

Muscle strength/intensive care unit acquired weakness in COVID-19 and non-COVID-19 patients

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Abstract

Background: Intensive care unit acquired weakness (ICU-AW) affects both coronavirus disease 19 (COVID-19) and non-COVID-19 patients. ICU-AW can result in a variety of consequences, including increased patient mortality.

Aims: The current study aimed to compare muscle strength and ICU-AW in COVID-19 and non-COVID-19 patients.

Study Design: This was a cross-sectional, descriptive-analytical pilot study.

Methods: Fifteen conscious COVID-19 patients and 15 conscious non-COVID-19 patients admitted to the ICUs of a public hospital were selected by convenience sampling. Muscle strength in arms and legs was assessed by a hand-held dynamometer (HHD), and ICU-AW was measured with the medical research council sum score (MRC-SS) scale on the first, fourth, and seventh days of admission to ICUs.

Results: The results showed that muscle strength in the arms and legs of the COVID-19 patients assessed by a HHD and MRC was significantly lower than that of non-COVID-19 patients. On the fourth day of ICU admission, 80% of the COVID-19 patients and 40% of the non-COVID-19 patients had ICU-AW. All COVID-19 patients and 86.8% of the non-COVID-19 patients had ICU-AW on the seventh day of ICU admission.

Conclusions: Decreased muscle strength and ICU-AW are more likely in COVID-19 patients who must stay in the ICU compared with non-COVID-19 patients.

Relevance to Clinical Practice: Health systems should plan to provide rehabilitation facilities for COVID-19 patients and prevent prolonged complications of COVID-19.

KEYWORDS

dynamometer, intensive care unit, intensive care unit acquired weakness, muscle strength

1 | BACKGROUND

People on all continents are unimaginably affected by coronavirus disease 19 (COVID-19).¹ The epidemic has quickly become a major threat to human life and health.^{2,3} According to statistics provided by the World Health Organization on 4 August 2020, there are more than 18 142 000 confirmed cases of COVID-19 and more than 691 000 deaths worldwide.⁴ The latest statistics in Iran indicate the

spread of infection in Iranian society. The confirmed cases of COVID-19 were 1 131 077 and the number of deaths was 52 883 until 15 December 2020, which is increasing every day.⁵

Some COVID-19 patients develop life-threatening conditions, such as acute respiratory distress syndrome. Such patients need mechanical ventilation, which leads to their admission to the intensive care unit (ICU) or death.⁶ Some information is available about the occurrence and clinical characteristics of COVID-19 among critically ill

individuals. However, prolonged ICU stays are often associated with patients' physical dysfunction and neuromuscular complications.^{7,8}

Muscle atrophy and weakness are common complications in the ICU. Recent studies show muscle atrophy and loss of muscle mass in intubated and mechanically ventilated patients during their admission.⁹ Neuromuscular disorders (NMDs) are possible complications of the COVID-19 disease. Much more attention should be paid to neuromuscular complications during the COVID-19 epidemic. Such complications may be caused directly or indirectly by the COVID-19 infection.¹⁰

COVID-19 individuals have been reported to suffer from encephalitis, encephalopathy, cranial neuropathy, Guillain-Barré syndrome, and myositis/rhabdomyolysis.¹¹ Neuromuscular complications associated with COVID-19 can affect muscle strength and cause problems in patients admitted to the ICU. Numerous studies have suggested that many patients with COVID-19 will develop muscle weakness,¹² especially those admitted to the ICU. A significant prevalence of skeletal muscle weakness and impaired physical function has been found in COVID-19 patients admitted to the hospital.¹³ On the other hand, intensive medical management, including prolonged lung-protective ventilation, sedation, and the use of neuromuscular blocking agents, can increase the risk of intensive care unit acquired weakness (ICU-AW) in some COVID-19 patients admitted to the ICU.¹⁴

ICU-AW is a common problem in critically ill patients.¹⁵ The incidence of ICU-AW is approximately 50%.^{8,16} ICU-AW is common in 67% of the patients who have been mechanically ventilated for more than 10 days.¹⁷ ICU-AW includes critical illness myopathy (CIM), critical illness polyneuropathy (CIP), and a combination of both. Muscle dysfunction is thought to be the major cause of ICU-AW.¹⁸ Multiple organ failure dysfunction syndrome, immobilization, sepsis, hyperglycemia, corticosteroids and neuromuscular blocking agents, nutritional deprivation, and sleep disorder are risk factors for ICU-AW.^{9,19}

ICU-AW leads to muscle weakness in the limbs and respiratory system. ICU-AW complicates patients' weaning from the ventilator, prolongs ICU stays, and increases mortality.²⁰ Wieke et al. found that ICU-AW was independently associated with an increased risk of post-ICU mortality and poor physical function in ICU survivors for 6 months.²¹ Thomas et al. showed that physical and cognitive function and quality of life were not fully improved 1 year after rehabilitation.⁸

Nearly 32% of the COVID-19 patients require care and ICU admission during the COVID-19 pandemic²² and musculoskeletal dysfunction is probable in some COVID-19 patients,²³ so it is necessary to pay special attention to the COVID-19 patients admitted to the ICU and prevent complications, such as atrophy and decreased muscle strength. Compared with non-COVID-19 patients, COVID-19 patients can provide valuable information about the different effects of diseases and patient management on reducing ICU-AW. The aim of the present study was to compare muscle strength and ICU-AW in COVID-19 and non-COVID-19 patients admitted to the ICU to gain a deeper insight into the destructive effects of COVID-19.

What is known about the topic

- Patients admitted to intensive care units (ICUs) have variable degrees of muscular weakness.
- Muscle weakness and intensive care unit acquired weakness (ICU-AW) make it difficult to wean patients off the ventilator, lengthen ICU stays, and increase mortality.
- Muscle strength can be affected by COVID-19-associated neuromuscular problems.

What this paper adds

- Most of the extremities of COVID-19 patients were weaker than those of patients who did not have COVID-19.
- During the research period, both the COVID-19 and non-COVID-19 groups' median and mean medical research council sum score (MRC-SS) values went down by the same amount.
- Four-fifths of the COVID-19 patients and two-fifths of the non-COVID-19 patients developed ICU-AW on the fourth day of ICU admission.
- On the seventh day after being admitted to the ICU, all COVID-19 patients and most non-COVID-19 patients got ICU-AW.

2 | METHODS

2.1 | Study design and setting

This cross-sectional pilot study was performed on conscious COVID-19 and non-COVID-19 patients admitted to the ICUs of Afzalipour hospital in Kerman, southeastern Iran. Afzalipour hospital has 5 ICUs (general ICU with 10 beds, surgical ICU with 7 beds, poisoning ICU with 7 beds, COVID-19 ICU₁ with 12 beds, COVID-19 ICU₂ with 7 beds).

2.2 | Sample size and sampling

Patients were divided into COVID-19 and non-COVID-19 groups based on in vitro results of real-time reverse transcriptase-polymerase chain reaction (RT-PCR) or computed tomography.²⁴ The diagnosis was confirmed by an infectious disease doctor. Non-COVID-19 patients were sampled in the general ICU, the surgical ICU, and the poisoning ICU, while COVID-19 patients were sampled in ICU Corona-1 and ICU Corona-2. Then, patients who met the inclusion criteria were included by using the conventional method. Inclusion criteria included patients aged ≥ 18 , who was on the first day of ICU admission (invasive mechanically ventilated patients, non-invasive

TABLE 1 Comparison of demographic and clinical variables between ICU COVID-19 patients and ICU non-COVID-19 patients

Group variables	ICU COVID-19 patients (n = 15)		ICU non-COVID-19 patients (n = 15)		Independent t test	p value
	Mean	SD	Mean	SD		
Age (year)	52.00	16.30	42.87	17.72	-1.47	.15
FOUR score (first day of ICU admission)	14.87	0.74	15.40	0.51	2.30	.03
SOFA (first day of ICU admission)	2.13	1.46	1.93	1.03	-0.43	.67
APACHE II (first day of ICU admission)	9.27	3.41	7.73	3.83	-1.16	.26
	N	%	N	%	Chi-Square/Fisher's exact test	p value
Sex						
Female	7	46.7	8	53.3	0.13	.72
Male	8	53.3	7	46.7		
Length of hospital stay before ICU admission						
1	5	33.3	7	46.7	2.48	.29
2	9	60.0	5	33.3		
3 and 4	1	6.7	3	20.0		
History of addiction						
Yes	6	40.0	6	40.0	-	-
No	9	60.0	9	60.0		
History of chronic disease						
Yes	11	73.3	7	46.7	2.22	.14
No	4	26.7	8	53.3		
History of ICU admission						
Yes	1	6.7	2	13.3	0.37	.54
No	14	93.3	13	86.7		
Nutrition (first day of ICU admission)						
NPO	12	80.0	12	80.0	-	-
PO	3	20.0	3	20.0		
Respiratory support						
Face mask	1	6.7	8	53.3	14.14	.003
Non-rebreathing mask	3	20.0	5	33.3		
Invasive mechanical ventilation ^a	3	20.0	2	13.3		
High flow nasal cannulation	8	53.3	0	0		

Abbreviations: APACHE II, acute physiology age adjustment chronic health evaluation; COVID-19, coronavirus disease 19; FOUR, full outline of unresponsiveness; ICU, intensive care unit; NPO, non per os (Nothing by mouth); PO, per os; SD, standard deviation; SOFA, sequential organ failure assessment. ^aWith endotracheal tube.

mechanically ventilated patients, and patients who were not mechanically ventilated), and patients with a Full Outline of Unresponsiveness (FOUR) score ≥14.

Exclusion criteria included amputation, fractures in lower and upper extremities, neuromuscular diseases (myasthenia gravis, Guillain-Barre, botulism, and pesticide poisoning),⁸ deep vein thrombosis,²⁵ metabolic disorders (hypocalcemia, hypophosphatemia, hypomagnesemia), as well as the patient's death or transfer to the ward while being studied.

According to G*Power software version 3.1.9.2. (power = 80%, $p = .05$, number of groups = 2, and number of measurements = 3), 28 participants were required to detect an effect size of 0.45. On the other hand, 28 participants were required to determine a significant

high difference in muscle strength between COVID-19 and non-COVID-19 ICU patients. Sampling started in June 2020 and ended in November 2020.

2.3 | Data collection tools

In this study, the demographic and background information questionnaire (Table 1) includes the variables of age, sex, length of hospital stay before admission to ICU, diagnosis at the time of admission, history of addiction, history of previous illnesses, history of admissions to ICUs, use of renal replacement therapies, state of consciousness based on FOUR and Glasgow scales, nutritional status, respiratory

status, information about device settings (invasive mechanical ventilation, non-invasive mechanical ventilation, high flow), daily medications taken by the patient in the ICU, the Acute physiology Age adjustment Chronic health evaluation score (APACHE II) and the Sequential Organ Failure Assessment score (SOFA).

2.4 | Medical research council sum score

Medical research council sum score (MRC-SS) was used to measure muscle strength in this study. This scale is used only by patients who are aware of the time and place and need cooperation.²⁶ The MRC-SS measures muscle strength in the upper and lower extremities using a manual muscle test. Target muscles in the upper extremities include right and left shoulder abduction, right and left elbow flexion, and right and left wrist extensions, while target muscles in the lower extremities include right and left hip flexion, right and left knee extensions, and dorsiflexion of the right and left ankles. Each organ score was between 0 and 5. The strength score is obtained according to the force applied to the resistance: 0: no contraction, 1: vibration or low amount of contraction, 2: active motion with no gravity, 3: active motion against gravity, 4: active motion against gravity and resistance, 5: normal strength, and 60: the perfect score, with scores less than 48 indicating ICU-AW.^{27,28}

A physiotherapist trained the rater on how to measure MRC during three 2-h sessions. To determine the intrarater reliability, the rater evaluated 15 patients admitted to the ICUs of Afzalipour hospital twice (with an interval of 2 h). The intraclass correlation coefficient (ICC) rate was 0.99 ($p < .001$ and confidence interval = 0.992–0.999). A single person performed all the measurements.

2.5 | Hand-held dynamometer

A hand-held dynamometer (HHD; Sharif-Exo Model M-201, made in Iran) was used to evaluate muscle strength in this study. Target muscles in the upper extremities include the right and left deltoid, right and left biceps brachii, and right and left wrist extensor, while target muscles in the lower extremities include the right and left rectus femoris, right and left quadriceps femoris, and left and right tibialis anterior.

Muscle strength was measured three times for each patient, and the maximum score was considered. To determine the intrarater reliability, the rater learned how to work with the dynamometer under the supervision of a trained physiotherapist during three 2-h sessions and performed the evaluation after the approval of an expert. The rater evaluated 15 patients admitted to the ICU of Afzalipour hospital twice (with an interval of 2 h). The ICC for all muscles was more than 0.99 ($p < .001$). All measurements were performed by one person.

2.6 | Data collection

After receiving the code of ethics, the researcher first coordinates the research with the hospital and ICUs' management. After obtaining

informed written consent from the patients, she completed the demographic and background information of the patients who met the inclusion criteria. Using the MRC scale and a HHD, a single rater evaluated muscle strength of the upper and lower extremities on the first, fourth, and seventh days of admission to ICUs at 8 PM. Sampling lasted from June to November 2020.

2.7 | Statistical analysis

Data analysis was carried out using IBM SPSS Statistics 24 (IBM Corp., Armonk, NY). Descriptive statistics (frequency, percentage, mean, and standard deviation) were used to describe the demographic characteristics and clinical history of patients. Median, mean, and standard deviation were used to describe the MRC and muscle strength scores. Chi-square, Fisher's exact, and independent *t* tests were used to evaluate the similarity of the two groups in terms of study variables. Repeated measures analysis of variance (ANOVA) was used to compare the MRC and muscle strength scores within and between the two groups. In addition, the Bonferroni post hoc test was used to compare MRC and muscle strength scores between the two groups at different times. Bivariate logistic regression was used to check the probability of developing ICU-AW at different times. A significance level of <0.05 was considered.

2.8 | Ethics approval and consent to participate

The ethics committee of Kerman University of Medical Sciences approved the study protocol (IR.KMU.REC.1398.558). We have complied with the Declaration of Helsinki statements of ethical principles for medical research involving human subjects. After receiving the code of ethics, we coordinated research with the hospital management. The purpose of the research was fully explained to the participants, who could withdraw from the study at any time. They were told that participating in or withdrawing from the study would not affect their course of treatment and that their personal information would be kept confidential. Written informed consent was obtained from all participants. In addition, all methods were carried out in accordance with relevant guidelines and regulations.

3 | RESULTS

3.1 | Baseline characteristics of the participants

Totally, 45 participants were assessed for eligibility, of whom 35 eligible participants were allocated to the two groups (excluded due to: admission to ICU <7 days [$n = 3$] and decreased level of consciousness [$n = 2$]). Finally, 30 participants finished the study. Table 1 shows demographic and background information about the participants. As expected, there were significant differences in the FOUR score and the type of respiratory support on the first day of ICU admission between the two groups (Table 1).

TABLE 2 Comparison of muscle strength in the right and left hands of the ICU COVID-19 patients and ICU non-COVID-19 patients

Group muscle strength (kg)		ICU COVID-19 patients (n = 15)		ICU non-COVID-19 patients (n = 15)		Mean difference		p value ^a	Effect size
		Mean	SD	Mean	SD	Mean	SE		
Right deltoid	T1	11.48	1.66	13.20	2.41	-1.72	0.76	.03	0.16
	T2	11.23	1.85	13.04	2.45	-1.81	0.79	.03	
	T3	10.71	1.94	12.66	2.55	-1.95	0.83	.025	
Right biceps	T1	11.63	2.06	14.05	2.62	-2.42	0.86	.009	0.23
	T2	11.38	2.20	13.93	2.64	-2.55	0.89	.008	
	T3	11.04	2.14	13.62	2.55	-2.58	0.86	.006	
Right wrist	T1	6.37	1.09	8.59	1.81	-2.22	0.55	<.001	0.35
	T2	6.24	0.99	8.36	1.77	-2.11	0.52	<.001	
	T3	6.08	1.05	7.92	1.72	-1.84	0.52	.001	
Left deltoid	T1	11.41	1.66	12.92	2.32	-1.51	0.74	.05	0.15
	T2	11.10	1.79	12.83	2.28	-1.73	0.75	.03	
	T3	10.71	1.88	12.42	2.34	-1.71	0.78	.04	
Left biceps	T1	11.74	2.01	13.89	2.54	-2.16	0.84	.02	0.21
	T2	11.37	2.15	13.75	2.52	-2.39	0.86	.01	
	T3	11.03	2.14	13.41	2.49	-2.38	0.85	.009	
Left wrist	T1	6.38	1.03	8.48	1.82	-2.10	0.54	.001	0.35
	T2	6.17	0.88	8.27	1.77	-2.11	0.51	<.001	
	T3	6.03	0.96	7.83	1.71	-1.80	0.51	.001	

Abbreviations: ANOVA, analysis of variance; COVID-19, coronavirus disease 19; ICU, intensive care unit; SD, standard deviation; SE, standard error; T1, first day of ICU admission; T2, fourth day of ICU admission; T3, Seventh day of ICU admission.

^aRepeated measure ANOVA: Adjustment for multiple comparisons: Bonferroni.

There were significant differences in receiving cardiovascular and antihypertensive drugs ($\chi^2 = 6.0$, $p = .01$), corticosteroids ($\chi^2 = 4.62$, $p = .03$), and gastrointestinal medication ($\chi^2 = 10.99$, $p = .001$) between the two groups. It should be noted that 40% ($n = 6$), 33.3% ($n = 5$), and 26.7% ($n = 4$) of the non-COVID patients in ICUs were diagnosed with respiratory problems, surgery, and drug poisoning, respectively.

3.2 | Muscle strengths

According to Table 2, muscle strength in the right hand of COVID-19 patients admitted to ICU was significantly lower than that of the non-COVID patients at three-time points (T1: first day, T2: fourth days, and T3: seventh days of ICU admission) ($p < .05$). In addition, muscle strength in the left hand of the ICU COVID-19 patients was significantly lower than that of the ICU non-COVID-19 patients at three-time points ($p < .05$).

According to Table 3, muscle strength in the right leg of the ICU COVID-19 patients was significantly lower than that of the ICU non-COVID-19 patients at three-time points ($p < .05$). In addition, muscle strength in the left leg of the ICU COVID-19 patients was significantly lower than that of the ICU non-COVID-19 patients at three-time points ($p < .05$).

3.3 | Medical research council score and ICU-AW

The median scores of MRC-SS in COVID-19 and non-COVID-19 patients were 48.0 (interquartile range [IQR] = 6) and 54.0 (IQR = 10), respectively, on the first day of ICU admission. The median scores of MRC-SS in the COVID-19 and non-COVID-19 patients were 46.0 (IQR = 6) and 52.0 (IQR = 6), respectively, on the fourth day of ICU admission. Therefore, 80% ($n = 12$) of the COVID-19 patients and 40.0% ($n = 6$) of the non-COVID-19 patients had ICU-AW on the fourth day of ICU admission (odds ratio = 6.0, 95% confidence interval = 1.17–30.72, $p = .03$). The median scores of MRC in COVID-19 and non-COVID-19 patients were 42.0 (IQR = 6) and 48.0 (IQR = 6), respectively, on the seventh day of ICU admission ($p = .03$) (Figure 1). All COVID-19 patients ($n = 15$) and 86.8% ($n = 13$) of the non-COVID-19 patients had ICU-AW on the seventh day of ICU admission.

4 | DISCUSSION

The current study aimed to compare muscle strength and ICU-AW in COVID-19 and non-COVID-19 patients and evaluate the effects of COVID-19 disease on patients admitted to the ICU. To the best of our knowledge, we compared muscle strength and ICU-AW in COVID-19 and non-COVID-19 patients for the first time. The findings

TABLE 3 Comparison of muscle strength in the right and left legs of the ICU COVID-19 patients and ICU non-COVID-19 patients

Group muscles strength (kg)		ICU COVID-19 patients (n = 15)		ICU non-COVID-19 patients (n = 15)		Mean difference		p value ^a	Effect size
		Mean	SD	Mean	SD	Mean	SE		
Right rectus	T1	12.13	1.24	14.15	2.03	-2.02	0.61	.003	0.28
	T2	11.68	1.45	13.80	2.12	-2.12	0.66	.003	
	T3	11.24	1.45	13.49	2.19	-2.25	0.68	.003	
Right quadriceps	T1	12.33	1.86	14.10	1.87	-1.77	0.68	.02	0.20
	T2	11.85	2.19	13.75	1.94	-1.90	0.76	.02	
	T3	11.42	2.07	13.49	1.99	-2.07	0.74	.009	
Right tibialis	T1	7.05	1.58	8.97	1.65	-1.92	0.59	.003	0.27
	T2	6.67	1.76	8.78	1.69	-2.10	0.63	.002	
	T3	6.45	1.84	8.48	1.79	-2.03	0.66	.005	
Left rectus	T1	12.16	1.32	14.11	1.95	-1.96	0.61	.003	0.29
	T2	11.57	1.53	13.70	1.91	-2.14	0.63	.002	
	T3	11.19	1.47	13.338	2.01	-2.19	0.64	.002	
Left quadriceps	T1	12.36	1.79	13.96	1.91	-1.60	0.68	.02	0.17
	T2	11.89	2.13	13.60	1.97	-1.72	0.75	.03	
	T3	11.47	2.0	13.37	2.06	-1.90	0.74	.02	
Left tibialis	T1	7.0	1.54	8.90	1.70	-1.91	0.59	.003	0.26
	T2	6.65	1.81	8.67	1.68	-2.02	0.64	.004	
	T3	6.40	1.77	8.39	1.78	-1.98	0.65	.005	

Abbreviations: ANOVA, analysis of variance; COVID-19, coronavirus disease 19; ICU, intensive care unit; SD, standard deviation; SE, standard error; T1, first day of ICU admission; T2, fourth day of ICU admission; T3, Seventh day of ICU admission.

^aRepeated measure ANOVA: Adjustment for multiple comparisons: Bonferroni.

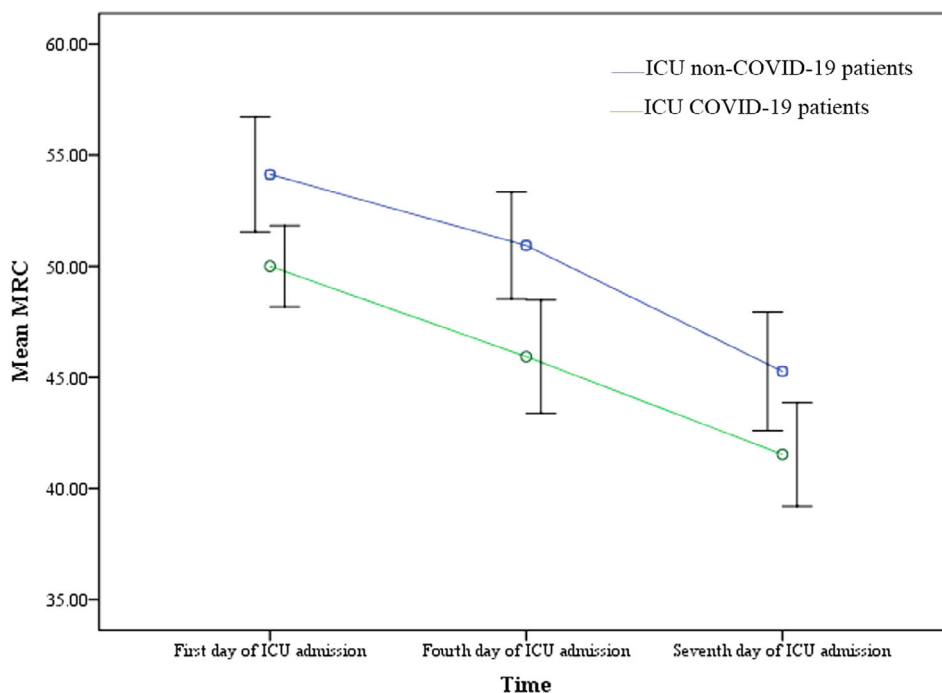


FIGURE 1 Comparison of Medical Research Council (MRC) score between the ICU COVID-19 patients and ICU non-COVID-19 patients. COVID-19, coronavirus disease 19; ICU, intensive care unit

of the present study showed that muscle strength in the arms and legs of the COVID-19 patients was significantly less than that of the non-COVID-19 patients in all three measurements. Median and mean

values for the MRC-SS were reduced equally in both the COVID-19 and non-COVID-19 groups in the study period, indicating that they may be related to the COVID-19 disease.

Patients' muscle strength and problems affecting the musculoskeletal system in COVID-19 patients depend on several factors. Primary studies have shown significant musculoskeletal dysfunction in some patients with COVID-19. Various studies have reported muscle weakness in COVID-19 patients and considered rhabdomyolysis,²⁹ myalgias,³⁰ and myopathy³¹⁻³³ as causes of muscle weakness. These findings emphasize the various and complex mechanisms associated with COVID-19 disease in patients admitted to ICUs.

Past studies have also shown direct and indirect effects of severe acute respiratory syndrome (SARS) on several organ systems, including the musculoskeletal system. Tsai et al. reported four patients with SARS who developed neuromuscular problems after the onset of symptoms, with a definitive diagnosis of polyneuropathy.³⁴

COVID-19 infection and treatment may cause new neuromuscular complications (such as Guillain-Barré syndrome, myositis and polyneuropathy), autoimmune and degenerative disorders, risk of immunosuppressive/immunomodulatory treatments and risks of treatment with hydroxychloroquine and chloroquine such as toxic neuropathy and myopathy.¹⁰ Mao et al. reported myalgias in half of the patients with COVID-19.³⁰ Chan et al. showed that two COVID-19 patients had typical symptoms of rhabdomyolysis, including general weakness and muscle pain, but no fever or respiratory symptoms in the early manifestations.²⁹ Rhabdomyolysis is characterized by the triple syndrome of muscle weakness/pain, red urine colour, and skeletal muscle damage. Necrosis releases intracellular chemicals into the blood circulation, which might be an indication of musculoskeletal system impairment.^{35,36}

Zhang et al. described a 58-year-old woman with symptoms of inflammatory myopathy and facial, bulbar, and proximal weakness and showed that COVID-19 was associated with myositis in this patient.³¹ Bagnato et al. also described a 62-year-old woman with severe CIM-induced muscle weakness and showed that COVID-19 was associated with myopathy.³² Myopathy has also been reported with increased creatine kinase (CK) levels in patients with SARS.³⁷

Ishkanian et al. described a 58-year-old woman with COVID-19 who had dysphagia, speech disorders, and left upper extremity weakness and showed that COVID-19 might cause myositis.³⁸ Viral infection, including influenza A and B, has been a known cause of myositis.³⁹ Since the causes of muscle disease are unknown, muscle involvement receives less attention in infections. However, muscle damage in COVID-19 patients may be attributed to electrolyte disorders, sepsis, prolonged bed rest, or hypoxia rather than a direct viral attack on myocytes.⁴⁰ Further in-depth studies on muscle disease associated with COVID-19 infection are needed.

Corticosteroids can exacerbate musculoskeletal system problems in COVID-19 patients because they have adverse effects on skeletal muscle and bone. A number of immunotherapeutic methods, such as IL-1 and IL-6 inhibitors, are used to treat acute inflammation in patients with COVID-19.⁴¹ However, they may affect musculoskeletal function. Sepsis can also be considered as a common complication that causes multiple organ dysfunction, destroys proteins and inhibits muscle protein synthesis, leads to loss of mitochondria and dysfunction, and causes skeletal muscle atrophy by increasing proteolysis in critically ill patients with COVID-19.¹²

Although these findings addressed the effects of COVID-19 on the musculoskeletal system, some studies have not reported a significant effect. Cabañes-Martínez et al. studied the presence of myopathy and neuropathy in 12 patients with COVID-19 admitted to the ICU and found no distinct features in the studies done on ICU patients with COVID-19.⁴²

Pitscheider et al. also showed that patients with influenza CK had a higher baseline than those with COVID-19, and 35.7% of the ICU patients had CK levels >1000 U/L compared with 4.7% of the COVID-19 patients. HyperCKemia also occurred at a similar frequency in COVID-19 and influenza infections.⁴³ CK level is strongly associated with disease severity and markers of inflammation and it is a stronger indicator of muscle injury than myalgia.⁴⁴ In addition, it can be assumed that COVID-19 may not specifically target muscles. On the other hand, it is not clear whether hyperCKemia is due to an inflammatory response caused by a virus or direct muscle poisoning.⁴³ Therefore, further studies are needed to determine whether COVID-19 affects the musculoskeletal system. Furthermore, no comparison has been made between COVID-19 and non-COVID-19 patients admitted to the ICU in this regard.

Another finding of the present study was the lack of a difference in wrist muscle strength between the two groups at different times (ICU COVID-19 patients vs. ICU Non-COVID-19 patients: T1: 50.00 ± 3.29 vs. 54.13 ± 4.69 , T2: 45.93 ± 4.60 vs. 50.93 ± 4.33 and T3: 41.53 ± 4.22 vs. 45.27 ± 4.82). However, direct muscle injury caused by COVID-19 has been reported in some viral infections, such as influenza,⁴⁵ human immunodeficiency virus⁴⁶ and SARS,³⁴ but studies have not proven direct muscle injury induced by the virus. Studies have shown that microvascular, electrical, metabolic, and bioenergetic changes interact in complex ways and cause muscle weakness or atrophy.⁴⁷ According to the present study, it is not possible to determine the effects of the disease on different muscle types. However, prolonged follow-up studies have not yet been conducted in this regard.

Another important finding of the present study was that the level of ICU-AW among COVID-19 patients was significantly higher than that in non-COVID-19 patients. Sixty-six point seven of the COVID-19 patients and 26.7% of the non-COVID-19 patients had ICU-AW on the first day of admission, and all COVID-19 patients and 86.8% of the non-COVID-19 patients had ICU-AW on the seventh day of admission. Van Aerde et al. supported the results of the present study and showed that muscle weakness at awakening, ICU, and hospital discharge was 72%, 52%, and 27%, respectively.⁴⁸ In their study, Paneroni et al. found that many COVID-19 patients had problems with their muscle strength and physical function.¹³

Therefore, ICU-AW may occur in COVID-19 patients who need long-term sedation. The reported incidence of ICU-AW in non-COVID-19 patients varies depending on the patient population. The incidence of ICU-AW was reported to be 60% in patients with acute respiratory distress syndrome.⁴⁸ One study found that 11% of the patients admitted to ICU for at least 24 h had ICUAW,⁴⁹ and 24%–55% of the patients who were in ICU for more than 7–10 days had ICU-AW.^{49,50} Other studies showed that weakness at awakening

occurred in 26% and 65% of the patients who were mechanically ventilated for 5 and 7 days, respectively.^{51,52}

ICU-AW is often associated with muscle loss. Sodium channelopathy refers to impaired muscle contraction and action due to loss of excitability of the muscle membrane. Mitochondrial dysfunction also causes muscle weakness and fatigue.¹² It is necessary to evaluate and follow up COVID-19 patients to confirm ICU-AW. Abdelnour et al. reported peripheral neuropathy following COVID-19 in a 69-year-old man,⁵³ showing the destructive effects of COVID-19 disease on the skeletal muscles of patients due to problems in the peripheral nerve, neuromuscular junction, and skeletal muscle fibre. A study on the relationship between neuropathy and myopathy showed that CIP and CIM were not separate, and they developed in the form of critical illness neuromyopathy as a result of multiple organ dysfunction.¹² Since many COVID-19 patients require prolonged and severe ventilation, more cases of CIP, CIM, or critical illness polyneuropathy and myopathy are expected in the future.⁴² Further studies are needed to determine why ICU-AW occurs in COVID-19 patients.

For various reasons, it is not possible to measure the exact rate of ICU-AW. Concerning the infectious nature and severity of COVID-19, a number of patients died without diagnostic studies, and unnecessary studies were delayed or even cancelled. In addition, limited resources during the sudden outbreak of COVID-19 have influenced research in this area. Therefore, it is necessary to pay more attention to ICU-AW among patients. Social awareness of these complications helps health-care providers consider these complications, and diagnose and treat them timely. Rehabilitation programs can also be used to reduce ICU-AW, especially in COVID-19 patients.³² Healthcare systems should provide more comprehensive planning for the screening and rehabilitation of the ICU-AW-prone COVID-19 patients and prevent prolonged complications of COVID-19.

4.1 | Limitations

We have to admit that our study has some limitations. First, the number of patients in our study is limited, and studies in larger groups are needed for more accurate conclusions. In addition, for results to be confirmed, muscle biopsy has not been done in our study, so future studies should pay attention to physiological and pathological effects. Our study focused on conscious COVID-19 patients with a short follow-up period, so future studies should consider mechanically ventilated patients with severe COVID-19 and with a longer follow-up period. Based on our results, the participants in the COVID-19 group were older than the participants in the non-COVID group. Although the age difference between the two groups was not statistically significant, it could be a possible confounding factor, so care should be taken in interpreting the results. Finally, our study was conducted in a small part of Iran at a specific time, and the result should be generalized to other regions and times with caution. Given the heterogeneous population in this study (intubated in MV, SV with non-rebreather mask or high flow, etc.) and the lack of comparison of the ICU acquired weakness among different groups, caution should be

taken in interpreting the findings. Separate studies should be undertaken and compared for each of these groups.

4.2 | Implications of findings

The findings of this study revealed that COVID-19 patients had poorer muscular strength prior to ICU admission than non-COVID patients. Despite the fact that muscular strength decreased equally in both the COVID-19 and non-COVID-19 groups during the course of the research, the ICU-AW manifested earlier in most of the COVID-19 patients than in non-COVID-19 patients. In order to effectively allocate suitable medical therapies and patient care, the condition of COVID-19 patients and the problems connected with this disease should be evaluated. Nurse managers and ICU nurses' attention to the special conditions and complications of COVID-19 patients admitted to ICU, the provision of facilities and rehabilitation support for patients, as well as proper human resource management, can assist nurses to meet patients' care needs. But these results need to be tested and confirmed in future studies, and COVID-19 patients need effective ways to improve their muscle strength and stop COVID-19's long-term effects.

5 | CONCLUSION

The present study showed that the muscular strength of the arms and legs of COVID-19 patients during 7 days was significantly lower than that of non-COVID-19 patients, indicating that they may be related to the COVID-19 disease. However, there was no difference in wrist muscle strength between the two groups at different times. Therefore, it is not possible to determine the effects of COVID-19 disease on different muscle types. We tried to perceive the reasons for the decrease in muscle strength and ICUAW in COVID-19 patients and emphasized its identification and follow-up. However, concerning the critical condition of COVID-19 patients, it is difficult and even impossible to assess muscle weakness and ICU-AW in the ICU. Currently, the only possible way to reduce the prevalence of ICU-AW in critical COVID-19 patients is to control risk factors and perform early and timely rehabilitation. More research is needed to discover effective solutions for the diagnosis, prevention, and treatment of muscle weakness and ICU-AW.

AUTHOR CONTRIBUTIONS

Elham Rahiminezhad, Mohammad Ali Zakeri, and Mahlagha Dehghan designed the study. Elham Rahiminezhad collected data. Elham Rahiminezhad, Mohammad Ali Zakeri, and Mahlagha Dehghan contributed to the study design, they provided critical feedback on the study and statistical analysis and inputted the draft of this manuscript. Elham Rahiminezhad and Mohammad Ali Zakeri wrote the manuscript. All authors have read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

The datasets used for the current study are available from the corresponding author upon request.

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