Intensive Care Unit Acquired Weakness in Patients With COVID-19: Occurrence and Associated Factors

ICU Acquired Weakness in Patients With COVID-19

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KEYWORDS: COVID-19; Critical Illness; Muscle Weakness; Risk Factors

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Abstract

Objective. The primary objective of this study was to identify the occurrence and factors associated with intensive care unit (ICU)–acquired weakness (ICUAW) in patients with COVID-19. Secondarily, we monitored the evolution of muscle strength and mobility among patients with ICUAW and patients without ICUAW and the association of these variables with length of stay, mechanical ventilation (MV), and other clinical variables.

Methods. In this prospective observational study, patients admitted to the ICU for >72 h with COVID-19 were evaluated for muscle strength and mobility at 3 times: when being weaned from ventilatory support, discharged from the ICU, and discharged from the hospital. Risk factors for ICUAW were monitored.

Results. The occurrences of ICUAW at the 3 times evaluated among the 75 patients included were 52%, 38%, and 13%. The length of the ICU stay (29.5 [16.3–42.5] versus 11 [6.5–16] days; $P \leq .001$), the length of the hospital stay (43.5 [22.8–55.3] versus 16 [12.5–24] days; $P \leq .001$) and time on MV (25.5 [13.8–41.3] versus 10 [5–22.5] days; $P \leq .001$) were greater in patients with ICUAW. Muscle strength and mobility were lower at all times assessed in patients with ICUAW ($P < .05$). Bed rest time for all patients (relative risk = 1.14; 95% CI = 1.02–1.28; $P = .03$ per week) and use of corticosteroids (relative risk = 1.01; 95% CI = 1.00–1.03; $P = .01$ per day) for those who required MV were factors independently associated with ICUAW. Muscle strength was found to have a positive correlation with mobility and a negative correlation with lengths of stay in the ICU and hospital and time on MV.

Conclusions. The occurrence of ICUAW was high upon patients' awakening in the ICU but decreases throughout hospitalization; however, strength and mobility remained compromised at hospital discharge. Bed rest time and use of corticosteroids (for those

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who needed MV) were factors independently associated with ICUAW in patients with COVID-19.

Impact. Patients who had COVID-19 and developed ICUAW had longer periods of ICU stay, hospital stay, and MV. Bed rest time and use of corticosteroids (for those who required MV) were factors independently associated with ICUAW.

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Introduction

Patients with severe COVID-19 cases may develop hypoxemic respiratory failure and acute respiratory distress syndrome, leading to the need for hospitalization in intensive care units (ICUs).[1,2] These patients may need organ support, particularly advanced ventilatory support and consequently need deep sedation and neuromuscular blocking agents,[3-5] some of which are known risks for the development of ICU-acquired weakness (ICUAW) in patients who are critically ill.[6]

ICUAW is a common complication of critical illness, with an incidence of around 43%, varying according to the population studied, risk factors, timing and methods used for diagnosis.[7,8] It is associated with an increase in mortality, a need for prolonged mechanical ventilation (MV), and a longer hospital stay.[9,10] A recent study including 12 patients with severe acute respiratory distress syndrome caused by SARS-CoV-2 and with muscle weakness and difficulty being weaned from MV showed that 11 patients had alterations in the neurophysiological study, 63.6% were compatible with critical myopathy, and 36.4% were compatible with neuropathy.[11] In another study with 50 patients who had COVID-19 and required invasive MV (IMV), 72% had ICUAW when awakening, 52% had ICUAW on discharge from the ICU, and 27% had ICUAW on discharge from the hospital.[12]

Considering the importance of understanding the aspects involved in the development of ICUAW in patients with COVID-19, the primary objective of the present study was to identify the occurrence and factors associated with the development of ICUAW in patients hospitalized because of COVID-19. To accomplish this aim, we specifically examined the association between the development of ICUAW and the level of mobility, time on MV, length of hospital stay, length of ICU stay, rate of readmission

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to the ICU, and other clinical variables. We also monitored and compared the evolution of muscle strength and mobility during hospitalization among patients who developed ICUAW and those who did not.

[H1]Methods

[H2]Study Design and Patients

This was a prospective observational study carried out in a COVID-19-specific ICU, from May to August 2020 and approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (CAAE: 31080820.0.0000.5327).

Patients who were older than 18 years of age, had confirmed SARS-CoV-2 infection (through a real-time reverse transcription-polymerase chain reaction), and required ICU admission for at least 72 hours were included in the study. Patients who had muscle weakness secondary to neurological or musculoskeletal disease prior to admission were excluded (information was obtained by reviewing the patients' medical records and interviewing their guardians at the time of obtaining authorization for inclusion in the study), as were those who were unable to communicate and follow the examiner's commands for the proposed assessments. Furthermore, patients who could not complete all of the proposed assessments were excluded from the comparison analysis over time. All patients included had their participation authorized by their guardians through an informed consent form, and patient consent was obtained at the moment of assessment (when the patient was awake).

[H2]Assessment and Outcomes

The patients were monitored daily by the researchers for clinical evolution and awakening. For assessments, the patient had to be calm, awake, and able to obey at least

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3 of the De Jonghe 5 command criteria (open and close your eyes; look at me; open your mouth and stick your tongue out; shake your head “yes”; raise your eyebrows when I count to 5).[13] The assessments were carried out by 4 physical therapists and researchers who had experience in the care of patients admitted to the ICU and who were previously trained to administer the assessment instruments. The assessments were carried out 3 times during the hospital stay.

Assessment 1 (weaning from ventilatory support) was performed when the patient was awake and being weaned from ventilatory support (patients with intubation: assessed under extubation conditions; patients with tracheostomy: assessed when they started periods of spontaneous ventilation; patients on noninvasive ventilation: assessed when they could tolerate reductions in pressure and oxygen concentration for at least 24 hours without the need to increase these parameters; patients with a high-flow nasal cannula: assessed when they tolerated reductions in the flow and oxygen concentration parameters, without the need to increase these parameters for at least 24 hours).

Assessment 2 (ICU discharge) was performed up to 24 hours before ICU discharge.

Assessment 3 (hospital discharge) was performed up to 24 hours before hospital discharge.

The following outcomes were assessed in the 3 periods described above.

Peripheral muscle strength was assessed with the Medical Research Council (MRC) score. This score, with a maximum of 60 points, assesses 12 muscle groups in the upper and lower extremities. Patients with a score of <48 were considered to have ICUAW.[13]

For handgrip strength of the dominant hand, 3 evaluations were performed using a handheld hydraulic dynamometer (SH5001 Hand Dynamometer; Saehan Corp, Masan,

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Korea) with the elbow positioned at 90 degrees, The best result was considered for analysis and compared with the values predicted for the Brazilian population.[14]

Mobility was assessed with the Perme Intensive Care Unit Mobility Score (Perme Score), which includes an assessment of mental status, potential barriers to mobility, functional strength, mobility in bed, transfers, assistive devices for walking, and resistance measures. The final score varies between 0 and 32 points, with a low score indicating more mobility barriers and greater need for assistance for mobilization.[15]

The level of mobility was assessed with the ICU Mobility Scale, which consists of 11 mobility stages scored from 0 to 10, where 0 = lying in bed and 10 = independent walking without the aid of a walking device.[15]

The following variables were also assessed: lengths of hospital stay and ICU stay; need for ventilatory support and time on MV; rate of readmission to the ICU; rates of weaning failure (intolerance in the spontaneous breathing test) and extubation failure (need for restitution of the artificial airway within 48 hours after extubation); and mortality in the ICU and hospital. Demographic data, preexisting comorbidities, Simplified Acute Physiology Score III measured at ICU admission, and treatments and complications during the ICU stay were collected from the patients' electronic medical records. The monitored treatments were need for and duration of use of sedation, neuromuscular blocking agents (NMBA), antibiotics, corticosteroids, vasopressors, insulin, renal replacement therapy, occurrence and time of hyperglycemia (glycemia level of >180 mg/dL), need for a prone position, use of extracorporeal membrane oxygenation, bed rest time (defined as the time until leaving the bed for the first time), need for deep sedation (score of −4 or −5 on the Richmond Agitation-Sedation Scale), and number of physical therapy sessions.

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[H2]Data Analysis

The sample size was calculated using the sampling book version 1.2.2 of the *R* program, after a pilot study with 25 patients was performed in the weeks prior to the study, finding 24% of occurrence of ICUAW. Considering a 95% confidence level, a 10% margin of error and an occurrence of ICUAW (at ICU discharge) of 24%, the sample size was 71 patients.

Data normality was assessed using the Kolmogorov-Smirnov test. Data were expressed as the mean and SD or the median and interquartile range for continuous variables and as the absolute number and percentage for categorical variables. For data analysis, patients were classified into 2 subgroups according to the MRC score at discharge from the ICU: patients with ICUAW (scores of <48) and patients without ICUAW (scores of ≥48).

To compare the subgroups (patients with ICUAW and patients without ICUAW), we used the Student *t* test (for independent samples) for independent groups for parametric variables, the Mann-Whitney *U* test for independent samples for nonparametric variables, and the Pearson chi-square test for categorical variables.

We used the Poisson regression model, initially performing univariable regression including variables that were investigated in previous studies as risk factors for ICUAW[6,8,9]. From that, factors that had *P* values of <.05 were added to a multivariable regression model. The relative risk and 95% CI were presented together with the *P* value. The Friedman test was used to compare variables (muscle strength and mobility) over time (assessments 1, 2, and 3). Correlations were assessed using the Spearman test; correlation coefficients between 0.9 and 1 were considered very strong, those from 0.7 to 0.89 were considered strong, and those from 0.5 to 0.69 were considered moderate.[16] For

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data analysis, the software Statistical Package for the Social Sciences, version 20.0 (IBM SPSS, Chicago, IL, USA), was used, and a *P* value of <.05 was considered significant.

[H2]Role of the Funding Source

The funders played no role in the design, conduct, or reporting of this study.

[H1]Results

One hundred fifty-six patients were assessed throughout the study period, and of these, 75 were included according to the flowchart shown in Figure 1. Most patients were men, with a mean age of 53 (SD = 13) years and more than 2 preexisting comorbidities, the most prevalent being obesity, systemic hypertension, and diabetes mellitus (Tab. 1).

[H2]Occurrence of ICUAW

The occurrence of ICUAW in the first assessment (when patients were awakened in the ICU for weaning from ventilatory support) was 52%, decreasing to 38% on discharge from the ICU and to 13% on hospital discharge. The lengths of stay in the ICU and the hospital, the rates of use of IMV, the time on MV, the time to first leaving bed rest, and the number of physical therapy sessions were higher in patients with ICUAW (Tab. 2). In addition, patients with ICUAW used sedatives, NMBA, antibiotics, corticosteroids, and vasopressors for longer periods; received more renal replacement therapy; were more often in a prone position; remained in deep sedation (Richmond Agitation-Sedation Scale score of −4 or −5) for more days; and had more complications while in the ICU (Tab. 3). As for muscle strength and mobility, patients with ICUAW showed lower results at all times assessed than patients without ICUAW (*P* < .05).

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[H2]Risk Factors for ICUAW

Univariable regression analysis found the following factors associated with the development of ICUAW: higher Simplified Acute Physiology Score III; sepsis; need for insulin, aminoglycosides and renal replacement therapy; and duration (in days) of IMV, sedation, NMBA, corticosteroids, vasopressors, hyperglycemia, deep sedation, and bed rest. Each week of use of IMV, sedation, NMBA, deep sedation, and bed rest increased the risk of ICUAW by 24.0%, 35.0%, 30.0%, 34.0%, and 34.0%, respectively (Tab. 4).

In a multivariable regression analysis, the development of ICUAW was used as a dependent variable, and the independent variables were those that were significant in the univariate analysis but were not found to have a very strong correlation among them and that had been reported in previous studies as risk factors for ICUAW [6,8,9] (Simplified Acute Physiology Score III, sepsis, use of aminoglycosides, renal replacement therapy, hyperglycemia, and bed rest time). Bed rest time was the only factor independently associated with ICUAW (relative risk = 1.14; 95% CI = 1.02–1.28; *P* = .03 for each immobile week).

Considering only the patients who were under IMV, the occurrence of ICUAW at ICU discharge was 46.0%, and the following factors were shown to be independently associated: days on bed rest (relative risk = 1.02; 95% CI = 1.00–1.03; *P* = .01 for each week on rest) and days on corticosteroids (relative risk = 1.01; 95% CI = 1.00–1.03; *P* = .01).

[H2]Muscle Strength, Mobility, and ICUAW

As for the evolution throughout hospitalization, patients with ICUAW were found to have an increase in muscle strength according to the MRC score (Fig. 2a) and handgrip test (Fig. 2b) at all assessed times. In patients without ICUAW, there was an increase in

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muscle strength only from assessment 1 to assessment 2 according to both the MRC score and the handgrip test ($P < .05$). Patients reached, on average, 31.0% of the predicted value for handgrip strength in the dominant hand upon awakening, 41.0% at ICU discharge, and 53.0% at hospital discharge.

Regarding mobility, both groups showed an increase in the Perme Score (Fig. 2c) at all assessments ($P < .05$), suggesting progressively higher levels of mobility. According to the ICU Mobility Scale (Fig. 2d), both groups had an increase in mobility levels from assessment 1 to assessment 2 ($P < .05$); however, from assessment 2 to assessment 3, this increase was observed only in the patients without ICUAW ($P \leq .001$). At hospital discharge, 67.0% of patients without ICUAW walked independently, versus 30.0% of patients with ICUAW.

Finally, muscle strength assessed with the MRC score at ICU discharge showed a strong positive correlation with the Perme Score (0.716; $P \leq .001$), a moderate correlation with the level of mobility on the ICU Mobility Scale (0.689; $P \leq .001$), and a moderate negative correlation with the lengths of stay in the ICU and the hospital and the time on IMV (−0.674, −0.650, and −0.637, respectively; $P \leq .001$).

[H1]Discussion

ICUAW is a frequent complication in patients who are critically ill with COVID-19 and are admitted to the ICU. Patients with ICUAW had longer ICU stays, hospital stays, and time on MV, received more physical therapy sessions, and had lower levels of strength and mobility upon awakening, at ICU discharge, and at hospital discharge. Several clinical variables to which patients who were critically ill were exposed were associated with ICUAW, but time on bed rest for all patients and the time of use of

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corticosteroids for those who needed IMV were factors independently associated with ICUAW.

This study showed that the occurrence of ICUAW was 52.0% when patients were awakened for weaning, decreasing throughout hospitalization, 38.0% at ICU discharge and 13.0% at hospital discharge. A recent study investigated the incidence of ICUAW among patients who had COVID-19 and required MV and found rates of 72.0%, 52.0%, and 27.0% upon awakening, ICU discharge, and hospital discharge, respectively[12]; these rates are considerably higher than the values found in the present study. This difference could be explained by the fact that the present study also included patients who used noninvasive ventilation and a high-flow nasal cannula; however, when analyzing only the patients who needed IMV, the occurrences were 52.0% upon awakening, 46.0% at ICU discharge, and 15.0% at hospital discharge. The age of the patients had been reported as a predictor for ICUAW [17] and may explain this difference, since the study by Van Aerde et al assessed patients who were older than those included in the present study.[12] Corroborating previous studies with patients who are critically ill with COVID-19, [2,18] we observed a high rate of previous comorbidities.

Patients with ICUAW had longer ICU and hospital stays, with a duration similar to that observed in the study by Van Aerde et al (30 [19–42] days), [12] who also did not observe differences in ICU readmission and mortality rates between groups. The longer hospital stays can be explained by the longer duration of ventilatory support, the greater number of weaning failures and the need for a tracheostomy. The duration of MV was a factor associated with ICUAW, and this may be a reciprocal relationship, since prolonged MV increases the risk of ICUAW and diaphragmatic dysfunction, which, in turn, increases the risk of prolonged MV. [8] An analysis of 7 studies revealed longer time on

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MV in patients with ICUAW with a median of 25 days (12–33 days),[7] a value similar to that observed in the present study.

Several independent risk factors for the development of ICUAW have been identified and described in the literature, but there are still no studies assessing these factors in patients with COVID-19. The severity of the critical illness and the occurrence of sepsis were considered predictive for ICUAW in previous studies[6]; these data were reinforced by the findings of our study. Hyperglycemia was also a factor associated with ICUAW in the studied population, as already evidenced in studies with clinical and surgical patients admitted to the ICU.[6]

Some drugs used to treat patients who are critically ill are associated with ICUAW. In the present study, time on vasopressors, corticosteroids, antibiotics, NMBA, and sedatives was associated with ICUAW. The use of vasoactive drugs and aminoglycosides and the length of time on antibiotics has been reported as a factor associated with ICUAW.[19-22] As for corticosteroids, a systematic review suggested an association with ICUAW, recommending that exposure to this drug should be reduced.[23] In the treatment of patients who are critically ill with COVID-19, the use of dexamethasone was recommended, as it results in lower mortality in patients who needed oxygen or MV[24] and was, therefore, a treatment used in most patients in the present study. Time on corticosteroids was an independent factor associated with ICUAW in patients who needed IMV.

The occurrence of hypoxemic respiratory failure and acute respiratory distress syndrome leads to the need for deep sedation and prolonged use of neuromuscular blocking agents.[1-5] The association between ICUAW and NMBA, found in the present study, had already been reported by Yang et al in studies in the general population (overall risk = 2.03; 95% CI = 1.22–3.4; I^2 = 72.9%).[6] The use of NMBA associated with deep

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sedation also tended to increase the risk of ICUAW compared to lighter sedation targets.[25] It is difficult to isolate the direct effects of drugs from the harmful impact of bed rest and inactivity caused by sedation. These associated factors induce severe muscle inactivity with consequent atrophy due to disuse and impaired physical mobility.[26] The need for longer periods of bed rest in patients with COVID-19 has been evidenced by McWillians et al, who reported an average time of 14 days until first mobilization.[18] In the present study, bed rest was a factor independently associated with ICUAW, reinforcing what was evidenced previously in patients who were critically ill.[27]

Patients with ICUAW had significant improvement in muscle strength during hospitalization. All patients underwent an intensive rehabilitation program, based on early mobilization and walking, as soon as they showed enough clinical stability for this. The feasibility and effectiveness of rehabilitation measures for patients who were critically ill with COVID-19 during hospitalization were previously reported by McWillianns et al.[18]

Mobility in patients with ICUAW, assessed with the Perme Score, was lower at all assessed times, showing the negative impact of ICUAW on the mobility of patients who were critically ill. In the ICU Mobility Scale assessment, however, there was no statistically significant difference between the times of ICU discharge and hospital discharge in patients with ICUAW; still, when the clinical relevance of this finding is analyzed, it becomes significant, since patients could walk from the bed to a chair at ICU discharge and could walk (for at least 5 m) with the help of 1 person at hospital discharge.

[H2]Limitations

This study had some limitations. Since this was an exploratory cohort study, it was not possible to determine causality, only the association between factor and outcome.

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Another limitation was the sample size, which did not allow us to address and control all potential confounding factors. The present study, however, may serve as a precursor to larger studies to further investigate risk factors for ICUAW in patients with COVID-19, as the literature on this research question is still scarce.

Because of the need to transfer patients to lower complexity hospitals, not all patients (18.7%) could be assessed at hospital discharge. Some factors that have been pointed out in the literature as being risk factors for ICUAW could not be assessed in the present study, such as lactate levels, doses of medications, and some inflammatory markers. The impact of rehabilitation on the evolution of strength and mobility could not be explored further. We point out the need for studies that assess the impact of ICUAW in the medium and long terms on levels of mobility and functionality in patients with COVID-19.

[H1]Conclusions

A high occurrence of ICUAW was observed in patients with COVID-19 upon awakening in the ICU, with a reduction during the hospital stay. Patients with ICUAW had longer stays in the ICU and hospital used more invasive ventilatory support for longer periods, and also had difficulty being weaned from MV. These patients had lower levels of muscle strength and mobility at hospital discharge. Finally, bed rest time for all patients and the time of use of corticosteroids for those who needed IMV were factors independently associated with ICUAW in patients who were critically ill with COVID-19.

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Author Contributions

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Ethics Approval

This study was approved by the Research Ethics Committee of the Hospital de Clínicas de Porto Alegre (CAAE: 31080820.0.0000.5327).

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Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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References:

1. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet.* 2020; 395: 1054-1062. https://doi.org/10.1016/S0140-6736(20)30566-3.
2. Xu J, Yang X, Yang L et al. Clinical course and predictors of 60-day mortality in 239 critically ill patients with COVID-19: a multicenter retrospective study from Wuhan, China. *Crit Care.* 2020; 24: 394. https://doi.org/10.1186/s13054-020-03098-9
3. Grasselli G, Pesenti A, Cecconi M. Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast During an Emergency Response. *JAMA.* 2020; 323: 1545-1546. https://doi.org/10.1001/jama.2020.4031
4. Yang X, Yu Y, Xu J et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med.* 2020; 8: 475-481. https://doi.org/10.1016/S2213-2600(20)30079-5
5. Kapp CM, Zaeh S, Niedermeyer S et al. The Use of Analgesia and Sedation in Mechanically Ventilated Patients With COVID-19 Acute Respiratory Distress Syndrome. *Anesth Analg.* 2020; 131: 198-200 https://doi.org/10.1213/ANE.0000000000005131
6. Yang T, Li Z, Jiang L et al. Risk factors for intensive care unit-acquired weakness: A systematic review and meta-analysis. *Acta Neurol Scand.* 2018; 138: 104-114. https://doi.org/10.1111/ane.12964.
7. Fan E, Cheek F, Chlan L et al. An official American Thoracic Society Clinical Practice guideline: the diagnosis of intensive care unit-acquired weakness in

UNCORRECTED MANUSCRIPT

adults. *Am J Respir Crit Care Med.* 2014; 190: 1437-46. https://doi.org/10.1164/rccm.201411-2011ST

8. Vanhorebeek I, Latronico N, Van den Berghe G. ICU-acquired weakness. *Intensive Care Med.* 2020; 46:637-653. https://doi.org/ 10.1007/s00134-020-05944-4.
9. Stevens RD, Dowdy DW, Michaels RK et al. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med.* 2007; 33:1876-9. https://doi.org/ 10.1007/s00134-007-0772-2.
10. Wieske L, Dettling-Ihnenfeldt DS, Verhamme C et al. Impact of ICU-acquired weakness on post-ICU physical functioning: a follow-up study. *Crit Care*. 2015; 19:196. https://doi.org/10.1186/s13054-015-0937-2
11. Cabanes-Martinez L, Villadóniga M, González-Rodríguez L et al. Neuromuscular involvement in COVID-19 critically ill patients. *Clin Neurophysiol.* 2020; 131:2809-2816. https://doi.org/ 10.1016/j.clinph.2020.09.017
12. Van Aerde N, Van den Berghe G, Wilmer A et al. Intensive care unit acquired muscle weakness in COVID-19 patients. *Intensive Care Med.* 2020; 46:2083-2085. https://doi.org/ 10.1007/s00134-020-06244-7
13. De Jonghe B, Sharshar T, Lefaucheur J et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA.* 2002; 288:2859-67. https://doi.org/10.1001/jama.288.22.2859
14. Novaes RD, Miranda AS, Silva JO et al. Reference equations for predicting of handgrip strength in Brazilian middle-aged and elderly subjects. *Fisioterapia e Pesquisa.* 2009; 16:217-22. https://doi.org/10.1590/S1809-29502009000300005
15. Kawaguchi YM, Nawa RK, Figueiredo TB et al. Perme Intensive Care Unit Mobility Score and ICU Mobility Scale: translation into Portuguese and cross-

UNCORRECTED MANUSCRIPT

cultural adaptation for use in Brazil. *J Bras Pneumol.* 2016; 42: 429-434. https://doi.org/10.1590/S1806-37562015000000301

16. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. *Malawi Med J*. 2012; 24: 69-71.
17. Wieske L, Witteveen E, Verhamme C et al. Early prediction of intensive care unit-acquired weakness using easily available parameters: a prospective observational study. *PLoS One.* 2014; 9:e111259. https://doi.org/10.1371/journal.pone.0111259
18. McWilliams D, Weblin J, Hodson J et al. Rehabilitation Levels in Patients with COVID-19 Admitted to Intensive Care Requiring Invasive Ventilation. An Observational Study. *Ann Am Thorac Soc*. 2021; 18:122-129. https://doi.org/10.1513/AnnalsATS.202005-560OC
19. Wolfe KS, Patel BK, MacKenzie EL et al. Impact of Vasoactive Medications on ICU-Acquired Weakness in Mechanically Ventilated Patients. *Chest.* 2018; 154:781-787. https://doi.org/10.1016/j.chest.2018.07.016
20. Nanas S, Kritikos K, Angelopoulos E et al. Predisposing factors for critical illness polyneuromyopathy in a multidisciplinary intensive care unit. *Acta Neurol Scand*. 2008; 118:175-81. https://doi.org/10.1111/j.1600-0404.2008.00996.x
21. Wieske L, van Hest RM, Witteveen E et al. Is gentamicin affecting the neuromuscular system of critically ill patients? *Intensive Care Med.* 2015; 41:727-8. https://doi.org/10.1007/s00134-015-3731-3
22. Yang T, Li ZQ, Li HL et al. Aminoglycoside use and intensive care unit-acquired weakness: A systematic review and meta-analysis. *PLoS One.* 2020; 15:e0230181. https://doi.org/10.1371/journal.pone.0230181

UNCORRECTED MANUSCRIPT

23. Yang T, Li Z, Jiang L et al. Corticosteroid use and intensive care unit-acquired weakness: a systematic review and meta-analysis. *Crit Care*. 2018; 22:187. https://doi.org/10.1186/s13054-018-2111-0

24. Horby P, Lim WS, Emberson JR et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021; 384:693-704. https://doi.org/10.1056/NEJMoa2021436

25. Moss M, Ulysse CA, Angus DC et al. Early Neuromuscular Blockade in the Acute Respiratory Distress Syndrome. Reply. *N Engl J Med.* 2019; 381:787-788. https://doi.org/10.1056/NEJMc1908874

26. Foster J. Complications of sedation and critical illness. *Crit Care Nurs Clin North Am.* 2005; 17: 287-96. https://doi.org/10.1016/j.ccell.2005.04.012

27. Fan E, Dowdy DW, Colantuoni E et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med*. 2014; 42:849-59. https://doi.org/10.1097/CCM.0000000000000040

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Table 1. Patient Baseline Characteristics[a]

Characteristic	Overall(N = 75)	With ICUAW(n = 28)	Without ICUAW(n = 47)	*P*[b]
Age, y, mean (SD)	52.6 (12.6)	54.5 (13.4)	51.4 (12.1)	.32
Men, no. (%)	43 (57.3)	16 (57.1)	27 (57.4)	.98
White, no. (%)	60 (80.0)	23 (82.1)	37 (78.7)	.54
BMI, kg/m^2, mean (SD)	32.3 (6.8)	32.9 (7.2)	31.9 (6.7)	.57
SAPS III, mean (SD)	56.8 (14.0)	63.4 (17.1)	52.8 (10.1)	.005
Preexisting comorbidities, no. (%) of patients				
Obesity, BMI ≥ 30 kg/m^2	39 (52.0)	16 (57.1)	23 (48.9)	.49
Hypertension	35 (46.7)	14 (50.0)	21 (44.7)	.66
Diabetes mellitus	29 (38.7)	11 (39.3)	18 (38.3)	.93
Asthma	8 (10.7)	2 (7.1)	6 (12.8)	.44
Heart disease	5 (6.7)	1 (3.6)	4 (8.5)	.41
Chronic kidney disease	5 (6.7)	2 (7.1)	3 (6.4)	.89
COPD	3 (4.0)	2 (7.1)	1 (2.1)	.28
No. of comorbidities				
Median (IQR)	2 (1–3)	2 (2–3)	2 (1–3)	.33
No. (%) of patients				
0	9 (12.0)	1 (3.6)	8 (17.0)	
1	14 (18.7)	5 (17.9)	9 (19.1)	
2 or 3	35 (46.7)	16 (57.1)	19 (40.4)	

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>3	17 (22.7)	6 (21.4)	11 (23.4)	
Smoking, no. (%) of patients	13 (17.3)	7 (25.0)	6 (12.8)	.18
Alcohol abuse, no. (%) of patients	5 (6.7)	3 (10.7)	2 (4.3)	.28

[a]To compare the subgroups (with intensive care unit [ICU]–acquired weakness [ICUAW] and without ICUAW), we used the Student *t* test (for independent groups) for parametric variables, the Mann-Whitney *U* test for independent samples and nonparametric variables, and the Pearson χ^2 test for categorical variables. BMI = body mass index; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; SAPS III = Simplified Acute Physiology Score III.

[b]For comparison of with ICUAW versus without ICUAW.

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Table 2. Outcomes, Ventilatory Support, and Physical Therapy Rehabilitation[a]

Parameter	Overall (N= 75)	With ICUAW (n = 28)	Without ICUAW (n = 47)	*P*[b]
Outcome				
ICU admission, d, median (IQR)	14 (8.5–30)	29.5 (16.3–42.5)	11 (6.5–16)	≤.001
Hospital admission, d, median (IQR)	21 (14–36.5)	43.5 (22.8–55.3)	16 (12.5–24)	≤.001
ICU mortality, no. (%) of patients	1 (1.3)	0 (0)	1 (2.1)	.32
Hospital mortality, no. (%) of patients	2 (2.7)	1 (3.6)	1 (2.1)	.36
ICU readmission, no. (%) of patients	4 (5.3)	3 (10.7)	1 (2.1)	.11
Ventilatory support[c]				
NIV only	3 (4.0)	0 (0)	3 (6.4)	
HFNC only	6 (8.0)	0 (0)	6 (12.8)	
NIV + HFNC	4 (5.3)	0 (0)	4 (8.5)	
IMV	62 (82.7)	28 (100)	34 (72.3)	.01
NIV postextubation	25 (33.3)	15 (53.6)	10 (21.3)	
Time on IMV, median (IQR)	8 (5–14.25)	25.5 (13.8–41.3)	10 (5–22.5)	≤.001
Weaning failure	16 (21.3)	12 (42.9)	4 (8.5)	≤.001
Extubation failure	12 (16.0)	5 (17.9)	7 (14.9)	.73

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Need for tracheostomy	11 (14.7)	9 (32.1)	2 (4.3)	≤.001
Physical therapy sessions, median (IQR)				
In the ICU	34 (22–63.5)	63.5 (39.5–96.8)	26 (17.5–38.5)	≤.001
In a hospital inpatient non-ICU unit	5 (2–10)	10 (5–15.5)	4 (2–7)	≤.001
Total	41 (24.5–72.5)	77 (45.5–105)	29 (22.5–45)	≤.001

[a]The Mann-Whitney *U* test for independent samples was used to compare nonparametric variables; the Pearson χ^2 test was used to compare categorical variables. HFNC = high-flow nasal cannula; ICU = intensive care unit; ICUAW = ICU-acquired weakness; IMV = invasive mechanical ventilation; IQR = interquartile range; NIV = noninvasive ventilation.

[b]For comparison of with ICUAW versus without ICUAW.

[c]Number (percentage) of patients unless otherwise indicated.

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Table 3. Treatments and Complications During Intensive Care Unit (ICU) Admission[a]

Treatment or Complication	Overall (N = 75)	With ICUAW (n = 28)	Without ICUAW (n = 47)	*P*[b]
Sedation	62 (82.7)	28 (100)	34 (72.3)	.01
Days under sedation, median (IQR)	12 (8–24)	19 (11–28.8)	9 (5.8–14)	≤.001
NMBA	55 (73.3)	28 (100)	27 (57.4)	≤.001
Days on NMBA, median (IQR)	6 (2–13.5)	8.5 (4–15.8)	3 (2–6)	.01
Antibiotics	75 (100)	28 (100)	47 (100)	1
Days on antibiotics, median (IQR)	12 (7–19.5)	20.5 (14.3–30)	8 (6–12)	≤.001
Aminoglycosides	9 (12.0)	9 (32.1)	0 (0)	≤.001
Days on aminoglycosides, median (IQR)	6 (3–8)	6 (3–8)	0 (0–0)	
Corticosteroids	67 (89.3)	25 (89.3)	42 (89.4)	.99
Days on corticosteroids, median (IQR)	10 (8–13)	11 (10–18.5)	10 (7–10.3)	.02
Vasopressors	55 (73.3)	24 (85.7)	31 (66.0)	.06
Days on vasopressors, median (IQR)	5 (311.3)	7.5 (4.3–18.5)	4 (2–6)	.01
RRT	19 (25.3)	13 (46.4)	6 (12.8)	≤.001
Days on RRT, median (IQR)	12 (9–18)	15 (10–19.5)	9 (4–13)	.06

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Hyperglycemia	48 (64.0)	22 (78.6)	26 (55.3)	.04
Days of hyperglycemia, median (IQR)	12 (7–20)	16 (9.5 – 22)	10.5 (5.2–14.7)	.01
Use of insulin	39 (52.0)	19 (67.9)	20 (42.6)	.08
Prone position	27 (36.0)	16 (57.1)	11 (23.4)	.01
ECMO	2 (2.7)	2 (7.1)	0 (0)	.06
Days of RASS score of −4 or −5, median (IQR)	10 (5.5–19)	15.5 (9.7–25.7)	6.5 (4–10.3)	≤.001
Days until leaving the room, median (IQR)	12 (5 – 22.5)	22.5 (14 – 31)	8 (4– 12)	≤.001
Sepsis	47 (62.7)	24 (85.7)	23 (48.9)	≤.001
Focused respiratory sepsis, no. (%) of patients with sepsis	36 (76.6)	16 (66.7)	20 (87.0)	
Severe ARDS	35 (46.7)	20 (71.4)	15 (31.9)	.01
VAP	41 (54.7)	24 (85.7)	17 (36.2)	≤.001
Acute renal failure	26 (34.7)	16 (57.1)	10 (21.3)	.01
Pulmonary embolism	9 (12.0)	5 (17.9)	4 (8.5)	.23
Deep-vein thrombosis	6 (8.0)	3 (10.7)	3 (6.4)	.50
Pressure sores	25 (33.3)	18 (64.3)	7 (14.9)	≤.001
Pneumothorax	7 (9.3)	5 (17.9)	2 (4.3)	.05

[a]Data are reported as number (percentage) of patients unless otherwise indicated. The Mann-Whitney *U* test for independent samples was used to compare nonparametric variables; the Pearson χ^2 test was used to compare categorical variables. ARDS = acute

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respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ICUAW = ICU-acquired weakness; IQR = interquartile range; NMBA = neuromuscular blocking agents; RASS = Richmond Agitation-Sedation Scale; RRT = renal replacement therapy; VAP = ventilator-associated pneumonia.

[b]For comparison of with ICUAW vs without ICUAW.

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Table 4. Poisson Regression Analysis (Univariable) of Risk Factors for the Development of ICUAW in Patients Admitted to the ICU With COVID-19[a]

Variable	RR	95% CI	*P*
SAPS III	1.03	1.01–1.04	≤.001
Sepsis	3.57	1.38–9.23	.01
Days of hyperglycemia	1.03	1.01–1.05	≤.001
Days on IMV	1.03	1.01–1.04	≤.001
Weeks on IMV	1.24	1.14–1.34	≤.001
Days on sedation	1.04	1.03–1.06	≤.001
Weeks on sedation	1.35	1.19–1.52	≤.001
Days on neuromuscular blocking agents	1.04	1.02–1.06	≤.001
Weeks on neuromuscular blocking agents	1.30	1.14–1.49	≤.001
Days on corticosteroids	1.04	1.02–1.06	≤.001
Days on vasopressors	1.05	1.02–1.09	≤.001
Use of insulin	2.07	1.05–4.10	.04
Days on antibiotics	1.06	1.03–1.08	≤.001
Use of aminoglycosides	3.47	2.37–5.07	≤.001
Renal replacement therapy	2.55	1.50–4.33	≤.001
Days on renal replacement therapy	1.04	1.00–1.08	.003
Days on deep sedation	1.04	1.02–1.06	≤.001
Weeks on deep sedation	1.34	1.17–1.53	≤.001
Days on bed rest	1.04	1.03–1.06	≤.001
Weeks on bed rest	1.34	1.22–1.47	≤.001

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[a]ICU = intensive care unit; ICUAW = ICU-acquired weakness; IMV = invasive mechanical ventilation; RR = relative risk; SAPS III = Simplified Acute Physiology Score III.

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Figure Captions

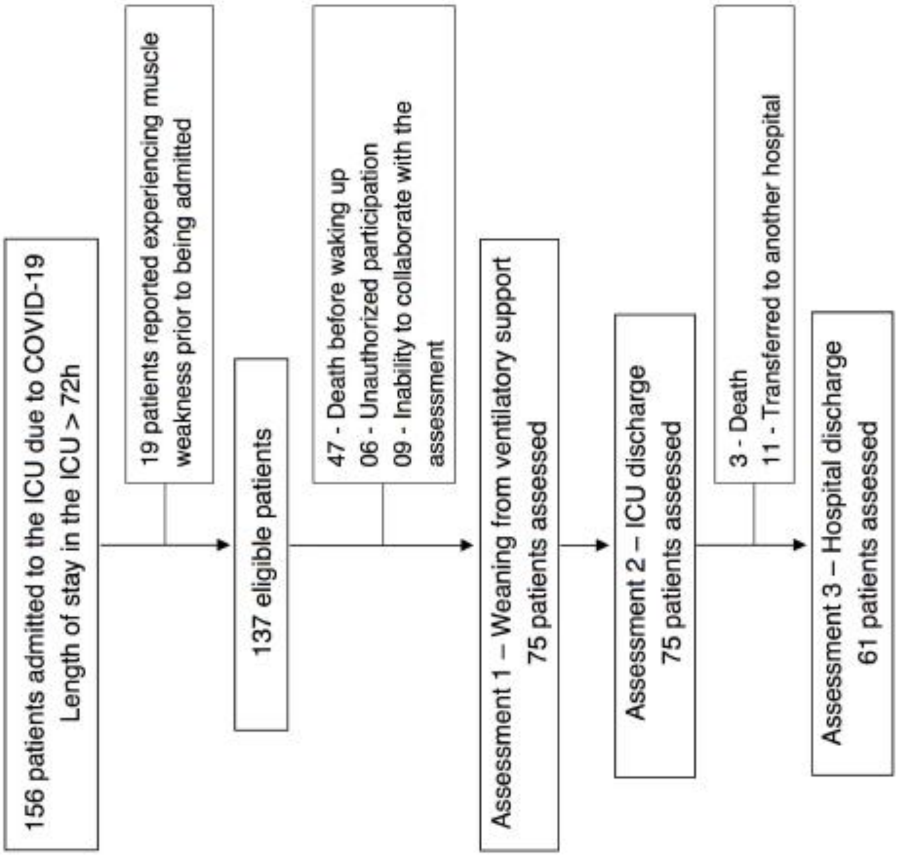

Figure 1. Flowchart of patients included in the study. ICU = intensive care unit.

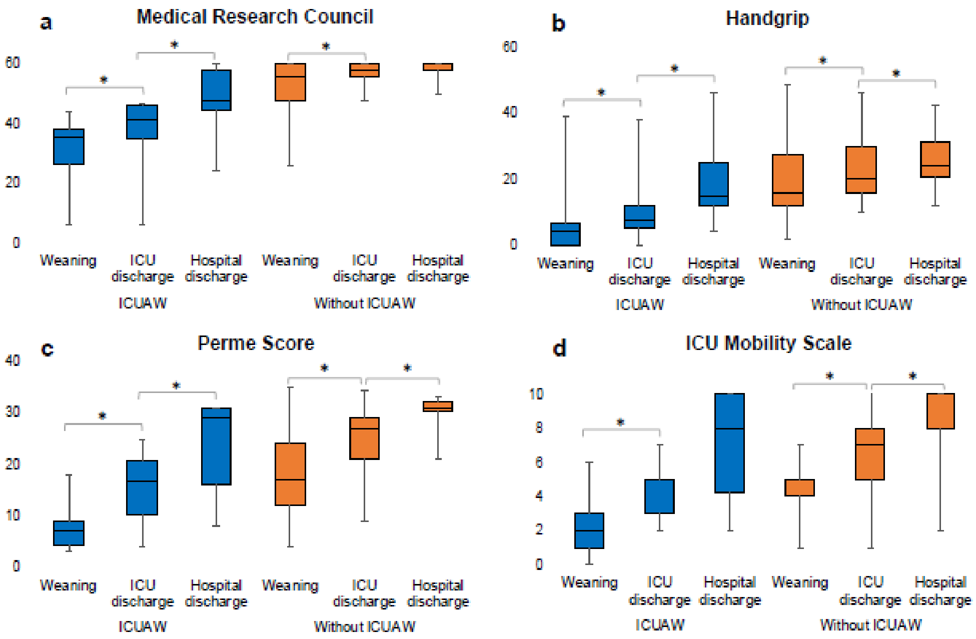

Figure 2. Evolution of muscle strength and mobility of patient subgroups when awake, discharged from the intensive care unit (ICU), and discharged from the hospital. The Friedman test was used to compare variables over time. ICUAW = ICU–acquired weakness. *$P < .05$.

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