Acute and Critical Care

Acute and Critical Care 2025 August 40(3):361-372
https://doi.org/10.4266/acc.001450

| pISSN 2586-6052 | eISSN 2586-6060

Intensive care unit-acquired muscle atrophy and weakness in critical illness: a review of long-term recovery strategies

Nobuto Nakanishi

Division of Disaster and Emergency Medicine, Department of Surgery Related, Kobe University Graduate School of Medicine, Kobe, Japan

Intensive care unit (ICU)-acquired muscle atrophy and weakness are key contributors to post-intensive care syndrome (PICS), which can lead to long-term functional impairments. Although the ICU survival rate has improved, many patients continue to experience persistent functional impairments that hinder their reintegration into society. This review summarizes a series of observational and interventional studies conducted as part of the Muscle Atrophy Zero Project, focusing on the etiology, assessment, and prevention of ICU-acquired muscle atrophy and weakness. The project findings highlight the critical role of inflammation, particularly neutrophil infiltration, in the pathogenesis of muscle atrophy. Muscle damage can be assessed using ultrasound, bioelectrical impedance analysis, and urinary titin. Among them, ultrasound demonstrates high diagnostic accuracy for detecting low muscularity, and urinary titin has emerged as a promising biomarker of muscle degradation. Preventive strategies include early rehabilitation, neuromuscular electrical stimulation, vibration therapy, and nutritional support, especially protein supplementation. These multimodal interventions have shown efficacy in mitigating ICU-acquired muscle atrophy and weakness. However, follow-up systems for PICS remain underdeveloped. A continual multimodal intervention approach that combines physical rehabilitation with nutritional therapy is essential. The development of structured follow-up programs is vitally needed to confront the long-term challenges posed by PICS.

Key Words: electrical stimulation therapy; intensive care units; muscle; ultrasonography; vibration

Review Article

Received: May 16, 2025
Revised: July 10, 2025
Accepted: August 2, 2025

Corresponding author
Nobuto Nakanishi
Division of Disaster and Emergency Medicine, Department of Surgery Related, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki, Chuo-ward, Kobe, 650-0017, Japan
Tel: +81-78-382-5015
Fax: +81-78-382-5050
Email: nobuto_nakanishi@yahoo.co.jp

INTRODUCTION

Recent advances in critical care have reduced the mortality rate of critical illness by approximately 35% during the past few decades [1]. However, more than one-third of survivors experience persistent physical, cognitive, and psychological impairments for months after their hospital discharge [2]. Even 5 years after intensive care, many patients have not regained their pre-illness levels of physical function [3]. These prolonged impairments are collectively called

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Infographics Acute and Critical Care

Intensive care unit-acquired muscle atrophy and weakness in critical illness : a review of long-term recovery strategies

Intensive care unit (ICU)-acquired muscle atrophy and weakness leads to long-term functional impairments.

Early detection and comprehensive interventions are essential to prevent ICU-acquired muscle atrophy and weakness.

post-intensive care syndrome (PICS) [4]. As a result of PICS, many patients face difficulties in returning to their daily lives and previous occupations [5]. A major contributor to PICS is intensive care unit (ICU)-acquired muscle atrophy and weakness [6].

ICU-acquired muscle atrophy and weakness are commonly caused by prolonged immobilization and systemic inflammation, which accelerate catabolic processes and muscle protein degradation [7]. Critically ill patients can lose up to 2% of their muscle mass per day during the acute phase of illness [8]. ICU-acquired weakness encompasses both critical illness polyneuropathy and critical illness myopathy, and it is clinically diagnosed as newly developed bilateral muscle weakness [9]. This condition is associated with persistent physical disability, even 5 years after hospital discharge [10].

ICU-acquired muscle atrophy and weakness can be mitigated through rehabilitation and nutritional interventions [11,12]. My colleagues and I have conducted a series of studies within the framework of the Muscle Atrophy Zero Project to explore the etiology, assessment, and prevention of muscle atrophy and weakness in critically ill patients. Our research has demonstrated that inflammation and immune responses are central to the development of muscle atrophy. Muscle status can be assessed using ultrasound, bioelectrical impedance analysis (BIA), and biomarkers. Preventive strategies include rehabilitation and nutritional interventions such as electrical muscle stimulation, vibration therapy, and protein supplementation. The prevention of PICS requires a continual chain of interventions, from assessment and monitoring to prevention, treatment, and follow-up (Figure 1). In this review, I summarize our research journey to elucidate ICU-acquired muscle atrophy and weakness and confront the burden of PICS (Table 1).

KEY MESSAGES

- Intensive care unit -acquired muscle atrophy and weakness are major contributors to post-intensive care syndrome (PICS).
- Ultrasound and urinary titin are non-invasive tools to assess muscle damage.
- Rehabilitation, nutrition intervention, and PICS follow-up systems are important to confront PICS.

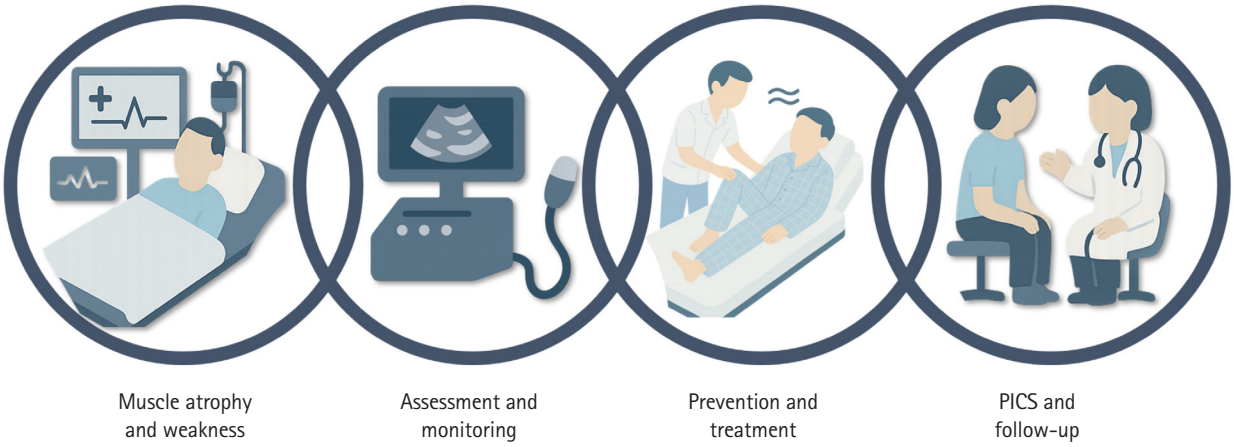

Figure 1. The continual chain to prevent post-intensive care syndrome (PICS). Intensive care unit (ICU)-acquired muscle atrophy and weakness can develop after ICU admission, and assessment and monitoring are essential to prevent and treat it. After hospital discharge, patients with PICS require ongoing follow-up.

MUSCLE ATROPHY AND WEAKNESS

Muscle Loss

Critically ill patients begin to experience muscle atrophy immediately after ICU admission [12]. Muscle mass decreases by 13.2%–16.9% in the upper limbs and 18.8%–20.7% in the lower limbs over the course of a single week [13]. This atrophy is associated with impaired physical function and in-hospital mortality. Muscle atrophy at ICU discharge is associated with decreases in hand grip strength (r=0.50–0.62, P≤0.01), Medical Research Council (MRC) score (r=0.46–0.47, P≤0.02), and Functional Status Score in the ICU (FSS-ICU) (r=0.56, P<0.01) [14]. Furthermore, muscle atrophy observed on days 5 and 7 was associated with increased in-hospital mortality, with area under the curve (AUC) values of 0.71 on day 5, and 0.79–0.84 on day 7 [14]. Muscle atrophy occurs not only in the limbs but also in the respiratory muscles [15]. In two thirds of mechanically ventilated patients, we observed atrophy in both the diaphragm and intercostal muscles during the course of ventilation. This respiratory muscle atrophy is associated with delayed liberation from mechanical ventilation [16]. Even in patients with septic shock who were not mechanically ventilated, we found impaired diaphragm function, likely due to systemic inflammation [17].

Cause and Pathophysiology

The primary cause of muscle atrophy and weakness during the acute phase of a critical illness is inflammation, rather than immobilization [18]. In healthy bedridden volunteers, the rate of muscle atrophy was reported to be 0.4% per day [19], and in astronauts, it is 0.03% per day [20]; in contrast, critically ill patients exhibit a markedly higher rate of approximately 2% per day. The difference is attributed to inflammation and other ICU-specific factors, including insufficient nutritional support, the use of medications such as neuromuscular blockers and corticosteroids, and hyperglycemia [21].

Immune dysregulation plays a critical role in muscle damage [22]. Among immune cells, neutrophils are essential for defending against microbial invasion [23]. However, following sepsis or acute respiratory distress syndrome, abnormal neutrophil activation contributes to multiple organ failure, including the lungs and kidneys [24]. Similarly, neutrophils infiltrate into skeletal muscle and contribute to muscle damage. In one study, neutrophil depletion prevented muscle atrophy and weakness in a murine model of sepsis [25], which suggests that suppressing aberrant neutrophil activation could be a potential way to prevent muscle damage in critically ill patients.

ASSESSMENT AND MONITORING

Ultrasound

Ultrasound is an emerging tool for assessing muscle mass [26]. Unlike other imaging modalities, ultrasound allows direct visualization of muscle tissue. Importantly, ultrasound-based

assessment is not affected by fluid balance because fluid tends to accumulate in subcutaneous tissue, rather than in the muscle itself [27]. The gold standard measurement site is the rectus femoris muscle in the supine position. At ICU admission, the cross-sectional area of the rectus femoris muscle measured by ultrasound demonstrated an AUC of 0.76 (95% CI, 0.65–0.88), and the thickness of the quadriceps muscle measured by ultrasound demonstrated an AUC of 0.84 (95% CI, 0.74–0.94), for identifying low muscularity, as assessed by computed tomography (CT) as the reference standard [28]. Consistently, upper limb muscle thickness showed an AUC of 0.77 (95% CI, 0.63–0.91) in detecting low muscularity, and a thickness index relative to height had an AUC of 0.80 (95% CI, 0.68–0.93) [29]. Our group established reference values for upper and lower limb muscle measurements to facilitate their application in clinical practice [30]. However, a notable challenge in using ultrasound for muscle mass assessment is its technique dependency [31]. Unlike other imaging tests, the accuracy and reliability of ultrasound measurements are highly influenced by the examiner's skill. Factors such as probe angle, compression pressure, and the patient's posture can all significantly affect measurement outcomes [32]. Therefore, proper training in ultrasound techniques is essential. To support such training, we developed a phantom model of the quadriceps femoris muscle. Using that model, various healthcare providers were able to acquire the necessary skills in just one hour, and those skills were retained several days after training [32]. Ultrasound devices and their functions are also evolving. Some portable ultrasound devices are now available at more affordable prices than older machines (Figure 2A). A new ultrasound function, the panoramic mode, can be used if the width of the ultrasound probe is insufficient to capture the entire muscle [33]. This mode enables full muscle imaging by moving the probe horizontally across the surface of the limb. According to a re-

Figure 2. Devices to prevent intensive care unit (ICU)-acquired muscle atrophy and weakness in critical illness. This figure illustrates various devices that are essential for the prevention of ICU-acquired muscle atrophy and weakness in critically ill patients. These devices support early rehabilitation and mobilization, which are key strategies for mitigating muscle loss during prolonged ICU stays. (A) Ultrasound: PortaSound, Terumo Medical Care Solutions. (B) Bioelectrical impedance analysis (BIA): Ratchet, Terumo Medical Care Solutions. (C) High function bed shown facilitating smooth mobilization: ProCuity, Stryker Medical. (D) High function bed shown facilitating safe sitting position: ProCuity, Stryker Medical. (E) Neuromuscular electrical stimulation (NMES): SOL-1, Minato Medical Science. (F) NMES: SOL-M01 Minato Medical Science. (G) Vibration therapy: BW-750, BodyGreen (photo from Goshin, Shimane, Japan). (H) Vibration therapy: BX-2, BodyGreen.

cent survey, ultrasound is most commonly used by physicians and physical therapists [34]; however, it is also suitable for use by other healthcare professionals. In recent years, nutritional status has increasingly been assessed using the Global Leadership Initiative on Malnutrition criteria, an international consensus framework [35]. Because muscle mass is a key component of that assessment, ultrasound has been proposed as a bedside tool for use by registered dietitians [36].

Bioelectrical Impedance Analysis

BIA uses an undetectable electrical current to evaluate lean body mass and muscle mass (Figure 2B) [37]. Muscle mass is estimated through a proprietary equation based on the resistance and reactance of the electrical current. BIA is noninvasive and can be used at the bedside without requiring specialized techniques, so it is widely used by various health care providers [38]. However, BIA has two major limitations: the use of undisclosed equations and the influence of fluid balance. Because the equations used to estimate muscle mass are not publicly disclosed and vary across devices, muscle mass estimates can differ between devices [39]. A more critical issue is the influence of fluid status. In our previous study, BIA-based muscle mass estimates were significantly affected by fluid changes in critically ill patients admitted to the ICU [27]. Although single time-point muscle mass estimates correlated with CT-based measurements, BIA was not useful for tracking changes in muscle mass over time, similar to body weight, due to dynamic fluid shifts in the ICU. In those conditions, the phase angle might offer a more reliable assessment of muscle. The phase angle reflects muscle quality by quantifying the relationship between resistance and reactance [40]. In our basic research using mice, we compared the phase angle between young and aged mice and found that it was significantly lower in aged mice [41]. Interestingly, although the aged mice had greater body weight, they showed lower phase angle values, consistent with reduced grip strength and muscle weight relative to body weight. Those findings suggest that the phase angle can be used to detect declines in muscle quality. Yabe et al. also reported that phase angle is a useful indicator for assessing ICU-acquired weakness [42].

Urinary Titin

No reliable biomarker is currently available to assess muscle atrophy and weakness [43]. Muscle tissue is composed of sarcomeres, which include the contractile proteins actin and myosin. However, the direct measurement of actin and myosin content is not feasible. However, titin, another crucial sarcomere component, can be measured [44]. Titin plays an essential role in muscle contraction, acting as a spring that connects actin and myosin [45]. The breakdown product of titin can now be measured in urine using an enzyme-linked immunosorbent assay [46]. We evaluated urinary titin levels in critically ill patients and found them to be elevated to more than 10 times the normal values [47]. Furthermore, the urinary titin level was associated with ICU-acquired muscle atrophy and weakness. Notably, the titin level measured on day 2 of ICU admission predicted the presence of ICU-acquired weakness at ICU discharge, with a sensitivity of 78% and specificity of 81%. Urinary titin has the advantage of rapidly reflecting muscle breakdown. We also evaluated urinary titin levels in patients with stroke, a condition in which the onset time is clearly defined, unlike critical illness, in which the onset is often unclear [48]. Interestingly, an elevated urinary titin level was observed as early as two hours after stroke onset, indicating its rapid responsiveness to muscle breakdown. Another key advantage of urinary titin as a biomarker is its noninvasiveness. Because it requires only a urine sample, no blood draws are needed, making it particularly suitable for use in pediatric and neonatal intensive care. We assessed the utility of urinary titin in neonates and found that it reflected catabolic states in this population [49]. In general, iatrogenic blood loss is the leading cause of ICU-acquired anemia [50]. Therefore, a noninvasive biomarker that does not contribute to blood loss is especially beneficial for monitoring muscle in critically ill patients during the acute phase. In addition to skeletal muscle, urinary titin is also useful for evaluating cardiac muscle breakdown. We found that urinary titin was a helpful diagnostic tool for myocardial infarction [51]. This noninvasive biomarker might thus have potential applications in monitoring cardiac muscle necrosis following acute myocardial infarction, as well as in assessing ICU-acquired muscle atrophy and weakness.

PREVENTION AND TREATMENT

Rehabilitation

Rehabilitation and mobilization are essential strategies to

prevent ICU-acquired muscle atrophy and weakness [52]. Current guidelines recommend initiating rehabilitation and mobilization within 72 hours of ICU admission to prevent PICS [53]. Although early, enhanced rehabilitation has shown promise, two recent randomized controlled trials reported that such early interventions were associated with an increase in adverse events [54,55]. To ensure the safety of rehabilitation in critically ill patients, it is crucial to adhere to clearly defined initiation and termination criteria. In response to that need, the Japanese Society of Intensive Care Medicine developed the Japanese Clinical Practice Guidelines for Rehabilitation in Critically Ill Patients 2023 (J-ReCIP 2023) [56]. These guidelines include specific criteria for starting and pausing rehabilitation and advocate for protocolized rehabilitation and mobilization interventions at least twice daily. Protocolized mobilization has been shown to reduce the length of ICU stay while minimizing the risk of adverse events. Rehabilitation should also be performed multiple times per day. Although both the intensity and frequency of rehabilitation are reportedly important [57], the optimal levels of each remain unclear. Therefore, we are currently conducting the IMPAMICS (ICU Multicenter Physical Activity Dosing, Muscle Mass, Physical Outcome) study to determine the appropriate dose and frequency of rehabilitation interventions in the ICU setting [58].

In-Bed and Bedside Rehabilitation

Rehabilitation should begin with bedside interventions, including proper positioning and range of motion exercises. A European group has published guidelines on positioning in the ICU [59]. Those guidelines recommend elevating the head of the bed to more than 40° to prevent ventilator-associated pneumonia [60], and regular repositioning changes are important to prevent pressure ulcers [61]. High function beds can be beneficial for critically ill patients because they facilitate head-up positioning, and some models offer automatic repositioning. Furthermore, those features can support the transition from in-bed rehabilitation to mobilization at the bedside (Figure 2C and D). Some high-function beds also have a tilt-up function, which has been reported to be useful in preventing muscle weakness [62].

Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation is a therapeutic modality that induces muscle contraction through the application of electrical stimulation (Figure 2E and F) [63]. It can be safely used as a form of passive rehabilitation in bedridden, critically ill patients [64]. Lago et al. [65] reported that neuromuscular electrical stimulation did not affect the metabolic rate in patients during the acute phase of septic shock. Based on that finding, we conducted a randomized controlled trial to evaluate the efficacy of an early neuromuscular electrical stimulation intervention initiated in critically ill patients during the very acute phase [66]. The intervention was initiated upon ICU admission and continued through ICU day 5. Neuromuscular electrical stimulation was applied to both the upper and lower limbs to promote muscle activation and prevent muscle atrophy. As a result, patients in the intervention group demonstrated significantly reduced muscle atrophy and a shorter hospital stay than the controls. Furthermore, in a meta-analysis that included our study, neuromuscular electrical stimulation was shown to be effective in preventing ICU-acquired muscle atrophy and weakness [67]. However, an adverse effect of the intervention was a pricking sensation experienced by some patients, which affects comfort and should be considered when implementing neuromuscular electrical stimulation. Both the Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2024 (J-SSCG 2024) [68] and J-ReCIP 2023 [56] recommend the use of neuromuscular electrical stimulation in critically ill patients as part of early rehabilitation protocols. Although neuromuscular electrical stimulation has demonstrated potential benefits in critically ill patients, many studies have been limited by small sample sizes, which could reduce the generalizability of their findings. Clinicians should interpret these data with caution when considering its use in clinical practice.

Vibration Therapy

Vibration therapy has been used for decades across various medical fields [69]. It stimulates muscle spindles and can affect the entire body (Figure 2G). In a previous in vitro study, vibration was shown to decrease myostatin, a negative regulator of muscle growth, and promote muscle hypertrophy [70]. Furthermore, vibration therapy improves blood circulation by increasing the production of nitric oxide [71], and it increases the levels of anabolic hormones such as testosterone and growth hormone [72]. In human subjects, Wu et al. [73] reported that

vibration therapy contributed to the reduction of sarcopenia. We investigated whether vibration therapy could improve physical function in critically ill patients without causing adverse events [74]. When vibration therapy was applied to the feet in a sitting position, it did not affect the vital signs of these patients [75]. It was also widely accepted as a comfortable intervention in the ICU setting and contributed to the reduction of fatigue. Although vibration therapy did not improve the total FSS-ICU score, it did enhance the ability to move from a supine to a sitting position. Another study applied a vibration device to the lower limbs of bedridden critically ill patients and reported no adverse effects [76]; they also found that a physiotherapy intervention that included vibration therapy contributed to the prevention of muscle atrophy. We applied the vibration device to the lower limbs; however, its use is not limited to this region. Other vibration devices can also be applied to the upper limbs, warranting further investigation (Figure 2H). Vibration therapy has emerged as a promising therapeutic option; however, further research is needed to establish its efficacy.

Protection for Diaphragm

Ventilator settings play a crucial role in preventing muscle atrophy and weakness [77,78]. Key strategies include promoting spontaneous breathing and avoiding excessive inspiratory support [79]. However, in our previous study, spontaneous breathing was not significantly associated with diaphragm muscle atrophy [80]. This finding suggests that factors such as patient-ventilator asynchrony and other underlying mechanisms might contribute to diaphragmatic atrophy. Veno-venous extracorporeal membrane oxygenation might help prevent not only lung injury but also diaphragm injury. In particular, veno-venous extracorporeal membrane oxygenation has been reported to reduce muscle damage and diaphragm atrophy, as described in a case report [81]. Once diaphragm impairment and dysfunction are evident, a high-flow nasal cannula can serve as a non-invasive method for supporting diaphragm function [82].

Nutritional Support

Nutrition intervention is essential to prevent ICU-acquired muscle atrophy and weakness [83]. The Japanese Critical Care Nutrition Guideline 2024 (JCCNG 2024) strongly recommends early (within 48 hours of ICU admission) enteral nutrition and weakly recommends a high protein dosage [84]. Early enteral nutrition contributes to the prevention of intestinal mucosal atrophy and the activation of gut-associated immune function, reducing infectious complications [85]. To maximize the benefits of enteral nutrition, it is important to consider the administration method, patient selection, and dosage, including protein [86]. In a meta-analysis, a protein dose of more than 1.0 g/kg/day during the first 4 to 10 days of an ICU stay helped to prevent muscle atrophy and slightly improved activities of daily living without statistical significance [87].

PICS AND FOLLOW-UP

PICS Follow-up System

The presence of PICS symptoms should be assessed using scientifically validated assessment tools: (1) the 6-minute walk test, MRC score, and handgrip strength for physical function; (2) Montreal Cognitive Assessment, Mini-Mental State Examination, and Short-Memory Questionnaire for cognitive function; and (3) Hospital Anxiety and Depression Scale, Impact of Event Scale-Revised, and Patient Health Questionnaire-9 for mental health [88]. To facilitate those assessments, practical examples of integrating them into routine workflows include incorporating screening checklists at the time of discharge or during follow-up visits. Following a comprehensive assessment, patients identified as having PICS should receive ongoing follow-up and appropriate interventions until they are successfully reintegrated into society [89]. A PICS follow-up clinic should be organized as a multidisciplinary team that includes physiotherapists for rehabilitation and registered dietitians for nutritional management [90]. The J-SSCG recommends continual rehabilitation after hospital discharge to prevent PICS [68]. However, PICS follow-up clinics remain rare, and many patients continue to struggle with returning to their previous daily lives and occupations [91]. Successful multidisciplinary follow-up programs require adequate staffing, interprofessional training, and a robust coordination infrastructure [92]. Anticipated challenges, such as limited resources, can be mitigated through strategies such as the use of telemedicine [93,94]. Our long journey to create such systems and confront PICS is still ongoing.

Table 1. The summary of strategies to confront PICS

Category	Description	Reference
Muscle atrophy and weakness		
Muscle loss		
Upper limb muscle atrophy	13.2%–16.9% of muscle mass loss over 1 week	[13]
Lower limb muscle atrophy	18.8%–20.7% of muscle mass loss over 1 week	[13]
Diaphragm thickness atrophy	Two thirds of mechanically ventilated patients	[16]
Cause and pathophysiology	Neutrophil infiltration into muscle	[25]
Assessment and monitoring		
Ultrasound	Noninvasive, high accuracy in detecting low muscle mass	[28,29]
Bioelectrical impedance analysis	Influenced by fluid changes in the ICU	[27]
Urinary titin	Reflects muscle atrophy and weakness	[47]
Prevention and treatment		
Rehabilitation	Early rehabilitation and mobilization are recommended to prevent PICS.	[68]
On-bed rehabilitation	Positioning and smooth transition to mobilization	[59]
Neuromuscular electrical stimulation	Recommended in the supplemental intervention to prevent ICU-acquired muscle atrophy and weakness	[67]
Vibration therapy	Safe and effective to improve physical functions	[75]
Protection for diaphragm	Excessive ventilatory support should be avoided to prevent diaphragm atrophy.	[79]
Nutritional support	Protein supplementation reduces muscle atrophy.	[87]
PICS and follow-up		
PICS follow-up system	Assessment tools and the construction of follow-up system	[88,90]

PICS: post-intensive care syndrome; ICU: intensive care unit.

CONCLUSIONS

To mitigate the long-term effects of ICU-acquired muscle atrophy and weakness, early detection and comprehensive interventions are essential. A multidisciplinary approach that integrates physical rehabilitation, nutritional support, and long-term follow-up should be implemented to prevent PICS.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

FUNDING

None.

ACKNOWLEDGMENTS

None.

ORCID

Nobuto Nakanishi https://orcid.org/0000-0002-2394-2688

AUTHOR CONTRIBUTIONS

All the work was done by Nobuto Nakanishi.

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