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Early urea-to-creatinine ratio to predict rapid muscle loss in critically ill patients with sepsis: a single-center retrospective observational study

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Abstract

Background Patients with sepsis in the intensive care unit (ICU) often experience rapid muscle loss. The urea-to-creatinine ratio (UCR) is thought to reflect muscle breakdown (creatinine) and catabolism (urea) and is commonly used to assess nutritional and metabolic status. This study aimed to investigate whether changes in UCR (ΔUCR) can predict the development of rapid muscle loss in patients with sepsis.

Methods This retrospective observational study was conducted in a university ICU between 2014 and 2021, involving adult patients (≥ 18 years) diagnosed with sepsis. The primary outcome was the incidence of rapid muscle loss during ICU hospitalization. Changes in the cross-sectional muscle area at the third lumbar vertebra (L3SMA) were measured using CT images to evaluate muscle loss. Rapid muscle loss was defined as a change in ΔL3SMA greater than 2% per day. Multivariable logistic regression was used to examine the association between UCR or ΔUCR and rapid muscle loss. The area under the receiver operating characteristic curve (AUC) was calculated to assess the predictive performance of UCR or ΔUCR for rapid muscle loss.

Results Of the 482 patients, 141 (29.2%) experienced rapid muscle loss during their ICU stay. Multivariable logistic regression analysis revealed that ΔUCR was significantly associated with an increased risk of rapid muscle loss, with an odds ratio (OR) of 1.02 [95% CI: 1.01, 1.02]. The AUC for ΔUCR in predicting rapid muscle loss was 0.76 [95% CI: 0.68–0.83], with a threshold value of 19.4 μmol urea/μmol creatinine for ΔUCR.

Conclusion The results demonstrate that ΔUCR is independently associated with rapid muscle loss in patients with sepsis and the AUC of the ROC curve for the ability of ΔUCR to predict rapid muscle loss was 0.76. Though additional prospective data are needed, our results suggest that ΔUCR may be useful in the early identification of critically ill patients with sepsis at risk of rapid muscle loss.

Keywords Sepsis, Skeletal muscle wasting, Urea-to-creatinine ratio, ICU acquired weakness

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Introduction

During the first week of hospitalization in the intensive care unit (ICU), there may be significant muscle loss of over 10%, which often leads to functional decline and weakness among ICU survivors [1, 2]. Skeletal muscle mass is crucial in immune function, glucose processing, protein synthesis, and mobility; therefore, acute loss of skeletal muscle mass can lead to excessive

physiological damage [3–5], and even lead to weakness in the ICU. ICU-acquired weakness (ICUAW) is a serious and recurrent complication originating from critical illness, with an incidence rate ranging from 25 to 75% [6]. Sepsis is one of the most important risk factors for ICUAW, with a prevalence of 25–30% in non-patients with sepsis and as high as 48–86% in patients with sepsis [7–9]. The acute loss of skeletal muscle mass leads to long-term dependence on mechanical ventilation and prolonged hospitalization, thereby increasing medical expenses and mortality. In addition, it is associated with sustained impairment of health-related quality of life, which may persist for several years after discharge from the ICU [10–14].

Skeletal muscle mass can be estimated by various techniques and adjusted based on height or body mass index (BMI) [15]. Magnetic resonance imaging (MRI) and computed tomography (CT) are considered the gold standards for non-invasive assessment of muscle mass. In particular, the CT images of specific lumbar spine markers (L3) are significantly correlated with overall muscularity, which has been proven to be practical and accurate for measuring body composition [16–18]. Therefore, this imaging method has been used to detect muscle mass loss. Though CT is highly accurate for measurement of muscle size and is available in most ICUs in developed countries, CT is rarely performed clinically for the purpose of diagnosing muscle wasting due to the cost, radiation exposure, and logistic challenges involved.

The urea-to-creatinine ratio (UCR) reflects protein metabolism, and its sustained increase reflects muscle catabolism, muscle bioenergy depletion, and ongoing muscle atrophy [5]. Thus, it helps in assessing nutritional metabolic status. Recently, Haines reported [19] that elevated UCR can be used as a potential biomarker of muscle catabolism after severe trauma and persistent critical illness. Although protein digestion and amino acid absorption are relatively normal, critically ill patients' ability to utilize ingested protein for muscle protein synthesis is significantly impaired [20]. In patients with severe sepsis, the protein degradation rate can be as high as 160% [21], potentially leading to an increase in UCR.

Due to systemic inflammatory response, oxidative stress, and various other factors, early acute muscle mass loss in sepsis patients is the result of increased catabolic metabolism and decreased synthetic metabolism, which may lead to an increase in UCR. The purpose of this study was to investigate whether early elevated UCR could predict acute skeletal muscle wasting in patients with sepsis.

Methods

Study population

This is a single-center retrospective observational study on patients with sepsis admitted to the ICU of a university hospital from January 2014 to December 2021. Sepsis was diagnosed according to the sepsis-3 criteria [22]; in brief, patients with documented or suspected infection and an acute change in total Sequential Organ Failure Assessment (SOFA) score of ≥ 2 points were considered to have sepsis. Patients were eligible if they were 18 years of age or older, and at least 5 days of ICU stay, had undergone an abdominal CT examination within 24 h of admission, and had at least two serial CT datasets during hospitalization, including the abdomen. We excluded patients if (1) they had creatinine > 4 mg/dl on ICU admission, (2) received renal replacement therapy (RRT), (3) There was gastrointestinal bleeding within the three days before admission, (4) failed to match to complete data records, (5) transferred from another ICU, and (6) the interval between two serial CT datasets shorter than 5 days. The study was approved by the ethics committees of Zhongda Hospital, Affiliated to Southeast University (Number 2021ZDSYLL225-P01) and performed in accordance with STROBE [23] guideline for observational research.

Data collection

For all patients, the following demographic and clinical data were collected from electronic health records: sex, age, height and weight, sequential organ failure assessment (SOFA) score, acute physiology and chronic health evaluation (APACHE) II score, chronic comorbidities, admission diagnosis, and infection site. We recorded the creatine kinase, myoglobin, hemoglobin, albumin (ALB), prognostic nutrition index (PNI), blood glucose, lymphocyte count, procalcitonin (PCT), and lactate on day 1 after ICU admission. Blood urea nitrogen (BUN), and serum creatinine were extracted on day 1 and day 3. In addition, we collected the mode of nutritional support, daily non-protein caloric intake, neuromuscular blockers use, Richmond agitation-sedation scale (RASS) score, and insulin dose. PNI was calculated as $10 \times$ serum ALB level (g/L) $+ 0.005 \times$ total lymphocyte count (/mm3).

L3 skeletal muscle area analysis

CT images of the third lumbar vertebra (L3) were evaluated. For all patients included, skeletal muscle area at L3 slices (L3SMA) includes the psoas, erector spine, quadratus lumborum, transverse abdominous, external and internal obliques, and rectus abdominous. Images were analyzed by a trained specialist (J.J) with Image J software [6] version 1.48 (https://imagej.nih.gov/ij/index.html; NIH, Bethesda, MD, USA), which used predetermined

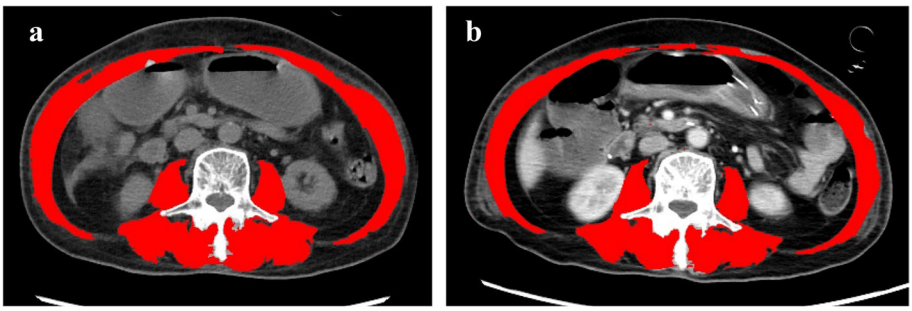

Fig. 1 Typical transverse CT images at L3 of the same patient. **a** ICU admission; **b**, the tenth day after ICU admission. The total skeletal muscle area (red)

thresholds (−29 to + 150 Hounsfield units) to demarcate skeletal muscle tissues [6]. Tissue boundaries were manually corrected if needed. L3SMA was calculated automatically by summing the skeletal muscle-tissue pixels and multiplying them by the surface area of each pixel. Figure 1 shows the before and after changes in L3SMA (red) on transverse CT images in the same patient. L3SMA was adjusted for the square of the height (SMA/ height^2), which was referred to as the skeletal muscle index (L3SMI). L3SMI = L3SMA/ height 2. L3SMA was assessed on ICU admission and at least one more in-ICU follow-up CT. If the patient had ≥ 2 upper abdominal CT scans during the ICU stay, only the first and second CT scan results were evaluated. In Fazzini's (2023) meta-analysis [24], four studies used CT methods to measure the L3SMA, with data provided by three of these studies. Lambell [25] reported a 3.1%/day decrease in L3SMA, Haines [19] found a decrease of 2.1%/day, and Jung [26] observed a 0.8%/day decrease in L3SMA. Based on these findings, along with data from other muscle ultrasound studies, a threshold of 2%/day was set. We define rapid muscle loss as a change in L3SMA (△L3SMA) > 2% per day, calculated from the difference between admission and follow-up CT L3 muscle areas, as follows:

$$\Delta\ \text{L3SMA} = \frac{\text{admission CT L3SMA} - \text{Follow up CT L3SMA}}{\text{admission CT L3SMA}}$$

Primary exposures and Outcomes

The primary exposures were UCR on day 1 (UCR_D1), which was calculated as [urea nitrogen*1000/ creatinine], UCR on day 3 (UCR_D3), and the difference in UCR between day 3 and day 1 (ΔUCR). The primary outcome was the incidence of rapid muscle loss during ICU hospitalization. The secondary outcomes included ICU and hospital length of stay, ICU mortality, 28-day mortality, hospital mortality, and ventilation-free days (VFDs) on day 28.

Statistical analysis

Values are presented as the mean (standard deviation) or median [interquartile range (IQR)] for continuous variables as appropriate and as the total number (percentage) for categorical variables. Comparisons between rapid muscle loss and no rapid muscle loss patients were made using the X2 test or Fisher's exact test for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables as appropriate. The Shapiro–Wilk test was used to assess the normality of continuous variables.

A Spearman rank correlation test was conducted to assess the relationship between ΔUCR and ΔL3SMA. We first employed three multivariable logistic regression models to explore the association between UCR or ΔUCR and rapid muscle loss. Variables based on previous studies and clinical correlations including age, gender, BMI, SOFA score, Lactate, PCT, L3SMA, and PNI were entered into the model. We calculated the area under curve (AUC) of the receiver operating characteristic (ROC) curve to quantify the performance of UCR or ΔUCR in predicting rapid muscle loss. The optimal cut-off value of UCR or ΔUCR was determined by the Youden Index (sensitivity + specificity −1). We also calculated the AUROCs after adjusting for the above confounders. The AUCs were compared by using the bootstrap test for each two ROC curves.

Several subgroup analyses were performed according to sex, age (≥ 60, < 60), Diabetes mellitus, BMI (≥ 24, < 24), SOFA score (≥ 8, < 8), PNI (≥ 34, < 34), L3SMI (≥ 40, < 40), use of mechanical ventilation, insulin, nutrition supports (whether the patient fasted within 3 days of admission), neuromuscular blocker and vasopressor.

We used Stata software version 15.0 (Stata Corp) and R software (IBM, Armonk, NY version 4.0.3) for all analyses. 2-tailed P < 0 0.05 was considered to be statistically significant.

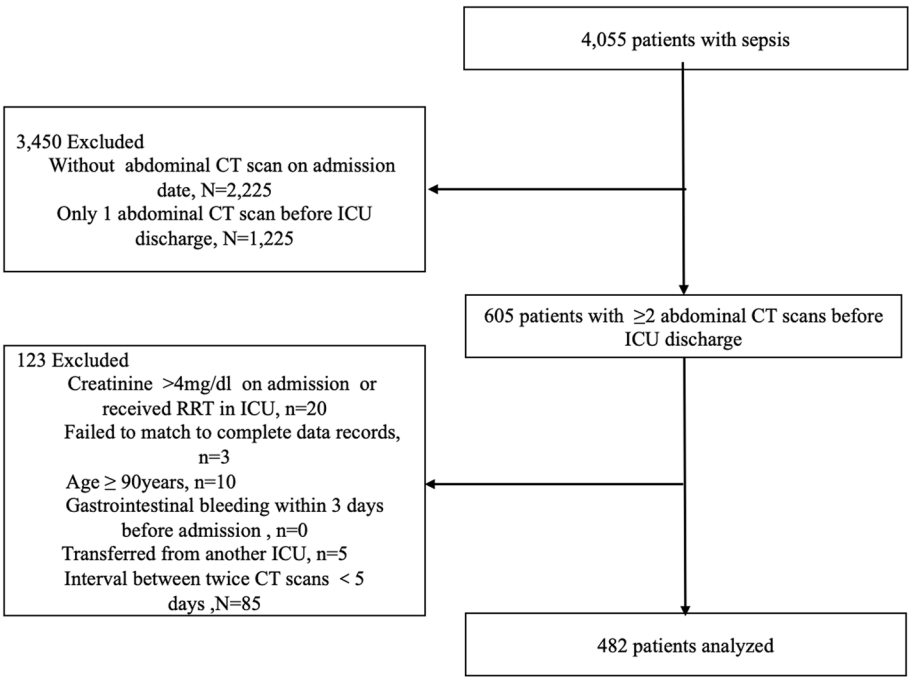

Fig. 2 Flowchart of the patients included in the study. RRT, renal purification therapy; CT, computerized tomography; ICU, intensive care unit

Result

Baseline characteristics and clinical outcomes

A total of 482 patients were included in the final analysis. The flow diagram of study patients is presented in Fig. 2. The median (IQR) age of the included patients was 62.0 (51.0, 74.0) years, with 350 males and 132 females (Table 1). Patients had a median SOFA score of 8 (6, 11) and a median APACHE II score of 19(14, 24). Among them, 141 patients (29.2%) had Rapid muscle loss during ICU stay. There was no significant difference in L3SMA between the two groups upon admission, and subsequently, L3SMA in both groups tended to decrease. However, the rapid muscle loss group showed a greater decrease in L3SMA, Δ L3SMA is (20.7 [0.6], 14.5 [0.5], $P<0.01$) (Figure S1 and Table S1). In the group that underwent repeat CT scan within one week, the rate of decline was faster than in the group that underwent repeat CT more than a week later (1.9 [0.9], 1.6 [0.6], $P<0.01$) (Table S2). Table 1 and Table S3 summarize the clinical characteristics of the rapid muscle loss group and the group without rapid muscle loss. Compared with the group without rapid muscle loss, patients with rapid muscle loss had a lower average age (56.0 [50.0, 71.0], 64.0 [51.0, 75.0], $P=0.02$), the proportion of male patients is higher (118 [83.7%], 232 [68.1%], $P<0.01$), UCR-D3 and Δ UCR significantly increased (Figure S2). There was no significant difference between the two groups in terms of 28-day mortality, ICU mortality, and length of hospitalization.

In addition, a separate analysis of 176 patients who underwent CT re-examination within one week revealed that 67 patients (38.1%) had rapid muscle loss. There was no significant difference in 28-day mortality or ICU mortality between patients with and without rapid muscle loss, but the length of hospitalization was longer than in patients without rapid muscle loss (28.5 [2.1], 21.9 [1.16], $P<0.01$) (Table S4).

Association between UCR and rapid muscle loss

The results showed a significant correlation between ΔUCR and ΔL3SMA, with Spearman's $\rho=0.41$ ($p<0.01$). The multivariable logistic regression analysis showed that UCR_D1 and UCR_D3 were not associated with an increased risk of rapid muscle loss, while there was a significant association between ΔUCR and rapid muscle loss, with an OR of 1.02 [95% CI: 1.01,1.02] (Table 2). The comparisons were similar after adjusting for confounders.

In patients who underwent CT re-examination within one week, ΔUCR is still associated with rapid muscle loss (Table S5). Analysis of the predictive values of UCR_D1, UCR_D3 and ΔUCR for rapid muscle loss showed that UCR_D1 and UCR_D3 had poor predictive accuracy (AUROC 0.46 and 0.57). ΔUCR had the highest predictive accuracy (AUROC 0.76) (Fig. 3). ΔUCR had an optimal threshold of 19.4 μmol urea/μmol creatinine for the prediction of rapid muscle loss, with sensitivity and specificity of 60% (49–83) % and 84% (61–95) %, respectively.

Table 1 Baseline characteristics and clinical outcomes of patients

Characteristics	All patients (*N* = 482)	Rapid muscle loss group(*N* = 141)	Non rapid muscle loss group (*N* = 341)	*p*
Age (year) (median [IQR])	62.0 (51.0, 74.0)	56.0 (50.0, 71.0)	64.0 (51.0, 75.0)	0.02*
Male (n) (%)	350 (72.6)	118 (83.7)	232 (68.0)	< 0.01*
Infection site				
Respiratory (n) (%)	295 (61.2)	81 (57.4)	214 (62.8)	0.28
Abdominal (n) (%)	127 (26.4)	44 (31.2)	83 (24.3)	0.12
Genitourinary (n) (%)	13 (2.7)	4 (2.8)	9 (2.6)	0.9
Skin/soft tissue (n) (%)	7 (1.5)	1 (0.7)	6 (1.8)	0.38
Bloodstream (n) (%)	22 (4.6)	6 (4.3)	16 (4.7)	0.83
Central nervous system (n) (%)	15 (3.1)	4 (2.8)	11 (3.2)	0.82
Other (n) (%)	3 (0.6)	1 (0.7)	2 (0.6)	0.88
BMI (median [IQR])	23.7 (21.7, 26.1)	24.5 (22.9, 27.3)	23.4 (20.9, 25.3)	0.21
APACHE II (median [IQR])	19.0 (14.0, 24.0)	18.0 (13.0, 23.0)	19.0 (14.0, 24.0)	0.63
SOFA (median [IQR])	8.0 (6.0, 11.0)	8.0(6.0, 11.0)	8.0 (6.0, 11.0)	0.59
Shock (n) (%)	276 (57.4)	157 (57.9)	119 (56.4)	0.74
Comorbid conditions				
Hypertension (n) (%)	213 (44.2)	52 (36.9)	161 (47.2)	0.04*
Coronary artery disease (n) (%)	62 (12.9)	14 (9.9)	48 (14.1)	0.22
Heart failure (n) (%)	60 (12.5)	15 (10.7)	45 (13.2)	0.44
Chronic obstructive pulmonary disease (n) (%)	27 (5.6)	8 (5.7)	19 (5.6)	0.96
Diabetes mellitus (n) (%)	119 (24.7)	33 (23.4)	86 (25.2)	0.67
Solid malignant tumors (n) (%)	71 (14.7)	14 (9.9)	57 (16.7)	0.05
Hematologic cancer (n) (%)	6 (1.3)	1 (0.7)	5 (1.5)	0.49
Cirrhosis (n) (%)	7 (1.5)	2 (1.4)	5 (1.5)	0.97
Other (n) (%)	11 (2.3)	3 (2.1)	8 (2.4)	0.91
Admission vital signs				
Temperature (°C) (median [IQR])	37.2 (36.5, 38.5)	37.4 (36.5, 38.3)	37.2 (36.5, 38.5)	0.69
RR (median [IQR])	21(12, 28)	20(12, 28)	21(13, 28)	0.66
Heart rate (beats/min) (median [IQR])	111(73, 126)	111(80, 125)	111(72, 127)	0.90
MAP (mmHg) (median [IQR])	75.0 (71.0, 78.0)	76.0 (72.0, 78.0)	75.0 (70.0, 78.0)	0.54
Admission blood tests (median [IQR])				
Creatinine (umol/L) (median [IQR])	78.0 (59.0, 107.0)	82.0 (63.0, 109.0)	77.0 (56.0, 103.0)	0.73
Urea (mmol/L) (median [IQR])	6.9 (4.7, 10.4)	6.8 (5.1, 9.2)	6.9 (4.6, 10.7)	0.17
Urea: creatinine (median [IQR])	88.6 (61.4, 123.1)	84.2 (62.5, 110.5)	92.5 (61.4, 132.7)	0.02*
Lactate (mmol/L) (median [IQR])	1.6 (1.1, 2.5)	1.5 (1.1, 2.3)	1.6 (1.1, 2.6)	0.86
PCT (ng/ml) (median [IQR])	0.9 (0.1, 4.8)	1.1 (0.2, 3.2)	0.9 (0.1, 5.7)	0.23
Albumin (g/L) (median [IQR])	30.2 (27.0, 34.0)	29.9 (27.0, 33.8)	30.2 (26.9, 34.0)	0.68
Lymphocyte count ($\times 10^9$/L) (median [IQR])	0.7 (0.5, 1.1)	0.7 (0.5, 1.2)	0.7 (0.5, 1.1)	0.21
Hemoglobin (g/L) (median [IQR])	106.0 (91.0, 123.0)	105.0 (89.0, 125.0)	106.0 (92.0, 122.0)	0.93
Admission L3SMA (cm2) mean (SD)	118.9 (32.3)	141.7 (30.1)	109.6 (28.3)	< 0.01*
ΔL3SMA/day (cm2/day)	1.7(0.8)	2.5 (0.5)	1.3 (0.3)	< 0.01*
Hospital length of stay (day) (mean [SD])	31.4 (20.6)	28.8 (17.1)	32.5(21.8)	0.08
ICU length of stay (day) (median [IQR])	16.2 (11.5, 26.2)	15.5 (10.8, 24.5)	17.6 (11.8,26.9)	0.13
Hospital mortality (n) (%)	105 (21.8)	24 (17.1)	81 (23.8)	0.10
ICU mortality (n) (%)	92 (19.1)	20 (14.2)	72 (21.1)	0.08
28-day mortality (day) (%)	76 (15.8)	21 (14.9)	55 (16.1)	0.74
Alive and VFDs-28-day (day) (median [IQR])	20.4(7.6)	20.5 (7.3)	20.3 (7.7)	0.85

BMI body mass index, *APACHE II* acute physiology and chronic health evaluation II, *SOFA* sequential organ failure assessment, *UCR* urea-to-creatinine ratio, *PCT* procalcitonin, *RR* Respiratory rate, *MAP* mean arterial pressure, *L3SMA* skeletal muscle area at L3 slices, *VFDs-28-day* mechanical ventilation free days to day28. * $p < 0.05$

Table 2 Multivariable logistic regression exploring the impact of UCR on the risk of rapid muscle loss

	Adjusted for UCR_D1		Adjusted for UCR_D3		Adjusted for ΔUCR	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	0.99 (0.97,1.00)	0.03*	0.99 (0.99,1.00)	0.02*	0.99 (0.99,0.99)	0.02*
Male	0.95 (0.58,1.56)	0.85	0.99 (0.61,1.63)	0.98	0.95 (0.58,1.56)	0.99
BMI	0.96 (0.89,1.03)	0.25	0.96 (0.90,1.03)	0.29	0.96 (0.89,1.03)	0.31
SOFA	0.99 (0.94,1.06)		0.99 (0.93,1.05)	0.79	0.99 (0.94,1.06)	0.65
L3SMA on Day 1	1.00 (0.99,1.01)	0.76	1.00 (0.99,1.01)	0.86	1.00 (0.98,1.01)	0.89
Lactate	1.00 (0.92,1.09)	0.96	1.02 (0.93,1.11)	0.69	1.00 (0.91,1.09)	0.69
PCT	0.98 (0.95,1.01)	0.16	0.98 (0.95,1.01)	0.22	0.98 (0.95,1.01)	0.13
PNI	0.99 (0.97,1.02)	0.68	0.99 (0.97,1.02)	0.68	0.99 (0.68,1.02)	0.75
UCR_D1	1.00 (0.99,1.01)	0.07	—	—	—	—
UCR_D3	—	—	1.00 (0.99,1.00)	0.61	—	—
ΔUCR	—	—	—	—	1.02 (1.01,1.02)	< 0.01*

The reference group was non rapid muscle loss. *OR* odds ratio, *CI* Confidence interval, *SOFA* sequential organ failure assessment, *BMI* body mass index, *PCT* procalcitonin, *PNI* prognostic nutritional index, *L3SMA* skeletal muscle area at L3 slices, *UCR* urea-to-creatinine ratio, *UCR_D1* urea-to-creatinine ratio on day1, *UCR_D3* urea-to-creatinine ratio on day3, *ΔUCR* difference in UCR between day 3 and day 1. *: $p < 0.05$

The positive predictive value was 70% (67–93) % and the negative predictive value was 77% (68–85) %. The Youden index was 0.44 (Table 3).

Subgroup analyses

Regardless of the subgroup, ΔUCR was associated with a higher probability of rapid muscle loss. No significant differences were observed among the subgroups. However, subgroup analysis in patients who underwent CT re-examination within one week showed that in the age subgroup, the AUROC of rapid muscle loss predicted by Δ UCR was significantly higher in patients aged ≥ 60 years than in patients aged < 60 years (0.82 [95% CI 0.74–0.91] vs. 0.67 [95% CI 0.55–0.79], $P = 0.04$). In the nutritional support subgroup, the AUROC of rapid muscle loss predicted by Δ UCR was significantly higher in patients without nutritional support than in patients with nutritional support (0.79 [95% CI 0.72–0.87 vs 0.58 [95% CI 0.39–0.78], $P = 0.04$) (Table S6 and Figure S3).

Discussion

In this study, we found that 29.2% of patients experienced rapid muscle loss during their ICU stay. The rate of decline was faster in the early stages of ICU (within a week) than in the later stages. Patients who showed rapid muscle loss within one week of ICU admission had longer hospitalization. ΔUCR was confirmed to be independently associated with rapid muscle loss by analyzing patients' abdominal CT scans and biochemical markers.

An early increase in the ΔUCR would help predict the occurrence of rapid muscle loss in patients with sepsis. Haines reported [19] that in patients after major trauma with ICU stay ≥ 10 days, UCR on day 10 had increased by 133%. Elevated UCR was a biochemical marker indicating persistent critical illness after major trauma and was seen in association with the wasting of skeletal muscle. In other investigations on nutrient metabolism, the UCR had also been found to be a usable clinical biomarker of muscle catabolism conditions in critical diseases [27–29].

Possible mechanisms for rapid muscle loss in patients with sepsis include reduced levels of anabolic hormones and increased levels of catabolic hormones [30, 31], as well as mechanical unloading due to fixation or denervation. These factors contribute to a metabolic disorder characterized by increased protein catabolism and decreased anabolic metabolism [1]. Elevated protein catabolism results in higher urea production, while also contributing to a reduction in total muscle mass and creatinine levels. This ultimately leads to an increase in the UCR. These mechanisms are thought to contribute to ICUAW, although the development of ICUAW is complex and influenced by various factors, such as nutritional interventions and pharmacological treatments. Despite these insights, our understanding of ICUAW remains incomplete.

We conducted a separate analysis on patients who underwent CT re-examination within one week of staying in the ICU. The results showed that early increase in the ΔUCR had a higher accuracy in predicting rapid muscle loss in CT re-examination within one week group. This result may be potentially explained by the findings of our subgroup analysis. Subgroup analysis showed that the implementation of enteral nutrition would reduce the value of ΔUCR in predicting rapid muscle loss. With the extension of ICU stay time, including the implementation of nutritional support and protein intake, the body has shifted from early catabolism to a complex state of coexistence of catabolism and

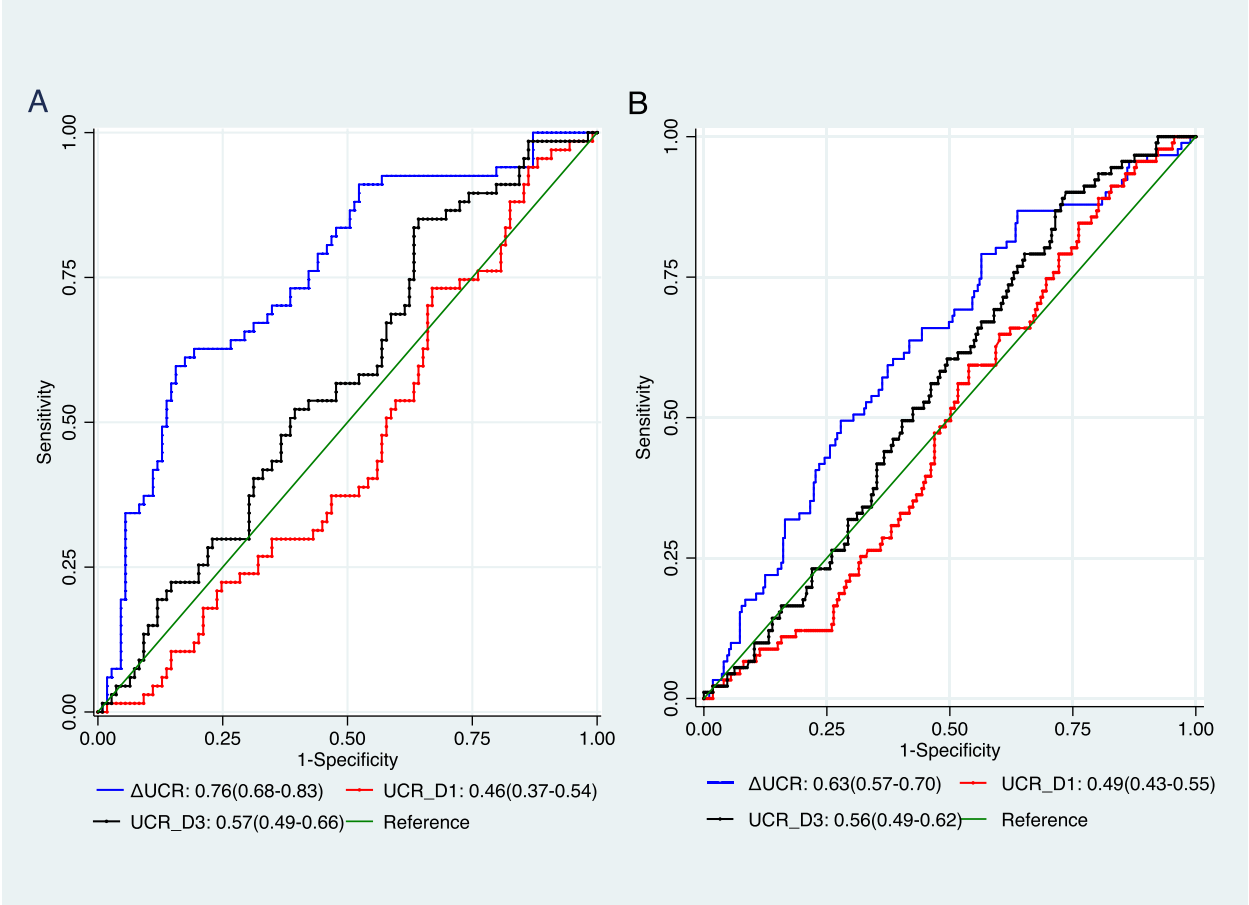

Fig. 3 AUROC of predicting rapid muscle loss in patients with sepsis. **A** AUROC curves for UCR or ΔUCR after adjusting for confounders. **B** unadjusted AUROC curves for UCR and ΔUCR. AUROC curves for UCR, ΔUCR. AUROC, area under the receiver operating characteristic; CI, confidence interval; UCR, urea-to-creatinine ratio; ΔUCR, difference in UCR between day 3 and day 1

Table 3 The accuracy of UCR to predict rapid muscle loss in CT re-examination within one week group

	AUROC	Threshold	Sensitivity, %	Specifcity, %	Positive predictive value, %	Negative predictive value, %
UCR_D1	0.46 (0.37–0.54)	> 48.1	0.88 (0.76–0.97)	0.17 (0.12–0.37)	0.39 (0.31–0.69)	0.68 (0.52–0.75)
UCR_D3	0.57 (0.49–0.66)	> 70.7	0.84 (0.49–0.91)	0.37 (0.29–0.73)	0.45(0.36–0.54)	0.78 (0.69–0.83)
ΔUCR	0.76 (0.68–0.83)	> 19.4	0.60 (0.49–0.83)	0.84 (0.61–0.95)	0.70 (0.67–0.93)	0.77 (0.68–0.85)

AUROC area under the receiver operating characteristic, *UCR* urea-to-creatinine ratio, *UCR_D1* urea-to-creatinine ratio on day1, *UCR_D3* urea-to-creatinine ratio on day3, *ΔUCR* difference in UCR between day 3 and day 1

synthetic metabolism, masking the early protein metabolism disorder in patients with sepsis. Furthermore, blood urea nitrogen levels arise from either nutrient protein intake or the breakdown of endogenous proteins, such as muscle protein. Consequently, nutritional interventions may interfere with the use of this ratio to assess muscle breakdown metabolism. As ICU stay prolongs, the predictive value of ΔUCR as a biomarker for protein catabolism diminishes.

It is important to note that the AUC of Δ UCR in predicting rapid muscle loss is 0.76, indicating a moderate level of predictive performance. Therefore, the significance of this result should be interpreted with caution. In other words, the discriminative ability of Δ UCR alone in predicting rapid muscle loss is limited. To improve predictive accuracy, it may be beneficial to combine Δ UCR with other established methods, such as additional

muscle metabolism-related biomarkers, ultrasound, and other relevant tools [32–34].

Critically ill patients may develop rapid muscle loss as early as the day after admission to ICU [35], and the incidence increases as the length of ICU stay increases. 24%–55% of patients develop ICUAW when the length of ICU stays is extended to 5–7 days, and the incidence can further increase to 75% [36] when the length of ICU stay exceeds 10 days. The incidence of rapid muscle loss of critically ill patients with sepsis in this study is similar to that in the above studies. In terms of prognosis, we discovered that in the rapid muscle loss group patients had longer hospital stays, which is consistent with other relevant studies [10]. Previous studies [13, 14, 37–39] have shown that rapid muscle loss affects not only the short-term prognosis of patients but also the long-term quality of life in survivors after discharge; yet, the present study failed to follow up on the long-term prognosis of the patients.

The study has several limitations. First, Patients who experience rapid muscle loss during ICU hospitalization not only face an increased risk of short-term mortality but also tend to recover slowly after discharge, resulting in prolonged weakness and reduced long-term survival rates. This study focused solely on the 28-day survival rate and did not evaluate the broader, long-term consequences of rapid muscle loss. Second, patients who underwent RRT were excluded from this study because it was considered that the removal of urea and creatinine by RRT would interfere with the study results, which may lead to population bias. These patients may be at particularly increased risk of ICUAW due to the inflammatory and metabolic effects of AKI and the non-selective removal of amino acids by RRT [40]. Third, the main basis for using 2% per day as the threshold for rapid muscle loss is Fazinni's meta-analysis, which primarily included studies using muscle ultrasound. Applying these results to this study may introduce potential errors. Fourth, this study only evaluated muscle loss and did not assess changes in patient muscle strength, so it cannot be determined whether the patient has developed ICUAW. Finally, this is a single-center retrospective observational study, which limits the ability to draw clear causal conclusions and limits the generalizability of our findings.

Conclusion

Approximately one-third (29.2%) of critically ill patients with sepsis will experience rapid muscle loss. Though additional prospective data are needed, our results suggest that ΔUCR may be useful in the early identification of critically ill patients with sepsis at risk of rapid muscle loss, especially in patients aged 60 years or older and those who do not receive early nutritional support.

Abbreviations

CT	Computed tomography
ICUAW	Intensive care unit-acquired weakness
SOFA	Sequential organ failure score
RRT	Renal replacement therapy
UCR	Urea-to-creatinine ratio
ΔUCR d3-d1	UCR on day 3 minus UCR on day 1
ΔUCR d5-d1	UCR on day 5 minus UCR on day 1
SMI	Skeletal muscle index
L3	Third lumbar spine
L3SMA	Skeletal muscle area at the third lumbar vertebra slices
L3SMI	Skeletal muscle index at the third lumbar vertebra slices
APACHE II	Acute Physiology and Chronic Health Evaluation II
ICU	Intensive care unit
LOS	Length of stay
IQR	Interquartile range
OR	Odds ratio
PCT	Procalcitonin
PNI	Prognostic nutritional index
RASS score	Richmond Agitation-Sedation Scale score
CRP	C-reactive protein
BMI	Body Mass Index
VFDs	Mechanical ventilation free days
AUROC	Area under the receiver operating characteristic
CI	Confidence interval

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
F.G.: Designed the study. J.J.:Writing a manuscript. J.X., P.C. and H.C.: Assist in editing and reviewing manuscripts. S.M.: Help for data collection and analysis. All authors have contributed to the article and agree to the submitted version.

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Data availability
The datasets generated and analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
This study was approved by the Ethics Committees for Clinical Research of Zhongda Hospital, Southeast University (Number 2021ZDSYLL225-P01). All participants or their legal representatives have signed informed consent. The study complied with the Declaration of Helsinki and its amendments.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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