Higher Mortality in Pediatric Liver Transplant Candidates With Sarcopenia

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Little is known about the impact of sarcopenia (reduced muscle mass and function) in pediatric chronic liver disease. We compared psoas muscle surface area (PMSA), measured at the 4th lumbar vertebrae, in children listed for liver transplantation (LT) to that of healthy controls and studied the impact of sarcopenia on transplant-associated outcomes. The effect of PMSA (raw value and *z* score) on survival was studied using multivariable proportional hazards, whereas the impact of PMSA on other transplant-associated outcomes was assessed by multivariable linear or logistic regression. The correlation of PMSA with anthropometric values and markers of disease severity was studied using Spearman's rank-order correlation. Mean PMSA was significantly lower in LT candidates (n = 57, 699.4 ± 591.9 mm^2 [mean ± SD]) than controls (n = 53, 1052.9 ± 960.7 mm^2; $P = 0.02$). For LT candidates, there was an increased risk of death (either while on the waiting list or following transplantation) with lower PMSA (hazard ratio [HR], 1.6 per 100 mm^2 [$P = 0.03$]; 95% confidence interval [CI], 1.1-2.8), amounting to a 4.9 times higher risk of death for every 1 unit decrease in PMSA z score (HR, 4.9 [$P = 0.05$], 95% CI, 1.2-34.5), adjusting for age and sex. PMSA did not correlate with posttransplant length of intubation, hospital length of stay, or perioperative complications. PMSA also did not correlate with calculated ($r = 0.10$, $P = 0.60$) or appealed Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease scores ($r = 0.10$, $P = 0.69$). Pediatric LT candidates have a significant reduction in muscle compared with controls. LT candidates with lower PMSA experience significant increases in mortality. As such, sarcopenia may provide a novel indicator of disease severity in children with chronic liver disease.

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Sarcopenia, a reduced quantity and quality of skeletal muscle, is a common and significant comorbidity in adults with chronic liver disease. Sarcopenia occurs in up to 70% of adults who require liver transplantation (LT), with profound adverse effects on patient outcomes.[1] These include higher waitlist mortality, higher posttransplant mortality, and more frequent serious postoperative complications, including bleeding, sepsis, renal failure, bile leaks, and respiratory failure.[2-9] Little is known about the impact of sarcopenia in pediatric chronic liver disease.

The physiologic differences between adult and pediatric patients are vast, particularly in regard to nutrition and body composition. Weight, height, and muscle mass vary greatly as children age. Thus, the understanding of sarcopenia in adults with chronic liver disease cannot be directly applied to the pediatric population. A small single-center study suggested that children with end-stage liver disease (ESLD) have a smaller psoas muscle surface area (PMSA) than healthy controls.[10] Another study showed that even in children who underwent LT, their estimated skeletal muscle mass remained low, with 41% of children having a skeletal muscle mass *z* score ≤−2 by dual energy

Abbreviations: ACLF, acute-on-chronic liver failure; BMI, body mass index; CI, confidence interval; CT, computed tomography; EMR, electronic medical record; ESLD, end-stage liver disease; HAT, hepatic artery thrombosis; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; LT, liver transplantation; MAC, mid-arm circumference; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; MSOF, multisystem organ failure; N/A, not available; OR, odds ratio; PELD, Pediatric End-Stage Liver Disease; PMSA, psoas muscle surface area; PVT, portal vein thrombosis; SBP, spontaneous bacterial peritonitis; SD, standard deviation; TSF, triceps skinfolds.

X-ray absorptiometry measurement.[11] Those patients with reduced muscle mass had increased lengths of hospitalization and ventilator dependence. Although these studies are provocative in their novel assessment of sarcopenia in pediatric ESLD, the effects of pretransplant muscle wasting on LT outcomes have not been defined in children.

Given the significant negative impact of muscle wasting in adult LT, we sought to evaluate muscle mass in children listed for LT and its impact on outcomes. We hypothesized that PMSA would be significantly lower in children listed for LT than healthy controls, with a negative impact on LT-associated outcomes.

Patients and Methods

We studied all children (age 0-18 years) listed for LT because of chronic/progressive, fibrotic, or cholestatic liver disease at Children's Hospital Colorado between March 2009 and August 2018 who had cross-sectional abdominal imaging available within the 12 months before LT or listing (either computed tomography [CT] or magnetic resonance imaging [MRI]). We collected demographic, radiologic, and transplant-specific clinical data from the electronic medical records (EMRs). Children were excluded from the study if cross-sectional imaging was not available; if they required simultaneous kidney transplantation and LT; if they required an LT because of acute liver failure, hepatic malignancy, or an underlying metabolic disorder; or if they were listed for a retransplant. Age-matched and sex-matched controls with available CT abdominal imaging were identified from a radiology database at Children's Hospital Colorado. The EMRs were reviewed and controls were excluded if they had severe chronic lung disease, neuromuscular comorbidities, congenital heart disease, chronic kidney disease, chronic gastrointestinal disease, multiple congenital anomalies, <30 weeks' gestation, body mass index (BMI) z scores ≤−2, or were undergoing chemotherapy. Abdominal imaging in controls was obtained primarily for trauma (73%), with the remainder (27%) performed to assess for intra-abdominal pathology such as appendicitis or bowel obstruction. This study was approved by the Colorado Multiple Institutional Review Board.

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PMSA MEASUREMENTS

For both cases and controls, the surface areas of the right and left psoas muscles were measured at the 4th lumbar vertebrae (L4) on abdominal CT or MRI using Synapse 3D (Fujifilm Medical Systems USA, Lexington, MA). Both radiologic methodologies were used as CT and MRI have been shown to correlate well with each other in measuring cross-sectional muscle areas.[12] L4 was first identified on sagittal images, allowing for the identification of the corresponding level on axial images subsequently used for the PMSA measurement (Fig. 1). The left and right PMSA values were combined to calculate a total PMSA at L4. A second investigator performed PMSA measurements for a subset of patients chosen at random (n = 20). Interclass correlation was used to estimate the inter-rater reliability coefficient.

Adult studies of PMSA commonly measure muscle area at L3 or L4.[1,2,4,6] We measured PMSA at L4 because normative data have been previously derived for healthy children ages 1 to 20 years using this technique by the Morphomic Analysis Group at the University of Michigan School of Medicine.[13] The Morphomic Analysis Group previously computed reference z scores from quantile regression curves using the age-adjusted and sex-adjusted means of a healthy pediatric population who underwent abdominal CT at their institution: z = (value − 50th percentile)/([75th percentile − 25th percentile]/1.34).[13] Using this normative data, we calculated PMSA z scores in both LT candidates and controls. A PMSA z score of ≤−2 is 2 standard deviations (SDs) from the mean of the normative data and can reasonably be considered a definition of sarcopenia. However, as there are not clearly validated

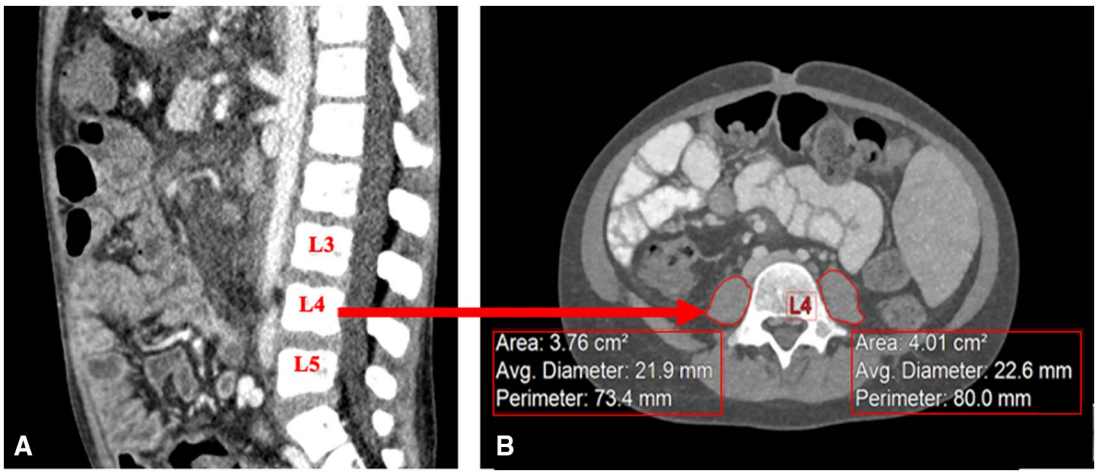

FIG. 1. Measurement of PMSA. (A) Midline sagittal CT abdominal image demonstrates the lumbar vertebrae, including L4; (B) the corresponding level is then located on the axial image allowing for PMSA measurement.

definitions of sarcopenia in pediatric liver disease, we studied PMSA and PMSA *z* score as continuous variables.

In the patients listed for LT, laboratory, anthropometric, and LT-associated outcome data were collected from the EMRs. The Pediatric End-Stage Liver Disease (PELD) score (used in patients <12 years old) or Model for End-Stage Liver Disease (MELD) score (used in patients ≥12 years old) were calculated at the time of LT and, if relevant, exception MELD/PELD scores were collected from the EMRs as well. Weight, height, weight-for-length (children <2 years), and BMI (children ≥2 years) were collected from the EMRs for both LT patients and controls at the available time point closest to the time of abdominal imaging. For patients in whom concurrent height was unavailable, height was extrapolated using prior height percentiles. LT candidates also had anthropometric measurements including mid-arm circumference (MAC) and triceps skinfolds (TSF) obtained from the EMRs. These measurements, performed by a trained dietician, are a part of our center's clinical standard of care for children awaiting LT.

The following outcomes were collected from the EMRs: death (on the waiting list, following removal from the waiting list, or after LT), length of intubation after LT, length of initial intensive care unit (ICU) stay, total hospital length of stay (LOS), perioperative complications during the initial transplant hospitalization (return to the operating room, hepatic artery thrombosis [HAT], portal vein thrombosis [PVT], biliary complication, serious infection), and number of hospital readmissions in the first 6 months after LT.

The effect of PMSA (both raw values [mm^2] and *z* score values) on survival was studied using multivariable proportional hazards, incorporating age and sex in the statistical model. The impact of muscle mass on other transplant-associated outcomes (length of intubation, ICU LOS, total hospital LOS, perioperative complications, and hospital readmissions) was assessed by multivariable linear or logistic regression. The correlation of PMSA with anthropometric values and MELD/PELD score was studied using Spearman's rank-order correlation. A *P* value of <0.05 was considered significant.

Results

Of the 114 patients listed for LT for indications other than acute liver failure during the study period, we studied 57 patients (median age at time of abdominal imaging, 1.3 years; interquartile range [IQR], 0.6-9.8 years; 51% female; Table 1). A total of 38 LT candidates were excluded from the analysis because of the lack of cross-sectional abdominal imaging within 12 months of LT or listing: 7 because of the need for retransplantation, 7 because their indication for LT was a liver tumor, 4 because their indication for LT was metabolic liver disease (without associated fibrosis or cirrhosis), and 1 because

TABLE 1. Demographics, Anthropometrics, and PMSA Measurements in LT Candidates and Age-Matched and Sex-Matched Controls

Variable at Time of Pretransplant Imaging	Listed for LT (n = 57)	Controls (n = 53)	Mean Difference	*P* Value
Median age at abdominal imaging, years	1.3 (0.6-9.8)	1.3 (0.7-11.1)	—	0.80
Female sex	51%	47%	—	0.70
Weight *z* score	–1.2 ± 1.2	0.1 ± 1.1	—	<**0.001**
Height *z* score	–1.4 ± 1.2	0.1 ± 1.0	—	<**0.001**
Weight-for-length *z* score*	–0.3 ± 0.9	–0.1 ± 1.1	—	0.40
BMI,† kg/m^2	17.3 ± 2.4	18.3 ± 4.4	—	0.12
BMI *z* score	0.0 ± 1.0	0.3 ± 1.2	—	0.37
Body surface area, m^2	0.7 ± 0.5	0.8 ± 0.6	—	0.26
Mean PMSA at L4, mm^2				
All ages	699.4 ± 591.9	1052.9 ± 960.7	353.5	**0.02**
≤1 year of age (N = 26)	341.0 ± 55.4	419.1 ± 53.4	78.1	<**0.001**
>1 year of age (N = 31)	999.9 ± 668.4	1577.4 ± 1040.4	577.5	**0.01**
z score	–1.5 ± 1.0	–0.3 ± 0.9	1.2	<**0.001**
Mean PMSA at L4 standardized to height, mm^2/cm	6.5 ± 2.6	8.7 ± 4.5	—	**0.003**
Mean PMSA at L4 standardized to BSA, mm^2/m^2	959.4 ± 224.8	1164.1 ± 285.7	—	<**0.001**

NOTE: Data are provided as mean ± SD or median (IQR).
*Weight-for-length used in patients <2 years of age.
†BMI used in patients ≥2 years of age.
P values listed in bold are significant at <0.05.

of the need for simultaneous kidney transplantation and LT (Fig. 2). Subjects excluded because of the lack of cross-sectional imaging were similar to the included subjects in age and sex (mean age, 5.4 versus 5.8 years [$P = 0.80$]; 55% female versus 51% female [$P = 0.65$]). The proportion of patients with biliary atresia, the leading indication for LT, was also similar between those included (49%) and excluded (32%) from the study ($P = 0.08$).

LT candidates were compared to 53 age-matched (median age, 1.3 years; IQR, 0.7-11.1 years; $P = 0.80$) and sex-matched (47% female; $P = 0.70$) healthy controls (Table 1). Concurrent height was only available in 54% of controls; therefore, height was extrapolated from the last recorded height percentile for all others. Weight *z* scores (–1.2 ± 1.2 for LT candidates versus 0.1 ± 1.1 for controls; $P < 0.001$) and height *z* scores (–1.4 ± 1.2 for LT candidates versus 0.1 ± 1.0 for controls; $P < 0.001$) at the time of imaging were significantly different between groups. However, the BMI *z* scores (0.0 ± 1.0 for LT candidates versus 0.3 ± 1.2 for controls; $P = 0.37$) and the weight-for-length *z* scores (–0.3 ± 0.9 for LT candidates versus –0.1 ± 1.1 for controls; $P = 0.40$) were similar.

The most common indication for LT was biliary atresia (58%; Table 2). Of the 57 patients listed, 49 underwent LT. A total of 7 patients died before transplant (4 died while on the waiting list and 3 were removed from the waiting list because they were too sick for transplantation; Table 3). One additional patient was removed from the waiting list because of improvement in autoimmune hepatitis with ongoing medical management. The median age at transplant was 1.9 years with a range from 5 months to 18 years. Of LT recipients, 41% (20/49) underwent transplant before 1 year of age. A total of 4 patients died following transplantation (Table 3).

For LT candidates, PMSA was measured on CT in 51 patients (89%) and on MRI in the remaining 6 patients (11%); all controls had CT imaging. Interrater reliability analysis of PMSA measurements performed by a second investigator in 20 patients indicated almost perfect agreement with an interclass correlation of 0.997 (95% confidence interval [CI], 0.992-0.999). Mean PMSA was significantly lower in children listed for LT (699.4 ± 591.9 mm^2 [mean ± SD]) than in controls (1052.9 ± 960.7 mm^2; $P = 0.02$). Even after PMSA was standardized to height and body surface area, muscle area remained significantly lower in LT candidates than controls (Table 1). LT recipients had a median wait time of 2.6 months (IQR, 1.3-5.1 months) from listing to transplant. At the time of transplant, the mean calculated PELD score (patients <12 years, n = 40) was 15.9 ± 9.3, and the mean calculated MELD

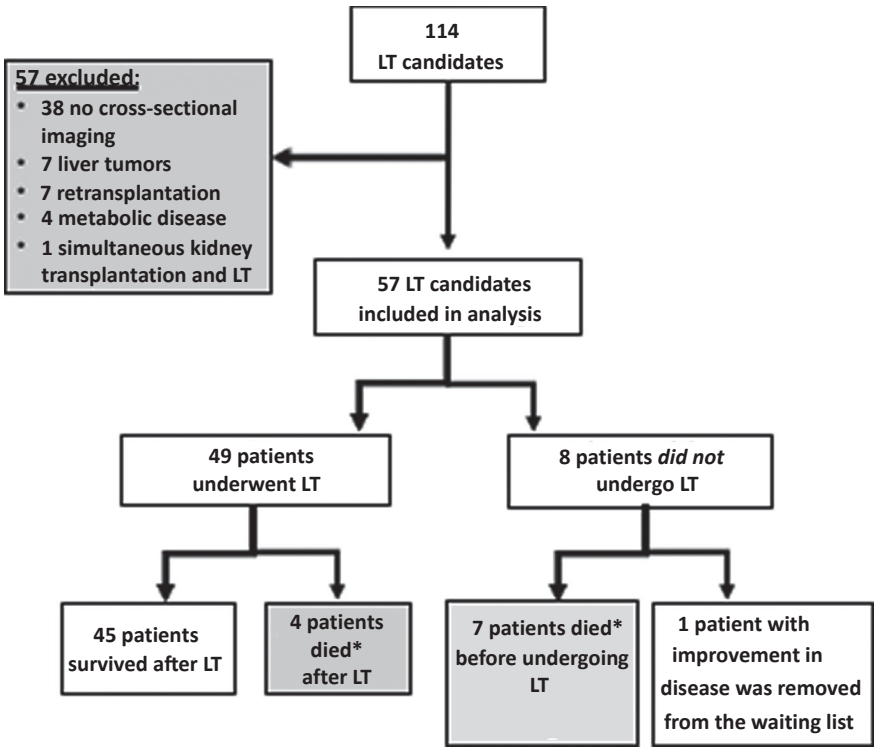

FIG. 2. Consort diagram of LT candidate study population. *Deaths included in the survival analysis (n = 11).

TABLE 2. Indications for LT and Mean Age for Each Indication

Indication for LT	Total Patients (n = 57)	Mean Age at Time of LT, Years (n = 49)*
Biliary atresia	33 (58)	3.2 ± 4.4
Autoimmune liver disease	8 (14)	13.6 ± 3.6
Autoimmune hepatitis	4	
Autoimmune hepatitis/primary sclerosing cholangitis overlap	4	
Alagille syndrome	4 (7)	5.6 ± 5.2
Cirrhosis, not otherwise specified	4 (7)	3.6 ± 5.1
Progressive familial intrahepatic cholestasis type 2	3 (5)	8.1 ± 7.2
Other	3 (5)	6.9 ± 5.7
Cystic fibrosis-associated liver disease	2 (4)	15.5 ± 0.6

NOTE: Data are given as n (%) or mean ± SD.
*Patients who did not undergo transplant (n = 8) were not included in the mean age at LT calculation.

score (patients ≥12 years, n = 9) was 14.7 ± 4.2. Of the 49 patients who underwent LT, 34 (69%) were allocated an organ based on exception points rather than their calculated score (mean appealed MELD/PELD was 26.9 ± 8.0). Abdominal imaging was obtained at a mean 3.1 ± 3.0 months before LT.

Survival analysis using Cox proportional hazards adjusted for age and sex showed an increased risk of death (either while awaiting LT or after LT) with smaller PMSA (hazard ratio [HR], 1.6 per 100 mm^2 [$P = 0.03$], 95% CI, 1.1-2.8). In other words, holding age constant and controlling for sex, the risk of death increased by 60% per 100 mm^2 decrease in PMSA. Of note, we observed a mean difference in PMSA between LT candidates and controls of 353.5 mm^2. We also observed this degree of difference among LT candidates. For example, a comparison of 2 patients with an age difference of 3 days, both LT candidates, had a PMSA difference of 391.3 mm^2.

After LT, patients spent a mean 1.2 ± 3.0 days intubated, 7.5 ± 8.8 days in the ICU, and 16.2 ± 11.6 days total in the hospital. In univariate analysis, lower PMSA correlated significantly with longer intubation ($r = -0.40$, $P = 0.004$), ICU LOS ($r = -0.52$, $P < 0.001$), and total hospital LOS ($r = -0.42$, $P = 0.003$) following transplantation. However, in multivariable analysis, once age was included in the

TABLE 3. Clinical Characteristics of Deceased Patients

Timing of Death	Primary Diagnosis	Calculated PELD or MELD* (Appealed)	Complications of Liver Disease	Cause of Death	Age at Time of Death	PMSA at L4 (mm^2)	PMSA *z* Score†
On the waiting list	Biliary atresia	18 (appealed PELD 40)	Malnutrition, ascites, and SBP	Sepsis, MSOF, cerebral hemorrhage	7 months	331.9	N/A
On the waiting list	Biliary atresia	17 (appealed PELD 27)	Malnutrition, variceal hemorrhage	Pulmonary and esophageal hemorrhage	11 months	253.4	N/A
On the waiting list	Biliary atresia	14 (appealed PELD 24)	Malnutrition, ascites, esophageal varices	Death at home, cause unknown	12 months	347.5	−0.0
On the waiting list	Cirrhosis, unknown etiology	10 (appealed PELD 27)	Variceal hemorrhage, hepatorenal syndrome	Sepsis, MSOF, pulmonary hemorrhage	12 months	338.9	N/A
After removal from the waiting list	Biliary atresia	26	Malnutrition, ascites, hepatorenal syndrome	Fungal sepsis, MSOF, cerebral edema, and herniation	8 months	265.6	N/A
After removal from the waiting list	Autoimmune hepatitis	31	Malnutrition, ascites, esophageal varices	Pneumonia, sepsis, ACLF	15 years	1224.3	−1.9
After removal from the waiting list	Autoimmune hepatitis	15 (appealed MELD 25)	Malnutrition, ascites, variceal hemorrhage	Pneumonia, sepsis, MSOF	17 years	532.6	−4.3
0 days after LT	Biliary atresia	24 (Status 1B)	Malnutrition, variceal hemorrhage	Severe coagulopathy, hemorrhagic shock	11 months	338.9	N/A
8 days after LT	Biliary atresia	9 (appealed PELD 30)	Malnutrition, recurrent cholangitis, ascites	Primary nonfunction, cerebral edema and herniation	5 years	360.0	−1.2
17 days after LT	Alagille syndrome	7 (appealed PELD 27)	Malnutrition, pruritus	MSOF, sepsis, cerebral hemorrhage and herniation	18 months	367.0	−1.9
46 days after LT	Langerhans histiocytosis, secondary sclerosing cholangitis	17 (appealed PELD 25)	Malnutrition, ascites	Intracranial infection with cerebral edema and herniation	2 years	366.5	−1.9

*Calculated MELD or PELD score closest to the time of abdominal imaging (appealed MELD/PELD listed in parentheses, if applicable).
†PMSA *z* score cannot be calculated for patients <1 year of age.

analytic model, PMSA no longer correlated with length of intubation (partial $r^2 < 0.01$, $P = 0.57$), ICU LOS (partial $r^2 < 0.01$, $P = 0.89$), or total hospital LOS (partial $r^2 < 0.01$, $P = 0.85$). Furthermore, PMSA did not have a significant effect on the odds of returning to the operating room (odds ratio [OR], 1.0 per 100 mm^2 [$P = 0.86$]; 95% CI, 0.6-1.3), HAT (OR, 1.0 per 100 mm^2 [$P = 0.87$]; 95% CI, 0.5-1.3), PVT (OR, 0.7 per 100 mm^2 [$P = 0.52$]; 95% CI, 0.2-1.6), biliary complications (OR, 0.8 per 100 mm^2 [$P = 0.74$]; 95% CI, 0.2-2.3), or hospital readmissions in the 6 months after LT (OR, 1.1 per 100 mm^2 [$P = 0.07$]; 95% CI, 1.0-1.3). The odds of developing serious infection after LT increased with higher PMSA (OR, 1.2 per 100 mm^2 [$P = 0.002$]; 95% CI, 0.8-1.7).

Using normative data from the Morphomic Analysis Group at the University of Michigan Medical School, we calculated *z* score values for PMSA in both LT candidates and controls (Fig. 3). This was only possible in patients >1 year old at the time of imaging as the normative data only exist for patients 1 to 20 years of age. LT candidates had a mean PMSA *z* score of −1.5 ± 1.0 compared with −0.3 ± 0.9 for controls ($P < 0.001$). Of the 31 LT candidates, 7 (22.6%) >1 year of age had a PMSA *z* score ≤−2 compared with only 1 of 29 controls (3.4%; $P = 0.05$). Cox survival analysis using PMSA *z* score as the predictor demonstrated a 4.9 times higher risk of death for every 1 SD decrease in PMSA *z* score (HR, 4.9 [$P = 0.05$]; 95% CI, 1.2-34.5). Figure 4 demonstrates the effect of PMSA *z* score on survival in LT candidates >1 year of age at 3 representative sample ages.

As seen with the raw PMSA value, PMSA *z* score did not correlate with ICU LOS ($r = -0.16$, $P = 0.43$) or total hospital LOS ($r = -0.19$, $P = 0.34$) and did not predict the following perioperative complications: return to the operating room (OR, 3.2 [$P = 0.18$]; 95% CI, 0.6-3.4), HAT (OR, 0.7 [$P = 0.64$]; 95% CI, 0.1-2.8), biliary complications (OR, 1.3 [$P = 0.82$]; 95% CI, 0.1-8.7), PVT (OR, 1.2 [$P = 0.82$]; 95% CI, 0.1-9.2), or hospital readmissions (OR, 1.2 [$P = 0.39$]; 95% CI, 0.7-2.7). PMSA *z* score also did not correlate with the calculated MELD/PELD score at the time of LT ($r = 0.10$, $P = 0.60$) or appealed MELD/PELD score ($r = 0.10$, $P = 0.69$) (Fig. 5). PMSA *z* score correlated significantly with weight *z* score ($r = 0.61$, $P < 0.001$), height *z* score ($r = 0.58$, $P < 0.001$), BMI *z* score ($r = 0.43$, $P = 0.03$), and MAC *z* score ($r = 0.42$, $P = 0.007$), but did not correlate with weight-for-length *z* score or TSF *z* score (Table 4).

Discussion

A growing body of evidence highlights the prevalence of sarcopenia in adults with chronic liver disease and

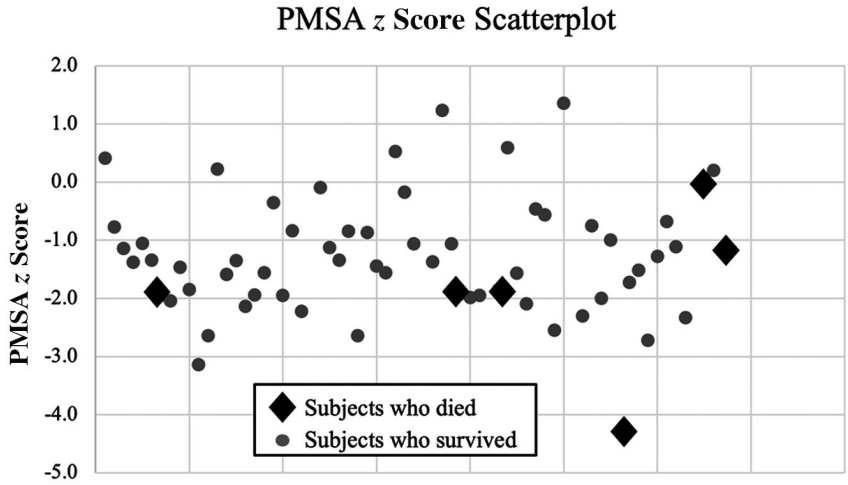

FIG. 3. PMSA *z* score scatterplot. This scatterplot provides a visual representation of the PMSA *z* score distribution for all patients >1 year of age who either survived (♦) or died (•) on the waiting list, after removal from the waiting list, or after LT). Only patients who were ≥1 year of age at the time of imaging are included, as *z* score calculations are not available for patients <1 year of age. The majority of patients who died had a PMSA *z* score of ≤−2.

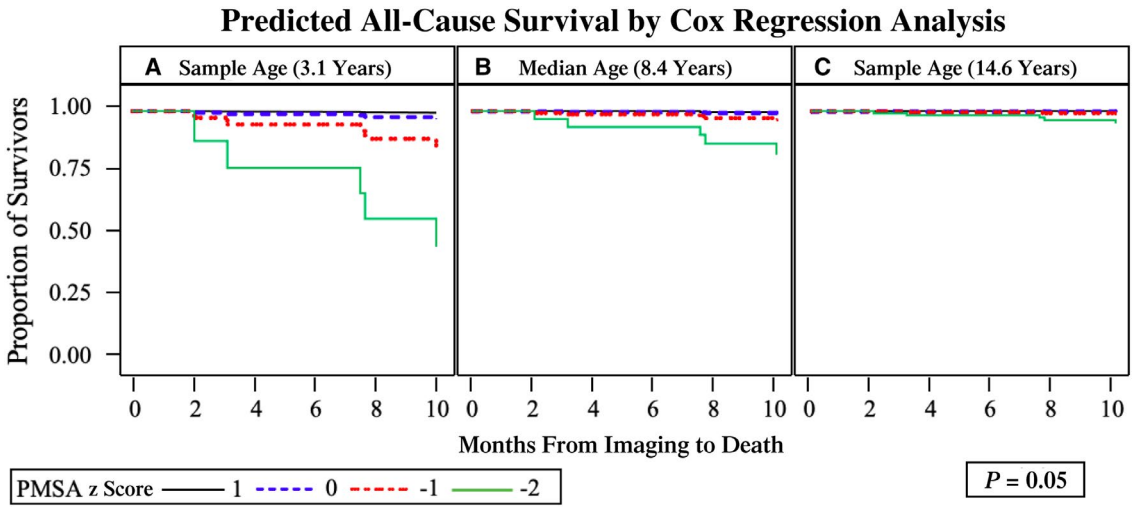

FIG. 4. Effect of PMSA *z* score on survival for LT candidates. This figure demonstrates the effect of PMSA *z* score on survival in LT candidates >1 year of age at the following 3 representative ages: (A) sample age 3.1 years, (B) median age 8.4 years, and (C) sample age 14.6 years. Survival was poorer for lower PMSA *z* scores (eg, *z* score −2 versus −1; $P = 0.05$). The effect of PMSA *z* score on survival was more pronounced in the younger age groups (A and B) than in the older age group (C).

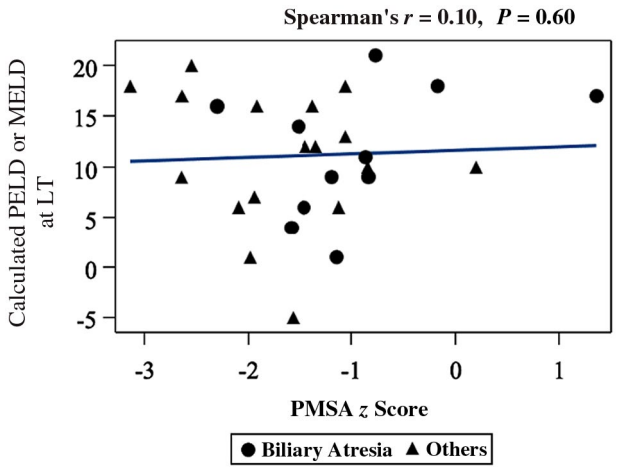

FIG. 5. Correlation between PMSA *z* score and calculated MELD/PELD score. There was poor correlation between the PMSA *z* score and the calculated MELD or PELD score at the time of LT, regardless of the underlying etiology of liver disease (ie, biliary atresia [●] or other primary liver disease [▲]).

TABLE 4. Correlation of PMSA *z* Score With Markers of Disease Severity and Anthropometrics

Correlation With PMSA *z* Score	Spearman's *r*	*P* Value
Calculated MELD/PELD	0.10	0.60
Adjusted MELD/PELD	0.10	0.69
Weight *z* score	0.61	**<0.001**
Height *z* score	0.58	**<0.001**
BMI *z* score	0.43	**0.03**
Weight-for-length *z* score	0.20	0.80
MAC *z* score	0.42	**0.007**
TSF *z* score	0.02	0.90

P values listed in bold are significant at <0.05.

the adverse impact on outcomes for those requiring LT. Given the vast physiologic differences between children and adults, the aforementioned literature cannot be applied to children. This study systematically identifies deficits in PMSA, indicating the presence of significant sarcopenia in pediatric LT candidates compared with healthy controls. Furthermore, the presence of sarcopenia (as reflected by lower PMSA) predicts higher mortality for children who require LT (while on the waiting list or after LT).

Significant differences between the height and weight of LT candidates and controls emphasize that malnutrition and stunting commonly plague children with chronic liver disease. In healthy children, BMI and weight-for-length are routinely used indicators of adequate nutrition and growth. Similarities in BMI and weight-for-length between LT candidates and controls, however, serve as critical reminders that these parameters often overrepresent the

nutritional adequacy of children with liver disease. The validity of these standard measurements is confounded by organomegaly, fluctuating ascites, and stunting of height progression, therefore not adequately reflecting malnutrition.[14] Measurement of PMSA allows for a novel assessment of nutritional status, unaffected by organomegaly and fluid overload. Practically, however, the correlation between PMSA *z* score and MAC *z* score supports the current use of MAC anthropometrics in clinical practice as a rapid and effective method to assess muscle bulk in the office setting.

PMSA had a significant detrimental effect on mortality for pediatric LT candidates. The risk of death (while on the waiting list or after LT) was 4.9 times higher for every 1 SD decrease in PMSA *z* score; for example, the risk of death would increase by 390% for a PMSA *z* score of −2 compared with a *z* score of −1. The limitation of this *z* score–based analysis, however, is that we are only able to study LT candidates >1 year of age, therefore excluding one-third of the studied LT candidates (the youngest and potentially most vulnerable subgroup of the at-risk population) and decreasing the sample size (likely contributing to the wide CI in this case). Given the importance of capturing the effect of muscle size on survival in this particularly vulnerable subpopulation, we also performed age-adjusted and sex-adjusted survival analyses of the entire LT cohort using raw PMSA values as opposed to the *z* score. When we examined the effect of the raw PMSA value on overall mortality in LT candidates, we found that the risk of death was 1.6 times as likely for every 100 mm^2 decrease in PMSA.

The effect of sarcopenia, as measured by PMSA, on mortality in pediatric LT candidates has not been studied previously. With 1 in 10 infants and 1 in 20 older children dying on the LT waiting list each year, there is an urgent need to further stratify children with ESLD who are at highest risk of death.[15] The MELD and PELD scores were designed to predict the risk of death without transplantation and therefore allocate organs to the sickest potential recipients first. In pediatrics, however, these scores often inadequately capture disease severity. Of our pediatric LT candidates, 69% received an organ based on MELD/PELD exception points rather than their calculated scores, similar to national data.[16] Interestingly, PMSA *z* score did not correlate with either the calculated MELD/PELD score at the time of LT ($r = 0.10$, $P = 0.60$) or the appealed MELD/PELD score ($r = 0.10$, $P = 0.69$). The pediatric transplant community needs a more robust tool that will adequately reflect the severity of liver disease and therefore potential risk of death in children requiring LT. The data provided in this study demonstrate that sarcopenia may provide an additional context for defining disease severity and risk of death in children with chronic liver disease.

Although CT and MRI measurements of PMSA have been used extensively in adults who require LT, this is a novel technique to assess outcomes in children with chronic liver disease. This study, however, has several limitations. Retrospective data collection resulted in nonuniform timing of imaging before LT used to assess PMSA. Furthermore, serial imaging was not available to determine if muscle size changed over time and with worsening disease severity as individual patients progressed toward LT. The differences in PMSA between LT candidates and controls ≤1 year of age was substantially smaller than in those >1 year of age (78.1 versus 577.5 mm^2), although both differences were statistically significant. In this study, we were unable to determine if this reflects less sarcopenia in younger patients because of the shorter length of illness before transplant versus an inherent reflection of their disease process. The heterogenous underlying disease conditions in the LT candidates may also impact the pathophysiology of muscle wasting; however, we only included children with chronic/progressive cholestatic and/or fibrotic liver disease. We excluded cases in which there was not underlying structural chronic liver disease, such as hepatic malignancy and metabolic disorders (eg, ornithine transcarbamylase deficiency, glycogen storage disease), as we suspect these diseases may affect muscle physiology differently. Factors beyond the underlying liver disease may also contribute to muscle wasting (eg, pulmonary status in a child with cystic fibrosis). In addition, the very small muscle size in the youngest children had the potential to amplify any variations in measurements. Although PMSA did not predict the occurrence of posttransplant complications (eg, return to the operating room and hepatic artery thrombosis), this may have been attributed to the small number of each of these individual events. Although the increased risk of infection with increasing PMSA size was unexpected (OR, 1.2 per 100 mm^2; 95% CI, 0.8-1.7), this result is statistically insignificant as the 95% CI crosses 1 and should be interpreted with caution.[17] Finally, given its retrospective nature, this study does not include a

measure of muscle function, another important component of sarcopenia.[18]

This study demonstrates significant sarcopenia in children with chronic liver disease with an alarming negative impact on survival. Little is known about the mechanisms of muscle loss (or perhaps lack of muscle gain) in this specific population. In adults with cirrhosis, myostatin, a myokine that inhibits protein synthesis and activates proteolysis, seems to play a key role.[19,20] Elevated ammonia upregulates myostatin expression in the muscle of adults with cirrhosis, and serum myostatin levels are elevated in these patients; furthermore, myostatin levels negatively correlate with muscle mass.[21] Other mechanisms under investigation include the role of hormonal factors (such as testosterone and growth hormone) and chronic inflammation, although this research is primarily in adults.[19-21] Multiple mechanisms likely overlap with resultant muscle loss in children with chronic liver disease. An improved understanding of the mechanisms driving sarcopenia in pediatric liver disease will be necessary to develop effective screening and intervention strategies for this vulnerable population.

In conclusion, children with chronic liver disease have significant reductions in muscle size. We have shown the negative impact on survival in LT candidates with lower PMSA. In the future, robust and well-designed prospective studies will be necessary to further understand the impact of sarcopenia on outcomes in pediatric chronic liver disease and the mechanisms by which muscle wasting occurs. This will require an ascertainment of changes in developmental status and body composition throughout childhood, which may help to improve our understanding of both nutritional and functional muscle status in pediatric chronic liver disease.

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