Assessing the Impact of Suboptimal Donor Characteristics on Mortality After Liver Transplantation: A Time-dependent Analysis Comparing HCC With Non-HCC Patients

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Background. Patients who receive a liver transplant for hepatocellular carcinoma (HCC) often receive poorer-quality livers. Tumor recurrence also has a negative effect on posttransplant outcomes. We compared mortality of HCC and non-HCC recipients in different posttransplant time periods (epochs) to separate the impact of these different risk factors on short-term and longer-term posttransplant survival. **Methods.** We identified a population-based cohort of first-time liver transplant recipients (aged ≥16 years) between 2008 and 2016 in the United Kingdom. We used Cox regression to estimate hazard ratios (HRs) comparing posttransplant mortality between HCC and non-HCC patients in 3 posttransplant epochs: 0 to 90 days, 90 days to 2 years, and 2 to 5 years, with adjustment first for recipient and later also for donor characteristics. **Results.** One thousand two hundred seventy HCC and 3657 non-HCC transplant recipients were included. Five-year posttransplant survival was 74.5% (95% confidence interval [CI] 71.2%–77.5%) in HCC patients and 84.6% (83.0%–86.1%) in non-HCC patients. With adjustment for recipient characteristics only, mortality of HCC patients was lower but not statistically significantly different in the first 90 days (HR, 0.76; 95% CI, 0.53–1.09; $P = 0.11$), but significantly higher thereafter (90 days to 2 years: HR, 1.99; 95% CI, 1.48–2.66; $P < 0.001$; 2 to 5 years HR, 1.77; 95% CI, 1.30–2.42; $P < 0.001$). Further adjustment for donor characteristics had little impact on these results. **Conclusions.** HCC recipients have poorer 5-year posttransplant survival than non-HCC recipients, most likely because of tumor recurrence. The more frequent use of poorer-quality donor organs for HCC does not explain this difference.

(*Transplantation* 2019;103: e89–e98)

Received 30 August 2018.

Accepted 3 November 2018.

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D.W. is funded by a Doctoral Research Fellowship from the National Institute of Health Research. J.v.d.M. is partly supported by the NHS National Institute for Health Research Collaboration for leadership in Applied Health Research and Care North Thames at Bart's Health NHS Trust. The funder of the study, National Institute for Health Research, had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication. D.W., K.W., and J.v.d.M. had full access to all the data in the study, take responsibility for the integrity of the data and the accuracy of the data analysis, and had final responsibility for the decision to submit for publication.

J.v.d.M. reports grants from Healthcare Quality Improvement Partnership during the conduct of the study. The other authors declare no conflicts of interest.

This report is independent research arising from a Doctoral Research Fellowship (DRF-2016-09-132) awarded to David Wallace and supported by the National Institute for Health Research. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, Health Education England or the Department of Health.

D.W. involved in the conception of project, literature review, data analysis, interpretation of results, and write up of the manuscript. K.W. involved in the conception of the project, data analysis, interpretation of results, and write up of the manuscript. S.C. involved in the interpretation of results and write up of the manuscript. A.S. involved in the interpretation of results and write up of the manuscript. A.G. involved in the interpretation of results and write up of the manuscript. I.R. involved in the interpretation of results and write up of the manuscript. C.C. involved in the interpretation of results and write up of the manuscript. N.H. involved in the interpretation of results and write up of the manuscript. J.v.d.M. involved in the conception of project, literature review, data analysis, interpretation of results, and write up of the manuscript. All authors have given final approval for this manuscript to be submitted to Transplantation.

Supplemental digital content (SDC) is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.transplantjournal.com).

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ISSN: 0041-1337/19/10304-0e89

DOI: 10.1097/TP.0000000000002559

<zdoi;10.1097/TP.0000000000002559>

INTRODUCTION

The rising incidence of hepatocellular carcinoma (HCC) has led to a marked increase in the number of patients with HCC receiving a liver transplant.[1] This has put pressure on transplantation services in many countries as they struggle to cope with transplanting patients with HCC in an acceptable oncological time frame given the limited availability of donor organs.[1] In response, livers with suboptimal donor characteristics are increasingly being used.[2]

It is unknown to what extent the increase in the number of liver transplants for HCC and the related increased use of marginal livers have affected posttransplantation outcomes. International consensus recommendations only indicate that posttransplant outcomes of patients transplanted for HCC should be comparable to those transplanted for non-HCC indications.[3]

A study including patients transplanted between 1988 and 2003 in a number of European countries suggested that posttransplant survival immediately after transplantation is often better in patients transplanted for HCC compared with those who had liver transplant for other reasons.[4,5] However, survival in HCC patients can deteriorate later during follow-up, most likely as a result of tumor recurrence. It has been argued that the introduction of the Milan criteria—a set of tumor characteristics introduced in the late 1990s to identify HCC patients in whom liver transplantation may provide curative treatment (1 lesion with a diameter ≤5 cm, or alternatively 3 lesions each with a diameter ≤3 cm)—will have reduced tumor recurrence and in that way will have canceled the reversal of HCC's impact on posttransplant outcomes.[5-7] There has been no recent large-scale study that has empirically tested this assertion.

In the United Kingdom, the Milan criteria for listing patients with HCC for liver transplantation were expanded in response to studies that suggested that less restrictive criteria would not negatively affect cancer recurrence rates and posttransplant survival.[8,9] As a result, a set of expanded criteria were formally accepted in the United Kingdom in 2008 (1 lesion with a diameter ≤5 cm, or up to 5 tumors each with diameter ≤3 cm, or 1 lesion with a diameter >5 and ≤7 cm with no evidence of tumor progression, extrahepatic spread, or new nodule formation over a 6-month period).[10,11]

Our aim was to examine the prognostic impact of HCC over different time periods (epochs) after liver transplantation using recent data from the Standard National Liver Transplant Registry. To correlate with the introduction of expanded selection criteria, our analysis focused on a cohort of patients who received a liver transplant between 2008 and 2016. We investigated whether the impact of HCC varied over 3 epochs of follow-up: patient survival up to 90 days was chosen to reflect the occurrence of surgical complications, primary nonfunction and acute rejection,[12] survival between 90 days and 2 years and between 2 and 5 years to reflect tumor recurrence and chronic rejection.[3,7,12,13] These results were first adjusted for recipient characteristics and in a second step also for donor characteristics to investigate the impact that the use of livers with suboptimal donor characteristics has on differences in posttransplant survival between HCC and non-HCC recipients. In a series of sensitivity analyses, we also tested whether the effect of HCC on mortality differed according to a previous diagnosis of hepatitis C (HCV) and, more specifically, whether mortality from tumor recurrence differed according to the use of donation after circulatory death (DCD) donors.

MATERIALS AND METHODS

Standard National Liver Transplant Registry

Since 1968, the Standard National Liver Transplant Registry contains information about all liver transplants done in the 6 liver transplant centers in England and 1 center in Scotland. The data set is managed by National Health Service (NHS) Blood and Transplant,[14] and regular checks indicate that the data are consistently >93% complete and accurate and results from several studies confirm the validity of the data set.[14-17]

Study Population

The study population included all recipients aged 16 years or older who received the first elective orthotopic liver transplant in the United Kingdom between January 1, 2008, and December 31, 2016. The diagnostic category of each patient was identified from the 3 diagnostic fields available in the Standard National Liver Transplant Registry and patients were categorized into 2 groups, patients transplanted with HCC and patients transplanted with other liver disease diagnoses according to their primary liver diagnosis at the time of transplantation (non-HCC patients). In the event of multiple diagnoses, patients were considered to have HCC if HCC was mentioned in any of 3 diagnosis fields. There was no information in the UK transplant registry on explant pathology.

To limit heterogeneity of the study cohort, patients who underwent transplantation for types of liver cancer other than HCC and those who underwent multivisceral, superurgent, domino, or living-related liver transplantations were excluded as well as those who received a liver transplant for acute liver failure (including auxiliary transplantation). We also excluded patients whose survival data were missing.

Donor and recipient characteristics and primary cause of death were compared between HCC and non-HCC recipients. Recipient's lifestyle activity was assessed using a 5-point scale ranging from able to carry out normal activity without restriction to completely reliant on nursing/medical care,[17] and United Kingdom Model for End-Stage Liver Disease (UKELD) was used to score the severity of the liver disease.[18] Cold ischemic time was defined as the duration between the start of cold perfusion in the donor to the start of blood flow through the organ in the recipient.[19] Values for ethnicity were grouped into white and non-white groups.

Statistical Analysis

To describe the prognostic impact of HCC, we included patients who received a liver transplant over a 9-year period between January 1, 2008, and December 31, 2016. Categorical variables were presented as proportions and compared using chi-squared tests and continuous variables presented as means with SDs and compared using *t* tests. Patients transplanted for non-HCC indications who were

subsequently found to have an HCC on explant pathology were analyzed on an intention-to-treat basis and remained in the non-HCC cohort.

The Kaplan-Meier method was used to compare posttransplant patient and graft survival in HCC and non-HCC recipients and to compare posttransplant patient and graft survival in patients with HCC who were transplanted within the Milan criteria and those transplanted within the expanded criteria. Follow-up data were available until December 31, 2016. Patients with a functioning graft or alive at their last follow-up visit were considered to be censored observations. Graft loss was defined as either retransplantation or patient death. Differences in survival were assessed with the log-rank test.

We used multifactorial Cox regression to build 3 separate models. All models were designed to examine the prognostic impact of HCC status on patient survival in 3 separate epochs of follow-up time: up to 90 days after transplantation, between 90 days and 2 years, and between 2 and 5 years. In the first model, hazard ratios (HRs) comparing posttransplant survival in liver transplant recipients with and without HCC were estimated without adjustment for the donor and recipient characteristics. In the second model, HRs were estimated with adjustment for recipient factors only, and in the final model, HRs were estimated after adjustment for both donor and recipient factors. We performed a series of sensitivity analysis that first explored the effect of partitioning the epochs into posttransplantation time periods that included 90 days to 1 year and 1 to 2 years and second determined whether the effect of HCC on mortality differed according to HCV status by testing the interaction between HCC and HCV.

In all Cox models, adjustment for specific tumor characteristics was not included as comparisons of posttransplantation survival in HCC patients were made with a cohort of non-HCC patients. All donor and recipient factors were selected on the basis of their clinical plausibility of being a risk factor for posttransplant survival.[16] The time dependency of HCC as a risk factor for posttransplant survival and the interaction effect between HCC and HCV were tested with Wald tests.

In the regression models in which we adjusted for donor and recipient characteristics, we also explored possible nonlinear relationships between the recipient and donor characteristics measured as continuous variables and posttransplant survival, by including these as both linear and quadratic terms in the model. Missing patient and donor characteristics were imputed using chained equations creating 10 complete data sets.[20] The Cox regression results for each of these data sets were pooled using Rubin rules.[20] No patient or donor characteristic had >15% of missing values.

Stata V15 (StataCorp, College Station, TX) was used for all statistical analyses. A P <0.05 was considered significant for each statistical analysis.

RESULTS

A total of 4927 first adult elective liver transplants were performed between 2008 and 2016, of which 1270 liver transplants were for HCC recipients and 3657 for non-HCC recipients (Figure 1). Compared with non-HCC recipients, those who received a liver transplantation for HCC between 2008 and 2016 were more likely to be male, from non-white ethnic backgrounds, and positive for HCV infection (Table 1). Despite being significantly older at the time of transplantation, HCC patients were physically more active (according to their recorded lifestyle activity), had better liver function (exhibited by lower UKELD scores), and were less likely to show signs of end-stage liver disease (varices, encephalopathy, and ascites). They were also less likely required ventilation or hospital admission immediately before transplantation and less likely to have undergone previous abdominal surgery. Patients with HCC received more grafts from organs DCD or grafts in which the appearance had been documented as abnormal or steatotic. Cold ischemic time was marginally lower in HCC recipients, and there were only small differences between the cohorts in the frequency of capsular damage in the donor organ. Of the 1270 HCC recipients who were included in our study, only 81 (6.4%) had tumor characteristics that were beyond the Milan but within the expanded criteria at the time of registration on the transplant waiting list.

Kaplan-Meier survival curves comparing outcomes in HCC and non-HCC patients showed that patient and graft survival in the first months following liver transplantation is very similar (Figure 2). After about 3 to 4 months, HCC patients seem to have progressively worse patient survival, resulting in a 5-year patient survival of 74.5% (95% CI, 71.2%–77·5%) for HCC patients and 84.6% (95% CI, 83.0%–86.1%, P < 0.001) for non-HCC patients. A similar time pattern was observed for prognostic impact of HCC on graft survival with corresponding 5-year estimates of 70.2% (95% CI, 66.8%–73.3%) for HCC patients and 79.1% (95% CI, 77.4%–80.7%, P < 0.001) for non-HCC patients.

We did not find a difference in the 5-year patient survival between the 1189 HCC patients who met the Milan criteria (74.6%; 95% CI, 71.1%–77.7%) and the 81 who did meet the expanded criteria (74.5%; 95% CI, 58.6%–85.0%; P = 0.76 (Figure 3). Neither did we find differences in graft survival between these patient groups (70.4%; 95% CI, 67.0%–73.6% and 67.8%; 95% CI, 55.2%–79.3%, respectively; P = 0.81).

The first Cox regression model, comparing HCC and non-HCC patients without adjustment for donor or recipient characteristics, did not find a statistically significant difference in survival in the first 90 days after transplantation (HR, 0.88; CI, 0.63–1.23; Table 2). In the subsequent 2 epochs of follow-up time, patients with HCC had a significantly poorer survival (HR, 2.27 between 90 days and 2 years and HR, 2.00 between 2 and 5 years). In the second Cox regression model, only adjusting for recipient characteristics did not dramatically change the impact of HCC on survival in either the first 90 days after transplantation (adjusted HR, 0.76; CI, 0.53–1.09) or in the 2 later epochs of follow-up time (adjusted HR, 1.99 between 90 days and 2 years and adjusted HR, 1.77 between 2 and 5 years). In the third Cox model, additional adjustment for donor characteristics also had little effect on the impact of HCC in each of the epochs of follow-up time (adjusted HR, 0.74 between 0 and 90 days; adjusted HR, 1.96 between 90 days and 2 years; and adjusted HR, 1.74 between 2 and 5 years). The results of the Cox regression analysis of graft

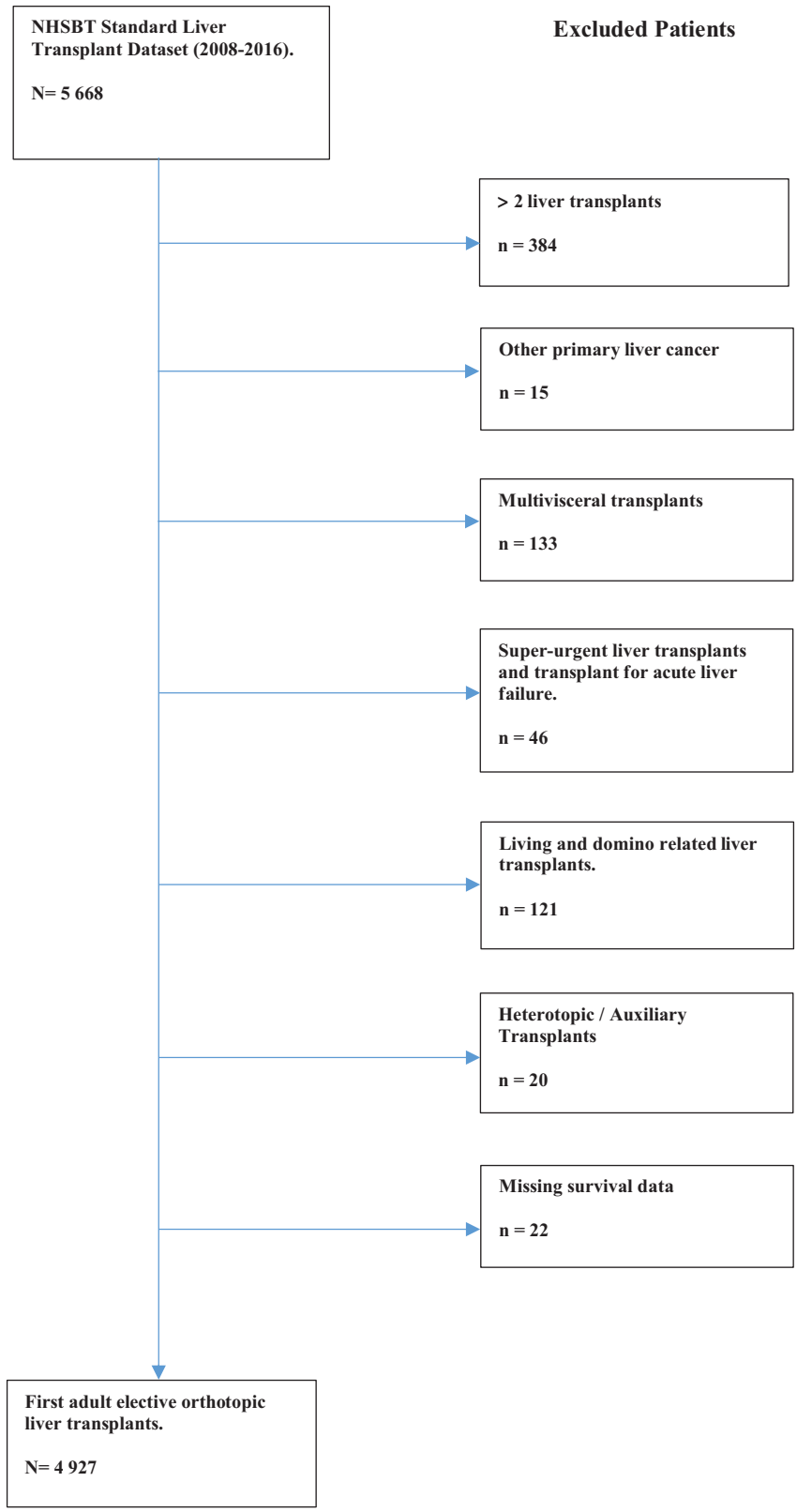

FIGURE 1. Flow chart detailing selection of study population (2008-2016). NHSBT, National Health Service Blood and Transplant.

survival (Table 3) closely mirrored the results found for patient survival (Table 2).

In the sensitivity analysis that explored the impact of HCC in 4 separate epochs, we found that it was highest between 90 days and 1 year after transplantation (adjusted HR, 2.10; 95% CI, 1.47–3.00) and that it remained at a very similar level thereafter (Table S5, SDC, http://links.lww.com/TP/B665). The sensitivity analysis testing the interaction between HCC and HCV status did not show that the effect of HCC on mortality differed significantly according

TABLE 1.

Donor and recipient patient characteristics (N = 4927)

Indication group	HCC	Non-HCC		
Number	n = 1270	n = 3657	Missing values[a]	*P*
Donor	% (N)	% (N)	N	
Sex				
Female	42.8% (544)	47.6% (1740)	0	0.003
Cause of death				
Trauma	9.1% (115)	7.7% (281)		0.21
Cerebrovascular accident	62.6% (796)	64.8% (2371)		
Others	28.3% (359)	27.5% (1005)	0	
Donor type				
DCD	31.9% (405)	21.2% (774)	0	<0.001
ABO match				
Identical	98.0% (1245)	98.6% (3606)		0.34
Compatible	1.9% (24)	1.3% (48)		
Incompatible	0.1% (1)	0.1% (3)	0	
Graft type				
Segmental	6.0% (76)	8.9% (324)	0	0.001
Organ appearance				
Abnormal	29.8% (308)	22.8% (709)	776	<0.001
Steatosis				
Presence	48.2% (604)	44.6% (1603)	84	0.03
Capsular damage				
Presence	14.3% (178)	14.1% (507)	92	0.91
Donor age, y				
Mean (SD)	50 (16)	49 (16)	0	0.07
Donor BMI, kg/m^2				
Mean (SD)	27 (5.0)	26 (5.0)	10	0.15
Cold ischemic time (min)				
Mean (SD)	502 (158)	517 (158)	392	0.01
Recipient				
Sex				
Female	19.8% (251)	37.3% (1363)	1	<0.001
Recipient ethnicity				
Non-white	16.5% (209)	11.1% (407)	2	<0.001
HCV status				
Positive	42.6% (509)	12.1% (418)	285	<0.001
Pretransplant in patient status				
Inpatient	4.9% (62)	16.6% (608)	6	<0.001
Ascites				
Presence	29.8% (378)	61.8% (2251)	17	<0.001
Encephalopathy				
Presence	15.2% (189)	36.1% (1300)	82	<0.001
Pretransplant renal support				
Yes	4.7% (60)	4.6% (170)	13	0.9
Pretransplant ventilation requirement				
Yes	0.2% (3)	0.9% (31)	8	0.02
Previous abdominal surgery				
Yes	10.0% (127)	12.4% (453)	17	0.02
Previous variceal bleed				
Presence	15.7% (199)	27.4% (1002)	56	<0.001
Life style activity				
Normal	12.9% (161)	3.8% (139)		<0.001
Restricted	44.2% (554)	31.5% (1136)		
Self-care	37.4% (469)	47.7% (1724)		
Reliant	4.5% (56)	14.0% (505)		
Confined	1.0% (13)	3.0% (107)	63	

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TABLE 1. (Continued)

Indication group	HCC	Non-HCC		
Number	**n = 1270**	**n = 3657**	**Missing values**	***P***
Age (y)				
Mean (SD)	58 (8.0)	51 (11.8)	0	<0.001
BMI, kg/m^2				
Mean (SD)	28 (4.8)	27 (5.3)	5	<0.001
UKELD				
Mean (SD)	51 (4.9)	56 (5.4)	38	<0.001

[a]No data item had >15% of missing values.
BMI, body mass index; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; HCV, hepatitis C; SD, standard deviation; UKELD, United Kingdom Model for End-Stage Liver Disease.

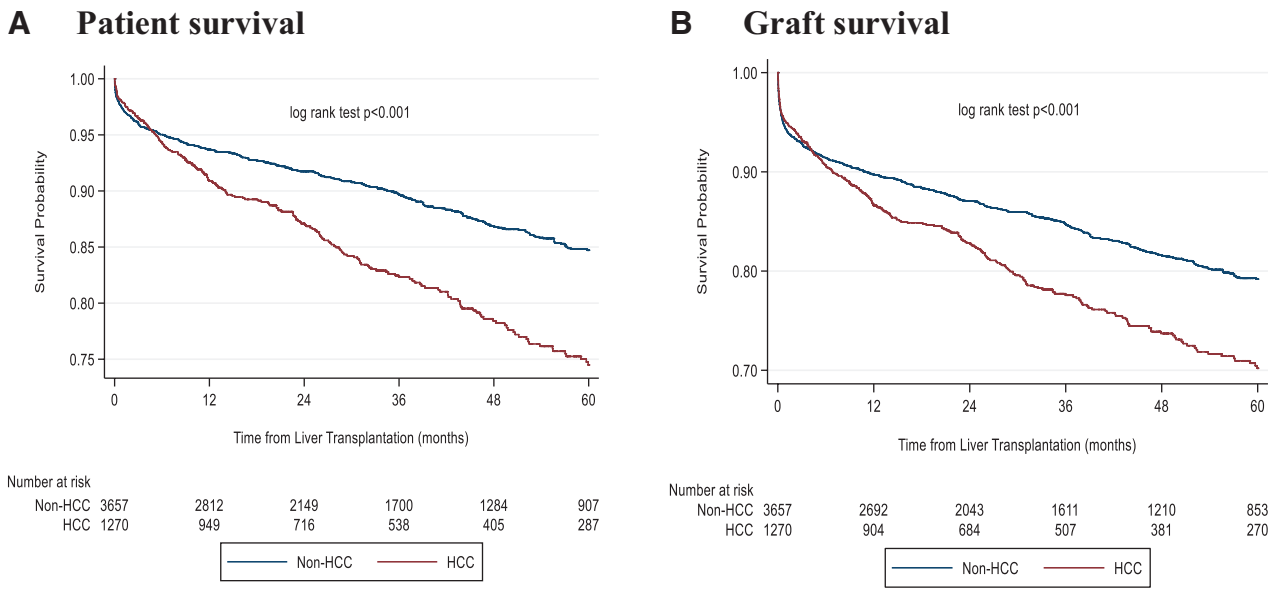

FIGURE 2. Five-year patient and graft survival stratified by hepatocellular carcinoma (HCC) status 2008-2016 (N = 4927).

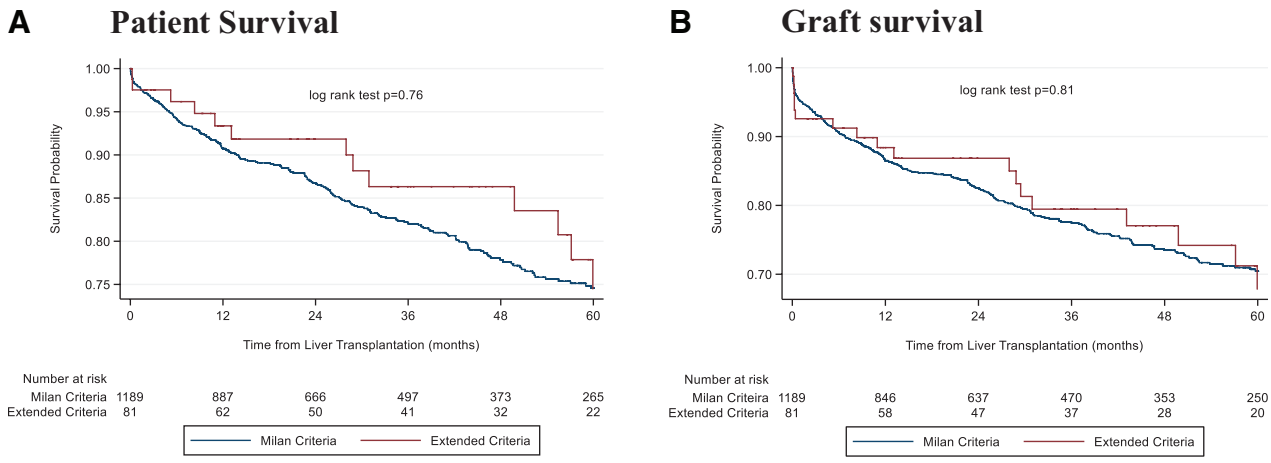

FIGURE 3. Five-year patient and graft survival for hepatocellular carcinoma (HCC) patients stratified by type of selection criteria 2006-2016 (N = 1270).

to HCV status (HCV+ve HR, 1.16; 0.87–1.56, and HCV–ve HR, 0.86; 0.64–1.15; *P* for interaction = 0.10).

In the first 90 days after transplantation, there were no statistically significant differences in the distribution of cause of death between HCC and non-HCC recipients and no patient died from tumor recurrence (recurrence of malignant primary disease; Table 4). In the subsequent posttransplant epochs, tumor recurrence in HCC recipients became a more frequent cause of death accounting for 23 of the 101 deaths (22.7%) between 90 days and

TABLE 2.

Impact of HCC on posttransplant patient survival in 3 separate epochs of follow-up time (N = 4927)

	HCC compared with non-HCC HR (95% CI)			
Posttransplant patient survival	0-3 Months	3-24 Months	24-60 Months	*P* time dependency[a]
Unadjusted analysis	0.88 (0.63–1.23)	2.27 (1.74–2.94)	2.00 (1.50–2.66)	<0.001
Adjusted for recipient characteristics[b]	0.76 (0.53–1.09)	1.99 (1.48–2.66)	1.77 (1.30–2.42)	<0.001
Adjusted for recipient and donor characteristics[b]	0.74 (0.52–1.07)	1.96 (1.46–2.62)	1.74 (1.27–2.31)	<0.001

[a]*P* values represent whether HRs in each epoch of follow-up time differ significantly from each other.
[b]Adjusted for (a) recipient characteristics: sex, ethnicity, HCV status, pretransplant inpatient status, ascites, encephalopathy, pretransplant renal support, previous abdominal surgery, varices, lifestyle activity, age, BMI (kg/m^2), and UKELD and (b) donor characteristics: sex, cause of death, donor type (donation after cardiac death or donation after brain death), ABO match, graft type, organ appearance, steatosis, capsular damage, age, BMI (kg/m^2), and cold ischemic time.
Tables S1 and S2, SDC, http://links.lww.com/TP/B665 in the supplemental information have HRs and 95% CI for all other donor and recipient characteristics.
BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C; HR, hazard ratio; UKELD, United Kingdom Model for End-Stage Liver Disease.

TABLE 3.

Impact of HCC on post-transplant graft survival in 3 separate epochs of follow-up time (N = 4927)

	HCC compared to non-HCC HR (95% CI)			
Posttransplant graft survival	0-3 Months	3-24 Months	24-60 Months	*P* time dependency[a]
Unadjusted analysis	0.95 (0.75–1.21)	1.84 (1.46–2.34)	1.82 (1.38–2.39)	<0.001
Adjusted for recipient characteristics[b]	0.89 (0.68–1.17)	1.74 (1.34–2.27)	1.72 (1.28–2.31)	<0.001
Adjusted for recipient and donor characteristics[b]	0.84 (0.65–1.11)	1.67 (1.28–2.17)	1.66 (1.23–2.23)	<0.001

[a]*P* values represent whether HRs in each epoch of follow-up time differ significantly from each other.
[b]Adjusted for (a) recipient characteristics: sex, ethnicity, HCV status, pretransplant inpatient status, ascites, encephalopathy, pretransplant renal support, previous abdominal surgery, varices, lifestyle activity, age, BMI (kg/m^2), and UKELD and (2) donor characteristics: sex, cause of death, donor type (donation after cardiac death or donation after brain death), ABO match, graft type, organ appearance, steatosis, capsular damage, age, BMI (kg/m^2), and cold ischemic time.
Tables S3 and S4, SDC, http://links.lww.com/TP/B665 in the supplemental information have HRs and 95% CI for all other donor and recipient characteristics.
BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C; HR, hazard ratio; UKELD, United Kingdom Model for End-Stage Liver Disease.

2 years and 12 of the 77 deaths (15.6%) between 2 and 5 years. When splitting cause of death into 4 epochs, we found that from 90 days onward the number of patients dying from tumor recurrence remained more or less constant (Table S6, SDC, http://links.lww.com/TP/B665).

Of the 35 HCC recipients who died of tumor recurrence, 9 (25.7%) had received a DCD liver compared with 396 of the 1235 other HCC recipients (32.1%; $P = 0.43$) which demonstrates that there is no evidence that the use of DCD livers is linked to an HCC recurrence risk. The proportion of patients who died from malignancies other than tumor recurrence was higher in the HCC recipients (2.9% or 37/1270) than in non-HCC recipients (1.1% or 41/3657), and this difference was most prominent in deaths from nonlymphoid malignancies (Table 4). Overall, recurrence of benign primary disease, which includes HCV, was infrequently reported as a cause of death (Table 4 and see Table S6, SDC, http://links.lww.com/TP/B665), irrespective of HCC status at the time of transplant or epoch of follow-up (Table 4 and see Table S6, SDC, http://links.lww.com/TP/B665).

DISCUSSION

Summary of Results

At the time of transplantation, HCC patients were on average in a better physical condition and had less signs of end-stage liver disease than non-HCC patients, but they received more often suboptimal grafts. We found that the survival of HCC and non-HCC recipients was similar in the first months after transplantation. Then the survival of HCC recipients deteriorated with the rate of mortality and graft failure being at least 50% higher than in non-HCC recipients, with tumor recurrence as the most important explanation. The difference in survival could not be explained by HCC recipients receiving a higher proportion of livers from DCD donors or from donors with other suboptimal characteristics.

Methodological Limitations

The key limitation of our analysis is that we used predefined posttransplant epochs (up to 90 days, between 90 days and 2 years, and between 2 and 5 years) to investigate the time dependency of the impact of HCC on patient and graft survival. This approach assumes that the prognostic impact of HCC on survival is constant within each of these epochs.[21] The advantage of this approach is that the HRs can be estimated using standard Cox regression methods and, more importantly, that the results are relatively easy to interpret. Its disadvantage is that the partitioning of the survival time in distinct epochs needs to be chosen in advance and that the number of separate epochs as well as their duration is arbitrary.

TABLE 4.

Primary cause of death following liver transplantation for HCC and non-HCC patients in 3 separate epochs of follow-up time (n = 620)

	0-90 days		91 days to 24 months		24 months to 60 months	
Cause of death	**HCC (n = 44)**	**Non-HCC (n = 144)**	**HCC (n = 101)**	**Non-HCC (n = 132)**	**HCC (n = 77)**	**Non-HCC (n = 122)**
Recurrent primary disease—malignant[a]	0% (0)	0% (0)	22.7% (23)	1.5% (2)	15.6% (12)	1.6% (2)
Recurrent primary disease—benign[b]	2.3% (1)	0.0% (0)	1.0% (1)	3.8% (5)	1.3% (1)	2.5% (3)
Malignancy—lymphoproliferative	2.3% (1)	0.0% (0)	3.0% (3)	4.5% (6)	1.3% (1)	4.9% (6)
Malignancy—nonlymphoproliferative	0.0% (0)	0.0% (0)	12.9% (13)	9.1% (12)	24.7% (19)	13.9% (17)
Sepsis	45.5% (20)	42.3% (61)	24.7% (25)	37.1% (49)	22.0% (17)	29.5% (36)
Graft failure	2.3% (1)	4.2% (6)	3.0% (3)	0.8% (1)	1.3% (1)	0.8% (1)
Hemorrhage	4.5% (2)	6.9% (10)	3.0% (3)	1.5% (2)	1.3% (1)	1.6% (2)
Pulmonary failure	2.3% (1)	6.3% (9)	3.9% (4)	9.9% (13)	9.1% (7)	5.8% (7)
Renal failure	0.0% (0)	0.7% (1)	0% (0)	0% (0)	0.0% (0)	0.8% (1)
Cardiac failure	9.1% (4)	9.7% (14)	3.0% (3)	6.1% (8)	1.3% (1)	6.6% (8)
Hepatic failure	2.3% (1)	0.7% (1)	0.0% (0)	1.5% (2)	2.6% (2)	1.6% (2)
Gastrointestinal	0% (0)	0.7% (1)	0.0% (0)	0% (0)	1.3% (1)	1.6% (2)
Infection	4.5% (2)	0.7% (1)	2.0% (2)	0% (0)	0.0% (0)	0.8% (1)
CVA	4.5% (2)	3.5% (5)	0.0% (0)	2.3% (3)	1.3% (1)	2.5% (3)
Other	20.4% (9)	22.2% (32)	10.9% (11)	15.9% (21)	10.4% (8)	10.7% (13)
Unknown	0% (0)	2.1% (3)	9.9% (10)	6.0% (8)	6.5% (5)	14.8% (18)
P[c]	0.38		<0.001		0.03	

[a]Recurrence of malignant disease for patients transplanted for non-HCC indications likely represents recurrence of an intrahepatic malignancy only identified on explant pathology or an error in the recording cause of death.
[b]Includes the recurrence of HCV and the cholestatic liver diseases (PSC and PBC).
[c]*P* value of chi-squared test comparing distribution of causes of death in HCC and non-HCC patients.
HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.

In our analysis, we compared HCC patients with a heterogeneous cohort of non-HCC patients. This approach may have masked specific survival patterns of individual primary liver diseases. However, the dichotomy in HCC and non-HCC patients reflects the difference in how HCC and non-HCC patients were selected for transplantation in the United Kingdom. While for most non-HCC patients, the urgency of transplantation was taken from their liver function according to the UKELD score, the urgency for HCC patients came from the need to avoid cancer progression before transplantation.

Comparison With Other Studies

We studied the prognostic impact of HCC on posttransplant survival in 3 distinct epochs, aiming to capture on the one hand that HCC patients are in a better physical condition at the time of transplantation—which may give them better surgical outcomes—but on the other that tumor recurrence may deteriorate survival in the later stages. Already 30 years ago, the importance of analyzing liver transplant outcomes in epochs of follow-up time was recognized, but this statistical approach is very rarely practised.[4,22] Our study is an example of how important it is to analyze posttransplant outcomes in distinct epochs of follow-up time, guided by the understanding of the relevant underlying clinical mechanisms. For example, risk factors for immediate surgical outcomes are predominantly linked to the recipients' physical condition and risk factors for longer-term outcomes to recurrence of the original disease that was the reason for transplantation.

It was expected that the introduction of the Milan criteria would lead to a decrease in recurrence rates in patients transplanted for HCC.[4] However, our study, which reflects the outcomes of modern liver transplantation practice, including a national population-based cohort of patients transplanted between 2008 and 2016, indicates that tumor recurrence remains an important risk factor for survival in the later stages after liver transplantation, which corresponds with earlier reports of posttransplant survival.[1-3]

Despite a formal adoption of expanded HCC selection criteria in 2008, we found that only 6.4% of HCC recipients were selected for transplantation within these expanded criteria and we could not demonstrate differences in posttransplant outcomes compared with those who were selected according to the Milan criteria. Reasons for why only a very small minority of HCC recipients were transplanted beyond the Milan criteria are difficult to explain and we must acknowledge that this analysis does not specifically address this question. However, a tendency for radiological assessment to understage some HCC patients before transplantation may have prohibited the aggressive use of the extended selection criteria, especially when other studies have indicated a linear relationship between tumor burden and posttransplantation survival.[23,24]

Explanation of Results

Our study found that HCC patients were more likely to receive suboptimal donor organs with characteristics previously proven to have poorer posttransplant outcomes.[2] This included donated livers that were either steatotic, abnormal in appearance, or that were from DCD donors. However, our analysis was specifically designed to test the impact of donor characteristics on posttransplant survival, and we observed that additional adjustment for donor characteristics had little effect on the differences in survival between HCC and non-HCC recipients in any of the epochs after transplantation.

The incidence of HCV recurrence after transplantation is also an unlikely explanation for the observed differences in survival. Previous studies have reported that, irrespective of HCC status at the time of transplantation, survival between those with and without HCV is similar up to 5 years after transplantation and worse thereafter.[25,26] In our own analysis, we did not find the effect of HCC on mortality to differ significantly according to whether the patient had a previous diagnosis of HCV nor did we find HCV recurrence to be frequently reported as a cause of death in the first 5 years after transplantation.

Similarly, differences in the incidence of acute rejection do not explain the differences in the survival patterns of HCC and non-HCC recipients. In efforts to reduce the risk of tumor recurrence, HCC recipients can be subjected to more conservative immunosuppression protocols,[27] and therefore, they may be at an increased risk of acute rejection. However, we have found that 1-year readmissions for acute rejection in patients transplanted in the United Kingdom between 2008 and 2016 occurred less frequently in HCC recipients (2.8% or 35/1270) than in non-HCC recipients (3.1% or 112/3657; $P = 0.57$), while acute rejection recorded as a cause of death was not identified at all within the study cohort (London School of Hygiene and Tropical Medicine, unpublished data, 2018).

We identified some differences in the proportion of HCC and non-HCC recipients who died of malignancies other than tumor recurrence. This cause of death, particularly nonlymphoid-related malignancies, were more frequent in HCC recipients and consistent with the existing literature there was a high incidence between 3 months and 2 years after transplantation.[28] However, the differences in the overall number of HCC and non-HCC recipients who died from malignancies other than tumor recurrence were too small to fully explain the differences in survival between the 2 cohorts.

Beyond 90 days, differences in survival are best explained by differences in deaths due to tumor recurrence and this remained so even when we further partitioned the follow-up period to include survival from 90 days to 1 year and from 1 to 2 years. Of the HCC patients who were recorded to have died of tumor recurrence within 1 year, only one was preoperatively staged according to the extended criteria with other early deaths potentially explained by aggressive tumor biology or radiological understaging of the HCC before transplantation.[13] In further analysis, we did not find the use of DCD livers to be associated with an increased risk of death from tumor recurrence.

In the past, HCC patients were found to have 90-day outcomes that were statistically significantly better than non-HCC patients.[5] Our results suggested that 90-day outcomes of HCC patients were better, but the difference with non-HCC patients was not statistically significant. One important explanation for not finding a significant difference is the substantial improvement in posttransplant outcomes in the last 30 years which considerably reduces the statistical power to detect differences.[29] Another explanation is that the impact of recipients' frailty at the time of transplantation has decreased given the improvements in perioperative care and the high dependency care immediately after transplantation.[30]

Implications of Findings

Our results demonstrate that outcomes in patients transplanted for HCC are worse than in those transplanted for non-HCC indications. This is not explained by the fact that we are using more DCD donors in HCC patients or that we are transplanting a significant proportion of patients who, at the time of transplantation, are beyond the Milan criteria. Instead, we must acknowledge that even with the stringent adoption of the Milan criteria in the United Kingdom, we are still selecting for transplantation a significant proportion of patients with HCC who are at risk of tumor recurrence. Therefore, until we can add to our selection criteria new parameters that better predict tumor recurrence, the poorer survival of HCC patients after liver transplantation will remain.

Until recently, many guidelines stipulated that patients with HCC should only receive a liver transplant if their predicted outcomes are comparable to non-HCC patients.[3] However, in the last decade, this has never been the case. This has been recognized by the service providers, and donor liver allocation schemes are now moving toward using criteria based on transplant benefit—in which they aim to maximize the net life years gained from the point of registration on the waiting rather than providing the greatest chance of surviving after transplantation.[31,32] However, the decision to offer HCC patients a liver transplant is further complicated as other treatments, including resection and ablation, have to be considered which is all the more important considering the impact that an increased use of liver transplantation in HCC patients will have on outcomes for non-HCC patients on the waiting list for transplantation given the ongoing donor organ shortage.[1,3]

CONCLUSIONS

Between 2008 and 2016, almost all HCC patients who received a liver transplant in the United Kingdom met the Milan criteria. Nevertheless, 1 in 4 HCC recipients died within 5 years compared with only 1 in 6 non-HCC patients, with tumor recurrence being the most likely explanation for this difference. These differences could not be explained by the increased use of poorer-quality donor organs in HCC patients. Donor allocation schemes based on transplant benefit schemes are likely to accommodate the poor posttransplant survival of HCC patients given their greater net gain in posttransplanted expected life years.

ACKNOWLEDGMENTS

The authors would like to thank all liver transplant centers for providing data to the Standard National Liver Transplant Registry. The authors would also like to thank all those involved in collecting and handling liver transplant data at National Health Service Blood and Transplant. The UK Liver Transplant Audit is supported by the NHS National Specialised Commissioning Group and NHS England.

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