


Intensive Care Unit- Acquired Weakness and Hospital Functional Mobility Outcomes Following Invasive Mechanical Ventilation in Patients with COVID-19: A Single-Centre Prospective Cohort Study

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Abstract

Background: Acute physical function outcomes in ICU survivors of COVID-19 pneumonia has received little attention. Critically ill patients with COVID-19 infection who require invasive mechanical ventilation may undergo greater exposure to some risk factors for ICU-acquired weakness (ICUAW). **Purpose:** To determine incidence and factors associated with ICUAW at ICU discharge and gait dependence at hospital discharge in mechanically ventilated patients with COVID-19 pneumonia. **Methods:** Single-centre, prospective cohort study conducted at a tertiary hospital in Madrid, Spain. We evaluated ICUAW with the Medical Research Council Summary Score (MRC-SS). Gait dependence was assessed with the Functional Status Score for the ICU (FSS-ICU) walking subscale. **Results:** During the pandemic second wave, between 27 July and 15 December, 2020, 70 patients were enrolled. ICUAW incidence was 65.7% and 31.4% at ICU discharge and hospital discharge, respectively. Gait dependence at hospital discharge was observed in 66 (54.3%) patients, including 9 (37.5%) without weakness at ICU discharge. In univariate analysis, ICUAW was associated with the use of neuromuscular blockers (crude odds ratio [OR] 9.059; $p = 0.01$) and duration of mechanical ventilation (OR 1.201; $p = 0.001$), but not with the duration of neuromuscular blockade (OR 1.145, $p = 0.052$). There was no difference in corticosteroid use between patients with and without weakness. Associations with gait dependence were lower MRC-SS at ICU discharge (OR 0.943; $p = 0.015$), older age (OR 1.126; $p = 0.001$), greater Charlson Comorbidity Index (OR 1.606; $p = 0.011$), longer duration of mechanical ventilation (OR 1.128; $p = 0.001$) and longer duration of neuromuscular blockade (OR 1.150; $p = 0.029$). **Conclusions:** In critically ill COVID-19 patients, the incidence of ICUAW and acute gait dependence were high. Our study identifies factors influencing both outcomes. Future studies should investigate optimal COVID-19 ARDS management and impact of dyspnea on acute functional outcomes of COVID-19 ICU survivors.

Keywords

COVID-19, critical care outcomes, muscle weakness, functional status, gait, neuromuscular blocking agents

Introduction

Coronavirus disease (COVID-19), the infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may lead to life-threatening illness and admission to intensive care unit (ICU) for invasive mechanical ventilation (IMV) due to interstitial pneumonia and associated acute respiratory distress syndrome (ARDS).^{1,2}

Prolonged ICU stay and supportive treatments for COVID-19 ARDS, such as the frequent use of neuromuscular blockers (NMBA) and regular corticosteroids,³⁻⁵ may put patients with COVID-19 at greater risk of developing neuromuscular complications, generally referred to as ICU-acquired weakness (ICUAW),⁶ and physical functioning impairments. Notably, ICUAW is a predictor of worse short-term ICU outcome, including delayed weaning,^{7,8} increased long-term

mortality^{9,10} and higher health-care cost.¹¹ Neuromuscular weakness is also associated with impaired short-term gait independence,¹² long-term functional disability^{10,13} and worse health-related quality of life (HRQOL) in critical illness survivors.^{14,15} Furthermore, reduced physical functioning, involving

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domains such as mobility and gait,¹⁶ may also lead to a need for continuing care following hospital discharge¹⁷ and to worse physical HRQOL.¹⁸

Vast numbers of patients have required ICU admission during the COVID-19 pandemic globally.¹⁹ Speculations anticipating the severity of the physical-related outcomes and rehabilitation needs of critically ill COVID-19 patients were made by clinical experts at the onset of the COVID-19 pandemic.^{20,21} However, further data on the specific epidemiology of acute physical outcomes of critically ill patients with COVID-19 based on direct cohort observation is still required. Furthermore, whereas risk factors for non-COVID-19 ARDS and general critically ill populations²² have been previously reported, it is yet unknown how these factors specifically influence the development of ICUAW in COVID-19 patients. Determinants of hospital functional outcomes have been less widely investigated, however they are equally important as reduced acute physical functioning affects short-term rehabilitation needs, and it is likely to influence long-term functional disability. Therefore, the purpose of this study was to describe the incidence of ICUAW and hospital functional mobility outcomes in a prospective cohort of critically-ill patients with COVID-19. It also aimed to examine the association of ICUAW at ICU discharge and gait dependence at hospital discharge with baseline and clinical variables.

Methods

Study design

This was a single-centre, prospective cohort study conducted at the tertiary care Ramón y Cajal University Hospital in Madrid, Spain. Ethical approval was obtained from the institutional Clinical Research Ethics Committee. Need for written consent was waived due to the minimal-risk, observational nature of the study. Nevertheless, verbal informed consent from patients was gained and recorded on electronic patient records. The study was conducted and reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines²³ and was registered in ClinicalTrials.gov: NCT04400461.

Study Cohort

Consecutive adult (≥ 18 years) subjects admitted to ICU for IMV ≥ 24 h due to laboratory-confirmed SARS-CoV-2 pneumonia between 27 July and 15 December, 2020 were screened for eligibility. Patients were recruited from the two on-site medical and surgical ICUs starting from the date the first patient with confirmed COVID-19 pneumonia was admitted to ICU at the beginning of the pandemic second surge ("second wave") and ending when ICU admission levels started to rise again ("third wave").²⁴

Exclusion criteria included: (1) loss of gait independence prior to hospitalisation (patient requiring the assistance of another person to walk or gait aid excluding a walking stick), (2) cognitive deficit that precluded cooperation with assessments (3) pre-

existing neuromuscular disorder, (4) communication/language barrier, (5) acute cerebrovascular accident complication (6) pregnancy and (7) injury or surgical procedure requiring medical bed rest or immobilisation.

Procedures and Data Collection

For each patient, baseline and clinical characteristics were collected from electronic medical records. Baseline characteristics were age, sex, Body Mass Index (BMI), co-morbidities, Charlson Comorbidity Index (CCI),²⁵ APACHE II scores,²⁶ and PaO₂/FiO₂ (worst value during the first 24 h of admission to ICU). Clinical characteristics included ICU and hospital characteristics: IMV duration (number of days on IMV, regardless of the duration of IMV for that day), occurrence of failed extubation (need for reintubation within 72 h), need for tracheostomy, need for at least one episode of prone positioning, length of stay (days) in the ICU, post-ICU and in hospital, number of physiotherapy sessions (total, ICU and ward), and discharge destination and continuation of care required (home with no physiotherapy follow-up, home with domiciliary physiotherapy, home with outpatient physiotherapy and in-patient rehabilitation facility). In addition, clinical characteristics regarding exposure to adjuvant drug therapies for ARDS were recorded: duration (days) and total cumulative doses (mg) of neuromuscular blocking agent (NMBA) continuous infusion, total cumulative doses (mg) of intravenous boluses, excluding tracheal intubation doses; and duration (days) and total cumulative doses (mg) of systemic corticosteroids administered in hospital during pre-ICU and ICU stay. Corticosteroid doses were converted to methylprednisolone equivalents using an online corticosteroid equivalence calculator (<https://www.mdcalc.com/steroid-conversion-calculator>) to obtain a total corticosteroid equivalent cumulative dose.

Detailed information regarding ICU drugs was collected from daily observation charts by an ICU registered nurse. When ICU charts were not available, medication data were collected from the electronic prescription order entry system (PrescriWin) and electronic medical records. Information regarding hospital corticosteroid administration pre- ICU admission was collected from electronic patient records.

Outcome Variables

Primary outcomes included the incidence of ICUAW at ICU discharge and at hospital discharge clinically evaluated by bedside manual muscle testing with the standardised Medical Research Council Sum Score (MRC-SS)²⁷ (range 0-60, higher scores indicate greater muscle strength). ICUAW is defined as the MRC-SS < 48 cut-off.²⁸ MRC-SS scores used to determine ICUAW were reported.

Secondary outcomes comprised patient functional mobility status and gait dependence, both measured upon hospital discharge. Functional mobility status at hospital discharge was assessed with the Spanish version of the Functional Status Score for the ICU (FSS-ICU)²⁹ (range 0-35, higher scores indicate better functional mobility) which examines the level of

dependence/assistance required to perform 5 tasks: rolling, supine to sit transfer, sitting on the edge of the bed, sit to stand transfer and walking. Gait dependence at hospital discharge was determined with the scores obtained within the 7-point FSS-ICU walking subscale, which is based on a combination of the distance the patient is able to walk and the level of physical assistance by another person required. Patients were dichotomised into: gait dependence (FSS-ICU walking score 0-5) and gait independent (FSS-ICU walking score 6-7) groups.

All outcome measurements were administered by two trained physiotherapists. Patient assignment to each researcher was done by alternation at study entry. All patients received routine daily physiotherapy treatment in the ICU (Monday to Sunday) as soon as they were able to cooperate and continued treatment in the ward (Monday to Friday). Physiotherapy sessions focused on early in-bed and progressive out-of-bed mobilisation during the ICU stay and on the ward according to patient clinical status. Physiotherapists delivering treatments were independent of research physiotherapists carrying out assessments, except for some patients receiving treatment in ICU (n = 16, 22.8%).

Statistical Analysis

Descriptive statistics are presented as medians (interquartile range [IQR]) for continuous variables, and absolute frequencies and percentages for categorical data. Patients were divided into two groups according to the occurrence of ICUAW at ICU discharge. Between-group comparisons were conducted using Mann-Whitney and Chi-square test or Fisher-exact test, as appropriate. Similarly, between-group differences of patients with and without gait dependence at hospital discharge were analysed. Univariate analysis to examine associations between baseline and clinical variables with ICUAW at ICU discharge, and with gait dependence at hospital discharge, as dependent variables, was conducted. The magnitude of the associations was expressed as crude odds ratios (OR) and 95% confidence intervals (95% CI). Two-sided p-values ≤ 0.05 were considered statistically significant for all tests. Analysis was performed in SPSS IBM statistical software for Windows (version 24.0). Data of non-survivors and excluded patients were not analysed.

Results

During the second COVID-19 outbreak, 113 patients with COVID-19 were admitted to ICU for IMV between 27 July, and 15 December, 2020. Twenty-eight (25%) died before ICU discharge and 14 (12%) met exclusion criteria. Reasons for exclusion were inability to cooperate with assessments (8%), cerebrovascular accident during current hospitalisation episode (4%) and injury requiring bed rest (1%) (Figure 1). One patient died on the ward due to cardiac arrest and was excluded from analysis. Thus, the final cohort consisted of 70 patients. Complete datasets were available for all included patients.

Cohort Characteristics and ICUAW Incidence

Cohort characteristics, incidence of ICUAW at ICU discharge and comparison between patients with and without ICUAW at ICU discharge are presented in Table 1. There was no significant difference in baseline characteristics upon ICU admission between weak and not-weak patients. ICUAW had developed in 46 patients (65.7%) at ICU discharge and persisted in 22 (31.4%) at hospital discharge. Patients with ICUAW at ICU discharge spent significantly longer on mechanical ventilation (17 days (d) [11–27] vs. 7 [5–10.5]); had longer length of stay in ICU (23 d [15–35] vs. 11.5 [9–16]), longer post-ICU stay (13 d [9–22] vs. 7 [6–11]) and longer stay in hospital (41 d [30.7–67.2] vs. 23 [20.2–31]). The number of patients having an episode of failed extubation was not different between groups. However, patients with ICUAW were more likely to undergo tracheostomy (32.6% vs. 0%). Most patients in both groups had at least one episode of prone ventilation, with weak patients having higher number of episodes (2 [1–3] vs. 1[1–1]). Moreover, patients with ICUAW at ICU discharge were more likely to require referral to an in-patient rehabilitation facility (37% vs. 8.3%).

Cisatracurium besylate was the drug of choice in all patients who received continuous neuromuscular blockade and IV boluses. A larger proportion of weak patients were treated with continuous NMBA (96% vs. 71%) for a longer median duration (6 d [3–9] vs. 3 [0–6]) and with greater total cumulative doses (941 mg [392–1977] vs. 493 [10–1089]). A total of 9 patients (2 [4.3%] in the ICUAW group and 7 [29%] in the non-ICUAW group) did not receive any neuromuscular blockers, either by continuous infusion or intravenous bolus doses, except for the initial tracheal intubation dose.

Dexamethasone was the most commonly administered corticosteroid pre-ICU and during ICU admission. Other systemic corticosteroids included methylprednisolone and hydrocortisone sodium phosphate. Treatment duration and total cumulative dosages of dexamethasone and total equivalent corticosteroids doses did not significantly differ between weak and not-weak patients.

Functional Mobility and Gait Dependence

Table 2 shows secondary outcomes. Overall FSS-ICU scores at hospital discharge were significantly lower in patients with ICUAW at ICU discharge (26 (19–31) versus 34 (29–35)). A total of 38 patients (54.3%) were discharged newly gait dependent, out of which, 11 (15.7%) were not able to attempt to walk (FSS walking = 0). Compared to patients without weakness at ICU discharge, weak patients were more likely to be discharged from hospital without the ability to walk independently (63% vs. 37.5%). A total of 9 (37.5%) patients without weakness at ICU discharge also presented with gait dependence at hospital discharge.

Associations

Table 3 presents results for univariate associations with outcomes. The odds of developing ICUAW at ICU discharge

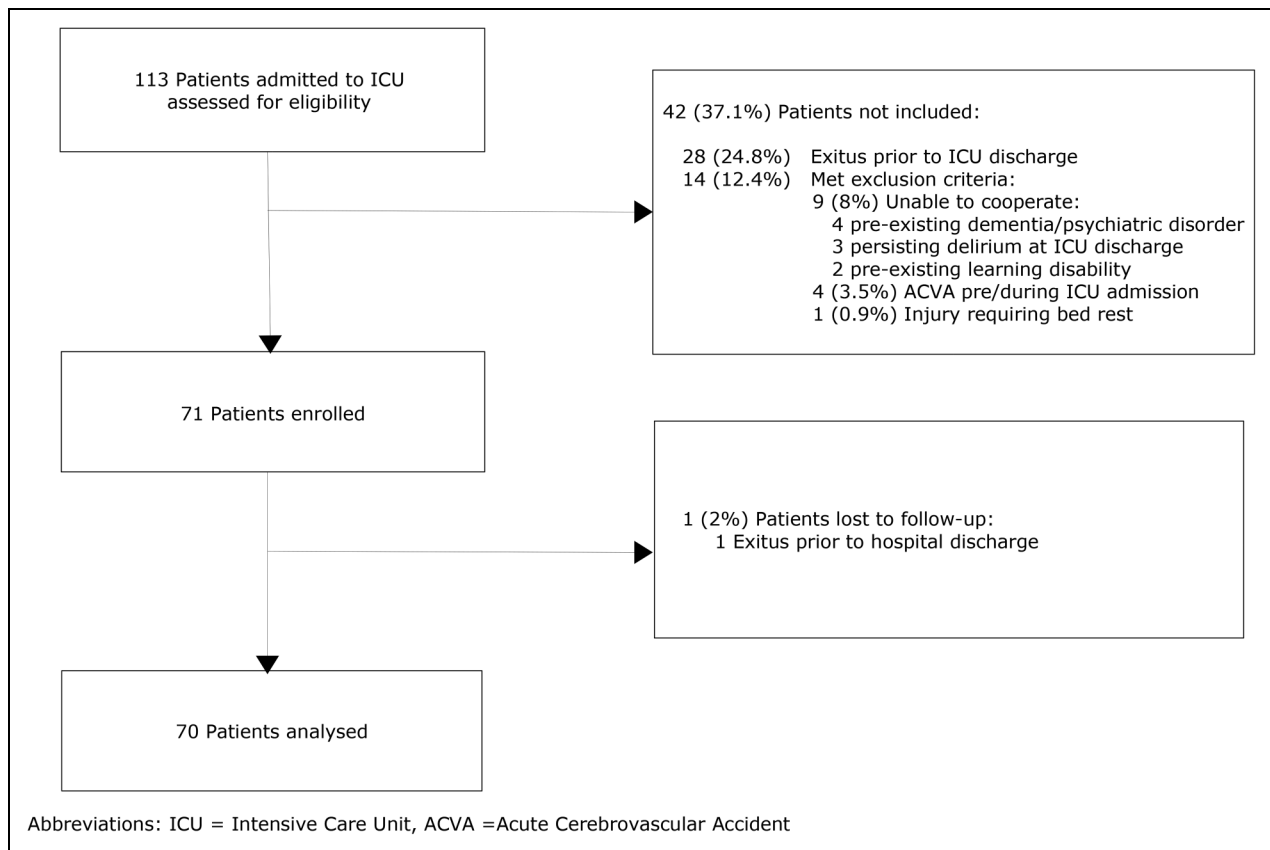


Figure 1. Study flow diagram.

Abbreviations: ICU = Intensive Care Unit, ACVA = Acute Cerebrovascular Accident.

were significantly higher in patients exposed to continuous NMBA (crude odds ratio [OR] 9.059 [95% CI 1.708–48.034]) and with a longer duration of IMV (OR 1.201 [95% CI 1.079–1.337]). Baseline characteristics, NMBA duration and NMBA dose were not significantly associated with ICUAW at ICU discharge. A post-hoc subgroup analysis revealed that patients receiving NMBA > 48 h did not show higher odds of ICUAW at ICU discharge.

On the other hand, worse MRC-SS score at ICU discharge (OR 0.943; [95% CI 0.9–0.989]), older age (OR 1.126 [95% CI 1.053–1.203]), worse CCI (OR 1.606 [95% CI 1.113–2.317]), longer duration of IMV (OR 1.128 [95% CI 1.050–1.212]) and longer duration of NMBA treatment (OR 1.150 [95% CI 1.014–1.304]) were identified as factors associated with an increase in the odds of presenting gait dependence at hospital discharge. Cohort characteristics according to the occurrence of gait dependence are available as supplemental material (Table 4).

Discussion

In this single-center, prospective, observational study of a chronologic cohort of 70 critically ill COVID-19 survivors who underwent mechanical ventilation during the second pandemic outbreak, our main findings were: (1) ICU-acquired weakness

was present in nearly two thirds of patients at ICU discharge and persisted in almost a third at hospital discharge; (2) the occurrence of ICUAW at ICU discharge was associated with the use of continuous neuromuscular blockade and with longer duration of mechanical ventilation, while there was no difference in corticosteroid use and doses between patients with and without ICU weakness; (3) about half (54.3%) presented with gait dependence at hospital discharge, including 9 (37.5%) patients without weakness at ICU discharge; (4) factors associated with gait dependence were lower MRC-SS scores at ICU discharge, older age, greater baseline comorbidity, prolonged mechanical ventilation, longer stay in ICU and longer duration of NMBA treatment. These findings further current knowledge concerning the adverse impact of critical illness on important acute physical outcomes in COVID-19 ICU survivors.

In agreement with our results, available studies reported high rates of ICUAW in mechanically ventilated adults with COVID-19. During the pandemic first surge, clinically-assessed ICUAW rates were 52% (n = 26/50)³⁰ and 100% (n = 35)³¹ at ICU discharge, in 2 retrospective studies; and 100% at awakening (n = 110)³² and 69% (n = 16/23) at the time of extubation³³ in two further prospective studies. Interestingly, these high rates contrast with lower event rates observed in earlier large historical trials of mechanically

Table 1. Cohort Characteristics, Incidence of ICUAW at ICU Discharge and Hospital Discharge and Comparison Between Groups with and Without ICUAW at ICU Discharge.

	All patients (n = 70)	ICUAW (n = 46)	No ICUAW (n = 24)	p value
BASELINE CHARACTERISTICS				
Age, years	63(57–70)	63 (58–69)	61 (52–70)	0.254
Sex, patient No.				
Male	38 (54.3%)	22 (47.8%)	16 (66.6%)	0.133
BMI, kg/m ²	31 (28–35)	31 (27–37)	29 (26–33)	0.428
BMI, patient No.				
Normal weight (18.5–24.9 kg/m ²)	12 (17.1%)	9 (19.6%)	3 (12.5%)	0.293
Overweight (25–30 kg/m ²)	21 (30%)	11 (23.9%)	10 (41.7%)	
Obese (>30 kg/m ²)	37 (52.9%)	26 (56.5%)	11 (45.8%)	
Charlson Comorbidity Index	2 (1–3)	2 (2–3)	2.5 (0–3)	0.518
Comorbidities, patient No.				
Dyslipidemia	30 (43%)	20 (43.5%)	10 (42%)	0.884
Hypertension	27 (38.6%)	20 (43.4%)	7 (29%)	0.243
Diabetes Mellitus	18 (25.7%)	9 (19.5%)	9 (38%)	0.103
Malignancy	10 (14.3%)	5 (10.8%)	5 (21%)	0.294
Cardiovascular Disease	5 (7.1%)	4 (8.6%)	1 (4%)	0.654
Chronic Kidney Disease	3 (4.3%)	1 (2.1%)	2 (8%)	0.269
COPD	4 (5.7%)	2 (4.3%)	2 (8%)	0.603
Asthma	3 (4.3%)	2 (4.3%)	1 (4%)	0.999
Stroke	4 (5.7%)	4 (8.6%)	0	0.291
Admission APACHE II Score	22 (15–26)	22 (17.5–25)	22 (11–27)	0.906
PaO ₂ /FiO ₂ ^a	81 (64–97.75)	77.5 (61.5–95)	91 (68–118)	0.142
PaO ₂ /FiO ₂ < 100 mm Hg, patient No.	53 (75.7%)	37 (80.4%)	16 (66.7%)	0.202
PaO ₂ /FiO ₂ 100–200 mm Hg, patient No.	17 (24.3%)	9 (19.6%)	8 (33.3%)	
CLINICAL CHARACTERISTICS				
ICU and hospital characteristics				
IMV duration, days	13 (7–22.5)	17 (11–27)	7 (5–10.5)	<0.001
At least 1 prone episode, patient No.	64 (91.4%)	44 (95.7%)	20 (83.3%)	0.171
Prone episodes, No.	2 (1–3)	2 (1–3)	1 (1–1)	0.001
Tracheostomy, patient No.	15 (21.4%)	15 (32.6%)	0 (0%)	0.002
Failed extubation, patient No.	3 (4.3%)	2 (4.3%)	1 (4.2%)	0.999
ICU Length of stay, days	18 (11.75–30)	23 (15–35)	11.5 (9–16)	<0.001
Post-ICU Length of stay, days	11 (7–16)	13 (9–22)	7 (6–11)	<0.001
Hospital Length of stay, days	33 (23–49)	41 (31–67)	23 (20–31)	<0.000
Physiotherapy sessions, No.	14 (9–24)	17 (12–27)	7 (5–10)	<0.000
ICU sessions	6 (4–11)	9 (5–15)	3.5 (2–6)	<0.001
Ward sessions	6 (4–10)	8 (5–14)	4 (2–6)	<0.000
Discharge destination, patient No.				
Home with no follow-up PT	35 (50%)	18 (39.1%)	17 (70.8%)	0.005
In-patient rehabilitation	19 (27%)	17 (37%)	2 (8.3%)	
Home with domiciliary PT	14 (20%)	11 (23.9%)	3 (12.5%)	
Out-patient PT	2 (3%)	0 (0%)	2 (8.3%)	0.409
O ₂ at Hospital discharge, patient No.	31 (44.3%)	22 (47.8%)	9 (37.5%)	
ICU drugs exposure				
NMBA use, patient No.	61 (87.1%)	44 (95.7%)	17 (70.8%)	0.006
NMBA duration, days	5 (2–8)	6 (3–9)	3 (0–6)	0.010
NMBA >2 days, patient No.	52 (74.3%)	37 (80.4%)	15 (62.5%)	0.103
NMBA cumulative dose, mg	739 (283–1425)	916 (372–1962)	483 (0–1066)	0.017
NMBA infusion and bolus cumulative dose, mg	744 (288.5–1501)	941 (392–1976)	493 (10–1088.5)	0.018
Corticoids use, patient No.	70 (100%)	46 (100%)	24 (100%)	–
Equivalent cumulative corticoids dose, mg ^b	420 (300–541)	420 (300–550)	405 (305–530)	0.651
Dexamethasone use, patient No.	69 (98.6%)	46 (100%)	23 (95.8%)	0.343
Days on dexamethasone	10 (9–11)	10 (9–11)	10 (9–12)	0.960

(continued)

Table 1. (continued)

	All patients (n = 70)	ICUAW (n = 46)	No ICUAW (n = 24)	p value
Cumulative dexamethasone dose, mg	60 (54–69)	60 (54–68)	60 (53–72)	0.866
Equ. cumulative dexamethasone dose, mg ^b	300 (270–346)	300 (270–341)	300 (263–358)	0.880
MUSCLE STRENGTH				
MRC Sum Score ICU	42 (33–52)	37.5 (30–42)	56 (52–60)	<0.001
MRC Sum Score hospital	52 (46–59)	47.5 (43–52)	60 (58–60)	<0.001
ICUAW at hospital discharge, patient No.	22 (31.4%)	22 (47.8%)	NA	<0.001

Abbreviations: ICU = Intensive care unit, ICUAW = ICU-acquired weakness (Medical Research Council (MRC) Sum Score <48/60), BMI = Body Mass Index, COPD = Chronic obstructive pulmonary disease, APACHE II = Acute Physiology and Chronic Health Evaluation (range 0–71, higher scores indicate more severe illness), PaO₂/FiO₂ = partial pressure of oxygen to fraction of inspired oxygen, IMV = invasive mechanical ventilation, PT = Physiotherapy, NMBA = Neuromuscular blocking agent (cisatracurium continuous perfusion), Equ. = Equivalent.

Data are presented as median (interquartile range). Between-group differences analysed using Mann-Whitney U test or X²/Fisher exact test, as appropriate.

a Worst values within 24 hours of ICU admission.

b Methylprednisolone-equivalent doses.

ventilated adults with non-COVID-19 ARDS ranging 34–36%^{34,35} consequently, our data raise the question of whether critically ill COVID-19 survivors experience ICU neuromuscular complications more frequently relative to other ARDS populations.

Emerging evidence indicates that critically ill patients with COVID-19 could have undergone greater exposure to previously investigated risk factors for neuromuscular dysfunction. Common adjunctive interventions for ARDS, such as neuromuscular blockade and prone positioning, together with deep sedation have been used more frequently and for longer duration in critically-ill patients with COVID-19 ARDS.^{3,4,36–39} In our cohort, 87% received continuous neuromuscular blockade. This percentage is higher than those reported in pre-pandemic large multi-centric trials with ARDS patients which observed rates of continuous paralysis between 26–42%.^{40,41} Furthermore, most patients in our cohort (74%) received a course of paralyzing agents beyond the 48-hours recommended by some guidelines for ARDS management.^{42,43} The adverse impact of NMBA on neuromuscular function remains controversial.^{44,45} In our study, patients receiving neuromuscular blockade had higher odds of developing ICUAW. The duration of NMBA treatment, however, did not reach statistical significance (p = 0.052). Given that our study was statistically underpowered to evaluate independent associations between NMBA and muscle weakness, these findings need to be carefully interpreted before further larger studies examine this relationship.

Patients in our cohort underwent prolonged mechanical ventilation which, unsurprisingly, was associated with a greater occurrence of ICUAW, as previously reported.⁴⁶ ICU length of stay is highly correlated with IMV duration and consequently, showed a significant association too. Furthermore, recent publications indicate that COVID-19 patients may have required substantially higher doses and longer administration of sedatives than other ARDS patients during IMV.^{37,38} We did not gather data to evaluate the possible myotoxic effects of sedatives.⁴⁷ However, delayed physiotherapy interventions due to lack of patient cooperation may have adversely contributed to higher ICUAW rates. Consequently, our study emphasises recommendations for optimal cooperative sedation targets, whenever save, to prevent

excessive immobilisation. Additionally, all patients in our cohort were exposed to systemic corticosteroids, which role in critical illness neuromuscular dysfunction remains inconclusive.⁴⁸ Updated clinical guidelines incorporated corticosteroids into treatment regimes for severe and critically ill patients with COVID-19.^{49,50} Hence, we did not find difference in exposure to corticosteroids between patients with and without weakness. Further studies with alternative study designs are needed to address this issue.

Our study showed that acute reduction in independent functional mobility was common among COVID-19 ICU survivors in line with recent studies with critically ill COVID-19 patients showing short-term impairments in physical functioning.^{32,33,51,52} Notably, functional mobility decline in our cohort was primarily attributable to impaired gait independence. Two previous studies found that 83–92% of COVID-19 survivors were discharged from hospital as autonomous walkers^{32,53} in contrast to the 45.7% of independent walkers in our cohort. Differences in effectiveness of local rehabilitation practices, longer length of stay in acute wards and the specific ceiling effects of the varying outcome measures used may have all contributed to this disparity.

Moreover, we have shown that critical illness neuromuscular weakness was associated with worse acute functional outcome. While previous studies have demonstrated that muscle weakness acquired in the ICU influences long-term physical function,^{10,54,55} our results confirm findings from earlier work showing also the impact of ICU weakness on gait ability from the early post-ICU phase.¹² Interestingly, more than one third of patients (n = 9, 37.5%) without weakness at ICU discharge did not recover their baseline independent gait status at hospital discharge. This could be partly explained by the barriers to ward rehabilitation imposed by room isolation restrictions which may have prevented optimal functional recovery. It is also possible that patients with subclinical weakness were undetected by bed-side assessments in ICU. A recent report on critically ill patients with COVID-19 indicated that MRC scores above 48 do not always rule out the presence of neuromuscular complications.⁵⁶ Incidentally, we suspect gait impairment may be also due to the exertional dyspnea

Table 2. Secondary Outcomes: Functional Mobility status and Gait Dependence at Hospital Discharge of Cohort and According to Patients with and Without ICUAW at ICU Discharge.

	All patients (n = 70)	ICUAW (n = 46)	No ICUAW (n = 24)	P value
FSS-ICU hospital	30 (23–34)	26 (19–31)	34 (29–35)	<0.001
Rolling	7 (6–7)	6 (6–7)	7 (7–7)	<0.001
Supine to sit transfer	6 (4–7)	5.5 (3.75–6)	7 (6–7)	<0.001
Sit to stand transfer	6 (4–7)	5.5 (3–6)	6 (2–7)	
Sitting on the edge of the bed	7 (7–7)	7 (7–7)	7 (7–7)	<0.001
Walking	4 (2–7)	2 (0.75–6)	6.5 (4–7)	0.014
Gait dependence hospital, Patient No. ^a	38 (54.3%)	29(63%)	9 (37.5%)	0.002
FSS-ICU Walking score, Patient No. ^b				0.042
0	11 (15.7%)	11 (23.9%)	0%	<0.001
1	6 (8.6)	6 (13%)	0%	
2	15 (21.4%)	8 (17.4%)	7 (29.2%)	
3	2 (2.9%)	2 (4.3%)	0%	
4	4 (5.7%)	2 (4.3%)	2 (8.3%)	
5	0 (0%)	0 (0%)	0 (0%)	
6	13 (18.6%)	9 (19.6%)	4 (16.7%)	
7	19 (27.1%)	8 (17.4%)	11 (45.8%)	

Abbreviations: ICUAW = intensive care unit acquired weakness (defined as MRC-SS < 48/ 60), ICU = Intensive Care Unit, FSS-ICU = Functional Status Score in the Intensive Care Unit (5 items, range 0-7; total sum score range 0-35, higher values indicate higher functional independence).

Data are presented as median (interquartile range). Between-group differences analysed using Mann-Whitney U test or X²/Fisher exact test, as appropriate.

a Gait dependence: patient is unable to attempt or complete the task of walking due to weakness or can walk with various degrees of assistance by 1 or 2 people or with supervision (FSS-ICU Walking score = 0-5).

b FSS walking subscale: 0 = unable to attempt to walk; 1 = <15 m with maximal assistance of 1-2 people; 2 = ≥15 m with maximal assistance of 1 person; 3 = ≥45 m with moderate assistance; 4 = ≥45 m with minimal assistance; 5 = ≥45 m with verbal cueing; 6 = ≥ 45 m with a walking aid; 7 = >45 m without a walking aid.

experienced by many patients during the early recovery phase, which influenced the observed walking distance during physical examination. Although our study was not designed to measure dyspnoea, 44% of patients were discharged from hospital with supplementary oxygen possibly reflecting a degree of underlying persistent respiratory failure. In fact, recent work has identified dyspnoea as a prevalent persisting symptom in hospitalised and ICU patients with COVID-19 pneumonia.⁵⁷ Future studies investigating acute functional outcomes in COVID-19 ICU survivors may need to consider not only the impact of muscle weakness but also the influence of exertional dyspnea.

Table 3. Univariate Logistic Regression: Associations Between ICUAW at ICU Discharge and Gait Dependence at Hospital Discharge with Baseline and Clinical Variables.

Dependent variable	Cohort characteristics	Odds ratios [95% CI]	P value
ICUAW	IMV duration (1 day)	1.201 [1.079–1.337]	<0.001
	ICU Length of stay (1 day)	1.159 [1.059–1.268]	<0.001
	NMBA use (yes/no)	9.059 [1.708–48.034]	0.010
	NMBA duration (1 day)	1.145 [0.999–1.313]	0.052
	NMBA total cum. dose (mg)	1 [1–1.001]	0.446
	Gait dependence	Age (years)	1.126 [1.053–1.203]
CCI (1 point)		1.606 [1.113–2.317]	0.011
MRC-SS at ICU discharge (1 point)		0.943 [0.9–0.989]	0.015
IMV duration (1 day)		1.128 [1.050–1.212]	<0.001
ICU Length of stay (1 day)		1.1 [1.037–1.168]	0.002
NMBA duration (1 day)		1.150 [1.014–1.304]	0.029
	NMBA total cum. dose (mg)	1 [1–1.001]	0.195

* Only independent variables with p < 0.05 in the between-group comparison are shown. Variables with not significant between-group differences did not reach statistical significance in the univariate analysis.

Abbreviations: ICUAW = intensive care unit acquired weakness, ICU = Intensive Care Unit, CI -Confidence Interval, PaO₂/FiO₂ = partial pressure of oxygen to fraction of inspired oxygen (worst values within 24 hours of ICU admission), IMV = invasive mechanical ventilation, NMBA = Neuromuscular Blocking Agents (continuous perfusion only), CCI = Charlson Comorbidity Index, APACHE II = Acute Physiology and Chronic Health Evaluation (range 0-71, higher scores indicate more severe illness), MRC- SS = Medical Research Council Sum Score (range 0-60, higher values indicate more strength).

Older age, worse baseline comorbidity status together with the correlated variables prolonged IMV and ICU stay, were also identified as explanatory factors potentially influencing decline in gait independence. This is in agreement with recent work showing reduced acute functional status in invasively ventilated COVID-19 patients.^{29,51,53} Previous studies in ARDS survivors and other critically ill patient populations also found that these are poor prognostic factors for long-term physical decline.^{58,59} Early recognition of patients most at-risk of functional mobility decline, and support with advance care planning and targeted rehabilitation interventions may help improve long-term outcome in COVID-19 survivors. The association between NMBA duration with reduced mobility status has not been reported before and it is probably mediated through muscle weakness acquired during ICU stay. The covariance between duration of NMBA and duration of IMV

could also account for this result which should be tested in future multivariable analyses.

This study has some strengths. We provide a comprehensive prospective dataset with lack of missing data and detailed medication information. We also admit several limitations. Firstly, our study is subject to common inherent biases of single-centre unmatched observational designs. Generalisability and capacity to infer cause-effect were limited. Secondly, due to a small cohort size, our study was underpowered to perform further multiple regression analysis to identify factors independently associated with outcomes. Additionally, we excluded patients with delirium and other neurocognitive disorders, which may have introduced a selection bias. Finally, the cut-off point to determine gait dependence within the FSS-ICU walking subscale has not been validated before, which may have affected internal consistency of observations.

Conclusions

In our study, COVID-19 ICU survivors experienced high rates of ICUAW and acute decline in functional mobility independence. Factors associated with ICUAW were the use of continuous neuromuscular blockade and duration of mechanical ventilation. Muscle weakness acquired in the ICU had an impact on impaired gait ability at hospital discharge. Other factors associated with gait dependence were older age, worse baseline comorbidity, prolonged IMV and longer duration of NMBA. Larger multicentre cohort studies are needed to confirm these findings which may inform effective ICU management strategies and rehabilitation interventions, and to evaluate the influence of dyspnea on acute functional outcomes COVID-19 ICU survivors.

Abbreviations

APACHE	Acute Physiology and Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
CCI	Charlson Comorbidity Index
FSS-ICU	Functional Status Score for the Intensive Care Unit
ICU	Intensive Care Unit
ICUAW	Intensive Care Unit – Acquired Weakness
IMV	Invasive Mechanical Ventilation
MRC-SS	Medical Research Council Sum Score
NMBA	Neuromuscular Blocking Agents
PaO ₂ /FiO ₂	partial pressure of oxygen to fraction of inspired oxygen
PT	Physiotherapy

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Author Contributions

María N. Núñez-Seisdedos: Conceptualisation, Methodology, Formal analysis, Writing- original draft, Project administration, Supervision.

Irene Lázaro-Navas: Formal analysis, review for editing.

All authors contributed to data collection and approved the final version of the manuscript.

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Ethical Approval

Not applicable, because this article does not contain any studies with human or animal subjects.

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