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DOI
10.1093/ptj/pzad039

Publication date
2023

Document Version
Final published version

Published in
Physical Therapy

License
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Link to publication

Citation for published version (APA):
Cijs, B., Valkenet, K., Heijnen, G., Visser-Meily, J. M. A., & Van Der Schaaf, M. (2023). Patients with and Without COVID-19 in the Intensive Care Unit: Physical Status Outcome Comparisons 3 Months after Discharge. *Physical Therapy*, *103*(7), Article pzad039. https://doi.org/10.1093/ptj/pzad039

PTJ: Physical Therapy & Rehabilitation Journal | *Physical Therapy*, 2023;103:1–10
https://doi.org/10.1093/ptj/pzad039
Advance access publication date April 20, 2023
Original Research

Patients With and Without COVID-19 in the Intensive Care Unit: Physical Status Outcome Comparisons 3 Months After Discharge

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Abstract

Objective. Many patients with coronavirus disease 2019 (COVID-19) infections were admitted to an intensive care unit (ICU). Physical impairments are common after ICU stays and are associated with clinical and patient characteristics. To date, it is unknown if physical functioning and health status are comparable between patients in the ICU with COVID-19 and patients in the ICU without COVID-19 3 months after ICU discharge. The primary objective of this study was to compare handgrip strength, physical functioning, and health status between patients in the ICU with COVID-19 and patients in the ICU without COVID-19 3 months after ICU discharge. The second objective was to identify factors associated with physical functioning and health status in patients in the ICU with COVID-19.

Methods. In this observational, retrospective chart review study, handgrip strength (handheld dynamometer), physical functioning (Patient-Reported Outcomes Measurement Information System Physical Function), and health status (EuroQol 5 Dimension 5 Level) were compared between patients in the ICU with COVID-19 and patients in the ICU without COVID-19 using linear regression. Multilinear regression analyses were used to investigate whether age, sex, body mass index, comorbidities in medical history (Charlson Comorbidity Index), and premorbid function illness (Identification of Seniors At Risk-Hospitalized Patients) were associated with these parameters in patients in the ICU with COVID-19.

Results. In total, 183 patients ($N = 92$ with COVID-19) were included. No significant between-group differences were found in handgrip strength, physical functioning, and health status 3 months after ICU discharge. The multilinear regression analyses showed a significant association between sex and physical functioning in the COVID-19 group, with better physical functioning in men compared with women.

Conclusion. Current findings suggest that handgrip strength, physical functioning, and health status are comparable for patients who were in the ICU with COVID-19 and patients who were in the ICU without COVID-19 3 months after ICU discharge.

Impact. Aftercare in primary or secondary care in the physical domain of postintensive care syndrome after ICU discharge in patients with COVID-19 and in patients without COVID-19 who had an ICU length of stay >48 hours is recommended.

Lay Summary. Patients who were in the ICU with and without COVID-19 had a lower physical status and health status than healthy people, thus requiring personalized physical rehabilitation. Outpatient aftercare is recommended for patients with an ICU length of stay >48 hours, and functional assessment is recommended 3 months after hospital discharge.

Keywords: COVID-19, Health Status, Intensive Care Unit, Physical Functioning, Physical Therapy, Rehabilitation

Received: May 12, 2022. **Revised:** December 16, 2022. **Accepted:** February 15, 2023

Introduction

In December 2019, a new coronavirus, called coronavirus disease 2019 (COVID-19), was identified in Wuhan, China. COVID-19 causes severe respiratory illness and is associated with intensive care unit (ICU) admission and high mortality.[1] The Netherlands experienced a multiple wave pattern in reported cases of COVID-19.[2] A systematic review including studies in multiple countries showed that 26% of patients hospitalized with a COVID-19 infection were admitted to the ICU.[3] Due to novelty of the new COVID-19 infection, little is known about the functional status of these patients several months after ICU discharge. On other timepoints, it is known that patients with COVID-19 who had a pneumosepsis perform worse on physical assessments on ICU discharge compared with patients without COVID-19 who had a pneumosepsis.[4] Furthermore, most patients with COVID-in the ICU have lower physical functioning than the general population 6 months after ICU discharge.[5] Moreover, at 6 months after ICU discharge, COVID-19–related ICU stays are not associated with a lower health–related quality of life compared with non–COVID-19–related ICU stays.[6]

Approximately half of the patients without COVID-19 in the ICU develop the post-intensive care syndrome (PICS). PICS includes new or worsening physical, cognitive, and/or mental health impairments arising after critical illness, persisting beyond ICU care.[7,8] Known possible predictive variables for poor physical recovery after ICU stay are older age, female sex (reported as male/female), a high body mass index (BMI), presence of comorbidities, a low self-reported premorbid function, and a higher severity of illness.[9,10] Rehabilitation seems to be a cornerstone in the management of PICS during all phases of recovery, starting at the ICU admission,[11] continuing on the general hospital ward, and after hospital discharge.[12] However, a Cochrane review, focusing on rehabilitation after hospital discharge, did not show an effect on physical functioning due to low study quality.[13]

Patient and clinical characteristics associated with physical impairments in patients without COVID-19 in the ICU might be different in patients with COVID-19 in the ICU, as the group of patients without COVID-19 in the ICU show a large heterogeneity with respect to diagnosis, age, comorbidities, and ICU treatment when compared with patients with a COVID-19 infection in the ICU.[14–16]

Currently, it remains unknown whether outcomes of physical status are comparable between patients with a COVID-19 infection and patients without COVID-19 several months after ICU discharge. Therefore, the first aim of this study is to compare physical status outcomes (handgrip strength, physical functioning, and health status) between these 2 groups 3 months after ICU discharge. The second aim is to investigate which demographic and patient characteristics are associated with the physical status outcomes in patients who had COVID-19 in the ICU. Gaining a better understanding about physical status might yield possibilities for physical therapy.

Methods

This observational, retrospective chart review used usual care data from the outpatient ICU aftercare clinic of the University Medical Center Utrecht. In outpatient ICU aftercare 3 months after ICU discharge, a physician assistant and a rehabilitation specialist assess physical, mental, and cognitive functioning and participation goals and, when necessary, provide advice for improving recovery. In this cross-sectional study, participants were included if they were 18 years old or older at ICU admission and visited the outpatient ICU aftercare of University Medical Center Utrecht between January 2020 and June 2021. Exclusion criteria were age $\geq$ 80 years, ICU length of stay $<$ 48 hours, neurological disease as ICU admission diagnosis, or ICU discharge with home-based mechanical ventilation. The data were obtained by the research group from the electronic health record programs HiX (HiX Digital Health Services, Amsterdam, the Netherlands) and Metavision (Prophesee Metavision, Paris, France), pseudonymized, and entered into an electronic data collection application (CASTOR EDC, New York, NY, USA).

Measurements

During the COVID-19 crisis, The Netherlands Society of Rehabilitation Medicine has recommended a set of measurement instruments to use in outpatient ICU aftercare.[17] In this study, data from measurements and questionnaires related to handgrip strength, physical functioning, and health status were used. Handgrip strength was measured with a JAMAR handheld dynamometer.[18] Handheld dynamometry has good validity in patients in the ICU and good interrater reliability for measuring handgrip strength.[19] The raw outcome values of the JAMAR handheld dynamometer were converted to a percentage of normative references by sex, age, and body height.[20] This percentage was used in the analyses of this study. Physical functioning was measured with the Dutch Short-Form Patient-Reported Outcomes Measurement Information System Physical Function (PROMIS-PF), a questionnaire measuring patient-reported physical functioning on a 5-point scale.[21] The total scores on the PROMIS-PF were transformed into normalized *t* values and used in the analyses of this study.[21,22] The validity and reliability of the PROMIS-PF are unknown for patients in the ICU; however, the PROMIS-PF is known to be sensitive to change in intervention studies on patients with chronic heart failure and cancer.[23] Furthermore, the PROMIS-PF is sensitive to change among different clinical samples.[23] Health status was measured with EuroQol 5 Dimensions 5 Levels (EQ-5D-5L), a questionnaire assessing mobility, self-care, daily activities, pain, and anxiety/depression.[24] Outcomes were transformed into an EQ-5D-5L index value and used in the analyses of this study. The EQ-5D-5L index is a valid extension of the EQ-5D-3L with improved discriminatory power and known-groups validity[25,26] and has shown to be a valid and responsive measure of health status in patients with COPD and asthma, patients after stroke, and patients with chronic hepatic diseases.[26–29] All outcome variables are continuous data.

For the secondary study aim, the following potential determinants for postdischarge physical status of the COVID-19 ICU group were selected based on earlier studies: age[9,10,30] (continuous), sex[10,30] (reported as male/female), BMI,[10,31] comorbidities in medical history, [9,10,30] and premorbid function[9,10] at ICU admission. BMI was calculated according to the continuous variable Quetelet Index.[32] The presence of comorbidities in medical history was measured by the continuous Charlson Comorbidity Index (CCI).[33] The CCI quantifies an individual's burden of disease and corresponding 1-year mortality risk. Premorbid function was measured by the ordinal variable Identification of Seniors At Risk-Hospitalized Patients (ISAR-HP).[34] The ISAR-HP is a screening instrument to predict 90-day functional decline in older patients who had an acute care admission to the department of internal medicine.[34]

Finally, patient characteristics and clinical data associated with the ICU stay were recorded to describe and compare the group of patients in the ICU without COVID-19 and the group of patients in the ICU with COVID-19. The severity of illness was scored with the Acute Physiology And Chronic Health Evaluation (APACHE) IV score.[10] The APACHE IV score is a method for predicting hospital mortality among adults who are critically ill. Furthermore, the duration of mechanical ventilation,[9,35] ICU length of stay, and hospital length of stay[35] were recorded in days, and organ dysfunction was measured with the Sequential Organ Failure Assessment score.[36,37] Furthermore, the presence of sepsis was indicated by the highest C-reactive protein level (CRP). A CRP level > 50 ng/ml indicates sepsis.[9,38] Finally, the presence of hyperglycemia was recorded, indicated by the blood glucose level during ICU stay. A blood glucose level > 150 mg/dl maintained for >5 days was defined as hyperglycemia.[39]

Results from the JAMAR handheld dynamometer measurements, the PROMIS-PF, the EQ-5D-5L, the CCI, the CRP level, and the glucose level were extracted manually from the electronic health records of participants and entered into an electronic data capturing tool. Other study parameters were automatically extracted and imported into the electronic data capturing tool. To prevent bias due to input errors, a second researcher randomly checked 5% of the entered data. Pseudonymized data from the electronic data collection application were exported into SPSS version 27 (SPSS Inc, Chicago, IL, USA) for analyses.[40]

Ethical Approval

Ethical approval for the usage of daily care data was obtained from the Medical Ethical Research Committee of University Medical Center Utrecht. Data from patients who signed an objection letter for the use of their health care data in research were excluded. The study complies with the Declaration of Helsinki.

Statistical Analyses

Descriptive statistics were performed to summarize demographic and clinical characteristics. These characteristics were compared between the non–COVID-19 ICU group and the COVID-19 ICU group by using univariate linear regression analyses.

To conduct the main analyses with complete data, multiple imputation was performed for missing data. For missing data qualified as missing completely at random and missing at random, 5 imputations were obtained. This gives an efficiency of 99% compared with using an infinite number of imputations.[41] Consistent with the guidelines for variable selection for multiple imputation, patient characteristics were included in the multiple imputation procedure.[42] Imputed variables and variables that were used as a predictor for imputation are described in the Supplementary Appendix.

Primarily, handgrip strength, physical functioning, and health status of patients in the ICU without COVID-19 and patients in the ICU with COVID-19 were compared—as well as demographic and clinical characteristics—using univariate linear regression analyses. Subsequently, these comparisons were repeated while correcting for time between ICU discharge and visitation of outpatient ICU aftercare using multivariate linear regression analyses. Furthermore, the mean handgrip strength, physical functioning, and health status of the non–COVID-19 ICU group and the COVID-19 ICU group were compared with reference values of healthy persons.[20,21,43]

Secondarily, to investigate which factors were associated with the dependent variables of handgrip strength, physical functioning, and health status in patients in the ICU with COVID-19, multilinear regression analyses were used, with age, sex, BMI, number of comorbidities in medical history, and premorbid function illness as independent variables.[9,27–29] Multicollinearity was checked for independent variables.

Furthermore, 2 post hoc analyses were performed. First, the multilinear regression analysis was repeated and supplemented with the variables that showed to be significantly different between the 2 groups in Table 1 as independent variables, to correct for differences at baseline. Second, the Netherlands experienced a multiple wave pattern in reported cases of COVID-19. During our inclusion period, the first 3 COVID-19 waves occurred. As the medical treatment of patients with COVID-19 in the ICU evolved, and as the proportion of hospitalized patients requiring ICU treatment and mechanical ventilation dropped, subgroup analyses per wave of reported cases were performed. Therefore, the COVID-19 ICU group was divided into 3 groups, depending on the time of ICU admission, namely, in the first wave (March 2020–June 2020), second wave (July 2020–January 2021), and third wave (since February 2021).[2] The total group of patients in the ICU without COVID-19 and each subgroup of patients in the ICU with COVID-19 were compared on handgrip strength, physical functioning, and health status using univariate linear regression analyses.

All analyses were conducted with SPSS 27 (IBM, Armonk, NY, USA). Statistical assumptions were examined prior to the analyses. Statistical results at level $P \leq .05$ were considered to be significant.

Sample Size Calculation

To determine the minimal sample size for the primary analyses, the effect size was set at 0.5, indicating a medium effect size. This effect size was chosen because there are no sufficient data available to calculate an effect size.[44] Based on a 2-tailed outcome, an α error probability of 0.95 and a power of 0.80 with an equal allocation ratio were set leading to a minimal sample size of 128 (64 per group). For the secondary analyses, the rule of thumb of a maximum of 1 independent variable per 10 events was followed.[45]

Results

We studied 183 patients (57 women) with a mean (SD) age of 57.6 (13.3) years. In total, 168 patients had a face-to-face consult at the outpatient ICU aftercare and, in the non–COVID-19 ICU group, 15 patients had an assessment conducted by phone due to the COVID-19 crisis. The COVID-19 ICU group consisted of 92 patients (27 women) with a mean (SD) age of 60.8 (10.5) years, and the non–COVID 19 ICU group consisted of 91 patients (30 women) with a mean (SD) age of 54.2 (15.1) years ($P = <.001$). The time between ICU discharge and visitation at the outpatient ICU aftercare appointment differed between the COVID-19 ICU group (mean [SD] = 84.6 [30.1] days) and the non–COVID

Table 1. Sample Characteristics ($N = 183$)[a]

Characteristic	Total Group (N = 183)		COVID-19 ICU Group (n = 92)		Non–COVID-19 ICU Group (n = 91)		P[b]
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	No. (%)	Mean (SD)	
Sex, women	57 (31.1)		27 (29.3)		30 (33.0)		.59
Age	182	57.6 (13.3)	92	60.8 (10.5)	90	54.2 (15.1)	**<.001**
Body mass index	182	27.3 (5.6)	91	28.0 (5.9)	91	26.5 (5.3)	.08
Embolism			32 (34.8)				
Diagnosis type					91		
Cardiac					11 (12.1)		
Pulmonary					11 (12.1)		
Neurologic					8 (8.8)		
Surgical					52 (57.1)		
Orthopedic					1 (1.1)		
Internal					6 (6.6)		
Gastroenterologic					2 (2.2)		
Oncologic					0 (0.0)		
Surgical type					52		
Cardiac					33 (63.5)		
Pulmonary					5 (9.6)		
Neurologic					2 (3.8)		
Orthopedic					3 (5.8)		
Internal					2 (3.8)		
Gastroenterologic					1 (1.9)		
Oncologic					6 (11.5)		
Physical consult at ICU aftercare	168 (91.8)		91 (98.9)		77 (84.6)		**<.001**
Time between ICU discharge and ICU aftercare, d	175	118.1 (70.4)	87	84.6 (30.1)	88	151.1 (82.4)	**<.001**
Premorbid functioning[c]	113	0.6 (0.1)	55	0.5 (0.9)	58	0.7 (1.1)	.54
Comorbidities[d]	181	2.6 (2.3)	91	2.6 (2.1)	90	2.6 (2.5)	.99
Hospital stay, d	154	32.5 (21.8)	74	30.3 (15.9)	80	34.5 (26.0)	.36
ICU stay, d	174	15.4 (13.9)	87	18.7 (13.1)	87	12.1 (14.0)	**<.001**
Severity of illness[e]	166	66.9 (22.3)	86	66.3 (19.5)	80	67.6 (24.9)	.72
Readmission to ICU	23 (12.6)		6 (6.5)		17 (18.7)		**.02**
Mechanical ventilation	167 (91.3)		83 (90.2)		84 (92.3)		.60
Reintubation	21 (11.5)		5 (5.4)		16 (17.6)		**.01**
Mechanical ventilation, d	157	11.8 (11.7)	77	15.8 (11.3)	80	8.0 (10.8)	**<.001**
ECLS/ECMO	15 (8.2)		2 (2.2)		13 (14.3)		**.003**
ECLS/ECMO, d	15	10.1 (8.6)	2	13.0 (9.8)	13	9.7 (8.7)	.62
CRP level[f]	158	223.7 (115.1)	72	235.5 (121.3)	86	213.9 (109.4)	.33
Blood glucose level[f]	160	12.5 (3.8)	72	12.5 (4.0)	88	12.6 (3.7)	.99
Multiorgan failure[g]	177	9.4 (2.8)	91	9.2 (2.8)	86	9.7 (2.9)	.24
Rehabilitation	181		91		90		.07
None	25 (13.8)		8 (8.8)		17 (18.9)		
Primary care	61 (33.7)		35 (38.5)		26 (28.9)		
Secondary care	44 (24.3)		26 (28.6)		18 (20.0)		
Tertiary care	51 (28.1)		22 (24.2)		29 (32.2)		
Discharge destination	181		91		90		**.03**
Home	103 (56.9)		43 (47.3)		60 (66.7)		
Care hotel	2 (1.1)		2 (2.2)		0 (0.0)		
Secondary care	40 (22.1)		26 (28.6)		14 (15.6)		
Tertiary care	36 (19.9)		20 (22.0)		16 (17.8)		

[a]CRP = C-reactive protein; ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit. [b]Values in bold type were significant at $P < .05$. [c]Determined with the Identification of Seniors at Risk–Hospitalized Patients instrument. [d]Determined with the Charlson Comorbidity Index. [e]Determined with the Acute Physiology and Chronic Health Evaluation IV. [f]Highest value during ICU stay. [g]Highest Sequential Organ Failure Assessment Score during ICU stay.

ICU group (mean [SD] = 151.1 [82.4] days) ($P = < .001$). Furthermore, patients in the COVID-19 ICU group were mechanically ventilated longer (15.8 days vs 8.0 days; $P = < .001$), and the use of extracorporeal life support/extracorporeal membrane oxygenation (ECLS/ECMO) was necessary less often (2.2% vs 14.3%; $P = <.003$). Patients in the non–COVID-19 ICU group were more often able to go home upon discharge (66.7%) than those in the COVID-19 ICU group (47.3%). In the COVID-19 group, 91.3% received some form of rehabilitation (primary care, 38.5%; secondary care, 28.6%; tertiary care, 24.2%), whereas in the non–COVID-19 group, 81.1% received some form of rehabilitation (primary care, 28.9%; secondary care, 20.0%; tertiary care, 32.2%). Demographic details and patient characteristics are provided in Table 1.

There were missing data on primary parameters for handgrip strength (37.7%), physical functioning (26.5%), and health status (32.2%) and on secondary parameters for age

Table 2. Comparison of Handgrip Strength, Physical Functioning, and Health Status Between the COVID-19 ICU Group and the Non–COVID-19 ICU Group (N = 183)[a]

Parameter	COVID-19 ICU Group		Non–COVID 19 ICU Group		Unadjusted[b]			Adjusted[c]		
	No.	Mean (SEM)	No.	Mean (SEM)	B	95% CI	P[d]	B	95% CI	P[d]
Handgrip strength[e]	90	74.2 (2.93)	89	84.2 (4.44)	−10.03	−22.41 to 2.35	.10	−5.4	−17.41 to 6.54	.36
Physical functioning[f]	91	39.0 (0.99)	90	39.8 (0.99)	−0.82	−3.59 to 1.95	.56	−1.87	−5.07 to 1.34	.25
Health status[g]	91	0.7 (0.03)	90	0.7 (0.03)	−0.00	−0.09 to 0.11	.85	0.00	0.00 to 0.00	.85

[a]ICU = intensive care unit; SEM = standard error of the mean. [b]Univariate linear regression. [c]Multivariate linear regression adjusted for time between ICU discharge and ICU aftercare. [d]Significance was set at $P < .05$. [e]Determined with a JAMAR handheld dynamometer and reported as percentages of reference values. [f]Reported as a Patient-Reported Outcomes Measurement Information System physical function t value. [g]Reported as a EuroQol 5 Dimensions 5 Levels index value.

(0.5%), BMI (0.5%), CCI (1%), and ISAR-HP (38.2%). All missing data were considered to be "missing completely at random," with exception of the 14 patients who had an ICU aftercare appointment by phone; those missing data were qualified as "missing at random." There were no missing values described as "missing not at random," and therefore all missing data were eligible for multiple imputation.

Univariate linear regression analyses showed no significant differences in handgrip strength (P = .104), physical functioning (P = .562), and health status (P = .848) between the 2 groups. These findings remained unchanged after adjustment for the time between ICU discharge and the visitation at the ICU aftercare appointment (Tab. 2). The handgrip strength of the patients in the COVID-19 ICU group (74.2% of normative values) and non–COVID-19 ICU group (84.2% of normative values) was lower than healthy people. [20] The physical functioning of both groups was 1 SD below average,[21] and the health status of both groups was lower than in healthy people (Fig. 1).[43]

The multivariate linear regression analyses showed a significant (P = .008) association between sex and physical functioning in the COVID-19 ICU group, where men showed a higher level of physical functioning than women showed. Furthermore, a significant association (P = .03) between the number of comorbidities and physical functioning in the COVID-19 ICU group was shown. No other significant associations were found (all P values > .05) (Tab. 3).

The post hoc multivariate linear regression analyses in the COVID-19 ICU group showed significant associations between handgrip strength and ICU length of stay (P = .035), physical functioning and comorbidities (P = .024), and ICU length of stay (P = .014), after correction in the secondary analyses for duration of mechanical ventilation and use of ECLS/ECMO. The significant association between physical functioning and sex remained (P = .003), where men had a higher physical functioning score than women did. No other significant associations were found (Tab. 4).

The post hoc univariate linear regression analyses showed patients in the COVID-19 ICU group of the first wave (n = 43) having a significant lower score on handgrip strength (P = .024) compared with patients in the non–COVID-19 ICU group (n = 89). These differences were not found in the second wave (n = 39) or the third wave (n = 8). Furthermore, no differences were found in physical functioning and health status between patients in the COVID-19 ICU group of the first wave, the second wave, and the third wave and patients in the non–COVID-19 ICU group (Tab. 5).

Discussion

In this cross-sectional study, the first aim was to compare handgrip strength, physical functioning, and health status between the COVID-19 ICU group and the non–COVID-19 ICU group about 3 months after ICU discharge. We found no significant differences between the groups. The secondary aim was to investigate which factors were associated with the physical status outcomes in the patients in the COVID-19 ICU group. The secondary analyses showed that the number of comorbidities and sex was associated with physical functioning, where men had better physical functioning than women.

Based on the differences in patient and clinical characteristics, as well as the course during ICU stay, between the patients in the COVID-19 ICU group and the patients in the non–COVID-19 group, we expected a different physical recovery 3 months after ICU discharge. There are several possible explanations why similar handgrip strength, physical functioning, and health status were found in the COVID-19 ICU group and the non–COVID-19 ICU group. First, the demographic and clinical characteristics of both groups showed fewer differences than expected.[14–16] Differences were confirmed only for age, duration of mechanical ventilation, and ICU length of stay. Although our post hoc analyses showed that a longer ICU length of stay was associated with a lower physical functioning after discharge in the COVID-19 ICU group, no significant difference in physical functioning was found between non–COVID-19 ICU group and the COVID-19 ICU group 3 months after ICU discharge. Perhaps these variables have less influence on physical functioning 3 months after ICU discharge than expected. Second, about 3 months after ICU discharge, the handgrip strength, physical functioning, and health status of patients in the COVID-19 ICU group and the non–COVID-19 ICU group were similar. In the non–COVID-19 ICU patient population, it is known that muscle strength and physical functioning increase mainly in the first 3 months and flatten between 3 and 6 months.[46,47] It is possible that differences existed in the first 3 months because of an older age,[9,10] a longer ICU length of stay,[10] and a longer duration of mechanical ventilation,[48] but these possible differences were no longer present at the time of measurement. Furthermore, our data showed that physical functioning and health status of patients in the COVID-19 ICU group were lower than in healthy people approximately 3 months after ICU discharge. An earlier study showed that the physical functioning of patients in the ICU with COVID-19 remains lower compared with healthy people 6 months after ICU discharge.[5] This may suggest that, in contrast to

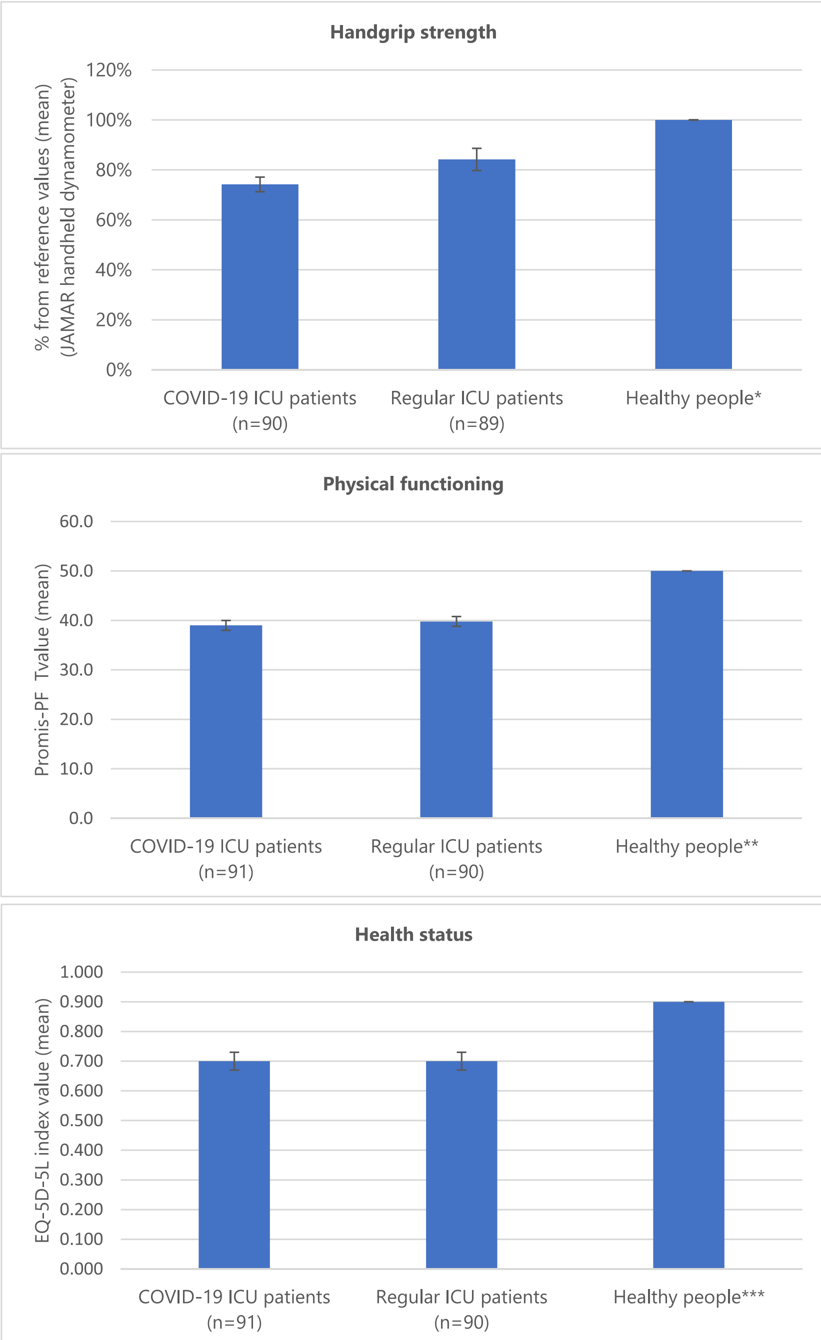

Figure. Comparisons of handgrip strength, physical functioning, and health status of COVID-19 ICU, regular ICU patients and healthy people. * Steiber N. Strong or weak handgrip? Normative reference values for the German population across the life course stratified by sex, age, and body height. PLoS One. 2016;11.[20] ** Terwee CB, Roorda LD, De Vet HCW, et al. Dutch-Flemish translation of 17 item banks from the Patient-Reported Outcomes Measurement Information System (PROMIS). Qual Life Res. 2014;23:1733–1741.[21] *** Hinz A, Kohlmann T, Stöbel-Richter Y, Zenger M, Brähler E. The quality of life questionnaire EQ-5D-5L: psychometric properties and normative values for the general German population. Qual Life Res. 2014 Mar 7;23:443–7.[43]

the flattening in patients in the ICU without COVID-19, there is still improvement in physical functioning and health status between 3 and 6 months after ICU discharge. Moreover, the current study showed that men had a better physical functioning (on PROMIS-PF) than women. Based on the current data, there is no explanation for this.

Although not statistically significant, the difference in handgrip strength between all patients in the ICU with COVID-19 (mean = 74.2% of normative values) and patients in the ICU without COVID-19 (mean = 84.2% of normative values) is considered clinically relevant as the MCID for HGS is smaller than the difference between these groups.[49] This indicates that muscle strength training might deserve additional attention during treatment in COVID-19 ICU patients.

Our post hoc analyses showed that patients in the COVID-19 ICU group who had an ICU admission in the first wave had a significant lower handgrip strength than patients in the non–COVID-19 ICU group. This difference disappeared in the second and third wave. In these waves, the handgrip strength of the patients with COVID-19 and the patients

Table 3. Associations Between Dependent Variables Handgrip Strength, Physical Functioning, and Health Status and Independent Variables in the COVID-19 ICU Group ($n = 92$)[a]

Independent Variable	Handgrip Strength ($n = 90$)[b]			Physical Functioning[c]			Health Status[d]		
	B	95% CI	P[e]	B	95% CI	P[e]	B	95% CI	P[e]
Age	−0.41	−1.18 to 0.36	.293	0.14	−0.12 to 0.39	.30	0.04	−0.003 to 0.01	.22
Sex	3.936	−11.99 to 19.86	.615	5.779	1.54 to 10.02	**.008**	0.04	−0.09 to 0.17	.50
Body mass index	−0.07	−0.97 to 0.96	.989	−0.23	−0.56 to 0.11	.18	−0.007	−0.02 to 0.002	.13
Premorbid functioning[f]	−3.85	−10.83 to 3.13	.265	0.84	−1.17 to 2.85	.83	−0.03	−0.03 to 0.10	.30
Comorbidities[g]	2.31	−3.38 to 8.01	.394	−1.37	−2.64 to −0.11	**.03**	−0.03	−0.07 to 0.01	.20

[a]ICU = intensive care unit. [b]Determined with a JAMAR handheld dynamometer and reported as percentages of reference values. [c]Reported as a Patient-Reported Outcomes Measurement Information System physical function t value. [d]Reported as a EuroQol 5 Dimensions 5 Levels index value. [e]Values in bold type were significant at $P < .05$. [f]Determined with the Identification of Seniors at Risk–Hospitalized Patients instrument. [g]Determined with the Charlson Comorbidity Index.

Table 4. Post Hoc Associations Between Dependent Variables Handgrip Strength, Physical Functioning, and Health Status and Independent Variables in the COVID-19 ICU Group ($n = 92$)[a]

Independent Variable	Handgrip Strength ($n = 90$)[b]			Physical Functioning[c]			Health Status[d]		
	B	95% CI #	P[e]	B	95% CI	P[e]	B	95% CI	P[e]
Age	−0.36	−1.08 to 0.41	.38	−0.18	−0.79 to 0.43	.18	0.005	−0.002 to 0.01	.19
Sex	4.72	−11.17 to 20.61	.62	6.46	2.22 to 10.70	**.003**	−0.04	−0.09 to 0.18	.53
Body mass index	−0.18	−1.15 to 0.79	.71	−0.32	−0.65 to 0.02	.07	−0.008	−0.02 to 0.0002	.11
Premorbid functioning[f]	−3.04	−10.19 to 4.11	.39	1.18	−1.04 to 3.40	.29	0.03	−0.03 to 0.10	.31
Comorbidities[g]	2.63	−2.97 to 8.22	.33	−1.43	−2.67 to −0.20	**.03**	−0.02	−0.07 to 0.02	.24
ICU length of stay, d	−0.53	−1.01 to −0.04	**.04**	−0.19	−0.34 to −0.04	**.01**	−0.002	−0.007 to 0.002	.30
Duration of mechanical ventilation, d	−6.13	−24.20 to 11.94	.51	4.94	−1.57 to 11.45	.14	−0.043	−0.23 to 0.14	.65
Use of ECLS/ECMO	11.18	−27.39 to 49.75	.57	2.70	−9.92 to 15.33	.68	0.09	−0.24 to 0.42	.59

[a]ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit. [b]Determined with a JAMAR handheld dynamometer and reported as percentages of reference values. [c]Reported as a Patient-Reported Outcomes Measurement Information System physical function t value. [d]Reported as a EuroQol 5 Dimensions 5 Levels index value. [e]Values in bold type were significant at $P < .05$. [f]Determined with the Identification of Seniors at Risk–Hospitalized Patients instrument. [g]Determined with the Charlson Comorbidity Index.

Table 5. Comparison of Handgrip Strength, Self-Reported Physical Functioning, and Health Status Between the COVID-19 ICU Group and the Non–COVID-19 ICU Group by Wave[a]

Parameter and Wave	COVID-19 ICU Group[b]		Non–COVID-19 ICU Group[c]		B	95% CI	P
	No.	Mean (SEM)	No.	Mean (SEM)			
Handgrip strength[d]							
First wave[e]	43	70.9 (3.30)	89	84.2 (4.44)	−13.37	−24.90 to −1.841	.02[f]
Second wave[g]	39	78.7 (5.49)	89	84.2 (4.44)	−5.57	−22.55 to 11.40	.49
Third wave[h]	8	70.5 (9.39)	89	84.2 (4.44)	−13.77	−39.23 to 11.69	.28
Physical functioning[i]							
First wave	44	40.4 (1.46)	90	39.8 (0.99)	0.66	−2.76 to 4.09	.70
Second wave	39	37.8 (1.47)	90	39.8 (0.99)	−1.97	−5.55 to 1.62	.28
Third wave	8	36.4 (2.90)	90	39.8 (0.99)	−3.38	−10.28 to 3.53	.34
Health status[j]							
First wave	44	0.8 (0.03)	90	0.7 (0.03)	0.05	−0.04 to 0.15	.28
Second wave	39	0.7 (0.05)	90	0.7 (0.03)	−0.03	−0.14 to 0.08	.55
Third wave	8	0.7 (0.10)	90	0.7 (0.03)	−0.03	−0.30 to 0.23	.80

[a]ICU = intensive care unit; SEM = standard error of the mean. [b]Patients in the specific wave were included. [c]All patients in the non–COVID-19 ICU group were included. [d]Determined with a JAMAR handheld dynamometer and reported as percentages of reference values. [e]First wave: March 2020–June 2020. [f]Significant at $P < .05$. [g]Second wave: July 2020–January 2021. [h]Third wave: Since February 2021. [i]Reported as a Patient-Reported Outcomes Measurement Information System physical function T value. [j]Reported as a EuroQol 5 Dimensions 5 Levels index value.

without COVID-19 was similar. This might be explained by the duration of mechanical ventilation, which was higher in the first wave compared with the second and third waves.[50] A prolonged mechanical ventilation increases the risk of muscle weakness.[48] Another explanation can be the ICU and hospital length of stay, which decreased for patients with COVID-19 in the Netherlands since the second wave.[51] In patients in the ICU without COVID-19, the association between muscle weakness and ICU length of stay was already known.[52] Muscle weakness is also associated with hospital length of stay.[53] The current post hoc analyses confirmed that handgrip strength was negatively associated with ICU stay in the patients with COVID-19.

No differences in handgrip strength, physical functioning, and health status were shown between the patients in the COVID-19 ICU group and the non–COVID-19 ICU group. In the Figure, the results of handgrip strength, physical functioning, and health status of both patient groups are compared with healthy people or normative values, based on literature. Both patient groups score lower than healthy people in handgrip strength, physical functioning, and health status.[20,21,43] Health status, measured with EQ-5D-5L, is highly correlated with performance-based outcomes, except for handgrip strength.[54] This is in line with the results on handgrip strength in our study.

Our study has several strengths. To our knowledge, it is the first published study to examine the differences in handgrip strength, physical functioning, and health status between patients with COVID-19 in the ICU and patients without COVID-19 in the ICU after ICU discharge, and all data were obtained from regular care. Furthermore, all the primary outcomes were standardized to reference values before analyses, which facilitated comparison with other studies on physical outcomes in these 2 patient populations. However, there are also some limitations. First, the sample size of this study is quite small for this kind of observational study. An increase in the number of inclusions may have increased the reliability and validity of the results; however, the minimum sample size was well reached. In the post hoc univariate linear regression analyses (Tab. 5), none of the subgroups reached the minimum group size as calculated in the power calculation. Therefore, these results should be interpreted accordingly. Second, the primary outcomes were measured only once. These outcome data collected on different time points would have increased the insight as to whether patients with COVID-19 in the ICU and patients without COVID-19 in the ICU have a different course in their recovery. Third, there might be selection bias due to multiple causes. It is possible that the patients without COVID-19 in this study differed from patients without COVID-19 before the pandemic because, due to the COVID-19 pandemic, surgeries requiring ICU admission were postponed. Furthermore, patients in the ICU were invited to receive outpatient ICU aftercare except for patients $\geq$80 years of age, with an ICU length of stay $<$48 hours, a neurological disease as ICU admission diagnosis, or ICU discharge with home-based mechanical ventilation. Selection bias may have occurred because not all of the patients visited the ICU outpatient aftercare service for multiple reasons. Practice shows that some patients give no importance to visiting ICU outpatient aftercare, some patients seem to be anxious, and some patients are followed up in another hospital or in primary care. Although there are no data to objectify this, aftercare attendance is subjectively rated as good by clinicians. It is likely that nonattendance is likely to be similar between groups and, therefore, selection bias is unlikely to differ between groups. Finally, data were collected in only one hospital. UMC Utrecht is an academic hospital and treats patients with higher complexity than those treated in community hospitals. For example, at UMC Utrecht, heart and lung transplants are performed more often, which could explain the more frequent use of ECLS/ECMO in the non–COVID-19 ICU group. It is, therefore, possible that the outcomes seen in the current study may differ from those of patients who have been admitted in a community hospital.

Our study shows that both the patients in the COVID-19 ICU group and the patients in the non–COVID-19 ICU group have a lower physical functioning and health status than healthy people around 3 months after discharge. Our study confirms the importance of tailored rehabilitation after ICU discharge in the patients who had COVID-19, as previously highlighted in the literature.[13,55,56] As with patients without COVID-19 in the ICU, a functional (re)assessment is recommended 3 months after hospital discharge, with referral to the appropriate rehabilitation or specialist services if the patient appears to be recovering at a slower rate than anticipated or if the patient has developed unanticipated physical (or nonphysical) morbidity that was not previously identified. In both patient groups, it is recommended to initiate rehabilitation on the physical domain of PICS during all phases of recovery. Furthermore, it is important to give support if the patient is not recovering as quickly as they anticipated.[12]

There are also recommendations for future research. First, to provide more tailor-made care to patients who were in the ICU with COVID-19, more insight must be gained into the course of the recovery of physical status during the first period following hospital discharge. Therefore, we recommend observational studies with physical, mental, and cognitive outcomes measured on multiple time points early after ICU discharge. Second, the current study focused on differences in physical status outcomes between patients with and without COVID-19 in the ICU. It is possible that both groups differ on other outcomes that might affect recovery. Future studies should, therefore, focus on participation outcomes and modifiable factors; for example, cognitive, emotional, and psychic functioning and societal participation.

Conclusion

Based on our observational study, we conclude that, at 3 months ICU postdischarge, handgrip strength, physical functioning, and health status are comparable both for patients who were in the ICU with COVID-19 and for patients who were in the ICU without COVID-19.

Both patient groups have a lower physical status and health status than healthy people, thus requiring personalized physical rehabilitation. We recommend aftercare in the physical domain of PICS after ICU discharge in patients who were in the ICU with or without COVID-19 with an ICU length of stay $>$48 hours, in primary and/or secondary care. Finally, we recommend performing a functional assessment for patients in both the COVID-19 and non–COVID-19 groups 3 months after hospital discharge.

Author Contributions

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Ethics Approval

Ethical approval for the usage of daily care data was obtained from the Medical Ethical Research Committee of University Medical Center Utrecht.

Funding

There are no funders to report for this study.

Disclosures

The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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