TITLE PAGE

Short and long-term mortality after liver transplantation in patients with and without hepatocellular carcinoma in the United Kingdom.

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ABSTRACT

Background: The increasing demand for liver transplantation has led to considerable changes in characteristics of donors and recipients. In this study, the short-term and long-term mortality of HCC and non-HCC recipients in the UK were evaluated between 1997 and 2016.

Methods: First-time elective adult liver transplant recipients in the UK were identified and four successive eras of transplantation were compared. Hazard ratios (aHR) comparing the impact of era on short-term (first 90 days) and ~~on~~ longer-term mortality (from 90 days to 5 years) were estimated with adjustment of recipient and donor characteristics.

Results: 1 879 HCC recipients and 7 661 non-HCC recipients were included. There was an increase in use of donors following circulatory death (DCD) from 0% in era 1 to 35.2% in era 4 for HCC recipients and from 0.2% to 24.1% for non-HCC recipients. 3-year mortality decreased from 28.3% in era 1 to 16.9% in era 4 (aHR: 0.47, 95%CI: 0.35-0.63) for HCC recipients and from 20.4% to 9.3% (aHR: 0.44, 0.36-0.53) for non-HCC recipients. Comparing era 1 and era 4, improvements in short-term mortality were more marked than in long-term mortality both for HCC (aHR 0-90 days: 0.20, 0.10-0.39; 90 days-5 years: 0.52, 0.35-0.75; p=0.04) and for non-HCC recipients (aHR 0-90 days: 0.32, 0.24-0.42; 90 days-5 years: 0.52, 0.40-0.67; p=0.02).

Conclusion: In last 20 years, mortality after liver transplantation has more than halved, despite an increasing use of DCD donors. Improvements in overall survival can be explained by decreases in short-term and longer-term mortality.

INTRODUCTION

The rise in incidence of hepatocellular carcinoma (HCC) and the introduction of selection criteria that identify patients with HCC who are likely to achieve acceptable results with liver transplantation have led to a marked increase in the number of patients with HCC who receive a liver transplant.[1-5] This has put pressure on transplantation services in many countries because it is felt to be more difficult to cope with transplanting both HCC and non-HCC patients in an acceptable time frame.[1] The chronic shortage of donor organs has led to an increase in the use of donors whose organs have a greater risk of initial poor function or failure, including organs donated after circulatory death (DCD).[6]

It is currently unknown to what extent the increase in the number of liver transplants for HCC and the related increased use of sub-optimal donors have affected post-transplantation outcomes. A study, carried out in the UK including patients transplanted between 2005 and 2010, has suggested that recipients of a DCD liver have poorer post-transplantation outcomes.[6] However, for some patients on the waiting list, especially those with HCC, transplantation with a DCD liver may still offer the best chance of curative treatment.[1] This is particularly relevant for organ allocation policies – like those used in the UK until recently – that do not use tumour characteristics to prioritise patients on the waiting list[7,8] or for countries who have a high waiting list mortality.[9,10]

It has previously been shown that patients who receive a liver transplant as treatment for HCC are on average in a better physical condition with less signs of end-stage liver disease than patients who receive a liver transplantation for other reasons. This in turn may have a positive effect on short-term post-transplant outcomes.[11] However, survival of HCC recipients in the longer term is negatively affected by recurrence of cancer.[11] Therefore, a national population-based cohort study that explored time trends in short-term and longer-term post-transplant mortality was carried out, separately for recipients with and without HCC.

PATIENTS AND METHODS

Standard National Liver Transplant Registry

Since 1984, the Standard National Liver Transplant Registry has assembled detailed information about all liver transplants performed in the seven liver transplant centres in the UK.[12] Regular checks indicate that the data are consistently more than 93% complete and accurate, and several studies have confirmed the validity of the dataset.[13-15]

Study Population

All patients aged 17 years or older who had received a first-time elective liver transplant between 1st January 1997 and 31st December 2016 were eligible for inclusion. Recipients were categorised into two groups: transplanted patients with HCC recorded in any of three diagnosis fields available in the Standard National Liver Transplant Registry (HCC patients) and transplanted patients with other liver disease diagnoses (non-HCC patients). To limit heterogeneity of the study cohort, patients who underwent transplantation for types of liver cancer other than HCC and those who underwent multi-visceral, super-urgent, domino or living-related liver transplantations were excluded (Figure S1) as well as those who received a liver transplant for acute liver failure (including auxiliary transplantation). Patients whose survival data were missing were also excluded. Information on explant pathology was not available.[12]

Patients were grouped according to date of transplantation into one of four successive 5-year transplantation periods ('eras'): era 1: 1st January 1997 – 31st December 2001; era 2: 1st January 2002 – 31st December 2006; era 3: 1st January 2007 – 31st December 2011; and era 4: 1st January 2012 – 31st December 2016. Recipients' functional status at the time of transplantation was assessed using a 5-point scale ranging from 'able to carry out normal activity without restriction' to 'completely reliant on nursing/medical care'.[15] The UKELD score, derived from INR, serum creatinine, serum bilirubin and serum sodium, was used to score the recipients' severity of liver disease[8] and values for ethnicity were dichotomised into white and non-white groups. Changes over time in overall donor quality were measured using the UK Donor Liver Index (DLI), derived from donor age, sex, height, type (DCD donor or not), serum bilirubin, smoking history, and whether the liver was split, with larger values representing poorer donor livers.[16]

UK allocation policy 1997-2016

During the study period, the allocation of DCD livers and livers donated following brainstem death (DBD) was organized locally and centres selected recipients according to local criteria.[7-8] Patients on local waiting lists were prioritised according to waiting list mortality predicted on the basis of a scoring system capturing the severity of liver disease. The scoring system did not award additional points to patients on the waiting list with HCC[7,8]

Statistical analysis

Categorical variables were presented as proportions and compared using chi-squared tests and continuous variables were presented as means with standard deviations and compared using t-tests. Patients transplanted for non-HCC indications who were subsequently found to have HCC, according to explant pathology, were analysed on an intention-to-treat basis and remained in the non-HCC group.

Kaplan-Meier methods were used to compare patient and graft survival between successive eras of transplantation. Follow-up was censored at 5 years after transplantation or on the last follow-up visit before 31st December 2016, whatever occurred earlier. Graft failure was defined as either re-transplantation or patient death. To account for limited follow-up in era 4, post-transplantation outcomes for all eras are presented up to 3 years after transplantation.

Multivariable Cox regression models were used to estimate hazard ratios (HRs) that represent the relative differences in the primary outcomes measures of post-transplant mortality and graft failure between eras of transplantation. Era 1 (1997-2001) was chosen as the reference value. To determine whether changes in donor and recipient characteristics had influenced the impact of era of transplantation on post-transplant survival, HRs were initially estimated without adjustment for recipient or donor characteristics, then with adjustment for recipient characteristics only, and finally with adjustments for both recipient and donor characteristics. All characteristics included in the risk-adjustment were based on clinical plausibility of being a potentially confounding factor for post-transplantation mortality or graft failure.

Interaction terms were included in the Cox regression models to determine whether the prognostic impact of era varied according to HCC status, hepatitis C virus (HCV) status in HCC patients only, and time-period after transplantation. Two post-transplant time periods were used: the first 90 days after transplantation reflecting occurrence of surgical complications, acute rejection and primary non-function[17] and from 90 days and 5 years reflecting longer term outcomes, including recurrence of primary liver disease.[17,18] The significance of interaction terms was tested using the Wald test.

Missing donor and recipient characteristics were imputed using chained equations creating ten complete datasets.[19] In the imputation procedure, the donor and recipient variables used in the case-mix adjustment were used to predict missing values, including outcome variables.[20] The Cox regression results for each of these datasets were pooled using Rubin's rules.[19] Stata V15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses. A p-value smaller than 0.05 was considered statistically significant.

RESULTS

Time trends in post-transplant mortality

Between 1st January 1997 and 31st December 2016, 9 540 first-time single-organ elective adult liver transplants were performed. Over this study period, the number of adult HCC recipients almost tripled from 275 out of a total number of 2 117 liver transplantations (13.0%) in era 1 (1997-2001) to 727 out of a total number of 3 042 (23.9%) in era 4 (2012-2016). The increase in total number of liver transplantations for the first 3 eras of transplantation was fully explained by the increase in the number of liver transplants performed in patients with HCC (Figure 1). In contrast, the proportion of all patients with HCC in England who received a liver transplant remained stable despite substantial increases in the number of patients diagnosed with HCC from 4 029 in era 1 to 12 142 in era 4 (Figure S2).

The use of DCD livers strongly increased during the study period from 0 in 275 HCC recipients and 4 in 1842 non-HCC recipients (0.2%) in era 1 to 256 in 727 HCC recipients (35.2%) and 557 in 2 315 non-HCC recipients (24.1%) in era 4 (Table 1). Over the entire study period, HCC recipients were slightly more likely to receive donor livers that were considered steatotic or abnormal in appearance (Table 1). These findings are in line with the trend in the DLI, which demonstrates that liver donor quality deteriorated over time for both cohorts, but the deterioration was most marked for HCC patients (Table 1).

There were decreases over time in the number of HCC patients who had HCV antibodies (from 49.5% in era 1 to 41.8% in era 4) and there were corresponding decreases for non-HCC recipients (from 19.4% in era 1 to 10.5% in era 4; Table 1). The mean time on the transplant waiting list time increased for HCC recipients from 105.1 days (SD 112.2) in era 1 to 146.1 days (SD 149.7) in era 4 and for non-HCC recipients from 145.4 days (SD; 160.2) in era 1 to 164.7 days (SD 220.8) in era 4.

Era-specific changes in post-transplantation outcomes

Kaplan-Meier survival analysis

Across the four eras of transplantation, successive improvements in post-transplantation patient and graft mortality were identified in both HCC and non-HCC recipients (Figure 2). In HCC recipients, 3-year patient mortality decreased from 28.3% (95% CI: 23.2% to 34.3%) in era 1 to 21.3% (95% CI: 17.1% to 26.3%) in era 2, 19.0% (95% CI: 16.0% to 22.6%) in era 3 and 16.9% (95% CI: 13.5% to 21.1%) in era 4 (Figure 2a). In non- HCC recipients, mortality decreased from 20.4% (95% CI: 18.6% to 22.4%) in era 1 to 15.8% (95% CI: 14.2% to 17.6%) in era 2, 11.3% (95% CI: 9.9% to 12.9%) in era 3 and 9.3% (95%CI: 7.9% to 10.9%) in era 4 (Figure 2b). Similarly, 3-year graft failure for HCC recipients decreased from 31.7% (95%CI: 26.4% to 37.7%) in era 1 to 22.0% (95%CI: 18.3% to 26.3%) in era 4 (Figure 3c) and for non-HCC recipients from 24.7% (95%CI: 22.7% to 26.8%) in era 1 to 15.0% (95%CI: 13.3% to 16.9%) in era 4 (Figure 3d).

Mortality in the first 90 days after transplantation decreased from 9.1% (95% CI: 6.3% to 13.2%) in era 1 to 2.2% (95% CI: 1.4% to 3.6%) in era 4 for HCC recipients and from to 9.6% (95% CI: 8.3% to 11.1%) in era 1 to

3.1% (95% CI: 2.5% to 3.9%) in era 4 for non-HCC recipients.

Cox regression analysis

Comparing era 1 to 4, post-transplant mortality in the first 5 years after transplantation decreased by 50% for HCC patients (unadjusted HR comparing era 1 with era 4, 0.50, 95%CI: 0.46 to 0.55; Table 2) and graft failure decreased by 42% (unadjusted HR 0.58, 95%CI: 0.45 to 0.76; Table 3). In non-HCC patients, mortality decreased by 56% (unadjusted HR comparing era 1 with era 4, 0.44, 95%CI: 0.37 to 0.53; Table 2) and graft failure decreased by 41% (unadjusted HR 0.59, 95%CI: 0.51-0.68; Table 3). Adjustment for recipient characteristics and for both recipient and donor characteristics combined had only a small impact on the time trends observed in post-transplant mortality or graft failure in both HCC and non-HCC recipients (Tables 2 and 3).

The effect of era on mortality and graft failure did not vary according to HCC status (p for interaction=0.27 and 0.37, respectively) and neither did the effect of era vary in HCC recipients according to whether or not they had a concomitant diagnosis of HCV (p for interaction=0.12, Table S1).

Over the years, In the first 90 days following transplantation, mortality decreased by 80% for HCC recipients (HR adjusted for both recipient and donor characteristics comparing era 1 with era 4, 0.20, 95%CI: 0.10 to 0.39) and 68% for non-HCC recipients (adjusted HR comparing era 1 with era 4, 0.32, 95%CI: 0.24 to 0.42; Figures 3a and 3b; Table S2 in Supplementary Information). In the subsequent follow-up time period – from 90 days to 5-years – decreases in mortality were not as substantial, decreasing 48% for both HCC and non-HCC patients (adjusted HR comparing era 1 with era 4, 0.52, 95%CI: 0.35 to 0.75 and 0.52, 95%CI: 0.40 to 0.67, respectively; Figures 3a and 3b; Table S2 in Supplementary Information). In both HCC and non-HCC recipients, the impact of era on mortality was found to be different for the two follow-up periods (p for interaction=0.04 and 0.02, respectively).

Similar differences were observed in the improvements of graft survival in the first 90 days and from 90 days to 5 years (Figures 3c and 4d, Table S2 in Supplementary Information) but the impact of era on graft survival did not differ between the two follow-up periods (p=0.13 and 0.19 for HCC and non-HCC recipients, respectively).

<u>Era-specific changes in causes of death</u>

The proportion of recipients with HCC who died of tumour recurrence within the first 5 years after transplantation remained stable during the first 3 eras of transplantation: era 1: 21.0% (21/100); era 2: 21.6% (19/88); era 3 18.5% (25/135; Table S3 in Supplementary Information). In era 4 (2012-2016), the proportion of HCC recipients who died of tumour recurrence was slightly lower at 14.3% (13/91). This decrease in era 4 is almost certainly explained by most patients in this cohort having been followed up for less than 5 years. Overall, 11 of the 78 HCC recipients who died of tumour recurrence (14.1%) had received a DCD liver

compared to 403 of the 1 801 HCC recipients who died of other reasons than tumour recurrence (22.4%, p=0.15). In non-HCC patients, sepsis was consistently the most common cause of death increasing from 34.5% (161/447) in era 1 to 39.6% (70/177) in era 4.

DISCUSSION

In the last 20 years, the number of first-time single-organ elective liver transplantations in adult recipients performed in the UK has continually increased, and until recently this increase has been driven by increases in the transplantation of HCC patients. In the same period, increases in the use of DCD and other sub-optimal donor livers have been identified, particularly in patients with HCC. However, mortality in the first 5 years after transplantation has more than halved both for HCC patients who need a liver transplant before disease progresses beyond transplantable criteria and for non-HCC patients who need a liver transplant because of deteriorating liver function related to end-stage liver disease. There were decreases in mortality in the first 90 days after transplantation as well as in the mortality between 90 days and 5 years.

A limitation of the study was that it compared HCC recipients with a heterogeneous cohort of non-HCC recipients. This approach may have masked specific post-transplant mortality patterns in non-HCC patients related to primary liver disease. However, the dichotomy in HCC and non-HCC recipients reflects the fundamental difference in why patients were selected for transplantation. A liver transplant is used in patients with HCC as a treatment to remove a malignancy with curative intent and it is used in patient with end-stage liver disease as a treatment of liver failure.[7,8]

A second limitation might be that adjustment for recipient and donor characteristics may not have fully captured variations in how patients were selected for liver transplantation over the 20 years of the study period. However, given that a wide range of characteristics were adjusted for it is rather unlikely that changes over time in patient selection and organ allocation criteria are major explanations for the substantial improvements in post-transplant survival that were observed.

In addition, the time after transplantation was arbitrarily divided into two time periods: within the first 90 days and between 90 days and 5 years to investigate whether there were differences in time trends for short-term and long-term post-transplant mortality. A 90-day time period is increasingly being used to capture short-term surgical outcomes. A study exploring timing of surgical outcomes after hepatopancreatobiliary surgery in 4 000 patients supports the legitimacy of the use of this 90-day limit because it demonstrated that surgery-related deaths accounted for all early deaths and that about 85% of all surgery-related death occurred in the first 90 days.[21] Also 90-day mortality is commonly used as a short-term outcome after liver transplantation because, in addition to surgical mortality, it reflects the occurrence of acute rejection and primary non-function of the donor liver.[22]

Studies from the US and Europe have described changes over time in the characteristics and outcomes of patients receiving a liver transplant.[23,24] An analysis of the United Network for Organ Sharing database in the US, including transplantations carried out between 1994 and 2009[23] and an analysis of the European Liver Transplant Registry between 1988 and 2009[24] demonstrated marked increases in the number of liver transplantations in patients with HCC. These studies also found that HCC recipients had worse long-term

patient survival compared to non-HCC recipients.[23,24] However, no study could be identified that explicitly investigated differences in time trends of short-term and longer-term post-transplant outcomes in HCC and non-HCC recipients nor could a study be identified that had quantified to what extent the increased use of DCD livers had affected time trends in outcomes separately for HCC and non-HCC recipients.

Explanation of results

It is important to note that between 1997 and 2016 the HCC incidence increased three-fold but that the proportion of HCC patients who received a potentially curative liver transplant remained static. As a result, the number of patients with HCC who received a liver transplant has gone up accordingly. Significant increases in the use of DCD livers reflect increases in the total number of liver transplantations, relative decreases in the overall donation of DBD livers,[24] and – for HCC recipients especially – the clinical requirement to provide liver transplantations in an acceptable time frame for patients on the waiting list. However, post-transplantation mortality across the 20-year study period more than halved for both HCC and non-HCC recipients.

The improvements in overall patient and graft survival are most likely explained by a combination of factors, which initially includes the introduction of the Milan criteria followed by better matching of donors and recipients, developments in immunosuppression and anaesthesia, decreases in cold ischaemic time, and more recently the introduction of directly acting antiviral medications for patients with HCV cirrhosis.[13,23] However, the current analysis was able to demonstrate more specifically than before that factors associated with early post-transplant outcomes, potentially including surgical technique and peri-operative care, are likely to have had a substantial impact on improved overall survival.

Adjustment for differences in recipient characteristics only or for both recipients and donor characteristics had minimal effects on the observed time trends in the post-transplantation outcomes of HCC and non-HCC recipients. Instead tumour recurrence was identified as the main factor responsible for the consistently poorer long-term survival identified in HCC recipients.[11,18] Accordingly, improvements in the longer-term survival of HCC recipients are more likely to be influenced by changes in the selection of HCC patients for liver transplantation than by donor related factors.[11,18]

There were decreases in the number of non-HCC patients with HCV cirrhosis receiving a liver transplant but increases in the number of recipients transplanted for HCV-induced HCC. This is consistent with the wider accessibility to the newer direct acting antiviral medications leading to a cascade of events that include further reductions in patients with HCV requiring a liver transplant and eventual reductions in the incidence of HCV induced HCC.[25-26]

Most importantly, this study demonstrate**d** that mortality in adult patients undergoing a first-time single-organ elective liver transplantation has more than halved in the last two decades, despite a marked increase in the use of DCD livers. Decreases in both short-term and long-term mortality are responsible for

improvements in overall survival, irrespective of whether recipients have HCC with relatively preserved liver function or a failure of liver function linked to end-stage liver disease.

The increasing use of DCD livers over a period with substantial improvement of post-transplant outcomes is a guiding example for countries with a high waiting list mortality and a low DCD utilisation[10] as well as for countries where a high proportion of liver transplant recipients have HCC.[1,23,24] In the context of the ongoing improvement of post-transplant outcomes, the risk of using DCD livers or livers from donors whose organs have a greater risk of failure must be balanced against the consequence of not using these potentially poorer livers with in turn higher waiting list mortality and drop-outs due to HCC progression.

Between 1997 and 2016, the number of patients receiving a liver transplant increased considerably. However, despite the rising use of sub-optimal donor organs, post- transplantation mortality for both HCC and non-HCC patients has more than halved. Improvements in overall survival have been driven by decreases in both short-term and longer-term mortality.

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NIHR Statement

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Data Statement

The Standard National Liver Transplant Registry is available on request from National Health Service Blood and Transplant.

Declaration of interests

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FIGURES:

Figure 1: Time trends in the number and proportion of HCC ~~vs~~ versus non-HCC liver transplants performed in the UK, stratified by era of transplantation (n=9 540).

Figure 2: Post-transplant patient and graft survival according to era of transplantation (n=9 540).

Figure 3: The impact of era of transplantation on ~~the~~ post-transplantation outcomes from 0 to 90 days and from 90 days to 5 years in HCC and non-HCC recipients (n= 9 540).

TABLES

Table 1: Donor and recipient characteristics according to era of transplantation.

		ERA OF TRANSPLANTATION				
		ERA 1: 1997-2001	**ERA 2: 2002-2006**	**ERA 3: 2007-2011**	**ERA 4: 2012-2016**	**Missing values**
Number	**HCC recipients**	**275**	**318**	**559**	**727**	
	Non-HCC recipients	**1 842**	**1 785**	**1 719**	**2 315**	
DONOR CHARACTERISTICS						
Female	HCC	17·0% (46)	18·6% (59)	19·0% (106)	19·1% (138)	**0.0% (0)**
	Non-HCC	41·9% (742)	40·7% (725)	38·8% (664)	36·2% (831)	**0.0% (0)**
Age (years) Mean (SD)	HCC	46·8 (14·1)	46·4 (15·5)	48·0 (15·6)	50·6 (15·9)	**0.0% (0)**
	Non-HCC	43·0 (14·9)	45·2 (14·9)	46·6 (15·7)	50·1 (16·3)	**0.0% (0)**
BMI (kg/M^2) Mean (SD)	HCC	25·4 (3·8)	25·6 (4·3)	26·6 (4·9)	26·5 (5·1)	**2.1% (40)**
	Non-HCC	24.8 (4·3)	25.6 (4·6)	26.0 (4·9)	26.4 (4·8)	**3.8% (290)**
Trauma as cause of death	HCC	22·6% (62)	13·5% (43)	11·3% (63)	8·9% (65)	**0.0% (0)**
	Non-HCC	21·6% (398)	15·4% (274)	11·2% (192)	6·0% (139)	**0.0% (0)**
DCD Donor*	HCC	0·0% (0)	5·0% (16)	25·4% (142)	35·2% (256)	**0.0% (0)**
	Non-HCC	0·2% (4)	4·4% (79)	15·8% (272)	24·1% (557)	**0.0% (0)**
Hepatic steatosis	HCC	47·0% (54)	41·7% (128)	47·6% (264)	46·9% (335)	**10.0% (187)**
	Non-HCC	36·6% (237)	40·3% (697)	44·5% (752)	44·8% (1 019)	**17.2% (1 320)**
Presence of capsular damage	HCC	17·3% (19)	10·2% (31)	12·1% (67)	15·9% (113)	**10.5% (1 879)**
	Non-HCC	13·8% (88)	13·5% (229)	14·8% (250)	13·1% (298)	**17.8% (1 362)**
Abnormal donor liver appearance	HCC	21·5% (59)	22·1% (64)	30·9% (136)	26·4% (164)	**13.5% (254)**
	Non-HCC	16·7% (307)	23·0% (384)	25·1% (348)	22·2% (445)	**9.9% (761)**
Segmental Graft Type	HCC	3·3% (9)	5·7% (18)	8·2% (46)	4·5% (33)	**0.0-% (0)**
	Non-HCC	4·2% (78)	7·9% (141)	9·7% (167)	8·5% (197)	**0.0% (0)**
Cold Ischaemic Time (mins) Mean (SD)	HCC	665·8 (174·6)	599·1 (163·6)	520·8 (163·3)	490·9 (156·0)	**7.3% (138)**
	Non-HCC	683·5 (187·8)	615·0 (169·2)	532·9 (153·7)	510·0 (159·1)	**5.2% (402)**
Donor Liver Index (DLI)** Mean (SD)	HCC	1.13 (0.23)	1.13 (0.23)	1.31 (0.41)	1.46 (0.49)	**14.8% (278)**
	Non-HCC	1.14 (0.32)	1.16 (0.28)	1.24 (0.37)	1.38 (0.45)	**20.% (1539)**
RECIPIENT CHARACTERISTICS						
Female	HCC	17·0% (46)	18·6% (59)	19·0% (106)	19·1% (138)	**0.4% (8)**
	Non-HCC	41·9% (742)	40·3% (725)	38·8% (664)	36·2% (831)	**1.3% (103)**
Age (Years) Mean (SD)	HCC	54·4 (8·7)	56·1 (8·6)	56·9 (7·7)	58·8 (7·8)	**0.0% (0)**
	Non-HCC	50·3 (10·9)	51·1 (11·0)	51·0 (11·6)	51·4 (12·0)	**0.0% (0)**
Non-white ethnicity	HCC	21·8% (60)	23·6% (75)	17·6% (98)	15·7% (114)	**0.1% (1)**
	Non-HCC	13·6% (251)	13·6% (242)	12·5% (214)	10·1% (234)	**0.01% (1)**
BMI (Kg/M^2) Mean (SD)	HCC	26.7 (3·6)	27.1 (4·6)	26.6 (5·0)	28.2 (4·9)	**2.3% (44)**
	Non-HCC	25.4 (4·9)	26.3 (4·9)	27.6 (4·6)	27.4 (5·4)	**4.1% (313)**
UKELD*** Mean (SD)	HCC	52.1 (5·5)	51.5 (4·7)	51.1 (4·9)	51.0 (4·9)	**2.3% (44)**
	Non-HCC	56.0 (5·8)	55.8 (5·6)	56.0 (5·7)	55.8 (5·3)	**2.8% (215)**
Functional status: Self-care****	HCC	49·1% (134)	55·2% (175)	39·5% (217)	37·7% (271)	**1.1% (20)**
	Non-HCC	58·9% (1 081)	62·8% (1 116)	49·0% (834)	47·6% (1 087)	**0.8% (61)**
Ascites	HCC	37·5% (103)	30·9% (98)	28·4% (159)	30·0% (218)	**0.1% (2)**
	Non-HCC	61·8% (1 132)	55·7% (993)	59·5% (1 021)	62·5% (1 439)	**0.4% (30)**
Previous variceal bleed	HCC	20·7% (57)	22·3% (71)	18·2% (101)	13·9% (100)	**0.6% (11)**
	Non-HCC	35·9% (662)	33·2% (590)	29·7% (511)	26·7% (608)	**0.8% (64)**
Encephalopathy	HCC	9·8% (27)	7·9% (25)	12·8% (71)	15·9% (113)	**1.3% (24)**
	Non-HCC	22·0% (406)	22·0% (392)	32·9% (562)	36·7% (834)	**0.8% (64)**
Presence of HCV antibodies	HCC	49·5% (136)	43·6% (129)	45·5% (235)	41·8% (291)	**5.6% (106)**
	Non-HCC	19·4% (357)	16·9% (262)	15·3% (243)	10·5% (233)	**7.1% (545)**

**Liver donated following circulatory death.*
***Includes donor factors; DCD, segmental graft, height, age, smoking status and bilirubin*
****United Kingdom Model for End-stage Liver Disease.*
*****3rd level of 5-point scale assessing patient's pre-transplantation functional status.*

Table 2: Post-transplant mortality of HCC (n=1 879) and non-HCC recipients (n=7 661) in the first 5 years after liver transplantation according to era of transplantation.

	ERA OF TRANSPLANTATION				
STATUS OF CASE-MIX ADJUSTMENT	**ERA 1: 1997-2001**	**ERA 2: 2002-2006**	**ERA 3: 2007-2011**	**ERA 4: 2012-2016**	**P-value for the effect of era**
	Hazard ratio				
HCC RECIPIENTS					
Unadjusted	**1**	0·67 (0·61-0·73)	0.58 (0.54-0.63)	0.50 (0.46-0.55)	<0.001
Adjusted for recipient characteristics only*	**1**	0·65 (0·48-0·87)	0.56 (0.43-0.73)	0.47 (0.35-0.63)	<0.001
Adjusted for recipient and donor characteristics**	**1**	0·65 (0·49-0·87)	0.54 (0.42-0.70)	0.44 (0.33-0.60)	<0.001
NON-HCC RECIPIENTS					
Unadjusted	**1**	0·85 (0·74-0·97)	0.60 (0.51-0.69)	0.44 (0.37-0.53)	<0.001
Adjusted for recipient characteristics only*	**1**	0·86 (0·74-0·98)	0.59 (0.50-0.69)	0.44 (0.36-0.53)	<0.001
Adjusted for recipient and donor characteristics**	**1**	0·83 (0·72-0·96)	0.56 (0.47-0.66)	0.41 (0.34-0.50)	<0.001

***** *Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M²), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery.*

****Adjusted for recipient characteristics listed above and donor characteristics: sex, age, BMI (Kg/m²), cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time.*

Table 3: Graft failure of HCC (n=1 879) and non-HCC recipients (n=7 661) in the first 5 years after liver transplantation according to era of transplantation.

STATUS OF CASE-MIX ADJUSTMENT	ERA OF TRANSPLANTATION				P-value for the effect of era
	ERA 1: 1997-2001	ERA 2: 2002-2006	ERA 3: 2007-2011	ERA 4: 2012-2016	
	Hazard ratio				
HCC RECIPIENTS					
Unadjusted	**1**	0.70 (0.53-0.92)	0.63 (0.50-0.81)	0.58 (0.45-0.76)	<0.001
Adjusted for recipient characteristics only*	**1**	0.69 (0.52-0.91)	0.63 (0.49-0.81)	0.57 (0.44-0.74)	<0.001
Adjusted for recipient and donor characteristics**	**1**	0.68 (0.52-0.90)	0.56 (0.44-0.73)	0.48 (0.37-0.65)	<0.001
NON-HCC RECIPIENTS					
Unadjusted	**1**	0.90 (0.79-1.01)	0.63 (0.55-0.72)	0.59 (0.51-0.68)	<0.001
Adjusted for recipient characteristics only*	**1**	0.91 (0.80-1.03)	0.63 (0.55-0.73)	0.60 (0.51-0.70)	<0.001
Adjusted for recipient and donor characteristics**	**1**	0.87 (0.76-1.00)	0.57 (0.49-0.67)	0.52 (0.44-0.62)	<0.001

***Adjusted for recipient characteristics: sex, age, ethnicity, BMI (Kg/M^2), functional status, ascites, varices, encephalopathy, HCV status, UKELD, pre-transplant inpatient status, pre-transplant renal support, previous abdominal surgery.*

***Adjusted for recipient characteristics listed above <u>and</u> donor characteristics: sex, age, BMI (Kg/m^2), cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemic time.*