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RESEARCH LETTER

Clinical outcomes of intensive care unit-acquired weakness in critically ill COVID-19 patients. A prospective cohort study

Alessandra Preisig Werlang[1], Viviane Martins Correa Boniatti[2], Carolina Tarantino Neuenfeldt[2], Luciana Carcuchinski da Silva[2], Gabriela Machado Costa[2], Michelle Carneiro Teixeira[2], Wagner Luis Nedel[2]

[1] Irmandade da Santa Casa de Misericórdia de Porto Alegre (RS), Brazil.
[2] Hospital Nossa Senhora da Conceição - Porto Alegre (RS), Brazil.

To the Editor

Intensive care unit-acquired weakness (ICUAW) is one of the most common neurological complications in ICU patients,[1,2] and the prevalence of ICUAW after developing coronavirus disease 2019 (COVID-19)-related acute respiratory distress syndrome (ARDS) was 70 - 100%.[3] The risk factors for ICUAW, such as the frequent use of neuromuscular blockers (NMBs) and the regular use of corticosteroids, are numerous and are well described in the COVID-19 population.[3-5] These ICUAW risk factors are similar to those in the non-COVID-19 population.[2] In particular, the ICUAW is associated with an increase in the number of days on mechanical ventilation (MV) and a prolonged stay in the ICU,[1] but few studies have evaluated clinical outcomes in the COVID-19 population.[5,6] Patients with critical COVID-19 may experience long-term functional disability;[7] therefore, the objective of this study was to evaluate the association between the presence of ICUAW and clinical outcomes in this population.

This prospective cohort study included patients admitted to a tertiary ICU between June 2020 and May 2021. This study was approved according to national guidelines (Plataforma Brasil 66240017.0.0000.5530).

We included patients admitted to the ICU with ARDS due to confirmed SARS-CoV-2 pneumonia who were receiving invasive MV. Data on the following clinical characteristics were collected: age, sex, comorbidities, Simplified Acute Physiology Score (SAPS 3), and Sequential Organ Failure Assessment (SOFA) score at admission to the ICU. The diagnosis of ICUAW was established in patients with a Medical Research Council (MRC) score <48 points, with an MRC score < 36 points considered to indicate severe ICUAW.[2] This score yields a global estimation of motor function by assessing six motor categories bilaterally in distinct muscle groups. We measured the MRC score at two time points: upon awakening from continuous IV sedoanalgesia, at which time the patient was able to obey commands at awakening (MRC 1), and upon discharge from the ICU (MRC 2). We calculated the variability of the MRC, defined as MRC 2 - MRC 1. The primary outcome of the study was in-hospital mortality. The secondary outcomes were the number of VFDs at 28 and 60 days and the need for a tracheostomy. Ventilatory-free days were defined as the number of days that patients were both alive and free of invasive MV. Patients who died were defined as having zero VFDs. The descriptive statistics included frequencies and percentages for categorical variables and means/medians ± standard deviations/interquartile ranges for continuous variables. We evaluated continuous variables with the Mann–Whitney test. We used one-way ANOVA to compare the VFDs on Day 60 between non-ICUAW, severe-ICUAW and ICUAW patients, with Tukey's post hoc test to compare differences between groups. To analyze categorical variables, we used the chi-square test. The association between variables and hospital mortality was evaluated using backward logistic regression, which showed odds ratios (ORs) and 95% confidence intervals (95%CIs), with hospital mortality as the dependent variable. We chose independent variables according to the differences between the groups, with $p < 0.2$ as the cutoff point. Statistical tests were two-tailed, with a p value < 0.05 considered to indicate statistical significance. For all analyses, we used jamovi 2.3.21.0.

We evaluated a total of 438 patients (mortality rate 13%) (Table 1). The median time on invasive MV was 14 (8 - 23) days. The median time for the measurement of MRC 1 was 10 (6 - 14) days. The median length of ICU stay was 17 (10 - 27) days, and the median length of hospital stay was 31 (20 - 47) days. All patients received corticosteroids for COVID-19 treatment: dexamethasone 6mg/day for 10 days.[8] Patients who needed NMB drugs had an increased chance of developing ICUAW (OR 4.74; 95%CI 2.49 - 9.01; p < 0.001). The median MRC 1 score was 36 (± 12) points, and the median MRC 2 score was 45 (± 10) points; 381 patients (86%) had ICUAW, and 185 (42%) had severe ICUAW. The median number of days between the two MRC measurements was 4 (2 - 7) days. Patients who survived had a higher MRC score of 1 than patients who died: 36 (12.6) *versus* 31 (12.2), with a mean difference of -4.8 (95%CI -8.9 to -0.7; p = 0.02). However, there was no difference in MRC variability between survivors and nonsurvivors, with a mean difference of 0 (95%CI -4 to 3; p = 0.82). According to multivariate analysis, an MRC score of 1 was associated with survival at hospital discharge (Table 1). There was a difference in the MRC 1 score between patients who required tracheostomy and those who did not: 28 (21 - 34) *versus* 38 (30 - 47); p < 0.01, respectively. However, there was no difference in MRC variability between those who required tracheostomy and those who did not require tracheostomy: 2 (0 - 10) *versus* 0.5 (-2 to 13), p = 0.96. Patients who did not present with ICUAW had a median of 53 VFDs on Day 60 (48 - 56), compared to those diagnosed with mild ICUAW (49 days, IQR 43 - 52) or those diagnosed with severe ICUAW (39 days, IQR 23 - 47); this difference was statistically significant (p < 0.01) (Figure 1). The patients who underwent tracheostomy (n = 98) had lower MRC 1 scores than those who did not (n = 340): 28 (20 - 34) *versus* 38 (30 - 47); p < 0.01.

In COVID-19 patients, ICUAW was associated with delayed time to functional independence. In our cohort, patients with ICUAW had greater mortality, fewer VFDs, and a greater need for tracheostomy. Our data highlight the clinical relevance of the presence of ICUAW in the population of patients with severe COVID-19 and are

Table 1 - Baseline variables and their associations with in-hospital mortality

Variable	Nonsurvivors (n = 59)	Survivors (n = 380)	Univariate analysis p value	Multivariate analysis OR (95%CI)
Sex (female)	50	40	0.87	
Age (years)	66 (58 - 75)	55 (42 - 63)	< 0.01	0.93 (0.89 - 0.98), p = 0.01
SAPS 3 score	74 (63 - 84)	63 (51 - 70)	< 0.01	0.97 (0.92 - 1.02), p = 0.24
SOFA score at admission to the ICU	9 (6 - 11)	7 (4 - 8)	< 0.01	0.87 (0.72 - 1.06), p = 0.19
Diabetes	43	36	0.37	
Ischemic heart disease	34	15	< 0.01	1.31 (0.43 - 3.9), p = 0.63
Hypertension	71	51	0.01	0.41 (0.13 - 1.31), p = 0.13
Asthma	5	5	0.76	
Stroke	13	3	0.01	1.91 (0.42 - 8.61), p = 0.39
COPD	19	8	0.02	1.21 (0.33 - 4.49), p = 0.76
Chronic kidney disease	26	8	< 0.01	0.61 (0.16 - 2.27), p = 0.46
Corticosteroid use	5	5	0.96	
Neoplasia	13	6	0.1	0.71 (0.16 - 2.98), p = 0.64
HIV	6	1	0.07	0.91 (0.06 - 11.89), p = 0.94
BMI	27.2 (24.1 - 31.2)	30.7 (27.7 - 35)	< 0.01	1.16 (1.05 - 1.27), p <0.01
NMB	71	83	0.05	1.07 (0.32 - 3.5), p = 1.07
MRC 1				1.04 (1.0 - 1.09), p = 0.03

OR - odds ratio; 95%CI - 95% confidence interval; SAPS - Simplified Acute Physiology Score; SOFA - Sequential Organ Failure Assessment; ICU - intensive care unit; COPD - chronic obstructive pulmonary disease; HIV - human immunodeficiency virus; BMI - body mass index; NMB - neuromuscular blocker; MRC 1 - Medical Research Council at awakening. The results are expressed as the percentage or median (interquartile range).

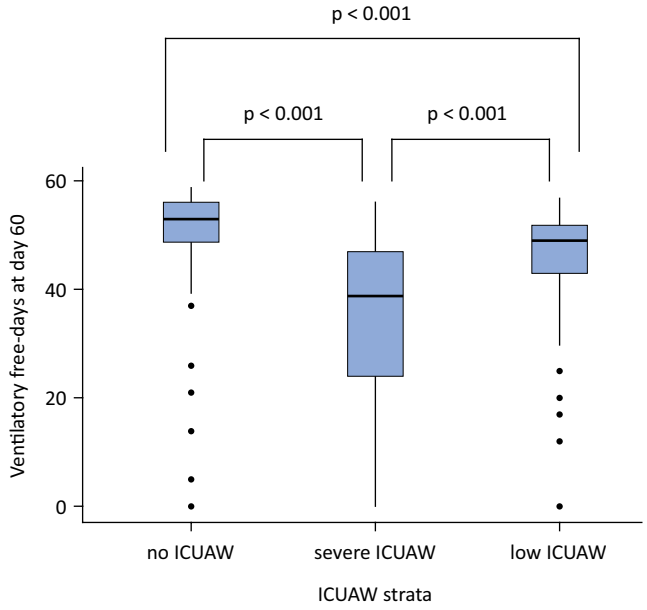

Figure 1 - Ventilatory free days on Day 60 according to intensive care unit-acquired weakness strata.
ICUAW - intensive care unit-acquired weakness.

similar to those of other cohorts in the literature.[3,5] The MRC score is the most widely used diagnostic criterion for ICUAW. This is a volitional technique, which has the drawback that patients must be awake and cooperative.[2] This technique limits the evaluation of patients with delirium or excessive sedation, and the low mortality rate found in this cohort of severely ill patients with COVID-19 could be justified by this fact. We also did not monitor the MRC after discharge from the ICU, which prevents us from determining the clinical trajectory of these patients, especially regarding long-term functional status. In this prospective cohort of patients with severe COVID-19, the presence of initial ICUAW was associated with unfavorable clinically relevant outcomes.

Publisher's note

Conflicts of interest: None.

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Corresponding author:
Wagner Luis Nedel
Unidade de Terapia Intensiva, Grupo Hospitalar Conceição
Av. Francisco Trein, 569
Zip code: 91350-200 - Porto Alegre (RS), Brazil
E-mail: wagnernedel@uol.com.br

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