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Predicting early diagnosis of intensive care unit-acquired weakness in septic patients using critical ultrasound and biological markers

Ling Lei[1†], Liang He[2†], Tongjuan Zou[1], Jun Qiu[1], Yi Li[1], Ran Zhou[1], Yao Qin[1] and Wanhong Yin[1*]

Abstract

Objective Early diagnosis of intensive care unit-acquired weakness (ICUAW) is crucial for improving the outcomes of critically ill patients. Hence, this study was designed to identify predisposing factors for ICUAW and establish a predictive model for the early diagnosis of ICUAW.

Methods This prospective observational multicenter study included septic patients from the comprehensive ICUs of West China Hospital of Sichuan University and 10 other hospitals between September and November 2023. Inclusion criteria were as follows: age over 18 years; expected ICU stay longer than 3 days; and voluntary informed consent. Patients were classified into ICUAW (MRC score < 48) and non-ICUAW (MRC score ≥ 48) groups based on muscle strength assessments. The analyzed key predictive factors encompassed demographic data, SOFA and APACHE II scores, inflammatory markers (PCT, IL-6, and CRP), and ultrasound measurements of muscle thickness and cross-sectional area. Logistic regression analysis was conducted for variable selection and nomogram model construction.

Results A total of 116 septic patients were included, comprising 77 males and 39 females (mean age: 56.94 ± 19.90 years). A nomogram model predicting ICUAW probability was developed, which involved vastus intermedius diameter, rectus femoris cross-sectional area, IL-6, and CRP. The AUC of the composite diagnostic ROC curve was 0.966 (95%CI: 0.936 – 0.996), with a sensitivity of 88% and a specificity of 95.8%.

Conclusions Conclusively, a nomogram model is constructed for diagnosing ICUAW in septic patients, which is simple and rapid and allows for visual representation, with excellent diagnostic capability.

Keywords Sepsis, Intensive care unit-acquired weakness, Critical ultrasound, Nomogram, Predictive model

†Ling Lei and Liang He contributed equally to this work.

*Correspondence:
Wanhong Yin
yinwanhong@wchscu.cn
[1]Department of Critical Care Medicine, West China Hospital, Sichuan University, 37 Guo Xue Xiang St, Chengdu 610041, Sichuan, China
[2]Department of Respiratory and Critical Care Medicine, Xindu District People's Hospital, 199 Yuying Road South, Chengdu 610500, Sichuan, China

Introduction

Sepsis represents a frequent life-threatening condition that usually culminates in multiple organ failure and death, which possesses typical features of disseminated intravascular coagulation and severe systemic inflammation [1]. The survival rate of sepsis has dramatically risen with advancements in critical care medicine [2]. Globally, around 14 million sepsis survivors are discharged from hospitals each year at present [3–5]. As the number of survivors grows, post-sepsis physical impairments, particularly intensive care unit (ICU)-acquired weakness (ICUAW), are becoming a prominent clinical issue [4, 6–9]. Sepsis survivors seldom regain the pre-illness functional status after discharge from ICUs. ICUAW also arises from critical illness-induced muscle weakness in addition to neurological disorders [10] and typically manifests as systemic and symmetrical weakness affecting respiratory muscles and limbs (primarily proximally rather than distally), but not ocular and facial muscles [11, 12]. In ICUAW patients, muscle tone is generally diminished, while deep tendon reflexes are either normal or weakened. Presently, ICUAW is frequently assessed with the Medical Research Council (MRC) score, which requires patients to be alert, fully comprehend the instructions of evaluators, and cooperate.

Electrophysiological assessments can be utilized for the diagnosis of comatose or uncooperative ICUAW patients. Nonetheless, electrophysiological assessments involve more intricate differential diagnosis processes, which limits their application. Imaging technologies, including computed tomography and magnetic resonance imaging, are used for evaluating muscle mass. Although these technologies can accurately detect fat infiltration in muscles and quantify lean muscle mass, they are costly and rely on specialized software and personnel [13, 14]. Additionally, computed tomography leads to exposure to high levels of radiation. Bioelectrical impedance analysis is a method for evaluating body composition, but its findings may be affected by edema, body position, or skin temperature [14].

Critical care ultrasonography is deemed the most promising assessment method for ICUAW and has been broadly utilized [13, 14], which is capable of evaluating muscle, tendon, and joint disorders [15]. Nevertheless, the sample size of available studies is small [13, 14], and meanwhile, cohort studies have not involved analyses classified by different critical illness etiologies. Herein, this cohort study aimed to identify core risk factors and risk weights for ICUAW in septic patients and develop a diagnostic model, thereby providing a basis for targeted clinical interventions for ICUAW in septic patients.

Methods

Materials: This prospective observational multicenter study analyzed the data of septic patients in the comprehensive ICUs of the West China Hospital of Sichuan University, the West China Tianfu Hospital of Sichuan University, the Affiliated Hospital of North Sichuan Medical College, the Affiliated Hospital of Southwest Medical University, the West China Longquan Hospital of Sichuan University, the Zigong Fourth People's Hospital, the West China Fourth Hospital of Sichuan University, the Mianyang Third People's Hospital, the Second People's Hospital of Yibin, the Second People's Hospital of Chengdu, and the Sichuan Provincial People's Hospital from September to November 2023. The inclusion criteria for participants were the following: (1) patients aged > 18 years; (2) patients with an expected hospital stay for more than 3 days; and (3) patients voluntarily participating in this study and providing informed consent. Exclusion criteria were as follows: (1) an ICU stay of less than 3 days; (2) transferring out of the ICU while not fully conscious; (3) inability to obtain muscle fat ultrasound images; and (4) incomplete clinical data. A total of 116 patients (77 males and 39 females; age: 56.94 ± 19.90 years) were included in the training set analysis. Three muscle groups in both the upper and lower limbs were evaluated with MRC scores [16, 17], which are a validated assessment tool for muscle strength. Each muscle group was scored from 0 (representing paralysis) to 5 (indicating normal muscle strength), with an overall score of 0 – 60. Scores below 48 illustrated the presence of ICUAW, whilst scores of 48 or above signified the absence of ICUAW. Patients were evaluated with MRC scores when they regained consciousness. The study strictly adhered to the ethical standards outlined in the World Medical Association Declaration of Helsinki, with informed consent from patients or authorized family members. The research protocol was ratified by the Biomedical Ethics Review Committee of West China Hospital of Sichuan University (Approval Number 2023 – 1422) and registered as a clinical trial (ChiCTR2300075581) on September 8, 2023.

The following research indicators were collected: (1) general data: age, gender, height, weight, body mass index (BMI), and estimated body surface area (BSA) based on height and weight; (2) scores: MRC scores, Sequential Organ Failure Assessment (SOFA; sepsis-related) scores, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores; (3) critical ultrasound indicators: rectus femoris muscle thickness (RF-MT), vastus intermedius muscle thickness (VITH), and rectus femoris cross-sectional area (RF-CSA); (4) inflammatory markers: procalcitonin (PCT), interleukin-6 (IL-6), and C-reactive protein (CRP); and (5) outcome indicators: mechanical ventilation duration and ICU stay length. All

test indicators were the results of the first test performed within 24 h following ICU admission.

Critical ultrasound measurement methods: Measurements were carried out within 24 h (D1) and on day 3 (D3) after ICU admission. During the measurements, the bed head was elevated by about 30°, and patients were placed in a supine position with their feet centered. As described in previous studies [18], RF-MT, VITH, and RF-CSA were measured with a linear array ultrasound probe (8 MHz, 5.6 cm) at the lower third of the line connecting the anterior superior iliac spine to the upper patellar edge. The decrease in muscle parameters compared to the baseline within 24 h after ICU admission was calculated with the formula (T3-T1)/T1. These indicators of all patients were measured by the same ultrasound physician, and the operators received training in the CCSUG advanced workshop. Each measurement was replicated three times and averaged.

Assessment method of ICUAW: The MRC scoring system was employed to assess the ability to lift the arms, flex the forearms, extend the wrists, flex the legs, extend the knee joints, and dorsiflex the feet. Each action was graded as 0 (non-visible contraction) – 5 (normal strength) for six muscle groups in four extremities, with an overall score of 60 (a score below 48 [19] or an average score below 4 [20] was indicative of ICUAW). Assessors were trained for MRC scoring, and the initial MRC score recorded throughout the ICU stay was utilized for research.

Statistical processing: SPSS 23.0 and R language (version 4.3.3) were adopted for statistical analysis. Normally distributed quantitative variables were presented as mean (SD), whereas non-normally distributed counterparts were summarized as the median (interquartile range). Qualitative variables were displayed as frequency (percentage). Inter-group comparisons of quantitative data were carried out with the Wilcoxon rank-sum test or independent sample *t*-test. Inter-group comparisons of categorical data were analyzed with the chi-square test or the Fisher's exact test (in the case of expected frequency < 5). Multivariate logistic regression analysis was conducted, from which variables were selected to construct a nomogram model. Area under the receiver-operating characteristic (ROC) curve (AUC), sensitivity, and specificity were calculated, and the decision curve analysis (DCA) was performed for assessing the clinical utility of the model, which quantified net benefits within a range of threshold probabilities. $p < 0.05$ stood for significant differences.

Results

A total of 116 patients were inclued in the final analysis (Fig. 1) and were allocated to ICUAW (92 patients) and non-ICUAW (24 patients) groups.

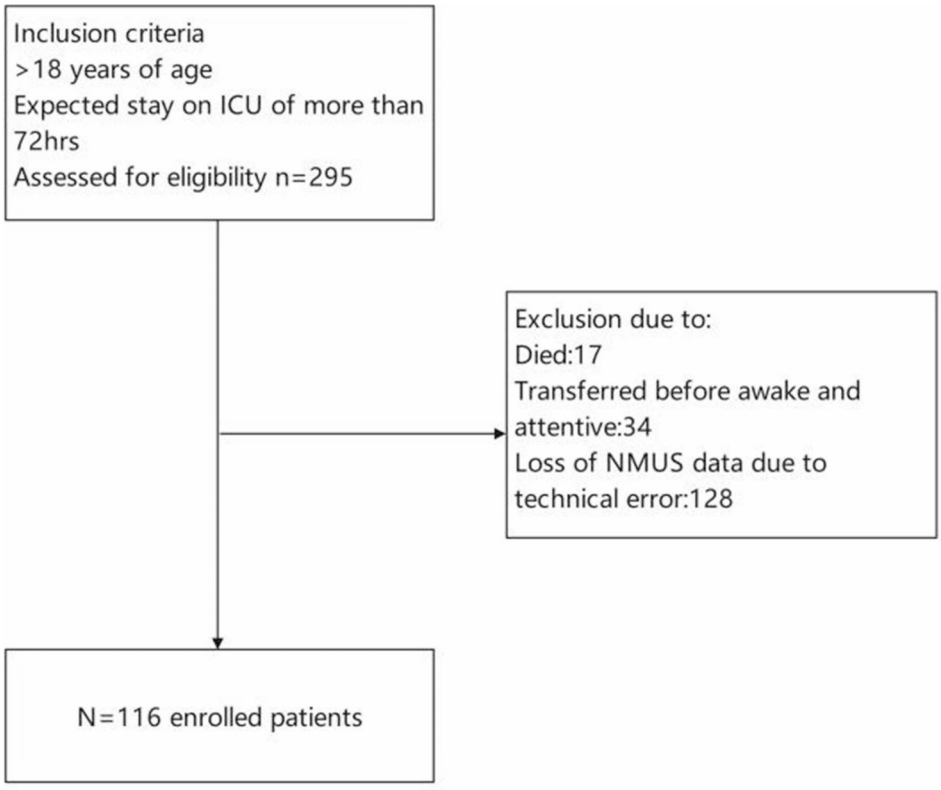

Fig. 1 The flowchart of patient selection

Table 1 Comparison of General Information between the ICUAW and Non-ICUAW groups

Parameters	ICUAW	Non-ICUAW	F/Z Value	*p* Value
n	92	24		
Age	58.22 ± 20.06	52.04 ± 18.88	0.031	0.860
Male	62 (67.4)	15 (62.5)	0.204	0.651
BMI	25.03 ± 19.98	23.62 ± 3.90	0.266	0.607
BSA	1.78 ± 0.18	1.77 ± 0.23	3.867	0.052
MRC	27.55 ± 16.54	51.58 ± 4.41	43.258	0.000
APACHE II	20.01 ± 7.83	15.00 ± 5.02	10.474	0.002
SOFA	7.49 ± 4.03	8.21 ± 4.67	0.728	0.395
Mechanical Ventilation Time	5.29 (1.25, 11.75)	5.50 (2.00, 9.75)	-0.236	0.813
Duration of ICU Stay	13.25 ± 11.80	12.38 ± 6.931	0.755	0.387

Note: mean (SD), median (IQR 1–3)

General information: Age, gender, BMI, BSA, and SOFA scores were not significantly different between both groups, whereas APACHE II scores showed significant differences between the two groups ($p < 0.05$, Table 1).

Critical ultrasound indicators: Differences in RF-MT, VITH, and RF-CSA were statistically significant between both groups ($p < 0.05$, Table 2).

Laboratory indicators: There was no statistically insignificant difference in PCT but statistically significant differences in IL-6 and CRP between the two groups ($p < 0.05$, Table 3).

Selection of predictive indicators: According to the logistic regression analysis, RF-MT, VITH, RF-CSA, IL-6, and CRP were included in the multivariate analysis. The results revealed that RF-CSA was markedly different ($p < 0.05$, Table 4).

Nomogram construction and validation: The total score was computed by summing individual scores of VITH, RF-CSA, IL-6, and CRP levels and then projected onto a lower scale to develop a nomogram for predicting the likelihood of ICUAW occurrence (Fig. 2). A composite diagnostic ROC curve was generated from the equation results (Fig. 3). The AUC value was 0.966 (95% confidence interval [95%CI]: 0.936–0.996), with a sensitivity of 88% and a specificity of 95.8%, indicating a robust composite diagnostic capability. The Hosmer–Lemeshow test demonstrated no statistically significant difference between actual and predicted probabilities of ICUAW ($\chi 2 = 5.377$, $p = 0.717$). The calibration curve exhibited high consistency between model prediction results and actual clinical observations (Fig. 4). Subsequent to 1000 bootstrap resamples for internal validation, the model maintained a high discriminative ability, as evidenced by an AUC value of 0.966 (95%CI: 0.933–0.991) and favorable consistency between predicted and actual clinical curves.

Table 3 Comparison of Laboratory indicators between the ICUAW and Non-ICUAW groups

Parameters	ICUAW	Non-ICUAW	F/Z Value	*p* Value
n	92	24		
PCT	1.32 (0.32, 7.96)	0.83 (0.18, 5.54)	1.788	0.184
IL-6	395.30 (84.55, 402.60)	38.40 (20.35, 82.30)	6.003	0.016
CRP	144.95 ± 93.63	73.52 ± 48.08	7.149	0.009

Note: mean (SD), median (IQR 1–3)

Table 4 Results of logistic regression analysis

Parameters	β Value	Sx^{-}	*p* Value	OR Value
const	-0.084	0.882	0.924	0.919
RF-MT	-0.008	0.017	0.645	0.992
VITH	-0.023	0.013	0.076	0.977
RF-CSA	-0.057	0.021	0.006	0.945
IL-6	0.014	0.007	0.054	1.014
CRP	0.002	0.008	0.813	1.002

Discussion

This study uncovered pivotal indicators for predicting the occurrence of ICUAW in septic patients. Despite no significant difference in age, gender, BMI, BSA, or SOFA scores between the two groups, the significant differences in APACHE II scores underlined that critically ill patients were at a higher risk of developing ICUAW. Statistically significant differences were observed in key ultrasound indicators, including RF-MT, VITH, and RF-CSA, underscoring their value in assessing muscle integrity in ICUs. Additionally, significant differences in laboratory markers, such as IL-6 and CRP, supported the role of inflammation in the progression of muscle atrophy in critically ill patients. The logistic regression analysis demonstrated RF-CSA as a robust predictor of ICUAW. The nomogram model constructed based on VITH, RF-CSA, IL-6, and CRP exhibited high sensitivity and specificity, with an AUC of 0.966, indicating excellent discriminatory ability and providing a promising tool to assess the risk of

Table 2 Comparison of critical Ultrasound data between the ICUAW and Non-ICUAW groups

Parameters	ICUAW	Non-ICUAW	F/Z Value	*p* Value
n	92	24		
RF-MT	-15.27 (-25.59, -3.09)	30.11 (-4.17, 53.63)	50.315	0.000
VITH	-15.85 (-29.48, 4.33)	23.74 (-0.90, 32.00)	23.390	0.000
RF-CSA	-15.99 (-36.42, -1.82)	26.84 (6.29, 106.71)	68.876	0.000

Note: median (IQR 1–3)

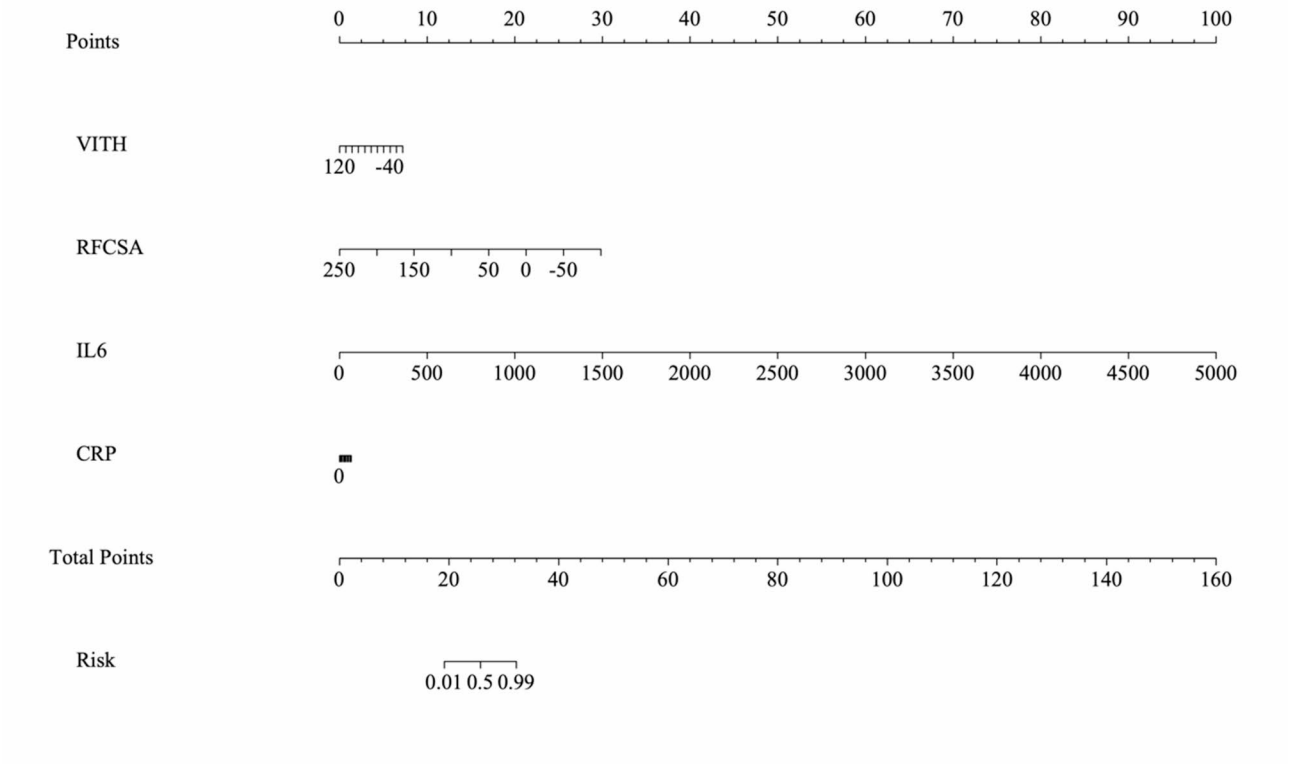

Fig. 2 A nomogram model for predicting the risk of ICUAW in septic patients

ICUAW. Furthermore, the calibration curve and Hosmer-Lemeshow test also validated the reliability of the model, suggesting that the model can accurately reflect clinical reality. These findings highlighted that the integration of ultrasound and laboratory biomarkers into routine assessments could substantially improve the outcomes of critically ill patients by advancing early intervention strategies to reduce the risk of ICUAW.

According to a systemic review involving 31 articles, ICUAW has a high incidence among septic patients, with an average prevalence of 43%. For critically ill patients, the balance of protein synthesis and breakdown is broken owing to factors including systemic inflammatory response syndrome, sepsis, and prolonged bed rest [21–26]. During sepsis-mediated muscle atrophy, the calpain system is activated, not only encouraging protein decomposition but also lowering Akt activities within the skeletal muscle to result in decreasing protein production [27]. The enhanced activity of calpain in sepsis models can diminish contractile function in the context of muscle atrophy [28]. Accordingly, calpain activation can boost protein degradation and muscle strength loss. Mitochondrial dysfunction constitutes an essential factor related to ICUAW occurrence, particularly during sepsis-related critical conditions [29]. A vicious cycle may occur in mitochondria, where increased free radicals attributed to sepsis exacerbate mitochondrial dysfunction, provoking excessive free radical generation [24]. Sepsis dramatically disrupts calcium homeostasis, which reduces calcium release in the sarcoplasmic reticulum, elevates contractile protein sensitivity to calcium, and affects skeletal muscle membrane excitability, eventually resulting in decreased muscle strength [30]. Myofibrillar structure disruption (resulting from tumor necrosis factor-alpha) or interference with mechanisms that regulate contraction may be factors inducing muscle strength weakness [24]. Nevertheless, sepsis impedes muscle satellite cell growth and differentiation, thus compromising damaged muscle repair and regeneration [31, 32]. Of note, cell aging has been recently demonstrated to be related to sepsis-mediated muscle weakness, which may contribute to the development of ICUAW [33].

The MRC score serves as an estimate of overall motor function, in which scores below 48 denote weakness and scores below 36 indicate severe weakness [16, 17]. As a useful tool for assessing muscle strength, the MRC scale also has several limitations. First, assessments may be impossible or delayed since critically ill patients generally lose consciousness or are uncooperative due to sedation or delirium. Second, this scale relies on clinician judgment, with different interpretations of muscle strength levels, which can introduce variability in scoring. Third, the sensitivity of the MRC scale is low, resulting in failure to detect subtle changes in muscle strength, particularly

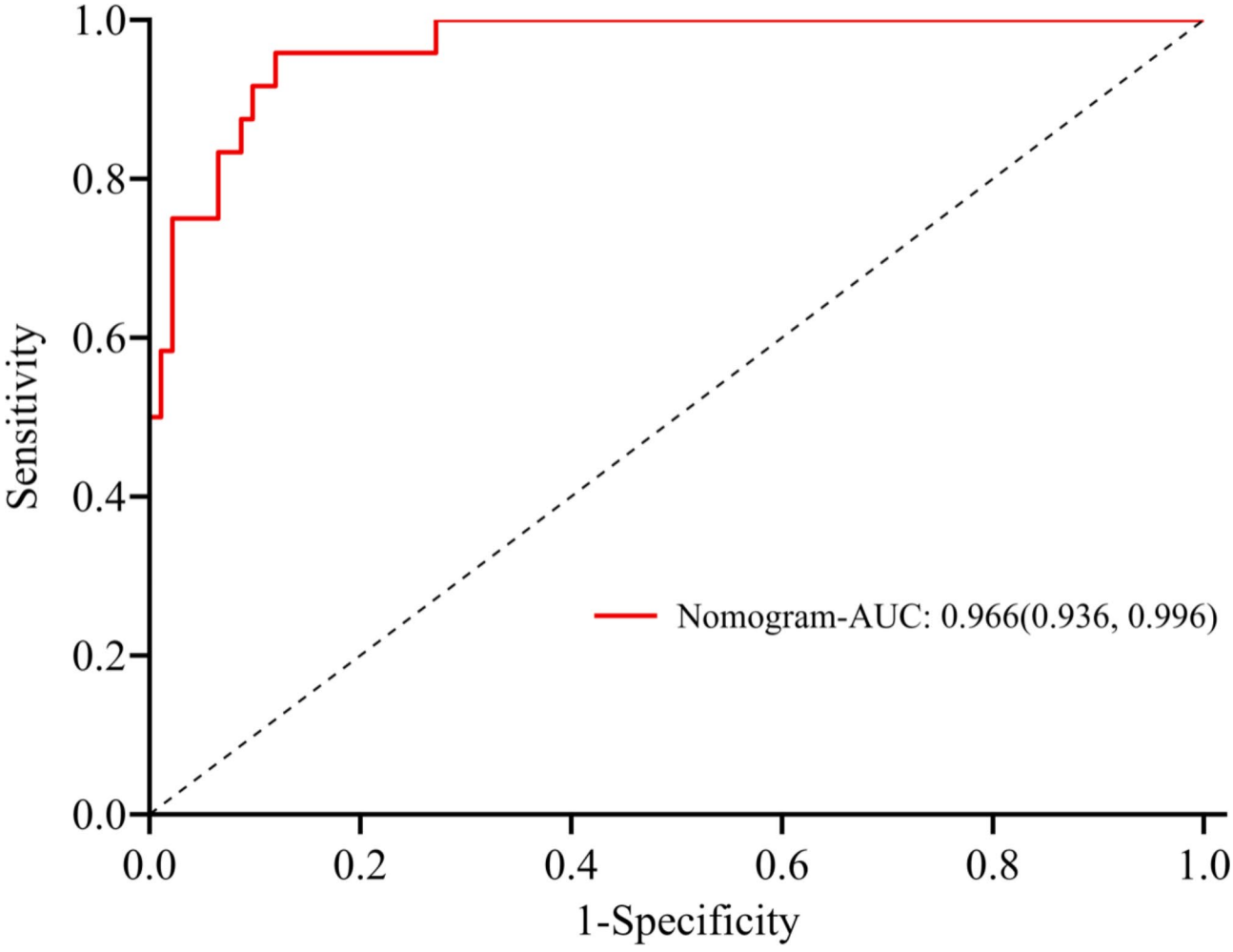

Fig. 3 ROC curves of the nomogram model

in patients with mild weakness or in the early stages of recovery. Fourth, the MRC scale primarily evaluates voluntary muscle strength and overlooks other important aspects, such as endurance, coordination, and overall functional status. Accordingly, although the MRC scoring system is valuable, it should be used in conjunction with other assessments for a comprehensive evaluation of muscle strength and function.

Critical ultrasound is increasingly utilized for assessing critically ill patients, which measures dimensions (such as cross-sectional area [34–36]) and evaluates structure by calculating the pennation angles of normal and pathological skeletal muscles [37, 38]. Although nerve and muscle biopsies offer valuable insights into mechanisms, they are invasive, may be associated with complications, and require specialized expertise to obtain samples and interpret results [13, 39–41]. Drawing from research on mechanisms underlying ICUAW in septic patients, this study developed a model for predicting ICUAW in septic patients by integrating muscle ultrasound and inflammatory markers, therefore laying the groundwork for early clinical assessment of weakness in septic patients and providing references for interventions and risk guidance. However, future basic research is warranted to further explore the pathogenesis of sepsis-related weakness.

The management of ICUAW primarily relies on prevention because no effective therapies are available for ICUAW at present. The present study showed a correlation between ICUAW occurrence in septic patients and inflammatory factors, emphasizing the significance of early prevention or treatment of infections and inflammation to lower the risk of ICUAW. Prompt infection treatment can directly or indirectly prevent inflammation-evoked muscle injury, driving early physical recovery and ultimately reducing the incidence of muscle weakness [42].

This study constructed a model for predicting ICUAW in septic patients by integrating muscle ultrasound measurements and inflammatory factors, all of which, particularly muscle ultrasound images, are readily obtained at the bedside. These indicators are highly repeatable and feasible, and their detection constitutes routine

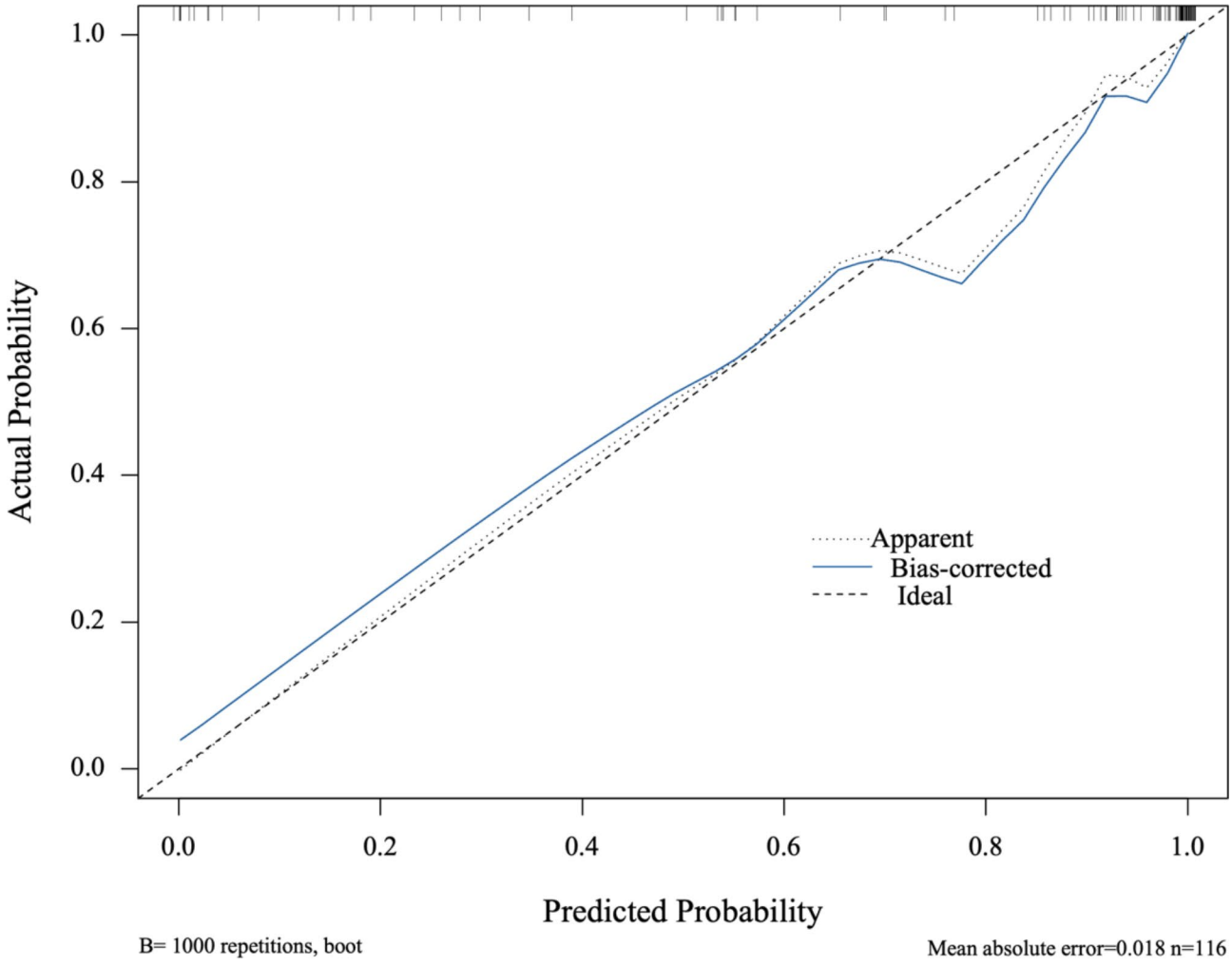

Fig. 4 Calibration curves of the nomogram model

examinations for septic patients without additional financial burden. This report presents the data of the training set in this study, with validation data to follow. Our nomogram model can be utilized as a clinical decision-making tool to enable the establishment of screening and early intervention protocols for high-risk patients, ensuring the timely implementation of personalized treatment plans and assisting in the development of more precise treatment strategies.

Furthermore, this study has several limitations. First, some data of participants, including comorbidities, use of neuromuscular blockers, and etiologies at admission were not considered in the initial design of our study. While the sample size was sufficient for model construction, a larger cohort can strengthen the generalizability of our findings. Second, this study is a multicenter study, where dedicated personnel are responsible for quality control to reduce operational biases. Nevertheless, different hospital ultrasound machine models may introduce measurement biases. Third, the constructed nomogram model requires external validation in diverse cohorts to confirm its predictive capability prior to widespread clinical application. Unmeasured confounding variables may affect the relationship between the identified risk factors and the occurrence of ICUAW. Consequently, our results may not be applicable to septic patients with different characteristics, such as those from diverse geographic locations or with varying disease severity.

In summary, through clinical data analyses, this study developed a nomogram model for diagnosing ICUAW in septic patients, which is simple and rapid and allows for visual representation, with favorable diagnostic capability. This model can function as a basis for the early diagnosis and treatment interventions of patients in the clinic.

Abbreviations

ICUAW	Intensive care unit-acquired weakness
MRC	Medical Research Council
ROC	Receiver operating characteristic
AUC	Area under the curve

DCA Decision curve analysis

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Author contributions
W. Y is responsible for guaranteeing manuscript content. L. L and L. H obtain our data, are in charge of data integrity and accuracy, study conception and design; and carried out literature review, data extraction and interpretation, methodological quality evaluation and manuscript drafting. T. Z，J. Q, Y. L, R. Z and Y. Q contributed to the study concept. Our authors approved our eventual version for submission.

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Data availability
The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The research protocol received approval from the Biomedical Ethics Review Committee of West China Hospital of Sichuan University (Approval Number 2023 – 1422). Written informed consent was obtained from all patients.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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