Functional Outcomes and Their Association With Physical Performance in Mechanically Ventilated Coronavirus Disease 2019 Survivors at 3 Months Following Hospital Discharge: A Cohort Study

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OBJECTIVES: We performed a comprehensive health assessment in mechanically ventilated coronavirus disease 2019 survivors to assess the impact of respiratory and skeletal muscle injury sustained during ICU stay on physical performance at 3 months following hospital discharge.

DESIGN: Preregistered prospective observational cohort study.

SETTING: University hospital ICU.

PATIENTS: All mechanically ventilated coronavirus disease 2019 patients admitted to our ICU during the first European pandemic wave.

MEASUREMENTS AND MAIN RESULTS: At 3 months after hospital discharge, 46 survivors underwent a comprehensive physical assessment (6-min walking distance, Medical Research Council sum score and handgrip strength), a full pulmonary function test, and a chest CT scan which was used to analyze skeletal muscle architecture. In addition, patient-reported outcomes measures were collected. Physical performance assessed by 6-minute walking distance was below 80% of predicted in 48% of patients. Patients with impaired physical performance had more muscle weakness (Medical Research Council sum score 53 [51–56] vs 59 [56–60]; $p < 0.001$), lower lung diffusing capacity (54% [44–66%] vs 68% of predicted [61–72% of predicted]; $p = 0.002$), and higher intermuscular adipose tissue area ($p = 0.037$). Reduced lung diffusing capacity and increased intermuscular adipose tissue were independently associated with physical performance.

CONCLUSIONS: Physical disability is common at 3 months in severe coronavirus disease 2019 survivors. Lung diffusing capacity and intermuscular adipose tissue assessed on CT were independently associated with walking distance, suggesting a key role for pulmonary function and muscle quality in functional disability.

KEY WORDS: coronavirus disease 2019; follow-up; functional outcomes; muscle function; pulmonary function

Long-term functional impairment is common among critically ill patients and represents a major challenge for intensivists and ICU survivors (1–3). Studies in survivors of acute respiratory failure have demonstrated the detrimental effects of prolonged mechanical ventilation, sedation, and

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neuromuscular blockade on respiratory and physical function (3, 4). The emergence of the current severe acute respiratory syndrome coronavirus 2 pandemic has resulted in a high number of coronavirus disease 2019 (COVID-19)–related ICU admissions characterized by severe hypoxemic respiratory failure requiring mechanical ventilation (5, 6). Prolonged periods of mechanical ventilation and respiratory and skeletal muscle injury sustained during ICU admission put severe COVID-19 survivors at increased risk for persistent functional disability (7–9). To what extent respiratory and skeletal muscle injury impacts the physical performance of mechanically ventilated COVID-19 survivors is yet to be determined.

Physical performance can be assessed by the 6-minute walking distance (6MWD) (10). The 6MWD is a standardized, objective assessment of physical performance, integrating cardiopulmonary and skeletal muscle function and is a widely used activity measure in COVID-19 outcome studies (11). Furthermore, it is the preferred measure for physical functioning as part of the extended core outcome measure set for respiratory failure survivors, together with handgrip strength and the Medical Research Council (MRC) sum score as measures of muscle function (12). In addition to muscle function, CT-derived skeletal muscle architecture can be obtained and is an established determinant of poor outcome in ICU patients (13, 14).

Data on functional outcomes of COVID-19 survivors are still sparse, and factors potentially contributing to worse functional outcomes are poorly characterized (15, 16). In the current study, we performed a comprehensive assessment of pulmonary and physical function in mechanically ventilated COVID-19 survivors at 3 months following hospital discharge. We hypothesized that both pulmonary function as well as CT-derived skeletal muscle architecture and function would be associated with physical impairment at 3 months in mechanically ventilated COVID-19 survivors.

METHODS

Participants

All patients admitted to our ICU requiring mechanical ventilation due to COVID-19 are consecutively included in a prospective cohort study (Maastricht Intensive Care Cohort [MaastrICCht] Intensive Care COVID cohort, Netherlands Trial Register NL8613) (17). Patients included in this cohort during the first European pandemic wave between March and June 2020 and who survived ICU admission were invited to attend a post-ICU clinic at 3 months following hospital discharge. At follow-up, participants underwent a full pulmonary function test (PFT), a high-resolution CT (HRCT) scan of the chest, a detailed physical assessment, and completed a bundle of questionnaires assessing health-related quality of life (QoL), fatigue, and mental health. Institutional Review Board approval was obtained for this study (METC azM/UM, METC 2020-1565 and METC 2020-2287), and written informed consent for data collection was obtained from all participants. Clinical information was collected during ICU admission (17, 18). During ICU admission, early physiotherapy with daily passive/active mobilization sessions with or without in-bed cycle ergometry was part of routine care. Nutritional support was provided according to current guidelines, with energy targets set at 25 kcal/kg/d and protein targets set at 1.3 g/kg/d (19).

Functional Outcomes

Physical Performance. Physical performance was the main outcome at 3 months follow-up and was assessed using the 6-minute walk distance (6MWD). The 6MWD was performed according to a standardized protocol (10). The absolute distance walked and relative values as a percentage of predicted are presented (20). Physical performance was considered to be impaired when 6MWD was below 80% of the predicted value for participants (21).

PFT. Participants underwent a full PFT according to American Thoracic Society and European Respiratory Society guidelines (22). Results are presented as absolute values and as a percentage of predicted based on age- and sex-matched controls using Global Lung Initiative reference values (23).

Muscle Function. Handgrip strength was assessed using a hand dynamometer (JAMAR; Sammons Preston Rolyan, Bolingbrook, IL) (24, 25). The MRC sum score evaluates bilateral strength for six muscle groups. Each group is scored on a five-point scale ranging from 0 (no visible contraction) to 5 (normal strength) per group and amount to a maximum score of 60 (26). Established cut offs were used to assess the presence of ICU acquired weakness (ICU-AW, MRC sum < 48) or moderate weakness with increased risk for morbidity (MRC sum ≤ 55) (27).

CT-Derived Skeletal Muscle Architecture. A HRCT scan of the chest was made to assess residual lesions of COVID-19 pneumonia. Axial slices were selected at the most cranial level of the 12th thoracic vertebra at the sight of both transverse processes. CT slices were analyzed based on their radiation attenuation values expressed in Hounsfield units (HUs) using sliceOmatic software (TomoVision, Magog, QC, Canada). Established attenuation ranges for skeletal muscle (–29 to 150 HU) and adipose tissue (–190 to –0 HU) were used to mark all skeletal muscle tissue (excluding the diaphragm) and intermuscular adipose tissue (IMAT) located within the erector spinae muscles (**Fig. 1**) (28). Total skeletal muscle area (SMA), skeletal muscle radiation attenuation (SM-RA) as a measure of intramuscular adipose tissue, and IMAT values were obtained (29).

Patient-Reported Outcome Measures. Health-related QoL was assessed using the Euro-QoL-5D (EQ-5D) 5-level based on five domains (mobility, self-care, daily activities, pain, and anxiety/depression) on a five-level scale (30). These results were converted to a country-specific Health Utility Score (EQ-5D HUS) ranging from 0 (death) until 1 (perfect health) using the Dutch-specific, validated index value set (31). In addition, participants rated their experienced QoL on a Visual Analogue Scale from 0 to 100. Fatigue was assessed using the multidimensional fatigue inventory (MFI), a 20-item scale ranging from 20 to 100 with increasing scores representing increasing fatigue (32). The Hospital Anxiety and Depression Scale (HADS) was used to assess psychologic consequences with subscores for anxiety and depressive symptoms, respectively (33). The Montreal cognitive assessment (MoCA) was used to screen for the presence of cognitive impairment, defined as a MoCA score below 26 (34).

Statistical Analysis

Data are presented as mean (± SD), median (first, third quartile), or count (percentages), as appropriate. Data analyses are performed in R (v3.6.2;

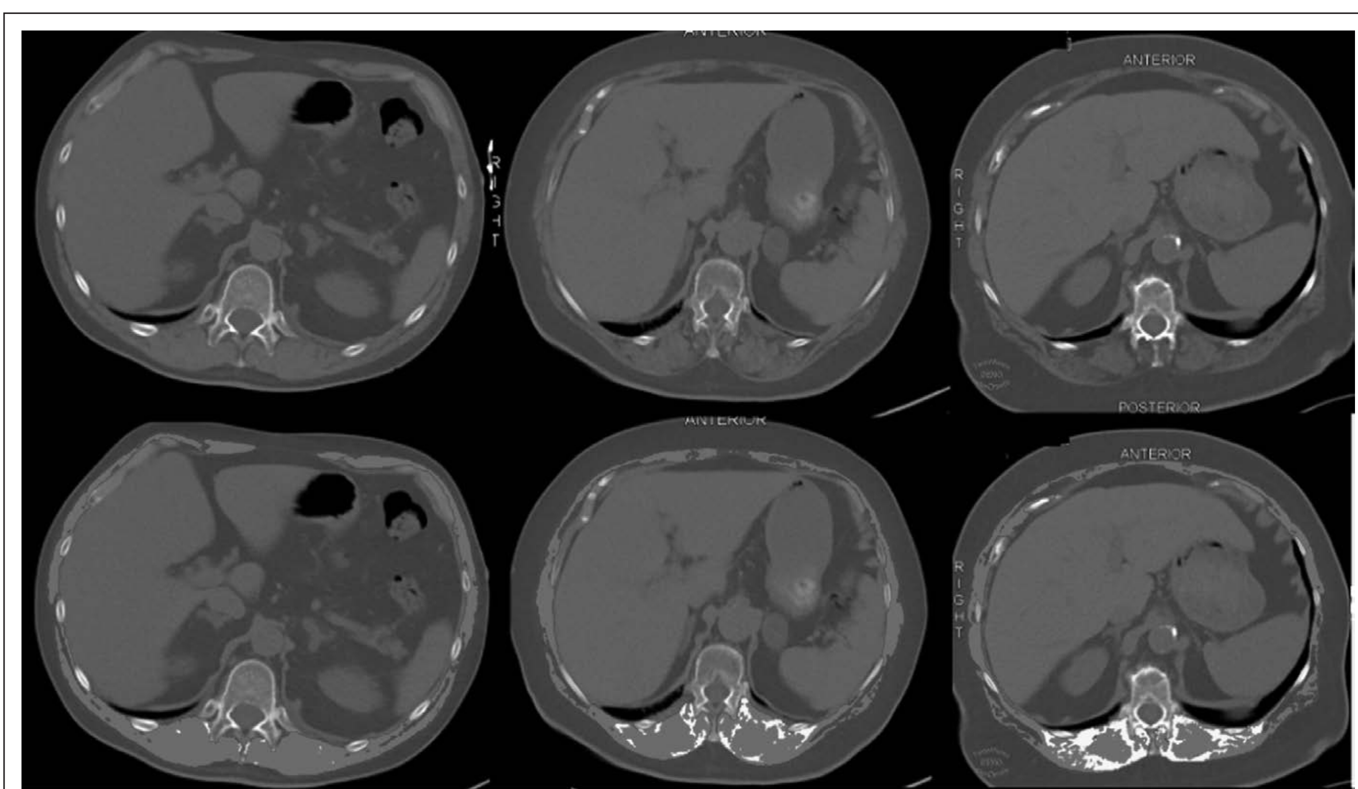

Figure 1. CT-derived skeletal muscle analysis at the 12th thoracic vertebrae level, showing skeletal muscle area and intermuscular adipose tissue surrounding erector spinae muscle. *Top row* shows high-resolution CT slices of three patients without tissue marking and *bottom row* shows the same slices with tissue marking in order of increasing intermuscular adipose tissue area.

https://cran.r-project.org/). Baseline characteristics and outcomes between patients with impaired and normal physical performance are compared using an independent *t* test, Mann-Whitney *U* or Fisher exact test as appropriate with statistical significance set at *p* value of less than 0.05.

Linear regression models were used to investigate the cross-sectional associations between pulmonary function (diffusing capacity for carbon monoxide adjusted for hemoglobin [DLCOc]) and walking distance (6MWD), between muscle function (handgrip strength) and walking distance, and between CT-derived skeletal muscle quality (IMAT) and walking distance. Associations are presented as crude models (model 1), age and sex adjusted (model 2), and for each of the main determinants (model 3). Both absolute values as well as relative values (% of predicted values) were used, with the exception of IMAT, for which no reference values are available. Model assumptions were checked by visual inspection of the plotted residuals versus predicted values, normal distribution of the standardized residuals, and the pp-plot. We present β with 95% CIs, with a *p* value of less than 0.05 considered statistically significant.

Additional Pulmonary Follow-Up

Between completion of follow-up and article submission, PFTs were repeated on clinical indication at 7 months following hospital discharge in a subset of patients. Clinical indications were determined by the pulmonologist based on respiratory function, complaints, and chest CT results.

RESULTS

Patients

During the first pandemic wave, 94 patients were admitted to our ICU and included into the MaastrICCht cohort between March and June 2020. Fifty-eight (62%) survived ICU admission, and 52 patients (55%) were alive at 3 months after hospital discharge. The six patients who did not survive after ICU discharge, all died in hospital following respiratory insufficiency and a "no reintubation" code after prolonged ICU stay. In total, 46 patients participated in the current study (**Fig. S1**, http://links.lww.com/CCM/G479; **legend:** patient flowchart detailing the number of patients admitted to the ICU and recruited into the study cohort and those that the full follow-up). Follow-up occurred at a median of 120 days (103, 135 d). Baseline characteristics and their distribution between patients with normal and impaired 6MWD (< 80% of predicted) are detailed in **Table 1**. All patients were supported by invasive mechanical ventilation (IMV) with a median IMV duration of 19 days (10, 29 d). Three patients received extracorporeal membrane oxygenation during admission. Following hospital discharge, the vast majority of ICU survivors (85%) were referred for clinical rehabilitation in a dedicated rehabilitation center. Three of them were still admitted to a rehabilitation center at the time of follow-up.

Physical Assessment at 3 Months

Functional outcomes at follow-up are shown in **Table 2**. Median 6MWD was 480 meters (380, 536 meters) , equivalent to 81% of predicted (70%, 99% of predicted) distance. Twenty-two participants (48%) had a 6MWD below 80% of predicted. Baseline demographics, disease severity scores, and admission characteristics were not significantly different between participants with normal or impaired 6MWD at follow-up (Table 1). However, participants with impaired 6MWD at 3 months follow-up had spent significantly more days on ventilatory support, in hospital, and at a rehabilitation facility (median 23 [14, 24] vs 9 d [4, 17 d]; $p = 0.003$).

Pulmonary Function

Reduced diffusing capacity was the dominant feature seen in pulmonary function, with a median DLCOc of 62% of predicted (51%, 70% of predicted). DLCOc was significantly lower in participants with impaired 6MWD. Both forced expiratory volume in 1 second, and total lung capacity (TLC) appeared less affected in participants at the 3-month follow-up.

Skeletal Muscle Strength

At follow-up, mean (± SD) handgrip strength was 29.4 (± 9.3) kg, corresponding to 81% (± 17) of predicted. Median MRC sum was 56 (53, 59). One participant met the criteria for ICU-AW (MRC sum < 48) at 3-month follow-up, whereas moderate weakness (MRC sum ≤ 55) was identified in 18 patients (40%). Survivors

TABLE 1.
Baseline Admission Characteristics and Their Distribution Between Patients With Normal and Impaired Physical Performance (< 80% of Predicted 6-min Walking Distance) at 3 Months Following Hospital Discharge

Characteristic	Overall ($n = 46$)	Physical Performance (6-min Walking Distance) Impaired ($n = 22$)	Normal ($n = 24$)	p
Age (yr), median (first, third quartile)	62 (55, 68)	62 (59, 73)	64 (54, 67)	0.291
Sex (male), n (%)	32 (69.6)	17 (77.3)	15 (62.5)	0.443
Body mass index (kg/m^2), median (first, third quartile)	27.7 (25.0, 30.5)	27.9 (25.2, 30.9)	27.4 (25.3, 28.5)	0.598
Charlson comorbidity index, median (first, third quartile)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	0.442
Current smoker (yes), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	Not applicable
Former smoker (yes), n (%)	21 (47.7)	8 (38.1)	13 (56.5)	0.357
Acute Physiology And Chronic Health Evaluation II score, median (first, third quartile)	15 (13, 18)	17 (13, 18)	14 (13, 16)	0.132
Simplified Acute Physiology Score II score, median (first, third quartile)	36 (30, 43)	34 (30, 41)	38 (30, 44)	0.291
Admission characteristics				
Pa_{O_2}/F_{IO_2} ratio (kPa), median (first, third quartile)	16 (12, 21)	15 (11, 19)	17 (14, 23)	0.290
Inspiratory pressure (cm H_2O), mean (SD)	26 (4)	26 (4)	26 (4)	0.826
Positive end-expiratory pressure (cm H_2O), median (first, third quartile)	14 (12, 14)	14.0 (13.5, 16.0)	14 (14, 16)	0.151
Dynamic compliance (mL/H_2O), mean (SD)	40.7 (14.4)	41.9 (15.7)	39.2 (13.0)	0.664
C-reactive protein (mg/L), median (first, third quartile)	191 (101, 262)	216 (101, 268)	182 (93, 243)	0.403
Leucocyte count (10E^{-9}/L), median (first, third quartile)	8.9 (7.8, 10.6)	9.1 (7.8, 11.1)	8.9 (8.0, 10.0)	0.733
Hemoglobin (mmol/L), mean (SD)	7.6 (1.2)	7.4 (1.3)	7.8 (1.2)	0.336
Thrombocyte count (10E^{-9}/L), mean (SD)	271 (104)	257 (90)	285 (116)	0.361
Albumin (g/L), mean (SD)	22.6 (5.6)	22.2 (5.0)	23.1 (6.4)	0.580
Urea (mmol/L), median (first, third quartile)	6.1 (4.3, 8.2)	5.6 (4.6, 7.8)	7.1 (4.3, 8.5)	0.428
Creatinine (µmol/L), median (first, third quartile)	69 (58, 90)	72 (63, 88)	64 (52, 89)	0.286

(*Continued*)

TABLE 1. (*Continued*).
Baseline Admission Characteristics and Their Distribution Between Patients With Normal and Impaired Physical Performance (< 80% of Predicted 6-min Walking Distance) at 3 Months Following Hospital Discharge

Characteristic	Overall ($n = 46$)	Physical Performance (6-min Walking Distance) Impaired ($n = 22$)	Normal ($n = 24$)	p
Discharge characteristics				
Invasive mechanical ventilation duration (d), median (first, third quartile)	19 (10, 29)	27 (16, 32)	16 (9, 22)	0.029[b]
Days receiving neuromuscular blocking agents, median (first, third quartile)	5 (1, 8)	3 (1, 6)	6 (1, 9)	0.241
Received corticosteroids? (yes), mean (SD)	14 (30.4)	6 (25.0)	8 (36.4)	0.606
Days in ICU, median (first, third quartile)	22 (11, 34)	31 (19, 42)	18 (10, 23)	0.013[b]
Days in hospital, median (first, third quartile)	32 (21, 41)	38 (32, 48)	28 (20, 34)	0.002[c]
Hospital discharge location, n (%)				0.164
Home	6 (13.0)	1 (4.5)	5 (20.8)	
Nursing home	1 (2.2)	1 (4.5)	0 (0.0)	
Rehabilitation center	9 (84.8)	20 (90.9)	19 (79.2)	
Days in rehabilitation center, median (first, third quartile)	15 (8, 28)	22 (14, 34)	8 (4, 17)	0.003[c]

[a]Three patients were still admitted to a rehabilitation center at follow-up.
[b]$p < 0.05$.
[c]$p < 0.01$.
Differences analyzed using *t* test, Mann-Whitney *U*, or Fisher exact test as appropriate.

with an impaired 6MWD had lower relative handgrip strength and MRC sum score (Table 2).

Skeletal Muscle Architecture

CT-derived muscle analysis and differences between subgroups are presented in Table 2. Neither SMA nor SM-RA was significantly different between patients with impaired or normal 6MWD. IMAT area was significantly higher in patients with an impaired 6MWD.

Patient-Reported Outcomes

Health-related QoL was significantly lower in patients with impaired 6MWD (0.593 [± 0.201] vs 0.754 [± 0.148]; $p = 0.004$). Similar distributions were found for both fatigue and HADS scores ($p < 0.001$). Sixteen patients (35%) had a HADS score above 10, indicating that anxiety or depression is likely present. Finally, mild cognitive dysfunction (MoCA < 26) was found in 12 patients, nine of which were patients with impaired 6MWD ($p = 0.014$).

Associations With Physical Performance

We found a significant association between pulmonary function assessed by DLCOc and physical performance assessed by 6MWD (**Table 3**). The associations remained significant after adjustment in all models. Handgrip strength was also associated with physical performance. After adjustment for sex, age, DLCOc, and IMAT, this association remained significant when handgrip strength and 6MWD were expressed

TABLE 2.
Functional Outcomes at 3 Months

Functional Outcome	Overall ($n = 46$)	Physical Performance (6MWD) Impaired ($n = 22$)	Physical Performance (6MWD) Normal ($n = 24$)	p
Days following intubation, median (first, third quartile)	118 (105, 133)	124 (111, 143)	112 (104, 119)	0.010[a]
6MWD (meters), median (first, third quartile)	480 (380, 536)	382 (238, 440)	536 (483, 568)	< 0.001[c]
6MWD (% of predicted), median (first, third quartile)	80.8 (69.1, 99.3)	67.8 (48.6, 71.7)	99.0 (87.0, 105.6)	< 0.001[c]
Pulmonary function testing				
FEV1 (L), mean (SD)	3.0 (0.8)	2.8 (0.9)	3.1 (0.6)	0.131
FEV1 (% of predicted), mean (SD)	92.3 (19.1)	84.2 (19.7)	99.3 (15.9)	0.010[a]
TLC (L), mean (SD)	5.7 (1.5)	5.5 (1.9)	5.9 (1.2)	0.460
TLC (% of predicted), mean (SD)	87.3 (19.1)	81.9 (20.6)	91.9 (16.7)	0.094
DLCOc (mmol/min/kPa), median (first, third quartile)	5.4 (4.7, 6.3)	4.7 (4.3, 5.6)	5.8 (5.3, 6.4)	0.010[a]
DLCOc (% of predicted), median (first, third quartile)	62.0 (51.0, 69.5)	54.0 (44.2, 66.2)	68.0 (61.0, 72.0)	0.002[b]
Muscle function				
Handgrip strength (kg), mean (SD)	29.4 (9.3)	26.9 (9.2)	31.6 (9.0)	0.088
Handgrip strength (% of predicted), mean (SD)	81.0 (17.7)	73.7 (17.3)	87.4 (15.7)	0.008[b]
Medical Research Council sum score, median (first, third quartile)	56 (53, 59)	53 (51, 56)	59 (56, 60)	< 0.001[c]
CT-derived skeletal muscle architecture				
Skeletal muscle area (cm^2), mean (SD)	86.6 (19.8)	84.2 (18.1)	89.0 (21.4)	0.448
Skeletal muscle radiation attenuation (Hounsfield units), mean (SD)	30.4 (7.1)	28.7 (7.8)	32.1 (5.9)	0.125
Intermuscular adipose tissue (cm^2), median (first, third quartile)	2.2 (1.4, 3.5)	3.3 (1.4, 4.2)	2.1 (1.4, 2.6)	0.037[a]
Patient-reported outcomes				
EQ-5D Health Utility Score, mean (SD)	0.673 (0.192)	0.593 (0.201)	0.754 (0.148)	0.004[b]
EQ-5D Visual Analogue Scale, median (first, third quartile)	60.0 (50.0, 70.0)	60 (45, 60)	70 (60, 79)	0.016[a]
Multidimensional fatigue index, mean (SD)	62.5 (19.2)	72.7 (13.6)	52.8 (19.0)	< 0.001[c]
HADS, median (first, third quartile)	7 (4, 15)	15 (6, 20)	4 (3, 8)	0.004[b]
HADS depression	3 (1, 9)	9 (3, 11)	1 (1, 3)	< 0.001[c]
HADS anxiety	4 (2, 7)	5 (3, 9)	4 (2, 5)	0.069
Cognitive impairment (Montreal cognitive assessment < 26), mean (SD)	12 (29.3)	9 (52.9)	3 (12.5)	0.014[a]

6MWD = 6-min walk distance, DLCOc = diffusing capacity for carbon monoxide adjusted for hemoglobin, EQ-5D = Euro-quality of life-5D, FEV1 = forced expiratory volume in 1 s, HADS = Hospital Anxiety and Depression Scale, TLC = total lung capacity.

[a] $p < 0.05$.

[b] $p < 0.01$.

[c] $p < 0.001$.

Differences analyzed using *t* test or Mann-Whitney *U* as appropriate. Missing: five patients did not undergo high-resolution CT or scans were incomplete for analysis, five patients did not complete full pulmonary function test, three patients did not complete questionnaires.

TABLE 3.
Linear Regression Analyses Results

	Physical Performance (6-min Walking Distance)					
Variable	**Absolute β**	**95% CI**	***p***	**Relative β**	**95% CI**	***p***
DLCOc						
Model 1: crude	35.5	(13.7–57.3)	0.002[b]	0.62	(0.14–1.11)	0.014[a]
Model 2: age and sex adjusted	32.5	(7.6–57.3)	0.012[a]	0.59	(0.10–1.08)	0.019[a]
Model 3: 2+ adjusted for hand grip strength, and IMAT	29.7	(5.8–53.7)	0.017[a]	0.52	(0.09–0.95)	0.019[a]
Handgrip strength						
Model 1: crude	8.7	(4.9–12.5)	< 0.001[c]	0.59	(0.20–0.97)	0.004[b]
Model 2: age and sex adjusted	8.4	(3.3–13.4)	0.002[b]	0.54	(0.14–0.94)	0.009[b]
Model 3: 2 + adjusted for DLCOc and IMAT	4.31	(-1.1–9.7)	0.111	0.40	(0.01–0.8)	0.044[a]
IMAT						
Model 1: crude	−38.7	(−55.9 to −21.5)	0.000[c]	−5.61	(−8.97 to −2.24)	0.002[b]
Model 2: Age and sex adjusted	−34.7	(−52.8 to −16.6)	< 0.001[c]	−6.63	(−9.94 to −3.31)	< 0.001[c]
Model 3: 2+ adjusted for DLCOc and hand grip strength	−27.1	(−46.0 to −8.2)	0.007[b]	−4.91	(−8.49 to −1.34)	0.009[b]

DLCOc = diffusing capacity for carbon monoxide adjusted for hemoglobin, IMAT = intermuscular adipose tissue.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.001$.
Separate models show associations based on absolute values and on relative values (% of predicted). As no relative values are available for IMAT, absolute values were used in both models.

as percentage of predicted, but not when absolute values were used. Finally, IMAT and physical performance were significantly associated in our models and remained significant after adjustment for sex and age and for DLCOc and handgrip strength.

Additional Pulmonary Follow-Up

Recovery of pulmonary function at 7 months was assessed in 28 patients (**Table 4**). The most notable change over time was a substantial increase in diffusing capacity (59% [46%, 86%] to 73% of predicted [65%, 86% of predicted]; $p < 0.001$). Consequently, the number of patients with disturbed diffusion capacity significantly decreased, whereas the number of patients with restrictive pulmonary dysfunction (impaired TLC) did not.

DISCUSSION

In this study, we assessed functional outcomes of mechanically ventilated COVID-19 survivors at 3 months following hospital discharge. We found that physical sequelae of COVID-19 are common at 3 months. Furthermore, they are determined multifactorial, at least by impaired lung function as well as by changes in skeletal muscle architecture. In addition, we observed that self-reported cognitive performance

TABLE 4.
Comparison of Pulmonary Function Tests at 3 and 7 Months Following Hospital Discharge

	Pulmonary Function Test Results (*n* = 28)			
	3-mo Follow-Up	7-mo Follow-Up	Change Over Time	*p*
Days after hospital discharge, mean (SD)	88 (13)	228 (33)	141 (34)	
Forced expiratory volume in 1 s				
FEV1 (L), mean (SD)	2.8 (0.8)	3.0 (0.9)	0.2 (0.2)	< 0.001[c]
FEV1 (% of predicted), mean (sd)	87.2 (19.1)	92.2 (19.4)	5.0 (6.3)	< 0.001[c]
FEV1 below LLN, *n* (%)	9 (32.1)	4 (14.3)		0.131
Total lung capacity				
TLC (liter), mean (SD)	5.4 (1.6)	5.3 (1.6)	0.1 (0.4)	0.293
TLC (% of predicted), mean (SD)	82.1 (19.5)	81.6 (19.8)	1.3 (6.9)	0.327
TLC below LLN, *n* (%)	19 (67.9)	18 (66.7)		1.000
Diffusing capacity				
DLCOc (mmol/min/kPa), median (first, third quartile)	4.9 (4.6, 6.0)	6.0 (5.3, 6.7)	1.1 (0.9)	< 0.001[c]
DLCOc (% of predicted), median (first, third quartile)	59.0 (46.0, 68.0)	73.0 (64.5, 85.5)	16.3 (9.6)	< 0.001[c]
DLCOc below LLN, *n* (%)	26 (96.3)	14 (51.9)		0.001[b]

DLCOc = diffusing capacity for carbon monoxide adjusted for hemoglobin, FEV1 = forced expiratory volume in 1 s, LLN = lower limit of normal, TLC = total lung capacity.
[a] $p < 0.01$.
[b] $p < 0.001$.
Changes over time compared using paired *t* test or Wilcoxon signed-rank test or McNemar test as appropriate.

and health-related QoL were diminished, and depressive symptoms were more prominent in patients with lasting physical impairment. This is one of the first studies reporting on such a broad and comprehensive spectrum of the consequences of an ICU admission requiring IMV for COVID-19 on physical, mental, and cognitive functioning.

The physical impairments found in our cohort are in line with early reports detailing impaired physical outcomes and muscle weakness in former COVID-19 patients (15, 35, 36). In contrast, a recent study performing a comprehensive health assessment at 3 months found overall normal 6MWD in COVID-19 survivors (37). Notably, the participants in the latter study consisted of both hospitalized as well as nonhospitalized patients indicating that these patients were less severely ill than the patients included in our study. Based on the MRC sum score, only one patient met the definition of ICU-AW at 3 months after hospital discharge. This is consistent with reports detailing that although ICU-AW is common at ICU discharge, improvement of ICU-AW likely continues after hospital discharge and further rehabilitation (38). ICU-related weakness was not completely resolved at 3 months, as an MRC sum score of 55 or lower was found in 40% of patients, which has been associated with poor long-term morbidity and mortality (27). In our models, muscle strength was significantly associated with physical performance at 3 months, but the strength of the association was reduced when adjusted for other components of physical performance such as pulmonary function and skeletal muscle architecture.

Common observations across studies investigating pulmonary outcomes in COVID-19 survivors are a decrease in diffusing capacity, with worse values reported in cohorts representing ICU patients only (15, 37, 39–41). Our findings suggest that impaired diffusing capacity is an important determinant of physical performance, independent of muscle strength and quality. Furthermore, diminished diffusing capacity might underly desaturations found during rehabilitation exercise, in turn limiting the ability to increase physical intensity during the early rehabilitation period in this specific group (42). Follow-up of pulmonary function at 7 months, in a selected subgroup of patients, demonstrated a substantial increase in diffusing capacity, demonstrating that recovery of pulmonary function over time is possible. This will likely translate into partial improvement of physical performance over time, but systematic follow-up of physical performance to support this assumption was unfortunately not performed. Notably, although diffusing capacity improved over time, TLC did not. This is likely due to irreversible structural changes such as fibrosis that likely underly restrictive pulmonary function (41).

In addition to skeletal muscle function, we analyzed CT-derived skeletal muscle architecture commonly used in other patient cohorts (43, 44). We did not find lower muscle mass in patients with low 6MWD. Rather, we found that the amount of IMAT was higher in patients with impaired 6MWD. These data suggest that markers of muscle quality and myosteatosis are more important in relation to physical performance than markers of muscle mass, a phenomenon increasingly witnessed in cachexia and sarcopenia research (45, 46). Increased IMAT could be the consequence of inflammation, altered lipid metabolism, and muscle necrosis, which have all been observed in muscle biopsies collected from critically ill patients (8, 47). However, we cannot rule out that that high IMAT seen in our cohort is not the result of injury sustained during ICU admission but rather a preexisting sign of poor muscle quality pre-ICU admission. Although a subset of patients did have a chest CT available at admission, the quality of the scans made in the acute phase was too poor for body-composition analysis, precluding their use for a valid comparison.

In our study, patients with impaired walking distance not only had more muscle weakness and diminished pulmonary function but also experienced worse health-related QoL, more fatigue, and more depression and anxiety symptoms. Overall EQ-5D HUS found in our study (0.677) appear similar to early results from a different cohort of mechanically ventilated COVID-19 survivors (Health Utility Score 0.752) at 3 months (48). For many ICU survivors, fatigue is a prominent symptom after ICU discharge. We found an overall mean MFI score of 62.5, which is similar to scores found in chronic critically ill patients following prolonged mechanical ventilation for more than 30 days (32, 49). These results reaffirm the importance of an integral vision on health at follow-up and rehabilitation of these patients (42).

The strength of our study is the high follow-up rate, with 88% of survivors participating in the follow-up assessment embedded in a prospective cohort design (17). Furthermore, we performed a comprehensive assessment integrating measures of physical performance, pulmonary function, skeletal muscle strength, and architecture, which allowed us to assess functional outcomes across multiple domains and their underlying associations. Finally, our study only included mechanically ventilated patients, reflecting outcomes on the severe end of the COVID-19 disease spectrum.

Limitations include assessment being performed at one timepoint only, meaning we cannot compare our results with prehospital functioning nor can we determine whether functional impairments found will persist or recover more long-term with the exception of pulmonary function, which was reassessed at 7 months following hospital discharge in a selected group of patients. Although CT-derived muscle analysis allows us to assess the role of muscle mass and quality in relation to functional outcomes, the 3rd lumbar vertebra level is normally the preferred method as an accurate reflection of lean body mass (28). Since these are not routinely included in chest CT scans performed for COVID-19, we assessed skeletal muscle architecture at the nearest available level (12th thoracic vertebra), which is the preferred alternative as it more closely relates to lean body mass than pectoral muscle area (50). Finally, the sample size of 46 patients limited the number of analyses we were able to conduct, as we lacked sufficient power to study sex stratified analyses (51).

CONCLUSIONS

We characterized physical performance, pulmonary function, skeletal muscle strength, and architecture in mechanically ventilated COVID-19 survivors at 3 months following hospital discharge. Lung diffusing capacity and IMAT assessed on CT were independently associated with walking distance, suggesting a key role for both pulmonary function and muscle quality in physical disability of severe COVID-19 survivors. There does appear to be significant recovery of lung diffusing capacity over time, but the subsequent impact on physical performance remains to be assessed.

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