Poor Performance Status Predicts Mortality After Living Donor Liver Transplantation

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Background/Aims: Performance status may adversely affect living donor liver transplantation (LDLT) outcomes. We present our data regarding performance status and posttransplantation survival in a large LDLT cohort. **Methods:** Patients with ABO incompatibility, of pediatric age, with acute liver failure, with hepatocellular carcinoma, and/or who had incomplete data were excluded. Two hundred sixty adults who had decompensated cirrhosis and underwent LDLT from January 2016 to March 2018 were included. Performance status was assessed by Karnofsky Performance Score (KPS). The data are depicted as number, mean (SD), or median (25–75 interquartile range [IQR]). **Results:** The cohort included 232 males and 28 females, aged 48.3 ± 9.8 years. Etiology of liver disease was hepatitis B in 33, hepatitis C in 19, alcohol related in 120, nonalcoholic steatohepatitis/cryptogenic in 68, and other etiologies in 20 patients. The mean Child's score was 9.6 ± 1.7 , Model for End-Stage Liver Disease (MELD) score was 18.0 ± 5.8 , and donor age was 33.4 ± 9.9 years. Forty-one recipients died at median follow-up of 11 months. The KPS was 100 in 6 (no deaths), 90 in 53 (2 deaths), 80 in 93 (12 deaths), 70 in 69 (14 deaths), 60 in 26 (8 deaths), and 50 in 13 (5 deaths) ($P = 0.003$). The area under the receiver operating characteristic curve of KPS to predict mortality was 0.698 ($P = 0.000$, 95% confidence interval [CI] = 0.616–0.780), and the best sensitivity (63%) and specificity (67%) were achieved at $KPS \leq 70$. The survivors and nonsurvivors had a significant difference with respect to KPS (77.6 ± 10.9 versus 69.5 ± 10.9 , $P = 0.000$), age of the patient (47.8 ± 9.4 versus 51.1 ± 11.7 ; $P = 0.047$), postoperative infections (53.8% versus 85.3%, $P = 0.001$), and need of packed red cells transfusion. Multivariate analysis (Cox proportional-hazard) showed KPS (hazard ratio [HR] = 0.96, 95% CI = 0.93–0.99, $P = 0.007$), postoperative infections (HR = 2.3, 95% CI = 1.04–5.1, $P = 0.038$), and recipient age (HR = 1.03, 95% CI = 1.002–1.07, $P = 0.039$) as predictors of mortality. **Conclusion:** Pretransplant performance status is one of the predictors of mortality after LDLT. (J CLIN EXP HEPATOL 2020;10:37–42)

In the last few years, there has been a renewed interest to assess nutritional, functional, and performance status of patients with cirrhosis. These factors not only affect survival but also predict risk of hospitalizations and transplant waitlist mortality. Efforts to improve the nutritional and functional status of patients with cirrhosis may increase their prospect of survival. The Karnofsky Performance Score (KPS) assesses the overall performance status of patients and has stood the test of time since almost 70 years of its inception into clinical medicine. Administered by health-care workers and self-reported by patients, KPS differentiates patients on a scale of 0–100%, in increments of 10, where 100% is normal activity, 0% is

dead, and decreasing values suggest progressive symptom burden and functional deterioration. KPS categories are further grouped into three broad subgroups: able to work (80–100; KPS A), unable to work but able to provide self-care (40–70; KPS B), and unable to care for self (10–30; KPS C). Although KPS is subjective in nature, it encompasses those aspects of health and frailty that are difficult to measure objectively.^{1,2} KPS has been used as an instrument to predict waitlist dropout due to death in recent studies.^{3–6} It has also shown to be robust in predicting post-liver transplantation (LT) outcomes.⁵ We aim to evaluate the role of KPS in predicting post-living donor liver transplantation (LDLT) mortality in the present study.

Keywords: performance status, MELD, infection, LDLT

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Abbreviations: BMI: body mass index; CTP: Child-Turcotte-Pugh; GRWR: graft-to-recipient weight ratio; KPS: Karnofsky Performance Score; LDLT: living donor liver transplantation; HCC: hepatocellular carcinoma; MELD: Model for End-Stage Liver Disease; MELD-Na: MELD sodium score

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MATERIAL AND METHODS

The study is a retrospective analysis of a prospectively collected database from January 2016 to March 2018. The data were analyzed until May 2018. The institutional review board approved the study. Of 495 transplantations in this defined period, a total of 260 consecutive recipients who underwent LDLT for

decompensated cirrhosis were included in the final analysis. Patients with ABO incompatibility, of pediatric age, with acute liver failure, with hepatocellular carcinoma (HCC), or who had incomplete data were excluded to keep a homogenous group of decompensated cirrhosis only as indication of LDLT. The KPS was measured at the time of case discussion (presentation) in multidisciplinary team (hepatology, anesthesia, and surgeons), which occurred < 1 week before LT. The donor and recipient selection criteria are described in detail elsewhere.^{7,8} In short, all donors were 18–55 years old, were blood group-matched relatives, and underwent detailed systemic, liver, and psychological evaluation. Donors were accepted when they were deemed suitable after an extensive four-phase evaluation. Suitability criteria included 18–55 years of age, normal biochemical laboratory values, hepatic steatosis <20%, body mass index (BMI) < 30, graft-to-recipient weight ratio (GRWR) > 0.8, future liver remnant >30%, exclusion of comorbidity, and either spouse or first- or second-degree relative as a donor. Informed written consent was obtained from all the donors about the potential morbidity and mortality associated with the procedure. Some potential liver donors with fatty liver were advised to repeat evaluation after weight reduction. Approval from a legal authorization committee, as required by the Indian Transplantation of Human Organs Act, was obtained for all. All recipients underwent a detailed pre-transplant evaluation to assess the extent of primary disease and any comorbidity, performance status, as well as renal, cardiac, and pulmonary function. The allocated Model for End-Stage Liver Disease (MELD) was the worst score within 4 weeks preceding the transplant. An LDLT setting allowed the patient to be optimized for transplantation. A policy of early extubation, early enteral feeding, removal of catheters and drainage tubes, and a need-based schedule of immunosuppression with tacrolimus, mycophenolate, and steroids was pursued postoperatively. While no prospective donor-recipient matching was done on the basis of donor age, suboptimal live donor grafts (grafts with low graft-to-recipient weight ratio, or GRWR, and steatosis) were used only in well-preserved patients, while an attempt was made to transplant the poorer risk patients with higher volume grafts of good quality. We aimed for GRWR >0.8 during pretransplantation workup. In selected cases, lower GRWR grafts with a portal pressure-reducing measure were accepted. Infections were defined as positive cultures in index admission. The posttransplant immunosuppression protocol consisted of a triple regimen including tacrolimus (or cyclosporine in some patients with tacrolimus toxicity), mycophenolate mofetil, and prednisolone. Steroids were stopped at 3 months in all recipients except those with a diagnosis of autoimmune hepatitis in whom prednisolone was continued at

Table 1 Comparison of KPS $\geq$ 80 (n = 152) and KPS $\leq$ 70, (n = 108).

Parameter	KPS $\geq$ 80 (n = 152)	KPS $\leq$ 70 (n = 108)	P
Age (years)	47.2 $\pm$ 9.8	49.8 $\pm$ 9.8	0.042
Sex, female: male	10:142	17:191	0.023
Child's score	9.4 $\pm$ 1.7	10.0 $\pm$ 1.6	0.007
MELD score	17.5 $\pm$ 5.5	18.8 $\pm$ 6.1	0.083
MELD sodium	18.5 $\pm$ 6.3	20.9 $\pm$ 7.4	0.006
BMI, kg/m ²	25.7 $\pm$ 4.0	25.0 $\pm$ 4.6	0.192
GRWR	0.91 $\pm$ 0.18	0.95 $\pm$ 0.21	0.149
Red blood cells transfusion (units)	5.1 $\pm$ 3.4	6.6 $\pm$ 3.7	0.002
Bilirubin, mg/dl	3.7 (2–6.8)	4 (1.9–8.7)	0.641
Albumin, g/dl	3.0 $\pm$ 0.44	2.9 $\pm$ 0.59	0.129
Creatinine, mg/dl	0.88 $\pm$ 0.35	1.0 $\pm$ 0.55	0.041
International normalized ratio (INR)	1.67 $\pm$ 0.58	1.67 $\pm$ 0.50	0.925
Sodium, meq/l	136.2 $\pm$ 5.2	133.8 $\pm$ 5.9	0.001
Hemoglobin, g/dl	9.9 $\pm$ 1.9	9.2 $\pm$ 1.4	0.002
Etiology			
Alcohol: hepatitis C: hepatitis B: others	68:13:24:47	52:6:9:41	0.201
Ascites, n (%)	131 (86.1%)	105 (97.2%)	0.002
History of hepatic encephalopathy in past, n (%)	68 (44.7%)	49 (45.3%)	1.000
Variceal bleed n (%)	49 (32.2%)	28 (25.9%)	0.334
Total ICU stay (days)	5.4 $\pm$ 1.7	6.1 $\pm$ 2.4	0.010
Hospital stay (days)	15.5 $\pm$ 5.6	18.2 $\pm$ 8.5	0.002
Infection	84 (55.2%)	69 (63.8%)	0.201

BMI: body mass index; GRWR: graft to-recipient weight ratio; ICU: intensive care unit; KPS: Karnofsky Performance Score; MELD: Model for End-Stage Liver Disease.

a dose of 5 mg per day. Tacrolimus level was maintained at 7–10 ng/ml in the first month and 5–8 ng/ml thereafter.

Statistical Methods

Data are shown as number, percentage, median (standard deviation [SD]), or median (25–75 interquartile range [IQR]). The Kaplan-Meier survival curve was used to show survival with time across various KPS groups for entire follow-up (median = 11 months) and for initial 3 months. Both survivors and nonsurvivor groups and KPS groups were compared with Fisher exact test/Chi-square test (categorical data) or student's *t* test (continuous data)/Mann-Whitney test (nonparametric data). Univariate and multivariate analyses (Cox proportional-hazard method) were

Figure 1 Posttransplant survival among various KPS groups for entire follow-up.

used to identify factors predictive of mortality. The factors with a P value < 0.05 in the univariate analysis were analyzed by multivariate analysis. A two-tailed P value < 0.05 is considered significant.

RESULTS

The study group comprised 260 adult LDLT recipients: 27 were females and 233 were males. The mean age of recipients was 48.3 ± 9.8 years. Etiology of liver disease was alcohol related in 120, nonalcoholic steatohepatitis/cryptogenic in 68, hepatitis B virus in 33, hepatitis C virus in 19, and others in 20 patients. The mean Child-Turcotte-Pugh (CTP) score was 9.6 ± 1.7 , and mean MELD score was 18.0 ± 5.8 . The mean donor age was 33.4 ± 9.9 years. The mean BMI of the study group was 25.4 ± 4.3 kg/m² (not corrected for ascites). GRWR was 0.93 ± 0.19 . A total of 41 recipients died at a follow-up of 11.6 ± 8.4 months. The KPS was 100 in 6 (no deaths), 90 in 53 (2 deaths), 80 in 93 (12 deaths), 70 in 69 (14 deaths), 60 in 26 (8 deaths), and 50 in 13 (5 deaths) ($P = 0.003$). The area under the receiver operating characteristic curve of KPS to predict mortality was 0.698 ($P = 0.000$, 95% CI = 0.616–0.780). The best sensitivity (63%) and specificity (67%) to predict postoperative mortality were achieved at a KPS cutoff of ≤ 70 . A total of 28 patients (10.7%) had acute-on-chronic liver failure, 3 of 14 died in the KPS ≥ 80 group, and 4 of 14 died in the KPS ≤ 70 group, $P = 1.0$.

Table 2 Comparison of Survivors ($n = 219$) and Nonsurvivors ($n = 41$).

Parameter	Survivors ($n = 219$)	Nonsurvivors ($n = 41$)	P value
Age	47.8 ± 9.4	51.1 ± 11.7	0.047
Sex, male:female	199:20	34:7	0.158
Donor age (years)	33.7 ± 9.9	31.5 ± 9.9	0.191
Child's score	9.6 ± 1.7	9.9 ± 1.7	0.990
MELD score	17.9 ± 5.6	18.9 ± 6.9	0.332
MELD sodium	19.3 ± 6.4	20.7 ± 8.9	0.230
BMI kg/m ²	25.3 ± 4.1	25.8 ± 5.0	0.484
GRWR	0.94 ± 0.19	0.89 ± 0.19	0.193
Cold ischemia time	118.9 ± 44.9	131.7 ± 46.1	0.108
Warm ischemia time	49.0 ± 16.3	50.9 ± 12.9	0.513
Red blood cell transfusion (units)	5.5 ± 3.5	7.0 ± 4.0	0.043
Bilirubin, mg/dl	$4.0 (2.1-7.3)$	$3.5 (1.5-5.4)$	0.714
Albumin, g/dl	3.0 ± 0.5	2.9 ± 0.5	0.625
Creatinine, mg/dl	0.91 ± 0.46	1.0 ± 0.3	0.154
INR	1.66 ± 0.53	1.70 ± 0.66	0.702
Sodium, meq/l	135.4 ± 5.6	134.1 ± 5.5	0.155
KPS	77.6 ± 10.9	69.5 ± 10.9	0.000
KPS ≤ 70 , n (%)	81 (36.9%)	27 (65.8%)	0.001
Etiology			
Alcohol:hepatitis C:hepatitis B:others	102:18:31:68	18:1:2:20	0.066
Ascites, n (%)	196 (89.5%)	40 (97.6%)	0.141
History of hepatic encephalopathy in past, n (%)	91 (41.6%)	26 (63.4%)	0.11
Variceal bleed n (%)	66 (30.1%)	11 (26.8%)	0.714
Total ICU stay (days)	5.6 ± 1.9	6.2 ± 3.7	0.122
Hospital stay (days)	15.9 ± 6.1	20.0 ± 10.5	0.001
Infection	118 (53.8%)	35 (85.3%)	0.001

BMI: body mass index; GRWR: graft-to-recipient weight ratio; ICU: intensive care unit; KPS: Karnofsky Performance Score; MELD: Model for End-Stage Liver Disease.

Parameters Associated with KPS ≤ 70

When patients with KPS ≤ 70 ($n = 108$) were compared with patients with KPS ≥ 80 ($n = 152$), patients with low KPS had significantly higher age, higher Child's score, higher MELD sodium score (MELD-Na), low serum sodium, higher creatinine level, and higher percentage of having ascites as shown in Table 1. It is important to note that MELD was not significantly different between the 2 groups. Patients in the KPS ≤ 70 group required a higher number of packed red blood cell (PRBC) transfusion and had significantly longer intensive care unit (ICU) and hospital stays (Table 1). Although a higher number of patients

Table 3 Univariate and Multivariate Analysis of Factors Predicting Mortality by Cox Proportional-Hazard Method.

Variables	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age	1.04 (1.00–1.07)	0.038	1.03 (1.002–1.07)	0.039
Sex	0.49 (0.22–1.11)	0.086		
Donor age	0.98 (0.95–1.01)	0.269		
Child's score	1.07 (0.90–1.28)	0.459		
MELD	1.03 (0.98–1.08)	0.300		
Graft-to-recipient weight ratio	0.24 (0.04–1.45)	0.121		
PRBC transfusion (units)	1.08 (1.00–1.15)	0.038	1.03 (0.95–1.11)	0.390
KPS	0.95 (0.93–0.98)	0.000	0.96 (0.93–0.99)	0.007
Postoperative infection	3.01 (1.39–6.50)	0.005	2.32 (1.04–5.1)	0.038

CI: confidence interval; HR: hazard ratio; KPS: Karnofsky Performance Score; PRBC, packed red blood cell.

in the KPS ≤ 70 group developed infections, it was not statistically different.

KPS and Survival

The Kaplan-Meier survival curves for recipients with various KPS are shown in [Figure 1](#) (entire follow-up) and [supplementary Figure 1](#) (initial 3 months). The risk of mortality increased as KPS decreased, as shown in [Figure 1](#) and [supplementary Figure 1](#). Comparison of survivors and nonsurvivors (during the entire follow-up) is shown in [Table 2](#). The survivors were significantly younger (47.8 ± 9.4 versus 51.1 ± 11.7 years, $P = 0.047$), had a better KPS (77.6 ± 10.9 versus 69.5 ± 10.9 , $P = 0.000$), and needed a less number of PRBC transfusion (entered as continuous data) during surgery. There was no significant difference with respect to the other parameters. The univariate and multivariate analyses are shown in [Table 3](#). The multivariate analysis showed KPS, postoperative infections, and recipient age as important predictors of mortality as shown in [Table 3](#). The majority of mortalities occurred in first three months, and infection was a major cause. Lower KPS was associated more commonly with infection. Infections occurred in 3 of 6 (50%) in the KPS 100 group, 30 of 53 (56.6%) in the KPS 90 group, 51 of 93 (54.8%) in the KPS 80 group, 39 of 69 (56.5%) in the KPS 70 group, 18 of 26 (69.2%) in the KPS 60 group, and 12 of 13 (92.3%) in the

KPS 50 group, although it was not statistically significant among various groups ($P = 0.143$). We performed a separate analysis of survivors and nonsurvivors for initial 3 months. The following were significantly different between survivors ($n = 230$) and nonsurvivors ($n = 30$): age of recipients (47.7 ± 9.6 years versus 52.8 ± 11.0 years, $P = 0.007$), KPS (77.1 ± 11.1 versus 70.0 ± 10.5 , $P = 0.001$), postoperative infections [$129/230$ (56%) versus $24/30$ (80%), $P = 0.012$] and PRBC transfusion (5.6 ± 3.5 versus 7.1 ± 4.2 , $P = 0.036$). On multivariate analysis, age [HR = 1.05 (95% CI = 1.01–1.09), $P = 0.013$] and KPS [HR = 0.96, (0.93–0.99), $P = 0.020$] were significant factors. Postoperative infection [HR = 2.25 (0.89–5.69), $P = 0.085$] and PRBC transfusion [HR = 1.04 (0.96–1.13), $P = 0.305$] were not significant on multivariate analysis.

DISCUSSION

The present study shows lower KPS and higher age of recipients are associated with mortality after LDLT. In fact, disease severity scores were not different in survivors and nonsurvivors. LDLT situation allowed optimization of recipients who had sepsis, renal dysfunction, and poor performance status. Recently, there has been abundant ongoing research in assessment of the nutritional, functional, and performance status of patients with cirrhosis, especially those awaiting LT. KPS is one of the many perspectives that look at frailty. Others include the Eastern Cooperative Oncology Group performance status, 6-min walk distance, sarcopenia, Fried Frailty Index, Activities of Daily Living Scale, and short physical performance battery, to name a few.^{9–12} KPS scoring has shown modest interobserver reliability, reproducibility, and validity in various clinical and research settings.^{13,14}

KPS predicts mortality in both pretransplant and post-transplant patient population. Orman *et al*⁴ used the United Network for Organ Sharing (UNOS) database to perform a retrospective study to identify the association between KPS and mortality in patients with cirrhosis. Of the 79,092 patients who were studied, 44% were categorized into KPS category A (KPS 80%–100%), 43% in category B (KPS 50%–70%), and 13% in category C (KPS 10%–40%). Understandably, the proportion with KPS B and C increased in transplant waitlisted patients, with a concomitant decrease in KPS A. As KPS critically worsened (90–100%), such patients were less likely considered for transplant by risk-averse programs given the negative impact on posttransplant outcomes. The authors concluded that for those without HCC, worsening KPS was associated with increased mortality and transplantation.⁴ The model including KPS and age was shown to be better than MELD score alone and MELD score + age to predict mortality in patients with cirrhosis.³ A recent study that included 50,417 patients listed with UNOS between 2006 and 2016 showed that KPS, before and after LT, is an

independent predictor of graft and patient survival after adjusting for other confounders. Patients with low KPS were relatively young, more obese, had grade 3–4 hepatic encephalopathy, higher serum creatinine and MELD scores, and lower serum albumin.⁵ A very low KPS (<20) is a risk factor for pulmonary thromboembolism and also contributes significantly to mortality after LT.¹⁵

We found that a higher Child's score (but not MELD) was associated with a low KPS. This is likely to be due to the inclusion of ascites and serum albumin in the score, as they reflect the general status of the patient much more than the 3 parameters in the MELD score. This is corroborated by the fact that we found ascites to be associated with low KPS. Apart from ascites and Child score, older age and low serum sodium were also associated with low KPS. These findings were somewhat predictable, as older patients with ascites and hyponatremia are sicker at equivalent MELD scores than patients without ascites or hyponatremia.¹⁶ The impact of hyponatremia is reflected by MELD-Na score, which was significantly higher in patients with poor KPS.

Several performance scores have been studied in patients with cirrhosis listed for LT. Six-minute walk distance has been shown to be useful in patients with cirrhosis, cardiac diseases, or lung diseases. Carey *et al.*¹⁷ showed that 6-min walking distance was significantly reduced in patients awaiting LT and a pretransplant 6-min walking distance <250 m was a risk factor for death for those on the waitlist. In another study of 213 patients, 6-min walking distance was better than sarcopenia to predict risk of mortality in patients awaiting LT.¹⁸ A combination of MELD-Na and frailty index (grip strength, chair stands, and balance) predicted mortality better than MELD-Na in a study by Lai *et al.*¹⁹ Frailty strongly predicted waitlist mortality and quality of life, even after adjustment for liver disease severity scores.^{9,20} Thus, performance scores add to understanding to severity of liver disease and risk of mortality in addition to currently available liver disease severity scores. It is to be seen if improvement of performance leads to improvement of outcomes. Because LDLT is a planned surgery, improving performance status can lead to improved outcomes after transplantation.

In our study, although prediction of post-LT mortality by KPS was modest, it was one of the important factors on multivariate analysis. However, KPS alone cannot accurately predict post-LT mortality as various factors such as surgical complications, infections, sarcopenia/nutritional status, and infections also play a major role. Although data regarding KPS and posttransplant mortality are available mainly in cadaveric liver transplant setting, the present study shows that it is applicable for setting of LDLT also despite opportunity to optimize patients before surgery.

Our study had a few limitations: It is retrospective and did not include other factors associated with functional

decline, such as nutrition, assessment of functional reserve, sarcopenia, and exercise tolerance. Being retrospective does not affect the primary outcome (mortality). In addition, KPS does not reflect nutritional status and sarcopenia. However, notwithstanding these caveats, KPS reflects the overall physical and mental well-being of patients with cirrhosis, a view that time-tested scoring systems such as Child-Turcotte-Pugh and MELD fail to address. KPS is also a useful modality to base important decision-making discussions with patient and their families. It is an easy-to-use, easy-to-understand, and no-cost point-of-care instrument, an advantage in cost-restricted health-care systems. Our study represents a large post-LDLT cohort from a single center (after exclusion of confounders, *e.g.*, HCC). What sets our study apart is that it was performed in an LDLT setting, whereas the Western data predominantly originate from cadaveric LT. We believe that patients with low KPS should be quickly optimized medically and LDLT should be performed before it is too late. Better prognostic scoring systems should be developed including KPS for prognostication in LDLT setting for posttransplant outcome and identifying patients who are too sick to transplant and should not be subjected to living donation when it is futile. The present study raises 2 vital questions that need to be answered by future studies: whether posttransplant mortality may be better predicted by adding KPS to other established parameters and if improvement in KPS can reduce the risk of post-LT mortality.

CONFLICTS OF INTEREST

The authors have none to declare.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jceh.2019.06.006>.