OBSERVATIONAL STUDY

OPEN

Exploring Peripheral and Respiratory Muscle Weakness and Functional Impairments in ICU Patients: Insights From a Resource-Constrained Setting

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IMPORTANCE AND OBJECTIVES: The aim of this study was to explore peripheral and respiratory muscle structure and strength from unit admission to hospital discharge among ICU patients in a resource-constrained setting.

DESIGN: Prospective, observational study.

SETTING: Tertiary academic hospital.

PARTICIPANTS: Newly intubated critically ill adults admitted to the medical and surgical ICUs and expected to be mechanically ventilated for more than 48 hours were included in the study.

MAIN OUTCOMES AND MEASURES: Ultrasonography of the right hemidiaphragm and quadriceps muscles were taken at admission for 3 consecutive days. Respiratory and peripheral muscle strength were evaluated using the Medical Research Council-Sum Score, dynamometry and maximal inspiratory pressure (MIP) at awakening, ICU discharge and hospital discharge.

RESULTS: Forty-five participants were included, with a median (interquartile range) age of 34.5 (24.3–47.4) years and 73% were male. Most of the change in diaphragm thickness was observed on day 3, with 5 (22%) participants showing a decrease of more than 10% from baseline. Minimal changes in rectus femoris cross-sectional area were noted during the first 3 days. Eleven participants (44%) presented with ICU-acquired weakness at awakening, which decreased to 7 (29%) participants at ICU discharge and 5 (24%) participants at hospital discharge. The mean ± SD percentage of predicted quadriceps force was 22.2 ± 5.1 N at hospital discharge. The mean ± SD percentage of predicted MIP scores was 29.6% ± 10.5% at ICU discharge and 29.1% ± 8.6% at hospital discharge.

CONCLUSIONS AND RELEVANCE: Patients discharged from the ICU in a resource-constrained setting presented with peripheral and respiratory muscle weakness, with minimal change in muscle structure shown by ultrasonography, despite short ICU stays, low Acute Physiology and Chronic Health Evaluation II scores, and a relatively young age. Future research should explore whether these findings indicate a distinct phenotype of critical illness in such environments.

KEYWORDS: critical care outcomes; ICU; muscle strength; physical activity; ultrasound

Improvements in ICU management have led to reduced mortality in ICU patients; however, ICU survivors often experience morbidity and impairments in physical function that persist beyond hospital discharge (1). A major contributing factor for these impairments is ICU-acquired weakness (ICU-AW) (2–4). ICU-AW is defined as "clinically detected weakness in critically ill patients where the only plausible etiology is critical illness itself." It is

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KEY POINTS

Question: What implication does critical illness have on ICU patients' peripheral and respiratory muscle structure and strength from unit admission to hospital discharge in a resource-constrained setting?

Findings: In this prospective observational study, ICU patients presented with peripheral and respiratory muscle weakness, as indicated by the mean reference values and percentages of predicted values, along with variations in structural changes of the peripheral and respiratory muscles.

Meaning: Patients discharged from an ICU in a research-constrained setting presented with peripheral and respiratory muscle weakness despite being young and having a short duration of mechanical ventilation and ICU stay.

diagnosed using the Medical Research Council-Sum Score (MRC-SS), with a score of less than 48 (2–4). Approximately 40% of ICU patients will present with ICU-AW during their ICU stay and is associated with an increased duration of mechanical ventilation, prolonged ICU and hospital length of stay (LOS) and an increased mortality (2–4). While ICU survivors recover from their critical illness, they often experience persistent muscle weakness, functional limitations, and a reduced quality of life (2, 3). This acquired morbidity has been shown to persist for up to 5 years after hospital discharge (5–9).

Post-ICU exercise-based interventions have attempted to address the acquired morbidity experienced by ICU survivors; however, recent systematic reviews have found that exercise-based rehabilitation following ICU discharge may have little to no effect on functional exercise capacity, muscle strength, quality of life, and mortality (10, 11). These findings suggest that early identification of patients at risk of muscle weakness and physical function impairments, along with timely interventions to address these risks, may be essential for improving long-term outcomes (10).

Currently, routine assessments of muscle structure and strength, and physical function are not performed early or frequently during ICU admission. This is often due to the need for ICU patients to be awake and oriented for certain assessments, or because the assessments are impractical to use in an ICU setting, requires specialized equipment and training, or involves invasive procedures. However, ultrasound has emerged as a minimally invasive tool frequently used by clinicians in the ICU. It is valuable for quantifying muscle mass and quality, which is important for nutritional therapy and physical therapy (12, 13). Additional methods, such as bio-electrical impedance, mid-arm muscle circumference and CT, may complement ultrasound assessments. However, these techniques have certain limitations. Bio-electrical impedance and mid-arm muscle circumference may be influenced by fluid shifts commonly observed in ICU patients, potentially affecting their accuracy. Meanwhile, CT is not ideal for ICU settings, as it is not typically available at the bedside and exposes patients to radiation (14–16).

The right hemi-diaphragm, rectus femoris (RF), and vastus intermedius (VI) muscles have been extensively studied in ICU patients from higher income countries (HICs) and validated in previous studies, demonstrating excellent inter-rater and intra-rater reliability (17–19). Furthermore, diaphragmatic thickening fraction (DTF), which reflects diaphragm function, has been widely used in as a predictor of successful extubation (20–22). Ultrasound detected changes in quadriceps muscle structure have also been associated with inflammation, organ failure, mortality, and functional status (13, 23, 24). Therefore, ultrasound could serve as a potential tool for early identification of patients at risk of long-term muscle weakness and physical function impairments.

Most research on ICU survivors has been conducted in HICs, where the reported data predominantly resemble older adults with medical diagnosis and comorbidities. There is limited data on ICU survivors from low-to middle-income countries (LMICs), indicating a need for further research across a broader range of resource settings (25). In South Africa, most ICU admissions in the public sector are due to surgical emergencies, often involving a younger population with trauma-related injuries (26–29). While traumatic injuries can lead to movement limitations that affect physical function, so can other reported patient or ICU-related factors affect physical function in ICU patients (30, 31). Therefore, further research is needed to better understand the interrelationship between these factors and their impact on physical function.

Additionally, South Africa has a high percentage of its population living with HIV and tuberculosis, who are malnourished and present with muscle wasting as compared with populations from HICs (32, 33).

Therefore, the aim of this study was to explore peripheral and respiratory muscle structure and strength, from unit admission to hospital discharge among ICU patients in a resource-constrained setting. We will also report on physical function at unit and hospital discharge.

MATERIALS AND METHODS

Study Design and Participants Eligibility

A prospective observational study was conducted at a Tertiary Academic Hospital in Cape Town, South Africa. Ethical approval for the study titled "The Impact of Critical Illness on Muscle Structure, Function, and Physical Capability" was obtained from the Stellenbosch University Health Research Ethics Committee (S16/09/173A) in June 2019. The study was conducted in compliance with the principles of the 1975 Declaration of Helsinki. Participants provided informed consent retrospectively upon successful extubation. If the legally authorized representative had initially provided informed consent, the participant was subsequently approached to provide their own informed consent upon successful extubation. If the participant declined consent, their data was discarded and excluded from the analysis. Newly intubated (less than 24 hr) adults admitted to the medical and surgical ICUs and expected to be mechanically ventilated for more than 48 hours were included in the study. Adults that presented with acute or chronic neuromuscular diseases, spinal cord injuries, new intracranial processes and pelvic or lower limb fractures where weight-bearing was contraindicated were excluded.

Procedures

All data was collected by the principal investigator (S.C.). Intra-rater and inter-rater reliability of measures was established a priori with intraclass correlation coefficients greater than 0.9 deemed acceptable. Baseline data was extracted from the medical records of each participant. Data included participant demographics, admission type, admission diagnosis, comorbidities, medication, the Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score, the Sequential Organ Failure Assessment (SOFA) score, length of ventilation (LOV), ICU LOS, hospital LOS, and the type of rehabilitation the participants received based on the ICU Mobility Scale (34).

Ultrasonography

Ultrasonography images of the right hemi-diaphragm, RF, and VI muscles were taken on unit admission for 3 consecutive days. The images were captured using a Phillips Lumify (Washington, DC) portable ultrasound machine in B-mode, utilizing a 7–12 MHz linear probe according to a method previously shown to be reliable (20, 35). Images were analyzed on a computer using ImageJ software (National Institutes of Health, Bethesda, MD). The average diaphragm thickness (Tdi) of each image was calculated by measuring three random points on the diaphragm at end-inspiration and end-expiration, respectively (20). The averages for end-inspiration and end-expiration were used to calculate the DTF. A standard square of 20 mm × 20 mm in the middle of the image and a computer-assisted quantitative grayscale was used for the analysis of echogenicity of the RF and VI muscle. If the area to be analyzed was smaller than 20 mm × 20 mm, the largest possible square within the anatomic boundaries of the muscle was then used for analysis (35). RF cross-sectional area (CSA) was measured along the border of the muscle belly. All measurements for Tdi of the right hemi-diaphragm, RF CSA, RF echogenicity, and VI echogenicity were performed in triplicate, with the average values used for analysis.

The following measures were assessed while the patient was in the ICU, either intubated or with a tracheostomy, and had a Richmond Agitation Sedation Scale score of 0 or a Standardised Five Questions score of 5 out of 5. These measures were also evaluated at ICU discharge and hospital discharge.

Medical Research Council–Sum Score (MRC-SS)

The MRC-SS was performed according to a standardized protocol (36, 37). The composite score was used in the analysis with a score of less than 48 indicating the presence of ICU-AW.

Dynamometry

Peak isometric knee extension force and hand grip strength were measured following a standardized protocol, using the Lafayette Manual Muscle Test System (Lafayette, LA) and the Jamar hydraulic handgrip dynamometer (Chicago, IL) (38, 39). The dominant limbs were assessed three times, and the best measurement were used for analysis.

Maximal Inspiratory Pressure

Maximal Inspiratory Pressures (MIPs) were assessed according to the European Respiratory Society/American Thoracic Society guidelines using the POWERbreathe KH1 device (40, 41). MIP measurements were performed in triplicate and the best MIP was used for analysis.

Chelsea Critical Care Physical Assessment Tool

The Chelsea Critical Care Physical Assessment Tool (CPAx) was used to measure physical function following a standardized protocol (42, 43). Individual scores for the 10 domains of physical function were collated and a total score out of 50 was obtained and used for analysis.

The de Morton Mobility Index

The de Morton Mobility Index (DEMMI) assessed 15 different aspects of mobility (44, 45). The total score out of 19 was converted with Rasch analysis to an interval score ranging from zero (poor mobility) to 100 (independent mobility) and was used for analysis.

Six-Minute Walk Test

The Six-Minute Walk Test (6-MWT) was performed according to the European Respiratory Society/American Thoracic Society guidelines (46, 47). Participants performed two 6-MWTs with a 30-minute rest interval between the two tests. The best six-minute walk distance (6-MWD) was used for analysis.

Data and Statistical Analysis

Data were analyzed using the IBM SPSS version 29 software (New York, NY) in consultation with a statistician. Data were tested for normality using the Shapiro-Wilk test. Data were presented as means and SD if normally distributed, or as medians and interquartile ranges (IQR) if skewed. Outliers were investigated using Z statistics. Changes in Tdi were categorized by an increase or a decrease of more than 10%, or no change (48, 49). The results for MRC-SS were presented as a number (percentage), quadriceps force and MIP as percentages of predicted values, and grip strength as percentages below mean reference values (50). Correlations between measures of muscle strength and physical function were assessed using Spearman correlation. A significance level of $p < 0.05$ was used. Correlations were interpreted as strong ($r > 0.7$), moderate ($0.5 < r < 0.7$) or weak ($0.3 < r \leq 0.5$).

RESULTS

Participants

Over a 7-month period, 525 participants were screened for eligibility. Fifty-seven participants were eligible for inclusion, but 12 participants did not provide consent. A total of 45 participants were enrolled in the study (**Fig. 1**). Due to the safety criteria applied for the measures of muscle structure and strength, physical function and exercise tolerance, not all 45 participants were assessed for each measure.

Demographics

The demographic data were not normally distributed (**Supplementary Table 1,** http://links.lww.com/CCX/B492). The median (IQR) age was 34.5 (24.3–47.4) years and 73% of the participants were male. Participants represented a severely critically ill cohort with a median (IQR) APACHE II score of 18.5 (12.8–25.3) and a mean ± SD SOFA score of 8.8 ± 2.8. The main admission diagnosis was trauma (*n* = 20/45; 44.4%). The median (IQR) LOV and ICU LOS were 3 (1–6) days and 3 (1–5) days, respectively. Only 36% of the participants (*n* = 16/45) received a mobility level of greater than 8 on the ICU mobility scale during their stay.

Muscle Structure

Most of the change in Tdi was observed on day 3, with 5 (22%) participants experiencing a decrease in Tdi of more than 10% from baseline. One (4%) participant had an increase in Tdi of more than 10% on day 2 and day 3 as compared with baseline (**Fig. 2**). The DTF was

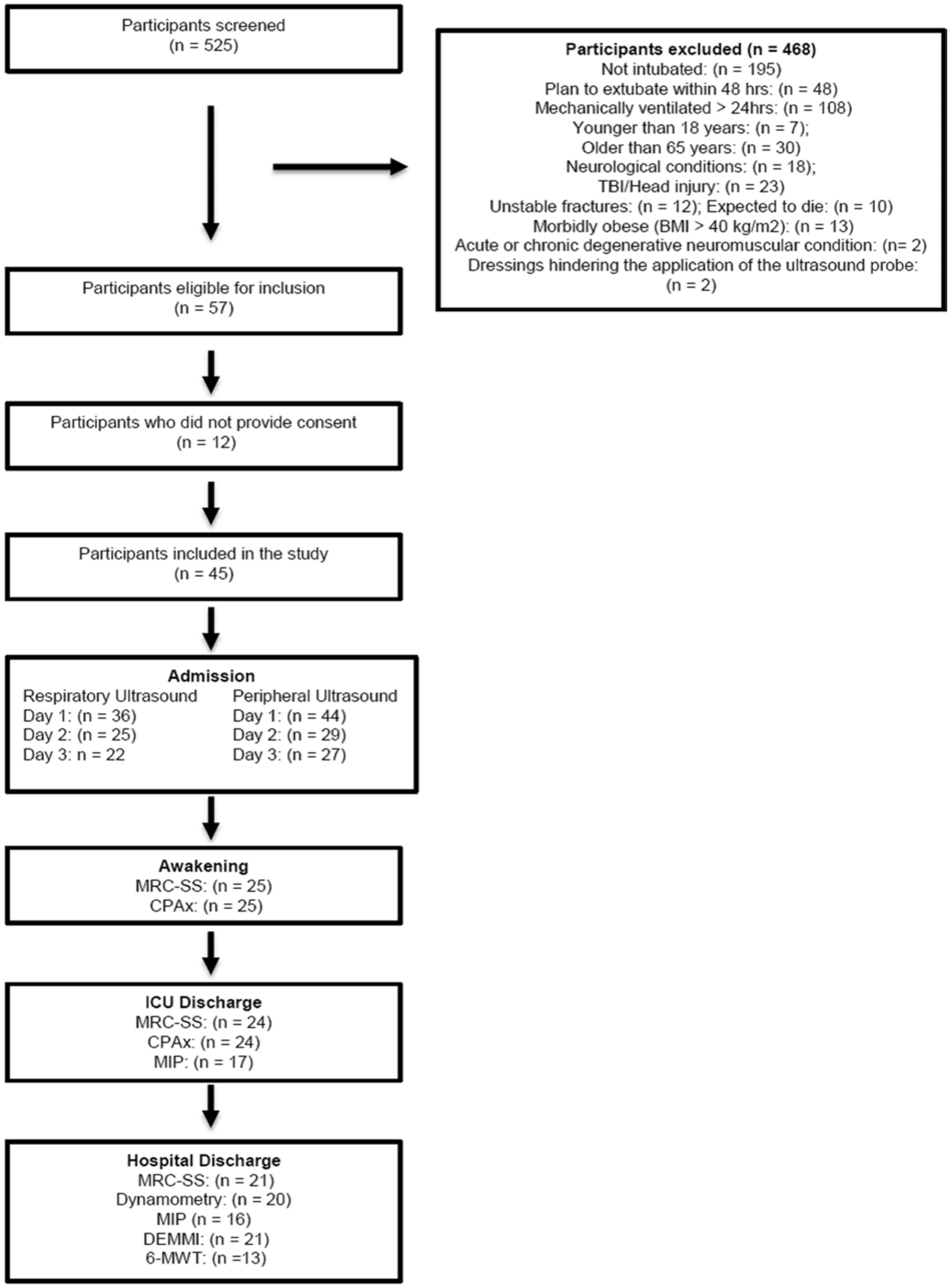

Figure 1. Flow diagram of the included participants.

low with a median (IQR) of 9.3 (6.2–13.6) % on day 1, median (IQR) of 8.7 (5.8–13.9) % on day 2 and a median (IQR) of 7.7 (5.9–14.2) % on day 3.

Minimal change in RF CSA was observed during the first 3 days (**Fig. 3**). There was no change in the echogenicity of the RF over the 3 days. A non-significant ($p = 0.27$) increase in echogenicity of the VI muscle was noted with median (IQR) of 23.7 (13–44.6) on day 1 to a median (IQR) of 36.1 (10.2–52.1) on day 3 (**Fig. 4**).

Muscle Strength and Physical Function

Forty-four percent ($n = 11$) of participants presented with ICU-AW (MRC-SS < 48) at awakening, which decreased to 29% ($n = 7$) at ICU discharge and 24%

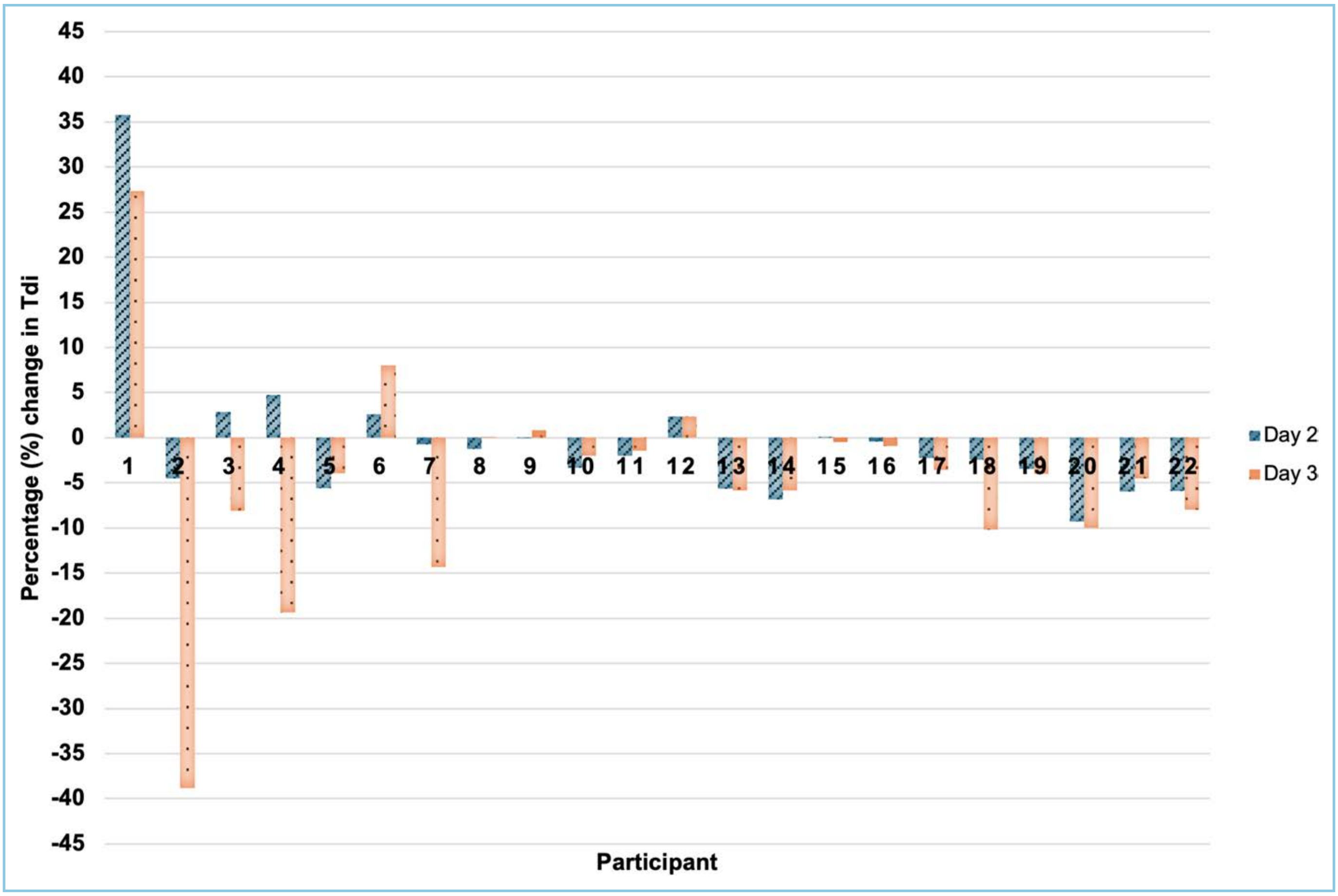

Figure 2. Percentage change in diaphragm thickness (Tdi) at end-inspiration on day 2 (stripes) and day 3 (dots) of mechanical ventilation as compared with baseline per participant.

(n = 5) at hospital discharge. Hand grip strength was below the mean reference values in 60% (n = 15) of participants at ICU discharge and 50% (n = 11) of participants at hospital discharge. The mean ± SD percentage of predicted MIP scores at ICU and hospital discharge was 29.6% ± 10.5% and 29.1% ± 8.6%, respectively. Three (17%) participants presented with both ICU-AW (MRC-SS < 48) and respiratory muscle weakness (MIP < 30 cmH_2O) at ICU discharge, and at hospital discharge this decreased to 2 (12 %) participants. A strong significant correlation was found between MIP and the 6-MWD (rho = 0.75; p = 0.01). No other strong significant correlations were found between muscle strength (MRC-SS, grip strength, quadriceps force) and 6-MWD (**Table 1**).

DISCUSSION

To the authors' knowledge, this was the first study to explore outcomes of respiratory and peripheral muscle structure and strength, as well as physical function, in a resource-constrained setting. Despite comprising a young population and having a short ICU LOS, this cohort presented with deficits in respiratory and peripheral muscle strength. While the RF CSA decreased over the 3 days, an increased in echogenicity was observed in the VI muscle. Notably, there were no changes in Tdi over the 3 days of mechanical ventilation, which is inconsistent with previously reported studies (48, 49). Furthermore, although participants had a low DTF and a short LOV, there were no failed extubation. In South Africa, the shortage of ICU beds and high demand for them in the public sector, primarily driven by surgical emergency admissions due to motor vehicle accidents and interpersonal violence, may explain the short LOV and ICU LOS observed in this study, as the majority of ICU admissions were related to emergencies (29, 32, 51). Despite these challenges, participants performed adequately in their physical function, with a CPAx score greater than 18 at ICU discharge being a strong predictor of ICU patients returning home (52).

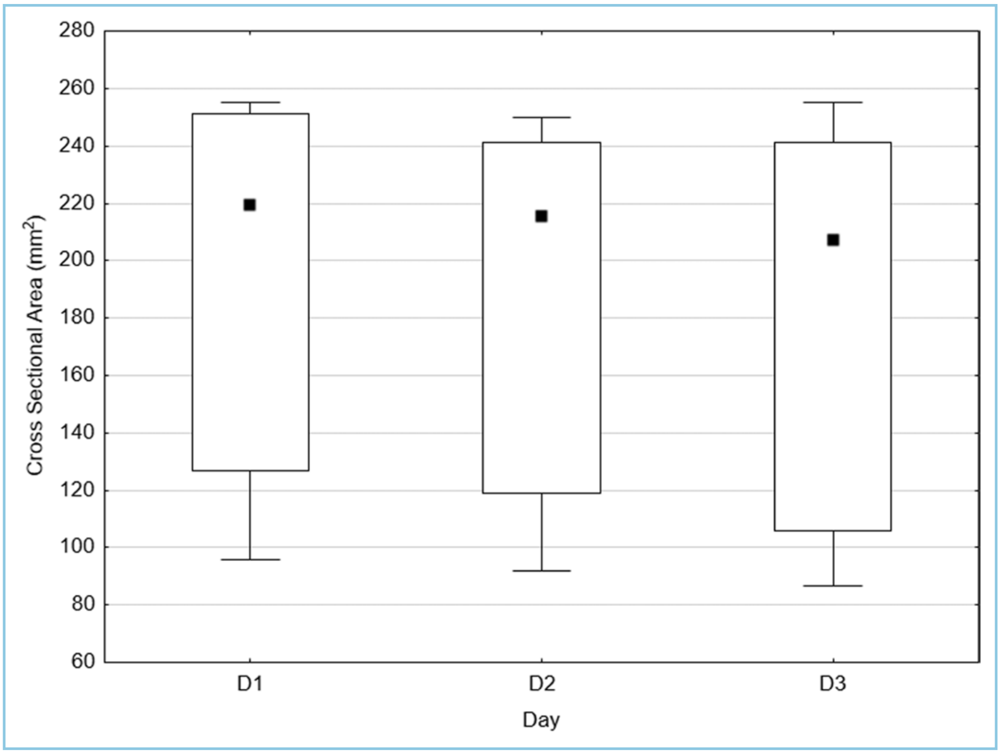

Figure 3. Rectus femoris cross-sectional area over the first 3 days of admission. Presented as medians (interquartile range) with minimum and maximum as follows: day 1: 237 (127–253.7) (99–255); day 2: 218.7 (118.5–241.5) (91.7–250); and day 3: 207 (104.5–241.7) (86.7–255).

Various measures are available to assess respiratory and peripheral muscle strength throughout the continuum of critically ill recovery (53, 54), but they do not appear to be correlated with each other. In this study, despite the low incidence of ICU-AW at ICU and hospital discharge, there were a higher number of participants who presented with peripheral and respiratory muscle weakness, as indicated by the low percentages of predicted values for knee extension force, grip strength, and MIP, which align with previous findings (55). Few studies have conducted similar assessments of both respiratory and peripheral muscle strength as in this study. While previous studies have reported improvements in MRC-SS during recovery (13, 56), there are limited data comparing MRC-SS with dynamometry or MIP in ICU survivors. This discrepancy observed in this study between the MRC-SS, dynamometry, and MIP could be due to the ceiling effect of the MRC-SS, as well as its variability in reliability for individual muscle testing, despite good reports of inter-rater reliability for the overall score (54). Furthermore, an MRC-SS of 48 may not accurately represent a patient's individual muscle strength, resulting in ICU patients in need of rehabilitation being overlooked. Therefore, alternative measures such as grip strength and dynamometry should be considered to identify patients with or at risk of acquiring muscle weakness early during ICU admission and hospital stay.

It is interesting to note the muscle wasting and the increase in echogenicity observed in the different muscle groups of the quadriceps complex which is consistent with findings from a previous study (35). In this study, there was a wide range in the reduction of RF CSA as compared with previously reported data showing a reduction of 10% to 12.5% (13, 23, 35). This contrast could be attributed to the older patient population as well as the longer durations of ventilation and ICU LOS observed in previous studies (13, 23, 35). RF is a fast twitch muscle and VI is a slow twitch muscle. Immobilization studies have reported greater loss of fast twitch muscle fibers, a conversion of slow twitch muscle fibers to fast twitch muscle fibers in postural muscles and the infiltration of noncontractile tissue such as connective tissue and edema in muscles (57). This could explain the muscle wasting of the RF muscle and partially explain the increase in echogenicity of the VI muscle. Studies have shown that ultrasound is a reliable tool and is able to diagnose ICU-AW (18, 19, 58). Therefore, perhaps the focus of ultrasound needs to shift on postural muscles due to exposure to microgravity such as bed rest and immobilization and consequent atrophy of the fast and slow twitch muscle fibers, resulting in a reduced resistance capacity (57).

Participants presented with respiratory muscle weakness regardless of a short LOV and with majority of the changes in Tdi were observed only on day 3. These findings differ from those of larger cohort studies, which reported an increased, decreased, or unchanged in Tdi

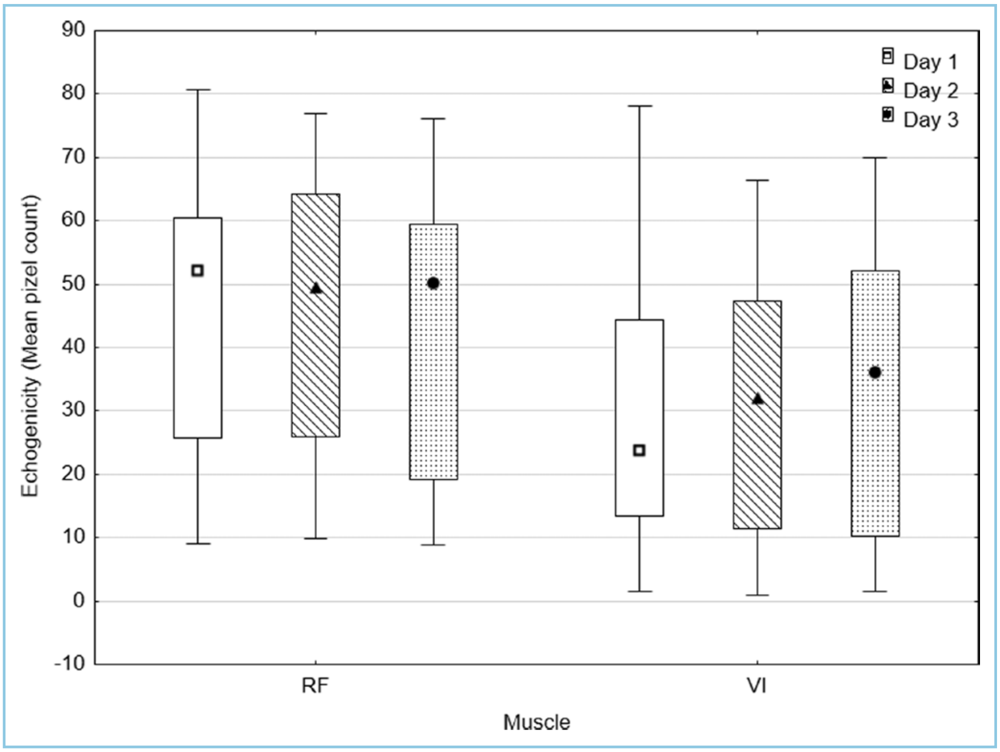

Figure 4. Echogenicity of rectus femoris (RF) and vastus intermedius (VI) muscles over the first 3 days following admission. Presented as medians (interquartile range [IQR]) as follows: RF—day 1: 52.2 (25.4–60.5); day 2: 49.5 (24–64.9); day 3: 50.1 (19.2–59.4); VI—day 1: 23.7 (13.2–44.6); day 2: 32 (10.4–48.4); and day 3: 36.1(10.2–52.1).

during the first week of ventilation (48, 49). This difference in results could be due to the limited sedation the participants received, the short LOV, or the uncertainty of what ultrasound measurements indicate. Similar results were observed in previous studies, where ICU survivors exhibited respiratory muscle weakness, as indicated by low MIP scores. However, these studies involved an older patient population, and the time points at which MIP assessments were conducted varied across the studies (59, 60). In this study, since participants presented with respiratory muscle weakness from ICU discharge that persisted to hospital discharge, the potential benefit of incorporating Inspiratory Muscle Training (IMT) as a rehabilitation intervention should be investigated (61–63). Given the association found between MIP and 6-MWD, MIP could potentially be a screening tool to identify not only patients who are difficult to wean from the ventilator or the elderly but also ICU patients who require early rehabilitation. Furthermore, incorporating IMT to address respiratory muscle weakness may also improve physical function.

Currently, there are no effective strategies to precondition muscles in ICU patients to enhance their response to muscle-preserving interventions. During the acute phase of critical illness, muscle mass loss is driven by various biological processes, including accelerated muscle protein degradation, metabolic reprogramming, bioenergetic depletion, and muscle contractile dysfunction, all of which have been extensively studied (2, 64). After ICU discharge, although proteolysis returns to baseline levels, ICU survivors may continue to experience impaired muscle contractility and abnormal muscle remodeling and regeneration, leading to sustained long-term muscle loss and impaired physical function (2, 64). The interplay of these complex factors makes it difficult for ICU patients to respond effectively to muscle-preserving interventions. Therefore, future research should focus on investigating biological factors alongside measures of respiratory and peripheral muscle structure and muscle strength. This approach will help identify specific ICU patient phenotypes, which will enable them to benefit from interventions aimed at preserving and restoring muscle mass.

This study has limitations. First, the resource-constrained setting, the high patient turnover and the short LOV led to a lost to follow-up, which may have resulted in missing participants in need of rehabilitation. Thus, early identification of these participants is crucial. Ultrasonography was not performed at ICU and hospital discharge, which limited the comparison of peripheral and respiratory muscle strength and physical function with muscle structure. Maximal expiratory pressure was also not assessed to determine the strength of the expiratory muscles, and its correlation with time on ventilation and extubation success.

This study has strengths as well. First, it highlights the need for more research in ICU populations from LMICs. Second, it emphasizes the importance of

TABLE 1.
Results of Respiratory and Peripheral Muscle Strength, and Physical Function

Measures	Awakening	ICU Discharge	Hospital Discharge
Peripheral muscle strength			
MRC-SS <48, *n* (%)	11 (44%)	7 (29%)	5 (24%)
Peak isometric knee extension force (percentage predicted)			
Dominant lower limb			22.2 ± 5.1
Nondominant lower limb			17 (13–23.7)
Grip strength, *n* (%) below mean reference values)		15 (60%)	11 (50%)
Respiratory muscle strength			
MIP (percentage predicted)		29.6 ± 10.5	29.1 ± 8.6
Co-occurrence of peripheral and respiratory muscle weakness, *n* (%)		3 (17%)	2 (12 %)
Physical function			
Chelsea Critical Care Physical Assessment Tool	33 (29–34)	35.5 (33.3–39)	
de Morton Mobility Index			60.9 ± 21.9
6-MWD (percentage predicted)			130.1 ± 62.7
Correlation between 6-MWD and MIP (rho, *p*)			0.75 (0.01*)
Correlation between 6-MWD and MRC-SS (rho, *p*)			0.57 (0.04*)
Correlation between 6-MWD and grip strength (rho, *p*)			0.50 (0.08)
Correlation between 6-MWD and quadriceps force (rho, *p*)			0.28 (0.36)

MIP = maximal inspiratory pressure, MRC-SS = Medical Research Council – Sum Score, 6-MWD = Six-minute Walk Distance, *p* = statistical significance, rho = Spearman correlation.
Results are represented as mean ± SD, median (interquartile range), or number (percentage).

screening for at risk patients and beginning with physical rehabilitation early during ICU admission and throughout a continuum, as ICU patients from LMICs tend to be younger, independent in their communities and can contribute significantly to the economic development of their community.

FUTURE RECOMMENDATION AND CONCLUSIONS

Future research should focus on investigating routine MIP assessment and its association with physical function in well-powered studies. The current definition of ICU-AW may need to be revisited, as an MRC-SS of less than 48 may not accurately represent a patient's peripheral muscle strength. Additionally, combining MRC-SS with ultrasound and hand-held dynamometry should be explored as a method for early identification of patients at risk of muscle loss and weakness during ICU admission Future studies should also investigate biological factors in specific groups of critically ill patients, alongside imaging and functional assessments, to improve the understanding of muscle loss. This could also support the development of interventions for preconditioning muscles and restoring muscle mass.

In conclusion, this study demonstrated that patients discharged from ICU in this resource-constrained setting presented with peripheral and respiratory muscle weakness at unit discharge. Muscle weakness occurred despite a short ICU stay and duration of mechanical ventilation, relatively low APACHE II scores, and younger patient age. The large variation in structural changes observed in both peripheral and respiratory muscles over the first 3 days of unit admission needs further scrutiny. While both peripheral and respiratory muscle strength was associated with functional capacity, the strength of the association indicates that other factors than muscle strength may be associated with functional impairments. Moving forward it is important to investigate whether these outcomes suggest a different phenotype of critical illness in resource-constrained environments.

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All authors were involved in designing the analysis, collecting and/or checking the data, performing the analysis, and writing the article.

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