TITLE PAGE

Assessing the time-dependent impact of performance status on outcomes after liver transplantation.

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All authors have been involved in revising the content of this work in preparation for manuscript submission and agree to be accountable for all aspects of the work. All authors have given final approval for be submission to Hepatology.

FOOTNOTE PAGE

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List of Abbreviations

ADL: Activities of daily living

ALF: Acute liver failure

CLD: Chronic liver disease

DBD: Brainstem death

DCD: Circulatory death

ECOG: Eastern Cooperative Oncology Group

HCC: Hepatocellular carcinoma

HCV: Hepatitis C

IRQ: Interquartile range

HR: Hazard ratio

PS: Performance status

SD: Standard deviation

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

UKELD: United Kingdom Model for End-Stage Liver Disease

ABSTRACT

Identifying how the prognostic impact of performance status (PS) differs according to the indication, era and time-period ('epoch') after liver transplantation (LT) could have implications for the selection and treatment of patients on the waitlist. We used national data from the UK and Ireland to assess the impact of PS on mortality separately for HCC and non-HCC recipients. We assessed pre-LT PS using the 5-point modified Eastern Cooperative Oncology Group (ECOG) scale and used Cox-regression methods to estimate hazard ratios (HR) that compared the post-transplantation mortality in different epochs of follow-up (0 to 90 days and 90 days to 1-year) and in different eras of transplantation (1995-2005 and 2006-2016). 2107 HCC and 10693 non-HCC patients were included. 1-year survival decreased with worsening PS in non-HCC recipients where 1-year survival was 91.9% (95%CI; 88.3%-94.4%) in those able to carry out normal activity (PS1) compared to 78.7% (76.7%-80.5%) in those completely reliant on care (PS5). For HCC patients, these estimates were 89.9% (85.4%-93.2%) and 83.1% (61.0%-93.3%) respectively. The reduction in survival in non-HCC patients with poorer PS was in the first 90 days after transplant, with no major effect seen between 90 days and 1 year. Adjustment for donor and recipient characteristics did not change the findings. Comparing era, post-LT mortality improved for HCC (adjusted HR 0.55, 0.40-0.74) and non-HCC recipients (0.48, 0.42-0.55) but this did not differ according to PS score (p=0.39 and 0.61, respectively). ***Conclusion:*** The impact on mortality of recipient's pre-transplant PS is limited to the first 3 months after liver transplant. Over time, mortality has improved for both HCC and non-HCC recipients and across the full range of PS.

INTRODUCTION

Patients with cirrhotic chronic liver disease (CLD) may develop multiple complications that impact upon their functional or performance status (PS) – the ability to perform activities of daily living (ADL).[1-3] This deterioration in condition reflects the development of a 'frail' state, with contribution from many of the clinical sequelae of liver cirrhosis including ascites, encephalopathy, sarcopenia, and hepatocellular carcinoma (HCC).[1, 4]

Measurements of PS are designed to capture a global assessment of health status as opposed to identifying the specific effects of particular organ dysfunction.[3,6-8] A variety of metrics are available to quantify PS and a subjective but reproducible one of these is through recording of PS scores – patient-reported or clinician recorded assessments of patients' ability to care for themselves.[3] In multiple epidemiological analyses, ratings of overall health status have been found to be powerful predictors of subsequent mortality with the suggestion that the computation of perceived health captures information beyond that identified through specific measurements of end-organ function.[8-9]

In patients on the transplant waitlist, impaired PS has been shown to have important adverse effects on quality of life as well as survival.[5-7] In patients who have received a liver transplant (LT), the impact of pre-transplant PS on post-transplant survival is less well described. One commonly used PS score shown to have a strong association with mortality in non-transplanted patients with CLD is the Eastern Cooperative Oncology Group (ECOG) scale.[10] The first published analysis of the impact of impaired PS on post-LT survival followed analysis of the UK liver transplant registry and found impaired PS to be a strong and independent risk factor post-transplant mortality.[3] However, this study used data from almost two decades ago and may not represent the current outcomes of LT.[3] Further, it only explored survival up to 90 days after transplantation and the longer-term impact of impaired PS on mortality remains relatively unknown.

Since that report, major advances in peri-operative care and immunosuppressive strategies[11] have occurred which may have altered the prognostic impact of impaired PS scores on post-transplant mortality. Determining how the association between PS scores and post-transplant mortality has changed over time and how it changes according to different post-transplantation time-periods ('epochs') could have important implications in the selection and counselling of patients and for the initiation of interventions on the waitlist and in the post-operative period. Similarly, in the last decade the number of recipients with hepatocellular carcinoma (HCC) has increased [11] yet the specific impact of PS on post-transplant mortality in this select group of patients also remains unknown.[12] This has the potential to be very different because at the time of transplantation HCC recipients are often in a better physical condition with fewer manifestations of end-stage liver disease than patients without HCC but with advanced CLD who have deteriorating liver function and its resulting complications.[11]

Given the increasing appreciation of the clinical impact of frailty on the outcome of transplantation in patients with CLD, we investigated impact of PS on post-transplant mortality, separately for recipients with and without HCC. Using data from the Standard National Liver Transplant Registry,[13] including all adult patients who had a liver transplantation between 1995 and 2016 in the UK and Ireland, the impact of PS on patient mortality was estimated in the short and longer-term and according to the era of transplantation

PATIENTS AND METHODS

Standard National Liver Transplant Registry

The Standard National Liver Transplant Registry contains detailed information about all liver transplants carried out since 1984 in the eight liver transplant centers in the United Kingdom and Ireland.[13] The dataset is currently managed by National Health Service Blood and Transplant (NHSBT), [13] 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. [3]

Study population

All adults (aged 18 years or older) who received a first liver transplant between 1st January 1995 and 31st December 2016 were eligible for inclusion (Figure 1). To select a sample of liver transplant recipients that were representative of clinical practice, recipients who underwent multivisceral transplants or super-urgent transplants, and those who required ITU support (ventilation and or dialysis) prior to transplantation were included. Those whose survival data was missing and those in which a PS score was not recorded prior to their transplant were excluded. Recipients were categorised into two groups: patients transplanted with HCC mentioned in any of three diagnosis fields available in the Standard National Liver Transplant Registry (HCC patients) and patients transplanted with other liver disease diagnoses (non-HCC patients).[13] Patients transplanted for non-HCC indications who were subsequently found to have HCC on explant pathology were analysed on an intention-to-treat basis and remained in the non-HCC cohort.[11]

A modified version of the Eastern Cooperative Oncology Group (ECOG) scale was used to measure recipients'

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performance status (PS) on a 5-point scale (Table 1) ranging from 'able to carry out normal activity without restriction' (PS1) to 'completely reliant on nursing/medical care' (PS5).[3,10] Measurements of PS were assessed by clinicians either at the time of transplantation or at the most recent clinic before surgery. Self-reports of functional ability were included in the assessment of patients' PS[3,13]

The severity of recipients' liver disease was assessed using the United Kingdom Model for End-Stage Liver Disease (UKELD) score.[14] Cold ischemic time (CIT) was defined as the duration between start of cold perfusion in the donor to start of blood flow through the organ in the recipient.[15] All livers that were donated after cardiac death (DCD) were procured under controlled circumstances where cardiac arrest either followed the planned withdrawal of life sustaining treatments (Maastricht III) or occurred in a patient who was brain dead (Maastricht IV).[16] Ethnic background was categorised into white and non-white groups.

Statistical Analysis

Donor and recipient characteristics and cause of death were described separately for HCC and non-HCC recipients, and according to the 5-point ECOG scale. Categorical variables were presented as proportions and continuous variables presented as medians with interquartile ranges (IQR). In accordance with recent Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines, we did not apply significance tests to the patient characteristics included in descriptive tables.[17]

Kaplan-Meier (KM) methods were used to compare patient survival between successive levels of PS score, separately for HCC and non-HCC patients. Follow-up was censored at 1 year after transplantation or on the last follow-up visit before 31st December 2016, whichever occurred earlier. Patients alive at their last follow-up visit were considered to be censored observations.

Multivariable Cox regression models were used to estimate the difference in post-transplant mortality across the different levels of PS, separately for HCC and non-HCC recipients, adjusting for all the donor and recipient characteristics in Table 2. Interaction terms were included in the Cox models to determine whether the prognostic impact of PS varied according to the time-period ('epoch')[18] after transplantation, and according to the era of transplantation. Epochs of 0 to 90 days and 90 days to 1-year post-transplant were chosen to reflect the impact of PS during the immediate post-operative period and its impact on longer term survival respectively. Partitioning eras of transplantations between 1995 and 2005 and 2006 and 2016 was chosen to capture the introduction of urgency based allocation policies in 2006 and the transplantation of patients with more severe liver disease.[19] In the Cox models that were used to test the time-dependent effect of PS, 'Self-care' (PS3) was used as the reference value as it was the largest group.[3] The statistical significance of the interaction terms in each model was tested using the global Wald test.

To assess the influence that liver disease severity had on the prognostic impact of PS, adjusted hazard ratios (HRs) for the effect of PS on post-transplant mortality were estimated with and without adjustment for: UKELD, ascites, varices and encephalopathy (with all other donor and recipient characteristics included in

both models). All risk adjustment included adjusting for differences across levels of the ECOG scale in those who received a multi-organ or super-urgent transplantation, those who had been transplanted in the presence of acute liver failure and or cirrhosis and those who required pre-operative ITU support.

Three sensitivity analyses were performed. First, the effect of PS on mortality was assessed having collapsed HCC and non-HCC patients with the worst PS scores (PS score of 4 or 5) into a single group, because of small numbers of HCC patients in these two groups. Second, the effect of PS of mortality was compared between Cox models that did and did not adjust for multivisceral transplants, super-urgent transplants, and those who required ITU support prior to transplantation. Third, additional adjustment for tumour characteristics were applied to the Cox model that assessed the impact of PS on mortality for HCC patients allowing us to specifically assess how tumour burden influenced the association between PS and post-transplant mortality. Included in this model were measurements of maximum tumour diameter, total tumour diameter, number of tumours, and alpha-feto protein levels (ng/mL).

Missing donor and recipient characteristics were imputed with multiple imputation using chained equations creating ten complete datasets.[20] In the imputation procedure all donor and recipient variables in the regression analyses were used to predict missing values, including the outcome variables.[20] The Hazard ratios for each of these datasets were pooled using Rubin's rules.[20] Stata V15 (StataCorp, College Station, Texas, USA) was used for all statistical analyses.

RESULTS

Patient characteristics

A total of 12 800 adult liver transplants were recorded as performed between 1995 and 2016, of which 2 107 were for HCC recipients and 10 693 for non-HCC recipients (Table 2). The number of HCC recipients increased from 29 in 1995 to 130 in 2016. PS was poorer for non-HCC patients, with almost a third of non-HCC patients having PS4 or 5 compared to only 1 in 15 for HCC patients. Those recipients who had poorer PS scores also had more severe liver disease (as captured by UKELD) and were more likely to have encephalopathy. They were also more frequently required to be inpatients or to require renal support prior to their transplant. HCC recipients were more likely to be male, older, and they also more often received grafts that were donated following circulatory death (DCD) or grafts in which the appearance had been documented as 'abnormal'.

Kaplan-Meier survival analysis

Kaplan-Meier survival curves showed that impaired PS was associated with poorer patient survival in non-HCC patients (log rank p<0.001, Figure 2) but not in HCC recipients (log rank p=0.17). For non-HCC patients, the difference in survival between recipients with PS1 and 5 appeared most marked in the first months after transplantation resulting in a 1-year patient survival of 91.9% (95%CI; 88.3% to 94.4%) and 78.7% (95%CI; 76.7% to 80.5%), respectively.

Multivariable Cox regression

Risk-adjustment did not change these findings (Figure 3 and Tables S1 and S2). In a multivariable Cox model comparing the impact of PS scores in the different epochs of follow-up, survival of non-HCC patients was progressively worse with poorer PS scores (Figure 3 and Table S1), with evidence of a larger effect in the first 3 months' post-transplant (p for interaction between PS and epoch <0.001). In the first 90 days following transplantation, mortality of non-HCC recipients with PS score of 5 was almost double that of recipients with PS3 (HR: 1.89, 95%CI: 1.42-2.61). There was no statistical evidence of any further effect of PS score on survival from 90 days to 1-year in non-HCC recipients overall, although an increased mortality was seen in those with PS4 compared to those with PS3 (HR: 1.41, 95%CI 1.05-1.90). No effect of PS score on survival was found in HCC recipients, either in the first 3 months or from 3 months to 1-year post-transplant (p for interaction between PS and epoch =0.44, Figure 3 and Table S2). Adjustment for measures of liver disease severity had little impact on these comparisons (Tables S1 and S2).

In the multivariable Cox model that compared the impact of PS over different eras of transplantation, improvements in overall mortality were observed in both HCC and non-HCC cohorts (Table 3). However, there was no evidence that improvements in survival over time differed between those with different PS scores and this was the same for both HCC and non-HCC recipients (p for interaction between era and PS =0.39 and 0.61, respectively). In the sensitivity analyses, the effect of combining those with the worst PS scores into one stratum had no impact on the analysis that assessed the impact of PS in different epochs or the analysis that assessed PS according to era (Table S3 and footnote of Table 3, respectively). Similarly, there was no difference in the pattern of results when comparing HR's of the Cox models that had or had not adjusted for multivisceral transplants, super-urgent transplants or pre-transplantation ITU support (Table S1, 2 & 4) or in the Cox model that for HCC patients had adjusted for tumour characteristics (Table S2 & S5). However, progressively poorer performance status was associated with recipients more frequently dying from sepsis in both HCC and non-HCC recipients (Table S6).

DISCUSSION

Summary of results

At the time of transplantation, almost one in three non-HCC patients were either confined to the bed or the chair (PS4) or completely reliant on care (PS5), compared to 1 in 15 HCC patients. PS at the time of transplantation was found to be independently associated with post-transplantation mortality, but only in non-HCC recipients and principally within the first 3 months following transplantation. Improvements in the post-transplant mortality of HCC and non-HCC recipients over time appear to have occurred equally across all levels of PS.

Comparison with other studies

Few studies have examined the association between PS scores prior to transplantation and subsequent mortality.

A national study in the UK and Ireland, published 16 years ago and using PS scores based on the ECOG scale taken from the same dataset as in this analysis, observed a similar pattern of results as described in our study.[3] They found that recipients who were completely reliant on care (PS5) prior to transplantation were significantly more likely to die within 90 days of their transplant than those capable of self care (PS3). A more recent US study, including 50 417 transplants identified in the United Network of Organ Sharing (UNOS) database between 2006 and 2016, also found pre-transplant measurements of PS (using the Karnofsky Score) to be independent predictors of post-transplant survival.[8]

However, to date no analysis has estimated the impact of PS on mortality separately for HCC and non-HCC patients or specifically investigated how that impact has changed according to epoch of follow-up or era of transplantation.

Explanation of results

There are several possible explanations for the association between pre-transplantation PS and shorter term post-transplant mortality in non-HCC recipients. It could be that PS scores are a more inclusive and accurate measure of a patient's health status than more specific measurements of organ dysfunction and some of the clinical sequelae of CLD, such as sarcopenia or under-nutrition. [3] PS scores may also better reflect behavior that influences the short-term outcome of transplantation.[3] For example, those with the poorer PS on the transplant waitlist are more likely to suffer from prolonged periods of immobilization, reduced physical activity and an increased risk of perioperative death.[1-2] Finally, the limited association of PS on mortality beyond the early post-transplant period may reflect the relatively rapid reversal of the clinical sequelae of severe liver dysfunction that follows restoration of liver function by transplantation, as opposed to other extra-hepatic chronic conditions that are not corrected and persist beyond the immediate post-transplant period and impact survival later.

In HCC recipients, there was no evidence of an association of PS and mortality. In the UK, HCC patients listed for transplantation tend to have more preserved liver function, fewer complications of end-stage liver disease, and low tumour burdens. This means that very few HCC patients have a significantly impaired PS at the time of transplantation, making it difficult to detect PS-specific differences in post-transplant mortality even if they do exist. Therefore, although our results suggest that PS has less of an association with post-transplant mortality in HCC patients, a larger sample of waitlist patients with PS scores of 4 or 5 who have HCC would be needed to confirm this.

It is likely that the improvements over time in post-transplant mortality reflect the effect of multiple interventions,[11] especially as for HCC and non-HCC patients these improvements were not found to differ according to PS score. Previous analysis by this research group has shown that, irrespective of PS, increased survival of both HCC and non-HCC recipients has largely been driven by a decreased rate of early post-operative death.[11] Advances in surgical technique, peri-operative care and more specifically in the prevention of sepsis-related complications are likely to be responsible for these improvements.[11,21]

Methodological limitations

A first limitation is that the PS scores that were used in this study were reported by clinicians in the eight-participating transplant centres. Although less prone to inter-observer error than the more complex measurements of PS, agreement between clinicians' scoring of the ECOG status of patients has varied between a coefficient of 0.91 in some studies to as low as 0.50 in others. [22-23] If we assume in our analysis that a level of disagreement - somewhere between these two coefficients – occurred to the same extent in patients who survived and in those who died, the true effect of pre-transplant PS on post-transplant mortality may have been larger than that observed in our study.[3]

Second, clinicians who were recording PS scores at the time of transplantation were not blinded to the other known risk factors of post-transplant mortality, including those measures of severe liver dysfunction.[3] This could have contributed to the observed association between PS and these risk factors. However, the association between the PS scores and post-transplant mortality remained even after extensive adjustment for pre-transplant factors, making it unlikely that a lack of blinding fully explains our findings.[3]

Finally, the small number of HCC patients who were reported to have the most severely impaired PS scores may have precluded the detection of significant differences in post-transplant mortality, especially in those patients who were reported to have a PS score of 4 or 5. However, when those with the worst PS score were collapsed into one stratum and a 4-level modified ECOG scale was used, no difference in the association of PS and post-transplant mortality was observed in either HCC or non-HCC recipients.

Clinical and methodological implications

Our observations in a national cohort of liver transplant recipients in the UK and Ireland suggest that considering the PS of patients prior to transplantation, in addition to other conventional risk factors, improves the ability to predict post-transplant survival. These are important findings that are relevant to the assessment of the suitability of potential liver transplant candidates in daily clinical practice. Also, despite an increasing reliance on complex prognostic models to predict outcome, these findings emphasize that asking patients traditional questions about their general health and well-being is still an important part of their clinical assessment that can help determine their suitability for transplantation and their risk of mortality after it.

The chief importance of the association between pre-transplantation PS and post-transplant mortality lies in the potential for its modification through pre- and post-transplant interventions. These may encompass medical optimisation, exercise therapies, nutritional and psychological support. However, if interventions to address functional impairment are considered we must acknowledge that the subjective nature of PS scores means that they may be best employed as screening tools that can be used in a 'frailty toolkit' alongside other more objective measures of PS.[24] In this utility, they could also be used to identify patients prior to transplantation who may benefit from targeted prehabilitative interventions,[2,24] or patients following transplantation who are most

vulnerable to early post-operative death. This is even more important now that it is known that beyond the first few months after transplantation even those with the most impaired PS prior to their operation can have similar outcomes to those who had a much better PS score.

PS scores therefore help to identify those patients at greater risk of a poor post-transplant outcome but do not definitively identify patients whose PS should preclude them from receiving a liver transplant. To aid in the selection of patients for liver transplantation further research is needed to identify whether the characteristics of patients with PS 5 which are associated with a poorer outcome are potentially modifiable with prehabilitative interventions.

Finally, this study re-established the importance of analysing post-transplant outcomes in distinct epochs of follow-up time.[18] By testing the prognostic impact of PS scores in different time-periods, the relative impact of functional status on post-transplant outcomes could be quantified for HCC and non-HCC recipients.[18] This method of time-dependent analysis re-introduces after decades an exemplar of statistical modelling that is likely to be informative for a wider range of questions about determinants of outcomes after liver transplantation.[18]

Conclusion
Considering PS scores prior to transplantation, in addition to other conventional risk factors, improves the ability to predict post-transplant survival. Measurements of PS, whilst subjective, are still important initial tools in assessing the suitability of patients for transplantation and for identifying those patients who may benefit from targeted pre-operative interventions that could improve their PS and subsequent post-transplant mortality.

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FIGURE LEGENDS

Figure 1: Flow chart presenting selection of study population (1st January 1995 to 31st December 2016).

Figure 2: Impact of performance status on post-transplant survival for HCC and Non-HCC patients (n= 12 800).

Figure 3: The impact of performance status on patient survival in two separate epochs of follow-up time in HCC and non-HCC patients (n=12 800).