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Ultrasound assessment of muscle mass has potential to identify patients with low muscularity at intensive care unit admission: A retrospective study

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SUMMARY

Background & aims: Muscle mass is an important biomarker of survival from a critical illness; however, there is no widely accepted method for routine assessment of low muscularity at intensive care unit (ICU) admission. We hypothesize that ultrasound-based partial muscle mass assessments can reflect the trunk muscle mass. Therefore, we aimed to investigate whether ultrasound muscle mass measurements could reflect trunk muscle mass and identify patients with low muscularity.
Methods: We performed a retrospective analysis of prospectively obtained ultrasound data at ICU admission. We included patients who underwent computed tomography (CT) imaging at the third lumbar vertebra (L3) within 2 days before and 2 days after ICU admission. Primary outcomes included the correlation between the femoral muscle mass measurements using ultrasound and the cross-sectional area (CSA) at L3 obtained by CT. Low muscularity was defined as a skeletal muscle index of 36.0 cm^2/m^2 for males and 29.0 cm^2/m^2 for females. Secondary outcomes included the correlation with the ultrasound measurements of the biceps brachii muscle mass and diaphragm thickness.
Results: Among 133 patients, 89 underwent CT imaging, which included the L3. The patient mean age was 72 ± 13 years, and 60 patients (67%) were male. The correlation between the femoral muscle ultrasound and CT was $\rho = 0.57$ ($p < 0.01$, $n = 89$) and $\rho = 0.48$ ($p < 0.01$, $n = 89$) for quadriceps muscle layer thickness and rectus femoris muscle CSA, and these had the discriminative power to assess low muscularity, with the areas under the curve of 0.84 and 0.76, respectively. The ultrasound measurements of the biceps brachii muscle mass and diaphragm thickness were correlated with CT imaging [$\rho = 0.57$–0.60 ($p < 0.01$, $n = 52$) and $\rho = 0.35$ ($p < 0.01$, $n = 79$)].
Conclusions: Ultrasound measurements of muscle mass were correlated with CT measurements, and the measurements of femoral muscle mass were useful to assess low muscularity at ICU admission.
Trial registration: UMIN000044032 (retrospectively registered on April 25, 2021).

1. Introduction

Muscle mass is an important biomarker of survival from a critical illness because low muscularity at intensive care unit (ICU) admission is associated with higher mortality and ICU-acquired weakness [1,2]. The notion that a state of low muscularity is representative of sarcopenia has recently been gaining increased attention [3]. The identification of low muscularity is important in planning nutrition and rehabilitation management

Abbreviations: ICU, intensive care unit; CT, computed tomography; L3, the third lumbar vertebra; CSA, cross-sectional area; AUC, area under the receiver operating characteristic curve; IQR, interquartile range; CI, confidence interval.

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strategies. Both are needed to maintain muscle mass during ICU hospitalization. However, to date, there is no widely accepted method for routine assessment of low muscularity at ICU admission.

Several methods have been used to assess muscle mass [4]. In general, dual-energy X-ray absorptiometry and bioelectrical impedance analyses have been used to assess whole-body muscle mass [5]. However, these indirect muscle mass assessments are inaccurate in critically ill patients because these are influenced by dynamic fluid changes [6–8]. Furthermore, it is challenging to transport patients to a dual-energy X-ray absorptiometry machine. During a critical illness, computed tomography (CT) is considered the gold standard to assess muscle mass because it can visually separate muscle mass from other tissues [9]. Although CT is a reliable method to measure muscle mass, prospective CT evaluation is infeasible because of patient transportation risks and radiation exposure [10]. By contrast, ultrasound is an emerging tool used to measure muscle mass noninvasively at the bedside [11]. Although ultrasound is used to assess limb muscles, it is unclear whether partial muscle mass assessments reflect trunk muscle mass in critically ill patients. To validate the ultrasound assessments of muscularity, it is important to show the measurement correlation between ultrasound and CT.

The femoral muscle is assessed commonly using ultrasound, in which muscle thickness or cross-sectional area (CSA) measurements are performed [4]. However, it is unclear whether these mass measurements reflect the trunk or partial muscle mass in critically ill patients. Given that a previous study reported that the CSA of the rectus femoris is preferable than thickness for physical functions [12,13], we hypothesized that CSA is associated with the trunk muscle mass. We retrospectively evaluated the muscle mass area at the level of the third lumbar vertebra (L3) using CT, and compared it with those obtained from prospectively obtained ultrasound data at ICU admission. This study aimed to investigate whether ultrasound muscle mass measurements were correlated with CT measurements, and could identify patients with low muscularity at ICU admission.

2. Materials & methods

2.1. Study design

This two-center retrospective study was conducted in the mixed medical/surgical ICUs of Tokushima University Hospital and Tokushima Prefectural Central Hospital. The study complied with the principles of the Declaration of Helsinki and was approved by the clinical research ethics committees of Tokushima University Hospital (approval number 2593) and Tokushima Prefectural Central Hospital (approval number 1739). Prospectively obtained data from May 2016 to June 2020 were retrospectively analyzed. This study was retrospectively registered at UMIN-Clinical Trials Registry (UMIN000044032). At the time of data acquisition, written informed consent was obtained from patients or their relatives. A part of this study was previously published [7,14,15].

2.2. Study population

We included patients who met the following criteria: (1) adults (≥18 years) admitted to ICU; (2) those expected to stay in ICU for >5 days; (3) those who underwent the ultrasound assessments of the rectus femoris muscle at the day of ICU admission; and (4) those who underwent the CT assessments of the L3 within 2 days before and after ICU admission. The following patients were excluded from the studies: those with (1) primary neuromuscular disease and (2) obstacles at the ultrasound measurement site.

2.3. Ultrasound

We used a linear transducer and performed B-mode imaging. The details of equipment were shown in Table S1. The measurements were performed at the dominant limb or right limb under no information. Elbows and knees were extended in the supine position, and the transducer was placed perpendicular to the long axis of the limbs. The measurements included the quadriceps muscle layer thickness and rectus femoris muscle CSA. Measurements were performed midway between the anterior superior iliac spine and the proximal end of the patella as a common landmark [4]. The quadriceps muscle layer thickness, including the rectus femoris and vastus intermedius muscles, was measured from the superficial fascia of the rectus femoris to the uppermost part of the femur (Fig. S1). CSA was measured by outlining the area shown in the transverse plane (Fig. S2). The elbow flexor muscle thickness and biceps brachii muscle CSA were measured at a distance equal to two-thirds of the distance from the acromion to the antecubital crease as a common landmark [16,17]. The elbow flexor muscle thickness, including the biceps brachii and brachialis muscles, was measured from the superficial fascia of the biceps brachii muscle to the uppermost part of the humerus. The diaphragm was measured at the end expiration on the right chest wall at the zones of apposition 0.5–2 cm below the costophrenic sinus between the antero-axillary and the midaxillary lines (Fig. S3) [18]. The ultrasound measurements were performed three times by a physician (N.N.), and the median value was used for evaluation. Generous amounts of contact gel was used for minimal compression because probe compression strength affects measurement accuracy [19]. The reliability of measurements was confirmed by another ICU physician, as reported previously (Table S2) [14,15].

2.4. CT

CT was used to evaluate muscle mass at the L3 level, which has been reported to correlate with the trunk muscle mass in patients with cancer [20]. A board-certified radiologist (A.Y.) retrospectively measured the total muscle mass in the CT image at the middle point of the L3 where transverse processes were visualized (Fig. S4). At this slice level, the total muscle area included the psoas, quadratus lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles. CT images acquired within 2 days before and after ICU admission were included in the analyses, and examinations performed closest to the day of ICU admission were used for comparisons in patients with multiple CT examinations. The radiologist was blinded to all clinical characteristics. All images were analyzed using ImageJ software (National Institutes of Health, Bethesda, MD, USA) [21]. The reliability of measurements was confirmed in 10 patients by 2 examiners (Y.A. and N.N.). The intraclass correlation coefficient was $\rho = 0.98$ ($p < 0.01$), and the interclass value was $\rho = 0.94$ ($p < 0.01$). The Bland–Altman plot yielded a bias of -1.24 ± 1.58 and -4.83 to 2.34 at the 95% confidence interval (CI) regarding intraobserver reproducibility and a bias of -0.94 ± 2.67 and -6.98 to 5.10 at the 95% CI regarding interobserver reproducibility.

Low muscularity was identified using the skeletal muscle index, which is calculated by dividing the CT image CSA at L3 by height squared. The sex-specific cutoff point was set to 36.0 cm^2/m^2 for males and 29.0 cm^2/m^2 for females, which are one of the commonly used cutoff points for low muscularity in the Asian population [22].

These cutoff points were previously reported to be important in Japanese patients with cancer [23].

2.5. Outcomes

The primary outcome was the relationship between the ultrasound assessments of the quadriceps muscle layer thickness or rectus femoris muscle CSA and the CT assessment of L3 CSA. We also assessed whether these ultrasound assessments can predict low muscularity in the same manner as that assessed by CT. Secondary outcomes of this study included the relationship with the ultrasound measurements of elbow flexor muscle thickness, biceps brachii muscle CSA, the sum of rectus femoris and biceps brachii muscle CSA, and diaphragm thickness.

2.6. Statistical analyses

Continuous variables were presented as the mean (standard deviations) or median values [interquartile ranges (IQRs)], whereas categorical data were presented as counts and proportions. Variables were compared using either the t-test or the Mann–Whitney U test. The Spearman correlation coefficient was used to investigate relationships in primary and secondary outcomes. The area under the receiver operating characteristic curve (AUC) was generated to determine the cutoff values of ultrasound assessments for low muscularity. Sample size was not calculated a priori and was based as per feasibility because of the retrospective nature of the study. For reproducibility, the Spearman correlation coefficient and the Bland–Altman plot were determined using JMP statistical software, version 13.1.0 (SAS Institute Inc., Cary, NC, USA).

3. Results

In total, 133 patients underwent ultrasound measurements of the femoral muscle mass. Among them, 89 patients underwent CT imaging at the L3 level within 2 days of ICU admission (Fig. 1). Fifty-nine patients underwent CT examinations immediately after ICU admission. CT examinations were performed in 10 and 4 patients on days 1 and 2 after ICU admission, respectively, and in 13 and 3 patients on days 1 and 2 days before ICU admission, respectively. The time between the ultrasound and CT assessments was 0 day (IQR, 0–1 day).

The patient characteristics are summarized in Table 1. The patient mean age was 72 ± 13 years, and 60 patients (67%) were male. The median Acute Physiology and Chronic Health Evaluation II score was 27 (IQR, 24–30), and the median length of ICU stay was 7 (IQR, 5–14) days. Seventy-eight (88%) patients were mechanically ventilated, and 15 (16%) were admitted postoperatively. Low muscularity, assessed by CT, was observed in 24 (27%) patients. The median thickness of the quadriceps muscle layer and CSA of the rectus femoris muscle were 2.4 (IQR, 1.8–3.1) cm and 4.9 (IQR, 3.9–6.5) cm^2, respectively. There was a significant difference in the body mass index ($p < 0.01$), quadriceps muscle layer thickness ($p < 0.01$), rectus femoris muscle CSA ($p < 0.01$), elbow flexor muscle thickness ($p < 0.01$), biceps brachii muscle CSA ($p < 0.01$), and muscle mass on CT between low and normal muscularity ($p < 0.01$).

The ultrasound measurements of the femoral muscle at ICU admission were correlated with the muscle mass at the L3 measured by CT (Fig. 2). The correlations of the quadriceps muscle layer thickness and rectus femoris muscle CSA were $\rho = 0.57$ ($p < 0.01$, $n = 89$) and $\rho = 0.48$ ($p < 0.01$, $n = 89$), respectively. The thickness of the quadriceps muscle layer thickness had the discriminative power to assess low muscularity at the AUC of 0.84 (95% CI, 0.74–0.94), in which the cutoff value of 2.0 cm had a sensitivity of 83.3% and specificity of 78.5% (Fig. 3). By contrast, the CSA of the rectus femoris muscle had the discriminative power to assess low muscularity at the AUC of 0.76 (95% CI, 0.65–0.88), in which the cutoff value of 4.7 cm^2 had a sensitivity of 79.2% and specificity of 66.2%.

Among the secondary outcomes, the elbow flexor muscle thickness, biceps brachii muscle CSA, the sum of rectus femoris and biceps brachii muscle CSA, and diaphragm muscles were assessed in 52, 52, 52, and 79 of the 89 patients, respectively (Fig. 4). The

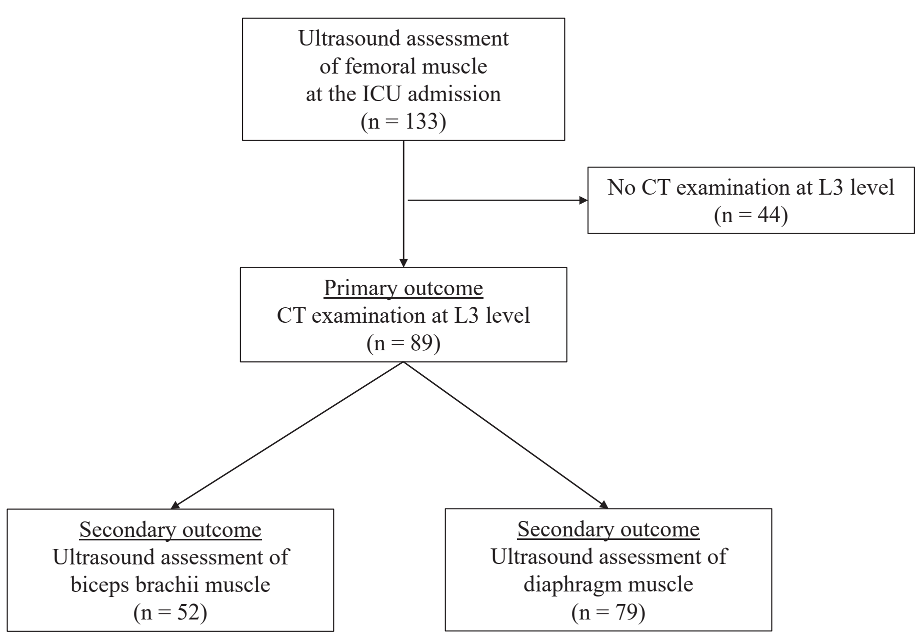

Fig. 1. Flowchart of patients included in this study. Among the 133 patients screened, 89 underwent computed tomography (CT) examinations at the level of the third lumbar vertebra. Secondary outcomes included the ultrasound assessments of the biceps brachii ($n = 52$) and diaphragm muscles ($n = 79$) (CT, computed tomography; L3, third lumbar vertebra).

Table 1
Patient characteristics.

Variables	All patients (n = 89)	Low muscularity[a] (n = 24)	Normal muscularity (n = 65)	p-value
Age, mean ± SD, y	72 ± 13	76 ± 11	70 ± 13.6	0.07
Male/Female	60/29	16/8	44/21	0.93
Body mass index, mean ± SD, kg/m^2	22.2 ± 4.4	18.6 ± 3.0	23.5 ± 4.0	<0.01
APACHE II score	27 (24–30)	28 (25–32)	27 (23–30)	0.31
SOFA	8 (6–11)	8 (6–11)	10 (6–12)	0.66
Sepsis (Sepsis-3 criteria), n (%)	40 (49)	24 (56)	16 (41)	0.27
Postoperative admissions, n (%)	14 (16)	1 (4)	13 (20)	0.07
Mechanical ventilation, n (%)	78 (88)	19 (79.2)	59 (90.8)	0.16
Length of ICU stay, d	7 (5–14)	6 (4–11)	7 (5–17)	0.13
Length of hospital stay, d	29 (18–51)	22 (15–44)	30 (21–51)	0.39
Mortality in the ICU, n (%)	16 (18.0)	4 (17)	12 (19)	0.85
Mortality in the hospital, n (%)	25 (28.1)	10 (41.7)	15 (23.1)	0.08
Ultrasound				
Quadriceps muscle layer thickness (cm)	2.4 (1.8–3.1)	1.7 (1.4–2.0)	2.8 (2.1–3.2)	<0.01
Rectus femoris muscle CSA (cm^2)	4.9 (3.9–6.5)	3.9 (2.9–4.6)	5.4 (4.1–7.1)	<0.01
Elbow flexor muscle thickness (cm)[b]	2.8 (2.3–3.1)	2.3 (2.0–2.7)	3.2 (2.8–3.4)	<0.01
Biceps brachii muscle CSA (cm^2)[b]	6.1 (4.6–8.6)	5.1 (3.6–5.4)	6.8 (5.1–9.0)	<0.01
Diaphragm thickness (mm)[c]	1.8 (1.4–2.1)	1.7 (1.3–2.0)	1.8 (1.5–2.2)	0.28
Computed tomography				
CSA at 3rd lumbar vertebra (cm^2)	102.8 (77.1–133.2)	69.2 (54.1–80.5)	118.9 (97.0–143.5)	<0.01

APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; SD: standard deviation; ICU: intensive care unit; IQR: interquartile range; CSA: Cross-sectional area.
Data were presented as median (IQR) unless otherwise indicated.
[a] Low muscularity was defined as skeletal muscle index <36.0 cm^2/m^2 for males and 29.0 cm^2/m^2 for female.
[b] Included number of patients was 52 with 13 of low muscularity and 39 of normal muscularity.
[c] Included number of patients was 79 with 22 of low muscularity and 57 of normal muscularity.

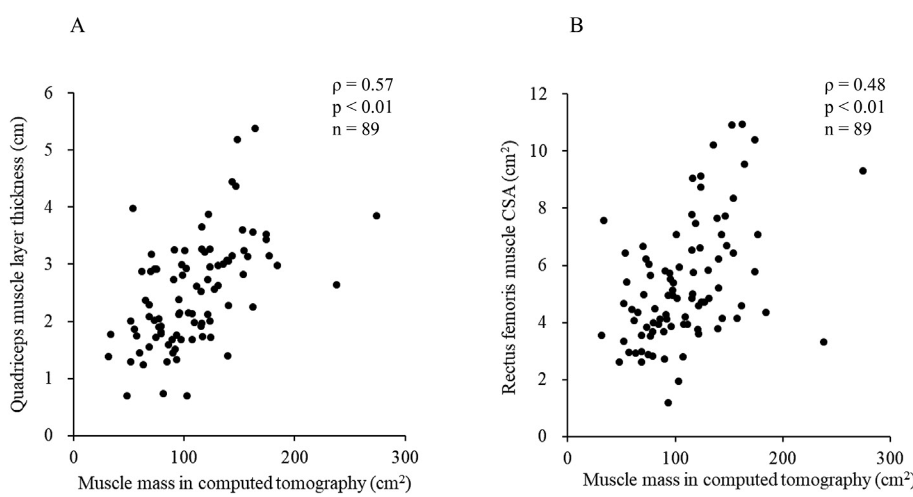

Fig. 2. Relationships between the ultrasound measurements of the quadriceps muscle layer thickness or rectus femoris muscle CSA and CT measurements of the cross-sectional area at the third lumbar vertebra. (A) Quadriceps muscle layer thickness and (B) Rectus femoris muscle CSA. The Spearman correlation coefficient was used to investigate the relationships. CSA: cross-sectional area, CT: computed tomography.

ultrasound measurements of these at ICU admission were correlated with the muscle mass at the L3 measured by CT. The elbow flexor muscle thickness and biceps brachii muscle CSA yielded the correlations of $\rho = 0.57$ ($p < 0.01$, n = 52) and $\rho = 0.60$ ($p < 0.01$, n = 52), respectively. The sum of rectus femoris and biceps brachii muscle CSA yielded the correlation of $\rho = 0.57$ ($p < 0.01$, n = 52). The thickness of the diaphragm yielded a correlation of $\rho = 0.35$ ($p < 0.01$, n = 79).

4. Discussion

In this study on 89 critically ill patients, we investigated whether ultrasound-based quadriceps muscle layer thickness and rectus femoris muscle CSA measurements are indicators of low muscularity. Contrary to our hypothesis, both the thickness and CSA were good indicators of low muscularity at ICU admission. Moreover, the biceps brachii muscle and diaphragm were weak-to-moderate indicators of trunk muscle mass. Given that CT is not routinely available to critically ill patients, the ultrasound measurement of the quadriceps muscle layer thickness and rectus femoris muscle CSA can be an alternative for the noninvasive assessment of low muscularity at ICU admission.

This study provides several important intellectual data. First, we found that both the quadriceps muscle layer thickness and rectus femoris muscle CSA are good indicators of the trunk muscle mass. Previous studies investigated the quadriceps muscle thickness and showed that its thickness was correlated with muscle mass measured using CT [24,25]. However, differences between the

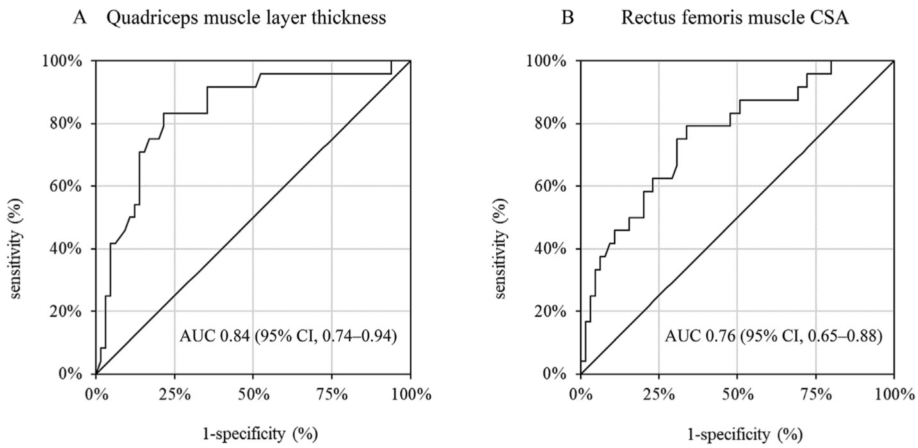

Fig. 3. Areas under the receiver operating characteristic curves (AUCs) were estimated to determine the cutoff values of ultrasound assessments for low muscularity. The Youden index was used to identify the optimal cutoff value. (A) Quadriceps muscle layer thickness and (B) Rectus femoris muscle CSA. (A) cutoff value was 2.0 cm at the sensitivity of 83.3% and the specificity of 78.5% and (B) cutoff value was 4.66 cm^2 at the sensitivity of 79.2% and the specificity of 66.2%. AUC: areas under the receiver operating characteristic curves, CSA: cross-sectional area, CI: confidence interval.

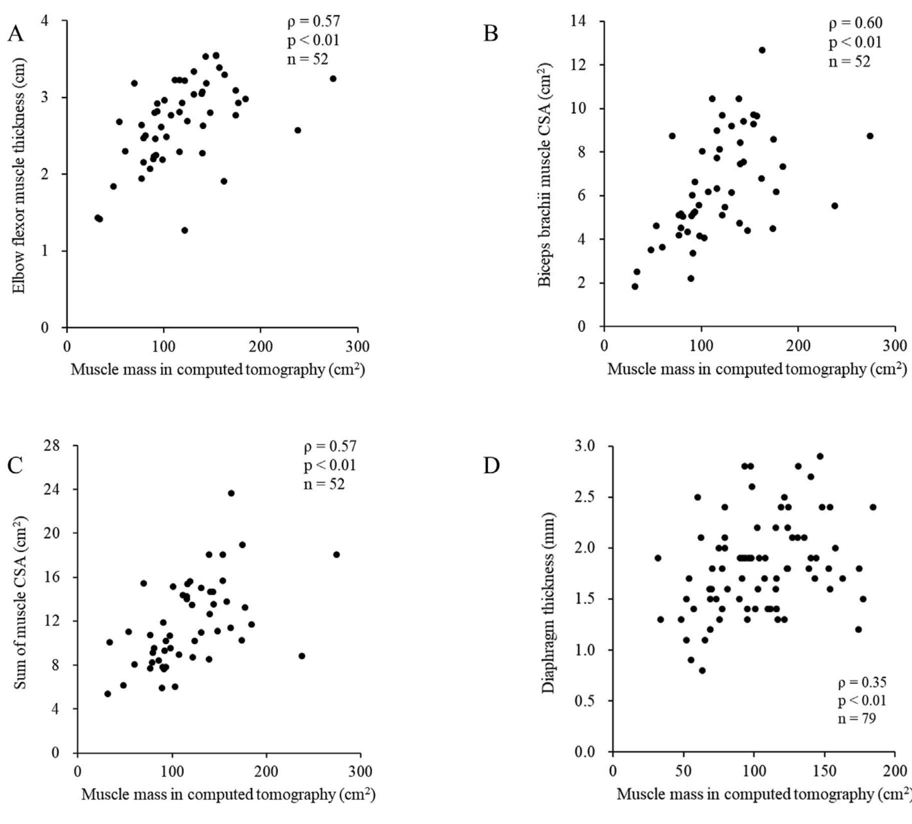

Fig. 4. Relationships with the ultrasound measurements of elbow flexor muscle thickness, biceps brachii muscle CSA, sum of rectus femoris and biceps brachii muscle CSA, and diaphragm thickness. (A) elbow flexor muscle thickness, (B) biceps brachii muscle CSA, (C) sum of rectus femoris and biceps brachii muscle CSA, (D) diaphragm thickness. CSA: cross-sectional area. Correlation between ultrasound and computed tomography measurements were evaluated. The Spearman correlation coefficient was used to investigate the relationships.

thickness and CSA had not been clarified in previous studies. Although thickness measurement is not correlated with functional impairments [12,13], the thickness measurement reflects the trunk muscle mass. Second, this study sets the standard values of the quadriceps muscle layer thickness and rectus femoris muscle CSA at ICU admission. Few studies have investigated subject groups using ultrasound at ICU admission. The quadriceps muscle layer thickness of 2.0 cm and the rectus femoris muscle CSA of 4.7 cm^2 can be set as cutoff values for low muscularity at ICU admission. Hida et al. investigated the cutoff value of the rectus femoris muscle for low muscularity in healthy volunteers; however, the values in critically ill patients have not been reported [26]. We showed the standard value of quadriceps muscle layer thickness and rectus femoris muscle CSA at ICU admission in all 133 patients (Table S3), which may contribute to the clinical application of ultrasound muscle mass assessment in critically ill patients.

Of note, the biceps brachii muscle mass was correlated with the trunk muscle mass. This finding is important because the muscle mass assessments of the biceps brachii muscle may replace the femoral muscle for muscularity assessments. The extension of the lower limb for femoral muscle measurements requires critically ill patients to be placed in a supine position because the bed angle affects lower limb extension [27]. During a critical illness, particularly at ICU admission, the flat position may be risky in some patients. By contrast, the biceps brachii muscle can be extended, regardless of the bed angle. Furthermore, the upper limb can be measured more easily because the biceps brachii muscle is exposed to the outside, whereas the femoral muscle measurements need preparation pertaining to the removal of the patient's clothing. The upper limb circumference has been used to calculate the upper limb muscle mass; however, it is not accurate to evaluate the muscle mass in critically ill patients [28]. This is reasonable because the circumference indirectly evaluates the upper limb muscle mass, whereas ultrasound evaluates it directly. Therefore, the ultrasound biceps brachii muscle measurement is a promising method for muscle mass assessments.

Contrary to previous studies [29,30], the sum of rectus femoris and biceps brachii muscle CSA did not improve the correlation with the trunk muscle mass. Campbell et al. reported that the sum of elbow flexor, anterior forearm, and quadriceps femoris thicknesses was useful to evaluate muscularity [29]. Likewise, Lambell et al. reported that the sum of elbow flexor, bilateral quadriceps femoris thicknesses, and patient characteristics improved the correlation with the trunk muscle mass [30]. The utility to add muscle mass may depend on the measurement site and the content to be added. We did not analyze which combination improves the correlation because this was not our primary purpose. Therefore, this result needs further investigation. However, at the very least, this result may indicate that a single site muscle mass measurement is sufficient to assess the trunk muscle mass in critically ill patients.

In addition to the biceps brachii muscle, the diaphragm was also correlated with muscularity. We found that the diaphragm thickness differs among critically ill patients. Sklar et al. reported that a diaphragm thickness of <2.3 mm is associated with prolonged mechanical ventilation and mortality [31]. Our finding suggests that patients with low muscularity are likely to have low diaphragm thickness. Hence, preventing further diaphragm atrophy is an urgent matter in such patients. Diaphragm atrophy may be prevented by avoiding excessive ventilatory support and inflammation [32,33]. Furthermore, diaphragm muscle training can preserve diaphragm muscle thickness [34]. The prevention and treatment of diaphragm atrophy are being investigated globally; however, few treatments exist [35]. Physical rehabilitation, such as mobilization, may contribute to treating diaphragm muscle atrophy as well as trunk muscle mass because of the associated relationship [36].

Based on the outcomes of the present study, we propose using ultrasound to assess muscularity at the time of ICU admission. The recognition of low muscularity at ICU admission is important for nutritional and rehabilitation intervention. Low muscularity at ICU admission harbors a risk of mortality and physical disability [37]. Early enteral nutrition and early mobilization are recommended in critically ill patients [38,39], and we propose that personalized management based on muscularity could prevent further muscle loss. Given that we provided the cutoff value of ultrasound assessments, it may be possible to assess low muscularity using ultrasound. Additional studies are, however, needed to confirm that ultrasound muscle mass assessments can be used to improve patient management in ICU.

4.1. Limitations

First, this was a retrospective analysis of an observational study. Therefore, prospective studies should be conducted to validate these findings. Second, the reliable cutoff value of low muscularity is unclear for the entire ICU population. Therefore, we used a cutoff value for Japanese patients with cancer to avoid ethnicity differences. Third, it is still unclear whether muscle CSA at the L3 assessed by CT is related to whole-body muscularity in ICU population. Fourth, CT and ultrasound examinations were performed within 2 days before and after admission and not on the same day. However, these examinations were performed in the difference of 0 days (IQR, 0–1 days). Thus, temporal differences were not considered influential.

5. Conclusions

We retrospectively evaluated the relationship between ultrasound and CT muscle mass assessments and found that ultrasound measurements of the quadriceps muscle layer thickness and rectus femoris muscle CSA can serve as indicators of low muscularity. Furthermore, the elbow flexor muscle thickness, biceps brachii muscle CSA, and diaphragm thickness had weak-to-moderate correlation to trunk muscle mass. At ICU admission, the ultrasound assessment of muscle mass can be a promising method to identify low muscularity.

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Authors' contributions

A.Y. participated in data acquisition and manuscript drafting. N.N. participated in study design, data acquisition, analysis, and manuscript drafting. The first two authors contributed equally to this study as first authors. Y.O. participated in manuscript revision. Profs. S.I., J.K., M.H., and J.O. supervised all aspects of this study. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2021.08.032.

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