

# Sarcopenia in Children With End-Stage Liver Disease on the Transplant Waiting List

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Sarcopenia predicts morbidity and mortality in adults with end-stage liver disease (ESLD) and is determined by total psoas muscle area (tPMA) measurement from computed tomography (CT) imaging. Recently developed pediatric age- and sex-specific tPMA growth curves provide the opportunity to ascertain prevalence and impact of sarcopenia in children awaiting liver transplantation (LT). This retrospective single-center study evaluated sarcopenia in children between 1 and 16 years with ESLD and a clinically indicated abdominal CT less than 3 months before first isolated LT. Sarcopenia was defined as tPMA  $z$  score less than  $-2$  measured at the intervertebral L4-5 level. Patient demographic, biochemical, and outcome data were recorded. tPMA was compared with other measures of nutritional status using univariate and multivariate logistic analyses. Outcome measures included 1-year morbidity events and mortality after LT. CT images from 25 (64% female) children with median age of 5.50 (interquartile range [IQR], 3.75-11.33) years were reviewed. Ten children (40%) had a tPMA  $z$  score less than  $-2$ . Sarcopenia was associated with lower  $z$  scores for weight (odds ratio [OR], 0.38;  $P = 0.02$ ), height (OR, 0.32;  $P = 0.03$ ), and nutritional support before LT (OR, 12.93;  $P = 0.01$ ). Sarcopenic children had a longer duration of pediatric intensive care unit (PICU) stay (3.50 [IQR, 3.00-6.00] versus 2.00 [IQR, 2.00-3.50] days;  $P = 0.03$ ). Sarcopenia was prevalent in 40% of children with ESLD awaiting LT, and lower tPMA  $z$  score was associated with deficient anthropometrics and need for nutritional support before LT. Post-LT PICU duration was increased in children with sarcopenia, reflecting adverse outcomes associated with muscle loss. Further studies are needed to elucidate the underlying mechanisms of sarcopenia in children with ESLD.

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Sarcopenia, defined as a decrease in skeletal muscle mass and function, is a frequent finding in adults with cirrhosis.<sup>(1-3)</sup> In a recent consensus statement by the North American Working Group on Sarcopenia in Liver Transplantation, computed tomography (CT)

assessment of total psoas muscle area (tPMA) was recommended as the gold standard technique to assess sarcopenia in patients with cirrhosis.<sup>(4)</sup> Unaffected by ascites, tPMA is linearly related to whole-body mass, providing an estimation of overall lean muscle mass in patients with end-stage liver disease (ESLD).<sup>(5,6)</sup> The prevalence of sarcopenia from cross-sectional CT images in adults on the waiting list for liver transplantation (LT) ranges between 40% and 70%.<sup>(2,7,8)</sup> Sarcopenia in adults is associated with increased waitlist morbidity and mortality caused by sepsis and infections<sup>(9)</sup> and impaired posttransplant outcomes, including decreased patient survival,<sup>(1,2,10-12)</sup> increased serious infection,<sup>(11,13-16)</sup> prolonged intubation<sup>(11,17)</sup> with a longer duration of intensive care unit (ICU) stay,<sup>(11,17,18)</sup> longer overall hospitalization,<sup>(11,19)</sup>

*Abbreviations: BA, biliary atresia; BCAA, branched chain amino acid; BMI, body mass index; CI, confidence interval; CT, computed tomography; DEXA, dual energy X-ray absorptiometry; ESLD, end-stage liver disease; HPS, hepatopulmonary syndrome; ICC, intraclass correlation coefficient; ICU, intensive care unit; INR, international normalized ratio; IQR, interquartile range; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NA, not applicable; NGT, nasogastric tube; OR, odds ratio; PELD, Pediatric End-Stage Liver Disease; PICU, pediatric intensive care unit; PMA, psoas muscle area; tPMA, total psoas muscle area; TPN, total parenteral nutrition.*

rejection,<sup>(20)</sup> decreased graft survival,<sup>(21)</sup> and postoperative complications.<sup>(14,18,22,23)</sup>

Sarcopenia contributes to impaired growth and outcomes in pediatric chronic conditions, such as leukemia, inflammatory bowel disease, and chronic liver/intestinal failure.<sup>(24-26)</sup> The “state of health” of children with ESLD on the waiting list for LT is influenced not only by the severity of liver disease but also by nutritional status, functional impairments, and the development of extrahepatic comorbidities.<sup>(3)</sup> Poor nutritional status is likely both a cause and effect of sarcopenia. Factors include decreased oral (protein, sodium, and/or volumes) intake and maldigestion and malabsorption with cholestasis as well as fasting for procedures.<sup>(27)</sup> There are alterations in metabolism, including shifts to gluconeogenesis, a proinflammatory state, and an

increase in proteolysis and a reduction in protein synthesis attributed to a decrease in circulating branched chain amino acids (BCAAs).<sup>(28)</sup> Physical activity is limited as a result of hospitalization, lines and tubes, and an unwell state. Pediatricians are attuned to assessing nutritional status using tools such as anthropometrics, growth parameters, and the subjective “eyeball test.” Commonly used nutritional biomarkers are unreliable in children with ESLD.<sup>(29,30)</sup> Ascites, edema, and organomegaly, known complications of portal hypertension, confound weight measurements.<sup>(30-33)</sup> Anthropometrics, such as triceps skinfold thickness and mid-arm circumference, are often not routinely performed and are operator dependent. Although experienced physicians may have a clinical gestalt for detecting patients at risk, there is a need for easily attainable and objective measures to fully capture the extent of malnutrition and poor health status and to aid risk stratification of children with ESLD on the pediatric LT waiting list.<sup>(4)</sup>

CT has wide availability, is commonly used clinically for surgical planning, is low cost, and offers rapid assessment of muscle mass compared with other modalities, such as dual energy X-ray absorptiometry (DEXA) and magnetic resonance imaging (MRI). Smaller measurements of tPMA at intervertebral lumbar levels are reported in children with ESLD compared with age-matched and sex-matched healthy controls.<sup>(34,35)</sup> We have recently derived pediatric growth curves for tPMA (mm<sup>2</sup>) at intervertebral lumbar L3-4 and L4-5 levels to enable calculation of z scores of tPMA from CT images for children aged between 1 and 16 years.<sup>(36)</sup> Sarcopenia was defined as a tPMA z score less than -2 measured at the intervertebral L4-5 level. The goal of this study is to determine the prevalence of sarcopenia in children with ESLD awaiting LT and explore its association with traditional markers of nutritional status as well as outcomes immediately and in the 1-year post-LT period.

## Patients and Methods

### STUDY POPULATION

Between January 2003 and June 2016, 269 pediatric patients younger than 18 years of age underwent first isolated LT at the Hospital for Sick Children in Toronto, Canada. Of these patients, 87 had a clinically indicated abdominal CT scan less than 3 months

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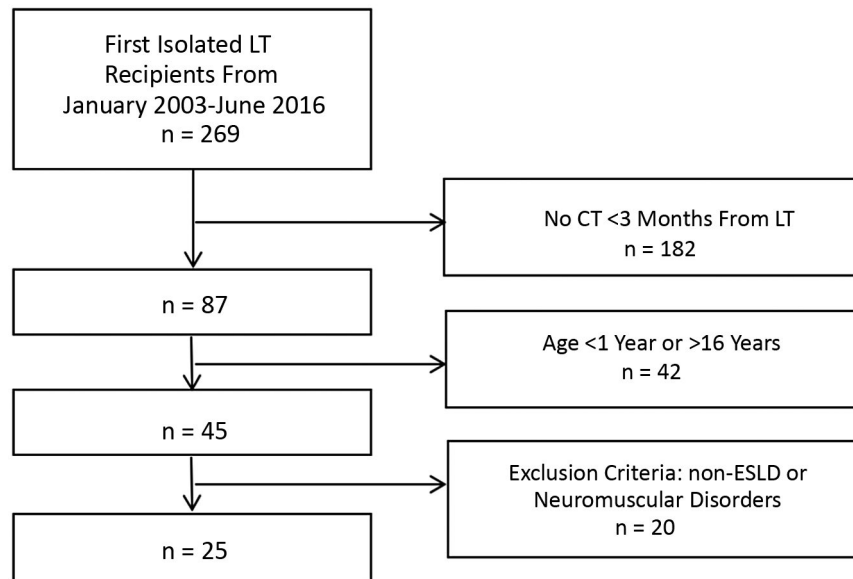


FIG. 1. CONSORT diagram of included study population.

before LT surgery. Children aged younger than 1 year or older than 16 years were excluded because reference ranges for  $z$  score calculations were not available for these age groups. Children with a primary indication for LT that was not chronic ESLD (such as hepatoblastoma, pediatric acute liver failure, or a metabolic liver condition) and those with preexisting neuromuscular disorders were excluded (Fig. 1). This study was approved by the Research Ethics Board at the Hospital for Sick Children, and a waiver of informed consent was granted.

## STUDY DESIGN

This was a retrospective single-center study. Charts were reviewed for patient demographic factors (age, sex, underlying diagnosis, and days on the waiting list), clinical manifestations (presence/absence of hepatorenal syndrome, hepatopulmonary syndrome [HPS]), and biochemical values, including complete blood count, bilirubin (conjugated, unconjugated, delta, and total), liver enzymes (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase), liver function (albumin, international normalized ratio [INR], ammonia), and renal function, on the date of CT imaging. Ultrasound findings (ie, ascites) were recorded before LT. At the time of CT, anthropometrics (height, weight, body mass

index [BMI]) with  $z$  scores, Pediatric End-Stage Liver Disease (PELD) scores, or Model for End-Stage Liver Disease (MELD) scores were recorded. Nutritional supplementation with a nasogastric tube (NGT), total parenteral nutrition (TPN), or both was collected before LT. The decision to start nutritional support by a NGT or TPN was at the discretion of the clinical care team. Graft type (live versus deceased donor organ) was recorded along with days on the waiting list.

The outcomes measured included early and late morbidities after LT. Early post-LT complications included biliary (biliary stricture or leak), vascular (hepatic artery thrombosis or stenosis), primary nonfunction, duration of ICU stay (days), intubation (days) following LT, and time to hospital discharge after LT. Late morbidities included number of culture-positive infections, histopathologic-confirmed allograft rejection, graft loss, and death up to 1 year after LT. A posttransplant infection was defined as the presence of a positive bacterial (blood or urine) culture, viral culture or test (ie, nasopharyngeal swab), stool culture (*Clostridium difficile*, bacterial, viral), chest X-ray-confirmed pneumonia, or other (ie, wound, cholangitis) infection with a positive culture and/or treatment with antibiotics. The number and type of infections, including identified organism, were collected. Episodes of acute cellular rejection of the graft were also recorded and were defined as a liver biopsy

with Banff criteria greater than 4/9.<sup>(37)</sup> Graft loss was defined by the decision for a patient to be listed for LT.

## tPMA MEASUREMENTS

Abdominal CT imaging was retrieved from our institution's Picture Archiving and Communication System. The right and left psoas muscle areas (PMAs) were measured using a geometric region-of-interest measurement tool on axial CT images at the L4-5 intervertebral disc level, as described.<sup>(17,34)</sup> Axial CT images through the corresponding disc level were identified by cross-referencing the level on coronal or sagittal plane reconstruction images. tPMA was expressed as the total sum of the left and right PMAs (mm<sup>2</sup>). All images were evaluated by a single radiologist (M.P.). A second radiologist (G.B.C.) independently measured 10% of randomly selected CTs to determine interobserver agreement. Analysis of agreement was performed using the intraclass correlation coefficient (ICC) to assess the reliability of the medical instruments measuring continuous outcomes.

Sarcopenia was defined as a tPMA *z* score of less than -2. The *z* scores for tPMA were calculated using recently developed age-specific and sex-specific reference ranges for healthy children using an online calculator tool.<sup>(36)</sup>

## STATISTICAL ANALYSIS

Baseline characteristics were examined using means and standard deviations for normally distributed data or medians and interquartile ranges (IQRs) for skewed data. Descriptive statistics are reported as medians with IQRs for continuous variables and frequencies and percentages for categorical variables. Comparative statistics were performed between patients with and without sarcopenia using RStudio Team.<sup>(38)</sup>

Independent-sample *t* tests were used to compare means, and when normality assumptions did not hold, nonparametric Mood median tests were used. Chi-square tests were used to compare frequencies, and when sample sizes were small (<5), Fisher's exact test was used. Correlation analysis was used to examine the relationship between traditional anthropometrics and tPMA. A *P* value of <0.05 was deemed to be significant for all tests. Univariate regression analysis was performed to determine if a patients' demographics and clinical measurements were associated with sarcopenia. Weight *z* score, height *z* score, and serum conjugated

bilirubin level at the time of CT were subsequently put into a multiple regression analysis to determine if there was an association with sarcopenia after adjusting for the other variables.

## Results

### STUDY POPULATION

A total of 25 children (64% female; median age, 5.50 [IQR, 3.75-11.33] years) comprised the study cohort (Fig. 1). All of the patients had chronic liver disease, with the most common indications for LT being biliary atresia (BA; *n* = 6; 24%) and primary sclerosing cholangitis (*n* = 6; 24%; Supporting Table 1). Table 1 provides demographic, clinical, and biochemical data. BMI was calculated in 19 patients (4 patients were younger than 2 years of age, and 2 others were missing height measurements). Ammonia values were not available for 8 (32%) of the patients. Complications of ESLD are reported in Table 1. Outcome measures are included in Table 2. Overall morbidity was low, and no patient was relisted or died during the study period (Table 2).

### STUDY POPULATION WITH SARCOPENIA AND COMPARATIVE ANALYSIS

The *z* score for tPMA at L4-5 was less than -2 in 10 (40%) patients (90% female; 70% living donor liver graft; median age, 5.00 [IQR, 3.00-11.25] years; days listed, 60.00 [IQR, 30.00-124.70]). Table 1 highlights the differences between patients with sarcopenia and patients without sarcopenia. Briefly, patients with sarcopenia were more likely to be girls (90.00% versus 46.70%; *P* = 0.07) and to have statistically lower weight *z* scores (-1.65 [IQR, -2.48 to -0.95] versus 0.35 [IQR, -1.09 to 0.97]; *P* = 0.00) as well as lower height *z* scores (-2.33 [IQR, -3.08 to -1.47] versus 0.71 [IQR, -0.98 to 1.59]; *P* = 0.01; Table 1). Pretransplant nutritional support was provided more frequently to patients with sarcopenia than to patients without sarcopenia (70.00% versus 15.60%; *P* = 0.01) and more often in the form of NGT feeding (60.00% versus 14.20%; *P* = 0.03; Table 1). There were no significant differences in age, diagnosis, graft type, time to transplant, biochemistry, or severity of disease (ie, PELD/MELD, ascites) between patients with and without sarcopenia (Table 1).



**TABLE 1. Demographics, Disease Factors, and Laboratory Values in the Study Population and Patients With and Without Sarcopenia**

Variable	Study Population (n = 25)	With Sarcopenia (n = 10)	Without Sarcopenia (n = 15)	P Value*
Patient demographics				
Female	16.00 (64.00)	9.00 (90.00)	7.00 (46.70)	0.07
Diagnosis				
BA	6.00 (24.00)	1.00 (10.00)	5.00 (33.33)	0.33
Age at CT, years	5.50 (3.75-11.33)	5.00 (3.00-11.25)	5.50 (3.96-9.67)	0.82
Date of listing to transplant	80.00 (36.00-125.00)	60.00 (30.00-124.70)	91.00 (66.50-121.00)	0.62
Live donor graft	19.00 (76.00)	7.00 (70.00)	12.00 (80.00)	0.92
Growth z score measurements				
Weight z score	-0.95 (-1.98 to 0.40)	-1.65 (-2.48 to -0.95)	0.35 (-1.09 to 0.97)	0.00 <sup>†</sup>
Height z score	-0.52 (-1.73 to 0.97)	-2.33 (-3.08 to -1.47)	0.71 (-0.98 to 1.59)	0.01 <sup>†</sup>
BMI z score	0.19 (-0.35 to 0.71)	-0.03 (-0.79 to 0.73)	0.61 (-0.28 to 0.91)	0.44
tPMA z score	-1.48 (-2.73 to -1.07)	-3.11 (-3.54 to -2.64)	-1.18 (-1.46 to -0.48)	0.00 <sup>†</sup>
Laboratory values				
Conjugated bilirubin (umol/L)	70.00 (0-142.00)	94.50 (19.50-160.20)	6.00 (0-119.00)	0.32
Platelets (×10 <sup>9</sup> /L)	131.00 (71.00-234.00)	228.00 (104.00-302.00)	95.00 (65.00-155.50)	0.09
Alanine aminotransferase (U/L)	104.00 (69.00-184.00)	99.50 (38.70-252.00)	104.00 (80.00-175.50)	0.42
PELD/MELD score	8.00 (3.00-10.00)	8.00 (6.25-9.75)	8.00 (-0.50 to 10.00)	0.46
Complications of ESLD				
Ascites	6.00 (24.00)	3.00 (30.00)	3.00 (20.00)	0.64
HPS	4.00 (16.00)	2.00 (20.00)	2.00 (13.33)	1.00
Nutritional support before LT				
NGT	8.00 (32.00)	6.00 (60.00)	2.00 (14.20)	0.03 <sup>†</sup>
TPN	4.00 (16.00)	2.00 (20.00)	2.00 (15.30)	1.00
NGT or TPN	9.00 (36.00)	7.00 (70.00)	2.00 (15.60)	0.01 <sup>†</sup>
NGT and TPN	3.00 (12.00)	1.00 (10.00)	2 (14.20)	1.00

NOTE: Data are provided as n (%) or median (IQR).

\*Analysis between sarcopenic and nonsarcopenic groups.

<sup>†</sup>Statistically significant.

**TABLE 2. Morbidity Outcome Factors 1 Year Following LT in the Study Population and Patients With and Without Sarcopenia**

Outcome Measure	Study Population (n = 25)	With Sarcopenia (n = 10)	Without Sarcopenia (n = 15)	P Value*
Intubation duration, days	1.00 (1.00-2.00)	2.00 (1.00-3.00)	1.00 (1.00-2.00)	0.15
ICU duration, days	3.00 (2.00-4.00)	3.50 (3.00-6.00)	2.00 (2.00-3.50)	0.03 <sup>†</sup>
Vascular complications	1.00 (4.00)	0 (0)	1.00 (6.67)	NA
Biliary complications	0 (0)	0 (0)	0 (0)	NA
Days to discharge	24.00 (17.00-36.00)	28.00 (19.50-34.50)	18.00 (16.50-36.00)	0.48
Number of infections	1.00 (0-2.00)	1.00 (0-2.00)	0 (0-2.00)	0.79
Number of rejections	0 (0-1.00)	0.50 (0-1.00)	0 (0-1.00)	1.00
Relisted	0 (0)	0 (0)	0 (0)	NA

NOTE: Data are provided as n (%) or median (IQR).

\*Statistics performed between sarcopenic and nonsarcopenic groups.

<sup>†</sup>Statistically significant.

## MEASURES OF NUTRITIONAL DEFICITS

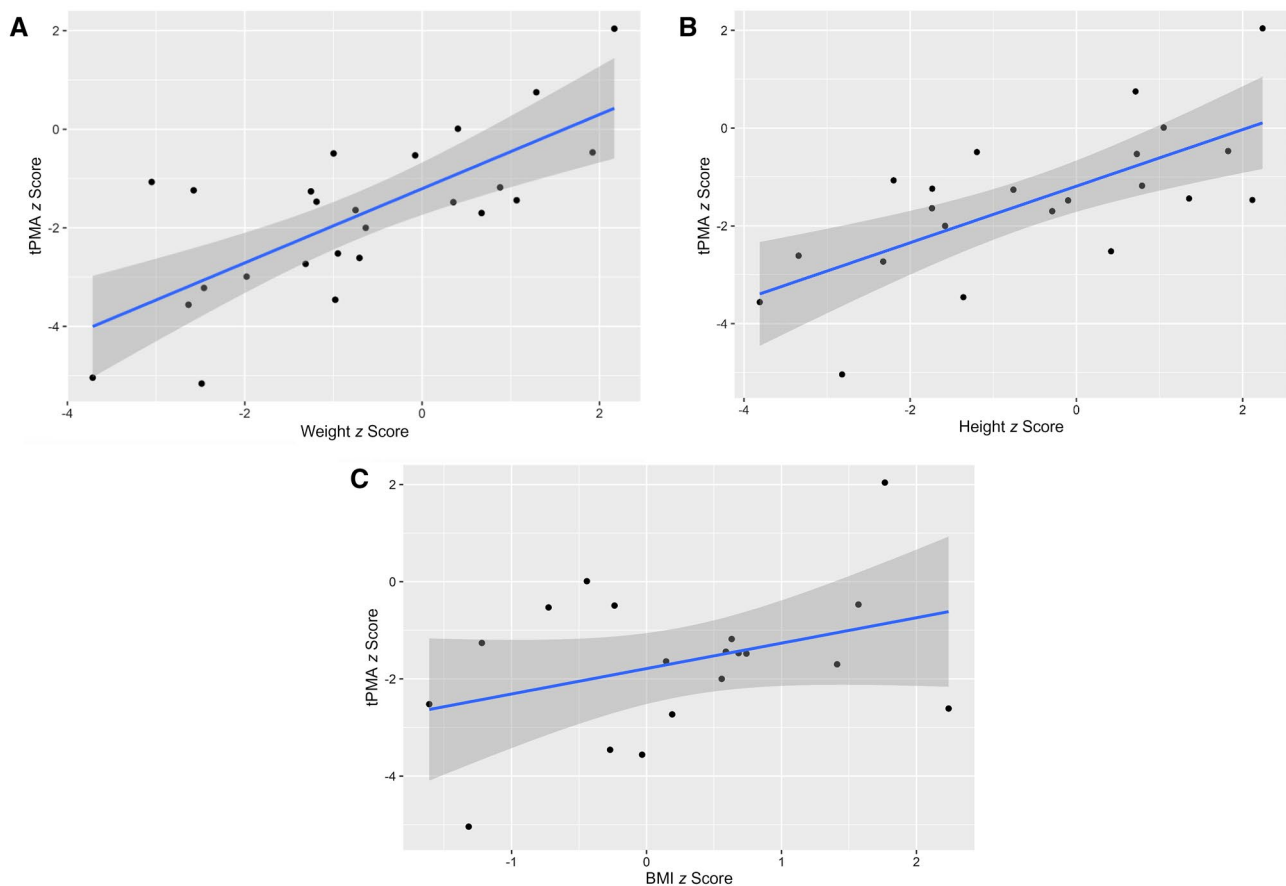
The traditional anthropometric measures of weight  $z$  score and height  $z$  score had moderate correlations with tPMA  $z$  scores (weight  $z$  score,  $R^2 = 0.73$  [ $P < 0.00$ ]; height  $z$  score,  $R^2 = 0.68$  [ $P < 0.001$ ]). BMI only weakly correlated with tPMA  $z$  score ( $R^2 = 0.36$ ;  $P = 0.12$ ; Fig. 2). There were 7 patients in the study cohort with tPMA not consistent with weight and height  $z$  scores. There were 2 patients whose tPMA was greater than  $-2$  ( $-1.07$  and  $-1.24$ ), but their weight  $z$  scores were less than  $-2$  ( $-3.05$  and  $-2.58$ ). Of the 10 patients, 5 with tPMA  $z$  scores less than  $-2$  had a weight  $z$  score greater than  $-2$ ; 2 of these patients also had a height  $z$  score that was greater than  $-2$  (Supporting Table 2).

Univariate analysis showed a significant association of weight  $z$  score (odds ratio [OR], 0.38; 95%

confidence interval [CI], 0.14-0.75;  $P = 0.02$ ), height  $z$  score (OR, 0.32; 95% CI, 0.10-0.72;  $P = 0.03$ ), and nutritional therapy before LT (NGT only; OR, 8.99; 95% CI, 1.43-18.1;  $P = 0.03$ ) and NGT or TPN (OR, 12.83; 95% CI, 1.97-18.6;  $P = 0.01$ ; Table 3) with sarcopenia. Multivariate analysis demonstrated that for each unit (1.00) decrease in weight or height  $z$  score, the risk of sarcopenia increased by 13% and 73%, respectively, although these were not statistically significant. There was no increased risk of sarcopenia with an increase in conjugated bilirubin (Table 4).

## OUTCOME MEASURES

Patients with sarcopenia had a significantly longer duration of ICU stay after LT (3.50 [IQR, 3.00-6.00] days) compared with patients without sarcopenia (2.00 [IQR, 2.00-3.50] days;  $P = 0.03$ ). Duration of intubation immediately after LT was longer in patients with



**FIG. 2.** Correlation analysis (A) between tPMA  $z$  score and weight  $z$  score (correlation coefficient, 0.73;  $P < 0.001$ ), (B) between tPMA  $z$  score and height  $z$  score (correlation coefficient, 0.68;  $P < 0.001$ ), and (C) between tPMA  $z$  score and BMI  $z$  score (correlation coefficient, 0.36;  $P = 0.12$ ).

**TABLE 3. Univariate Analysis of Patient Factors and Their Association With Sarcopenia**

Variable	OR	95% CI	P Value
Weight z score	0.38	0.14-0.75	0.02*
Height z score	0.32	0.10-0.72	0.03*
BMI z score	0.64	0.22-1.62	0.37
Live donor, yes	0.58	0.08-3.91	0.57
Days listed	0.99	0.98-1.00	0.72
PELD/MELD score	1.03	0.93-1.17	0.49
Conjugated bilirubin	1.00	0.99-1.01	0.29
Albumin	0.98	0.93-1.02	0.49
INR	0.44	0.01-2.08	0.48
Platelets	1.00	1.00-1.01	0.09
Hemoglobin	0.96	0.91-1.00	0.12
NGT use before transplant	8.99	1.43-18.1	0.03*
TPN use before transplant	1.37	0.14-13.5	0.77
NGT or TPN use before transplant	12.83	1.97-18.6	0.01*
NGT and TPN use before transplant	0.66	0.02-8.06	0.76

\*Statistically significant.

**TABLE 4. Multiple Logistic Regression Analysis Between a Patient's Weight z Score, Height z Score, Conjugated Bilirubin at Time of CT Before LT, and Sarcopenic Status**

Variable	OR	95% CI	P Value
Weight z score	0.87	0.17-4.06	0.85
Height z score	0.27	0.04-0.90	0.05
Conjugated bilirubin	0.99	0.97-1.01	0.30

sarcopenia (2.00 [IQR, 1.00-3.00] versus 1.00 [IQR, 1.00-2.00]); however, this was not statistically significant ( $P = 0.15$ ). There were no significant differences in other early or late post-LT morbidity outcome measures, vascular or biliary complications, time to discharge, infection, rejection, graft loss, or patient death at the 1-year follow-up (Table 2).

## tPMA ANALYSIS

Interrater reliability was excellent, with an overall ICC of 0.96 for all randomly selected subjects with an independent tPMA measurement by a second radiologist.

## Discussion

This is the first study to use tPMA z scores using CT cross-sectional imaging at the intervertebral L4-5 level in children with ESLD on the waiting

list for pediatric LT. Sarcopenia was prevalent in 40% of children, as determined by tPMA measured from clinically indicated CT scans performed within 3 months before LT. Children identified as having sarcopenia were more likely to receive nutritional support before LT and had longer pediatric intensive care unit (PICU) stays after LT. The correlation of tPMA z scores with weight and height z scores was moderate among children awaiting organ availability for LT.

Excellent long-term patient survival rates after LT have broadened the indications for pediatric LT to include etiologies such as metabolic liver diseases and liver malignancies, although infants and children with ESLD caused by BA and other cholestatic conditions still constitute the majority of waiting lists worldwide.<sup>(39)</sup> Malnutrition is a known predictor of poor outcomes in children undergoing LT.<sup>(40,41)</sup> However, the currently available armamentarium of clinical tools to accurately ascertain a poor nutritional state in children is limited by confounders such as ascites and organomegaly. Sarcopenia has been well studied in adults with cirrhosis, with sobering adverse outcomes of increased waitlist mortality and increased postoperative complications.<sup>(9-13,15,17,22,23)</sup> The assessment, definition, and effect of sarcopenia on outcomes cannot simply be extrapolated to children. Children with ESLD offer added complex challenges distinct from adults, including a time-limited opportunity for growth and development while awaiting a suitable donor organ. A recent commentary by LT experts prioritized sarcopenia and noninvasive nutritional biomarkers as high-yield gap areas for research to aid the risk stratification of patients on the pediatric LT waiting list.<sup>(42)</sup>

Cross-sectional CT imaging to assess tPMA has been reported as the gold standard for ascertaining sarcopenia in adults.<sup>(4)</sup> Multiple levels have been used, including discrete vertebral disc, intervertebral levels, and the umbilicus level. In our cohort, 40% of children with ESLD had a tPMA z score less than -2 at the L4-5 intervertebral level on a clinically indicated abdominal CT scan. We used a z score of less than -2 to define sarcopenia because this is 2 standard deviations below the healthy mean and is the generally accepted definition of sarcopenia based on muscle mass in an aging population.<sup>(43)</sup> It also aligns with a pediatric study that defined sarcopenia in children with chronic liver disease by a z score of less than -2 for skeletal muscle mass using DEXA.<sup>(44)</sup> Adult studies to date have defined sarcopenia in numerous ways,<sup>(3)</sup>

including sex-specific cutoffs in which a skeletal index is normalized to height<sup>(15,17)</sup> and stratification by tertiles.<sup>(13,14)</sup> In a growing pediatric patient, *z* scores are robust and relevant. The range of prevalence of 40% to 70% reported in the adult ESLD literature is likely secondary to variation in definitions of sarcopenia in different studies.

Although L3 is the most commonly reported level in adult patients, unequivocal identification of the mid-vertebral body level often requires multiplanar reformation, which may be time consuming.<sup>(45)</sup> Studies have also frequently used intervertebral disc space level.<sup>(17,34,35,46-52)</sup> There have been several advantages articulated in favor of using these levels, including the increased variability in the exact anatomic definition of the level when the vertebral body is used (top, mid, bottom) compared with the narrower and thinner intervertebral disc space, thereby enabling a more consistent level determination for measurement of the psoas muscle at the midpoint between the 2 vertebral bodies.<sup>(36)</sup> Second, intervertebral levels offer the best correlation of single-slice and volumetric measurement of skeletal muscle.<sup>(45)</sup> Third, for measurement of the psoas muscle, L4-5 may be the most clinically relevant because of its correlation with whole-body skeletal mass and adipose tissue<sup>(6)</sup> as well as the fact that it is easier and more accurate to measure in pediatric patients.<sup>(36)</sup> In support of this, the L4-5 level demonstrated almost perfect ICC versus that at L3-4 in 2 studies of more than 800 pediatric patients.<sup>(34,36)</sup> Reference ranges for tPMA now exist in pediatrics for L3-4,<sup>(36)</sup> L4,<sup>(53)</sup> and L4-5.<sup>(36)</sup> We used L4-5 for this study for the aforementioned reasons and because these reference ranges provided the ability to determine *z* scores. The reference ranges developed by Lurz et al.<sup>(36)</sup> are also more reflective of our local study population and generalizable because of the differences in weight and ethnicity for the L4 reference ranges.<sup>(53)</sup>

Weight and height *z* scores demonstrated a moderate association with the tPMA *z* score in this cohort. There is a linear increase of weight and height with the surface area size of the psoas muscle in children in a healthy normative population as they age.<sup>(36,53)</sup> Therefore, we expect there to be an association with traditional anthropometrics and muscle mass in healthy children because these are all markers of growth and nutritional status. However, ESLD poses unique challenges in determining this relationship between muscle mass and traditional measures of nutritional status

in children. There are well-described limitations to anthropometrics in pediatric patients with ESLD. Complications such as ascites and organomegaly can make weight unreliable, and decreased height may be intrinsic in underlying genetic disorders, such as Alagille syndrome.<sup>(29-33)</sup> Nearly one-fourth (24%) of our cohort had ascites, which can falsely elevate weight. This may explain why we saw a stronger association than what has been described in other studies, which showed no correlation between weight *z* score and tPMA size.<sup>(34)</sup> Although weight and height *z* scores have some association with sarcopenia, we suggest that tPMA *z* scores are a more sensitive and reliable marker for dynamic changes in muscle mass and are therefore a superior method to assess nutritional status in children with ESLD. This objective marker is particularly important for patients in whom these growth measurements are unreliable as a result of complications of cirrhosis, such as ascites. To this point, we had several patients whose tPMA *z* score was less than -2 with a normal weight *z* score (2 of which had ascites), suggesting that additional measures beyond anthropometrics are needed to comprehensively assess nutritional status. Furthermore, muscle mass is dynamic and can change more quickly than weight or height,<sup>(54)</sup> so it may have more clinical relevance during illness and may necessitate imaging to be performed within 3 months of LT.

Patients with sarcopenia were almost 4 times more likely than children without sarcopenia listed for LT to receive nutritional support before LT. Clinical judgment by an experienced medical team in addition to serial anthropometric measurements guided the decision making regarding the need for nutritional prehabilitation in this cohort. Interestingly, 3 patients with sarcopenia received supplemental nutrition before LT despite normal weight *z* scores, whereas 2 patients with sarcopenia did not receive any, which suggests that additional clinical parameters are being used to determine nutritional support, and weight alone does not and should not drive this decision. Although physicians and dietitians may be able to subjectively identify patients at risk, a need remains for reliable and objective measures. Detecting sarcopenia early is important in patients listed for LT to implement nutritional prehabilitation and interventions to try to improve outcomes. Although patients with sarcopenia received more nutritional support than patients without sarcopenia, greater morbidity after LT was seen, with an increase in PICU duration. Therefore, this nutritional



support likely was either too little and/or too late to modify outcomes in our patients. Modalities to reduce sarcopenia in adult patients have explored optimization of total caloric intake and macronutrient composition, timing of feeds,<sup>(55)</sup> supplementation with BCAAs,<sup>(56)</sup> and physical activity.<sup>(57)</sup> Studies are needed in children to decipher mechanisms of sarcopenia so that targeted nutritional interventions can be developed.

A major gap in pediatric ESLD is the lack of a mechanistic understanding of how sarcopenia develops and is maintained. Impaired hepatic protein synthesis secondary to alterations in hormonal pathways is currently being investigated. We identified that sarcopenia was more prevalent in girls, which is similar to the results of the Mager et al. study,<sup>(44)</sup> who, using DEXA, showed that sarcopenia occurred more often in female pediatric patients younger than 10 years of age than in males and older females. This is in contrast to adult studies, which report male sex to be a risk factor for sarcopenia.<sup>(10,15,17,58)</sup> In adults, this is presumed to be related to differences in body composition and hormones between the sexes, which are also involved in muscle homeostasis.<sup>(11,59-62)</sup> Normal growth and puberty are altered in children with ESLD because of malnutrition, the underlying disease state, and medical therapies. The exact role of hormones and muscle metabolomics has yet to be delineated, and understanding their roles may be important to help guide clinical treatment in pediatric patients awaiting LT.

Sarcopenia affects outcomes after LT. The duration of ICU stay after LT was 1.5 days longer in children with sarcopenia. This may be attributed to a median longer duration of intubation in these patients immediately after LT, although this was not statistically significant compared with the duration of patients without sarcopenia. It is unlikely that the longer duration of ICU stay in our study is attributed to perioperative complications or infections, as there was no difference between the 2 groups. We noted no differences in the PELD/MELD scores but acknowledge that sarcopenia is not reflected in MELD scoring in adult studies.<sup>(9,11)</sup> Growth failure has been shown to be associated with a greater risk of need for LT or death in infants with BA,<sup>(63)</sup> and the finding that patients with sarcopenia have a longer duration in ICU after LT has been similarly observed in adult studies<sup>(11,17,18)</sup> and in 17 children with sarcopenia ascertained by DEXA.<sup>(44)</sup> Identifying patients who are at a higher risk of poor outcomes has important implications for transplantation. This may affect the timing of listing and,

potentially, organ allocation. There were no other differences in 1-year morbidity (Table 2), and no deaths occurred in the 1-year follow-up period. Conversely, adult studies have shown an increase in mortality after LT in patients with sarcopenia,<sup>(11,13,17)</sup> however, the frequency of mortality is generally low in pediatrics following LT.<sup>(64,65)</sup> Furthermore, our cohort was small and wait times were relatively short (median <3 months for all subjects), which may explain the low morbidity and mortality observed. There may be lasting effects of sarcopenia on morbidity after LT,<sup>(44)</sup> but further prospective studies that explore longer term outcomes are needed in pediatrics.

The strengths of our study include the use of easily obtainable cross-sectional imaging and newly developed normal growth curves to ascertain tPMA *z* scores in a homogeneous population of children, all with ESLD within 3 months of LT. Limitations include those inherent in a retrospective study. Although our center performs living donor LT in approximately 50% of patients listed each year, CTs have become routine for surgical mapping planning during the past decade, which may account for a smaller than expected study cohort size and may have created a selection bias for our subject population. We were unable to study children younger than 1 year of age, which may be the most vulnerable population for malnutrition, and we did not have any assessments of muscle function. Finally, although muscle mass clearly is an important predictor of LT, the definition of sarcopenia in children has only just been more recently widened, with reference ranges now available. It is possible that our definition of a *z* score of less than -2 may have underestimated the clinical relevance of sarcopenia in this population with regard to outcomes. The median tPMA in our study (*n* = 25) was low compared with healthy individuals, with a *z* score of -1.48. A *z* score cutoff that predicts morbidity and mortality outcomes following pediatric LT has yet to be determined.

In conclusion, we demonstrate that sarcopenia is prevalent in 40% of children with ESLD awaiting pediatric LT and is associated with a longer duration of PICU stay following LT. With the availability of pediatric tPMA reference ranges, we suggest that tPMA measured on CT cross-sectional imaging is an objective measure enabling earlier detection of sarcopenia to enhance anticipatory guidance and aggressive nutritional prehabilitation therapies toward the goal of expedited recovery during the posttransplant course. Children with irreversible ESLD offer a complex

challenge that is distinct from adults because of their time-limited opportunity for growth and development. Although pediatric hepatologists are often well versed in the importance of preemptive optimizing nutritional rehabilitation therapies, the persistent prevalence of sarcopenia in children with ESLD supports the rationale of prioritizing continued efforts toward strategies to expedite diagnostic tools, understand underlying mechanisms, and identify novel molecular therapeutic targets.

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