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Original Research

Intensive Care Unit–Acquired Weakness in Patients With COVID-19: Occurrence and Associated 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 individuals with ICUAW and those 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, individuals admitted to the ICU for >72 hours 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 [IQR = 16.3–42.5] vs 11 [IQR = 6.5–16] days), the length of the hospital stay (43.5 [IQR = 22.8–55.3] vs 16 [IQR = 12.5–24] days), and time on MV (25.5 [IQR = 13.8–41.3] vs 10 [IQR = 5–22.5] days) were greater in patients with ICUAW. Muscle strength and mobility were lower at all times assessed in patients with ICUAW. Bed rest time for all patients (relative risk = 1.14; 95% CI = 1.02 to 1.28) and use of corticosteroids (relative risk = 1.01; 95% CI = 1.00 to 1.03) 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.

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

Keywords: COVID-19, Critical Illness, Muscle Weakness, Risk Factors

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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 (NMBA),[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 approximately 43%, varying according to the population studied, risk factors, timing, and methods used for diagnosis.[7,8] It is associated with increased mortality, a need for prolonged mechanical ventilation (MV), and a longer hospital stay.[9,10] A recent study including 12 participants 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 participants who had COVID-19 and required invasive MV (IMV), 72% had ICUAW on 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 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.

Methods

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).

Individuals who were older than 18 years, 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. Individuals who had muscle weakness secondary to neurological or musculoskeletal disease prior to admission were excluded (information was obtained by reviewing the individuals' 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, individuals who could not complete all the proposed assessments were excluded from the comparison analysis over time. Participation of all individuals included was authorized by their guardians through an informed consent form, and participant consent was obtained at the moment of assessment (when the individual was awake).

Assessment and Outcomes

The participants were monitored daily by the researchers for clinical evolution and awakening. For assessments, the participant had to be calm, awake, and able to obey at least 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 individuals 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 participant was awake and being weaned from ventilatory support (participants with intubation: assessed under extubation conditions; participants with tracheostomy: assessed when they started periods of spontaneous ventilation; participants 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; participants 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 <48 were considered to have ICUAW.[13]

For the evaluation of handgrip strength in the dominant hand, 3 evaluations were performed using a handheld hydraulic dynamometer (SH5001 Hand Dynamometer; Saehan Corp, Masan, 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, NMBA, antibiotics, corticosteroids, vasopressors, insulin, renal replacement therapy, occurrence and time of hyperglycemia (glycemia level >180 mg/dL), need for a prone position, use of extracorporeal membrane oxygenation, bed rest time (defined as the time in bed 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.

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 individuals was performed in the weeks prior to the study, finding 24% of occurrence of ICUAW. Considering a 95% CI, a 10% margin of error, and an occurrence of ICUAW (at ICU discharge) of 24%, the sample size was 71 participants.

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, participants were classified into 2 subgroups according to the MRC score at discharge from the ICU: those with ICUAW (scores <48) and those without ICUAW (scores ≥48).

To compare the subgroups (participants with ICUAW and those 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 with *P* values < .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 data analysis, the software Statistical Package for the Social Sciences, version 20.0 (IBM SPSS, Chicago, IL, USA), was used, and a *P* value < .05 was considered significant.

Role of the Funding Source

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

Results

A total 156 participants were assessed throughout the study period, and of these, 75 were included according to the flowchart shown in Figure 1. Most participants 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).

Occurrence of ICUAW

The occurrence of ICUAW in the first assessment (when participants 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 participants with ICUAW (Tab. 2). In addition, participants 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 ($P < .05$).

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 to 1.28; $P = .03$ for each immobile week).

Considering only the participants 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 to 1.03; $P = .01$ for each week on rest) and days on corticosteroids (relative risk = 1.01; 95% CI = 1.00 to 1.03; $P = .01$).

Muscle Strength, Mobility, and ICUAW

As for the evolution throughout hospitalization, participants with ICUAW were found to have increased muscle strength according to the MRC score (Fig. 2A) and handgrip test (Fig. 2B) at all assessed times. In participants without ICUAW, there was increased muscle strength only from assessment 1 to assessment 2 according to both the MRC score and the handgrip test ($P < .05$). Participants reached, on average, 31.0% of the predicted value for handgrip strength in the dominant hand on 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 increased mobility

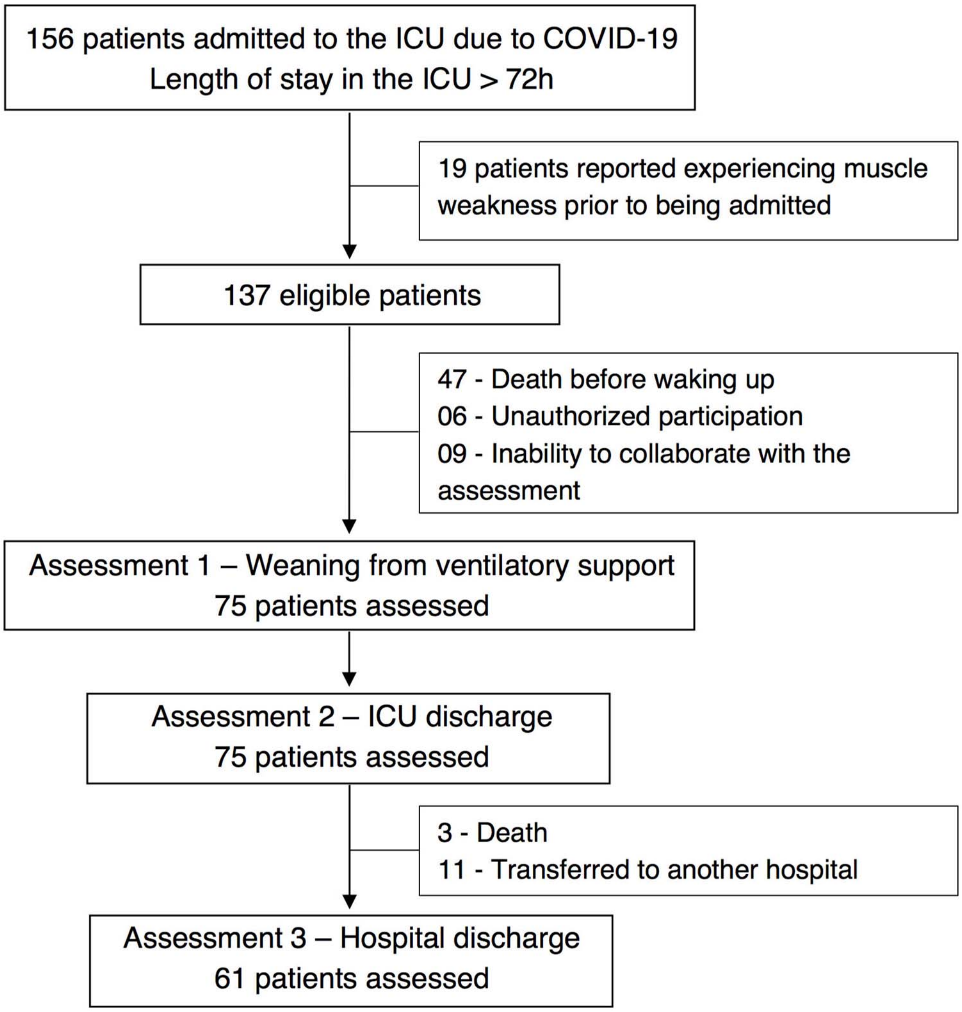

Figure 1. Flowchart of participants included in the study. ICU = intensive care unit.

levels from assessment 1 to assessment 2 ($P < .05$); however, from assessment 2 to assessment 3, this increase was observed only in the participants without ICUAW ($P \leq .001$). At hospital discharge, 67.0% of participants without ICUAW walked independently versus 30.0% of participants 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; $P \leq .001$).

Discussion

ICUAW is a frequent complication in individuals who are critically ill with COVID-19 and are admitted to the ICU. Participants 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 on awakening, at ICU discharge, and at hospital discharge. Several clinical variables to which participants who were critically ill were exposed were associated with ICUAW, but time on bed rest for all participants and the time of use of corticosteroids for those who needed IMV were factors independently associated with ICUAW.

This study showed that the occurrence of ICUAW was 52.0% when participants 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 participants who had COVID-19 and required MV and found rates of 72.0%, 52.0%, and 27.0% on 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 participants who used noninvasive ventilation and a high-flow nasal cannula; however, when analyzing only the participants who needed IMV, the occurrences were 52.0% on awakening, 46.0% at ICU discharge, and 15.0% at hospital discharge. The age of the participants had been reported as a predictor for ICUAW[17] and may explain this difference, because the study by Van Aerde et al assessed participants who were older than those included in the present study.[12] Corroborating previous studies with participants who were critically ill with COVID-19,[2,18] we observed a high rate of previous comorbidities.

Participants with ICUAW had longer ICU and hospital stays, with a duration similar to that observed in the study

Table 1. Patient Baseline Characteristics[a]

Characteristic	Overall (N = 75)	With ICUAW (n = 28)	Without ICUAW (n = 47)	P^b
Age, mean (SD), y	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, mean (SD), kg/m^2	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)	
>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 ICUAW and without ICUAW), we used the Student *t* test (for independent groups) for parametric variables, Mann–Whitney *U* test for independent samples and nonparametric variables, and Pearson χ^2 test for categorical variables. BMI = body mass index; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; ICUAW = acquired weakness–acquired weakness; IQR = interquartile range; SAPS III = Simplified Acute Physiology Score III. [b]For comparison of with ICUAW versus without ICUAW.

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, median (IQR), d	14 (8.5–30)	29.5 (16.3–42.5)	11 (6.5–16)	≤.001
Hospital admission, median (IQR), d	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
Need for tracheostomy	11 (14.7)	9 (32.1)	2 (4.3)	≤.001
Physical therapy sessions, median (IQR)				
In ICU	34 (22–63.5)	63.5 (39.5–96.8)	26 (17.5–38.5)	≤.001
In 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 = intensive care unit–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.

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, because 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 MV in participants 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 individuals with COVID-19. The severity of the critical illness and the

Table 3. Treatments and Complications During 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
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 respiratory distress syndrome; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; ICUAW = intensive care unit–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 versus without ICUAW.

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

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

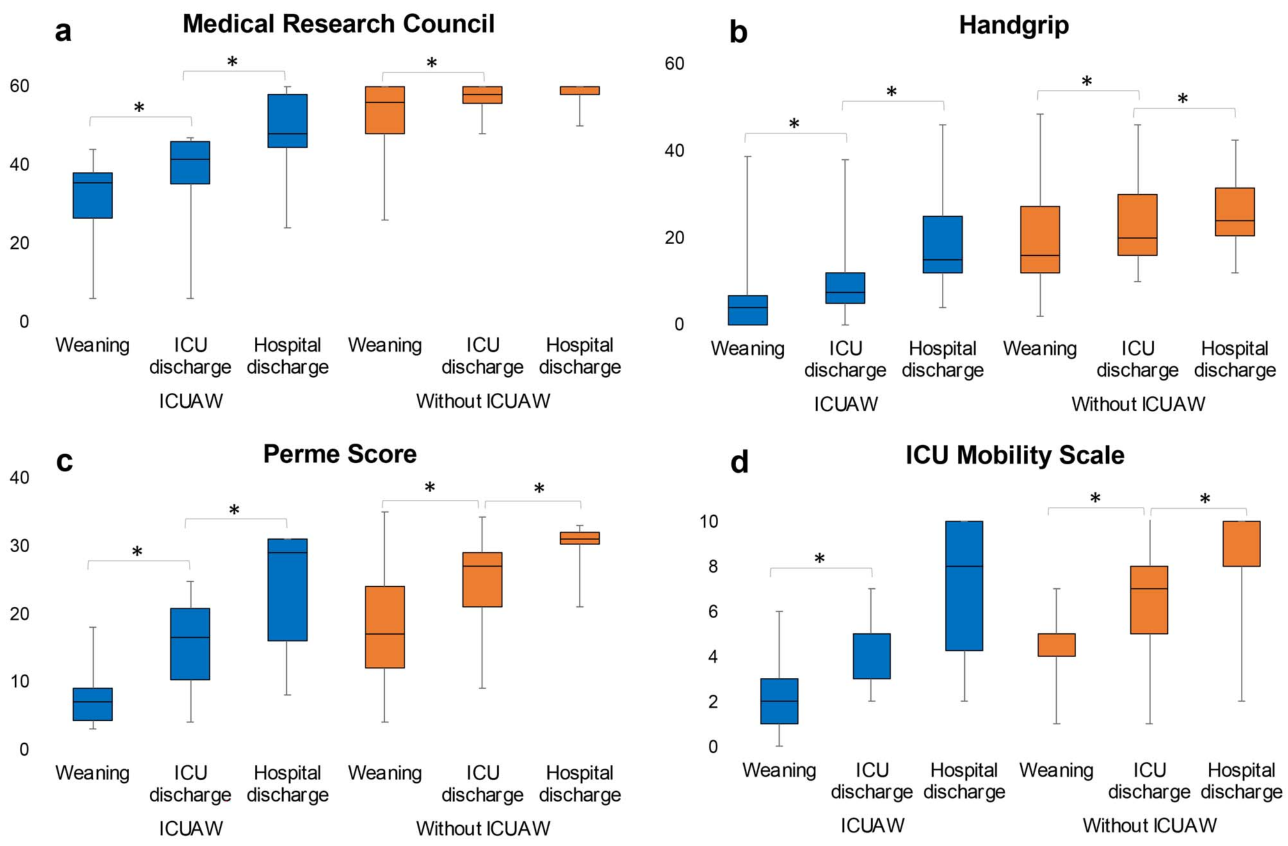

Figure 2. Evolution of muscle strength and mobility of participant subgroups when awake, discharged from the intensive care unit (ICU), and discharged from the hospital. The Friedman test was used to compare variables over time. ICUAW = ICU–acquired weakness. * $P < .05$.

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 individuals 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 individuals who are critically ill with COVID-19, the use of dexamethasone was recommended, because it results in lower mortality in individuals who needed oxygen or MV[24] and was, therefore, a treatment used in most participants 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 NMBA.[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 to 3.4; $I^2 = 72.9\%$).[6] The use of NMBA associated with deep sedation also tended to increase the risk of ICUAW compared with 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 individuals with COVID-19 has been evidenced by McWilliams 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 participants who were critically ill.[27]

Participants with ICUAW had significant improvement in muscle strength during hospitalization. All participants 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 individuals who were critically ill with COVID-19 during hospitalization were previously reported by McWilliams et al.[18]

Mobility in participants with ICUAW, assessed with the Perme Score, was lower at all assessed times, showing the negative impact of ICUAW on the mobility of participants 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 participants with ICUAW; still, when the clinical relevance of this finding is analyzed, it becomes significant, because participants 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.

Limitations

This study had some limitations. Because this was an exploratory cohort study, it was not possible to determine causality, only the association between factor and outcome. 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 individuals with COVID-19, because the literature on this research question is still scarce.

Because of the need to transfer patients to lower complexity hospitals, not all individuals (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 individuals with COVID-19.

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

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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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