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Functional status at listing predicts waitlist and post-transplant mortality in pediatric liver transplant candidates

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Abstract

Functional impairment is associated with mortality in adult liver transplant candidates. This has not been studied in pediatric liver transplant candidates. UNOS STAR files were used to investigate functional status, waitlist mortality, and post-transplant outcomes in children<18, listed 2006–16 for primary liver transplant. Functional status was categorized using the Lansky play-performance scale (LPPS), as normal/good (80–100%), moderately impaired (50–70%), or severely impaired (10–40%) by center assessment. Among 3,250 children not listed as Status 1A, 62% had LPPS 80–100 at listing, 25% were 50–70, 13% were 10–40. Children with LPPS 10–40 at listing were more likely to die on the waitlist (SHR 1.85, 95% CI 1.09–3.13, p=0.02) in analyses adjusting for being on a ventilator, breathing support, or dialysis and other illness severity measures. For the 2,565 children transplanted, LPPS 10–40 *at listing* drastically increased mortality risk by 1 year *post-transplant* (HR 5.77, 95%CI 3.05–10.91, p<0.0005). LPPS 10–40 and 50–70 both increased the risk of graft loss by 1 year. Functional status is an independent predictor of waitlist and post-transplant mortality in pediatric liver transplant candidates. Validated tools for assessment of functional status in these children would improve our ability to predict mortality risk—and to appropriately prioritize them for transplant.

INTRODUCTION:

Impaired functional status is increasingly recognized as a risk factor for morbidity and mortality in adult liver transplant candidates, both on the waitlist and post-transplant, but has not been thoroughly investigated in pediatric liver transplant candidates. In adults, Karnofsky Performance Status (KPS) is a widely used metric of functional impairment. KPS is scored by a healthcare provider or staff as 0–100%, in increments of 10, ranging from 100% (normal, no limitations) to 0% (dead). In analyses of the United Network for Organ Sharing (UNOS) database, KPS at listing predicts waitlist mortality in adult liver transplant

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candidates, even after adjusting for Model End-Stage Liver Disease (MELD) score and other risk factors. For transplanted patients, low KPS at transplant predicts post-transplant mortality—within 90 days and 1 year--graft loss,[1–3] as well as increased health care resource utilization.[4]

The UNOS registry currently includes data on functional status in pediatric liver transplant candidates using the Lansky Play-Performance Scale (LPPS), which parallels the KPS. The LPPS was developed and validated to measure global functional status specifically in children with cancer, aged 1–16 years.[5] It has been used to assess functional status in various groups of children with chronic disease,[6–9] but it has never been validated for a general or solid-organ transplant pediatric population. Although LPPS has been collected by UNOS since 2005 on all pediatric liver transplant candidates over age one, its utility as a predictor of poor outcomes has been minimally explored in these children.[10]

Improved quantitative metrics are sorely needed for risk assessment and outcome prediction in pediatric liver transplant candidates. The Pediatric End Stage Liver Disease (PELD) significantly underestimates children's actual risk of waitlist mortality and has poor precision for mortality prediction.[11] Reflecting recognition that the current PELD/MELD system is inadequate for prioritizing children, transplant centers request exception points for 44% of children listed by PELD/MELD score; these exceptions are based on subjective narratives and unstandardized Regional Review Board decisions.[12]

One option for improving the accuracy of risk prediction is to identify other variables or risk categories that predict outcomes but are not captured by current score or Status categories. Data from adult liver transplant candidates on KPS and other frailty metrics suggest that objective, at least semi-quantitative measures of functional status are independent predictors of mortality risk.[13,14] The LPPS itself is likely of limited utility in liver transplant practice and policy given its subjective nature and lack of validation. However, we sought to assess whether even this limited measure of functional status provided risk information beyond PELD, MELD, and other illness severity measures. We hypothesized that functional status at listing, as measured by the LPPS, would be associated with waitlist but not post-transplant mortality.

METHODS:

We utilized UNOS Standard Transplant Analysis and Research (STAR) files to examine the relationship between functional status and outcomes in children aged 1–17 years at listing for liver transplant. We included children listed for liver transplant 2006–2016, to capture children with LPPS likely available at listing and allow for follow-up for at least 1 year post-transplant (n=7,750). We used OPTN data as of 3/9/2018. We excluded children multiple-listed for heart, lung, or intestinal transplant (n=262), those less than 1 year of age at listing (n=2,601) since their functional status is not recorded, those with repeat listing during the study period (n=478), those with previous transplants (n=289), those with functional status missing or categorized as "unknown" at transplant (n=204), and those listed as Status 1A (n=666). To avoid bias introduced by intra-patient correlation, only the patient's first listing within the study period was used.

The Lansky Play Performance Scale (LPPS) is reported as a percent functional status for each patient by their transplant center. (TABLE 1) Since 2005, UNOS has reported functional status at waitlist registration, at transplant, and in annual post-transplant follow-up. We did examine LPPS as an ordinal variable. But given the score's subjectivity—and our concern that its gradations were applied inconsistently across children and centers (i.e., an LPPS score of 60 for one patient may not be truly equivalent to LPPS 60 for another) —we chose to condense these risk categories to LPPS 80–100, 50–70, and 10–40 as has been conventionally done in analysis of Karnofsky scores in adult liver transplant.[1,2,4,15]

UNOS submissions by each transplant center does describe each patient as "on life support" or not, with the type of life support optionally specified. We defined a composite "life support" variable as children on a ventilator, breathing support, or dialysis; children for whom enteral or parenteral nutrition was the only form of life support listed were not included in this category. Center volumes reflect the average annual number of pediatric liver transplant centers over the study period, using the candidate's listing center for waitlist analysis and transplant center for post-transplant analysis. Categorization of UNOS regions as high, medium, and low median MELD at transplant was based on median allocation MELD/PELD for children and adults transplanted during the study period.

Statistical analysis

Variables with $p<0.10$ in univariate analysis were considered for inclusion in multivariate models. Variables with $p<0.05$ were retained in multivariate models. Backward stepwise regression was used to generate final models. Risk of waitlist mortality, defined as a death or waitlist removal for being too sick to transplant, was evaluated using Fine and Gray competing risks regression.[16] Observation time was measured from the date of listing for transplant to waitlist death (event), liver transplant (competing risk), or last date on the waiting list for patients still waiting or removed for other reasons (censored).

Risk of post-transplant outcomes, patient death and graft loss (defined as re-transplant or death), within 1 year of transplant were evaluated using Cox proportional hazards regression.[17] Follow-up time was measured from the date of transplant to the first event, re-transplant (for graft loss) or death, or last follow-up within 1 year of transplant (censored). For post-transplant models, all variables retained in the final model were examined as potential time-varying covariates to evaluate whether their impact on the outcome attenuated with increasing time since transplant.

All multivariate models were adjusted for UNOS Region (https://optn.transplant.hrsa.gov/members/regions), using the Region with the highest volume of pediatric liver transplants, Region 5, as the reference. All data analysis was completed using Stata/IC 14 (StataCorp, College Station, TX).

RESULTS:

Functional status at listing

Our analysis included 3,250 liver transplant candidates who were aged 1 to 17 years at listing. At listing, 62% had good functional status with LPPS 80–100, 25% had moderate

impairment with LPPS 50–70, and 13% had severely impaired functional status with LPPS 10–40. Children with LPPS 10–40 at listing were younger, more likely to be on intubated, on breathing support, or on dialysis, and more likely to have encephalopathy. The prevalence of children of Black race, on public insurance, and at lower-volume transplant centers was also highest in those with LPPS 10–40 at listing. (TABLE 2) Children with severely impaired functional status spent significantly fewer days on the waitlist.

The distribution of LPPS scores at listing among these children not listed as Status 1A varied substantially by region, with the prevalence of LPPS 10–40 ranging from 2% in Region 6 to 21% in Region 5. (FIGURE 1) Children with LPPS 10–40 at listing had a lower prevalence of exceptions at transplant (34%, vs. 45% for those with LPPS 50–70 and 45% for those with LPPS 80–100, p=0.003). This includes standard and non-standard exceptions.

Functional status and waitlist mortality

LPPS was 10–40 at listing for 30% of children who died on the waitlist, compared to 12% of those transplanted, 13% of those removed from the waitlist for other reasons, and 5% of those who remained on the waitlist at censoring (p<0.0005). Children with LPPS 10–40 at listing were more likely to die on the waitlist than those with higher functional status in univariate (SHR 3.30, 95% CI 2.18–5.00, p<0.0005) and multivariate analysis (SHR 1.85, 95% CI 1.09–3.13, p=0.02). Kaplan-Meier survival curves, adjusted for being on life support at listing, are shown in Figure 2A. When LPPS was examined as an ordinal variable (LPPS 100 vs. 10, 100 vs. 20, etc) LPPS 10, 20, 30, and 40 at listing were each associated with a significantly increased risk of waitlist mortality (FIGURE S1). LPPS 50–70 did not confer increased risk of waitlist mortality in univariate or multivariate analysis. (TABLE S1, TABLE 3)

Additional data relating to children's cognitive or physical function on the waitlist is limited to one variable on academic level at waitlist registration, recorded only for children 5 and older. Children with LPPS 10–40 had the highest percentage of missing data for this variable (14%), but the distribution of academic level was similar across functional status groups. (TABLE 2)

Post-transplant graft loss and mortality:

By December 2016, 2,565 children in the cohort had been transplanted as pediatric candidates (age<18). By 1 year post-transplant, 15% of children with listing LPPS 10–40 lost their graft, compared to 10% with listing LPPS 50–70 and 6% with listing LPPS 80–100 (p<0.0005, Log-rank test). Listing LPPS 10–40 and 50–70 were independent predictors of graft loss within one year, in univariate analysis and in multivariate analysis adjusting for demographics, severity of illness measures, and transplant characteristics. (TABLE S2, TABLE 4) When examined as an ordinal variable, LPPS categories 10 through 70 were each significantly associated with an increased risk of post-transplant graft loss and death compared to LPPS 100. (FIGURE S1)

Children with lower LPPS at transplant were again less likely to have active exceptions. At transplant, 32% of children with LPPS 10–40 at transplant had active exceptions, versus

48% with LPPS 50–70, and 44% with LPPS 80–100 (p<0.0005). Of note, children with LPPS 10–40 had significantly higher PELD/MELD scores at transplant. (TABLE 2)

Death within 1 year post-transplant occurred in 11% of children with listing LPPS 10–40, compared to 5% with listing LPPS 50–70 and 3% with listing LPPS 80–100 (p<0.0005). In multivariate analysis, listing LPPS 10–40 dramatically increased the risk of post-transplant death. (TABLE 4) Univariate analyses are detailed in TABLE S2. Kaplan-Meier curves, shown in Figure 2B–C, demonstrate that most graft loss and death occurred within 30 days post-transplant.

Functional status at listing

Although analyses focused on LPPS at listing, we also examined the impact of LPPS at transplant on post-transplant outcomes. Only 2.4% of transplanted children were missing LPPS at transplant; 68% of these had listing LPPS 80–100 and 3% were on a ventilator, breathing support, or dialysis at transplant. Of transplanted children that were on a ventilator, breathing support, or dialysis at listing (n=41), 51% were also on it at transplant. For those who did have LPPS at transplant recorded, LPPS distribution at transplant was similar to that at listing: 55% were LPPS 80–100 at transplant, 29% LPPS 50–70, and 16% LPPS 10–40. Of children listed with LPPS 80–100, 73% were transplanted with LPPS 80–100. Of those listed with LPPS 10–40, 63% were transplanted with LPPS 10–40. Of those with listing LPPS 50–70, 56% were transplanted in this category, 27% improved to LPPS 80–100, and 16% worsened to LPPS 10–40.

Children with LPPS 10–40 at transplant had an increased risk of graft loss (HR 3.25, 95% CI 2.22–4.74, p<0.0005) and death (HR 7.68, 95% CI 3.87–15.227, p<0.0005) within 1 year post-transplant in multivariate analysis (data for other variables not shown). In the analysis of post-transplant mortality, LPPS at transplant was a time-varying covariate; its impact on survival decreased with time since transplant (data not shown). LPPS 50–70 at transplant was not associated with increased risk of post-transplant graft loss (HR 1.39, 95% CI 0.972.00, p=0.07 in multivariate analysis) or mortality (HR 1.72, 95% CI 0.78–3.81, p=0.18 in multivariate analysis).

DISCUSSION:

Although the UNOS registry has included data on functional status since 2005, this is the first analysis to focus on its significance for pediatric liver transplant candidates. In children aged 1–17 years awaiting liver transplantation, severely impaired functional status at waitlist registration (LPPS 10–40) is an independent predictor of death on the waitlist. For those who survive to transplant, LPPS 10–40 predicts graft loss and death within 1 year after liver transplantation. Moderate functional impairment at listing (LPPS 50–70) conferred an increased risk of graft loss within 1 year post-transplant but was not consistently associated with mortality.

These associations between impaired functional status and poor outcomes were attenuated but did not disappear after adjusting for other illness severity measures. Thus, these other measures—including being on “life support” (on a ventilator, breathing support, or dialysis),

PELD/MELD score, and being in the ICU at transplant—did not fully account for the impact of functional status on outcomes. Most graft loss and post-transplant death in the children with impaired functional status at listing occurred within 30 days post-transplant. This suggests that factors already present at listing, or accumulated during time on the waitlist, left these children particularly vulnerable to severe consequences of post-transplant complications.

This analysis suggests that quantitative, validated measures of functional status could improve risk prediction for pediatric liver transplant candidates. However, we do not advocate for incorporation of the LPPS itself into PELD. LPPS is scored only on children aged 1–17 years old at listing, thus excluding the approximately 1/3 of pediatric candidates listed prior to age one. The LPPS is inherently limited by subjectivity and vulnerability to observer bias in its assessment. Impaired functional status by LPPS has been identified as a risk factor for mortality in children with some oncologic conditions, including some solid tumors and after stem cell transplant for Hodgkin lymphoma,[6,7] but it has not been widely validated. For pediatric liver and other solid-organ transplant candidates, LPPS has never been validated, nor has interobserver agreement been tested.

LPPS is not a widely used metric in pediatric hepatology or general pediatrics; pediatric transplant providers are not generally trained in its application. It does not adjust for developmental disabilities that may limit activity. There is limited assessment of other functional domains in the UNOS registry—for example, physical, cognitive or academic function—and these are also subjectively assessed with non-validated tools. We suspect that the training, role, and experience of the individuals scoring LPPS varies widely across transplant centers, but there is currently no way to confirm our suspicion.

Given the weaknesses of the LPPS, future research should focus on developing objective, accurate tools to measure functional status in pediatric liver transplant candidates. Measuring nutritional status and muscle mass, two of the dominant factors that contribute to poor functional status – for children of all ages—may offer more objective options. This has been done for adults with the Liver Frailty Index.[18] One recent study examined the utility of Fried Frailty Criteria in children with chronic liver disease.[19] Frailty scores were lower in children with end-stage liver disease than in those with compensated chronic liver disease and did not correlate with MELD-Na—suggesting that the score captured currently unaccounted for factors. However, children less than 5 years of age or with significant physical impairment had to be excluded due to expected inability to complete the tasks. More than half of children are transplanted under age 5. In children that could participate, testing required a median 1 hour per subject. Growth or sarcopenia measures may offer a more broadly applicable proxy for functional status. Another recent pilot study reported on sarcopenia, as measured by CT in the psoas muscle, as an objective measure of children's nutritional status.[20] Sarcopenia correlates with performance-based assessments of physical function in adult liver transplant candidates, but the latter more strongly predicts mortality;[21] this association has not yet been studied in children.

Beyond associations between functional status and survival, our analyses reveal additional observations that should be considered in future research on functional measures in this

population. The distribution of LPPS varied significantly by UNOS region. It is not clear whether these variations represent true differences in case mix or some bias in how patients' function is assessed by this provider-assessed instrument. Of even greater interest, severely impaired functional status was reported more often in children of Black race, those with public insurance, and those in lower volume transplant centers. We cannot determine if this reflects inherent case mix, delays in presentation to care or listing for transplant, differences in the evaluation and scoring of LPPS, or other factors. But it suggests disparity in the system deserving of additional investigation. As with other transplant measures, it is key that functional status metrics offer objective measurement across demographic and geographic categories.

The pathways by which functional status impairment lead to poor outcomes are also in need of future investigation. UNOS has limited details about causes of death and graft loss, so we could not fully evaluate specific vulnerabilities of children with LPPS 10–40. In considering post-transplant outcomes, for example, it is possible that they received poorer quality grafts because of their illness severity.

Our data suggests that tools validated for assessing functional impairment in pediatric liver transplant candidates may enhance our ability to predict mortality risk—and thus to appropriately prioritize children for liver transplant. Perhaps even more importantly, given that functional status is potentially modifiable, integration of objective tools to measure functional status may allow us to develop effective interventions that target functional impairment and the factors that contribute to it (e.g., malnutrition, physical inactivity, muscle wasting), improve functional status, and ultimately reduce mortality in the most vulnerable children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CI	Confidence interval
HR	Hazard Ratio
INR	International Normalized Ratio
KPS	Karnofsky Performance Status

LPPS	Lansky Play-Performance Scale
MELD	Medical End-Stage Liver Disease
MV	Multivariate
PELD	Pediatric End-Stage Liver Disease
SHR	Standardized Hazard Ratio
UNOS	United Network for Organ Sharing

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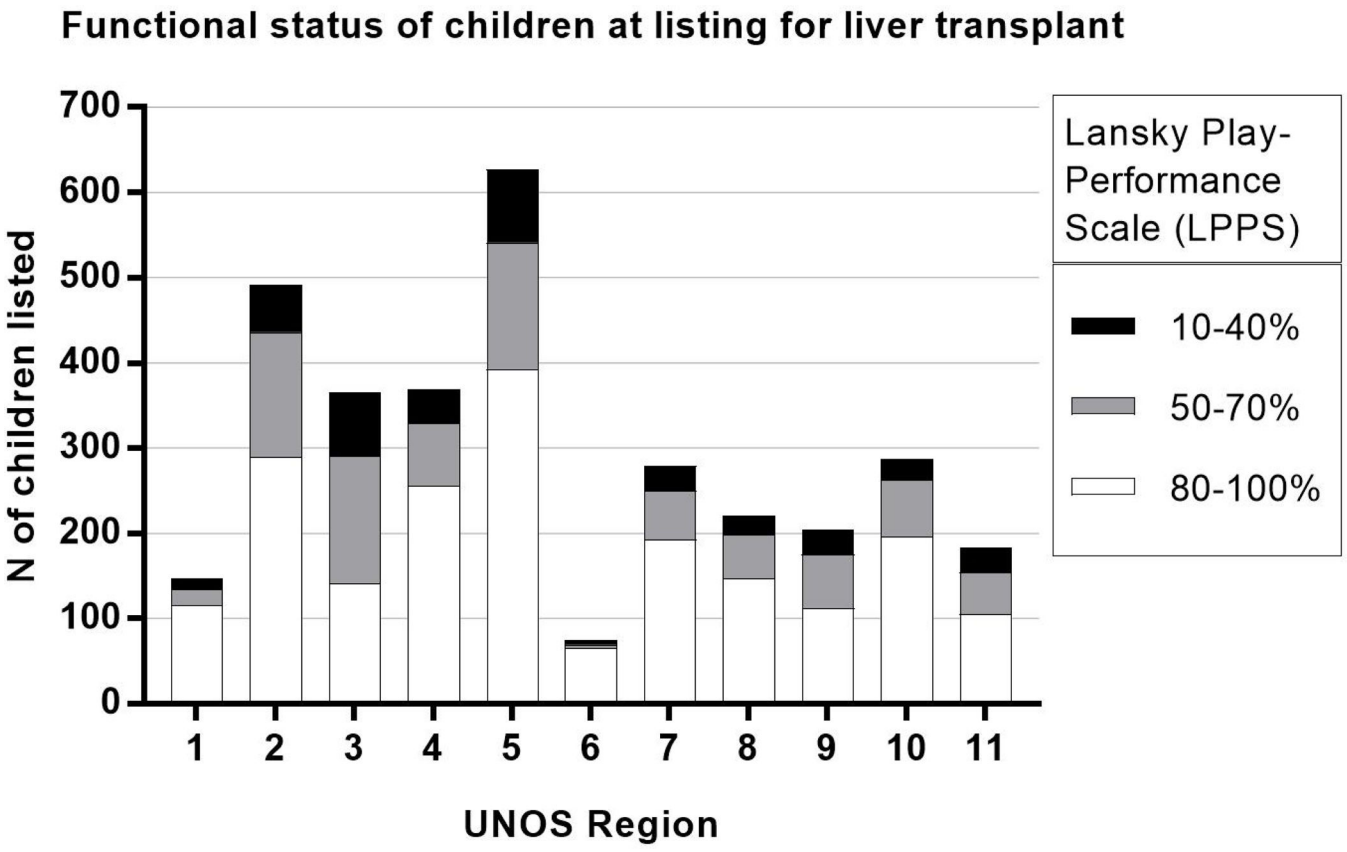
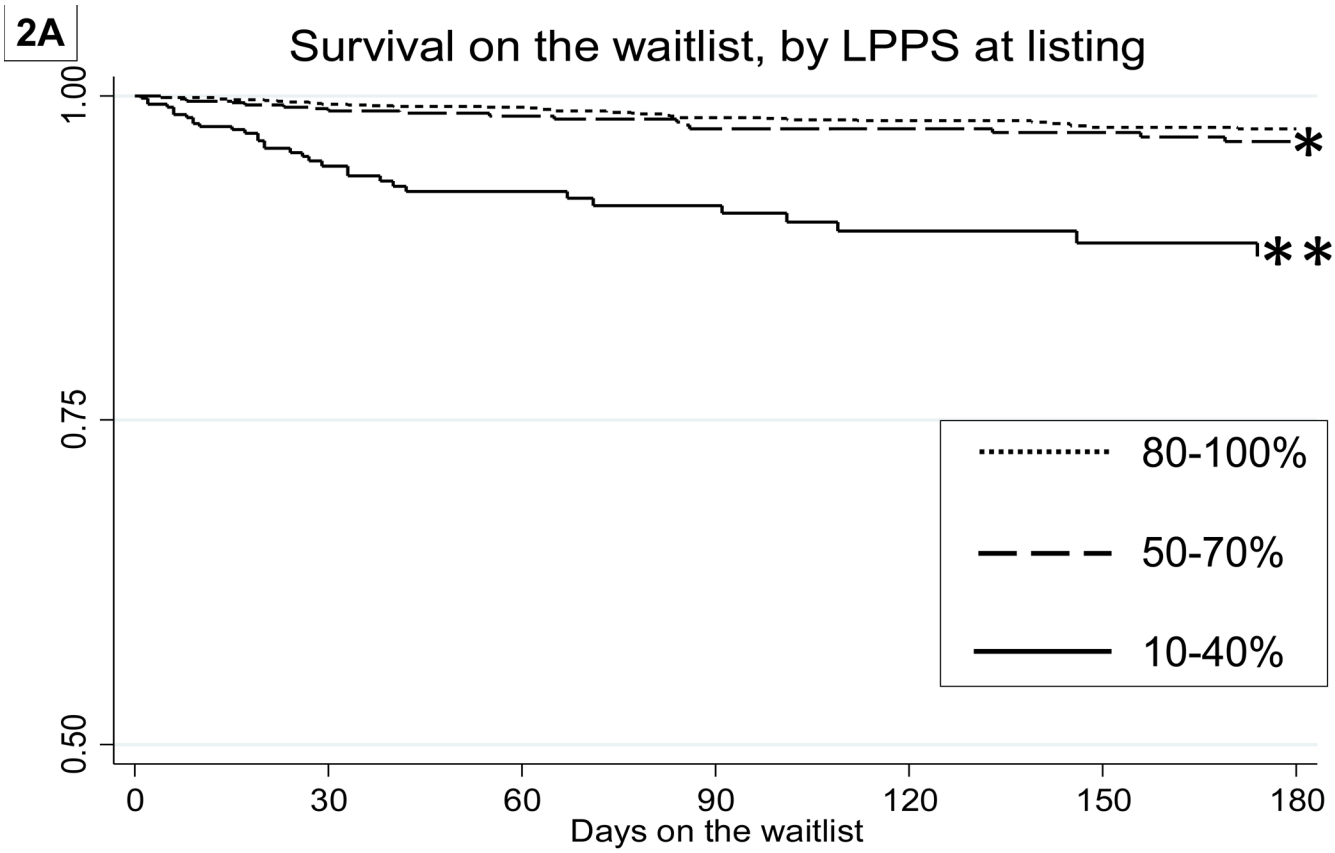
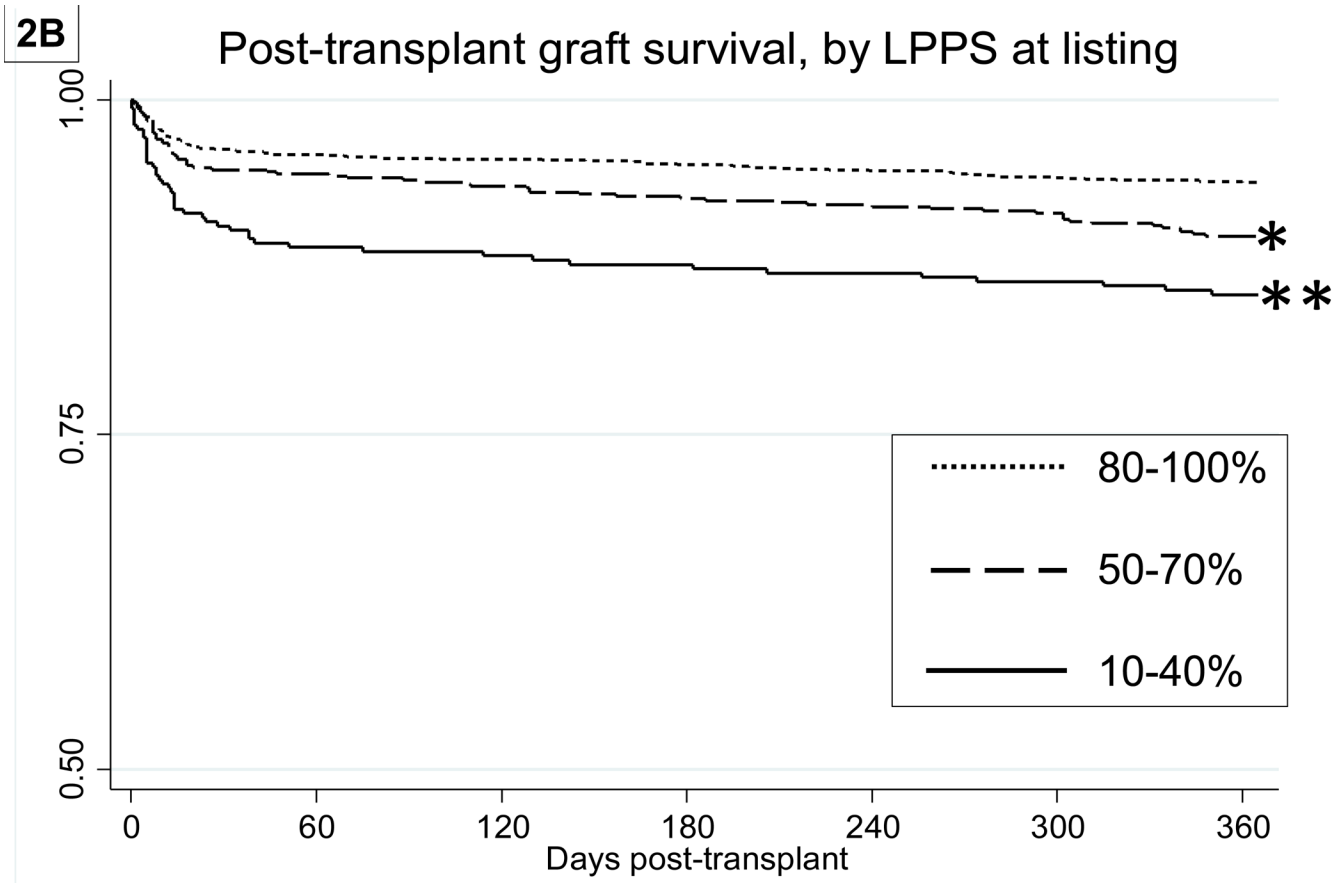


FIGURE 1:

Distribution of functional status scores, as measured by the Lansky Play-Performance Scale, in children at listing for liver transplant by UNOS Region. Figure represents children listed for transplant 2006–2016 who were not Status 1A at listing (n=3,250).





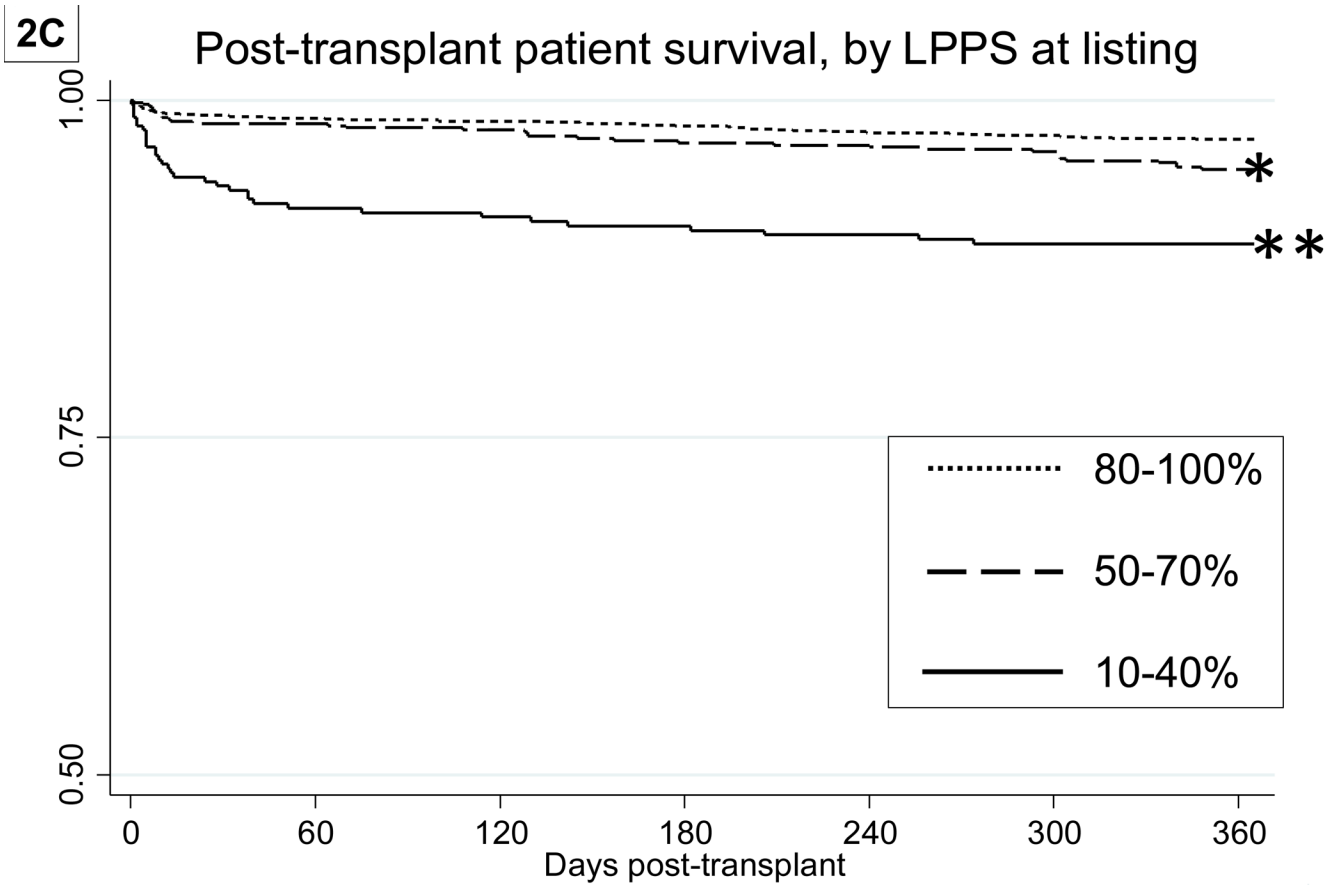


FIGURE 2:

Functional status at listing, as measured by the Lansky Play-Performance Scale, as a predictor of (A) waitlist mortality (n=3,244) (B) graft survival post-transplant (n=2,420) (C) patient survival post-transplant (n=2,420) in pediatric liver transplant candidates. All analyses are adjusted for being on life support (on a ventilator, breathing support, or dialysis) at listing. *p<0.01 vs. LPPS 80–100; **p<0.0005 vs. LPPS 80–100 using the stratified log-rank test for equality of survivor functions.

TABLE 1:

Lansky Play-Performance Scale (LPPS)*

100%	Fully active, normal
90%	Minor restrictions in physically strenuous activity
80%	Active, but tires more quickly
70%	Both greater restriction of, and less time spent in, active play
60%	Up and around, but minimal active play; keeps busy with quieter activities
50%	Can dress, but lies around much of the day; no active play; can take part in quiet play and activities
40%	Mostly in bed, participates in quiet activities
30%	In bed, needs assistance even for quiet play
20%	Often sleeping, play entirely limited to very passive activities
10%	No play, does not get out of bed

* As described in UNOS STAR files documentation, provided with dataset through 3/9/2018. LPPS as published by Lansky et al. included a “0%, Unresponsive” but this category is not included in the UNOS STAR File documentation and was not utilized for any children in the database.

TABLE 2:

Pediatric liver transplant candidates 2006–2016, by functional status at listing [*]

Recipient characteristics		LPPS 10–40% (n=412)	LPPS 50–70% (n=828)	LPPS 80–100% (n=2,010)	p-value
Female		51%	50%	49%	0.62
Age at listing (years)					
	1–2	40%	27%	30%	<0.0005
	3–11	32%	39%	38%	
	12–17	28%	34%	32%	
Ethnicity					
	White	44%	55%	57%	<0.0005
	Black	19%	15%	13%	
	Hispanic	28%	23%	21%	
	Asian	6%	5%	6%	
	Other	3%	2%	3%	
Transplant indication [†]					
	Biliary atresia	15%	14%	22%	<0.0005
	Other cirrhotic	31%	43%	41%	
	Acute liver failure	28%	6%	5%	
	Non-cirrhotic	26%	37%	32%	
Public insurance		58%	50%	48%	0.002
Academic level at listing					
	+/− 1 grade level for age	33%	44%	48%	<0.0005
	Delayed grade level	5%	6%	2%	
	Special education	4%	6%	3%	
	Missing data	58%	44%	47%	
Status at listing					0.02
	1A	--	--	--	
	1B	7%	5%	4%	
	MELD/PELD	92%	94%	94%	
	Inactive	1%	1%	2%	
On a ventilator, breathing support, or dialysis at listing [‡]		12%	0.2%	0.4%	<0.0005
On a ventilator at listing		11%	0.2%	0.4%	<0.0005
MELD/PELD lab score		15 (2 – 27)	7 (−3 – 15)	5 (−4 – 13)	0.0001
Encephalopathy at listing					
	None	52%	67%	63%	<0.0005
	Stage 1–2	22%	8%	6%	
	Stage 3–4	5%	1%	0.5%	
	Missing	21%	24%	30.5%	

Recipient characteristics		LPPS 10–40% (n=412)	LPPS 50–70% (n=828)	LPPS 80–100% (n=2,010)	p-value
Labs at listing for transplant					
	Bilirubin (mg/dL)	8.4 (1.3–18.7)	1.6 (0.5–7.9)	1.3 (0.5–5.4)	0.0001
	Creatinine (mg/dL)	0.4 (0.2–0.6)	0.4 (0.3–0.6)	0.4 (0.3–0.5)	0.2
	INR	1.5 (1.1–2.4)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	0.0001
	Albumin (mg/dL)	3.0 (2.6–3.5)	3.4 (2.9–3.9)	3.6 (3.0–4.1)	0.0001
	Sodium (mEq/L)	137 (135–140)	138 (136–140)	138 (136–140)	0.0001
Total days on waiting list		29 (7–108)	81 (24–247)	131 (45–411)	0.0001
Active MELD/PELD exception at waitlist removal		28%	41%	37%	<0.0005
Median regional MELD at transplant					
	≥29	31%	28%	31%	<0.0005
	25–28	37%	40%	47%	
	<25	32%	32%	22%	
Listing center volume, average annual pediatric liver transplants					
	<6	21%	13%	15%	<0.0005
	6–15	34%	28%	31%	
	>15	45%	59%	54%	
Transplanted children		n=313	n=697	n=1555	
Medical condition at transplant (n=2,522)					
	Not hospitalized	43%	79%	86%	<0.0005
	Hospitalized, not ICU	20%	13%	9%	
	ICU	37%	8%	5%	
On life support at transplant‡		17%	5%	2%	<0.0005
MELD/PELD lab score		14 (1 – 27)	9 (−2 – 18)	7 (−3 – 14)	0.0001
Allocation MELD/PELD (not Status 1, 7 at removal, n=1,943)		30 (23–35)	27 (17–32)	24 (14–30)	0.0001
Transplant Type (n=2,522)					
	Living donor	11%	9%	10%	0.72
	Cadaveric (whole)	73%	77%	75%	
	Cadaveric (split)	16%	14%	15%	
Share type (n=2,522)					
	Local	44%	46%	49%	0.01
	Regional	44%	44%	41%	
	National	12%	10%	10%	
Cold ischemia time (hrs, n=2,449)		6.0 (4.7–8.0)	6.3 (4.8–8.0)	6.3 (4.9–8.2)	0.72

*Continuous variables reported as median (interquartile range). P-value calculated using Kruskal-Wallis test for continuous variables, chi-squared testing for categorical variables.

†Other cirrhotic disease includes: Alagille syndrome, alpha-1-antitrypsin deficiency, choledochal cyst, cystic fibrosis, glycogen storage disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, primary sclerosing cholangitis or primary biliary cirrhosis, idiopathic cholestasis, congenital hepatic fibrosis, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis C cirrhosis, non-alcoholic steatohepatitis cirrhosis, unknown cirrhosis, chronic rejection/graft failure, inborn errors in bile acid metabolism, Wilson's disease. Other non-cirrhotic disease

includes: tumors without underlying cirrhosis, primary hyperoxaluria, maple syrup urine disease, trauma, urea cycle defects, mitochondrial disease/encephalopathy, ethylmalonic encephalopathy, Budd-Chiari, Crigler-Najjar, tyrosinemia, hyperlipidemia/homozygous hypercholesterolemia. Acute liver failure includes, diagnoses coded or text-described as “acute liver failure”, “fulminant liver failure”, or “fulminant” without other specifying diagnosis.

[≠]In the UNOS data entry forms, this category is labelled “on life support” with options including being on a ventilator, receiving breathing support, or receiving dialysis. Patients listed as “on life support” for whom mode of life support was specified only as enteral or parenteral nutrition were excluded from this category.

TABLE 3:

Predictors of waitlist mortality in pediatric liver transplant candidates, multivariate analysis *

		SHR	95% CI	p
Functional status at listing (LPPS)				
	80–100%	REF	REF	REF
	50–70%	1.15	0.73–1.82	0.54
	10–40%	1.85	1.09–3.13	0.02
On ventilator, breathing support, or dialysis (at listing)		2.45	1.19–5.08	0.02
Public insurance		2.12	1.45–3.09	<0.0005
Transplant indication				
	Biliary atresia	REF	REF	REF
	Other cirrhotic disease	1.94	1.05–3.60	0.03
	Acute liver failure	0.46	0.17–1.24	0.13
	Other non-cirrhotic disease	2.34	1.22–4.45	0.01
MELD/PELD at listing (per 1 point)		1.05	1.03–1.07	<0.0005
MELD/PELD exception, any type		0.16	0.08–0.31	<0.0005

* Model adjusted for UNOS region (REF = Region 5). No statistically significant differences between SHR for Region 5 and any other UNOS Region (data not shown). Only variables significant in multivariate analyses listed here; see Supplemental Table for univariate analyses. Six children listed and removed from the waitlist on the same day excluded from analysis.

TABLE 4:

Predictors of death and graft loss within 1 year post-transplant in pediatric liver transplant recipients, multivariate analysis*

		Death			Graft Loss		
		HR	95% CI	p	HR	95% CI	p
Functional status at listing (LPPS) †							
	80–100%	REF	REF	REF	REF	REF	REF
	50–70%	1.20	0.59–2.44	0.61	1.58	1.14–2.19	0.006
	10–40%	5.77	3.05–10.91	<0.0005	2.17	1.46–3.23	<0.0005
On ventilator, breathing support, or dialysis (at transplant)		3.09	1.67–5.71	<0.0005	2.52	1.53–4.15	<0.0005
Age at transplant (per 1 year)					0.97	0.94–0.99	0.01
Transplant indication							
	Biliary atresia	REF	REF	REF	REF	REF	REF
	Other cirrhotic disease	1.17	0.56–2.44	0.68	1.14	0.72–1.81	0.58
	Acute liver failure	0.37	0.12–1.09	0.071	0.54	0.26–1.12	0.10
	Other non-cirrhotic disease	4.55	2.24–9.23	0.003	2.51	1.59–3.97	<0.0005
MELD/PELD at transplant (per 1 point)		1.03	1.01–1.05	0.003	1.02	1.00–1.03	0.02
Serum sodium (at transplant, meq/L) †							
	<135	0.64	0.24–1.70	0.37	0.80	0.51–1.26	0.34
	135–145	REF	REF	REF	REF	REF	REF
	>145	5.39	2.75–10.56	<0.0005	2.16	1.34–3.50	0.002
Transplant type							
	Deceased donor, whole liver				REF	REF	REF
	Deceased donor, split liver				1.79	1.24–2.59	0.002
	Living donor				1.77	1.02–3.06	0.04
Transplant center volume, average annual							
	≤ 15 pediatric liver transplants				REF	REF	REF
	> 15 pediatric liver transplants				0.59	0.43–0.81	0.001
Donor share type							
	Local				REF	REF	REF
	Regional				1.20	0.86–1.66	0.28
	National				1.80	1.11–2.93	0.02
	Foreign				9.86	1.29–75.10	0.03

*Only variables significant in multivariate analyses listed here; see Supplemental Table for univariate analyses. Both models adjusted for UNOS region (REF = Region 5). HR for mortality was significantly different only in Region 8 (HR 2.79, 95% CI 1.42–5.48, p=0.003; other Regions not shown). HR for graft loss was significantly different only in Region 8 (HR 2.21, 95% CI 1.34–3.40, p=0.001) and Region 9 (Region 9 (HR 1.84, 95% CI 1.07–3.19, p=0.03; others not shown).

†Time-varying covariate in mortality model. The impact of listing LPPS 10–40% and of hypernatremia decreased with time since transplant (p=0.04, p=0.03 for interaction with time respectively). All other variables in both models tested for an interaction with time, with no statistically significant interaction.