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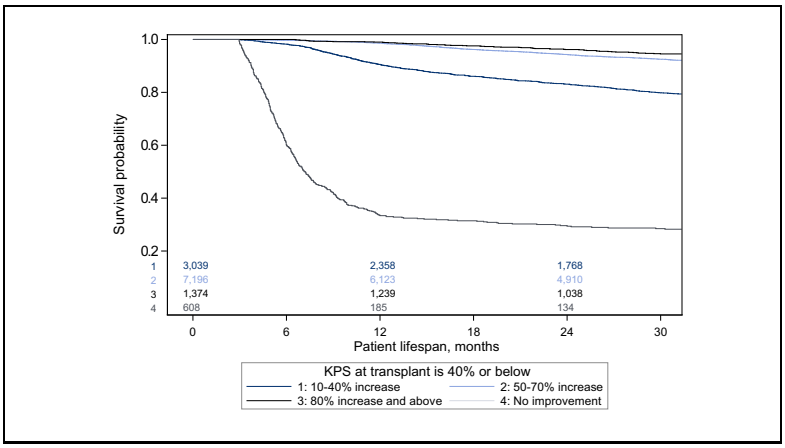
Karnofsky performance status before and after liver transplantation predicts graft and patient survival

Graphical abstract



Highlights

- The Karnofsky Performance Status (KPS) has been used for almost 70 years in clinical practice.
- We determined the trends in KPS before and after liver transplant, and survival probabilities based on KPS.
- KPS scores declined between listing and transplantation, but were significantly improved after transplantation.
- The KPS was an independent predictor of graft and patient survival.
- Those who did not show an improvement in post-liver transplant KPS scores had worse outcomes.

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Lay summary

The overall health of liver transplant recipients could be assessed by a simple clinical assessment tool called the Karnofsky performance status, which assesses an individual's overall functional status on an 11-point scale, in increments of 10, where a score of 0 is considered dead and 100 is considered perfect health. In this study, using a large dataset, we show that the performance status before and after liver transplant is a predictor of survival. More importantly, those who have low performance status before transplant and do not show an improvement in performance status between 3–12 months after liver transplant have very poor survival.

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Karnofsky performance status before and after liver transplantation predicts graft and patient survival

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Background & Aims: The Karnofsky performance status (KPS) has been used for almost 70 years for clinical assessment of patients. Our objective was to determine whether KPS is an independent predictor of post-liver transplant (LT) survival after adjusting for known confounders.

Method: Adult patients listed with the United Network for Organ Sharing (UNOS) from 2006 to 2016 were grouped into low (10–40%, n = 15,103), intermediate (50–70%, n = 22,183) and high (80–100%, n = 13,131) KPS groups based on KPS scores at the time of LT, after excluding those on ventilators or life support. We determined the trends in KPS before and after LT, and survival probabilities based on KPS.

Results: There was a decline in KPS scores between listing and LT and there was significant improvement after LT. The graft and patient survival differences were significantly lower (p <0.0001) in those with low KPS. After adjusting for other confounders, the hazard ratios for graft failure were 1.17 (1.12–1.22, p <0.01) for the intermediate and 1.38 (1.31–1.46, p <0.01) for the low group. Similarly, hazard ratios for patient failure were 1.18 (1.13–1.24, p <0.01) for the intermediate and 1.43 (1.35–1.52, p <0.01) for the low group. Other independent negative predictors for graft and patient survival were older age, Black ethnicity, presence of hepatic encephalopathy and donor risk index. Those who did not show significant improvements in post-LT KPS scores had poorer outcomes in all three KPS groups, but it was most obvious in the low KPS group with one-year patient survival of 33%.

Conclusion: The KPS, before and after LT, is an independent predictor of graft and patient survival after adjusting for other important predictors of survival.

Lay summary: The overall health of liver transplant recipients could be assessed by a simple clinical assessment tool called the Karnofsky performance status, which assesses an individual's overall functional status on an 11-point scale, in increments of 10, where a score of 0 is considered dead and 100 is considered perfect health. In this study, using a large dataset, we show that the performance status before and after liver transplant is a predictor of survival. More importantly, those who have low performance status before transplant and do not show an improvement in performance status between 3–12 months after liver transplant have very poor survival.

Introduction

The Karnofsky performance status (KPS) has been used for almost 70 years in clinical practice as a subjective 'eyeball' assessment of the overall performance status of patients. The KPS scores, administered by the provider or support staff, assign scores to patients on a scale of 0–100%, in increments of 10, where 100% is normal activity and 0% is dead.[1] It is widely used in general oncology practice as a prognostic predictor and also for the selection of patients in clinical trials.[4–10] The inter-observer reliability, validity and reproducibility of KPS scores in multiple clinical settings have shown to be excellent.[2,10,11] Recently, the KPS was shown to be a useful tool for predicting survival in patients admitted to hospitals with complications of cirrhosis and was shown to be a predictor of transplant wait-list mortality.[12,13]

The model for end-stage liver disease (MELD) scores is objective, but does not incorporate many variables that may predict outcomes before and after liver transplantation including malnutrition or morbid obesity, mobility and performance status. Despite its subjectivity, KPS scores reflect the overall assessment of a patient's performance status that may include some of the subjective tools that are difficult to quantify in an objective manner.[2] Recently, there have been attempts to develop objective tools, such as frailty index, six-minute walk distance and sarcopenia, to assess patients with liver diseases, but their utility in epidemiological studies remain unknown.[14–18]

The Eastern Cooperative Oncology Group (ECOG) performance status score, also widely used in cancer research, was found to be associated with 90-day post-LT survival in a study based on the United Kingdom and Ireland transplant registry.[19] To our knowledge, there have been no systematic studies exploring the utility of KPS before and after LT in predicting post-LT outcomes. The objective of our study was to determine whether KPS scores before and after LT independently predicted post-LT outcomes in an unselected patient population.

Patients and methods

We included patients listed for LT with the United Network for Organ Sharing (UNOS) between January 1, 2006 and September

Keywords: Karnofsky Performance Status; Liver transplant; Post-liver transplant survival; UNOS.
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30, 2016. The start date of January 1, 2006 was selected as KPS scores were consistently collected since 2006. Prior to 2006, for most patients, performance status was categorized into three categories, whereas the KPS scores are entered as an 11-point scale ranging between 0% and 100%. Our preliminary analysis suggested that combining these two variables into a single performance status measurement would introduce a bias, and hence we limited our analysis for those who were listed from January 1, 2006. We excluded patients younger than 18 years old, those listed for multiple organ transplantation or re-transplantation, those on life support or mechanical ventilation, and those with missing KPS scores (Flow Chart, Fig. 1). Based on KPS scores at the time of transplantation, patients were stratified into three groups: low (KPS scores 10–40%; unable to care for self and requires substantial assistance), intermediate (KPS scores 50–70%; unable to work and requires varying assistance) and high KPS (KPS scores 80–100%; able to work and no assistance required).[2] We collected KPS scores at the time of listing, at the time of transplant and at different intervals while awaiting LT and after LT for up to five years. We assessed differences in KPS at the time of listing and at LT; similarly, we assessed the differences in KPS at the time of LT and follow-up.

We collected data including age, sex, ethnicity, body mass index (BMI), serum creatinine, presence of diabetes mellitus, MELD score, presence of hepatic encephalopathy, cause of liver disease and donor risk index (DRI). The DRI was estimated according to a method proposed by Feng *et al.*[20] We estimated graft and patient survival after censoring patients at the time of re-transplantation or death based on KPS scores at the time of transplant. We also explored the survival differences based on post-LT changes (between 3–12 months) in KPS scores. Additionally, we examined the pre- and post-LT variables that could predict a non-improvement in KPS after the liver transplant.

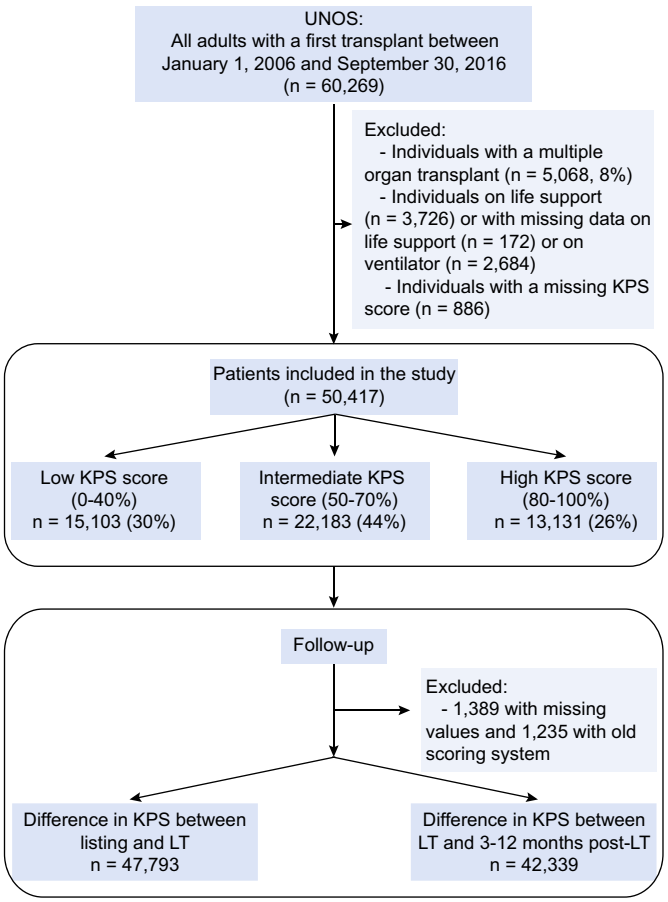

Fig. 1. Flow diagram of the inclusion/exclusion patients in the study. KPS, Karnofsky performance status; LT, liver transplant; UNOS, United Network for Organ Sharing.

Statistical methods

The baseline characteristics at the time of transplant were compared using *t* tests for continuous variables and Chi-squared tests for categorical variables. The post-transplant graft and patient survival probabilities were estimated using Kaplan-Meier survival analysis; the log-rank test was used to examine differences in survival probabilities between the three groups. The strength of the associations with the risk factors including demographic, clinical and graft quality characteristics was estimated via hazard ratios using Cox proportional hazard regressions. For this analysis, those variables that were significant at $p \leq 0.1$ by univariate analysis were included into a multivariate model. The variables that we included in the univariate analysis were age, gender, race, morbid obesity (BMI >40), MELD scores, stage 3–4 encephalopathy, etiology of liver disease, DRI, transplant center volume and KPS scores. The relative risk of graft and patient failure were adjusted for the differences in distributions of the risk factors between the three groups and are expressed as hazard ratios (HRs) with 95% confidence intervals.

For changes in KPS score from listing to LT and following LT, up to five years, we have summarized the results as descriptive statistics and histograms. The survival probabilities based on improvement in KPS were estimated by Kaplan-Meier estimates for three groups (defined as low, intermediate and high based on KPS at the time of LT) separately. For this analysis, KPS scores for the first three months of LT were excluded as patients are in the recovery phase after surgery and only those KPS scores assessed between 3–12 months were used to stratify the patients. The criteria of improvement differed among three groups. For patients with a high KPS score at transplant (80–100%), patients were stratified into two groups: a decrease of KPS scores by at least 10% or an improvement by ≥0%. Those with an intermediate KPS score at transplant (50–70%) were stratified into three groups: no improvement (≤0%), improvement by 10–20% or ≥30%. Patients with a low KPS score at transplant (≤40%) were stratified into four groups: no improvement (≤0%), improvement by 10–40%, 50–70% or ≥80%. These differences in stratification were to accommodate for the plausible differences in improvement/worsening of KPS scores within the three groups. To identify pre- and post-LT variables that could potentially predict a decline or lack of improvement in KPS after LT, we used logistic regression with a forward stepwise model.

Results

During the study period, 57,885 patients were listed for LT (after excluding 5,068 listed for more than one organ), and of these we excluded 6,582 (3,726 patients on life support, 2,684 on ventilator, 172 missing data on life support) patients as it was not possible to reliably assess KPS score and 886 because of missing data on KPS scores. Our final sample size was 50,417 individuals, with follow-up data for up to 10 years. Based on KPS scores at the time of LT, there were 15,103 with

low scores, 22,183 with intermediate scores and 13,131 with high scores (Fig. 1).

The demographic and clinical characteristics are shown (Table 1). The low KPS score group comprised relatively younger patients and a higher proportion of women and Hispanics. Morbid obesity, prevalence of dialysis and stage 3–4 hepatic encephalopathy were more common in those with low KPS scores. Similarly, serum creatinine and MELD scores were higher and serum albumin was lower in the low KPS score group. There were fewer patients with hepatocellular carcinoma in the low KPS group.

To compare KPS at listing and LT, we excluded 1,235 patients who had functional status assessed by an old scoring system (3 categories) and 1,389 who had missing KPS scores at listing. Among the 47,793 evaluable patients, KPS scores remained unchanged in 19%, improved in few and decreased in most during the waiting period (Fig. 2A). The KPS was assessed at the time of listing and transplantation for all patients (only one observation at each time point), and the median time between the assessments was 97 (22; 274) days. The decline in KPS worsened with longer duration on the waiting list (Table S2). For post-LT follow-up, we excluded KPS that was assessed within three months of LT (n = 5,853).

We had complete post-LT data on 42,339 patients at one year and 30,291 at two years. As shown (Fig. 2B), the KPS score improved in more than 90% of patients after LT (Fig. 2B). The KPS scores were assessed multiple times after LT; for our study we included KPS assessment between 3–12 months after LT. The median interval between LT and follow-up KPS assessment was 223 (186–265 IQR) days. While 22,334 patients only had KPS assessment, 19,947 had two KPS scores. A minority of LT recipients (n = 58) had three or more. When more than one KPS score was available between 3–12 months, the average score was calculated. The median improvement at one year was 20% (mean 23 ± 29%), and there was no further improvement after that (Table S3).

The graft and patient survival showed worsening survival probabilities in those with intermediate and low KPS score groups (Fig. 3A, B). The maximum difference in patient survival was less than 6% at every time interval after LT in the low KPS score group compared to the high KPS score group (Table S1). Multivariate analysis, after adjusting for other confounders, showed that poor performance status at the time of transplant was associated with lower graft and patient survival in those with intermediate and low KPS scores (Table 2 and Table S4). The HRs for graft failure were 1.17 (1.12–1.22, p <0.01) for the intermediate group and 1.38 (1.31–1.46, p <0.01) for the low group. Similarly, HRs for patient failure were 1.18 (1.13–1.24, p <0.01) for the intermediate group and 1.43 (1.35–1.52, p <0.01) for the low group. Other independent negative predictors of graft and patient survival were older age, presence of hepatic encephalopathy, and DRI. The etiology of liver disease was also an independent predictor. Hispanics and Asians had a better survival and Blacks had poorer survival when compared

Table 1. Patient characteristics at the time of liver transplant.

	High KPS (80–100)	Intermediate KPS (50–70)	*p* value (high KPS *vs.* intermediate KPS)	Low KPS (0–40)	*p* value (high KPS *vs.* low KPS)
N	13,131	22,183		15,103	
Age, mean (SD)	55.5 (10.1)	55.8 (9.4)	0.005	54.0 (10.3)	<0.0001
Female, n (%)	3,486 (26.5)	7,116 (32.1)	<0.0001	5,439 (36)	<0.0001
Ethnicity, n (%)			<0.0001		<0.0001
White	9,446 (71.9)	16,403 (73.9)		10,581 (70.1)	
African-American	1,174 (8.9)	1,869 (8.4)		1,477 (9.8)	
Hispanic	1,461 (11.1)	2,777 (12.5)		2,299 (15.2)	
Asian	896 (6.8)	859 (3.9)		540 (3.6)	
Other	154 (1.2)	275 (1.2)		206 (1.4)	
BMI, mean (SD)	28.2 (5.3)	28.5 (5.6)	<0.0001	28.8 (6.0)	<0.0001
Morbid obesity, n (%)	312 (2.4)	716 (3.2)	<0.0001	678 (4.5)	<0.0001
DM Type II, n (%)	2,443 (19.3)	4,913 (22.8)	<0.0001	3,018 (20.6)	0.005
Serum creatinine, mean (SD)	1.03 (0.6)	1.17 (0.8)	<0.0001	1.82 (1.3)	<0.0001
Dialysis, n (%)	169 (1.3)	444 (2)	<0.0001	2,118 (14)	<0.0001
Albumin, mean (SD)	3.14 (0.7)	3.0 (0.7)	<0.0001	3.04 (0.8)	<0.0001
MELD score, mean (SD)	15.4 (7.3)	18.3 (8)	<0.0001	28.0 (10.2)	<0.0001
Encephalopathy 3–4 grade, n (%)	399 (3.1)	1,322 (6)	<0.0001	2,445 (16.3)	<0.0001
Encephalopathy, n (%)	5,795 (44.5)	13,538 (61.5)	<0.0001	11,311 (75.4)	<0.0001
Diagnosis, n (%)			<0.0001		<0.0001
HCC	7,020 (53.5)	9,107 (41.1)		3,187 (21.1)	
HCV	1,919 (14.6)	4,543 (20.5)		3,936 (26.1)	
Alcoholic cirrhosis	880 (6.7)	2,424 (10.9)		2,496 (16.5)	
Autoimmune hepatitis	220 (1.7)	410 (1.8)		459 (3)	
NASH and cryptogenic cirrhosis	1,075 (8.2)	2,587 (11.7)		2,144 (14.2)	
PBC and PSC	1,030 (7.8)	1,515 (6.8)		1,046 (6.9)	
Other	987 (7.5)	1,597 (7.2)		1,835 (12.1)	
Donor risk index, mean (SD)	1.82 (0.46)	1.83 (0.46)	0.22	1.79 (0.43)	<0.0001
Transplant center by volume			<0.0001		<0.0001
<20 LT/year	576 (4.4%)	681 (3.1%)		499 (3.3%)	
20–50 LT/year	3,099 (23.6%)	5,411 (24.4%)		3,661 (24.2%)	
>50 LT/year	9,456 (72%)	16,091 (72.5%)		10,943 (72.5%)	

Two-sample *t* tests were used for continuous variables and Chi-square tests were used for categorical variables to compare the differences between the groups. BMI, body mass index; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; KPS, Karnofsky performance status; LT, liver transplant; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

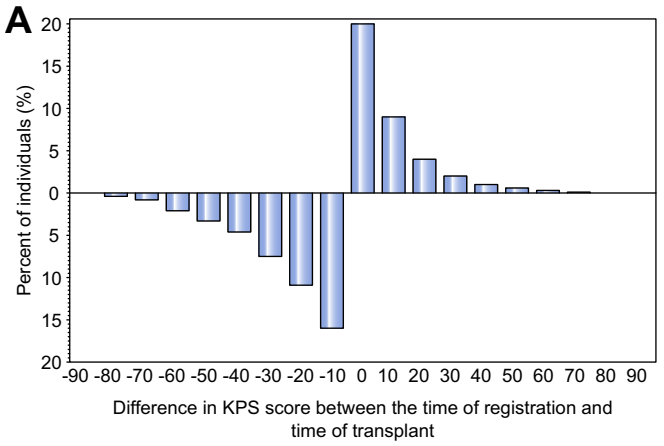

Fig. 2. The distribution of the absolute differences in KPS scores. (A) From the time of listing to liver transplant. The positive values indicate an improvement in KPS score relative to the time of listing. (B) From the time of transplant to follow-up. The positive values indicate an improvement in KPS score relative to the time of transplant. KPS, Karnofsky performance status.

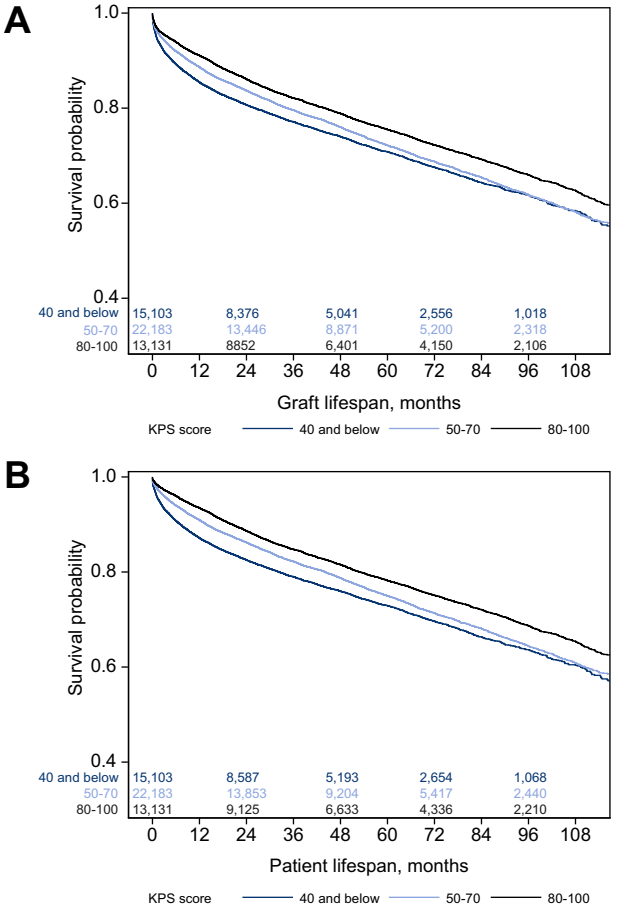

Fig. 3. Graft and patient survival probability by Kaplan-Meier survival analysis. (A) Graft survival probability by KPS score by Kaplan-Meier survival analysis (p value from log-rank test <0.0001). (B) Patient survival probability by KPS score by Kaplan-Meier survival analysis (p value from log-rank test <0.0001). KPS, Karnofsky performance status.

to Whites. The effect of transplant center was analyzed in two different ways in this study: by grouping based on the number of LT performed per year (<20, 20–50 and >50 per year) or random center effect. Both analyses showed that the transplant center had no impact on our graft or patient survival outcomes (Tables S5–8).

We further analyzed survival based on changes in KPS scores after LT. Patient survival based on changes in KPS score in low, intermediate and high groups are shown (Fig. 4). The one-year survival was only 33% in those with no improvement in KPS scores between 3–12 months after LT compared to 91% to 99% in those who had improved scores (Fig. 4A, Table 3). Similarly, in the intermediate group, one-year survival was 75% in those without improvement compared to 98% to 99% in those with improvement (Fig. 4B, Table 4). Even in the high KPS score group, there was a difference in survival, with one-year survival rates of 86% in those with a decrease in KPS score and 99% in those with no change or an improvement in KPS score (Fig. 4C, Table 3).

Since the KPS scores after LT had a major impact in the low KPS group, we examined this group in more detail to identify potential risk factors that could predict the non-improvement in KPS after LT (Table 4). The patients that showed no improvement (n = 608) in KPS were older, and had lower international normalized ratio, creatinine, bilirubin, albumin and MELD scores; this group also had a higher proportion of patients with type 2 diabetes mellitus, hepatocellular carcinoma (HCC) and hepatitis C virus (HCV). In addition, moderate ascites, dialysis, primary biliary cholangitis, primary sclerosing cholangitis and alcoholic cirrhosis were less common in the group that showed no improvement in KPS after LT. The interval between listing and transplantation was also higher in those who did not improve, and majority of these patients (75.5%) had their LT in centers that performed more than 50 transplants/year ($p = 0.0003$).

To identify independent risk factors for non-improvement in KPS after LT, we performed a logistic regression (forward selection) for the group with low KPS that did not show an improvement in KPS after LT, compared to those with an improvement of 50% or more (Table S9). We included all confounding risk factors and found that older age (odds ratio [OR] 1.02; 95% CI 1.01–1.03; p <0.0001), total bilirubin <12 mg/dl at LT (OR 1.27; CI 1.02–1.59; $p = 0.03$), MELD less than 30 (OR 1.28; CI 1.03–1.59; $p = 0.02$), serum albumin at LT (OR 0.84; CI 0.75–0.95; $p = 0.005$), presence of HCV (OR 1.5; CI 1.22–1.84; $p = 0.0001$) or HCC (OR 1.46; CI 1.16–1.83; $p = 0.0001$), and acute rejection episodes between LT and discharge from the hospital (OR 1.63; CI 1.14–2.35; $p = 0.008$) were associated with a higher probability of having no improvement in KPS after LT. These findings may suggest that the lack of improvement in KPS is multifactorial and could not be explained by more severe liver disease.

Table 2. Multivariate analysis of patient failure based on risk factors at the time of liver transplant.

	HR (unadjusted)	*p* value	HR (adjusted)	*p* value
Age	1.02 (1.02–1.02)	<0.01	1.02 (1.02–1.02)	<0.01
Gender				
Male	1.00		1.00	
Female	0.94 (0.91–0.98)	<0.01	0.98 (0.94–1.02)	0.3
Race				
White	1.00		1.00	
Black	1.30 (1.23–1.38)	<0.01	1.30 (1.23–1.39)	<0.01
Hispanic	0.94 (0.88–0.99)	0.02	0.88 (0.83–0.93)	<0.01
Asian	0.73 (0.66–0.81)	<0.01	0.68 (0.61–0.76)	<0.01
Other	0.88 (0.73–1.05)	0.2	0.89 (0.74–1.07)	0.2
Morbid obesity	1.06 (0.96–1.18)	0.2		
MELD score	1.00 (1.00–1.004)	0.03	1.00 (1.001–1.007)	<0.01
Encephalopathy	1.07 (1.03–1.11)	<0.01	1.04 (1.00–1.09)	0.08
Diagnosis				
PBC and PSC	1.00		1.00	
HCV	1.77 (1.61–1.93)	<0.01	1.65 (1.50–1.82)	<0.01
Alcoholic cirrhosis	1.34 (1.21–1.49)	<0.01	1.22 (1.10–1.37)	<0.01
Autoimmune hepatitis	1.35 (1.15–1.58)	<0.01	1.37 (1.16–1.62)	<0.01
HCC	1.83 (1.67–2.00)	<0.01	1.80 (1.62–1.98)	<0.01
NASH and cryptogenic cirrhosis	1.43 (1.29–1.58)	<0.01	1.23 (1.10–1.37)	<0.01
Other	1.26 (1.13–1.40)	<0.01	1.26 (1.12–1.42)	<0.01
KPS score				
80–100%	1.00		1.00	
50–70%	1.18 (1.13–1.24)	<0.01	1.18 (1.13–1.24)	<0.01
0–40%	1.36 (1.30–1.43)	<0.01	1.43 (1.35–1.52)	<0.01
Donor risk index	1.30 (1.25–1.35)	<0.01	1.34 (1.29–1.40)	<0.01
Transplant center volume				
<20 LT/year	1.0		1.0	
20–50 LT/year	1.02 (0.92–1.14)	0.2	1.00 (0.9–1.12)	0.9
>50 LT/year	0.9 (0.83–1.02)	0.1	0.90 (0.8–1.01)	0.07

The Cox proportional hazards regressions were used in univariate (unadjusted HRs) and multivariate (adjusted HRs) analyses. HCC, hepatocellular carcinoma; HCV, hepatitis C virus; KPS, Karnofsky performance status; LT, liver transplant; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

Discussion

In this study, we have shown a lower post-LT survival in patients with intermediate and low KPS scores when compared to those with high KPS scores. We also showed that KPS scores are independent predictors of graft and patient survival after LT after adjusting for other confounders. The improvement in KPS scores after LT reached a plateau at one year and thereafter there was no significant improvement. Those who did not demonstrate significant improvement in KPS scores after LT had worse outcomes, and this was most obvious in the low KPS group.

The interaction between performance status, as assessed by any subjective tools, and outcomes is very complex and has been debated in medical literature in detail before.[2–9] Despite its subjectivity, performance status has been shown to be predictor of survival in many conditions including in patients with cirrhosis.[2–9,12,13,21,22] We believe that the performance status adds another dimension to complete patient assessment in those with advanced cirrhosis. The KPS is perhaps a reflection of the overall physical and mental status of the patients with cirrhosis that could not be quantified by objective parameters or disease severity indices such as MELD and Child-Pugh scores. In our study, KPS score was an independent predictor of graft and patient survival after adjusting for other known recipient and donor confounders. Additionally, those who did not show significant improvement in KPS three months after LT had relatively poor outcomes. These differences were most obvious in those who had poor KPS at the time of LT and in that group only 33% survived for one year if they had no improvement in KPS scores. We may have underestimated the impact of KPS since we had excluded KPS scores assessed within three months of LT, as patients are considered to be recovering from surgery, and additionally, we had excluded those on life support (those on vasopressors for circulatory failure) or mechanical ventilation at the time of LT. Our data show that those who have low KPS at the time of LT and do not show any improvement in KPS three months after LT will have very poor survival outcomes.

We tried to identify pre- and post-LT risk factors that could predict the lack of improvement in KPS after LT in the low KPS group. Our analysis identified a few potential risk factors including older age, HCV, HCC and acute rejection episodes after LT, but counterintuitively, those who did not improve had less severe liver disease at the time of LT. We also examined the effect of transplant center volume and found no association. Low serum albumin was associated with non-improvement in KPS after LT, and one could only speculate whether this was a reflection of sarcopenia. It is possible that there are other potential post-LT complications and comorbidities that are not captured in the UNOS dataset that could explain the non-improvement and higher mortality in this group. Future studies should explore the reasons, especially the role of comorbidities, for this observation in a prospective manner. If modifiable reasons are identified, we may be able to intervene.

Recently there has been a renewed interest in nutritional and functional status of patients with advanced liver diseases and those awaiting LT. Many potential tools have been proposed including assessment of sarcopenia, frailty index and

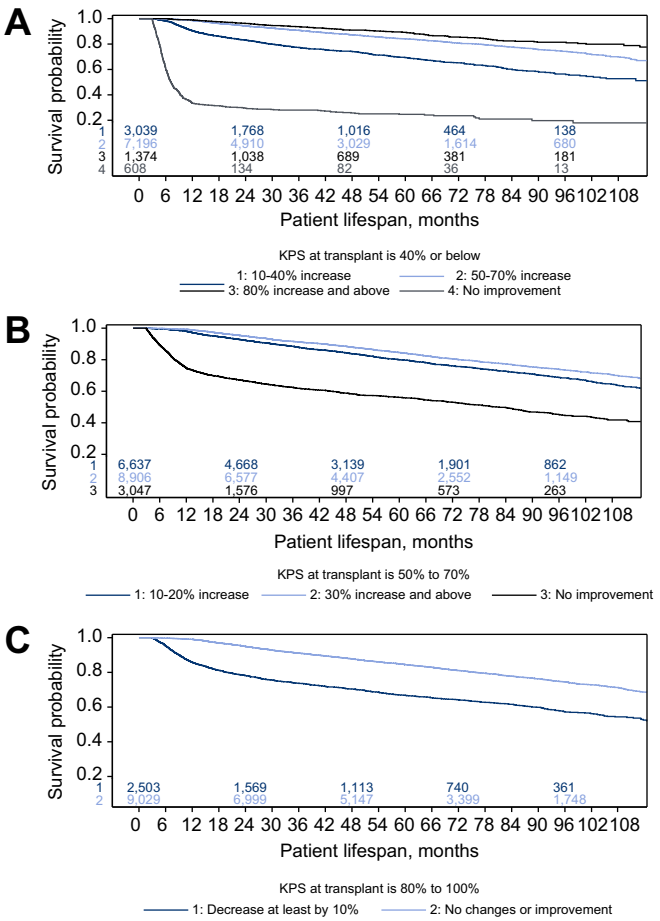

Fig. 4. The post-transplant survival probability for patients with low, intermediate and high KPS scores. (A) Patients with low KPS scores (≤40%) at the time of transplant by Kaplan-Meier survival analysis (*p* value from log-rank test <0.0001). (B) Patients with intermediate KPS scores (50–70%) at the time of transplant (*p* value from log-rank test <0.0001). (C) Patients with high KPS scores (80–100%) at the time of transplant (*p* value from log-rank test <0.0001). KPS, Karnofsky performance status.

six-minute walking distance, but it is not known whether these tools could be applied for epidemiological studies in potential LT recipients.[14–18,23–26] The KPS scores, although subjective, can be easily administered and repeated many times without significant inter-observer variability. Based on our study, we believe that KPS scores could be a useful tool for assessment of patients with advanced liver disease.[3,4,12,13] This is further supported by a recent study of 954 hospitalized patients with cirrhosis where Tandon *et al.* showed that low KPS scores, assessed a week after hospital discharge, were associated with very high mortality; the mortality rates were 23%, 11% and 5% in the low, intermediate and high KPS score groups respectively.[12] Moreover, three-month post discharge mortality could be predicted using a model that included KPS scores, age and MELD, and this model was better than MELD score alone in predicting three-month mortality. In another elegant study using UNOS data, Orman *et al.* showed that low KPS scores were associated with a higher waitlist mortality after adjusting for other important confounders.[13] As discussed earlier, a study from the United Kingdom and Ireland had shown that ECOG performance status scores were associated with 90-day post-LT survival.[13] In that study that included 3,973 LT recipients, post-LT mortality increased from 5.3% in those with functional status 1 (able to carry out normal activity without restriction) to 24.8% in status 5 (completely reliant on nursing and medical care). In another study that examined post-LT outcomes in older adults (≥50 years), poor pre-LT functional status was found to be associated with increased five-year mortality.[27] Our study corroborates the above observations in a large unselected cohort of liver transplant recipients from the USA, and moreover shows that post-LT KPS scores also predict survival.

One of the limitations of using KPS scores is the lack of evidence for reliability in patients with cirrhosis, where the presence of hepatic encephalopathy could influence KPS score assessment. In multivariate analysis, we adjusted survival for hepatic encephalopathy, and yet KPS scores remained predictive of outcomes. The reliability and reproducibility of KPS scores is well established in cancer literature.[2–4] Moreover, we believe that the variability in the assessment is significantly diminished by grouping them into low, intermediate and high KPS scores. Another limitation of our study is the lack of granularity in post-LT complications that could have a significant impact on KPS scores. The consistency in assessment of KPS at defined intervals after LT is also a matter of concern. Despite the above limitations, our observations suggest that KPS before and after LT is a useful predictor of survival.

In conclusion, we have shown that low KPS scores are associated with worse outcomes after LT. Moreover, the absence of improvement on KPS scores is associated with poor survival especially in those with low KPS at the time of LT. Multidisciplinary approaches to improve performance status should be tested in a prospective manner to determine whether survival outcomes could be improved in LT candidates.

Table 3. The survival probabilities stratified by a KPS score at transplant based on post-LT KPS scores at 3–12 months.

	Low KPS at LT (≤40%)				Intermediate KPS at LT (50–70%)			High KPS at LT (80–100%)	
Time since transplant	No improvement (≤0%)	10–40% increase	50–70% increase	≥80% increase	No improvement (≤0%)	10–20% increase	≥30% increase	No improvement (<0%)	≥0% increase
6 months	0.62	0.98	1.0	1.0	0.89	1.0	1.0	0.95	1.0
1 year	0.33	0.91	0.99	0.99	0.75	0.98	0.99	0.86	0.99
2 years	0.29	0.83	0.94	0.96	0.67	0.93	0.95	0.78	0.95
3 years	0.28	0.77	0.91	0.94	0.62	0.88	0.92	0.74	0.91
5 years	0.25	0.69	0.84	0.89	0.56	0.8	0.85	0.67	0.84
10 years	0.18	0.48	0.64	0.74	0.4	0.61	0.67	0.51	0.68

The survival probabilities were estimated using Kaplan-Meier analysis for the three groups (low, intermediate and high KPS score) at the time of LT, and stratified by changes in KPS score between the time of transplant and 3–12 months post-transplant. KPS, Karnofsky performance status; LT, liver transplant.

Table 4. Characteristics of patients for the group with a low KPS (≤40%) at the time of liver transplant stratified by changes in KPS between 3–12 months after LT.

Variables	Low KPS at LT ≤40%						
	Changes in KPS between LT and during (3–12 months) follow-up*						
	≤0% KPS change (declined) n = 608	*p* value	10–40% KPS increase n = 3,039	*p* value	50–70% KPS increase n = 7,196	*p* value	≥80 KPS increase n = 1,374
Age, mean (SD)	55.5 (10)	<0.0001	55.3 (9.3)	<0.0001	53.7 (10.2)	<0.0001	49.8 (12.2)
Female, n (%)	228 (37.5%)	0.3	1,026 (33.8%)	<0.0001	2,592 (36%)	0.004	551 (40.1%)
Ethnicity, n (%)							
White	425 (69.9%)	0.08	2,189 (72%)	<0.0001	4,975 (69.1%)	0.02	906 (65.9%)
African-American	62 (10.2%)	0.7	291 (9.6%)	0.2	717 (10%)	0.3	148 (10.8%)
Hispanic	101 (16.6%)	0.9	431 (14.2%)	0.03	1,142 (15.9%)	0.4	231 (16.8%)
Asian	14 (2.3%)	0.02	79 (2.6%)	0.0005	274 (3.8%)	0.2	63 (4.6%)
Other	6 (1%)	0.1	49 (1.6%)	0.5	88 (1.2%)	0.05	26 (1.9%)
BMI, mean (SD)	28.27 (5.9)	0.2	28.76 (5.9)	0.7	28.73 (5.96)	0.8	28.69 (6.22)
Morbid obesity, n (%)	23 (3.8%)	0.3	126 (4.1%)	0.3	304 (4.2%)	0.3	67 (4.9%)
Type 2 DM, n (%)	130 (21.8%)	0.0002	725 (24.6%)	<0.0001	1,334 (19.1%)	0.0004	201 (15%)
Moderate/severe ascites, n (%)	244 (40.5%)	0.004	1,222 (40.4%)	<0.0001	3,111 (43.5%)	0.006	644 (47.6%)
INR, mean (SD)	2.18 (1.01)	<0.0001	2.13 (1.45)	<0.0001	2.34 (1.5)	<0.0001	2.78 (1.89)
INR ≥2.5, n (%)	175 (28.8%)	<0.0001	785 (25.8%)	<0.0001	2,410 (33.5%)	<0.0001	659 (48%)
Serum creatinine, mean (SD)	1.73 (1.2)	<0.0001	1.61 (1.15)	<0.0001	1.83 (1.36)	<0.0001	2.14 (1.53)
Creatinine ≥2, N (%)	167 (27.6%)	<0.0001	752 (24.8%)	<0.0001	2,334 (32.4%)	<0.0001	570 (41.5%)
Dialysis, n (%)	74 (12.2%)	<0.0001	285 (9.4%)	<0.0001	993 (13.8%)	<0.0001	308 (22.4%)
Albumin, mean (SD)	2.97 (0.73)	0.08	3.01 (0.75)	0.3	3.06 (0.77)	0.4	3.04 (0.79)
Bilirubin, mean (SD)	11.51 (11.9)	<0.0001	10.76 (12.1)	<0.0001	14.06 (13.4)	<0.0001	19.6 (14.1)
Bilirubin ≥12, n (%)	193 (31.7%)	<0.0001	888 (29.2%)	<0.0001	2,953 (41%)	<0.0001	836 (60.8%)
MELD score, mean (SD)	26.4 (9.8)	<0.0001	24.9 (10.2)	<0.0001	28.08 (10.15)	<0.0001	33.4 (8.3)
MELD score ≥30, n (%)	234 (38.5%)	<0.0001	1,010 (33.2%)	<0.0001	3,432 (47.7%)	<0.0001	969 (70.5%)
Encephalopathy 3–4 grade, n (%)	91 (15.1%)	<0.0001	425 (14.1%)	<0.0001	1,107 (15.5%)	<0.0001	333 (24.6%)
Diagnosis, n (%)							
HCC	158 (26%)	<0.0001	842 (27.7%)	<0.0001	1,476 (20.5%)	<0.0001	142 (10.3%)
HCV	190 (31.3%)	<0.0001	834 (27.4%)	<0.0001	1,935 (26.9%)	<0.0001	296 (21.5%)
Alcoholic cirrhosis	79 (13%)	0.023	472 (15.5%)	0.2	1,208 (16.8%)	0.8251	234 (17%)
Autoimmune hepatitis	14 (2.3%)	0.09	73 (2.4%)	0.01	228 (3.2%)	0.2391	52 (3.8%)
NASH and cryptogenic cirrhosis	84 (13.8%)	0.3	425 (14%)	0.09	970 (13.5%)	0.1845	167 (12.2%)
PBC and PSC	33 (5.4%)	0.04	183 (6%)	0.01	513 (7.1%)	0.2144	111 (8.1%)
Other	50 (8.2%)	<0.0001	210 (6.9%)	<0.0001	866 (12%)	<0.0001	372 (27.1%)
Time to transplant in days, median (Q1; Q3)	66 (11; 239)	<0.0001	87 (17; 305)	<0.0001	41 (8; 210)	<0.0001	13 (4; 102)
Donor risk index, mean (SD)	1.82 (0.43)	0.04	1.8 (0.44)	0.1	1.78 (0.43)	0.6224	1.78 (0.41)
Acute rejection episode between LT and discharge, n (%)	38 (6.3%)	0.4	171 (5.6%)	0.6	320 (4.4%)	0.2	72 (5.2%)
Transplant center by volume							
<20 LT/year	17 (2.8%)	0.002	68 (2.2%)	<0.0001	251 (3.5%)	<0.0001	83 (6%)
20–50 LT/year	132 (21.7%)	0.02	836 (27.5%)	0.5	1,729 (24%)	0.04	366 (26.6%)
>50 LT/year	459 (75.5%)	0.0003	2,135 (70.3%)	0.05	5,216 (72.5%)	<0.0001	925 (67.3%)

* *p* values are for inferences relative to the group with KPS improved by ≥80%. BMI, body mass index; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; KPS, Karnofsky Performance Status; LT, liver transplant; MELD, model for end-stage liver disease; NASH, non-alcoholic steatohepatitis; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Paul Thuluvath, Avesh Thuluvath and Yulia Savva contributed to the study concept, design, analysis, interpretation of data, drafting of manuscript.

Yulia Savva did the statistical analysis.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jhep.2018.05.025.

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