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

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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

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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 to 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 (cm²) 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 (cm²) 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 vertebral body 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 RFMA₉₀₅ (PMA + BSA or psoas muscle area normalized by BSA), and (3) RFMA + (Height)² or rectus femoris muscle normalized by height-squared (RFMA₁₂₅) (PMA + [Height]² or PMA₁₂₅, 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 cm² by US RFMA measurement [in cm²/m² for RFMA₉₀₅ and RFMA₁₂₅] 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) RFMA₉₀₅, and (3) RFMA₁₂₅ 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...
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. All analyses were conducted using the R 3.6.3., and figures were produced using the package "ggplot2." 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 cm² (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 cm² (n = 50; IQR, 1.13–2.01), and the median of all US RFMA measurements was 1.34 cm² (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 cm² (95% CI, 0.000-0.034; P = 0.054), 0.011 cm²/m² (95% CI, 0.003-0.018; P = 0.005), and 0.009 cm²/m² (95% CI, 0.004-0.015; P = 0.002), respectively, for each day, the patient was in the ICU and that RFMA_{BSA} was lower by 0.047 cm²/m² (95% CI, 0.008-0.086; P = 0.019) for each cm²/m² 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 cm²/m² (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 cm²/m² (95% CI, 0.032-0.093; P < 0.001) for each cm²/m² 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                                      | Alive (n = 34) | Death/hospice (n = 16) | Total (n = 50) | P       |
|-----------------------------------------------------|----------------|------------------------|----------------|---------|
| Age (y)                                             | 56.5 (48.2–63.8) | 54.0 (43.5–63.2) | 56.5 (45.5–63.8) | 0.52    |
| Sex                                                 |                |                        |                | 0.98    |
| Female (%)                                          | 13 (38)        | 6 (38)                 | 19 (38)        |         |
| Male (%)                                            | 21 (62)        | 10 (62)                | 31 (62)        |         |
| Caucasian                                           |                |                        |                | 0.78    |
| No (%)                                              | 22 (65)        | 11 (69)                | 33 (66)        |         |
| Yes (%)                                             | 12 (35)        | 5 (31)                 | 17 (34)        |         |
| Height (m)                                          | 1.7 (1.6–1.7)  | 1.7 (1.6–1.8)          | 1.7 (1.6–1.8)  | 0.47    |
| Admission weight (kg)                               | 81.0 (74.3–103.7) | 86.3 (77.0–98.2) | 81.4 (76.6–102.3) | 0.70    |
| BSA (m²)                                            | 1.9 (1.8–2.2)  | 1.9 (1.8–2.2)          | 1.9 (1.8–2.2)  | 0.27    |
| Admission BMI (kg/m²)                               | 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            | 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                         | 38.0 (35.0–42.5) | 40.0 (38.0–42.0) | 38.0 (35.8–42.0) | 0.47    |
| Alcoholic liver disease                             |                |                        |                | 0.98    |
| No (%)                                              | 15 (44)        | 7 (44)                 | 22 (44)        |         |
| Yes (%)                                             | 19 (56)        | 9 (56)                 | 28 (56)        |         |
| Hepatocellular carcinoma                           | 29 (85)        | 15 (94)                | 44 (88)        | 0.39    |
| No (%)                                              | 5 (15)         | 1 (6)                  | 6 (12)         |         |
| Yes (%)                                             |                |                        |                |         |
| Diabetes mellitus                                   | 25 (74)        | 8 (50)                 | 33 (66)        | 0.10    |
| No (%)                                              | 9 (26)         | 8 (50)                 | 17 (34)        |         |
| Renal disease                                       |                |                        |                | 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                                        |                |                        |                | 0.71    |
| No (%)                                              | 21 (62)        | 9 (56)                 | 30 (60)        |         |
| Yes (%)                                             | 13 (38)        | 7 (44)                 | 20 (40)        |         |
| Ascites                                             |                |                        |                | 0.83    |
| No (%)                                              | 5 (15)         | 2 (12)                 | 7 (14)         |         |
| Yes (%)                                             | 29 (85)        | 14 (88)                | 43 (86)        |         |
| Encephalopathy                                      |                |                        |                | 0.51    |
| No (%)                                              | 4 (12)         | 3 (19)                 | 7 (14)         |         |
| Yes (%)                                             | 30 (88)        | 13 (81)                | 43 (86)        |         |
| PMA (cm²)                                           | 14.5 (11.8–18.7) | 13.9 (9.3–17.6) | 14.5 (11.2–18.3) | 0.46    |
| Infection                                           |                |                        |                | 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 area normalized by height-squared; US, ultrasound.
DISCUSSION

Hospitalized patients, particularly those requiring ICU care, are distinctly susceptible to the rapid development or progression of sarcopenia. Puthucheary et al. 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. We chose to evaluate US RFMA in ICU-bound ESLD patients because of their increased risk for time-dependent critical illness-associated muscle loss, 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.

**TABLE 2.** Multivariable mixed-effects linear regression models to identify characteristics associated with muscle mass as assessed by ultrasound RFMA measurements

| Characteristic | First model (crude RFMA) |  | Second model (RFMA_{BSA}) |  | Third model (RFMA_{h2}) |  |
|---------------|--------------------------|---|---------------------------|---|--------------------------|---|
|                | 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 (cm²)      | 0.066 0.034 to 0.098     | <0.001 | 0.047 0.008−0.086       | 0.019 | 0.063 0.032−0.093       | <0.001 |
| PMA_{BSA} (cm²/m²) | —                  | —  | 0.047 0.008−0.086       | 0.019 | 0.063 0.032−0.093       | <0.001 |
| PMA_{h2} (cm²/m²) | —                  | —  | 0.047 0.008−0.086       | 0.019 | 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

| Characteristic | 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}) |
|                | HR 95% CI P                | HR 95% CI P                | HR 95% CI P                | HR 95% CI P                | HR 95% CI P                | HR 95% CI P                |
| Crude RFMA     | 0.86 0.25-2.98 0.81        | —                         | —                         | 0.58 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       | —                         | —                         | —                         |
| 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.
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.15,16 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 absorptometry.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,31 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,19 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$_{BSA}$) 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$_{L3}$ 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 mass 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.

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