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### 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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## **ABBREVIATIONS PAGE**

BMI, body mass index

CIT, cold ischaemic time

DCD, donation after circulatory death

HCC, hepatocellular carcinoma

HCV, hepatitis C

HR, hazard ratios

MELD, Model for End-Stage Liver Disease

NHSBT, National Health Service Blood and Transplant

UKELD, United Kingdom Model for End-Stage Liver Disease

ACCEPTED

## ABSTRACT

**Background:** Patients who receive a liver transplant for hepatocellular carcinoma (HCC) often receive poorer quality livers. Tumour recurrence also has a negative effect on post-transplant outcomes. We compared mortality of HCC and non-HCC recipients in different post-transplant time periods ('epochs') to separate the impact of these different risk factors on short and longer term post-transplant survival.

**Methods:** We identified a population-based cohort of first-time liver transplant recipients (aged  $\geq 16$  years) between 2008 and 2016 in the UK. We used Cox regression to estimate hazard ratios (HR) comparing post-transplant mortality between HCC and non-HCC patients in three post-transplant 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:** 1 270 HCC and 3 657 non-HCC transplant recipients were included. 5-year post-transplant survival was 74.5% (95%CI 71.2% to 77.5%) in HCC patients and 84.6% (83.0% to 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, 1.48-2.66,  $P<0.001$ ; 2 to 5 years HR 1.77, 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 post-transplant survival than non-HCC recipients, most likely because of tumour recurrence. The more frequent use of poorer quality donor organs for HCC does not explain this difference.

## 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.<sup>1</sup> 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.<sup>1</sup> In response, livers with sub-optimal donor characteristics are increasingly being used.<sup>2</sup>

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 post-transplantation outcomes. International consensus recommendations only indicate that post-transplant outcomes of patients transplanted for HCC should be ‘comparable’ to those transplanted for non-HCC indications.<sup>3</sup>

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

In the UK, 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 post-transplant survival.<sup>8,9</sup> As a result, a set of expanded criteria were formally accepted in the UK in 2008 (one lesion with a diameter  $\leq 5$  cm, or up to five tumours each with diameter  $\leq 3$  cm, or one lesion with a diameter  $>5$  cm and  $\leq 7$  cm with no evidence of tumour progression, extrahepatic spread or new nodule formation over a 6-month period).<sup>10,11</sup>

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 three epochs of follow-up: patient survival up to 90 days was chosen to reflect the occurrence of surgical complications, primary non-function and acute rejection,<sup>12</sup> survival between 90 days and 2 years and between 2 and 5 years to reflect tumour recurrence and chronic rejection<sup>3,7,12,13</sup> 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 sub-optimal donor characteristics has on differences in post-transplant 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 tumour recurrence differed according to the use of 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 six liver transplant centers in England and one centre in Scotland. The dataset is managed by National Health Service Blood and Transplant (NHSBT),<sup>14</sup> and regular checks indicate that the data are consistently more than 93% complete and accurate and results from several studies confirm the validity of the dataset.<sup>14-17</sup>

### **Study population**

The study population included all recipients aged 16 years or older who received a first elective orthotopic liver transplant in the UK between 1<sup>st</sup> January 2008 and 31<sup>st</sup> December 2016. The diagnostic category of each patient was identified from the three diagnostic fields available in the Standard National Liver Transplant Registry and patients were categorised into two groups, patients transplanted with HCC and patients transplanted with other liver disease diagnosis 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 three 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 multi-visceral, super-urgent, 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 was missing.

Donor and recipient characteristics, 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')<sup>17</sup> and UKELD was used to score the severity of the liver disease.<sup>18</sup> Cold ischaemic time was defined as the duration between start of cold perfusion in the donor to start of blood flow through the organ in the recipient.<sup>19</sup> 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 1<sup>st</sup> January 2008 and 31<sup>st</sup> December 2016.

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

The Kaplan-Meier method was used to compare post-transplant patient and graft survival in HCC and non-HCC recipients and to compare post-transplant 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 31<sup>st</sup> December 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 re-transplantation or patient death.

Differences in survival were assessed with the log-rank test.

We used multifactorial Cox regression to build three separate models. All models were designed to examine the prognostic impact of HCC status on patient survival in three 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 post-transplant 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 post-transplantation time-periods that included 90 days to 1 year and 1 year 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 tumour characteristics were not included as comparisons of post-transplantation survival in HCC patients were made with a cohort non-HCC patients. All donor and recipient factors were selected on the basis of their clinical plausibility of being a risk factor for post-transplant survival.<sup>16</sup> The time-dependency of HCC as a risk factor for post-transplant 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 non-linear relationships between the recipient and donor characteristics measured as continuous variables and post-transplant survival, by including these as both linear and quadratic terms in the model. Missing patient and donor characteristics were imputed using chained equations creating ten complete datasets.<sup>20</sup> The Cox regression results for each of these datasets were pooled using Rubin's rules.<sup>20</sup> No patient or donor characteristic had more than 15% of missing values.

Stata V15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses. A p-value < 0.05 was considered significant for each statistical analysis.

## **RESULTS**

A total of 4 927 first adult elective liver transplants were performed between 2008 and 2016, of which 1 270 liver transplants were for HCC recipients and 3 657 for non-HCC recipients (Figure 1). Compared to 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 require ventilation or hospital admission immediately prior to transplantation and less likely to have undergone previous abdominal surgery. Patients with HCC received more grafts from organs donated following circulatory death (DCD), or grafts in which the appearance had been documented as 'abnormal' or 'steatotic'. CIT 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 1 270 HCC recipients who were included in our study, only 81 (6.4%) had tumour 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 three to four months, HCC patients seem to have progressively worse patient survival, resulting in a 5-year patient survival of 74.5% (95%CI 71.2 to 77.5%) for HCC patients and 84.6% (95%CI 83.0 to 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 to 73.3%) for HCC patients and 79.1% (95%CI 77.4 to 80.7%,  $p < 0.001$ ) for non-HCC patients. We did not find a difference in the 5-year patient survival between the 1 189 HCC patients who met the Milan criteria (74.6%, 95%CI 71.1% to 77.7%) and the 81 who did meet the expanded criteria (74.5%, 95%CI 58.6% to 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% to 73.6% and 67.8%, 95% CI 55.2% to 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 following transplantation (HR 0.88 CI; 0.63-1.23, Table 2). In the subsequent two 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 following transplantation (adjusted HR 0.76 CI; 0.53-1.09) or in the two 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 0-90 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 survival (Table 3) closely mirrored the results found for patient survival (Table 2).

In the sensitivity analysis that explored the impact of HCC in four separate epochs, we found that it was highest between 90 days and 1 year after transplantation (adjusted HR: 2.10 95% CI: 1.47 to 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 to HCV status (HCV+ve HR 1.16, 0.87-1.56, HCV-ve HR; 0.86, 0.64-1.15,  $p$  for interaction =0.10).

In the first 90 days following 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 tumour recurrence (recurrence of malignant primary disease; Table 4). In the subsequent post-transplant epochs, tumour recurrence in HCC recipients became a more frequent cause of death accounting for 23 of the 101 deaths (22.7%) between 90 days and 2 years and 12 of the 77 deaths (15.6%) between 2 and 5 years. When splitting cause of death into four epochs we found that from 90 days onwards the number of patients dying from tumour recurrence remained more or less constant (Table S6, SDC, <http://links.lww.com/TP/B665>). Of the 35 HCC recipients who died of tumour recurrence, nine (25.7%) had received a DCD liver compared 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 tumour 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 non-lymphoid 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 'sub-optimal' grafts. We found that survival of HCC and non-HCC recipients was similar in the first months after transplantation. Then survival of HCC recipients deteriorated with the rate of mortality and graft failure being at least 50% higher than in non-HCC recipients, with tumour

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 sub-optimal characteristics.

### **Methodological limitations**

The key limitation of our analysis is that we used pre-defined post-transplant 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.<sup>21</sup>

The advantage of this approach is that the hazard ratios 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.

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 were selected for transplantation in the UK. Whilst 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 post-transplant survival in three 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 tumour recurrence may deteriorate survival in the later stages. Already 30 years ago, the

importance of analysing liver transplant outcomes in epochs of follow-up time was recognised, but this statistical approach is very rarely practised.<sup>4,22</sup> Our study is an example of how important it is to analyse post-transplant outcomes in distinct epochs of follow-up time, guided by an 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.<sup>4</sup> However, our study, which reflects outcomes of modern liver transplantation practice, including a national population-based cohort of patients transplanted between 2008 and 2016, indicates that tumour recurrence remains an important risk factor for survival in the later stages after liver transplantation, which corresponds with earlier reports of post-transplant survival.<sup>1-3</sup>

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 post-transplant outcomes compared to 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 prior to transplantation may have prohibited the aggressive use of the extended selection criteria, especially when other studies have indicated a linear relationship between tumour burden and post-transplantation survival.<sup>23,24</sup>

## Explanation of results

Our study found that HCC patients were more likely to receive sub-optimal donor organs with characteristics previously proven to have poorer post-transplant outcomes.<sup>2</sup> 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 post-transplant 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 following transplantation.

The incidence of HCV recurrence following 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 following transplantation and worse thereafter.<sup>25,26</sup> 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 a diagnosis of HCV nor did we find HCV recurrence to be frequently reported as a cause of death in the first five 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 tumour recurrence, HCC recipients can be subjected to more conservative immunosuppression protocols<sup>27</sup> 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 UK 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,  $p=0.57$ ) whilst 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 observations).

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

Beyond 90 days, differences in survival are best explained by differences in deaths due to tumour 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 year to 2 years. Of the HCC patients who were recorded to have died of tumour recurrence within 1-year, only one was pre-operatively staged according to the extended criteria with other early deaths potentially explained by aggressive tumour biology and or radiological understaging of the HCC prior to transplantation.<sup>13</sup> In further analysis, we did not find the use of DCD livers to be associated with an increased risk of death from tumour recurrence.

In the past, HCC patients were found to have 90-day outcomes that were statistically significantly better than non-HCC patients.<sup>5</sup> 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 post-transplant outcomes in the last 30 years which considerably reduces the statistical power to detect differences.<sup>29</sup> Another explanation is that the impact of recipients' frailty at the time of transplantation has decreased given the improvements in peri-operative care and the high-dependency care immediately after transplantation.<sup>30</sup>



## 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 UK, we are still selecting for transplantation a significant proportion of patients with HCC who are at risk of tumour recurrence. Therefore, until we can add to our selection criteria new parameters that better predict tumour 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.<sup>3</sup> However, in the last decade this has never been the case. This has been recognised by the service providers and donor liver allocation schemes are now moving towards using criteria based on transplant ‘benefit’ – in which they aim to maximise the net life years gained from the point of registration on the waiting rather than providing the greatest chance of surviving after transplantation.<sup>31,32</sup> 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.<sup>1,3</sup>

## **CONCLUSION**

Between 2008 and 2016, almost all HCC patients who received a liver transplant in the UK met the Milan criteria. Nevertheless, one in four HCC recipients died within five years compared to only one in six non-HCC patients, with tumour 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 post-transplant survival of HCC patients given their greater net gain in post-transplanted expected life years.

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## REFERENCE LIST

- 1) Bruix J, Gores GJ, Mazzaferro V. Clinical frontiers in hepatocellular carcinoma; Clinical frontiers and perspectives. *Gut*. 2014;63:844-855.
- 2) Callaghan CJ, Charman SC, Muiesan P, et al. UK Liver Transplant Audit. Outcomes of transplantation of livers from donation after circulatory death donors in the UK: a cohort study. *BMJ Open*. 2013;3:e003287.
- 3) Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A; OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol*. 2012;13:e11-22.
- 4) Bird SM, Calne RY, Sharples LD. Analyse transplant outcomes in distinct epochs of follow-up. *Lancet*. 2006;367:1816.
- 5) Burroughs AK, Sabin CA, Rolles K, et al. 3-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. *Lancet*. 2006;367:225-32.
- 6) Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *New Engl J Med*. 1996;334:693-9.
- 7) Davis E, Wiesner R, Valdecasas J, Kita Y, Rossi M, Schwartz M. Treatment of recurrent hepatocellular carcinoma after liver transplantation. *Liver Transpl*. 2011;17:162-6
- 8) Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology*. 2001;33:1394-1403.

- 9) Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol.* 2009;10:35-43.
- 10) Menon KV, Hakeem AR, Heaton ND. Review article: liver transplantation for hepatocellular carcinoma - a critical appraisal of the current worldwide listing criteria. *Aliment Pharmacol Ther.* 2014;40:893-902.
- 11) [http://odt.nhs.uk/pdf/advisory\\_group\\_papers/LAG/HCC\\_recommendations\\_IR\\_TS\\_b\\_NAS\\_Work\\_in\\_Progress.pdf](http://odt.nhs.uk/pdf/advisory_group_papers/LAG/HCC_recommendations_IR_TS_b_NAS_Work_in_Progress.pdf). Accessed 12th Jan 2018.
- 12) Tovikkai C, Charman SC, Praseedom RK, Gimson AE, van der Meulen J. Time-varying impact of comorbidities on mortality after liver transplantation: a national cohort study using linked clinical and administrative data. *BMJ Open.* 2015;5:e006971.
- 13) Zimmerman MA, Ghobrial RM, Tong MJ, et al. Recurrence of hepatocellular carcinoma following liver transplantation: a review of preoperative and postoperative prognostic indicators. *Arch Surg.* 2008;143:182-8.
- 14) [http://odt.nhs.uk/pdf/advisory\\_group\\_papers/LAG/Provision\\_of\\_Standard\\_Data\\_Set\\_for\\_Liver\\_Transplant\\_v4.pdf](http://odt.nhs.uk/pdf/advisory_group_papers/LAG/Provision_of_Standard_Data_Set_for_Liver_Transplant_v4.pdf). Accessed January 9, 2018.
- 15) Dawwas MF, Gimson AE, Lewsey JD, Copley LP, van der Meulen JHP, on behalf of the UK and Ireland Liver Transplant Audit. Survival after liver transplantation in the United Kingdom and Ireland compared with the United States. *Gut.* 2007;56:1606–1613.
- 16) <https://www.rcseng.ac.uk/-/media/files/rcs/library-and-publications/non-journal-publications/liver-transplant-audit-report-2012.pdf>. Accessed June 10, 2018.

- 17) Jacob M, Copley LP, Lewsey JD, et al. Functional status of patients before liver transplantation as a predictor of posttransplant mortality. *Transplantation*. 2005;80:52-7
- 18) Barber K, Madden S, Allen J, et al. Elective liver transplant list mortality: development of a United Kingdom end-stage liver disease score. *Transplantation*. 2011;92:469-76.
- 19) Pan ET, Yoeli D, Galvan NTN, et al. Cold ischemia time is an important risk factor for post-liver transplant prolonged length of stay. *Liver Transpl*. 2018;24:762-768.
- 20) White I, Royston P, Wood A. Multiple imputation by chained equations: issues and guidance for practice. *Stat Med*. 2011;30:377–399.
- 21) Lehr S, Schemper M. Parsimonious analysis of time-dependent effect in the Cox model. *Stat Med*. 2007;26:2686-2698.
- 22) Gore SM, Barroso E, White DJG. Risk factors in orthotopic first liver transplantation. In: Calne R, ed. *Liver transplantation*, 2<sup>nd</sup> edn. London: Grune and Stratton, 1987: 513-30.
- 23) Germani G, Gurusamy K, Garcovich M, et al. Which matters most: Number of Tumours, Size of the Largest Tumour, or total tumour volume. *Liver Transpl*. 2011;17:S58-S66.
- 24) Marelli L, Grasso A, Pleguezuelo M, et al. Tumour size and differentiation in predicting recurrence of hepatocellular carcinoma after liver transplantation: external validation of a new prognostic score. *Ann Surg Oncol*. 2008;15:3503-3511.
- 25) Gane EJ, Portmann BC, Naoumov NV. Long-term outcome of Hepatitis C Infection after liver transplantation. *N Engl J Med*. 1996;334:815-821.
- 26) Vinaixa C, Rubin A, Aguilera V, Berenguer M. Recurrence of hepatitis C after liver transplantation. *Ann Gastroenterol*. 2013;26:304-313.

- 27) Khorshandi SE, Heaton N. Optimization of immunosuppressive medication upon liver transplantation against HCC recurrence. *Transl Gastroenterol Hepatol*. 2016;1:25.
- 28) Collet D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the incidence of malignancy in recipients of different types of organ: A UK Registry Audit. *Am J Transplant*. 2010;10:1889-1896.
- 29) Adam R, Karam V, Delvart V, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol*. 2012;57:675-88.
- 30) Singal AK, Gurusu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation*. 2013;95:755-760.
- 31) Schaubel DE, Guidinger MK, Biggins SW, et al. Survival benefit-based deceased-donor liver allocation. *Am J Transplant*. 2009;9:970-81.
- 32) [http://odt.nhs.uk/pdf/advisory\\_group\\_papers/AGCHC/Liver\\_National\\_Allocation-Scheme.pdf](http://odt.nhs.uk/pdf/advisory_group_papers/AGCHC/Liver_National_Allocation-Scheme.pdf). Accessed June 1, 2018.

## FIGURES

**Figure 1: Flow chart detailing selection of study population (2008-2016).**

**Figure 2: Five-year patient and graft survival stratified by HCC status 2008-2016 (n=4 927).**

**Figure 3: Five-year patient and graft survival for HCC patients stratified by type of selection criteria 2006-2016 (n=1 270).**

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**Table 1: Donor and recipient patient characteristics (n= 4927)**

| Indication Group                       |              | HCC           | Non-HCC       | Missing values | P value |
|--|--------------|---------------|---------------|----------------|---------|
| Number                                 |              | N = 1 270     | N = 3 657     |                |         |
| DONOR                                  |              | % / N         | % / N         | N              |         |
| Sex                                    | Female       | 42.8% (544)   | 47.6% (1 740) | 0              | 0.003   |
| Cause of death                         | Trauma       | 9.1% (115)    | 7.7% (281)    |                | 0.21    |
|  | CVA          | 62.6% (796)   | 64.8% (2 371) |                |         |
|  | Others       | 28.3% (359)   | 27.5% (1 005) | 0              |         |
| Donor Type                             | DCD          | 31.9% (405)   | 21.2% (774)   | 0              | <0.001  |
| ABO Match                              | Identical    | 98.0% (1 245) | 98.6% (3 606) |                | 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% (1 603) | 84             | 0.03    |
| Capsular damage                        | Presence     | 14.3% (178)   | 14.1% (507)   | 92             | 0.91    |
| Donor age, years                       | Mean (SD)    | 50 (16)       | 49 (16)       | 0              | 0.07    |
| Donor BMI, kg/m <sup>2</sup>           | Mean (SD)    | 27 (5.0)      | 26 (5.0)      | 10             | 0.15    |
| Cold Ischaemic Time (mins)             | Mean (SD)    | 502 (158)     | 517 (158)     | 392            | 0.01    |
| <b>RECIPIENT</b>                       |              |               |               |                |         |
| Sex                                    | Female       | 19.8% (251)   | 37.3% (1 363) | 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 |
| Pre-transplant in patient status       | Inpatient    | 4.9% (62)     | 16.6% (608)   | 6              | < 0.001 |
| Ascites                                | Presence     | 29.8% (378)   | 61.8% (2 251) | 17             | < 0.001 |
| Encephalopathy                         | Presence     | 15.2% (189)   | 36.1% (1 300) | 82             | < 0.001 |
| Pre-transplant renal support           | Yes          | 4.7% (60)     | 4.6% (170)    | 13             | 0.9     |
| Pre-transplant 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% (1 136) |                |         |
|  | Self-care    | 37.4% (469)   | 47.7% (1 724) |                |         |
|  | Reliant      | 4.5% (56)     | 14.0% (505)   |                |         |
|  | Confined     | 1.0% (13)     | 3.0% (107)    | 63             |         |
| Age (years)                            | Mean (SD)    | 58 (8.0)      | 51 (11.8)     | 0              | < 0.001 |
| BMI, Kg/m <sup>2</sup>                 | Mean (SD)    | 28 (4.8)      | 27 (5.3)      | 5              | < 0.001 |
| UKELD                                  | Mean (SD)    | 51 (4.9)      | 56 (5.4)      | 38             | < 0.001 |

\*No data item had more than 15% of missing values\*



**Table 2: Impact of HCC on post-transplant patient survival in three separate epochs of follow-up time (n=4 927).**

| Post-transplant patient survival                               | HCC compared to non-HCC<br>Hazard ratio (95% CI) |                  |                  | P value time dependency* <sup>2</sup> |
|--|--|------------------|------------------|---------------------------------------|
|  | 0 to 3 months                                    | 3 to 24 months   | 24 to 60 months  |                                       |
| 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* <sup>1</sup>           | 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* <sup>1</sup> | 0.74 (0.52-1.07)                                 | 1.96 (1.46-2.62) | 1.74 (1.27-2.31) | <0.001                                |

\*<sup>1</sup> Adjusted for a) Recipient characteristics: sex, ethnicity, HCV status, pre-transplant inpatient status, ascites, encephalopathy, pre-transplant renal support, previous abdominal surgery, varices, lifestyle activity, age, BMI (Kg/M<sup>2</sup>), 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<sup>2</sup>), cold ischaemic time.

\*<sup>2</sup> P-values represent whether HR's in each epoch of follow-up time differ significantly from each other.

\*<sup>3</sup> 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.

**Table 3: Impact of HCC on post-transplant graft survival in three separate epochs of follow-up time (n=4 927).**

| Post-transplant graft survival                                       | HCC compared to non-HCC<br>Hazard ratio (95% CI) |                  |                  | P value time dependency* <sup>2</sup> |
|--|--|------------------|------------------|---------------------------------------|
|  | 0 to 3 months                                    | 3 to 24 months   | 24 to 60 months  |                                       |
| <b>Unadjusted analysis</b>   | 0.95 (0.75-1.21)                                 | 1.84 (1.46-2.34) | 1.82 (1.38-2.39) | <0.001                                |
| <b>Adjusted for recipient characteristics*<sup>1</sup></b>           | 0.89 (0.68-1.17)                                 | 1.74 (1.34-2.27) | 1.72 (1.28-2.31) | <0.001                                |
| <b>Adjusted for recipient and donor characteristics*<sup>1</sup></b> | 0.84 (0.65-1.11)                                 | 1.67 (1.28-2.17) | 1.66 (1.23-2.23) | <0.001                                |

\*<sup>1</sup> Adjusted for a) Recipient characteristics: sex, ethnicity, HCV status, pre-transplant inpatient status, ascites, encephalopathy, pre-transplant renal support, previous abdominal surgery, varices, lifestyle activity, age, BMI (Kg/M<sup>2</sup>), 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<sup>2</sup>), cold ischaemic time.

\*<sup>2</sup> P-values represent whether HR's in each epoch of follow-up time differ significantly from each other.

\*<sup>3</sup> 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.

**Table 4: Primary cause of death following liver transplantation for HCC and non-HCC patients in three separate epochs of follow-up time (n=620).**

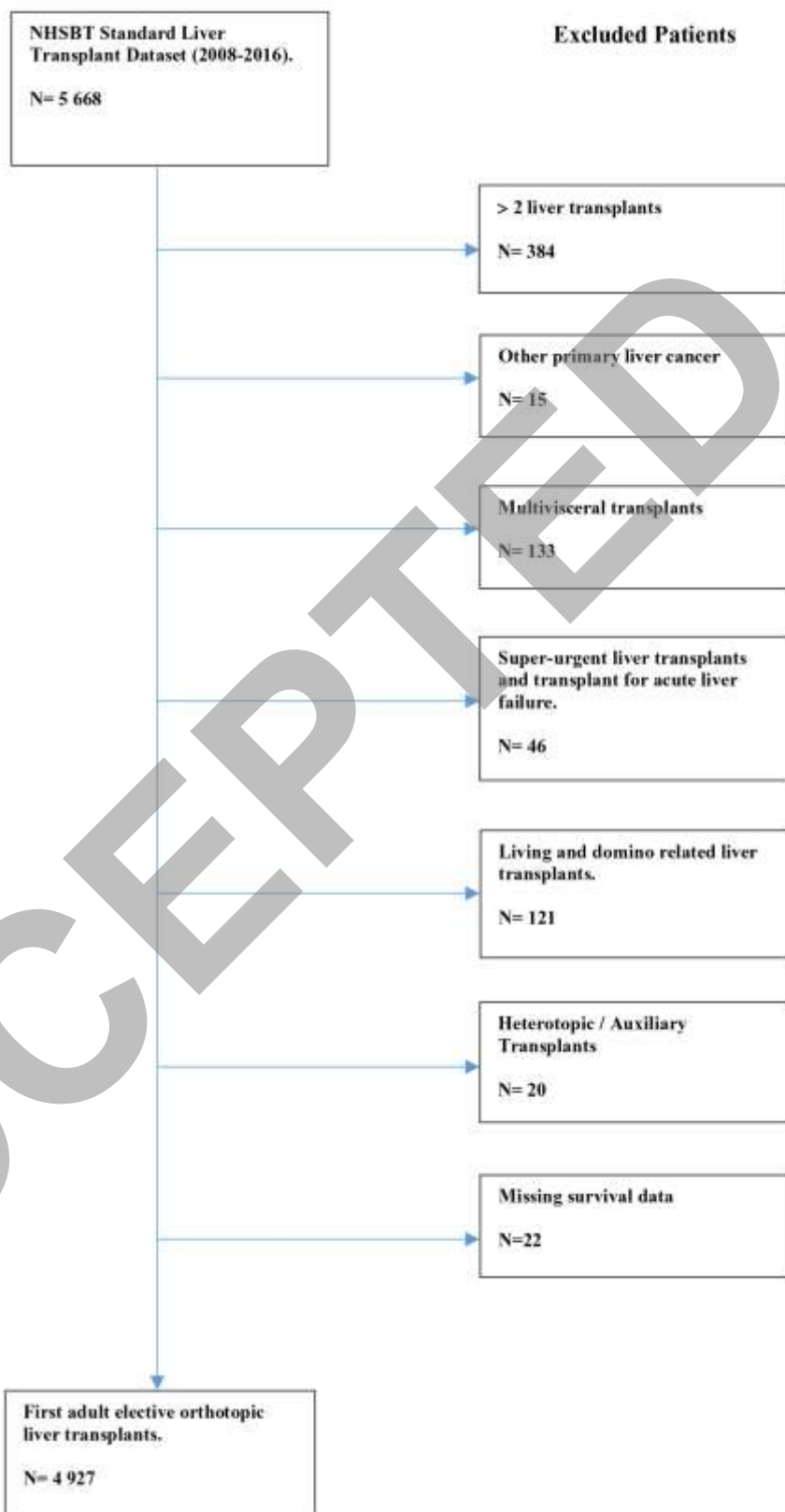
| Cause of Death                                      | 0-90 days   |                 | 91 days – 24 months |                 | 24 months – 60 months |                 |
|---|-------------|-----------------|---------------------|-----------------|-----------------------|-----------------|
|   | HCC (n=44)  | Non-HCC (n=144) | HCC (n=101)         | Non-HCC (n=132) | HCC (n=77)            | Non-HCC (n=122) |
| Recurrent primary disease - malignant* <sup>1</sup> | 0% (0)      | 0% (0)          | 22.7% (23)          | 1.5% (2)        | 15.6% (12)            | 1.6% (2)        |
| Recurrent primary disease - benign* <sup>2</sup>    | 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 – Non Lymphoproliferative                | 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)        |
| Haemorrhage   | 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)      |
| <b>P-value*<sup>3</sup></b>                         | <b>0.38</b> |                 | <b>&lt;0.001</b>    |                 | <b>0.03</b>           |                 |

\*<sup>1</sup> Recurrence of malignant disease for patients transplanted for non-HCC indications likely represents recurrence of a intrahepatic malignancy only identified on explant pathology or an error in the recording cause of death

\*<sup>2</sup> Includes the recurrence of HCV and the cholestatic liver diseases (PSC and PBC).

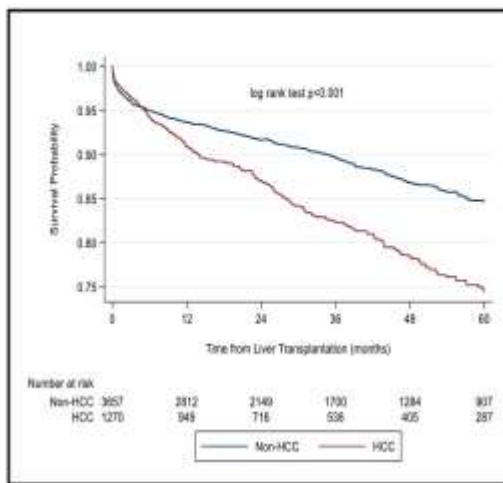
\*<sup>3</sup> p value of chi squared test comparing distribution of causes of death in HCC and non-HCC patients.

Figure 1: Flow chart detailing selection of study population (2008-2016).

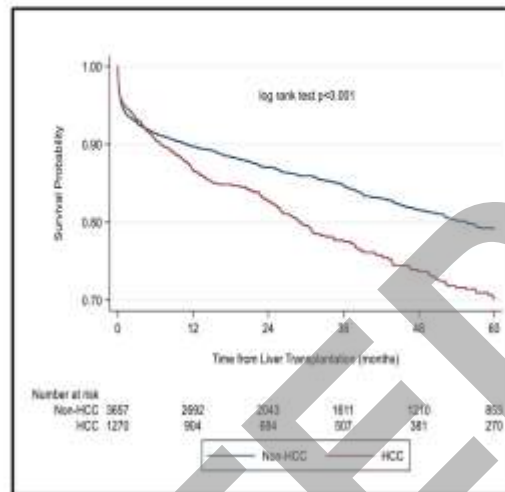


**Figure 2: Five-year patient and graft survival stratified by HCC status 2008-2016 (n=4 927).**

**a) Patient survival**



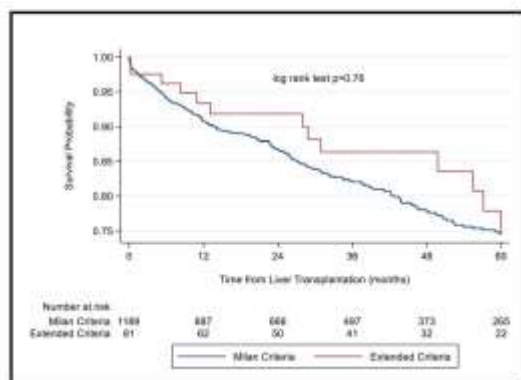
**b) Graft survival**



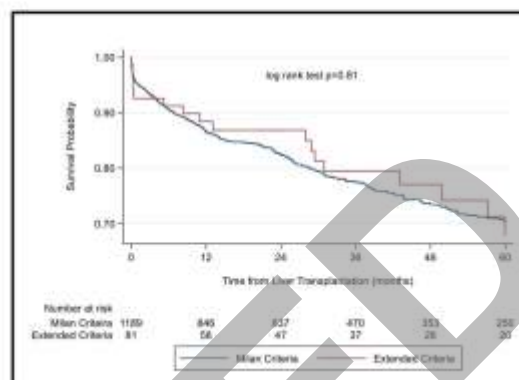
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**Figure 3: Five-year patient and graft survival for HCC patients stratified by type of selection criteria 2006-2016 (n=1 270).**

**a) Patient Survival**



**b) Graft survival**



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