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ORIGINAL RESEARCH

Effects of SARS-CoV-2 on changes in muscle mass and muscle strength in the intensive care unit setting: a single-center, unblinded, prospective study

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Abstract

The prevalence of sarcopenia increases in the intensive care unit (ICU) and critically ill patients. In this study, we aimed to evaluate the muscle mass and muscle strength changes in patients diagnosed with coronavirus disease 19 (COVID-19) pneumonia in the ICU setting using anthropometric and ultrasonographic measurements. A total of 30 patients with COVID-19 pneumonia hospitalized in the ICU between June 2021 and December 2021 were included in this single-center, unblinded, prospective study. Thigh circumference and muscle mass of the rectus femoris were measured and anthropometric and ultrasonographic examination were performed. The muscle strength was evaluated using the Medical Research Council (MRC) grading system in non-intubated patients. All measurements were recorded on Days 1, 7, 14, and 21. All patients were followed for 21 days. At the end of 21 days, the muscle mass of the right and left rectus femoris decreased by 47% and 52.8%, respectively based on ultrasonographic examination. In addition, the muscle mass of the right and left rectus femoris decreased by 25.3% and 25.4%, respectively based on anthropometric measurements. The muscle strength of the thigh of the lower limb was evaluated using the MRC scores and each parameter decreased by one unit: the muscle strength was 5/5 at the time of ICU admission, while it regressed to 3/5 at week 2 and 2/5 at week 3. Intensive care unit-acquired weakness (ICU-AW) may develop in critically ill patients with COVID-19 due to the disease itself or treatment methods. A special attention should be paid to accurately assess and treat ICU-AW in this patient population.

Keywords

Intensive care unit; Muscle weakness; COVID-19; Sarcopenia; Muscle loss

1. Introduction

Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has dramatically affected lives of individuals all over the world since December 2019 [1]. The disease usually presents with fever, dry cough, muscle pain, and fatigue, while some patients may suffer from severe complications requiring intensive care including acute respiratory distress syndrome [2].

Several studies have shown that muscle weakness may develop in patients infected with novel coronavirus 2019 disease (COVID-19) in the intensive care unit (ICU) setting [3]. Neuromuscular complications related to COVID-19 may affect the muscle strength in patients followed in the ICU. The disease, itself, is associated with many problems affecting the muscle strength and musculoskeletal system. Severe SARS-CoV-2 infection is characterized by dysregulated host response, which can directly affect neuronal function and various inflammatory cytokines and immune cells that contribute to muscle atrophy. Concomitant physical inactivity and, in some cases, hypoxemia and malnutrition are contributing factors to changes in skeletal muscle structure and function. Muscle weakness and exercise intolerance lead to more inactivity in vicious cycle [4]. COVID-19 disease is known to be associated with significant systemic inflammation and causes a severe cytokine response in some patients. Serum concentrations of inflammatory cytokines, including Tumor Necrosis Factor Alpha (TNF-α), have been shown to be higher in COVID-19 patients requiring intensive care therapy [5]. This has negative consequences on muscle protein synthesis; TNF-α reduces messenger Ribonucleic Acid (mRNA) translation efficiency through changes in the availability of Eukaryotic translation initiation factor 4E (eIF-4E). This causes a state of anabolic resistance that requires a higher protein intake requirement to stimulate muscle protein synthesis [6].

Preliminary studies have shown that COVID-19 may lead to musculoskeletal dysfunction in some cases [7]. Several studies have reported muscle weakness in COVID-19 patients which

can be attributed to rhabdomyolysis, myalgia, and myopathy [7]. Taken together, COVID-19 is considered to be associated with several complex mechanisms in ICU patients [7]. In addition, lung protective ventilation, sedation, the administration of intravenous corticosteroids or neuromuscular junction blocking agents, intensive care have been shown to be linked to the increased risk of ICU-acquired weakness (ICU-AW) in COVID-19 patients [4].

Muscle atrophy and weakness are common complications in ICU patients. Recent studies have demonstrated that intubated patients receiving mechanical ventilation support may develop muscle atrophy and muscle mass loss from the beginning of hospital admission [8]. Muscle weakness may be related to primary neuromuscular disorders such as Guillain-Barre syndrome and myasthenia gravis or secondary conditions such as life-threatening events [9]. As the exact etiology of neuromuscular dysfunction in ICU patients still remains unclear, the term "ICU-AW" has been proposed to attribute the condition to critical illness and treatments applied [10]. Of note, ICU-AW related diaphragm weakness may result in extubation failure, reintubation, prolonged intubation duration, and increased morbidity and mortality [9]. During the COVID-19 pandemic, a special attention should be paid to neuromuscular complications, as such complications may directly or indirectly result from COVID-19 infection [11].

Bioelectrical impedance analysis, anthropometric measurements, and radiological studies are the most commonly utilized methods to assess the muscle mass [12]. Ultrasonography has certain advantages, as it is a non-invasive and pain-free method and does not require patient participation. Neuromuscular ultrasonography has been widely used recently to evaluate quantitative alterations in the skeletal muscles in ICU patients [13]. Muscle mass changes in each muscle or muscle groups can be assessed by this method and rectus femoris (cross-sectional area (CSA) or thickness) and vastus lateralis (thickness) or rectus femoris and vastus intermedius or the muscle limb thickness can be measured [14]. In recent years, ultrasonographic measurement of the rectus femoris muscle mass has been increasingly adopted [14–16].

In the present study, we aimed to evaluate the decrease in muscle mass and muscle strength changes in patients diagnosed with COVID-19 pneumonia in the ICU setting based on anthropometric and ultrasonographic measurements.

2. Materials & methods

This single-center, unblinded, prospective study was conducted at Istanbul Eyüpsultan State Hospital, Department of COVID-19 Intensive Care Unit between 01 June 2021, and 01 December 2021. The center has a six ICU bed capacity. Inclusion criteria were as follows: >18 years of age, hospitalization in the ICU setting, and having a diagnosis of COVID-19 as confirmed by polymerase chain reaction (PCR). Exclusion criteria were as follows: <18 years of age, pregnancy, lower limb amputation, severe venous insufficiency or major injuries in the lower limbs, known neuromuscular disorder or malignancy. The study flowchart is shown in Fig. 1.

The day the patients were admitted to the intensive care unit was included in the study and recorded as the 1st day. All patients were followed during ICU stay up to 21 days maximum.

The thigh circumference and muscle mass of the rectus femoris were measured on Days 1, 7, 14, and 21 both anthropometrically and ultrasonographically while the leg is extended 15 cm over the patella. A linear probe was used (Esaote S.p.A., Italy) for the measurements and muscle mass of bilateral rectus femoris (from the anthropometric measurement area) was measured ultrasonographically and the results were recorded (Fig. 2).

The muscle strength was evaluated using the Medical Research Council (MRC) grading system in non-intubated patients. All measurements were recorded on Days 1, 7, 14, and 21. The Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II), and Nutrition Risk Screening 2002 (NRS-2002) scores were recorded for each patient in the first day of ICU admission. Nutritional care was provided by the hospital dietician. Total calorie need was calculated according to the American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines. At the end of Week 1, all patients were expected to reach the target calorie and protein.

During follow-up, C-reactive protein (CRP), procalcitonin, complete blood count (CBC), and biochemistry test results during diagnosis, treatment, and follow-up were recorded. In addition, the need for positive inotropic and vasopressor support, need for diuretics (amount, if available), dialysis requirement, the amount of low-molecular-weight heparin (LMWH), corticosteroid, neuromuscular blockers, the amount of daily fluid intake and daily urine output were noted. The route of feeding (enteral/parenteral) was also recorded. At the end of follow-up, the length of ICU stay, duration of intubation and extubation were analyzed. Patients receiving or not receiving mechanical ventilation who met the inclusion criteria were included. Duration of mechanical ventilation was recorded in intubated patients (Table 1).

3. Statistical analysis

Statistical analysis was performed using the SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were presented in number and frequency. The normality assumption was checked using the Shapiro-Wilk test. Repeated measures analysis of variance was used to examine the normal distribution of variables over time, while the Friedman test was used to analyze non-normally distributed data. p value of < 0.05 was considered statistically significant.

4. Results

Initially, a total of 70 patients with COVID-19 who were followed in the ICU setting were screened. Per inclusion and exclusion criteria, 30 patients were included in this study. The mean age of the patients was 63.72 ± 11.68 (Mean ± SD). Of the patients, 66.7% were males and 56% had comorbid diseases such as diabetes mellitus, hypertension, and chronic

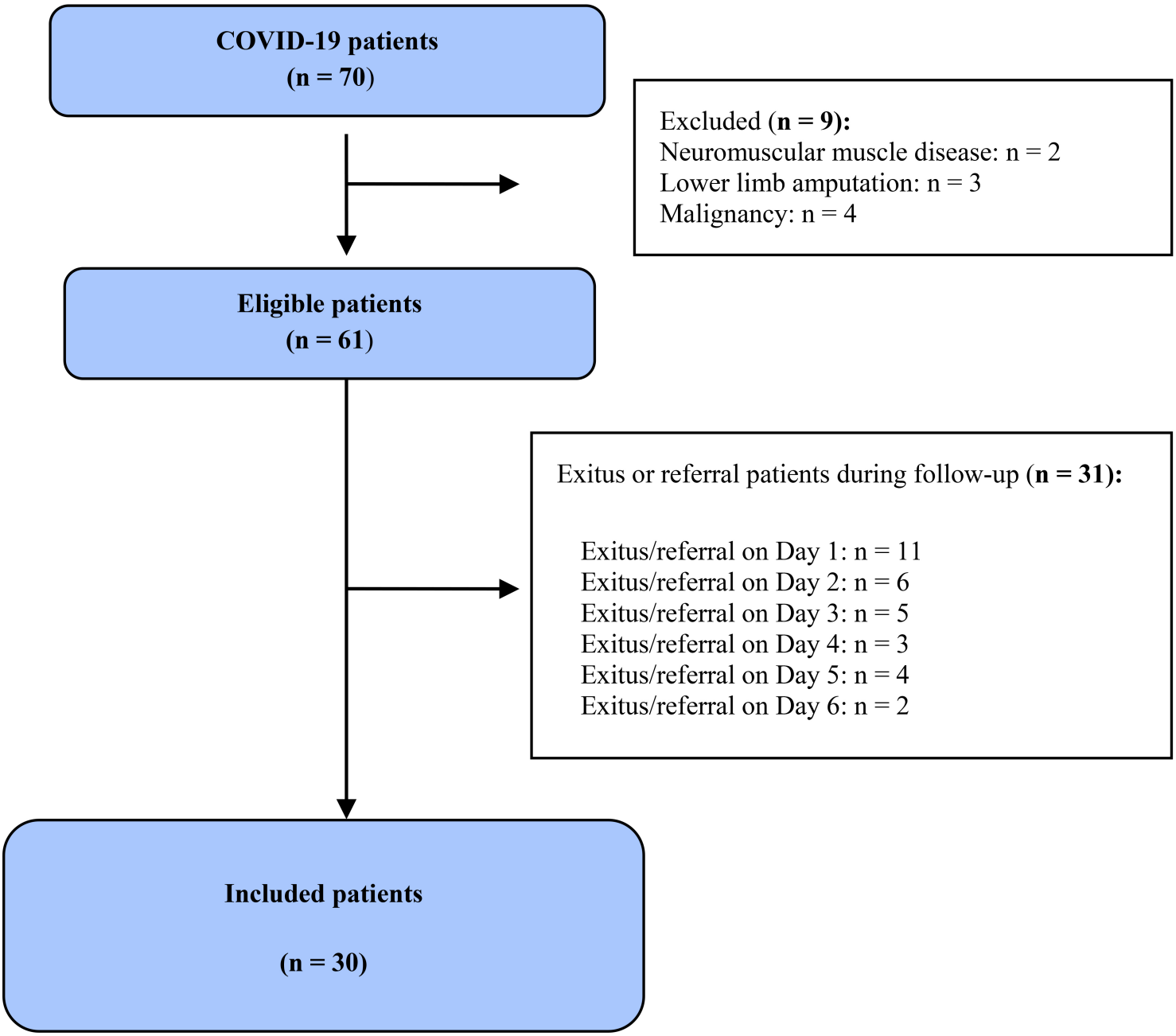

FIGURE 1. Study flowchart. COVID: coronavirus disease.

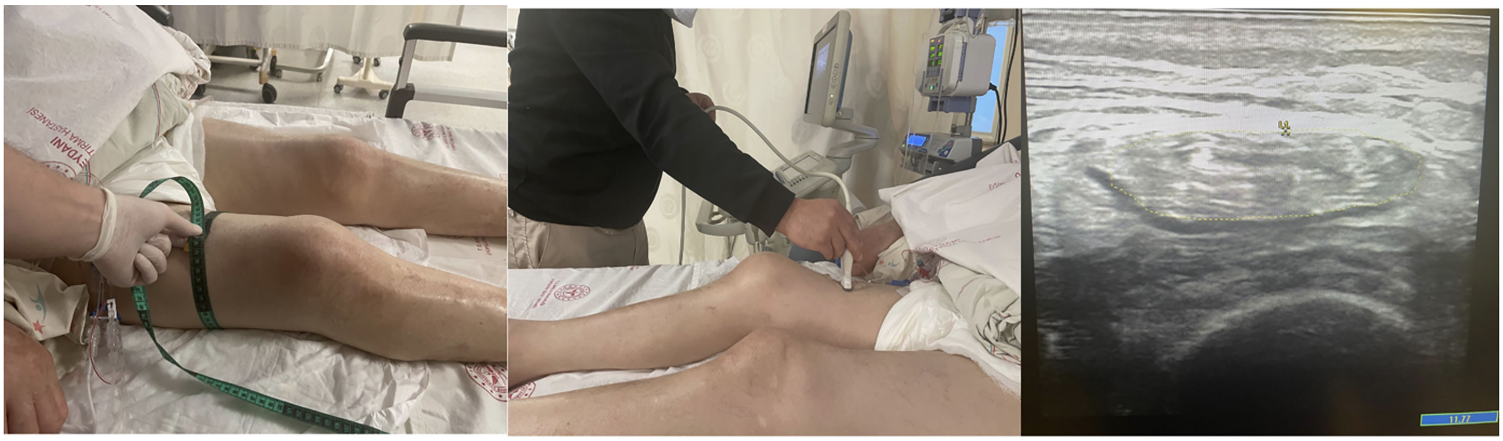

FIGURE 2. Anthropometric and ultrasonographic measurements of the muscle mass of bilateral rectus femoris muscles.

obstructive pulmonary disease. The majority of the patients (96.7%) used LMWH, while 93.3% did not use any diuretics, 100% received corticosteroid treatment, 96.7% were administered enteral feeding, and 90% of the patients achieved the target protein level during ICU stay. None of the patients used neuromuscular blockers. Half of the patients (50%) were discharged after treatment (Table 1).

The mean ultrasonographic measurement of the muscle mass of the right rectus femoris significantly differed over time ($p < 0.001$). The muscle mass loss of the right rectus femoris was 16.8% at Week 1, 19.7% at Week 2, 33.4% at Week 3, indicating an overall loss of 47.9% (Table 2). The mean ultrasonographic measurement of the muscle mass of the left rectus femoris significantly differed over time ($p < 0.001$). The muscle mass loss of the left rectus femoris was 12.7% at Week 1, 16.7% at Week 2, 35% at Week 3, indicating an overall loss of 52.8% (Table 2).

The mean anthropometric measurement of the muscle mass of the right rectus femoris significantly differed over time ($p < 0.001$). The muscle mass loss of the right rectus femoris was 4.3% at Week 1, 10.7% at Week 2, 12.6% at Week 3, indicating an overall loss of 25.3% (Table 2). The mean anthropometric measurement of the muscle mass of the left rectus femoris significantly differed over time ($p < 0.001$). The muscle mass loss of the left rectus femoris was 4.9% at Week 1, 16.25% at Week 2, 14.9% at Week 3, indicating an overall loss of 25.4% (Table 2).

The median MRC score of the right lower limb significantly differed over time ($p = 0.009$). The median MRC score of the right lower limb was 5 (range, 5 to 5), on Day 1, 4 (range, 3 to 5) on Day 7, 3 (range, 3 to 4) on Day 1 and 3 (range, 2 to 3) on Day 21 (Table 2). The median MRC score of the left lower limb significantly differed over time ($p = 0.009$). The median MRC score of the left lower limb was 5 (range, 5 to 5), on Day 1, 4 (range, 3 to 5) on Day 7, 3 (range, 3 to 4) on Day 1 and 3 (range, 2 to 3) on Day 21 (Table 2).

The median fluid intake-output difference significantly differed over time ($p = 0.009$). The median fluid intake-output difference was −200 mL (range, −2290 mL to −1000 mL) on Day 1, −500 mL (range, −2000 mL to −1100 mL) on Day 7, −500 mL (range, −3600 mL to −1440 mL) on Day 14, and −942 mL (−2000 mL to −200 mL) on Day 21 (Table 3).

The median corticosteroid dose used in the treatment significantly differed over time ($p < 0.001$). The median corticosteroid dose was 240 mg methylprednisolone on Day 1, 160 mg methylprednisolone on Day 7, 80 mg methylprednisolone on Day 14, and 40 mg methylprednisolone on Day 21 (Table 3).

There was no statistically significant difference in the SOFA (p: 0.605) and creatine kinase (p: 0.960) values during follow-up (Table 3).

5. Discussion

Intensive care unit-acquired weakness is associated with several adverse outcomes such as prolonged weaning from mechanical ventilation and its effects may persist even years after discharge due to impaired physical functions [17]. Some of the major risk factors for ICU-induced muscle weakness are time spent in the ICU, age, female gender, systemic inflammation, and sepsis. Muscle weakness can result from muscle atrophy, decreased specific tension (strength for size), or both [18]. Several studies have shown that critical illness may lead to involuntary muscle mass loss, as well as severe neuromuscular dysfunction and ICU-AW [19, 20]. In the present study, we evaluated rectus femoris muscle mass of ICU patients with COVID-19 both ultrasonographically and anthropometrically. Our study results showed that the muscle mass loss of the rectus femoris was 23% weekly and 25% at Week 3 based on ultrasonographic measurements, while the muscle mass loss was 9.2% weekly and 25.4% at Week 3 based on anthropometric measurements. In addition, the MRC scores of the lower limb decreased by one unit every week.

Ultrasonography is a widely used tool to measure the muscle both qualitatively and quantitatively. It is a non-invasive and pain-free method and does not require patient participation [13]. In a study including 21 critically ill patients, Puthucheary *et al.* [21] evaluated the patients by serial ultrasonography and reported a 10.3% decline in the CSA of the rectus femoris between Days 1 and 7. On Day 7, the decline was more prominent in patients with multiple organ failure than those with single organ failure (15.7% *vs.* 27.7%; $p < 0.001$) [21]. In another study including 41 critically ill patients, Mayer *et al.* [22] found a 19% decline in the CSA of the rectus femoris in the first week of critical illness. In our study, the ultrasonographic CSA measurement showed a higher decline in the muscle mass of the rectus femoris in patients with COVID-19 pneumonia than the study of Puthucheary *et al.* [21], but a lower decline than the study of Mayer *et al.* [22] this discrepancy between our study and the aforementioned studies can be attributed to the clinical status of the patients as assessed by the SOFA and APACHE II, additional treatments, and patient adherence to physical therapy. Despite controversial results in the muscle mass loss between the studies, prolonged ICU stay is associated with a higher muscle mass loss [23].

Intensive care unit-acquired weakness is diagnosed by manual bedside testing of the muscle strength in awake and cooperated patients and the severity is scored by the MRC sum scores [24]. Three muscle groups in the lower and upper limbs are assessed. The muscle power is graded using the muscle scale ranging from 0 to 5 with 0 being no muscle contraction and 5 being normal muscle strength, giving a maximum score of 60. A sum MRC muscle strength score of <48 indicates ICU-AW. In a recent study by Rahiminezhad *et al.* [7], 15 patients with COVID-19 pneumonia were compared with 15 critically ill patients without COVID-19 in the ICU setting. Using the hand dynamometer and MRC scores, the muscle strength of the lower and upper limb of the patients infected with COVID-19 was significantly lower than those without COVID-19. On Day 4 of the ICU stay, 80% of the COVID-19-positive patients and 40% of the COVID-19-negative patients were diagnosed with ICU-AW. Overall, 86.8% of the patients were diagnosed with ICU-AW on Day 7. In the current study, we were unable to evaluate all muscle groups, but only the muscle strength of the upper leg was assessed based on MRC scores. According to our results, each parameter decreased by one unit: the muscle strength was 5/5 at the time of ICU admission, while it regressed to 3/5 at Week 2 and 2/5 at Week 3. Based on anthropometric measurements,

TABLE 1. Descriptive data of patients.

	n	%
Sex		
Female	10	33.3
Male	20	66.7
Comorbid diseases		
DM	4	23.5
HT	9	52.9
DM + HT	3	17.6
Asthma/COPD	1	5.9
Inotropic support		
No	30	100.0
LMWH		
Yes	29	96.7
No	1	3.3
Diuretics		
Yes	2	6.7
No	28	93.3
Corticosteroids		
Yes	30	100.0
Enteral feeding		
Yes	29	96.7
No	1	3.3
Parenteral feeding		
Yes	2	6.7
No	28	93.3
PaO_2/FiO_2		
Mild ($\geq$300 PaO_2/FiO_2 >200)	13	43.3
Moderate ($\geq$200 PaO_2/FiO_2 >100)	15	50.0
Severe (PaO_2/FiO_2 $\leq$100)	2	6.6
Neuromuscular blockers		
No	30	100.0
Targeted protein		
Yes	27	90.0
No	3	10.0
Exitus	n = 12	40.0
	Mean $\pm$ SD	Median (min-max)
Age	63.72 $\pm$ 11.68	63.5 (45–83)
LOS before ICU admission (day)	1.56 $\pm$ 0.70	1 (1–3)
GCS	14.89 $\pm$ 0.47	15 (13–15)
CRP	44.23 $\pm$ 45.39	32 (3–186)
SOFA	7.39 $\pm$ 2.40	7 (4–12)
qSOFA	1.11 $\pm$ 0.32	1 (1–2)
APACHE II	12.11 $\pm$ 3.12	11.5 (7–18)

TABLE 1. Continued.

	n	%
NIMV (day)	6.39 ± 6.79	3 (1–21)
qSOFA	1.11 ± 0.32	1 (1–2)
APACHE II	12.11 ± 3.12	11.5 (7–18)
NIMV (day)	6.39 ± 6.79	3 (1–21)
IMV (day)	9.06 ± 5.60	7.5 (2–20)
LOS in the ICU (day)	16.28 ± 5.95	16 (7–23)
NRS-2002	2.50 ± 1.29	3 (1–4)

DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; LMWH: low-molecular-weight heparin; PaO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; LOS: length of stay; ICU: intensive care unit; GCS: Glasgow Coma Scale; APACHE II: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; NIMV: non-invasive mechanical ventilation; IMV: invasive mechanical ventilation; NRS-2002: Nutrition Risk Screening 2002; SD: standard deviation; CRP: C-reactive protein.

TABLE 2. Comparison of ultrasonographic and anthropometric parameters at different time points.

	Mean ± SD	Median (min-max)	Test statistics	*p* value
Ultrasonographic measurement of right rectus femoris muscle mass				
Day 1	2.19 ± 0.67	2.07 (1.23–3.89)	36.691	<0.001*
Day 7	1.82 ± 0.55	1.85 (0.72–2.9)		
Day 14	1.46 ± 0.38	1.50 (0.8–2.15)		
Day 21	1.14 ± 0.44	1.23 (0.5–1.69)		
Ultrasonographic measurement of left rectus femoris muscle mass				
Day 1	2.12 ± 0.53	1.98 (1.2–2.99)	25.593	<0.001*
Day 7	1.85 ± 0.52	1.82 (0.95–2.83)		
Day 14	1.54 ± 0.48	1.52 (0.75–2.68)		
Day 21	1.00 ± 0.42	1.05 (0.25–1.55)		
Anthropometric measurement of right rectus femoris muscle mass				
Day 1	50.93 ± 7.74	51.5 (32–72)	100.472	<0.001*
Day 7	48.70 ± 7.33	49.0 (30–67)		
Day 14	43.57 ± 7.68	44.0 (27–60)		
Day 21	38.00 ± 6.96	38.0 (30–49)		
Anthropometric measurement of left rectus femoris muscle mass				
Day 1	51.07 ± 7.68	52.5 (33–70)	89.972	<0.001*
Day 7	48.53 ± 7.20	49.0 (30–66)		
Day 14	43.69 ± 7.89	43.0 (28–62)		
Day 21	38.00 ± 6.22	39.0 (30–48)		
Right upper limb MRC score				
Day 1	5.00 ± 0.0	5 (5–5)	11.500	0.009**
Day 7	4.18 ± 0.50	4 (3–5)		
Day 14	3.40 ± 0.52	3 (3–4)		
Day 21	2.67 ± 0.52	3 (2–3)		
Left upper limb MRC score				
Day 1	5.00 ± 0.0	5 (5–5)	11.500	0.009**
Day 7	4.14 ± 0.47	4 (3–5)		
Day 14	3.40 ± 0.52	3 (3–4)		
Day 21	2.67 ± 0.52	3 (2–3)		

**Repeated measures analysis of variance. **Friedman test. SD: standard deviation; MRC: Medical Research Council.*

TABLE 3. Comparison of tracked parameters at different time points.

Parameters				
Total calorie intake (kcal/day)				
Day 1	1861.07 ± 340.53	1940 (900–2500)	2.288	0.515**
Day 7	1914.00 ± 337.70	2000 (950–2500)		
Day 14	1876.19 ± 357.99	2000 (950–2500)		
Day 21	1888.89 ± 242.10	2000 (1500–2200)		
SOFA score				
Day 1	7.33 ± 2.14	7 (4–12)	1.846	0.605**
Day 7	8.30 ± 3.12	8 (4–15)		
Day 14	9.48 ± 4.12	10 (4–15)		
Day 21	9.22 ± 3.77	10 (3–15)		
Creatine kinase (U/L)				
Day 1	197.54 ± 189.82	144 (25–690)	0.300	0.960**
Day 7	193.86 ± 517.49	76.5 (22–2794)		
Day 14	110.89 ± 135.36	65 (16–567)		
Day 21	125.83 ± 99.31	121.5 (26–250)		
Fluid intake-output difference (mL)				
Day 1	−292.70 ± 582.32	−200 (−2290–1000)	11.533	0.009**
Day 7	−433.27 ± 686.11	−500 (−2000–1100)		
Day 14	−602.14 ± 958.44	−500 (−3600–1440)		
Day 21	−1079.11 ± 685.34	−942 (−2000–−200)		
Prednizolon (mg)				
Day 1	234.48 ± 20.63	240 (160–240)	25.588	<0.001**
Day 7	146.90 ± 44.49	160 (20–240)		
Day 14	80.48 ± 54.45	80 (20–250)		
Day 21	42.22 ± 23.33	40 (20–80)		

*Data are given in mean ± SD or median (min-max), unless otherwise stated. *Repeated measures analysis of variance. **Friedman test. SOFA: Sequential Organ Failure Assessment.*

the muscle strength decreased by 4% at the end of the first week, indicating a discrepancy between the ultrasonographic and anthropometric measurements. This can be attributed to edema related to corticosteroid treatment and localized edema related to prone position.

Intensive care unit-acquired weakness is a clinical condition characterized by underlying critical illness such as polyneuropathy, myopathy, and muscle atrophy. In particular, acute respiratory distress syndrome, sepsis, prolonged mechanical ventilation and prolonged hospital stay is associated with ICU-AW [25]. Physical impairments due to ICU-AW may cause short- and long-term functional sequelae, adversely affecting the daily living activities of the patients and prolonging the duration of return to work [13]. As of December 2019, COVID-19 pandemic has had major effects worldwide and COVID-19 pneumonia is a critical illness with varying clinical presentations. Severe COVID-19 patients are at an increased risk of muscle mass loss due to ICU-AW, as they have multiple risk factors such as ARDS, sepsis, and multiple organ failure [13].

Severe COVID-19 has been shown to be associated with the prolonged ICU stay (10.6 days on average, ranging from 1.3 to 30.8% for 95% of patients) and prolonged duration of mechanical ventilation (7.3 days on average) [26, 27]. In a meta-analysis including 14 studies, the incidence of ICU-AW was higher in patients with prolonged mechanical ventilation (33% for ≤5 days *vs.* 43% for ≥7 days) [28]. Therefore, this patient population should be paid a special attention for ICU-AW. In our study, the patients were followed for 16 days on average in the ICU and needed mechanical ventilation support for about nine days. Consistent with previous studies, prolonged ICU stay and mechanical ventilation is associated with ICU-AW.

Many studies have already been conducted in the ICU, with some examining the association between muscle changes and ICU-acquired weakness (ICU-AW) or mortality from muscle ultrasound results over time. One study showed that decreased muscle thicknes or CSA in the lower extremities at 10 days (15% and 12%, respectively) had good diagnostic accuracy for ICU-AW while another study showed that an elevated echo intensity (EI) of the rectus femoris (RF) muscle at 7 days predicted ICU-AW at hospital discharge. In terms of mortality,

a recent study found that a decrease in quadriceps muscle thickness (MT) at 7 days was an independent predictor of 60-day mortality, whereas another study of patients with COVID-19 found that reduced CSA and EI of the RF at 7 days were also associated with death during ICU stays [29]. In our study, if we did not evaluate whether muscle loss is directly related to death, we see that 40% of the patients died. It is possible that muscle wasting is associated with death, supporting other studies, and more extensive studies should be conducted.

Corticosteroids are standard of care for COVID-19 patients. Compared to placebo, systemic corticosteroid treatment has been reported to be lower 28-day all-cause-mortality rates among COVID-19 patients [30]. However, the effect of corticosteroids on ICU-AW still remains to be elucidated. Long-term corticosteroid treatment may lead to myopathies and inhibit the protein synthesis of the muscle, thereby contributing to the development of ICU-AW and muscle mass loss [13]. Andrade-Junior *et al.* [31] found a weak correlation between the hydrocortisone dose and hand grip strength ($r = -0.49$, $p = 0.003$) and MRC scores ($r = 0.50$, $p = 0.003$), while there was no significant correlation between the CSA of the rectus femoris, thickness of the anterior compartment of the quadriceps muscle, and echogenicity in 32 ICU patients with COVID-19. In our study, all patients were administered high-dose corticosteroid treatment (prednisolone 240 mg) and maintained routine treatment with down-titrated doses [31].

Although there is an evident link between physical inactivity, chronic inflammation, oxidative stress, and muscle dysfunction, the effect of COVID-19-related hypoxemia on the muscle mass has not been much studied. In an animal study, Agrawal *et al.* [32] evaluated chronic hypobaric hypoxia (CHH)-exposed mice. The CHH exposed rats showed significantly lower skeletal muscle weights and tibia length ratio than the control rats. On Day 0 to 7, an 18.5% decrease was observed, increasing up to 23% on Day 14. This finding indicates the time-dependent muscle mass loss [32]. In addition, skeletal muscle creatine phosphokinase activity (CPK) in response to CHH was measured. Compared to the control rats, a significant decrease (45%) in the CPK content in the muscle homogenate was observed within 14 days after CHH exposure. In our study, 46% of the patients had mild hypoxemia, while the remaining patients had moderate or severe hypoxemia. On Day 14, we observed a 50% decrease in the CPK levels in these patients.

Nonetheless, there are some limitations to this study. The study center has only a six ICU bed capacity for COVID-19 patients. In addition, the patients were followed for only three weeks. The lack of personnel for COVID-19 ICU and time-wasting procedures for the ultrasonographic and anthropometric measurements are the other limitations. Furthermore, as our ICU is a Level 2 ICU, no critical illness other than COVID-19 can be followed. Thus, all patients were evaluated in a single group, which can be considered another limitation. Another limitation is that the evaluation of muscle strength and muscle thickness of the patients after the intensive care unit could be followed up in the long term. However, this follow-up was not possible due to the restriction of the patients admitted to the hospital due to the pandemic conditions and the efforts to ensure that the patients were discharged as soon as possible.

Of note, during the COVID-19 pandemic, there is a paradigm shift in the treatment algorithms of ARDS [33]. It is well known that ICU-AW may result from both COVID-19-related critical illness and treatments applied. Considering the effect of individual differences, clinical status of patients, and controllable and uncontrollable factors on muscle groups, further large-scale, prospective studies are warranted.

6. Conclusions

In conclusion, COVID-19 pandemic has affected many aspects of individual's lives worldwide. A substantial number of patients required hospitalization, leading to a major public health emergency. The majority of hospitalized patients required intensive care due to critical illness. Based on our study results, ICU patients with COVID-19 should be evaluated for ICU-AW as those with critical illness and a structured treatment plan should be developed for this special patient population. Early mobilization and treatment approaches may be helpful to avoid functional impairments. All patients should be provided rehabilitation protocols and services to enhance recovery and meet functional needs during both acute and chronic illness.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

AUTHOR CONTRIBUTIONS

HC—conceptualization, methodology, software, formal analysis, data collection, data interpretation, writing, original draft, review & editing; GCC—conceptualization, methodology, software, formal analysis, data collection, data interpretation, writing, original draft, review & editing; OK—formal analysis, data collection, data interpretation, writing, original draft, review & editing; FU—methodology, supervision. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Haseki Training and Research Hospital Clinical Research Ethics Committee with the Approval No: 26-2021 and Date: 26 May 2021. All patients and/or legal guardians of the patients were informed about the nature of the study and a written informed consent was obtained. The study was conducted in accordance with the CONSORT checklist and principles of the Declaration of Helsinki. The study was registered at ClinicalTrials.gov with the number NCT05008562.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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