PILOT STUDY:

"Operator Validation and Inter-Rater Variability in Diagnostic Strategies for ICU-Acquired Weakness"

October 8, 2024

Version number 2

Óscar Arellano-Pérez

Benito Arévalo Pereda

Nicole Peña León

Paola Llanos Vidal

Abstract

Background:
Intensive Care Unit-Acquired Weakness (ICU-AW) is characterized by muscle weakness that may result from critical illness polyneuropathy (CIP), critical illness myopathy (CIM), or a combination of both. This condition is a frequent complication that increases mortality and hospital length of stay, and contributes to post-intensive care syndrome, leading to long-term cognitive and physical dysfunction. Early diagnosis is crucial, as muscle mass loss and electrophysiological alterations can occur within the first 10 days of hospitalization. Muscle ultrasound has been used to support early detection, since electrophysiological tests are costly and not always available. Peripheral nerve ultrasound emerges as an effective alternative for differentiating between CIM and neuropathy. This study aims to evaluate the feasibility of quadriceps muscle and peripheral nerve ultrasound as assessment tools for physical therapists in the critical care setting, as well as their inter-rater reliability, with the goal of facilitating early diagnosis and timely therapeutic strategies in hospitalized patients.

Methods:
This study will be conducted in patients admitted to the critical care unit at Clínica INDISA. Inter-rater reliability will be assessed using the intraclass correlation coefficient (ICC) across several quadriceps muscle and peripheral nerve ultrasound variables, as measured by three experienced physical therapists. Variables will include anterior quadriceps complex thickness, cross-sectional area (CSA) of the rectus femoris and vastus intermedius (transverse view), and pennation angle of the vastus lateralis (longitudinal view). For peripheral nerve ultrasound, CSA and echogenicity will be evaluated. Echogenicity will be analysed using ImageJ software. Inter-rater agreement of the MRC Sum Score (MRC-SS) and the Functional Status Score for the ICU (FSS-ICU) will also be assessed using Kendall's W coefficient. Finally, ultrasound findings will be correlated with clinical scale scores using Pearson or Spearman correlation coefficients, as appropriate. All procedures will comply with bioethical standards and be approved by the Research Ethics Committee of Clínica INDISA.

Expected Results:

We expect to find sufficient inter-rater agreement in quadriceps and peripheral nerve ultrasound measurements performed by physical therapists in the ICU setting. Additionally, MRC-SS and FSS-ICU scale results are expected to demonstrate reliable agreement and correlate with the ultrasound findings.

Introduction

ICU-AW is a neuropathy and/or myopathy characterized by symmetrical proximal-predominant muscle weakness[1,2], without involvement of facial or ocular muscles[2,3], and may affect respiratory muscles[3,4], leading to diaphragmatic dysfunction associated with mechanical ventilation (VIDD) and difficulty weaning from ventilatory support[5]. CU-AW may be triggered by a) a neurogenic disorder known as critical illness polyneuropathy (CIP); b) a muscular disorder known as critical illness myopathy (CIM); and/or c) the coexistence of both[3,6–9]. CIP is an acute, acquired sensory-axonal neuropathy caused by peripheral nerve inflammation[5,10]. CIM is characterized by alterations in muscle mass and contractility[6,12], and presents pathognomonic features such as preserved sensation, elevated creatine kinase levels[10], and most notably, preferential loss of myosin relative to actin in muscle biopsy samples[5,11,12]. Since muscle atrophy and impaired contractility are the main features associated with increased mortality[13–17] and physical disability[18,19], most studies have focused on CIM and skeletal muscle degradation pathways[20]

Importance of ICU-AW

ICU-AW is a common complication in critically ill patients[16,21,22] and is associated with increased mortality[8,10,21,23–25], prolonged hospital stays[8,9,23,25], longer duration of mechanical ventilation[9,24], higher healthcare-related costs, and reduced long-term physical function and quality of life[8,9,21,24,26]. Moreover, this condition can progress into post-intensive care syndrome (PICS), which may result in persistent cognitive, mental, and physical dysfunction[3,25,27]. A multicentre study conducted in Chile evaluated the functional and cognitive sequelae of PICS in patients who experienced critical illness due to COVID-19, determining that a high percentage of survivors will present some degree of disability after hospital discharge[28]. **Therefore, early identification of ICU-AW is crucial to designing both pharmacological and non-pharmacological therapeutic strategies.**

Diagnosis of ICU-AW

Regarding the diagnosis of critical illness myopathy (CIM), there are strategies available for both cooperative and non-cooperative patients[2].

Medical Research Council Sum Score (MRC SS)

Clinical quantification of muscle strength in awake and cooperative patients is commonly performed using the Medical Research Council Sum Score (MRC-SS)[2,8,29]. his score assigns a value from 0 (no muscle contraction) to 5 (normal strength) to each of 12 muscle groups. These include muscles responsible for shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion, all evaluated bilaterally[30]. A score of ≤48 indicates the presence of muscle weakness, while a score below 36 indicates severe weakness [3,29,31]. However, this scale has several limitations. First, **it does not identify the underlying cause of weakness and cannot distinguish between CIP and CIM.** Moreover, it requires patients to be fully awake and cooperative—criteria that many ICU patients do not meet[30]. Although most studies have reported good reproducibility in critically ill patients[32–35], **further research is still needed to support this assertion.**

Electrophysiology

Another important aspect is the differential diagnosis between CIM and CIP. Electrophysiological evaluation is also used to diagnose ICU-AW and can be applied in unconscious or uncooperative patients, as well as to differentiate between CIP and CIM[31,36]. Nerve conduction studies assess the reduction of the compound muscle action potential (CMAP). In cases where CIP and CIM coexist, sensory nerve action potentials (SNAPs) may also be reduced, while nerve conduction velocity is typically normal or only slightly decreased[37]. Both CIP and CIM may show spontaneous electrical activity on electromyography (EMG). Voluntary muscle contraction—requiring patient cooperation—or more complex electrophysiological methods such as direct muscle stimulation can be used to differentiate between CIP and CIM[38]. However, these techniques do not allow for early diagnosis during the initial phase of ICU-AW development. **Full electrophysiological testing**

is often unavailable in many ICUs, is time-consuming, and costly [30]. Furthermore, the clinical significance of electrophysiological abnormalities in the absence of muscle weakness remains unclear[37].

Biopsies

Nerve and muscle biopsies can provide valuable mechanistic insights and allow for differential diagnosis between CIP and CIM. However, biopsy is an invasive procedure and is not recommended for routine clinical use; it is therefore advised only within the context of scientific research[29,31].

Imaging-Based Diagnosis of ICU-Acquired Weakness

In non-cooperative patients, various imaging techniques have been used to assess muscle mass as a surrogate for muscle strength in the diagnosis of ICU-AW. Computed tomography (CT) and magnetic resonance imaging (MRI) allow for visualization of muscle quality, detection of fatty infiltration, and quantification of lean muscle mass [15]; However, these are high-cost techniques that require specialized personnel and software[15,31]. **Quadriceps muscle ultrasound is considered the most promising approach, as it enables rapid and repeatable bedside assessments, allowing the evaluation of both muscle quantity (muscle thickness, anatomical and physiological cross-sectional area) and quality (echogenicity and muscle architecture)**[17,31,39].

Muscle Ultrasound

Diagnosis of CIM through muscle ultrasound is based on changes in ultrasound-derived variables within 7 to 10 days of critical illness onset. These changes include a 20% decrease in muscle thickness, a 10% reduction in cross-sectional area, a 5% decrease in pennation angle, and an 8–10% increase in echogenicity[16,17,39]. Regarding percent changes in ultrasound parameters over time, a study by Formenti et al. reported a significant decrease in pennation angle within the first 7 days of critical illness among patients who developed ICU-acquired

weakness [40]. Additionally, increased echogenicity of the rectus femoris during the first 7 days of ICU stay has been shown to be a predictor of ICU-AW[17].

Early diagnosis is crucial, as protein degradation, muscle mass loss[41,42], y and electrophysiological alterations[43] occur within the first 10 days in the ICU. Given the importance of early detection, some critical illness severity scores have been used alongside ultrasound evaluation to raise suspicion and consider the presence of this clinical condition[44–47]. **However, further research is needed to support this strategy.**

Differential Diagnosis Between CIM and CIP Using Ultrasound

As previously mentioned, the differential diagnosis between CIM and CIP has traditionally been made using electrophysiological evaluation[2]. However, **this method is not available in all centres and is rarely feasible at the bedside.**

D Since various neuropathies have been assessed using ultrasound[48] this technique has been proposed as an alternative approach to address this challenge[49]. In a study by Gruber et al.[49], the Ultrasonic Pattern Sum Score (UPSS)[50] was used to demonstrate that peripheral nerve ultrasound can differentiate between pure CIM and neuropathy in ICU-AW patients, with a sensitivity of approximately 84%[49]. Although the authors noted that this method does not distinguish between sensory and motor neuropathy, peripheral nerve ultrasound emerges as a reliable tool for identifying neuropathy in these patients[49]. This strategy could facilitate the detection of neuropathy in ICU-AW and aid in identifying its coexistence with CIM. **However, further studies are needed to validate and strengthen this approach.**

Based on the aforementioned evidence, although several strategies exist for diagnosing ICU-acquired weakness (ICU-AW), there remains a pressing need to promote early detection, as muscular alterations[41,42] occur within the first days of critical illness. One promising solution is the validation of muscle and peripheral nerve ultrasound to detect ICU-AW at an early stage. **This would allow for a more accurate differential diagnosis and facilitate the selection of the most appropriate therapeutic strategy.**

This pilot study aims to assess the usefulness and inter-rater reliability of ultrasound in the early diagnosis of ICU-acquired weakness, as well as the consistency of standardized clinical assessment scales. The results will support the validation of physical therapists as qualified operators for future research projects and contribute to strengthening physiotherapy interventions for hospitalized patients in critical care settings.

Hypothesis

Considering the aforementioned background, the hypothesis of this research project is: **Quadriceps muscle and peripheral nerve ultrasound is a feasible technique for physical therapists in the critical care unit and demonstrates good inter-rater reliability.**

General Objective

To assess the feasibility of quadriceps muscle and peripheral nerve ultrasound as a technique for physical therapists in the critical care unit, as well as to determine its inter-rater reliability.

Specific Objectives

- **SO1:** To evaluate the inter-rater variability of quadriceps muscle ultrasound measurements performed by physical therapists in the critical care unit.
- **SO2:** To assess the feasibility and inter-rater variability of peripheral nerve ultrasound in the same clinical setting.
- **SO3:** To evaluate the inter-rater variability of the MRC-SS and FSS-ICU clinical scales and correlate their results with findings from quadriceps muscle and peripheral nerve ultrasound.

Study Design

SO1: To evaluate the inter-rater variability of quadriceps muscle ultrasound measurements performed by physical therapists in the critical care unit.

Rationale: ICU-AW is a frequent complication in critically ill patients[16,21,22], associated with prolonged hospital stays[8,9,23,25], increased mortality[8,10,21,23–25], higher healthcare costs, and long-term functional impairments[8,9,21,24,26]. Protein degradation and muscle mass loss can begin within the first 10 days of critical illness[41,42] , highlighting the importance of early diagnosis. In non-cooperative patients, quadriceps muscle ultrasound has been proposed as an effective tool for early detection of ICU-AW[44–47]. Although ultrasound has shown good inter-rater reliability [51–54], these findings mostly reflect the consistency of the method itself, not of the individual operators—underscoring the need to validate operator reliability.

Experimental Approach: To address this objective, inter-rater variability will be assessed using the intraclass correlation coefficient (ICC) for various quadriceps muscle ultrasound variables, measured by three physical therapists experienced in the technique. In the transverse view, the following variables will be assessed: anterior quadriceps complex thickness, rectus femoris thickness, vastus intermedius thickness, and their respective cross-sectional areas (CSA). In the longitudinal view, the pennation angle of the vastus lateralis fibers relative to the superficial aponeurosis of the vastus intermedius will be evaluated. In addition, echogenicity will be assessed using histogram analysis via ImageJ software.

Expected Results: We anticipate sufficient inter-rater agreement in quadriceps muscle ultrasound measurements performed by physical therapists in the critical care unit.

SO2: To assess the feasibility and inter-rater variability of peripheral nerve ultrasound in the same clinical setting.

Rationale: Although the differential diagnosis between CIM and CIP is commonly performed using electrophysiological assessment[31,36], this tool is not widely available in all healthcare centres and is even less accessible at the patient's bedside. To address this limitation,

peripheral nerve ultrasound has been proposed as a strategy to evaluate changes in cross-sectional area (CSA) and echogenicity in specific peripheral nerve segments[49].

Experimental Approach: To address this objective, inter-rater variability will be assessed using the intraclass correlation coefficient (ICC) for various peripheral nerve ultrasound variables evaluated by three physical therapists who have received recent training in the technique. The variables to be analysed will include the cross-sectional area (CSA) and echogenicity of peripheral nerves, the latter of which will be evaluated using histogram analysis in ImageJ software.

Expected Results: We expect to observe sufficient inter-rater agreement in the peripheral nerve ultrasound measurements performed by physical therapists in the critical care unit.

SO3: To assess the inter-rater variability of the MRC-SS and FSS-ICU scales, and to correlate their results with findings from muscle and peripheral nerve ultrasound.

Rationale: The Medical Research Council Sum Score (MRC-SS) is the most commonly used tool to assess muscle strength in cooperative critically ill patients and is employed to diagnose both critical illness myopathy and ICU-acquired weakness (ICU-AW)[2]. The Functional Status Score for the ICU (FSS-ICU) evaluates patients' physical functionality during ICU stay[2]. Although both scales have demonstrated good inter-rater reliability[32,55,56], this reliability primarily refers to the measurement method and not to the evaluators themselves, underscoring the need to validate this aspect. Given that muscle mass loss begins within the first 10 days of critical illness and that severely ill patients are often unable to participate in scale-based evaluations due to impaired consciousness, quadriceps muscle ultrasound has been proposed as an early detection strategy for ICU-AW. Additionally, ultrasound findings indicative of muscle alterations—such as increased echogenicity—may correlate with poorer functional outcomes on the MRC-SS and FSS-ICU scales.

Experimental Approach: To address this objective, inter-rater variability for the MRC-SS and FSS-ICU scales will be assessed using Kendall’s coefficient of concordance (W) among three physical therapists. The findings from these clinical scales will be correlated with muscle and

nerve ultrasound parameters using Pearson or Spearman correlation coefficients, depending on the distribution of the variables.

Expected Results: We expect to find sufficient inter-rater agreement in the MRC-SS and FSS-ICU scores evaluated by physical therapists in the critical care unit. Additionally, we anticipate that these clinical scores will correlate with ultrasound findings.

General Methodology

Study Design

This is a quantitative, analytical, non-experimental, and cross-sectional study.

Patients

Inclusion criteria: Adult patients admitted to the Critical Care Unit who are able to provide informed consent and sign the corresponding consent form will be selected. *Exclusion criteria:* For ultrasound assessments, patients with a known allergy to ultrasound gel or a body mass index (BMI) ≥ 30 will be excluded. For the MRC-SS and FSS-ICU scale assessments, exclusion criteria include a history of malnutrition or cachexia, pre-existing neuromuscular disorders, coagulopathies (such as severe liver disease or continuous dialysis), thrombocytopenia <20,000/µL, lower limb amputations, lower limb fractures, ongoing chemotherapy, pregnancy, uncontrolled epileptic status, or prolonged corticosteroid use.

All enrolled patients will undergo quadriceps and peripheral nerve ultrasound assessments, as well as evaluation using the MRC-SS and FSS-ICU scales. While the timing of these evaluations may vary, all assessments will be performed on the same day. Safety criteria will follow the expert consensus guidelines established by Hodgson et al. [57], and include continuous monitoring of clinical parameters such as hemodynamic and respiratory variables.

Clinical Recruitment Site

All patients will be recruited from the Adult ICU of Clínica INDISA. Each enrolled participant will have a clinical file in which all relevant clinical data will be recorded. All patient information will be kept strictly confidential.

Sample Size Calculation

The sample size was determined based on the intraclass correlation coefficient (ICC), which evaluates agreement between continuous quantitative variables and requires a larger sample size than Kendall's W coefficient. These continuous variables include measurements obtained from quadriceps muscle ultrasound (cross-sectional area [CSA], muscle thickness, pennation angle) and peripheral nerve ultrasound (CSA and echogenicity). Assuming 80% power, a two-sided alpha of 0.05, a 10% attrition rate, three raters, a minimum acceptable ICC of 0.6, and an expected ICC of 0.8—as reported in previous studies[51,53], the required sample size is 37 patients.

Evaluators

The methodology involves the assessment of quadriceps muscle ultrasound and the MRC-SS and FSS-ICU scales by physical therapists working in the Critical Care Unit at Clínica INDISA. All evaluators either have experience or are currently undergoing training in these methods.

Statistical Analysis

To assess inter-rater reliability among physical therapists, ICC and Kendall's W coefficient will be applied. Results will be visualized using Bland–Altman plots. A p-value <0.05 will be considered statistically significant. Correlation between the results of Objectives 1 and 2 with those of Objective 3 will also be assessed. Depending on the distribution of variables (analysed using the Shapiro–Wilk test), Pearson or Spearman correlation coefficients will be used. All statistical analyses and graphics will be conducted using R Studio and Stata software.

Ultrasound Procedures

Quadriceps Muscle Ultrasound

For the transverse measurement, patients will be placed in the supine position with the knee joint in a neutral resting position. A line will be drawn from the anterior superior iliac spine (ASIS) to the superior border of the patella, and the measurement site will be located at the

junction between the middle and lower thirds of this line. At this site, the thickness of the anterior quadriceps compartment, rectus femoris (RF), and vastus intermedius (VI), as well as their cross-sectional areas (CSA), will be measured. Images will also be acquired for echogenicity analysis using ImageJ software. For longitudinal measurements, the probe will be positioned 5 cm lateral to the transverse measurement point to evaluate the pennation angle of the vastus lateralis fibers on the superficial aponeurosis of the vastus intermedius. All ultrasound examinations will be performed using a linear transducer (4–12 MHz) on a Sonosite™ system.

Peripheral Nerve Ultrasound

Peripheral nerve segments will be assessed using a standardized protocol at predefined anatomical sites. The ultrasound probe will be positioned perpendicular to the nerve path to minimize measurement error of CSA. Cross-sectional areas will be determined by manually tracing the nerve's contour, including the epineurium. Echogenicity changes—indicative of neuropathy—will also be evaluated. Based on literature evidence regarding accessibility and changes seen in critical illness polyneuropathy (CIP), the following nerves will be evaluated:

a) Median nerve: upper arm, cubital fossa (medial to the brachial artery), and mid-forearm

b) Ulnar nerve: mid-arm (medial) and mid-forearm

c) Fibular nerve: proximal popliteal fossa

d) Tibial nerve: proximal popliteal fossa and ankle (near the flexor tendons at the medial malleolus)

Ultrasound will be performed using a linear transducer (4–12 MHz) on a Sonosite™ system.

Ethical Considerations

Social Value

ICU-acquired weakness (ICU-AW) is characterized by muscle atrophy and impaired contractility, conditions that contribute to increased mortality[13–17], prolonged hospital stays [8,9,23,25], longer durations of mechanical ventilation [9,24], higher healthcare-related costs [8,9,21,24,26]

and greater long-term physical disability [18,19]. Given that muscle protein degradation and electrophysiological abnormalities occur within the first 10 days of ICU stay [42,43], early and timely rehabilitation is critical in critically ill patients. Therefore, the identification of diagnostic strategies is essential to enable early detection and the development of targeted pharmacological and non-pharmacological therapeutic interventions. Research into critical illness myopathy and neuropathy could ultimately benefit the broader population by informing public policies that support expanded physical therapy and rehabilitation programs in intensive care units across the country.

Protection of Vulnerable Populations

This study focuses on validating evaluations conducted by physical therapists and, as a pilot project, will include only patients who are cognitively able to provide informed consent. Therefore, it does not involve any inherently vulnerable populations. Moreover, the study is free from biases related to sex, race, or age.

Adverse Events

Ultrasound evaluation, which is a routine procedure in ICU settings [58], will be used in this study. Although rare, cases of contact dermatitis due to ultrasound gel have been reported [59–64]. Accordingly, the skin at the site of ultrasound evaluation will be monitored after each session. Additionally, the exclusion criteria proposed in this study aim to minimize the likelihood of adverse events.

Risk/Benefit Ratio

The potential for significant risks is minimized by the defined exclusion criteria. Physical therapy assessments performed by kinesiologists in the ICU at Clínica INDISA are routine procedures carried out under strict safety criteria in accordance with current literature[57]. Obtaining additional neuromusculoskeletal assessment data on hospitalized ICU patients may enhance early detection of ICU-AW, allowing attending physicians to address this condition with an integrated and multidisciplinary approach.

Privacy Protection

All information collected will be securely stored by the principal investigator. Participant data will be recorded in an Excel spreadsheet, and results will be presented anonymously. No identifying information will be disclosed or shared with third parties.

Ethical Oversight

Any issues that arise during the study or any amendments to the protocol will be reported to the ethics committee. In accordance with Article 10 of Chilean Law No. 20.120, “Any serious adverse event that occurs during the study must be reported by the investigator to the Ethics Committee and the Director of the institution where the study is being conducted.” **Feasibility**

This study has the full support of the Adult Critical Care Unit at Clínica INDISA, which will serve as the recruitment site from the second semester of 2024 through the end of 2025. No external funding is required for its implementation.

References

1. De Jonghe, B. Paresis Acquired in the Intensive Care Unit. A Prospective Multicenter Study. *JAMA* **288**, 2859 (2002).
2. Vanhorebeek, I., Latronico, N. & Van den Berghe, G. ICU-acquired weakness. *Intensive Care Med* **46**, 637–653 (2020).
3. Chen, J. & Huang, M. Intensive care unit-acquired weakness: Recent insights. *Journal of Intensive Medicine* **4**, 73–80 (2024).
4. Kress, J. P. & Hall, J. B. ICU-Acquired Weakness and Recovery from Critical Illness. *New England Journal of Medicine* **370**, 1626–1635 (2014).
5. Schefold, J. C. *et al.* Muscular weakness and muscle wasting in the critically ill. *J Cachexia Sarcopenia Muscle* **11**, 1399–1412 (2020).
6. Wang, W., Xu, C., Ma, X., Zhang, X. & Xie, P. Intensive Care Unit-Acquired Weakness: A Review of Recent Progress With a Look Toward the Future. *Front Med (Lausanne)* **7**, (2020).
7. Barreiro, E. Models of disuse muscle atrophy: therapeutic implications in critically ill patients. *Ann Transl Med* **6**, 29–29 (2018).
8. Fan, E. *et al.* An Official American Thoracic Society Clinical Practice Guideline: The Diagnosis of Intensive Care Unit–acquired Weakness in Adults. *Am J Respir Crit Care Med* **190**, 1437–1446 (2014).
9. Stevens, R. D. *et al.* A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med* **37**, S299–S308 (2009).
10. Wilcox, S. R. Corticosteroids and neuromuscular blockers in development of critical illness neuromuscular abnormalities: A historical review. *J Crit Care* **37**, 149–155 (2017).
11. Derde, S. *et al.* Muscle atrophy and preferential loss of myosin in prolonged critically ill patients*. *Crit Care Med* **40**, 79–89 (2012).
12. Stibler, H., Edström, L., Ahlbeck, K., Remahl, S. & Ansved, T. Electrophoretic determination of the myosin/actin ratio in the diagnosis of critical illness myopathy. *Intensive Care Med* **29**, 1515–1527 (2003).
13. Zhang, X.-M. *et al.* Sarcopenia as a predictor of mortality among the critically ill in an intensive care unit: a systematic review and meta-analysis. *BMC Geriatr* **21**, 339 (2021).
14. Yanagi, N. *et al.* Assessment of Sarcopenia in the Intensive Care Unit and 1-Year Mortality in Survivors of Critical Illness. *Nutrients* **13**, 2726 (2021).
15. Giani, M. *et al.* Low skeletal muscle index and myosteatosis as predictors of mortality in critically ill surgical patients. *Nutrition* **101**, 111687 (2022).
16. Hrdy, O. *et al.* Incidence of muscle wasting in the critically ill: a prospective observational cohort study. *Sci Rep* **13**, 742 (2023).
17. Mayer, K. P. *et al.* Acute skeletal muscle wasting and dysfunction predict physical disability at hospital discharge in patients with critical illness. *Crit Care* **24**, 637 (2020).
18. Rodriguez, B., Larsson, L. & Z'Graggen, W. J. Critical Illness Myopathy: Diagnostic Approach and Resulting Therapeutic Implications. *Curr Treat Options Neurol* **24**, 173–182 (2022).

19. Vongchaiudomchoke, W., Sathitkarnmanee, B., Thanakiattiwibun, C., Jarungjitaree, S. & Chaiwat, O. The association between sarcopenia and functional outcomes after hospital discharge among critically ill surgical patients. *Asian J Surg* **45**, 1408–1413 (2022).

20. Friedrich, O., Diermeier, S. & Larsson, L. Weak by the machines: muscle motor protein dysfunction - a side effect of intensive care unit treatment. *Acta Physiologica* **222**, e12885 (2018).

21. Kanova, M. & Kohout, P. Molecular Mechanisms Underlying Intensive Care Unit-Acquired Weakness and Sarcopenia. *Int J Mol Sci* **23**, 8396 (2022).

22. Appleton, R. T., Kinsella, J. & Quasim, T. The incidence of intensive care unit-acquired weakness syndromes: A systematic review. *J Intensive Care Soc* **16**, 126–136 (2015).

23. Tortuyaux, R., Davion, J.-B. & Jourdain, M. Intensive care unit-acquired weakness: Questions the clinician should ask. *Rev Neurol (Paris)* **178**, 84–92 (2022).

24. Latronico, N. *et al.* The ICM research agenda on intensive care unit-acquired weakness. *Intensive Care Med* **43**, 1270–1281 (2017).

25. Nakanishi, N., Takashima, T. & Oto, J. Muscle atrophy in critically ill patients : a review of its cause, evaluation, and prevention. *The Journal of Medical Investigation* **67**, 1–10 (2020).

26. Batt, J., Mathur, S. & Katzberg, H. D. Mechanism of ICU-acquired weakness: muscle contractility in critical illness. *Intensive Care Med* **43**, 584–586 (2017).

27. Sidiras, G. *et al.* Long term follow-up of quality of life and functional ability in patients with ICU acquired Weakness – A post hoc analysis. *J Crit Care* **53**, 223–230 (2019).

28. Castro-Ávila, A. C., Merino-Osorio, C., González-Seguel, F., Camus-Molina, A. & Leppe, J. Impact on Mental, Physical and Cognitive functioning of a Critical care sTay during the COVID-19 pandemic (IMPACCT COVID-19): protocol for a prospective, multicentre, mixed-methods cohort study. *BMJ Open* **11**, e053610 (2021).

29. Friedrich, O. *et al.* The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. *Physiol Rev* **95**, 1025–1109 (2015).

30. Hermans, G. & Van den Berghe, G. Clinical review: intensive care unit acquired weakness. *Crit Care* **19**, 274 (2015).

31. Vanhorebeek, I., Latronico, N. & Van den Berghe, G. ICU-acquired weakness. *Intensive Care Med* **46**, 637–653 (2020).

32. Hough, C. L., Lieu, B. K. & Caldwell, E. S. Manual muscle strength testing of critically ill patients: feasibility and interobserver agreement. *Crit Care* **15**, R43 (2011).

33. Hermans, G. *et al.* Interobserver agreement of medical research council sum-score and handgrip strength in the intensive care unit. *Muscle Nerve* **45**, 18–25 (2012).

34. Connolly, B. A. *et al.* Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. *Crit Care* **17**, R229 (2013).

35. Connolly, B. A. *et al.* Clinical predictive value of manual muscle strength testing during critical illness: an observational cohort study. *Crit Care* **17**, R229 (2013).

36. Stevens, R. D. *et al.* A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med* **37**, S299–S308 (2009).

37. Latronico, N. & Bolton, C. F. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. *Lancet Neurol* **10**, 931–941 (2011).

38. Lefaucheur, J.-P. Origin of ICU acquired paresis determined by direct muscle stimulation. *J Neurol Neurosurg Psychiatry* **77**, 500–506 (2006).

39. Formenti, P., Umbrello, M., Coppola, S., Froio, S. & Chiumello, D. Clinical review: peripheral muscular ultrasound in the ICU. *Ann Intensive Care* **9**, 57 (2019).

40. Paolo, F. *et al.* The possible predictive value of muscle ultrasound in the diagnosis of ICUAW in long-term critically ill patients. *J Crit Care* **71**, 154104 (2022).

41. Lad, H. *et al.* Intensive Care Unit-Acquired Weakness: Not Just Another Muscle Atrophying Condition. *Int J Mol Sci* **21**, 7840 (2020).

42. Puthucheary, Z. A. *et al.* Acute Skeletal Muscle Wasting in Critical Illness. *JAMA* **310**, 1591 (2013).

43. Hickmann, C. E. *et al.* Impact of Very Early Physical Therapy During Septic Shock on Skeletal Muscle: A Randomized Controlled Trial. *Crit Care Med* **46**, 1436–1443 (2018).

44. Elkalawy, H., Sekhar, P. & Abosena, W. Early detection and assessment of intensive care unit-acquired weakness: a comprehensive review. *Acute and Critical Care* **38**, 409–424 (2023).

45. Weber-Carstens, S. *et al.* Risk factors in critical illness myopathy during the early course of critical illness: a prospective observational study. *Crit Care* **14**, R119 (2010).

46. Weber-Carstens, S. *et al.* Critical Illness Myopathy and GLUT4. *Am J Respir Crit Care Med* **187**, 387–396 (2013).

47. Vijayan, D., Thomas, S. M. & Rajagopal, K. Association of SOFA Score with Severity of Muscle Wasting in Critically Ill Patients: A Prospective Observational Study. *Indian Journal of Critical Care Medicine* **27**, 743–747 (2023).

48. Beekman, R. & Visser, L. H. High-resolution sonography of the peripheral nervous system – a review of the literature. *Eur J Neurol* **11**, 305–314 (2004).

49. Gruber, L. *et al.* Differentiation of Critical Illness Myopathy and Critical Illness Neuropathy Using Nerve Ultrasonography. *Journal of Clinical Neurophysiology* **40**, 600–607 (2023).

50. Grimm, A., Décard, B. F., Axer, H. & Fuhr, P. The Ultrasound pattern sum score – UPSS. A new method to differentiate acute and subacute neuropathies using ultrasound of the peripheral nerves. *Clinical Neurophysiology* **126**, 2216–2225 (2015).

51. Mittal, S., Hadda, V., Khilnani, G. C., Dhunguna, A. & Khan, M. A. Intra- and Inter-Observer Reliability of Quadriceps Muscle Thickness Measured with Bedside Ultrasonography by Critical Care Physicians. *Indian Journal of Critical Care Medicine* **21**, 448–452 (2017).

52. Di Matteo, A. *et al.* Reliability assessment of ultrasound muscle echogenicity in patients with rheumatic diseases: Results of a multicenter international web-based study. *Front Med (Lausanne)* **9**, (2023).

53. Pardo, E. *et al.* Reliability of ultrasound measurements of quadriceps muscle thickness in critically ill patients. *BMC Anesthesiol* **18**, 205 (2018).

54. Karapınar, M., Atilla Ayyıldız, V., Ünal, M. & Fırat, T. Ultrasound imaging of quadriceps muscle in patients with knee osteoarthritis: The test-retest and inter-rater reliability and

concurrent validity of echo intensity measurement. *Musculoskelet Sci Pract* **56**, 102453 (2021).

55. Turan, Z., Topaloglu, M. & Ozyemisci Taskiran, O. Medical Research Council-sumscore: a tool for evaluating muscle weakness in patients with post-intensive care syndrome. *Crit Care* **24**, 562 (2020).

56. González-Seguel, F. *et al.* Inter-observer reliability of trained physiotherapists on the Functional Status Score for the Intensive Care Unit Chilean-Spanish version. *Physiother Theory Pract* **38**, 365–371 (2022).

57. Hodgson, C. L. *et al.* Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults. *Crit Care* **18**, 658 (2014).

58. Messina, A. *et al.* Head to toe ultrasound: a narrative review of experts' recommendations of methodological approaches. *Journal of Anesthesia, Analgesia and Critical Care* **2**, 44 (2022).

59. Chasset, F. *et al.* Contact dermatitis due to ultrasound gel: A case report and published work review. *J Dermatol* **43**, 318–320 (2016).

60. Cacciapuoti, S., Masarà, A., Fabbrocini, G. & Patruno, C. Contact Urticaria to Ultrasound Gel: A Case Report. *Dermatitis* **29**, 93–93 (2018).

61. Martínez Antón, M. D. *et al.* Two cases of allergic contact dermatitis to different elements in identical ultrasound gels. *Contact Dermatitis* **85**, 477–478 (2021).

62. Villa, A., Venegoni, M. & Tiso, B. Cases of contact dermatitis caused by ultrasonographic gel. *Journal of Ultrasound in Medicine* **17**, 530–530 (1998).

63. KESSLER, J., SCHAFHALTERZOPPOTH, I. & GRAY, A. Allergic Contact Dermatitis Caused by Ultrasonic Gel. *Reg Anesth Pain Med* **31**, 480–481 (2006).

64. Chasset, F. *et al.* Contact dermatitis due to ultrasound gel: A case report and published work review. *J Dermatol* **43**, 318–320 (2016).