Original article

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

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Background: The increasing demand for liver transplantation has led to considerable changes in characteristics of donors and recipients. This study evaluated the short- and long-term mortality of recipients with and without hepatocellular carcinoma (HCC) in the UK 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 (HRs) comparing the impact of era on short-term (first 90 days) and longer-term (from 90 days to 5 years) mortality were estimated, with adjustment for recipient and donor characteristics.

Results: Some 1879 recipients with and 7661 without HCC were included. There was an increase in use of organs donated after circulatory death (DCD), from 0 per cent in era 1 to 35·2 per cent in era 4 for recipients with HCC, and from 0·2 to 24·1 per cent for non-HCC recipients. The 3-year mortality rate decreased from 28·3 per cent in era 1 to 16·9 per cent in era 4 (adjusted HR 0·47, 95 per cent c.i. 0·35 to 0·63) for recipients with HCC, and from 20·4 to 9·3 per cent (adjusted HR 0·44, 0·36 to 0·53) for those without HCC. Comparing era 4 with era 1, improvements were more marked in short-term than in long-term mortality, both for recipients with HCC (0–90 days: adjusted HR 0·20, 0·10 to 0·39; 90 days to 5 years: adjusted HR 0·52, 0·35 to 0·75; $P = 0·043$) and for non-HCC recipients (0–90 days: adjusted HR 0·32, 0·24 to 0·42; 90 days to 5 years: adjusted HR 0·52, 0·40 to 0·67; $P = 0·024$).

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

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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 patients with HCC and those without HCC 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 suboptimal donors have affected post-transplantation outcomes. A study[6] 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. 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 prioritize patients on the waiting list[7,8], or for countries with a high waiting list mortality[9,10].

It has been shown previously that patients who receive a liver transplant as treatment for HCC are on average in better physical condition with fewer 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 recipients with HCC in the longer term is affected negatively 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 those without HCC.

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 per cent complete and accurate, and several studies[13–15] have confirmed the validity of the data set.

Study population

All patients aged 17 years or older who received a first-time elective liver transplant between 1 January 1997 and 31 December 2016 were eligible for inclusion. Recipients were categorized into two groups: transplanted patients with HCC recorded in any of three diagnosis fields available in the Standard National Liver Transplant Registry (HCC group) and transplanted patients with other liver disease diagnoses (non-HCC group). To limit heterogeneity of the study cohort, patients who had transplantation for types of liver cancer other than HCC and those who underwent multivisceral, superurgent domino or living-related liver transplantations were excluded (*Fig. S1*, supporting information), 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: era 1, 1 January 1997 to 31 December 2001; era 2, 1 January 2002 to 31 December 2006; era 3, 1 January 2007 to 31 December 2011; and era 4, 1 January 2012 to 31 December 2016. Recipients' functional status at the time of transplantation was assessed using a five-point scale ranging from 'able to carry out normal activity without restriction' to 'completely reliant on nursing/medical care'[15]. The UK Model for End-stage Liver Disease score, derived from the international normalized ratio, and serum creatinine, serum bilirubin and serum sodium levels, was used to score the recipients' severity of liver disease[8]. Ethnicity was dichotomized 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 concentration, smoking history, and whether the liver was split; larger values represented poorer donor livers[16].

UK allocation policy, 1997–2016

During the study interval, the allocation of DCD livers and livers donated after brainstem death (DBD) was organized locally and centres selected recipients according to local criteria[7,8]. Patients on local waiting lists were prioritized 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 with HCC on the waiting list[7,8].

Statistical analysis

Categorical variables are presented as proportions and were compared using χ^2 tests; continuous variables are presented as mean(s.d.) and were analysed 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 31 December 2016, whichever occurred earlier. Graft failure was defined by either retransplantation 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) representing relative differences in the primary outcome measures post-transplant mortality and graft failure between eras of transplantation. Era 1 (1997–2001) was chosen as the reference group. To determine whether changes in donor and recipient characteristics 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 the HCC group only, and time interval after transplantation. Two post-transplant intervals were used: the first 90 days after transplantation, reflecting the occurrence of surgical complications, acute rejection and primary non-function[17], and from 90 days to 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 data sets[19]. In the imputation procedure, the donor and recipient variables used in the case-mix adjustment were used to predict missing values, including those for outcome variables[20]. The Cox regression results for each of these data sets were pooled using Rubin's rules[19]. $P < 0{\cdot}050$ was considered statistically significant. Stata® version 15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses.

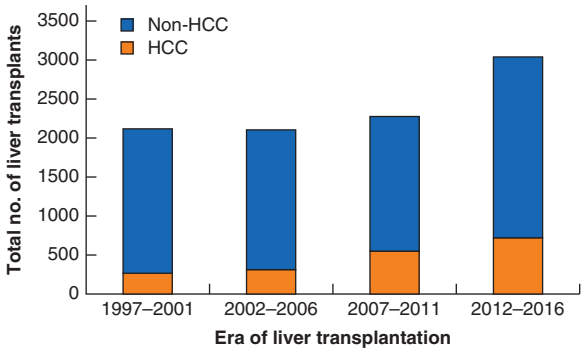
Results

Time trends in post-transplant mortality

Between 1 January 1997 and 31 December 2016, 9540 first-time single-organ elective adult liver transplants were performed. Over this interval, the number of adult recipients with HCC almost tripled, from 275 of a total of 2117 liver transplantations (13·0 per cent) in era 1 (1997–2001) to 727 of 3042 (23·9 per cent) in era 4 (2012–2016). The increase in total number of liver transplants for the first three eras of transplantation was fully explained by the increase in the number of liver transplants in patients with HCC (*Fig. 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 4029 in era 1 to 12 142 in era 4 (*Fig. S2*, supporting information).

The use of DCD livers greatly increased during the study period from 0 among 275 recipients with HCC and four among 1842 recipients without HCC (0·2 per cent) in era 1 to 256 of 727 (35·2 per cent) and 557 of 2315 (24·1 per cent) respectively in era 4 (*Table 1*). Over the entire study interval, recipients with HCC 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 showed that liver donor quality deteriorated over time in both cohorts, but that the deterioration was most marked in the HCC group (*Table 1*).

Fig. 1 Time trends in the number of liver transplants in patients with or without hepatocellular carcinoma performed in the UK, stratified by era of transplantation



The analysis included a total of 9540 transplants. HCC, hepatocellular carcinoma.

The number of recipients with HCC who had HCV antibodies decreased over time (from 49·5 per cent in era 1 to 41·8 per cent in era 4) and there was a corresponding decrease for those without HCC (from 19·4 to 10·5 per cent respectively) (*Table 1*). The mean(s.d.) time on the transplant waiting list increased from 105(112) days in era 1 to 146(150) days in era 4 among recipients with HCC, and from 145(160) to 165(221) days respectively for recipients without HCC.

Era-specific changes in post-transplantation outcomes

Kaplan–Meier survival analysis

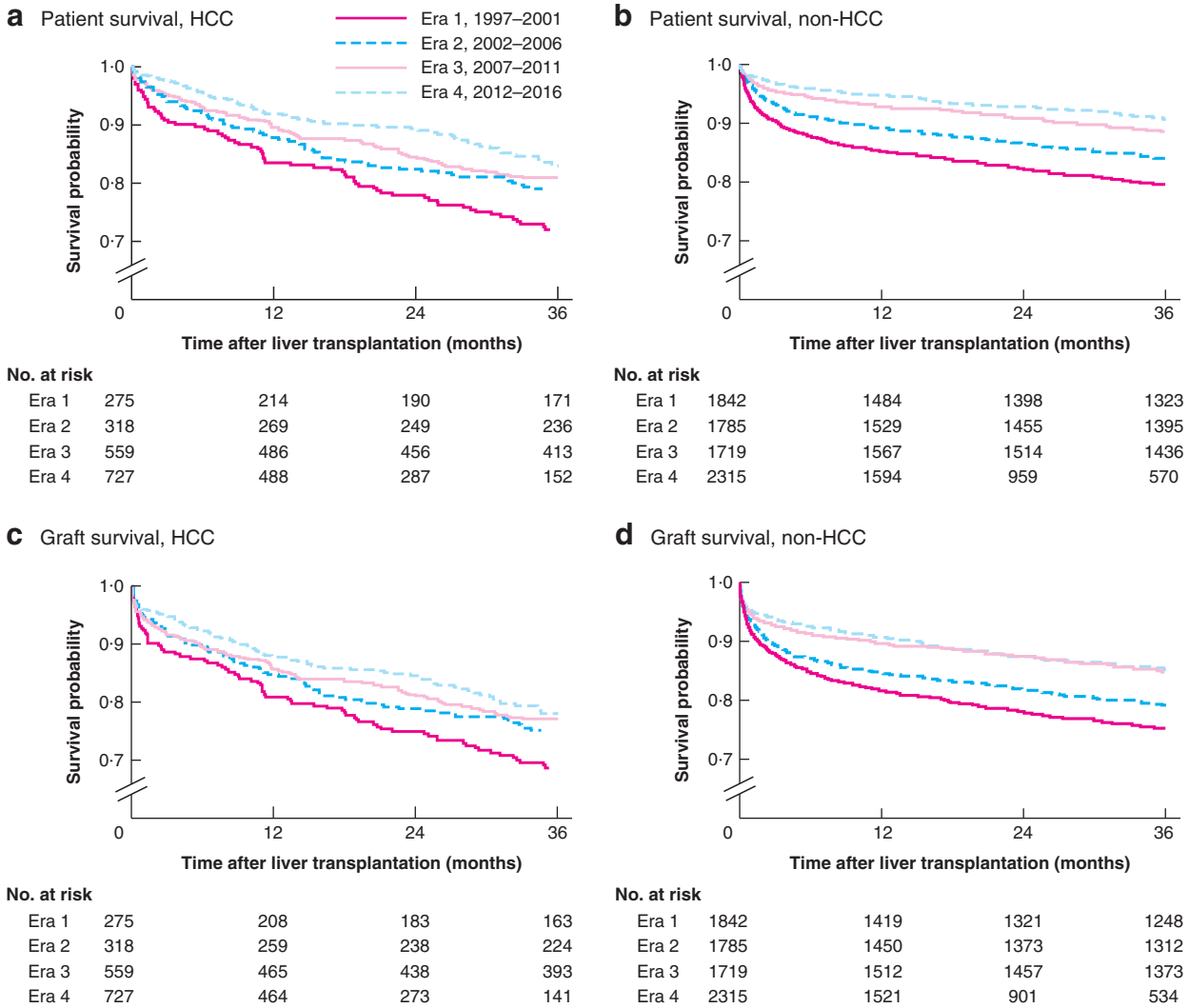
Across the four eras of transplantation, successive improvements in post-transplantation patient and graft survival were identified in both HCC and non-HCC recipients (*Fig. 2*). In recipients with HCC, the 3-year mortality rate decreased from 28·3 (95 per cent c.i. 23·2 to 34·3) per cent in era 1 to 21·3 (17·1 to 26·3) per cent in era 2, 19·0 (16·0 to 22·6) per cent in era 3 and 16·9 (13·5 to 21·1) per cent in era 4 (*Fig. 2a*). In recipients without HCC, mortality decreased from 20·4 (18·6 to 22·4) per cent in era 1, to 15·8 (14·2 to 17·6), 11·3 (9·9 to 12·9) and 9·3 (7·9 to 10·9) per cent in eras 2, 3 and 4 respectively (*Fig. 2b*). Similarly, the 3-year graft failure rate decreased from 31·7 (26·4 to 37·7) per cent in era 1 to 22·0 (18·3 to 26·3) per cent in era 4 (*Fig. 3c*) among recipients with HCC, and from 24·7

Table 1 Donor and recipient characteristics according to era of transplantation

		Era of transplantation				
	Recipient group	Era 1 1997–2001	Era 2 2002–2006	Era 3 2007–2011	Era 4 2012–2016	Missing values
No. of transplants	HCC	275	318	559	727	
	Non-HCC	1842	1785	1719	2315	
Donor characteristics						
Women	HCC	46 (16·7)	59 (18·6)	106 (19·0)	138 (19·0)	0 (0)
	Non-HCC	742 (40·3)	725 (40·6)	664 (38·6)	831 (35·9)	0 (0)
Age (years)*	HCC	46·8(14·1)	46·4(15·5)	48·0(15·6)	50·6(15·9)	0 (0)
	Non-HCC	43·0(14·9)	45·2(14·9)	46·6(15·7)	50·1(16·3)	0 (0)
BMI (kg/m^2)*	HCC	25·4(3·8)	25·6(4·3)	26·6(4·9)	26·5(5·1)	40 (2·1)
	Non-HCC	24·8(4·3)	25·6(4·6)	26·0(4·9)	26·4(4·8)	290 (3·8)
Trauma as cause of death	HCC	62 (22·6)	43 (13·5)	63 (11·3)	65 (8·9)	0 (0)
	Non-HCC	398 (21·6)	274 (15·4)	192 (11·2)	139 (6·0)	0 (0)
DCD donor	HCC	0 (0)	16 (5·0)	142 (25·4)	256 (35·2)	0 (0)
	Non-HCC	4 (0·2)	79 (4·4)	272 (15·8)	557 (24·1)	0 (0)
Hepatic steatosis	HCC	54 (47·0)	128 (41·7)	264 (47·6)	335 (46·9)	187 (10·0)
	Non-HCC	237 (36·6)	697 (40·3)	752 (44·5)	1019 (44·8)	1320 (17·2)
Presence of capsular damage	HCC	19 (17·3)	31 (10·2)	67 (12·1)	113 (15·9)	197 (10·5)
	Non-HCC	88 (13·8)	229 (13·5)	250 (14·8)	298 (13·1)	1362 (17·8)
Abnormal donor liver appearance	HCC	59 (21·5)	64 (22·1)	136 (30·9)	164 (26·4)	254 (13·5)
	Non-HCC	307 (16·7)	384 (23·0)	348 (25·1)	445 (22·2)	761 (9·9)
Segmental graft type	HCC	9 (3·3)	18 (5·7)	46 (8·2)	33 (4·5)	0 (0)
	Non-HCC	78 (4·2)	141 (7·9)	167 (9·7)	197 (8·5)	0 (0)
Cold ischaemia time (min)*	HCC	666(175)	599(164)	521(163)	491(156)	138 (7·3)
	Non-HCC	6845(188)	615(169)	533(154)	510(159)	402 (5·2)
Donor Liver Index*†	HCC	1·13(0·23)	1·13(0·23)	1·31(0·41)	1·46(0·49)	278 (14·8)
	Non-HCC	1·14(0·32)	1·16(0·28)	1·24(0·37)	1·38(0·45)	1539 (20·1)
Recipient characteristics						
Female	HCC	46 (17·0)	59 (18·6)	106 (19·0)	138 (19·1)	8 (0·4)
	Non-HCC	742 (41·9)	725 (40·3)	664 (38·8)	36·2 (831)	103 (1·3)
Age (years)*	HCC	54·4(8·7)	56·1(8·6)	56·9(7·7)	58·8(7·8)	0 (0)
	Non-HCC	50·3(10·9)	51·1(11·0)	51·0(11·6)	51·4(12·0)	0 (0)
Non-white ethnicity	HCC	60 (21·8)	75 (23·6)	98 (17·6)	15·7 (114)	1 (0·1)
	Non-HCC	251 (13·6)	242 (13·6)	214 (12·5)	10·1 (234)	1 (< 0·1)
BMI (kg/m^2)*	HCC	26·7(3·6)	27·1(4·6)	26·6(5·0)	28·2(4·9)	44 (2·3)
	Non-HCC	25·4(4·9)	26·3(4·9)	27·6(4·6)	27·4(5·4)	313 (4·1)
UKELD score*	HCC	52·1(5·5)	51·5(4·7)	51·0(4·9)	51·0(4·9)	44 (2·3)
	Non-HCC	56·0(5·8)	55·8(5·6)	56·0(5·7)	55·8(5·3)	215 (2·8)
Functional status: self-care‡	HCC	134 (49·1)	175 (55·2)	217 (39·5)	271 (37·7)	20 (1·1)
	Non-HCC	1081 (58·9)	1116 (62·8)	834 (49·0)	1087 (47·6)	61 (0·8)
Ascites	HCC	103 (37·5)	98 (30·9)	159 (28·4)	218 (30·0)	2 (0·1)
	Non-HCC	1132 (61·8)	993 (55·7)	1021 (59·5)	1439 (62·5)	30 (0·4)
Previous variceal bleed	HCC	57 (20·7)	71 (22·3)	101 (18·2)	100 (13·9)	11 (0·6)
	Non-HCC	662 (35·9)	590 (33·2)	511 (29·7)	608 (26·7)	64 (0·8)
Encephalopathy	HCC	27 (9·8)	25 (7·9)	71 (12·8)	113 (15·9)	24 (1·3)
	Non-HCC	406 (22·0)	392 (22·0)	562 (32·9)	834 (36·7)	64 (0·8)
Presence of HCV antibodies	HCC	136 (49·5)	129 (43·6)	235 (45·5)	291 (41·8)	106 (5·6)
	Non-HCC	357 (19·4)	262 (16·9)	243 (15·3)	233 (10·5)	545 (7·1)

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †Includes the following donor factors: donated after circulatory death (DCD), segmental graft, height, age, smoking status and bilirubin level. ‡Third level of five-point scale assessing patient's functional status before transplantation. HCC, hepatocellular carcinoma; UKELD, UK Model for End-stage Liver Disease.

Fig. 2 Post-transplant patient and graft survival according to era of transplantation



a,**b** Patient and **c**,**d** graft survival among 1879 patients with hepatocellular carcinoma (HCC) (**a**,**c**) and 7661 without (**b**,**d**). **a**–**d** $P < 0{\cdot}001$ (log rank test).

(22·7 to 26·8) to 15·0 (13·3 to 16·9) per cent respectively in the non-HCC group (*Fig. 3d*).

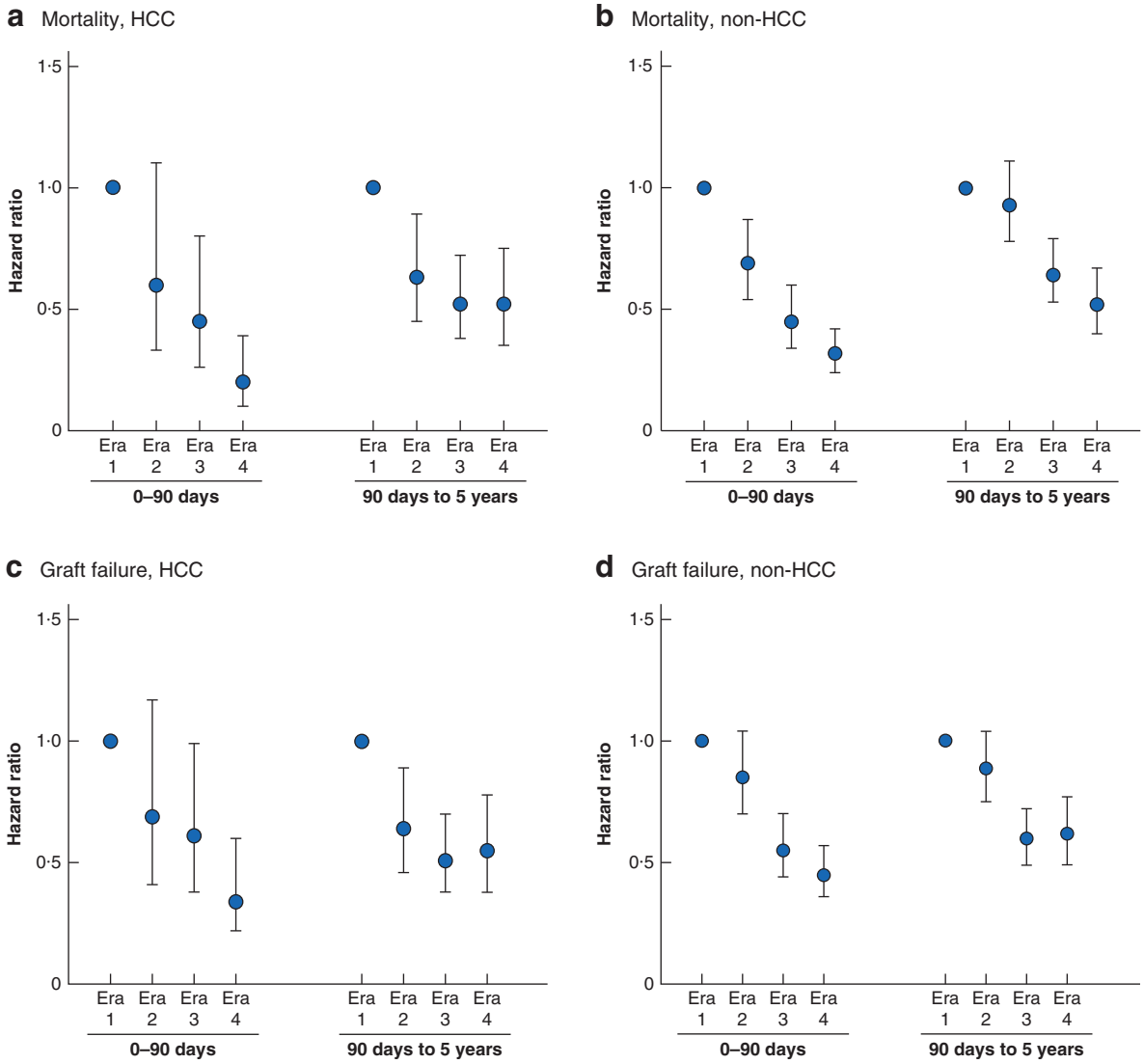
The mortality rate in the first 90 days after transplantation decreased from 9·1 (6·3 to 13·2) per cent in era 1 to 2·2 (1·4 to 3·6) per cent in era 4 for recipients with HCC, and from to 9·6 (8·3 to 11·1) to 3·1 (2·5 to 3·9) per cent respectively for recipients without HCC.

Cox regression analysis

Comparing era 4 with era 1, post-transplant mortality in the first 5 years after transplantation decreased by 50 per cent for patients with HCC (unadjusted HR 0·50, 95 per cent c.i. 0·46 to 0·55) (*Table 2*) and graft failure decreased by 42 per cent (unadjusted HR 0·58, 0·45 to 0·76) (*Table 3*). Among patients without HCC, mortality decreased by 56 per cent (unadjusted HR 0·44, 0·37 to 0·53) (*Table 2*) and graft failure decreased by 41 per cent (unadjusted HR 0·59, 0·51 to 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 groups (*Tables 2* and *3*).

The effect of era on mortality and graft failure did not vary according to HCC status (P for interaction = 0·268

Fig. 3 Impact of era of transplantation on post-transplantation outcomes from 0 to 90 days and from 90 days to 5 years in patients with or without hepatocellular carcinoma



Hazard ratios, with 95 per cent confidence intervals, for **a**,**b** mortality and **c**,**d** graft failure among 1879 patients with hepatocellular carcinoma (HCC) (**a**,**c**) and 7661 without (**b**,**d**). Era 1 is the reference group. The analysis was adjusted for recipient characteristics (sex, age, ethnicity, BMI, functional status, ascites, varices, encephalopathy, hepatitis C virus status, United Kingdom Model for End-Stage Liver Disease score, pretransplant inpatient status, pretransplant renal support, previous abdominal surgery) and donor characteristics (sex, age, BMI, cause of death, donor type (donation after cardiac death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemia time).

and $P = 0{\cdot}373$ respectively), or according to whether recipients with HCC had a concomitant diagnosis of HCV (P for interaction = 0·124) (*Table S1*, supporting information).

Analyses adjusted for both recipient and donor characteristics showed that mortality in the first 90 days after transplantation decreased by 80 per cent between era 1 and era 4 for HCC recipients (adjusted HR 0·20, 0·10 to 0·39) and by 68 per cent for recipients without HCC (adjusted HR 0·32, 0·24 to 0·42) (*Fig. 3a*,*b*; *Table S2*, supporting information). In the subsequent follow-up period, from 90 days to 5 years, decreases in mortality between eras 1 and 4 were not as substantial, being 48 per cent for both HCC (adjusted HR 0·52, 0·35 to 0·75) and non-HCC (adjusted HR 0·52, 0·40 to 0·67) groups respectively. In both recipients with

Table 2 Cox regression analysis of risk of post-transplant mortality among 1879 recipients with and 7661 without hepatocellular carcinoma in the first 5 years after liver transplantation according to era of transplantation

	Hazard ratio (*versus* era 1, 1997–2001)			
	Era 2 2002–2006	Era 3 2007–2011	Era 4 2012–2016	*P* for effect of era
Recipients with HCC				
Unadjusted	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*	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†	0·65 (0·49, 0·87)	0·54 (0·42, 0·70)	0·44 (0·33, 0·60)	< 0·001
Recipients without HCC				
Unadjusted	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*	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†	0·83 (0·72, 0·96)	0·56 (0·47, 0·66)	0·41 (0·34, 0·50)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Adjusted for recipient characteristics (sex, age, ethnicity, BMI, functional status, ascites, varices, encephalopathy, hepatitis C virus status, UK Model for End-stage Liver Disease score, pretransplant inpatient status, pretransplant renal support, previous abdominal surgery). †Adjusted for recipient characteristics listed above and donor characteristics (sex, age, BMI, cause of death, donor type (donated after circulatory death or donated after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemia time). HCC, hepatocellular carcinoma.

Table 3 Cox regression analysis of risk of graft failure among 1879 recipients with and 7661 without hepatocellular carcinoma in the first 5 years after liver transplantation according to era of transplantation

	Hazard ratio (*versus* era 1, 1997–2001)			
	Era 2 2002–2006	Era 3 2007–2011	Era 4 2012–2016	
Recipients with HCC				
Unadjusted	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*	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†	0·68 (0·52, 0·90)	0·56 (0·44, 0·73)	0·48 (0·37, 0·65)	< 0·001
Recipients without HCC				
Unadjusted	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*	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†	0·87 (0·76, 1·00)	0·57 (0·49, 0·67)	0·52 (0·44, 0·62)	< 0·001

Values in parentheses are 95 per cent confidence intervals. *Adjusted for recipient characteristics (sex, age, ethnicity, BMI, functional status, ascites, varices, encephalopathy, hepatitis C virus status, UK Model for End-stage Liver Disease score, pretransplant inpatient status, pretransplant renal support, previous abdominal surgery). †Adjusted for recipient characteristics listed above and donor characteristics (sex, age, BMI, cause of death, donor type (donation after circulatory death or donation after brain death), steatosis, capsular damage, organ appearance, graft type, cold ischaemia time). HCC, hepatocellular carcinoma.

and those without HCC, the impact of era on mortality was different for the two follow-up periods (*P* for interaction = 0·043 and *P* = 0·024 respectively).

Similar differences were observed in improvements in graft survival in the first 90 days and from 90 days to 5 years (*Fig. 3c,d*; *Table S2*, supporting information), but the impact of era on graft survival did not differ between the two follow-up periods (*P* = 0·136 and *P* = 0·191 for HCC and non-HCC groups respectively).

Era-specific changes in causes of death

The percentage of recipients with HCC who died from tumour recurrence within the first 5 years after transplantation remained stable during the first three eras of transplantation: era 1, 21·0 per cent (21 of 100); era 2, 22 per cent (19 of 88); and era 3, 18·5 per cent (25 of 135) (*Table S3*, supporting information). In era 4 (2012–2016), the percentage of recipients with HCC who died from tumour recurrence was slightly lower at 14 per cent (13 of 91). This decrease in era 4 is almost certainly explained by the fact that most patients in this cohort had been followed up for less than 5 years. Overall, 11 of the 78 recipients with HCC who died from tumour recurrence (14 per cent) had received a DCD liver, compared with 403 of the 1801 recipients with HCC (22·4 per cent) who died from causes other than tumour recurrence (*P* = 0·154). In recipients without HCC, sepsis was consistently the most common cause of death, with the rate increasing from 36·0 per cent (161 of 447) in era 1 to 39·5 per cent (70 of 177) in era 4.

Discussion

The number of first-time single-organ elective liver transplantations in adult recipients performed in the UK has increased continually over the past 20 years, and until recently this rise has been driven by increases in the transplantation of patients with HCC. In the same period, increases in the use of DCD and other suboptimal 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 patients with HCC who need a liver transplant before disease progresses beyond transplantable criteria, and for those without HCC 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 between 90 days and 5 years.

A limitation of the study was that it compared recipients with HCC with a heterogeneous cohort of recipients without HCC. This approach may have masked specific post-transplant mortality patterns in the non-HCC group related to the primary liver disease. However, the dichotomy between recipients with and without HCC reflects the fundamental difference in why patients were selected for transplantation. A liver transplant is used to remove a malignancy with curative intent in patients with HCC, and as a treatment for liver failure in patients with end-stage liver disease[7,8].

A second limitation might be that the 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. However, given that a wide range of characteristics were adjusted for, it is unlikely that changes in patient selection and organ allocation criteria over time are major explanations for the substantial improvements in post-transplant survival.

In addition, the time after transplantation was divided arbitrarily into two intervals, within the first 90 days and between 90 days and 5 years, to investigate whether there were differences in time trends for short- and long-term post-transplant mortality. A 90-day time interval is being used increasingly to capture short-term surgical outcomes. A study[21] exploring the timing of surgical outcomes after hepatopancreatobiliary surgery in 4000 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 per cent of all surgery-related deaths occurred in the first 90 days. In addition, 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 USA[23] and Europe[24] have described changes over time in the characteristics and outcomes of patients receiving a liver transplant. Analyses of the United Network for Organ Sharing database in the USA, including transplantations carried out between 1994 and 2009[23], and 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 recipients with HCC had worse long-term patient survival than those without. However, no study could be identified that explicitly investigated differences in time trends of short- and longer-term post-transplant outcomes in recipients with and those without HCC, or one that quantified to what extent the increased use of DCD livers affected time trends in outcomes separately for HCC and non-HCC cohorts.

It is important to note that between 1997 and 2016 the incidence of HCC increased threefold but that the proportion of patients with HCC who received a potentially curative liver transplant remained static. As a result, the number of patients with HCC who received a liver transplant increased 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 recipients with HCC especially – the clinical requirement to provide liver transplantations in an acceptable time frame for those on the waiting list. However, post-transplantation mortality across the 20-year study interval more than halved for both recipients with and those without HCC.

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 ischaemia time, and, more recently, the introduction of directly acting antiviral medications for patients with HCV cirrhosis[13,23]. However, the present analysis was able to demonstrate more specifically than before that factors associated with early post-transplant outcomes, potentially including surgical technique and perioperative 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 post-transplantation outcomes of recipients with or without HCC. Instead, tumour recurrence was identified as the main factor responsible for the consistently poorer long-term survival among recipients with HCC[11,18]. Accordingly, improvements in the longer-term survival

of recipients with HCC are more likely to be influenced by changes in the selection of such patients for liver transplantation than by donor-related factors[11,18].

Over the study, the number of patients without HCC who had HCV cirrhosis receiving a liver transplant decreased, whereas the number of recipients transplanted for HCV-induced HCC increased. This is consistent with the wider accessibility to newer directly acting antiviral medications, leading to a cascade of events that includes further reductions in patients with HCV requiring a liver transplant and eventual reductions in the incidence of HCV-induced HCC[25,26].

Between 1997 and 2016, the number of patients receiving a liver transplant increased considerably. Most importantly, this study demonstrated that mortality in adult patients undergoing a first-time single-organ elective liver transplantation has more than halved in the past two decades, despite a marked increase in the use of suboptimal donor organs. Decreases in both short- 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 in post-transplant outcomes is a guiding example for countries with a high waiting list mortality and a low DCD utilization[10] as well as those in which a high proportion of liver transplant recipients have HCC[1,23,24]. In the context of the ongoing improvement in 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 leading to higher waiting list mortality and drop-outs owing to HCC progression.

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Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the article.