, and hepatitis C cirrhosis in the US (table 3).

Compared with their US counterparts, liver transplant recipients in the UK and Ireland were far more likely to be transplanted for acute liver failure or cancer, had a greater requirement for preoperative renal support, were less often mechanically ventilated immediately prior to transplantation, had a significantly longer donor organ cold ischaemic time, were more likely to receive grafts from older donors who had succumbed as a result of a cerebrovascular accident (as opposed to trauma) and had slightly lower mean MELD scores, except among patients transplanted for acute liver failure whose MELD scores were higher in the UK and Ireland. It is important to note, however, that MELD scores could not be calculated in 54.3% of US patients because their INR data were not available.

Post-transplant mortality

The 5-year mortality of patients transplanted for chronic liver disease in the UK and Ireland was similar to that observed in the US (27.1%; 95% CI 25.8% to 28.5% vs 28.3%; 95% CI 27.8% to 28.8%), whereas the 5-year mortality of those transplanted

Table 2 Distribution of clinical characteristics at time of transplantation in the UK and Ireland and the USA between 1 March 1994 and 31 March 2005

	Overall		Acute liver failure		Chronic liver disease	
Characteristic	**UK and Ireland**	**USA**	**UK and Ireland**	**USA**	**UK and Ireland**	**USA**
Number of recipients	5925	41 866	773	1507	5152	40 359
Recipient age (years)	48.6 (12.5)	50.4 (10.8)	36.5 (13.2)	38.5 (14.1)	50.4 (11.4)	50.8 (10.4)
Recipient gender (% male)	56.1	63.2	33.0	33.1	59.6	64.3
Recipient race (%)						
White	86.3	87.0	87.3	71.3	86.1	87.6
Non-white	13.7	13.0	12.7	28.7	13.9	12.4
Recipient BMI (kg/m^2)	25.4 (4.9)	27.7 (5.8)	24.3 (5.0)	26.8 (6.3)	25.5 (4.9)	27.7 (5.8)
Albumin (g/dl)	3.0 (0.7)	2.9 (0.7)	2.8 (0.9)	2.8 (0.6)	3.0 (0.6)	2.9 (0.7)
Bilirubin (mg/dl)	7.5 (9.6)	6.8 (9.6)	17.0 (12.5)	20.1 (12.5)	6.1 (8.2)	6.3 (9.1)
Creatinine (mg/dl)	1.5 (1.2)	1.3 (1.1)	2.8 (1.6)	2.2 (1.9)	1.3 (0.9)	1.3 (1.0)
Calculated MELD score	20.2 (11.0)	19.5 (9.6)	39.8 (9.6)	35.0 (9.0)	17.3 (7.9)	19.0 (9.1)
Preoperative renal support (%)	12.8	4.2	50.3	17.1	7.2	3.7
Preoperative ventilation (%)	11.0	5.9	73.7	52.4	1.6	4.1
Previous upper abdominal surgery (%)	18.3	35.8	8.1	18.8	19.9	36.3
Graft type (%)						
Whole	94.4	94.4	91.6	96.6	94.9	94.4
Segmental	5.6	5.6	8.4	3.4	5.1	5.6
Cold ischaemic time (min)	658.1 (190.1)	497.3 (240.7)	601.0 (190.1)	486.6 (242.2)	666.8 (188.6)	497.7 (240.6)
Donor age (years)	42.7 (15.0)	38.4 (17.4)	41.7 (15.6)	36.9 (17.7)	42.8 (14.9)	38.5 (17.4)
Donor type (%)						
Cadaveric heart-beating	98.6	94.6	99.9	97.8	98.5	94.4
Living	0.4	4.1	0	1.1	0.4	4.2
Cadaveric non-heart-beating	1.0	1.3	0.1	1.1	1.1	1.4
Donor cause of death (%)						
Trauma	21.1	45.1	20.8	44.6	21.1	45.1
Cerebrovascular accident	64.5	42.9	65.7	42.7	64.4	42.9
Cerebral anoxia	6.7	9.1	6.8	9.5	6.7	9.1
Other	7.7	2.9	6.7	3.2	7.8	2.9
Donor BMI (kg/m^2)	24.8 (4.3)	25.4 (5.8)	24.3 (4.0)	25.1 (5.9)	24.9 (4.3)	25.5 (5.8)
Donor–recipient gender match (%)						
Male–male	35.3	40.6	18.4	20.3	37.8	41.3
Female–male	20.8	22.5	14.6	12.7	21.8	22.9
Male–female	18.2	19.1	31.8	37.7	16.2	18.4
Female–female	25.7	17.8	35.2	29.3	24.2	17.4
Donor–recipient blood group match (%)						
Identical	89.8	91.7	67.0	66.6	93.2	92.6
Compatible	9.7	7.4	32.3	27.9	6.3	6.7
Incompatible	0.5	0.9	0.7	5.5	0.5	0.7
Donor–recipient CMV match (%)						
Positive match	64.2	68.2	52.2	71.1	65.7	68.0
Positive mismatch	17.7	18.9	24.8	16.4	16.8	19.0
Negative match	18.1	12.9	23.0	12.5	17.5	13.0
Re-transplantation requirement (%)	9.0	8.0	10.7	9.3	8.7	8.0
Annual transplant centre volume	95.5 (38.7)	67.7 (46.9)	96.9 (41.0)	68.7 (50.3)	95.3 (38.3)	67.7 (46.8)

Values are means (SD) unless indicated as percentages.
BMI, body mass index; CMV, cytomegalovirus; MELD, model for end-stage liver disease.

Table 3 Frequency (%) of liver disease categories in liver transplant recipients in the UK and Ireland and the USA between 1 March 1994 and 31 March 2005

Disease category	UK and Ireland n = 5925	USA n = 41 866
Overall	100.0	100.0
Acute liver failure (ALF)	13.1	3.6
Chronic liver disease (CLD)	86.9	96.4
Primary biliary cirrhosis (PBC)	15.2	5.7
Primary sclerosing cholangitis (PSC)	8.5	6.7
Alcoholic liver disease (ALD)	15.2	13.7
Autoimmune and cryptogenic disease (AID)	10.8	13.7
Hepatitis C cirrhosis (HCV)	13.1	37.7
Hepatitis B cirrhosis (HBV)	4.0	4.3
Cancer	11.7	6.9
Metabolic liver disease	4.7	4.8
Other liver diseases	3.7	2.9

for acute liver failure was higher in the UK and Ireland (34.1%; 95% CI 30.7% to 37.8% vs 29.1%; 95% CI 26.7% to 31.6%). A disease-specific comparison of the 5-year mortality within patients transplanted for chronic liver disease produced similar findings, with the exception of higher mortality among patients transplanted for primary sclerosing cholangitis in the UK and Ireland (fig 1).

In contrast, the 90-day mortality was higher in the UK and Ireland than in the US among both patients transplanted for acute liver failure (24.9%; 95% CI 22.0% to 28.1% vs 18.2%; 95% CI 16.3% to 20.2%) and those transplanted for chronic liver disease (9.4%; 95% CI 8.6% to 10.2% vs 8.0%; 95% CI 7.7 to 8.2%). A disease-specific comparison within patients transplanted for chronic liver disease revealed a similar pattern, except in patients with alcoholic liver disease who had slightly lower 90-day mortality in the UK and Ireland (fig 2).

In both cohorts, the 5-year mortality was lowest among primary biliary cirrhosis recipients and highest among patients transplanted for cancer, followed by those transplanted for acute liver failure and hepatitis C cirrhosis.

Risk-adjusted comparisons

Risk-adjusted mortality (fig 2) in the first 90 days was significantly higher in the UK and Ireland than in the US (HR 1.17; 95% CI 1.07 to 1.29, $p<0.001$), both for patients transplanted for acute liver failure (HR 1.27; 95% CI 1.01 to 1.60, $p<0.04$) and those transplanted for chronic liver disease (HR 1.18; 95% CI 1.07 to 1.31, $p<0.001$). Mortality between 90 days and 1 year was similar between the two overall cohorts. Compared with their US counterparts, patients who survived the first post-transplant year in the UK and Ireland had a lower overall risk-adjusted mortality (HR 0.88; 95% CI 0.81 to 0.96, $p<0.004$). This difference was observed among patients transplanted for chronic liver disease (HR 0.88; 95% CI 0.81 to 0.96, $p<0.003$) but not those transplanted for acute liver failure (HR 1.02; 95% CI 0.70 to 1.50, $p = 0.9$).

Disease-specific risk-adjusted comparisons largely reflected the overall results for chronic liver disease, although there were some notable exceptions. For example, the mortality between 90 days and 1 year was significantly higher in the UK and Ireland among patients transplanted for primary sclerosing cholangitis (HR 1.70; 95% CI 1.04 to 2.78, $p<0.03$).

Additional analyses

When paracetamol hepatotoxicity ($n = 278$ in the UK and Ireland vs $n = 160$ in the US) was included in the risk model, the mortality of patients transplanted for acute liver failure in the UK and Ireland remained significantly higher during the first 90 days than that of their US counterparts (HR 1.33; 95% CI 1.06 to 1.68, $p<0.02$).

Similarly, the differences in overall risk-adjusted mortality between the two cohorts persisted even after differences in transplant centre volume were accounted for in the risk model ($\leqslant$90 days, HR 1.22; 95% CI 1.01 to 1.47, $p<0.04$; 90 days to 1 year, HR 0.97; 95% CI 0.84 to 1.12, $p = 0.7$; >1 year, HR 0.89; 95% CI 0.80 to 0.99, $p<0.03$).

DISCUSSION

We found that the mortality in the first 90 days after adult first single organ liver transplantation was higher in the UK and Ireland than in the US, but lower in patients who survived the first year. This trend was apparent across most liver disease categories both with and without risk adjustment.

Methodological limitations

Well-recognised differences in the aetiology of acute liver failure exist between the two cohorts. Paracetamol hepatotoxicity is a far more common cause of acute liver failure necessitating liver transplantation in the UK and Ireland than the US (36.0% vs 10.6% in our study) and is also associated with poorer transplant outcomes than other causes of acute liver failure.[9] This could account for the greater preoperative requirements for renal and ventilatory support we observed among patients transplanted for acute liver failure in the UK and Ireland, However, it is unlikely that these case-mix differences have contributed to the higher early mortality of this group in the UK and Ireland given that the differences in mortality in the first 90 days between the two cohorts remained when we adjusted for paracetamol hepatotoxicity in the risk model.

A further limitation relates to potential differences in data quality between the two databases. However, both databases are mandatory national liver transplant registries and have robust quality assurance procedures ensuring high standards of timely and complete data submission, validation and ascertainment of post-transplant adverse events,[6–8 19] thereby making suboptimal data quality an unlikely explanation for the observed mortality differences. In particular, the inferior long-term mortality among US liver transplant recipients cannot be accounted for by differences in the percentage of patients who were lost to follow-up (3.9% in the UK and Ireland vs 8.1% in the US).

Explanations for the observed differences

Although our comparison was risk-adjusted, it is still conceivable that the observed mortality differences could be explained by residual confounding. For example, a number of clinically plausible risk factors were not included in the regression model that we used for risk adjustment, because they had high frequencies of missing data in either database (eg, MELD), were not recorded in a format that allows direct and reliable comparison (eg, encephalopathy) or were likely to be differently defined (eg, requirement for hospitalisation). However, we believe that residual confounding is an unlikely explanation because our risk model included the vast majority of previously identified recipient and donor risk factors of post-liver transplant outcome.[20 21] With regards to MELD, we[6] and others[22 23] have previously shown it to be a poor predictor of post-transplant mortality and, hence, its omission from the multivariable analyses is highly unlikely to have made a significant difference to our results. Similarly, although our analysis did not take account of waiting time for the procedure (which is considerably longer in the US[4]), it is inconceivable that this has influenced our results since previous studies have clearly demonstrated that longer waiting time does not predict

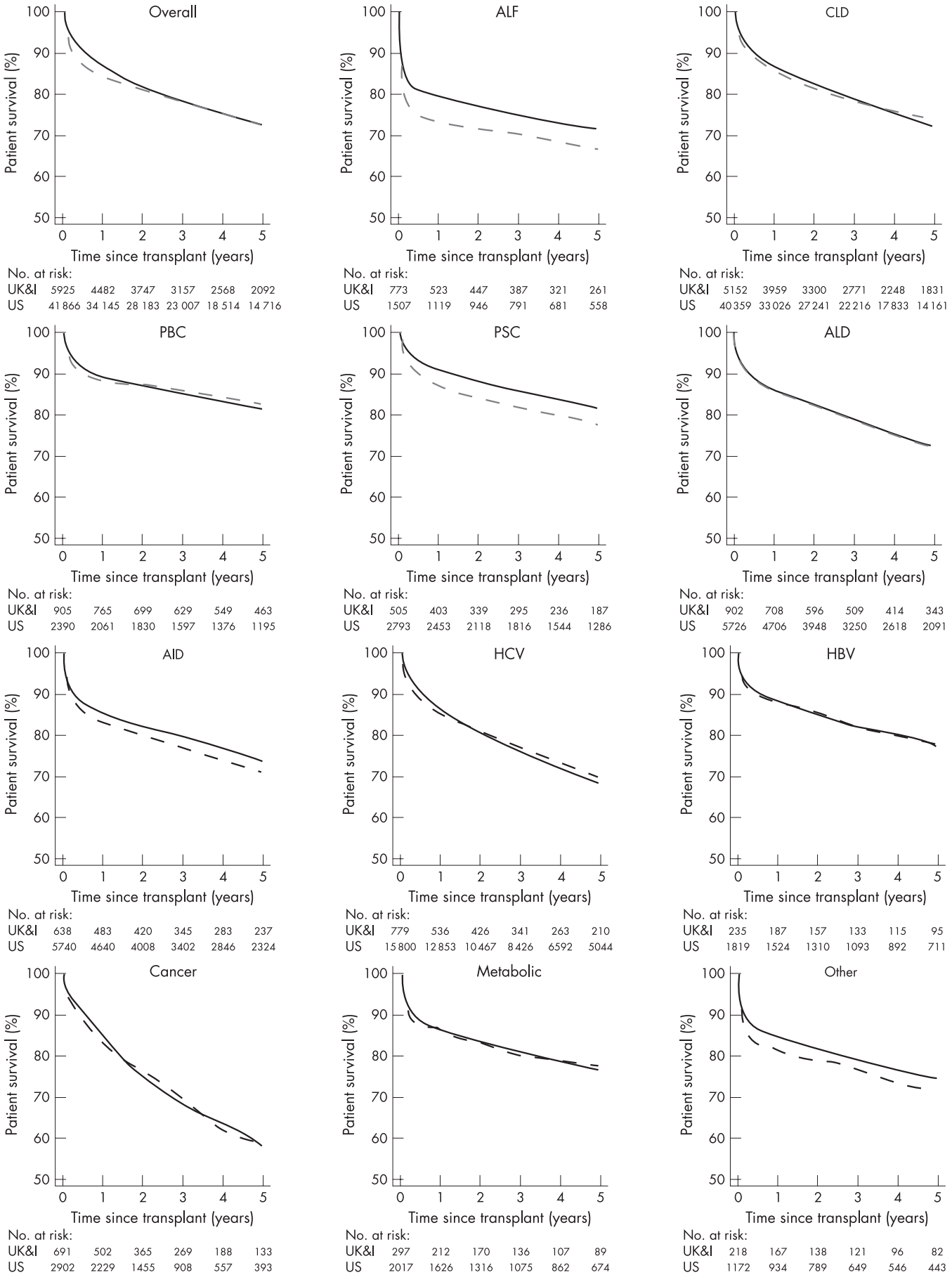

Figure 1 Kaplan–Meier survival graphs by liver disease category for liver transplant recipients in the UK and Ireland (dashed line) and the USA (solid line) between 1 March 1994 and 31 March 2005. ALF, acute liver failure; CLD, chronic liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; ALD, alcoholic liver disease; AID, autoimmune and cryptogenic disease; HCV, hepatitis C cirrhosis; HBV, hepatitis B cirrhosis; metabolic, metabolic liver disease; other, other liver diseases.

more severe liver disease at transplantation[6] or higher mortality either preoperatively or postoperatively.[24–28]

Whilst transplant centre volume has an important,[16 29] albeit waning,[17] influence on post-liver transplant outcomes, we felt it inappropriate to adjust for it in an international comparison of two health care systems because it potentially reflects the efficiency of organisation and delivery of a given country's health care system.[19] However, the results of our additional analyses, which incorporated this parameter in the risk models, suggest that it cannot explain the observed differences in post-transplant mortality between the two cohorts.

It is noteworthy that the cold ischaemic time, a measure of the efficiency of the organ procurement and distribution process and an important determinant of graft survival, is significantly longer in the UK and Ireland than in the US. The likely reasons for this require further study but might relate to logistic delays in organ retrieval and implantation. However, given the fact that it was included in the risk-adjustment, cold ischaemic time cannot account for the higher early mortality observed in the UK and Ireland.

The remaining explanation for the observed mortality differences is a genuine difference in quality of care. The observation that short-term mortality following liver transplantation is higher in the UK and Ireland than in the US is consistent with previously reported differences in risk-adjusted hospital mortality following major non-cardiac surgery.[2] Significant corresponding differences have been documented between the two health care systems in nurse–patient ratios[2 30 31] and provision of intensive care,[32–35] both of which have been shown to be inversely associated with excess surgical hospital mortality.[2 30 31 36–42] The observed early mortality differences could also reflect differences in donor appraisal and selection practices between the two cohorts. A survey of UK and US liver transplant surgeons in 2002[43] showed that American surgeons adopt a more conservative approach with regards to utilising steatotic donor livers, known to be associated with inferior short-term outcomes,[44–48] placing far greater emphasis on histological assessment than their British counterparts. Other factors that might affect the quality of care in this period could include differences in operator expertise and/or commitment to other surgical disciplines and differences in immunosuppressive and antibiotic protocols.

The higher risk-adjusted mortality among US survivors of the first post-transplant year, compared with those transplanted in the UK and Ireland, is likely to have other explanations. One possibility could be that US liver transplant programmes are good at prolonging, beyond the first post-transplant year, the survival of those high risk recipients who would have otherwise

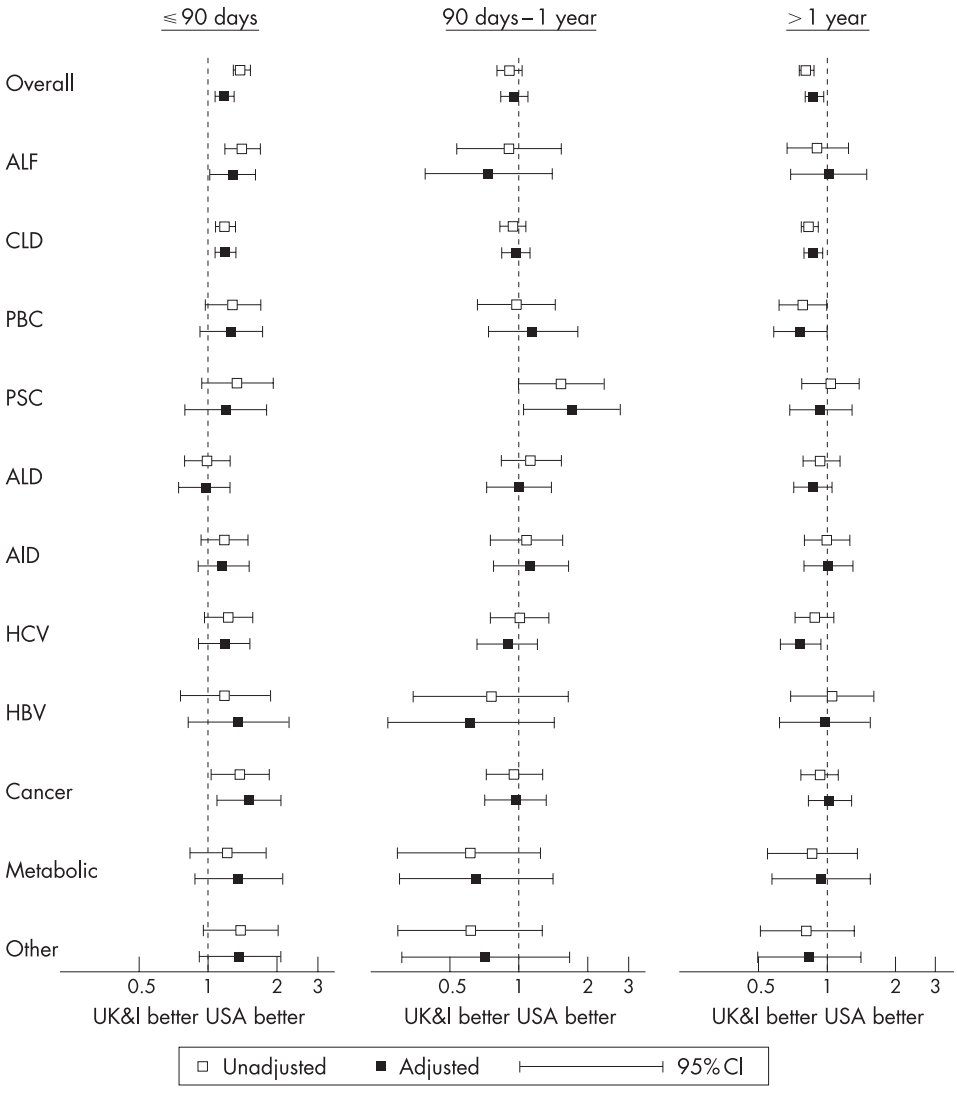

Figure 2 Unadjusted and adjusted HRs (and 95% CIs) for mortality in the first 90 days, 90 days to 1 year and beyond the first post-transplant year in the UK and Ireland (n = 5925) compared with the USA (n = 41 866) by liver disease category. The analysis was censored at 10 years post-transplantation. ALF, acute liver failure; CLD, chronic liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; ALD, alcoholic liver disease; AID, autoimmune and cryptogenic disease; HCV, hepatitis C cirrhosis; HBV, hepatitis B cirrhosis; metabolic, metabolic liver disease; other, other liver diseases.

died early had they been transplanted in the UK and Ireland. However, given the fact that risk-adjustment was equally applied to all time periods, we believe this possibility is unlikely.

The factors that predict long-term post-liver transplant mortality have been poorly investigated, but may include immunosuppressive strategies, management of complications of immunosuppression and disease recurrence, as well as management of co-morbidities. Some of these factors might be different in the two cohorts. For example, McGlynn *et al*[49] found that only 56% of Americans received recommended medical care for a range of chronic conditions, including diabetes, hypertension and hyperlipidaemia, all of which are known to be highly prevalent among liver transplant recipients.[50] Other possible explanations could relate to differences in strength of primary care infrastructure[51 52] as well as equity of access to, and costs of health care in, the two cohorts. The 2002 Commonwealth Fund International Health Policy Survey found that sicker adults in the US are far more likely than those in the UK to forgo medical care and fail to comply with recommended follow-up and treatment, because of costs.[53] More recently, a comparison of prevalence rates of self-reported illnesses and biological markers of disease in the two countries[54] concluded that US residents are much less healthy than their English counterparts, especially those at the bottom of the socio-economic hierarchy. Moreover, health insurance status was shown to be an independent predictor of 5-year mortality among US liver transplant recipients,[55] whereas the extension of Medicare insurance coverage of immunosuppressive medications beyond 1 year after kidney transplantation in the US resulted in a significant improvement of both patient and graft survival.[56 57]

Interestingly, similar findings to those found in our study were recently reported in a risk-adjusted comparison of mortality among survivors of the first year after kidney transplantation between the US and Canada,[58] another country with a universal health care system like that in the UK and Ireland.

The observed survival difference among those transplanted for primary sclerosing cholangitis, which unlike other diseases is apparent up to a year after transplantation, is intriguing. Whether this reflects differences in surgical technique[59] or is simply due to a type 1 error could not be ascertained from our data, and merits a further study.

Future

Whilst long-term survival in most disease categories was similar between patients transplanted in the UK and Ireland and the US, the time course of the mortality is different. The factors responsible for those differences and whether they continue beyond 10 years require more detailed analyses. Further research is also necessary to confirm our hypothesis that the observed differences in mortality after liver transplantation reflect more generic differences in perioperative and long-term care between the two health care systems.

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