OPEN

Feasibility of Serial Ultrasound Measurements of the Rectus Femoris Muscle Area to Assess Muscle Loss in Patients Awaiting Liver Transplantation in the Intensive Care Unit

Alejandro Pita, MD,[1] Ioannis A. Ziogas, MD,[2] Fei Ye, PhD, MSPH,[3] Yufan Chen, MPH,[3] Muhammad A. Rauf, MD,[2] Lea K. Matsuoka, MD, FACS,[2] Navpreet Kaur, MD, FACS,[1] Gilbert Whang, MD,[4] Shannon M. Zielsdorf, MD,[1] Gerasimos Bastas, MD,[5] Manhal Izzy, MD,[6] and Sophoclis P. Alexopoulos, MD, FACS[2]

Background. End-stage liver disease (ESLD) patients requiring intensive care unit (ICU) care before liver transplantation (LT) often experience significant muscle mass loss, which has been associated with mortality. In this exploratory study, we primarily aimed to assess the feasibility of serial ultrasound (US) rectus femoris muscle area (RFMA) measurements for the evaluation of progressive muscle loss in ICU-bound potential LT candidates and describe the rate of muscle loss as assessed by sequential US RFMA measurements. Secondarily, we sought to identify patient characteristics associated with muscle loss and determine how muscle loss is associated with survival. **Methods.** We prospectively enrolled 50 ESLD adults (≥18 y old) undergoing evaluation for LT candidacy in the ICU. A baseline computed tomography measurement of psoas muscle area (PMA) and serial bedside US measurements of RFMA were obtained. The associations between patient characteristics, PMA, RFMA, ICU stay, and survival were analyzed. **Results.** Rapid decline in muscle mass by RFMA measurements was ubiquitously present and correlated to baseline PMA and length of ICU stay. RFMA normalized by body surface area decreased by 0.013 cm^2/m^2 (95% confidence interval, 0.010-0.016; $P<0.001$) for each day in the ICU. Decreased RFMA normalized by body surface area was associated with poor overall survival (adjusted hazard ratio, 0.42; 95% confidence interval, 0.18-0.99; $P=0.047$). **Conclusions.** In this exploratory, prospective study, serial US RFMA measurements in ESLD patients in the ICU are feasible, demonstrate progressive time-dependent muscle loss, and are associated with mortality. Further large-scale assessment of this modality compared with static PMA or performance-based dynamic assessments should be performed.

(*Transplantation Direct* 2020;6: e618; doi: 10.1097/TXD.0000000000001067. Published online 20 October, 2020.)

INTRODUCTION

Sarcopenia, the progressive loss of muscle mass and strength, significantly contributes to frailty, a state of functional decline. These interrelated conditions are associated with increased morbidity and mortality in patients with end-stage liver disease (ESLD).[1-4] Cirrhotic patients

Received 4 September 2020.

Accepted 6 September 2020.

[1] Department of Surgery, Division of Hepatobiliary and Abdominal Transplant Surgery, University of Southern California, Los Angeles, CA.

[2] Department of Surgery, Division of Hepatobiliary Surgery and Liver Transplantation, Vanderbilt University Medical Center, Nashville, TN.

[3] Center for Quantitative Sciences and Department of Biostatistics, Vanderbilt University Medical Center, Nashville, TN.

[4] Department of Radiology, University of Southern California, Los Angeles, CA.

[5] Department of Physical Medicine & Rehabilitation, Vanderbilt University Medical Center, Nashville, TN.

[6] Department of Medicine, Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, Nashville, TN.

A.P. and I.A.Z. share first coauthorship to this work.

This study was supported by the One Legacy Foundation (grant ID 511520).

The authors declare no conflicts of interest.

A.P. and I.A.Z. participated in acquisition, analysis and interpretation of data, drafting article and critical revision, and final approval. F.Y., Y.C., M.A.R., and L.K.M. did analysis and interpretation of data, critical revision, and final approval. N.K. did project conception/design, analysis and interpretation of data, critical revision, and final approval. G.W., S.M.Z., G.B., and M.I. particpated in analysis and interpretation of data, critical revision, and final approval. S.P.A. project conception/design, analysis, and interpretation of data, drafting article and critical revision, and final approval.

Correspondence: Sophoclis P. Alexopoulos, MD, FACS, Department of Surgery, Division of Hepatobiliary Surgery and Liver Transplantation, Vanderbilt University Medical Center, 801 Oxford House, 1313 21st Ave S, Nashville, TN 37232. (sopho.alexopoulos@vumc.org).

ISSN: 2373-8731

DOI: 10.1097/TXD.0000000000001067

awaiting liver transplantation (LT) are particularly vulnerable to sarcopenia and frailty due to chronic protein-calorie malnutrition secondary to impaired nutrient intake, muscle catabolism, hypermetabolic state, neurocognitive changes, and critical care illness involving multiple organ systems, resulting in a combination of muscle loss and physical inactivity.[5-11] Multiple studies have demonstrated the association of sarcopenia and its severity with waitlist and overall mortality in patients awaiting or undergoing LT.[12-17] As a result, in recent years, there has been an ongoing effort to establish a consensus definition for sarcopenia and to characterize its deleterious effects in ESLD patients undergoing evaluation for LT.[18-21]

Multiple techniques have been used to measure muscle mass and function in patients with cirrhosis.[22] Despite existing procedural variability, the vast majority utilize static cross-sectional imaging in the form of computed tomography (CT) to measure total muscle cross-sectional area of psoas muscle area (PMA) to characterize the degree of preexisting sarcopenia.[15,23-26] Ultrasound (US) measurements of appendicular muscle area offer a viable alternative in patients who are hospitalized, especially those who are critically ill and receiving care in the intensive care unit (ICU).[27,28] In addition to the ease of use, low cost, bedside availability, and lack of exposure to ionizing radiation, serial US measurements can offer valuable insight into the progression of muscle wasting over time.

The primary aims of this exploratory study were to (1) assess the feasibility of bedside, serial US rectus femoris muscle area (RFMA) measurements for the evaluation of progressive muscle loss in critically ill ESLD patients, and (2) describe the rate of muscle loss as assessed by serial US RFMA measurements. Secondarily, we sought to (3) identify patient characteristics associated with muscle loss and (4) determine how muscle loss is associated with survival to ICU discharge and overall survival.

MATERIALS AND METHODS

Study Design and Population

This is a prospective, observational single-center study of adult patients (18 y or older) who underwent evaluation for potential listing or were listed for LT and were admitted in the ICU at the Keck Hospital of University of South California, CA (August 2017–December 2018). The study was approved by the University of Southern California Institutional Review Board.

Measurements

Rectus Femoris Muscle Cross-sectional Area

To conduct these measurements, participants were placed in the supine position. Measurement of the right RFMA was performed using a 5 cm–wide linear-array transducer, connected to a portable US unit. The transducer was placed on the anterior aspect of the thigh, ¾ of the distance from the anterior superior iliac spine to the superior aspect of the patella, perpendicular to its long axis (Figure 1A). Images were frozen, and the outline of the rectus femoris fascia was traced, and the area (cm^2) was calculated (Figure 1B). The area for each patient was determined by the average of 3 measurements. All US measurements were conducted by a single-experienced researcher to eliminate interobserver variability. Serial measurements were performed every 48–72 hours until LT, patient death, or hospital discharge (in those who were not transplanted).

Psoas Muscle Cross-sectional Area

The cross-sectional area (cm^2) of the right and left psoas muscles at the disc level between the third and fourth lumbar vertebrae was calculated in all participants. We first identified the lumbar vertebral bodies within each participant's CT scan and then selected the slice superior to the fourth vertebrae and outlined the borders of the right and left psoas muscles. The cross-sectional area of each psoas muscle was measured, and then the baseline PMA was calculated as the sum of the right and left psoas muscle cross-sectional areas.

Statistical Analysis

Continuous variables were summarized as medians and interquartile ranges (IQRs), and categorical variables as frequencies and percentages. Between-group comparisons were performed using the Mann-Whitney *U* test for continuous variables and the chi-squared test for categorical variables.

Because each patient had multiple US RFMA measurements depending on the length of ICU stay until an event occurred, a repeated-measures mixed-effects linear regression methodology controlling for patient characteristics was used.[29] Within the framework of this methodology, within-patient correlation was accounted for using patient ID, along with ICU stay (days), as random effects. Three multivariable repeated-measures mixed-effects linear regression models were fitted with ICU stay (d), degree of preexisting sarcopenia, and sex as the prespecified predictor variables for each the following as the dependent variables: (1) crude RFMA (PMA was used to represent the degree of preexisting sarcopenia), (2) RFMA ÷ body surface area (BSA) or $RFMA_{BSA}$ (PMA ÷ BSA or psoas muscle area normalized by BSA [PMA_{BSA}] was used instead of PMA), and (3) RFMA ÷ $(Height)^2$ or rectus femoris muscle normalized by height-squared ($RFMA_{h2}$) (PMA ÷ $[Height]^2$ or PMA_{h2}, also known as *Psoas Muscle Index*, was used instead of PMA). Linear regression coefficients with 95% confidence intervals (95% CI) represent the mean change in the dependent variables (in cm^2 by US RFMA measurement [in cm^2/m^2 for $RFMA_{BSA}$ and $RFMA_{h2}$]) for every 1 unit of change in the independent variable while holding other covariates in the model constant. The intraclass correlation coefficient was estimated to assess intraobserver variability.

To assess the effect of muscle loss as assessed by the US RFMA measurements on (1) survival to ICU discharge and (2) overall survival, we fitted prespecified Cox proportional hazards regression models and estimated the hazard ratios and 95% confidence intervals (95% CIs). US RFMA measurement was included as a time-dependent covariate, while sex and hemodialysis (clinically relevant parameters) were included as fixed covariates. Three Cox models were fitted to evaluate the effects of (1) crude RFMA, (2) $RFMA_{BSA}$, and (3) $RFMA_{h2}$, for each of the 2 endpoints of interest (survival to ICU discharge and overall survival). Survival to ICU discharge was defined as the duration from the date of ICU admission until the date of ICU discharge; death or disposition to hospice care was considered to be the event/composite outcome, while patients who underwent LT or were discharged to home/other facility were censored. Overall survival was defined as the duration from the date of ICU admission until either the date of death (either while in the ICU or after LT) or disposition to hospice

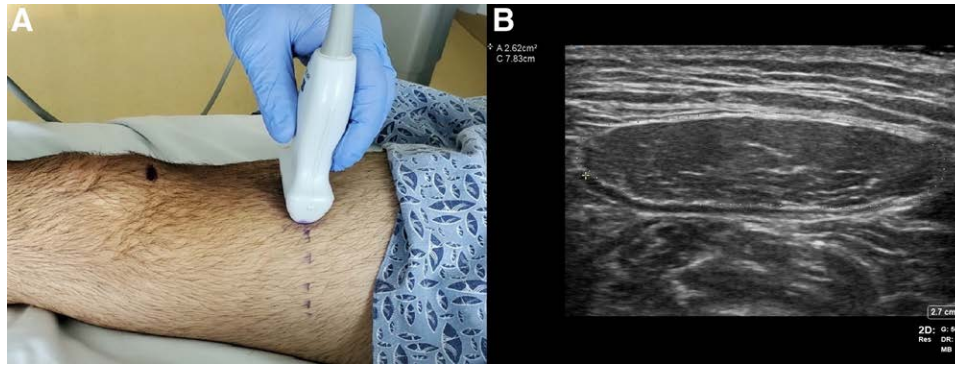

FIGURE 1. US RFMA measurement by placing the transducer at ¾ of the distance from the anterior superior iliac spine to superior border of the patella (A), and US image of the RFMA (B). RFMA, rectus femoris muscle area; US, ultrasound.

care (considered to be the event/composite outcome) or the date of last patient contact. The median follow-up time for the LT recipients was calculated using the reverse Kaplan-Meier method.[30]

All analyses were conducted using the R 3.6.3.,[31] and figures were produced using the package "ggplot2."[32] A 2-sided *P* value of <0.05 was used to determine statistical significance.

RESULTS

Patient Characteristics

A total of 50 patients with ESLD awaiting LT were enrolled upon admission to the ICU. The median age was 56.5 years (IQR, 45.5–63.8), 31 (62%) were male, and the median laboratory model for end-stage liver disease score upon ICU admission was 32.0 (30.0–36.8). The CT scan to assess baseline PMA was performed on a median of 2 days (IQR, 0–5) before the first US RFMA measurement, and the median baseline PMA was 14.5 cm^2 (IQR, 11.2–18.3). A total of 175 US measurements were performed over a median stay of 10.5 days (IQR, 8.0–14.8) in the ICU, the median first US RFMA measurement was 1.60 cm^2 (n = 50; IQR, 1.13–2.01), and the median of all US RFMA measurements was 1.34 cm^2 (n = 175; IQR, 0.98–1.95). The intraclass correlation coefficient was 0.945, which indicates the absence of intraobserver variability. The demographics and clinical characteristics did not differ between those who died/were discharged to hospice care and those who were alive on last patient contact (Table 1).

Muscle Mass as Assessed by US RFMA Measurements

Crude RFMA, $RFMA_{BSA}$, and $RFMA_{h2}$ measurements decreased by 0.017 cm^2 (95% CI, 0.000-0.034; $P = 0.054$), 0.011 cm^2/m^2 (95% CI, 0.003-0.018; $P = 0.005$), and 0.009 cm^2/m^2 (95% CI, 0.004-0.015; $P = 0.002$), respectively, for each day, the patient was in the ICU over the study period (Figure 2).

In multivariable mixed-effects linear regression, crude RFMA was associated with the number of days in the ICU and baseline PMA but not with sex. Specifically, we found that crude RFMA decreased by 0.026 cm^2 (95% CI, 0.020-0.031; $P < 0.001$) for each day, the patient was in the ICU and that crude RFMA was higher by 0.066 cm^2 (95% CI, 0.034-0.098; $P < 0.001$) for each cm^2 of baseline PMA (first model in Table 2).

Similarly, $RFMA_{BSA}$ was associated with the number of days in the ICU and PMA_{BSA} but not with sex. We found that $RFMA_{BSA}$ decreased by 0.013 cm^2/m^2 (95% CI, 0.010-0.016; $P < 0.001$) for each day, the patient was in the ICU, and that $RFMA_{BSA}$ was higher by 0.047 cm^2/m^2 (95% CI, 0.008-0.086; $P = 0.019$) for each cm^2/m^2 of baseline PMA_{BSA} (second model in Table 2).

Our results also showed that $RFMA_{h2}$ was associated with the number of days in the ICU and PMA_{h2}. Specifically, we found that $RFMA_{h2}$ decreased by 0.009 cm^2/m^2 (95% CI, 0.007-0.011; $P < 0.001$) for each day, the patient was in the ICU, and that $RFMA_{h2}$ was higher by 0.063 cm^2/m^2 (95% CI, 0.032-0.093; $P < 0.001$) for each cm^2/m^2 of baseline PMA_{h2}. Men had lower muscle mass than women as assessed by US $RFMA_{h2}$ measurements, and the association between sex and US $RFMA_{h2}$ was marginally statistically significant ($P = 0.056$) (third model in Table 2).

Survival to ICU Discharge

A total of 10 patients died or were discharged to hospice care, 34 underwent LT, and 6 were discharged to home or another facility. Subsequently, 2 of the 6 who were discharged to home or other facility underwent LT on a following admission (Figure 3A) after 41 and 66 days from discharge, respectively. When adjusting for sex and receipt of hemodialysis, neither crude RFMA nor normalized RFMA ($RFMA_{BSA}$, $RFMA_{h2}$) was associated with survival to ICU discharge (first, second, and third Model in Table 3).

Overall Survival

Thirty-six patients underwent LT (72%). In addition to the 10 patients who either died during the ICU admission or were discharged to hospice care, 1 patient discharged to another facility died on readmission. Additionally, 5 of the 36 LT recipients (13.9%) died over a median follow-up of 17 months (95% CI, 15.1-19.0) (Figure 3B).

In multivariable Cox regression, increasing $RFMA_{BSA}$ was associated with a decreased risk of death/discharge to hospice care (adjusted hazard ratios, 0.42; 95% CI, 0.18-0.99; $P = 0.047$), while sex and need for hemodialysis were not associated with overall survival (fifth model in Table 3). The lower risk of death/discharge to home hospice care in patients with $RFMA_{BSA}$ values in the highest tertile compared with those in lower tertiles is shown by means of a forest plot in Figure 3C. In comparison, when adjusting for sex and receipt of hemodialysis, neither crude RFMA nor $RFMA_{h2}$ was associated with overall survival (fourth and sixth models in Table 3).

TABLE 1.

Patient characteristics

Characteristic	n	Alive (n = 34)	Death/hospice (n = 16)	Total (n = 50)	*P*
Age (y)	50	56.5 (48.2–63.8)	54.0 (43.5–63.2)	56.5 (45.5–63.8)	0.52
Sex	50				0.96
Female (%)		13 (38)	6 (38)	19 (38)	
Male (%)		21 (62)	10 (62)	31 (62)	
Caucasian	50				0.78
No (%)		22 (65)	11 (69)	33 (66)	
Yes (%)		12 (35)	5 (31)	17 (34)	
Height (m)	50	1.7 (1.6–1.7)	1.7 (1.6–1.8)	1.7 (1.6–1.8)	0.47
Admission weight (kg)	50	81.0 (74.3–103.7)	86.3 (77.0–98.2)	81.4 (76.6–102.3)	0.70
BSA (m^2)	50	1.9 (1.8–2.2)	1.9 (1.8–2.2)	1.9 (1.8–2.2)	0.27
Admission BMI (kg/m^2)	50	30.3 (24.6–34.5)	30.7 (28.1–36.7)	30.7 (25.6–35.8)	0.46
Laboratory MELD score upon ICU admission	50	32.0 (30.0–36.8)	32.5 (30.0–36.8)	32.0 (30.0–36.8)	0.89
Laboratory MELD score at LT	36	38.0 (35.0–42.5)	40.0 (38.0–42.0)	38.0 (35.8–42.0)	0.47
Alcoholic liver disease	50				0.98
No (%)		15 (44)	7 (44)	22 (44)	
Yes (%)		19 (56)	9 (56)	28 (56)	
Hepatocellular carcinoma	50				0.39
No (%)		29 (85)	15 (94)	44 (88)	
Yes (%)		5 (15)	1 (6)	6 (12)	
Diabetes mellitus	50				0.10
No (%)		25 (74)	8 (50)	33 (66)	
Yes (%)		9 (26)	8 (50)	17 (34)	
Renal disease	50				0.52
No (%)		9 (26)	2 (12)	11 (22)	
Acute kidney injury (%)		17 (50)	9 (56)	26 (52)	
Chronic kidney disease (%)		8 (24)	5 (31)	13 (26)	
Hemodialysis	50				0.71
No (%)		21 (62)	9 (56)	30 (60)	
Yes (%)		13 (38)	7 (44)	20 (40)	
Ascites	50				0.83
No (%)		5 (15)	2 (12)	7 (14)	
Yes (%)		29 (85)	14 (88)	43 (86)	
Encephalopathy	50				0.51
No (%)		4 (12)	3 (19)	7 (14)	
Yes (%)		30 (88)	13 (81)	43 (86)	
PMA (cm^2)	50	14.5 (11.8–18.7)	13.9 (9.3–17.6)	14.5 (11.2–18.3)	0.46
Infection	50				0.88
No (%)		27 (79)	13 (81)	40 (80)	
Yes (%)		7 (21)	3 (19)	10 (20)	

BMI, body mass index; BSA, body surface area; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease; PMA, psoas muscle area.

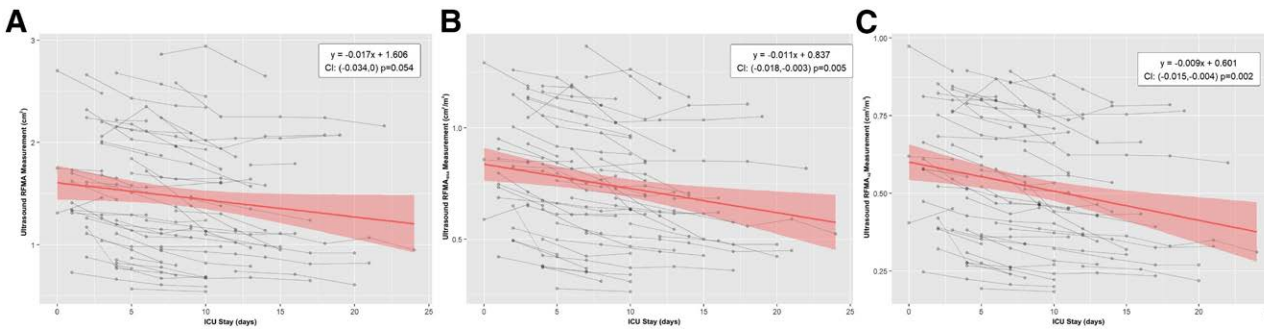

FIGURE 2. Spaghetti plots of ultrasound RFMA (A), $RFMA_{BSA}$ (B), and $RFMA_{h2}$ (C) measurements over days in the ICU based on repeated-measures mixed-effects linear regression models. ICU, intensive care units; RFMA, rectus femoris muscle area; $RFMA_{BSA}$, rectus femoris muscle area normalized by BSA; $RFMA_{h2}$, rectus femoris muscle normalized by height-squared; US, ultrasound.

TABLE 2.

Multivariable mixed-effects linear regression models to identify characteristics associated with muscle mass as assessed by ultrasound RFMA measurements

	First model (crude RFMA)			Second model ($RFMA_{BSA}$)			Third model ($RFMA_{h2}$)		
Characteristic	**Estimate (β)**	**95% CI**	***P***	**Estimate (β)**	**95% CI**	***P***	**Estimate (β)**	**95% CI**	***P***
ICU stay (d)	−0.026	−0.031 to −0.020	**<0.001**	−0.013	−0.016 to −0.010	**<0.001**	−0.009	−0.011 to −0.007	**<0.001**
PMA (cm^2)	0.066	0.034 to 0.098	**<0.001**	–	–	–	–	–	–
PMA_{BSA} (cm^2/m^2)	–	–	–	0.047	0.008–0.086	**0.019**	–	–	–
PMA_{h2} (cm^2/m^2)	–	–	–	–	–	–	0.063	0.032–0.093	**<0.001**
Male sex (ref: female)	−0.261	−0.630–0.107	0.160	−0.113	−0.288–0.063	0.202	−0.112	−0.227–0.003	0.056

BSA, body surface area; CI, confidence interval; ICU, intensive care unit; PMA, psoas muscle area; RFMA, rectus femoris muscle area; $RFMA_{BSA}$, rectus femoris muscle area normalized by BSA; $RFMA_{h2}$, rectus femoris muscle normalized by height-squared.

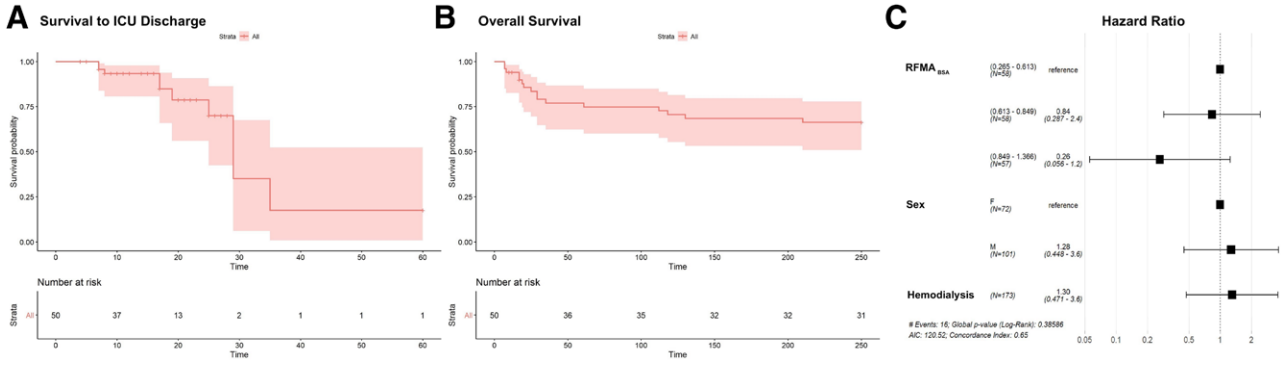

FIGURE 3. Kaplan-Meier curves for survival to ICU discharge (A) and overall survival (B); Forest plot demonstrating the effect of ultrasound $RFMA_{BSA}$ measurement (in tertiles) on overall survival when adjusting for sex and need for hemodialysis (visual representation of the fifth Cox Model in Table 3) (C). BSA, body surface area; ICU, intensive care units; $RFMA_{BSA}$, rectus femoris muscle area normalized by BSA.

TABLE 3.

Multivariable cox proportional hazards regression models to determine the effect of muscle mass as assessed by ultrasound RFMA measurements on survival to ICU discharge and on overall survival

	Survival to ICU discharge									Overall survival								
	First model (crude RFMA)			Second model ($RFMA_{BSA}$)			Third model ($RFMA_{h2}$)			Fourth model (crude RFMA)			Fifth model ($RFMA_{BSA}$)			Sixth model ($RFMA_{h2}$)		
Characteristic	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	
Crude RFMA	0.86	0.25-2.98	0.81	–	–	–	–	–	–	0.48	0.19-1.23	0.13	–	–	–	–	–	–
$RFMA_{BSA}$	–	–	–	0.68	0.20-2.30	0.54	–	–	–	–	–	–	0.42	0.18-0.99	**0.047**	–	–	–
$RFMA_{h2}$	–	–	–	–	–	–	0.71	0.20-2.56	0.60	–	–	–	–	–	–	0.43	0.16-1.11	0.08
Male sex (ref: female)	0.41	0.08-1.98	0.27	0.45	0.09-2.28	0.33	0.47	0.09-2.44	0.37	0.66	0.23-1.89	0.43	0.72	0.25-2.07	0.54	0.76	0.27-2.15	0.60
Hemodialysis (ref: no)	0.61	0.12-2.95	0.53	0.58	0.12-2.85	0.50	0.58	0.12-2.84	0.50	1.26	0.45-3.50	0.66	1.37	0.48-3.87	0.56	1.32	0.48-3.67	0.59

BSA, body surface area; CI, confidence interval; HR, hazard ratio; ICU, intensive care unit; RFMA, rectus femoris muscle area; $RFMA_{BSA}$, rectus femoris muscle area normalized by BSA; $RFMA_{h2}$, rectus femoris muscle normalized by height-squared.

DISCUSSION

Hospitalized patients, particularly those requiring ICU care, are distinctly susceptible to the rapid development or progression of sarcopenia. Puthucheary et al[33] observed that patients who are critically ill can experience >10% loss of rectus femoris muscle mass within a 7-day period, which can be accelerated by multiorgan system failure. Such progressive muscle loss has significant detrimental effects in ESLD patients, who are at increased risk for critical illness and often require pre-LT ICU care. In our exploratory study, we observed a progressive decline in RFMA, a large proximal extremity muscle, which we utilized as a surrogate for whole-body skeletal muscle mass.[34] We chose to evaluate US RFMA in ICU-bound ESLD patients because of their increased risk for time-dependent critical illness-associated muscle loss,[33] allowing us to demonstrate the feasibility of this modality through serial measurements in a short period of time. The use of US allowed quick, low cost, point-of-care, serial measurement of RFMA, which would be impractical with CT-based techniques. Finally, this patient group has a high incidence of peri-ICU mortality, allowing us to secondarily examine the association of US RFMA-determined muscle loss and survival.

Determination of who is clinically suitable for LT is one of the most challenging tasks for the LT clinician. The decision regarding when and if to transplant critically ill cirrhotic

patients is to some extent subjective and physician dependent. This has been most readily demonstrated with the early implementation of the model for end-stage liver disease score when some considered the transplantation of those with scores ≥40 to be futile.[35,36] Surgeons frequently utilize nonquantifiable judgment, often referred to as the "eye-ball" test aiming to assess the patient's function, skeletal muscle mass, nutritional status, and global health status and identify patients that will do well posttransplant. Most studies evaluating skeletal muscle mass have used some form of imaging for measurement of skeletal muscle mass, alone or in combination with functional assessment of physical performance or strength.[37] These include objective measurements such as cross-sectional imaging with CT, MRI, and density measurement by dual-energy x-ray absorptiometry.[12,22,38] While offering objectivity in the assessment of sarcopenia, PMA and L3 skeletal muscle index are static measurements that require a CT scan to measure skeletal muscle mass.[20] Considering that ICU patients lose muscle mass at a rapid rate,[33] the impracticality of performing repeated measurements puts into question the utility of these methods in this population. Similarly, dynamometric assessments require a cooperative patient and are effort dependent. In patients who are critically ill and require either mechanical ventilation, vasopressor support, continuous renal replacement therapy, or are otherwise encephalopathic or too debilitated to participate in these assessments, US RFMA measurements can offer invaluable information. US is a dynamic, reliable, reproducible, and affordable modality that can be performed independent of patient location or patient effort and without exposure to ionizing radiation to more objectively assist in the decision-making regarding patient status. Moreover, serial US measurements can offer real-time assessment of muscle mass loss over time and can be used to assess response to interventions aimed to ameliorate the progression of sarcopenia.

In addition to critically ill patients, the feasibility of US RFMA measurements to assess muscle mass has been previously described in patients with chronic kidney disease,[39] chronic obstructive pulmonary disease,[40] and coronary artery disease.[41] However, the present study is the first to evaluate the use of US RFMA measurements in potential LT candidates who were admitted to the ICU, and our results confirmed the occurrence of progressive muscle mass loss in this patient population. We observed a precipitous decline in US measurements of RFMA that was associated with baseline PMA and with the duration that patients remained critically ill in the ICU. However, this decline was independent of sex. While RFMA-based muscle mass (whether crude or $RFMA_{h2}$) did not appear to impact survival to ICU discharge when adjusting for sex and need for hemodialysis, decreased $RFMA_{BSA}$ was found to be associated with poor overall survival. Therefore, US $RFMA_{BSA}$ measurements can be a practical, dynamic, and convenient tool that can be applied to assess ESLD patients who are at increased risk of long-term mortality. Whether quantifying muscle mass by serial, bedside, point-of-care US RFMA measurements that are both easily performed at a low cost and in a consistent manner becomes a routine clinical assessment remains to be determined, but this method can provide an additional quantifiable way of clinically evaluating and describing the critically ill patient evaluated for LT.

Limitations of the study include its small sample size, partly due to its prospective, exploratory nature, which precluded performance of a sex-stratified analysis or adjustment for additional parameters including nutritional parameters that might be of clinical importance. Additionally, while the majority of the CT scans were performed within 48 hours of the initial US measurement, the rapid daily decline noticed on RFMA raises concerns about the validity of our PMA measurements to assess the initial sarcopenic state in our subjects. However, this highlights the advantage of US over other static modalities on which most studies on this subject are based. Finally, the known limitation of interobserver variability will have to be addressed as US RFMA measurements are more broadly implemented in future studies.

We used PMA, PMA_{BSA}, and PMA_{h2} as our baseline static assessment for sarcopenia as our study was already designed and actively enrolling patients before the implementation of L3 skeletal muscle index was more broadly supported.[18-20] Although the etiology of progressive muscle loss in this population is multifactorial, including ESLD and critical illness, our aim was to collectively assess muscle loss in this patient population. Because of its exploratory nature, we did not evaluate potential interventions that can slow the progression of sarcopenia in this patient population. This can be the focus of further research where US measurements can be used in real-time to assess the response to such interventions.

CONCLUSIONS

Sarcopenia has been identified as an important risk factor for poor outcomes in patients with ESLD. In the critically ill, there is a progressive loss of RFMA that is time-dependent and starting point dependent. Decreased $RFMA_{BSA}$ is associated with poor overall survival. Ultrasonography can be used as an effective modality to track changes in the extent of sarcopenia with important prognostic implications. Further studies on this subject should be conducted as CT-based sarcopenia measurements are static and expensive, while ICU patients are often unable to participate in dynamic measures of sarcopenia.

REFERENCES

1. Montano-Loza AJ, Meza-Junco J, Prado CM, et al. Muscle wasting is associated with mortality in patients with cirrhosis. *Clin Gastroenterol Hepatol.* 2012;10:166–73, 173.e1.
2. Lai JC, Feng S, Terrault NA, et al. Frailty predicts waitlist mortality in liver transplant candidates. *Am J Transplant.* 2014;14:1870–1879.
3. Hsu CS, Kao JH. Sarcopenia and chronic liver diseases. *Expert Rev Gastroenterol Hepatol.* 2018;12:1229–1244.
4. Hanai T, Shiraki M, Nishimura K, et al. Sarcopenia impairs prognosis of patients with liver cirrhosis. *Nutrition.* 2015;31:193–199.
5. Montano-Loza AJ. Muscle wasting: a nutritional criterion to prioritize patients for liver transplantation. *Curr Opin Clin Nutr Metab Care.* 2014;17:219–225.
6. Bhanji RA, Moctezuma-Velazquez C, Duarte-Rojo A, et al. Myosteatosis and sarcopenia are associated with hepatic encephalopathy in patients with cirrhosis. *Hepatol Int.* 2018;12:377–386.
7. Hayashi F, Matsumoto Y, Momoki C, et al. Physical inactivity and insufficient dietary intake are associated with the frequency of sarcopenia in patients with compensated viral liver cirrhosis. *Hepatol Res.* 2013;43:1264–1275.
8. Dasarathy S. Consilience in sarcopenia of cirrhosis. *J Cachexia Sarcopenia Muscle.* 2012;3:225–237.
9. Periyalwar P, Dasarathy S. Malnutrition in cirrhosis: contribution and consequences of sarcopenia on metabolic and clinical responses. *Clin Liver Dis.* 2012;16:95–131.
10. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol.* 2016;65:1232–1244.

11. Kim HY, Jang JW. Sarcopenia in the prognosis of cirrhosis: going beyond the MELD score. *World J Gastroenterol.* 2015;21:7637–7647.
12. Tandon P, Ney M, Irwin I, et al. Severe muscle depletion in patients on the liver transplant wait list: its prevalence and independent prognostic value. *Liver Transpl.* 2012;18:1209–1216.
13. Kalafateli M, Mantzoukis K, Choi Yau Y, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. *J Cachexia Sarcopenia Muscle.* 2017;8:113–121.
14. Englesbe MJ, Patel SP, He K, et al. Sarcopenia and mortality after liver transplantation. *J Am Coll Surg.* 2010;211:271–278.
15. van Vugt JL, Levolger S, de Bruin RW, et al. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. *Am J Transplant.* 2016;16:2277–2292.
16. Kuo SZ, Ahmad M, Dunn MA, et al. Sarcopenia predicts post-transplant mortality in acutely ill men undergoing urgent evaluation and liver transplantation. *Transplantation.* 2019;103:2312–2317.
17. Durand F, Buyse S, Francoz C, et al. Prognostic value of muscle atrophy in cirrhosis using psoas muscle thickness on computed tomography. *J Hepatol.* 2014;60:1151–1157.
18. Carey EJ, Lai JC, Wang CW, et al; Fitness, life enhancement, and exercise in liver transplantation consortium. A multicenter study to define sarcopenia in patients with end-stage liver disease. *Liver Transpl.* 2017;23:625–633.
19. Carey EJ, Lai JC, Sonnenday C, et al. A North American expert opinion statement on sarcopenia in liver transplantation. *Hepatology.* 2019;70:1816–1829.
20. Lai JC, Sonnenday CJ, Tapper EB, et al. Frailty in liver transplantation: an expert opinion statement from the American Society of Transplantation Liver and Intestinal Community of Practice. *Am J Transplant.* 2019;19:1896–1906.
21. Tandon P, Mourtzakis M. Reply. *Clin Gastroenterol Hepatol.* 2016;14:1672.
22. Kallwitz ER. Sarcopenia and liver transplant: the relevance of too little muscle mass. *World J Gastroenterol.* 2015;21:10982–10993.
23. Bush WJ, Davis JP, Maluccio MA, et al. Computed tomography measures of nutrition in patients with end-stage liver disease provide a novel approach to characterize deficits. *Transplant Proc.* 2018;50:3501–3507.
24. Cruz RJ Jr, Dew MA, Myaskovsky L, et al. Objective radiologic assessment of body composition in patients with end-stage liver disease: going beyond the BMI. *Transplantation.* 2013;95:617–622.
25. Esser H, Resch T, Pamminger M, et al. Preoperative assessment of muscle mass using computerized tomography scans to predict outcomes following orthotopic liver transplantation. *Transplantation.* 2019;103:2506–2514.
26. Golse N, Bucur PO, Ciacio O, et al. A new definition of sarcopenia in patients with cirrhosis undergoing liver transplantation. *Liver Transpl.* 2017;23:143–154.
27. Pardo E, El Behi H, Boizeau P, et al. Reliability of ultrasound measurements of quadriceps muscle thickness in critically ill patients. *BMC Anesthesiol.* 2018;18:205.
28. Mueller N, Murthy S, Tainter CR, et al. Can sarcopenia quantified by ultrasound of the rectus femoris muscle predict adverse outcome of surgical intensive care unit patients as well as frailty? A prospective, observational cohort study. *Ann Surg.* 2016;264:1116–1124.
29. Hedeker DR, Gibbons RD. *Longitudinal Data Analysis*. Hoboken, NJ: John Wiley & Sons; 2006.
30. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials.* 1996;17:343–346.
31. R Core Team. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2018. Available at http://www.r-project.org/.
32. Wickham H. *Ggplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer; 2009.
33. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA.* 2013;310:1591–1600.
34. Galindo Martín CA, Ubeda Zelaya RDC, Monares Zepeda E, et al. ROUNDS studies: relation of outcomes with nutrition despite severity-round one: ultrasound muscle measurements in critically ill adult patients. *J Nutr Metab.* 2018;2018:7142325.
35. Nekrasov V, Matsuoka L, Kaur N, et al. Improvement in the outcomes of MELD ≥ 40 liver transplantation: an analysis of 207 consecutive transplants in a highly competitive DSA. *Transplantation.* 2017;101:2360–2367.
36. Nekrasov V, Matsuoka L, Rauf M, et al. National outcomes of liver transplantation for model for end-stage liver disease score ≥40: the impact of share 35. *Am J Transplant.* 2016;16:2912–2924.
37. Montgomery J, Englesbe M. Sarcopenia in liver transplantation. *Curr Transplant Rep.* 2019;6:7–15.
38. Giusto M, Lattanzi B, Albanese C, et al. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. *Eur J Gastroenterol Hepatol.* 2015;27:328–334.
39. Souza VA, Oliveira D, Cupolilo EN, et al. Rectus femoris muscle mass evaluation by ultrasound: facilitating sarcopenia diagnosis in pre-dialysis chronic kidney disease stages. *Clinics (Sao Paulo).* 2018;73:e392.
40. Seymour JM, Ward K, Sidhu PS, et al. Ultrasound measurement of rectus femoris cross-sectional area and the relationship with quadriceps strength in COPD. *Thorax.* 2009;64:418–423.
41. Thomaes T, Thomis M, Onkelinx S, et al. Reliability and validity of the ultrasound technique to measure the rectus femoris muscle diameter in older CAD-patients. *BMC Med Imaging.* 2012;12:7.