8-26-2022

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Jyoti Sehjal

Linda D. Sharples

Ruth H. Keogh

Kate Walker

Andreas Prachalias

See next page for additional authors

Authors

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Time-varying Comparison of All-cause Mortality After Liver Transplantation Between Recipients With and Without Hepatocellular Carcinoma: A Population-based Cohort Study Using the United Kingdom Liver Transplant Registry

Jyoti Sehjal, MSc,[1] Linda D. Sharples, PhD,[1] Ruth H. Keogh, DPhil,[1] Kate Walker, PhD,[2] Andreas Prachalias, MD,[3] Nigel Heaton, FRCS,[3] Tommy Ivanics, MD, MPH,[4,5,6] Jan van der Meulen, PhD,[2] and David Wallace, PhD[2,3]

Background. Accurately identifying time-varying differences in the hazard of all-cause mortality after liver transplantation (LT) between recipients with and without hepatocellular carcinoma (HCC) may inform patient selection and organ allocation policies as well as post-LT surveillance protocols. **Methods.** A UK population-based study was carried out using 9586 LT recipients. The time-varying association between HCC and post-LT all-cause mortality was estimated using an adjusted flexible parametric model (FPM) and expressed as hazard ratios (HRs). Differences in this association by transplant year were then investigated. Non–cancer-specific mortality was compared between HCC and non-HCC recipients using an adjusted subdistribution hazard model. **Results.** The HR comparing HCC recipients with non-HCC recipients was below one immediately after LT (1-mo HR = 0.76; 95% confidence interval [CI], 0.59-0.99; $P = 0.044$). The HR then increased sharply to a maximum at 1.3 y (HR = 2.07; 95% CI, 1.70-2.52; $P < 0.001$) before decreasing. The hazard of death was significantly higher in HCC recipients than in non-HCC recipients between 4 mo and 7.4 y post-LT. There were no notable differences in the association between HCC and the post-LT hazard of death by transplant year. The estimated non–cancer-specific subdistribution HR for HCC was 0.93 (95% CI, 0.80-1.09; $P = 0.390$) and not found to vary over time. **Conclusion.** FPMs can provide a more precise comparison of post-LT hazards of mortality between HCC and non-HCC patients. The results provide further evidence that some HCC patients have extra-hepatic spread at the time of LT, which has implications for optimal post-LT surveillance protocols.

(*Transplantation* 2022;00: 00–00).

Received 7 March 2022. Revision received 1 June 2022.

Accepted 14 June 2022.

[1] *Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom.*

[2] *Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom.*

[3] *Institute of Liver Studies, King's College Hospital NHS Foundation Trust, London, United Kingdom.*

[4] *Division of General Surgery, Multi-organ Transplant Program, University Health Network, University of Toronto, Toronto, ON, Canada.*

[5] *Department of Surgery, Henry Ford Hospital, Detroit, MI.*

[6] *Department of Surgical Sciences, Akademiska Sjukhuset, Uppsala University, Uppsala, Sweden.*

This study was funded by the National Institute of Health Research (NIHR301023), which had no role in the study proposal, data collection, data analysis, data interpretation, write-up of the paper, or the decision to submit for publication.

J.S. is funded by a Pre-Doctoral Fellowship (NIHR301023) from the National Institute of Health Research (NIHR) for this research project. R.H.K. is funded by UK Research and Innovation (Future Leaders Fellowship MR/S017968/1). The views expressed in this publication are those of the authors and not necessarily those of the NIHR, UK Research, and Innovation, NHS, or the UK Department of Health and Social Care.

The authors declare no funding or conflicts of interest.

J.S. participated in the study proposal, data analysis, interpretation of results, and write-up of article. L.D.S. involved in study proposal, supervision of analysis, interpretation of results, and write-up of article. R.H.K. participated in interpretation of results and write-up of article. K.W., A.P., N.H., and T.I. participated in Interpretation of results and write-up of article

J.v.d.M. participated in study proposal, interpretation of results, and write-up of article.

D.W. participated in the interpretation of results and write-up of article.

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).

Correspondence: Jyoti Sehjal, MSc, Department of Medical Statistics, London School of Hygiene and Tropical Medicine, Keppel Street, London, WC1E 7HT, UK. (jyoti.sehjal@lshtm.ac.uk).

ISSN: 0041-1337/20/0000-00

DOI: 10.1097/TP.0000000000004282

INTRODUCTION

Liver transplantation (LT) has become the preferred curative treatment option for patients with early stage hepatocellular carcinoma (HCC).[1] The 5-y post-LT survival in HCC recipients whose preoperative tumor characteristics are within the Milan criteria (a single tumor with diameter ≤5 cm or at most three nodules each with diameter ≤3 cm with no angioinvasion or extra-hepatic involvement) is at least 70%.[2]

The long-term immunosuppressive management of LT recipients requires a prolonged and careful balancing of the risk of graft rejection and infection.[3] The post-LT hazard of death has a "bathtub" shape in that there is initially a high hazard of death from the surgery, primary nonfunction, and infection, followed by a period of low hazard, before the hazard increases again due to other issues, such as comorbidities and cancer recurrence.[4]

In this context, HCC is likely to have a greater impact on some recorded causes of death than others, so one cannot assume that the hazards of death for HCC and non-HCC recipients will be the same throughout the post-LT period.[5] Traditional proportional hazards models used to analyze survival data assume that the ratio of hazards for two groups is constant over time. This may not be appropriate, potentially resulting in a biased estimate of the hazard ratio (HR) for HCC and inaccurate predictions of (particularly long-term) survival.

Allowing for a time-varying association between HCC and the hazard of post-LT mortality can help clinicians determine the times at which HCC recipients have a higher hazard of death compared with non-HCC recipients. Adding time-varying interactions between HCC and transplant year also allows for the comparison of the association between HCC and the hazard of post-LT mortality over time to ascertain whether the significant changes in LT management has improved outcomes in these recipients. Investigating cause-specific mortality may help policymakers to better understand when recurrence following LT is most likely to be detectable and plan the surveillance of such patients accordingly.

The aims of this study were 2-fold. First, after adjusting for donor and recipient confounders, the hazard of post-LT all-cause mortality was compared between HCC and non-HCC recipients to identify the period for which the relative hazard of death was highest. Time-varying interactions between HCC and transplant year were then used to assess whether there were any differences in the association between HCC and the post-LT hazard of death between 1997 and 2016. Second, the association between HCC and non–cancer-specific mortality was estimated to provide further evidence that the increased relative hazard of death in HCC recipients was primarily due to post-LT HCC occurrence. To achieve these aims, a flexible parametric survival model for all-cause mortality and a subdistribution hazard model for non–cancer-specific mortality were applied to a dataset containing information on 9586 LT recipients from the United Kingdom Liver Transplant Registry (UKLTR).[6,7]

MATERIALS AND METHODS

The United Kingdom Liver Transplant Registry

The UKLTR contains data from a population-based cohort managed by the National Health Service Blood and Transplant (NHSBT). Data were extracted for all 11 926 adult elective transplants performed in the United Kingdom between January 1, 1995, and December 31, 2016. Patients attended regular post-LT examinations and were followed up until death or October 29, 2017, the date of data extraction.[6]

Study Population

The study population comprised recipients aged ≥17 (the age at which liver transplant recipients are considered to require adult-level treatment in the UK) who received their first elective orthotopic liver-only transplant in the UK between January 1, 1997, and December 31, 2016. Exclusion criteria were LT for acute liver failure, auxiliary transplant, primary liver cancer types other than HCC, domino or a living-donor transplant, or missing survival data.[8] Recipients with data entry errors were also excluded, for example, if the cause of death was reported but not the date of death or if their reported transplant date was earlier than the date of liver donation (Figure 1).

Data

The endpoint was recipient death, and survival time was recorded in days from LT. Recipients were censored if they were lost to follow-up or if they were alive at their last examination before data extraction.

Primary causes of death were grouped into HCC-specific, other cancers (including lymphoid and nonlymphoid malignancies possibly induced by immunosuppression), and non–cancer-specific causes using clinical knowledge (Table S1, SDC, http://links.lww.com/TP/C507).

The causal association between HCC and mortality was assessed by adjusting for previously established confounders (Table S2, SDC, http://links.lww.com/TP/C507).[7] Most confounders were measured objectively before LT. Recipient confounders that were adjusted for are age, sex, body mass index (BMI), ethnicity, previous abdominal surgery, ascites, renal support status, variceal bleed status, anti-hepatitis C virus (HCV) test result, hospital in-patient status, transplant year, encephalopathy, international normalized ratio, serum bilirubin, serum creatinine, serum sodium, serum albumin, and serum potassium. Donor confounders that were adjusted for are age, sex, BMI, cause of death, donor type, graft type, cold ischemia time, and organ appearance.

Liver disease diagnoses were grouped using a classification proposed by Roberts et al (Table S3, SDC, http://links.lww.com/TP/C507).[9] Recipients were assigned the diagnosis that would have most likely affected their post-LT prognosis using a disease hierarchy based on clinical knowledge.[9,10] HCC diagnosis was derived directly from liver disease etiology.

Statistical Analysis

Descriptive Analysis

Categorical and binary variables were tabulated to give frequencies and continuous variables were summarized by their mean, SD, median, and range. Histograms were produced for continuous variables to identify outlying and implausible values compared with published literature.[10,11] Implausible or outlying values were replaced as missing (Table S2, SDC, http://links.lww.com/TP/C507).

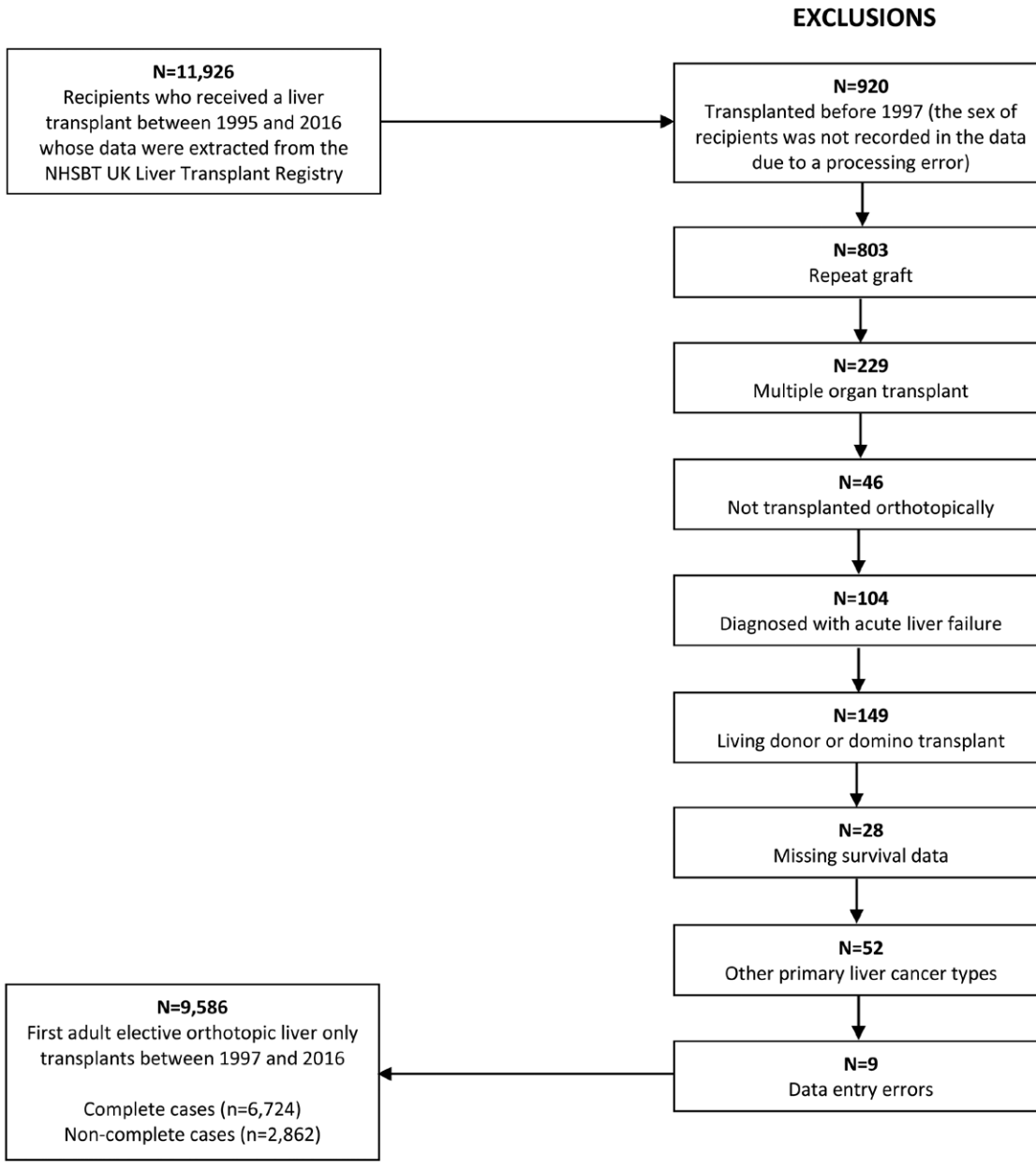

FIGURE 1. Flowchart of recipient numbers throughout the analysis. NHSBT, National Health Service Blood and Transplant; UK, United Kingdom.

Comparisons of other covariates between HCC and non-HCC recipients used chi-squared tests or Fisher's exact tests for categorical variables, ordinal logistic regression for ordered categorical variables (eg, recipient lifestyle activity score), and Student *t*-tests or Wilcoxon–Mann–Whitney tests for normally and nonnormally distributed continuous variables, respectively. Patients transplanted for non-HCC indications who were reported to have died from HCC occurrence were analyzed on an intention-to-treat basis and remained in the non-HCC cohort.

Kaplan–Meier survival curves were produced by levels of HCC and the other covariates to explore their univariable associations with recipient survival. Univariable log-rank tests were used to formally test for differences between the survival curves by levels of each variable.

Unadjusted cumulative incidence functions for each cause of death were produced by HCC diagnosis. They correspond to the marginal probability of dying from a certain cause.

Development of Multivariable Models

Although the main analysis used a flexible parametric model (FPM), a multivariable Cox proportional hazards model was used to determine how the adjustment variables were entered in the models. The scaled Schoenfeld test and residuals were used to assess the proportional hazards assumption.[12,13] The functional form of the linear predictor, conditional on the other variables, was investigated using Martingale residuals.[14] Interactions between HCC and each confounder were assessed individually and kept in the model if the *P* value was <0.05. Continuous covariates (except for transplant year) were centered around their median values and scaled for modeling. Stratified and Cox predicted survival curves at baseline values of the

TABLE 1.

Recipient characteristics by HCC diagnosis before LT (N = 9586)

Variable		HCC recipients (N = 1885)	Non-HCC recipients (N = 7701)	*P*
Age at transplant, y	Mean (SD)	57.1 (8.2)	51.0 (11.4)	<0.001
	Median (range)	58 (17, 74)	53 (17, 74)	
Sex	Male, n (%)	1525 (81.2)	4619 (60.8)	<0.001
	Female, n (%)	352 (18.8)	2979 (39.2)	
Ethnicity	White, n (%)	1535 (81.5)	6756 (87.7)	<0.001
	Non-White, n (%)	349 (18.5)	944 (12.3)	
BMI at registration, kg/m^2	Mean (SD)	27.6 (4.6)	26.5 (5.1)	<0.001
	Median (range)	27.1 (15.6, 45.9)	25.8 (11.6, 50.7)	
Transplant year	1997–2001, n (%)	275 (14.6)	1842 (23.9)	<0.001
	2002–2006, n (%)	321 (17.0)	1793 (23.3)	
	2007–2011, n (%)	561 (29.8)	1727 (22.4)	
	2012–2016, n (%)	728 (38.6)	2339 (30.4)	
Previous abdominal surgery	No previous surgery, n (%)	1651 (87.7)	6523 (85.0)	0.002
	Previous surgery, n (%)	231 (12.3)	1154 (15.0)	
Ascites	No ascites, n (%)	1301 (69.1)	3059 (39.9)	<0.001
	Ascites, n (%)	582 (30.9)	4611 (60.1)	
Ventilation status	Not ventilated, n (%)	1878 (99.7)	7646 (99.4)	0.079
	Ventilated, n (%)	5 (0.3)	47 (0.6)	
Renal support status	Not required, n (%)	1804 (96.0)	7308 (95.0)	0.092
	Required, n (%)	76 (4.0)	382 (5.0)	
Variceal bleed status	No variceal bleed, n (%)	1543 (82.4)	5251 (68.8)	<0.001
	Variceal bleed n, (%)	330 (17.6)	2386 (31.2)	
Encephalopathy	Not encephalopathic, n (%)	1623 (87.3)	5426 (71.0)	<0.001
	Encephalopathic, n (%)	237 (12.7)	2211 (29.0)	
Lifestyle activity score	Normal, n (%)	215 (11.5)	253 (3.3)	<0.001
	Restricted, n (%)	740 (39.7)	1963 (25.7)	
	Self-care, n (%)	800 (42.9)	4139 (54.2)	
	Confined, n (%)	93 (5.0)	1057 (13.8)	
	Reliant, n (%)	16 (0.9)	228 (3.0)	
Anti-HCV test result	Negative, n (%)	984 (55.4)	6056 (84.7)	<0.001
	Positive, n (%)	793 (44.6)	1097 (15.3)	
In-patient status	Out-patient, n (%)	1784 (94.7)	6489 (84.3)	<0.001
	In-patient, n (%)	99 (5.3)	1207 (15.7)	
INR	Mean (SD)	1.4 (0.7)	1.6 (0.9)	<0.001
	Median (range)	1.2 (0.7, 13.1)	1.4 (0.7, 18.6)	
UKELD score	Mean (SD)	51.2 (4.9)	55.9 (5.5)	<0.001
	Median (range)	50 (39, 72)	55 (40, 86)	

Serum creatinine, µmol/L	Mean (SD)	85.0 (27.1)	91.5 (45.6)	<0.001
	Median (range)	80 (30, 365)	83 (16, 915)	
Serum bilirubin, µmol/L	Mean (SD)	36.3 (47.6)	100.9 (130.4)	<0.001
	Median (range)	23 (2, 736)	55 (2, 1151)	
Serum potassium, mmol/L	Mean (SD)	4.2 (0.5)	4.2 (0.6)	<0.001
	Median (range)	4.1 (2.9, 6.9)	4.2 (2.1, 7.6)	
Serum sodium, mmol/L	Mean (SD)	138.2 (4.4)	136.1 (5.0)	<0.001
	Median (range)	139 (119, 158)	137 (112, 160)	
Serum albumin, g/L	Mean (SD)	33.5 (7.4)	30.6 (6.6)	<0.001
	Median (range)	34 (10, 52)	30 (8, 56)	

BMI, body mass index; CI, confidence interval; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; INR, international normalized ratio; LT, liver transplantation; UKELD, United Kingdom Model for End-Stage Liver Disease.

covariates were used to show that assuming proportional hazards for HCC was not appropriate.

Martingale residual plots showed that including recipient age-squared and BMI-squared improved the models. Likewise, serum bilirubin and serum creatinine were log-transformed for subsequent modeling. All other continuous variables were modeled linearly.

To produce a smooth curve for the association between HCC and all-cause mortality, an FPM with a time-varying effect of HCC was used.[15] The FPM uses a series of polynomial functions, joined together at specific points termed "knots," to analyze survival data.[16] These polynomials better describe how the baseline hazard changes over time in complex clinical settings, such as that observed post-LT, compared with other parametric models.

Akaike and Bayesian information criteria were used to determine the number of knots.[16] Knots were positioned at centiles of the distribution of the log event times to ensure an equal number of events in each interval.[16,17] The FPM was then extended to include a time-varying interaction between HCC and transplant year.

Fine and Gray's methods were used to obtain a subdistribution hazard ratio (SHR) to compare the non–cancer-specific mortality between HCC and non-HCC recipients and explain the shape of the HR for HCC over time estimated by the FPM.[18] By categorizing causes of death into cancer and non–cancer-specific, if one assumes that the increase in the hazard of post-LT mortality observed in the HCC recipients is due to HCC occurrence, then it is expected that the non–cancer-specific subdistribution hazard is similar in HCC and non-HCC recipients. A time-varying coefficient for HCC was used to investigate the proportionality of subdistribution hazards.

Missing Data

The percentage of missing records for most covariates was low, with organ appearance having the highest at 10.6%. Kaplan–Meier survival curves and log-rank tests were used to investigate whether missingness (in any variable) was associated with survival. Of the 9586 eligible recipients, 6724 patients (70.2%) had complete data for all covariates. Survival curves for complete and noncomplete cases were not significantly different ($P = 0.334$). The distributions of each variable were also similar for complete and noncomplete cases. Therefore, there was little evidence of a systematic difference between the two groups, justifying a complete-case analysis.[19] Descriptive analysis was carried out using the full data (Tables S4 and S5, SDC, http://links.lww.com/TP/C507) and multivariable models using the complete cases.

All statistical analysis was completed in Stata version 15.[20] This study obtained Health Research Authority (HRA) Research Ethics approval (17.LO.0231) and HRA CAG approval (17/CAG/0025).

RESULTS

Donor and Recipient Characteristics

Of the 9586 eligible recipients, 1885 were transplanted for HCC. Donor and recipient characteristics differed between HCC and non-HCC recipients (Tables 1 and 2). On average, HCC recipients were older, more likely to be male, of non-White ethnicities, and more

TABLE 2.

Donor characteristics by HCC diagnosis before LT (N = 9586)

Variable		HCC recipients (N = 1885)	Non-HCC recipients (N = 7701)	*P*
Age at donation, y	Mean (SD)	48.5 (15.5)	46.5 (15.7)	<0.001
	Median (range)	50 (12, 85)	48 (5, 86)	
Sex	Male, n (%)	1083 (57.5)	4044 (52.5)	<0.001
	Female, n (%)	802 (42.5)	3657 (47.5)	
BMI, kg/m^2	Mean (SD)	26.2 (4.7)	25.8 (4.8)	<0.001
	Median (range)	25.5 (14.3, 53.3)	25.2 (10.5, 67.6)	
Donor type	DBD, n (%)	1467 (77.8)	6781 (88.1)	<0.001
	DCD, n (%)	418 (22.2)	920 (11.9)	
Donor versus recipient blood group match	Identical, n (%)	1830 (97.1)	7481 (97.2)	0.688
	Compatible, n (%)	53 (2.8)	203 (2.6)	
	Incompatible, n (%)	2 (0.1)	16 (0.2)	
Graft type	Whole, n (%)	1779 (94.4)	7115 (92.4)	0.003
	Segment, n (%)	106 (5.6)	586 (7.6)	
Organ appearance	Healthy, n (%)	1205 (73.9)	5441 (78.4)	<0.001
	Abnormal, n (%)	426 (26.1)	1498 (21.6)	
CIT, hours	Mean (SD)	9.1 (2.9)	9.7 (3.0)	<0.001
	Median (range)	8.8 (0.8, 21)	9.5 (0, 23)	
Cause of death	Trauma, n (%)	235 (12.5)	1011 (13.2)	0.019
	CVA, n (%)	1201 (64.0)	5083 (66.2)	
	Other, n (%)	442 (23.5)	1579 (20.6)	

BMI, body mass index; CIT, cold ischemia time; CVA, cerebrovascular accident; DBD, donation after brain death; DCD, donation after circulatory death; HCC, hepatocellular carcinoma; LT, liver transplantation.

likely to have tested positive for HCV antibodies before LT (Table 1).

Despite HCC recipients being older, they tended to be in better overall health than non-HCC recipients (Table 1). They were physically more active, had a lower median United Kingdom End-Stage Liver Disease score, were less likely to have symptoms of end-stage liver disease (encephalopathy, variceal bleeding, and ascites), and were less likely to require ventilation, renal support, or have had previous abdominal surgery. However, HCC recipients were more likely to receive poorer quality livers, including those documented as having an abnormal appearance.

Nonparametric Survival Analysis

Recipients were followed for up to 20.3 y post-LT. Median time to death was 3.0 y in recipients who died, and median time to censoring was 4.8 y in those who were alive at their last examination before data extraction. For HCC recipients, these figures were 2.2 y and 3.8 y, and for non-HCC recipients, they were 3.3 y and 5.0 y, respectively.

For HCC recipients, unadjusted Kaplan–Meier survival estimates at 6 mo, 5 y, and 10 y were 93.0% (95% confidence interval [CI], 91.8%-94.1%), 71.7% (95% CI, 69.2%-74.0%), and 57.2% (95% CI, 53.8%-60.3%), respectively. These figures for non-HCC recipients were 92.2% (95% CI, 91.6%-92.8%), 79.8% (95% CI, 78.8%-80.8%), and 66.4% (95% CI, 65.0%-67.7%). Kaplan–Meier survival curves (Figure 2) showed that short-term survival was superior in HCC recipients up to approximately 8 mo compared with non-HCC recipients, with HCC recipients experiencing worse outcomes thereafter. The 95% CI for non-HCC estimates was narrow over the whole follow-up period, whereas the 95% CI for HCC estimates widened with time, reflecting the lack of recipient deaths after 15 y in this group. There was strong evidence of a difference between the survival curves ($P < 0.001$) (Figure 2).

Multivariable Cox Proportional Hazards Model

Adjusting for confounders, and assuming proportional hazards, the estimated HR for HCC relative to non-HCC was 1.27 (95% CI, 1.11-1.45; $P < 0.001$). A Schoenfeld test and residuals showed evidence against the proportional hazards assumption for HCC ($P = 0.044$). All other covariates were modeled as constant over time. No interactions were significant at the 5% level.

Stratified and Cox predicted survival curves at the baseline values of covariates by HCC diagnosis are shown in Figure 3. The Cox proportional hazards model predicted lower survival estimates in HCC recipients (light blue curve) compared with non-HCC recipients within the first year after LT, whereas the stratified survival estimates showed better survival for HCC recipients (dark blue curve). Thus, the Cox proportional hazards assumption does not accurately model short-term survival patterns by HCC.

Flexible Parametric Model

Figure 4 shows the adjusted HR and 95% CI for HCC over time after LT estimated from the FPM. The estimated hazard of death in HCC recipients was significantly lower than that in non-HCC recipients until the first month after LT (HR = 0.76; 95% CI, 0.59-0.99; $P = 0.044$). The HR then increased sharply to its maximum, observed at approximately 1.3 y (HR = 2.07, 95% CI, 1.70-2.52; $P < 0.001$), before decreasing. The HR crossed one at around 2 mo and 12.4 y after LT, so the hazards for all-cause mortality in HCC and non-HCC recipients were estimated to be identical at these times. There was evidence at the 5% level of an increased risk of death for HCC recipients compared with non-HCC recipients between 4 mo

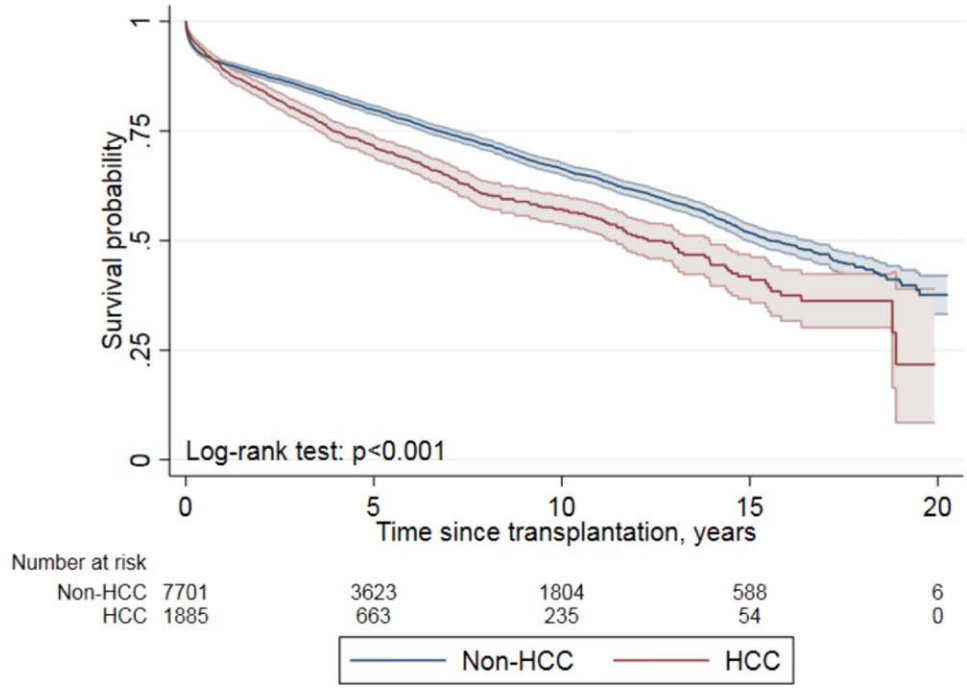

FIGURE 2. Unadjusted Kaplan–Meier estimates of survival after liver transplantation by HCC diagnosis. HCC, hepatocellular carcinoma.

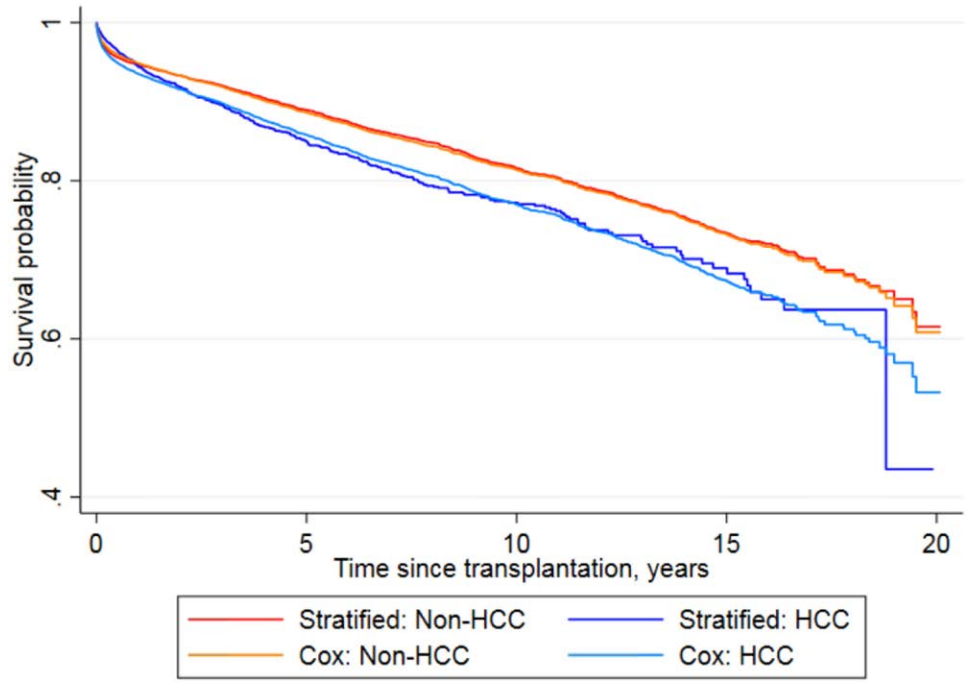

FIGURE 3. Stratified and Cox predicted survival estimates after liver transplantation by HCC diagnosis. HCC, hepatocellular carcinoma.

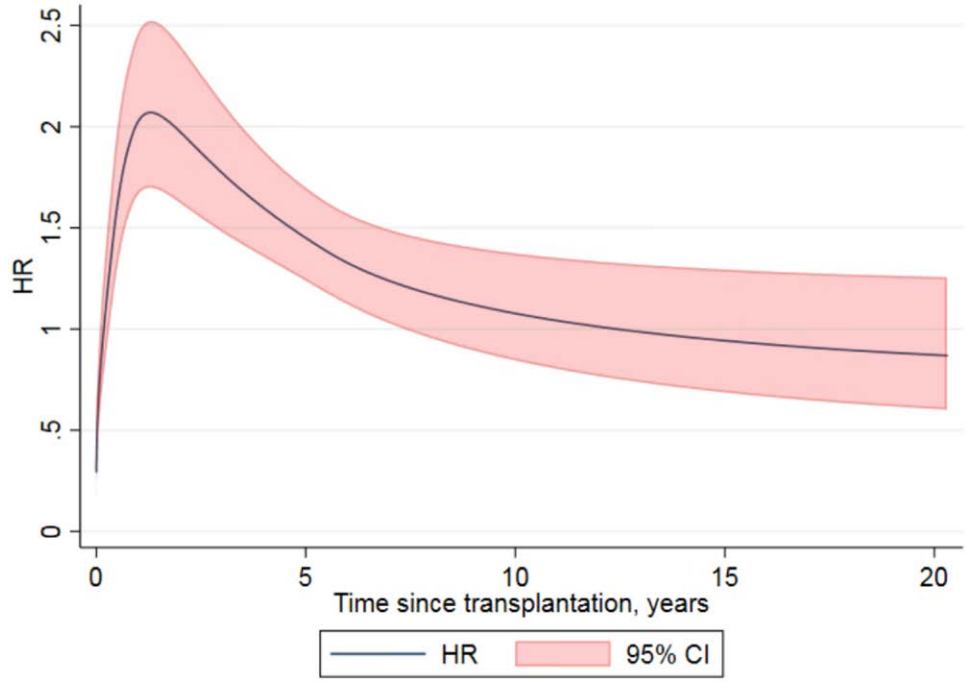

FIGURE 4. Adjusted time-varying HR for hepatocellular carcinoma recipients relative to non-HCC recipients after liver transplantation was estimated using the flexible parametric model. CI, confidence interval; HR, hazard ratio.

and 7.4 y (ie., the lower limit of the 95% CI was above 1). Estimated HRs for confounding variables, adjusting for the time-varying effect of HCC are in Table S6, SDC, http://links.lww.com/TP/C507. Because proportional hazards were assumed for confounders, their estimated HRs were very similar in the FPM and the Cox proportional hazards model (Table S7, SDC, http://links.lww.com/TP/C507).

Unlike the proportional hazards model (Figure 3), there was a very close agreement between the stratified and FPM predicted survival curves by HCC diagnosis (Figure 5).

Figure 6 shows the adjusted HR and 95% CI for HCC at different transplant years from the FPM with a time-varying interaction between HCC and transplant year. There are no marked differences in the association between HCC and the post-LT hazard of death, based on model extrapolations of the data. A test showed that this interaction was not significant at the 5% level (P = 0.231). The 95% CIs

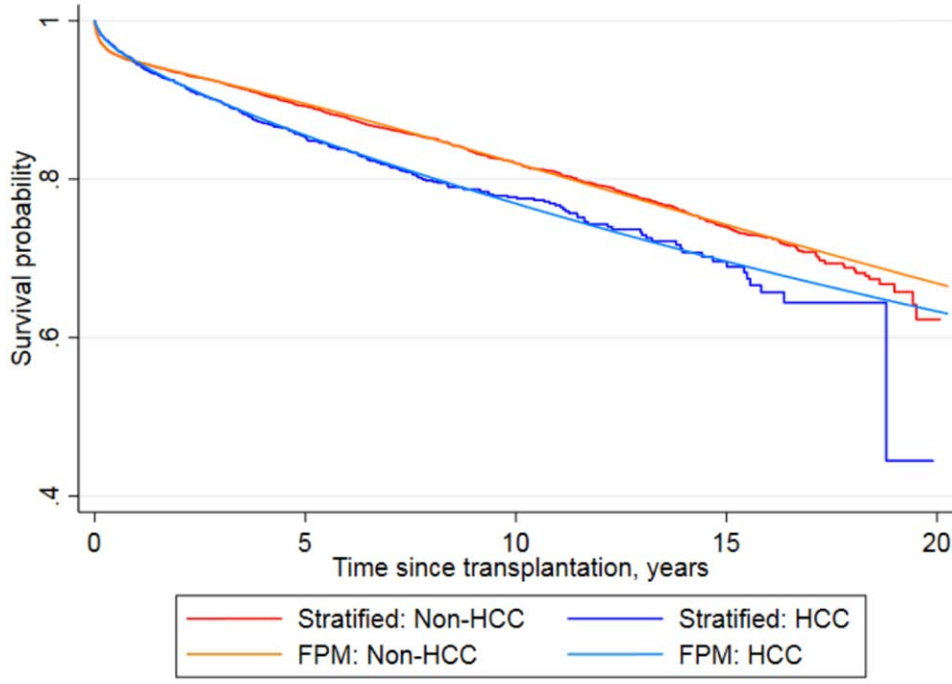

FIGURE 5. Stratified and FPM predicted survival estimates after liver transplantation by HCC diagnosis. FPM, flexible parametric model; HCC, hepatocellular carcinoma.

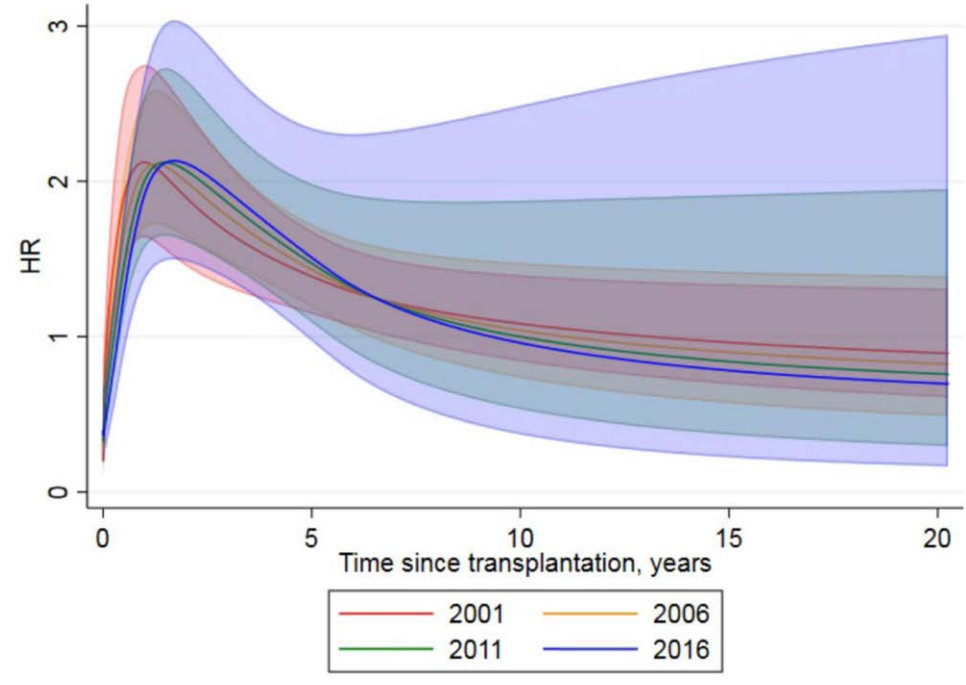

FIGURE 6. Adjusted time-varying HR for hepatocellular carcinoma recipients relative to non–hepatocellular carcinoma recipients after liver transplantation estimated from the flexible parametric model with a time-varying interaction between hepatocellular carcinoma diagnosis and transplant year. HR, hazard ratio.

widened with transplant year due to fewer events observed later in follow-up.

Competing Risks Analysis

Cause-specific Deaths in HCC and Non-HCC Recipients

Of the 566 HCC recipient deaths, 90 (15.9%) were due to HCC, 105 (18.6%) to other cancers, and 371 (65.5%) to noncancer. Of the 2146 non-HCC recipient deaths, 333 (15.5%) were due to other cancers and 1813 (84.5%) to noncancer. Distributions of event times were highly right-skewed; half of the deaths caused by post-LT HCC occurred within the first 1.8 y after LT, with the last such death observed at 14.4 y.

Figure 7 shows that the unadjusted cumulative incidence for noncancer mortality was similar in HCC and non-HCC recipients, possibly due to cohort selection and

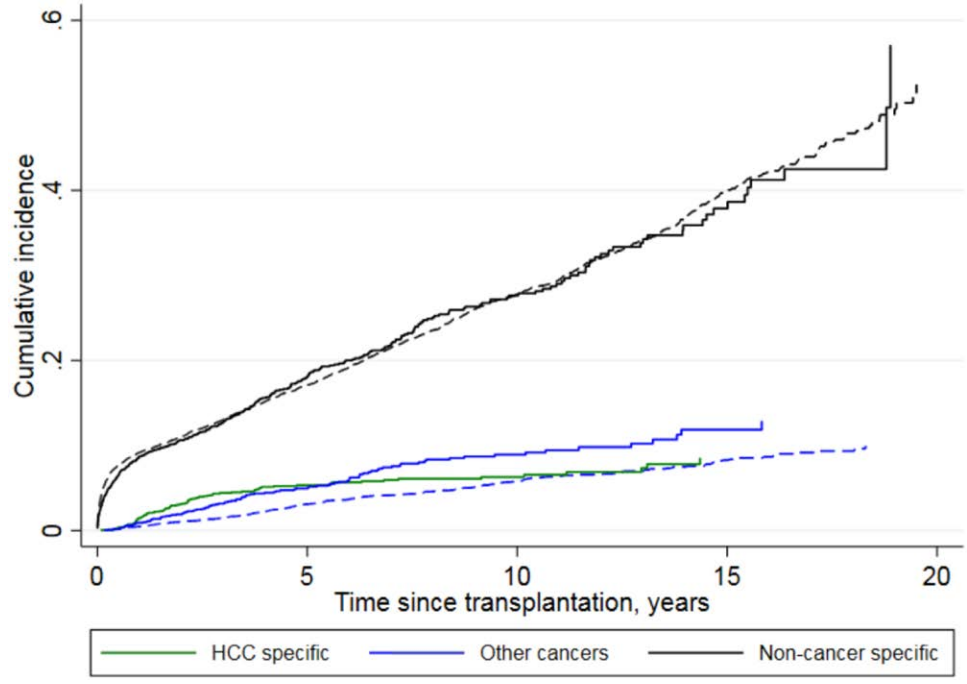

FIGURE 7. Cause-specific unadjusted cumulative incidence functions estimated in HCC (solid lines) and non-HCC (dashed lines) recipients after liver transplantation. HCC, hepatocellular carcinoma.

the frailty of patients in both groups, and for other cancers, only slightly higher in HCC recipients. It also shows that for HCC recipients, the unadjusted cumulative incidence for HCC mortality (solid green curve) was higher than that for other cancers (solid blue curve) between 2 and 6 y after LT. From 6 y onwards, the unadjusted cumulative incidence for other cancers mortality in the HCC recipients was higher. These results suggest that the increased hazard of post-LT mortality observed in HCC recipients is likely due to HCC occurrence.

Subdistribution Hazard Model for Non–cancer-specific Mortality

After adjustment for confounding, there was no evidence of a time-varying effect of HCC on the incidence of noncancer specific mortality ($P = 0.735$) and no evidence of a difference in the incidence of noncancer specific mortality between HCC and non-HCC recipients (SHR = 0.94; 95% CI, 0.80-1.09; $P = 0.390$).

DISCUSSION

Summary of Results

Using data on over 9586 recipients from the UKLTR, a time-varying comparison of post-LT all-cause mortality between recipients with and without HCC was subject to detailed survival analysis. Results from the Cox proportional hazards model were of limited value as associations between HCC and post-LT hazards of mortality varied over time.

Results from the FPM, which allowed for non–proportional hazards between HCC and non-HCC recipients, showed that the hazard was significantly lower in HCC recipients than in non-HCC recipients for the first month after LT. After that, the estimated HR for HCC increased to a maximum at around 1.3 y, at which the hazard for mortality was approximately twice that of non-HCC recipients. Extending this model by adding a time-varying interaction between HCC and transplant year showed no marked differences in the association between HCC and the post-LT hazard of death for different years of follow-up.

In further analysis, a subdistribution hazard model showed that non–cancer-specific mortality was not significantly different between HCC and non-HCC recipients, implying that post-LT HCC occurrence was likely to be the overriding cause of the increased hazard of death for HCC recipients between 4 mo and 7.4 y after LT.

Comparison With Other Studies

To the authors' knowledge, this is the first article in LT literature to assess the smoothed time-varying association between HCC and survival. Previously, Wallace et al considered a similar clinical question but used a simpler method that involved using clinical criteria to split follow-up time into discrete periods before applying Cox proportional hazards models.[8] This assumed constant relative hazards within each time period and discrete jumps between them, both of which may not be realistic.[8,21] Unlike previous studies, this one determines the post-LT time points at which HCC has a protective effect before changing to a detrimental effect on the post-LT hazard of death.

Explanation of Results

This analysis identifies that HCC recipients were more likely to receive suboptimal donor organs with characteristics that were proven to have poorer post-LT outcomes. This included livers that were either abnormal in appearance or from donors that were older, male, or DCD. In the UK, the donor liver index was introduced to measure the quality of donor's livers, based on several donor factors that were adjusted for in the models (eg, donor age, sex, type, and whether the liver was split).[22] However, adjustment for these donor factors, in addition to adjustment

for recipient factors, did not drastically change the HR for HCC.[8] This supports the conclusion from this study that post-LT HCC occurrence was primarily responsible for the higher relative hazard of death in HCC recipients, rather than the donor characteristics. The use of more marginal donors in HCC patients reflects the relative urgency to provide LT before their tumor progresses beyond transplantable criteria.[8]

These results also demonstrate that outcomes in patients transplanted for HCC are worse than in those transplanted for non-HCC indications, with a significantly higher hazard of death between 4 mo and 7.4 y. This is most likely explained by post-LT HCC occurrence, and it must be acknowledged that even with the adoption of the Milan criteria, a significant proportion of HCC patients who are at risk of tumor recurrence are still being selected for LT. In half of these recipients, death from HCC is occurring within 2 y post-LT.

Methodological Implications

FPMs have several advantages, and their use should be encouraged in future analyses of follow-up studies of transplant patients. With more precise long-term predictions of postoperative survival for HCC, the FPM could be applied to a wide range of other donor and recipient risk factors for survival after LT.

There are four main limitations of this study. First, organ appearance is a subjective measure of organ quality, determined by surgeons who visually inspect the liver at the time of retrieval. Though measurement bias may be introduced, organ appearance remains a robust prognostic marker of survival. The second limitation is that multiple imputations (MIs) could have been used to handle missing covariate values. However, there was little evidence of systematic differences in survival and distributions of covariates between complete and noncomplete cases. A complete-case analysis was deemed suitable for giving unbiased estimates without a large loss in efficiency. It is unlikely that conclusions would have been affected if MI had been used.[23] Third, despite rigorous risk adjustment, the potential for residual confounding remains in all observational studies. Fourth, the study did not have access to clinical data on baseline tumor characteristics and explant pathology. Hence, it was not possible to directly study which HCC patients have an increased risk of recurrence and require closer post-LT surveillance.

Clinical Implications

This study highlights two key clinical implications. The first is that HCC patients are being listed and transplanted at a stage beyond what is recommended for LT to be beneficial. In this context, early post-LT HCC is no recurrence at all but the undiagnosed extra-hepatic spread of original cancer at the time of LT. A better understanding of tumor biology (beyond the use of surrogate markers) and the ability to detect circulating extra-hepatic tumor cells could improve patient selection by identifying those who would not be best served by LT. The use of preoperative biopsy and assessment of tumor differentiation, as adopted by the Toronto criteria, may need to be given more consideration.[24]

The second implication is that post-LT surveillance of HCC recipients should start early and continue for many years to detect HCC recurrence. In this analysis, the first post-LT HCC death was observed at around 1.2 mo. Consistent practice of surveillance protocols ensures that measures—including adjuvant HCC-directed therapies (Sorafenib, locoregional therapies, liver resection)—to reduce mortality in patients whose cancer has recurred are not delayed.[25]

Currently, there is no defined protocol for post-LT surveillance of HCC in the UK and very little research conducted in this area. Due to the lack of standardization, transplant center protocols vary. In the United States, there is a 6-mo mandatory waiting period for LT in HCC patients, allowing for continuous monitoring and avoiding LT in patients whose cancer is likely to recur. This does not happen in the UK as many HCC patients are transplanted earlier using DCD organs. Also, many studies have developed risk scores to predict post-LT survival in these patients (eg, based on alpha-fetoprotein trends, history of locoregional therapy, etc) that could be extended to UK populations.[26,27]

Using the results from this analysis to help create a targeted surveillance program in the UK could reduce the number of outpatient appointments and improve accuracy in prognostication. This is important as it can benefit patient counseling because discussions of prognosis may be more optimistic if an HCC patient has survived the period of the highest relative hazard of death.

CONCLUSION

The post-LT hazard of death in HCC patients is significantly higher than in non-HCC patients between 4 mo and 7 y, which has implications for patient selection, organ allocation, and optimal post-LT surveillance protocols. FPMs can be more widely used to provide time-varying comparisons of post-LT hazards for other donor and recipient characteristics.

ACKNOWLEDGMENTS

This study was carried out using liver transplant data from the United Kingdom Transplant Registry held by NHS Blood and Transplant. The authors are grateful to all the transplant centers in the UK who contributed data on which this article is based. They would like to thank those involved in collecting and handling the data at NHS Blood and Transplant.

REFERENCES

1. British Liver Trust. *Liver cancer (hepatocellular carcinoma, HCC, or hepatoma)*. 2013. Available at https://britishlivertrust.org.uk/informationand-support/living-with-a-liver-condition/liver-conditions/liver-cancer/. Published November 22, 2013. Accessed September 29, 2021.
2. Clavien PA, Lesurtel M, Bossuyt PM, et al; OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol.* 2012;13:e11–e22.
3. British Liver Trust. *Life after having a liver transplant*. 2016. Available at https://britishlivertrust.org.uk/information-and-support/living-with-aliver-condition/liver-transplantation/lifeafterlivertransplant/. Published September 28, 2016. Accessed November 3, 2021.
4. Demiris N, Lunn D, Sharples LD. Survival extrapolation using the poly-Weibull model. *Stat Methods Med Res.* 2015;24:287–301.

5. Bird SM, Calne RY, Sharples LD. Analyse transplant outcomes in distinct epochs of follow-up. *Lancet.* 2006;367:1816.
6. NHS Blood and Transplant Organ Donation and Transplantation Directorate Liver Advisory Group. *Provision of standard data set for liver transplant*. March 2015. Available at http://odt.nhs.uk/pdf/advisory_group_papers/LAG/Provision_of_Standard_Data_Set_for_Liver_Transplant_v4.pdf. Accessed November 17, 2021.
7. NHS Blood and Transplant. *Annual report on liver transplantation: report for 2019/2020*. September 2020. Available at https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/19867/nhsbt-liver-transplant-report-1920.pdf. Accessed September 29, 2021.
8. Wallace D, Walker K, Charman S, et al. Assessing the impact of suboptimal donor characteristics on mortality after liver transplantation: a time-dependent analysis comparing HCC with non-HCC patients. *Transplantation.* 2019;103:e89–e98.
9. Roberts MS, Angus DC, Bryce CL, et al. Survival after liver transplantation in the United States: a disease-specific analysis of the UNOS database. *Liver Transpl.* 2004;10:886–897.
10. Dawwas MF, Gimson AE, Lewsey JD, et al. Survival after liver transplantation in the United Kingdom and Ireland compared with the United States. *Gut.* 2007;56:1606–1613.
11. Cullaro G, Hirose R, Lai JC. Changes in simultaneous liver-kidney transplant allocation policy may impact postliver transplant outcomes. *Transplantation.* 2019;103:959–964.
12. Cox DR. Regression models and life-tables. *J R Stat Soc Series B Stat Methodol*. 1972;34:187–202.
13. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994;81:515–526.
14. Therneau TM, Grambsch PM, Fleming TR. Martingale-based residuals for survival models. *Biometrika*. 1990;77:147–160.
15. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Stat Med.* 2002;21:2175–2197.
16. Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. *Stata J*. 2009;9:265–290.
17. Royston P, Lambert PC. *Flexible Parametric Survival Analysis Using Stata: Beyond the Cox Model*. Stata Press; 2011.
18. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94:496–509.
19. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009;338:b2393.
20. STATA. *Stata 15. Version 15*. StataCorp. 2017. Available at http://www.stata.com/. Accessed September 6, 2021.
21. Lehr S, Schemper M. Parsimonious analysis of time-dependent effects in the Cox model. *Stat Med.* 2007;26:2686–2698.
22. Collett D, Mumford L, Banner NR, et al. Comparison of the incidence of malignancy in recipients of different types of organ: a UK Registry audit. *Am J Transplant.* 2010;10:1889–1896.
23. Carpenter JR, Kenward MG. *Multiple Imputation and Its Application*. John Wiley & Sons; 2013.
24. Sapisochin G, Goldaracena N, Laurence JM, et al. The extended Toronto criteria for liver transplantation in patients with hepatocellular carcinoma: a prospective validation study. *Hepatology.* 2016;64:2077–2088.
25. Lin HS, Wan RH, Gao LH, et al. Adjuvant chemotherapy after liver transplantation for hepatocellular carcinoma: a systematic review and a meta-analysis. *Hepatobiliary Pancreat Dis Int.* 2015;14:236–245.
26. Sasaki K, Firl DJ, Hashimoto K, et al. Development and validation of the HALT-HCC score to predict mortality in liver transplant recipients with hepatocellular carcinoma: a retrospective cohort analysis. *Lancet Gastroenterol Hepatol.* 2017;2:595–603.
27. Goldberg D, Mantero A, Newcomb C, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma using the LiTES-HCC score. *J Hepatol.* 2021;74:1398–1406.