

What's going on following acute covid-19? Clinical characteristics of patients in an out-patient rehabilitation program

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Abstract.

BACKGROUND: Coronavirus disease 2019 (COVID-19) patients present long-lasting physical and neuropsychological impairment, which may require rehabilitation.

OBJECTIVES: The current cross-sectional study characterizes post COVID-19 sequelae and persistent symptoms in patients in an outpatient rehabilitation program.

METHODS: Thirty patients [16 post-ICU and 14 non-ICU; median age = 54(43.8–62) years; 19 men] presenting sequelae and/or persistent symptoms (>3 months after acute COVID-19) were selected of 41 patients referred for neurorehabilitation. Patients underwent physical, neuropsychological and respiratory evaluation and assessment of impact of fatigue and quality of life.

RESULTS: The main reasons for referral to rehabilitation were: fatigue (86.6%), dyspnea (66.7%), subjective cognitive impairment (46.7%) and neurological sequelae (33.3%). Post-ICU patient presented sequelae of critical illness myopathy and polyneuropathy, stroke and encephalopathy and lower forced vital capacity compared to non-ICU patients. Cognitive impairment was found in 63.3% of patients, with a similar profile in both sub-groups. Increased physical fatigue, anxiety and depression and low quality of life were prevalent irrespective of acute COVID-19 severity.

CONCLUSIONS: The variability of post COVID-19 physical and neuropsychological impairment requires a complex screening process both in ICU and non-ICU patients. The high impact of persistent symptoms on daily life activities and quality of life, regardless of acute infection severity, indicate need for rehabilitation.

Keywords: COVID-19, sequelae, persistent symptoms, neurological impairment, cognitive impairment

1. Introduction

The coronavirus disease 2019 (COVID-19) is considered primarily a respiratory disease caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The clinical spectrum of

acute COVID-19 infection is heterogeneous, with approximately 15% of cases being asymptomatic (Byambasuren et al., 2020), whereas about 73% of patients present symptoms of acute respiratory infection (fever, cough, dyspnea) (Argenziano et al., 2020; Suleyman et al., 2020), with higher risk of severe illness in older adults, males and individuals with baseline comorbidities (hypertension, obesity, diabetes, chronic pulmonary or kidney disease) (Argenziano et al., 2020; Richardson et al., 2020). A relevant proportion of patients develop extrapulmonary

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manifestations such as musculoskeletal (fatigue and myalgia), cardiovascular (arrhythmias and cardiac injury), gastrointestinal (nausea, vomiting, diarrhea and abdominal pain) and neurological and psychiatric (olfactory and gustatory dysfunctions, headache, cognitive impairment, anxiety and depression) among the most common symptoms (AlSamman, Caggiula, Ganguli, Misak, & Pourmand, 2020; Lechien et al., 2020; Negrini et al., 2020; Zhou et al., 2020). Only a small proportion of COVID-19 positive patients require admission to ICU due to severe hypoxemia and medical complications (acute respiratory distress syndrome, shock, myocardial dysfunction and acute kidney injury) (Phua et al., 2020). However, a significant number of individuals who survived severe COVID-19 may have persistent lung damage and long-term impairment of pulmonary function (Curci et al., 2020; Zhao, Shang, Song, & al., 2020) as well as sequelae associated with critical illness and neurologic complications (cerebrovascular events, altered mental status, peripheral nervous system and muscular alteration) (Varatharaj et al., 2020). Although most patients are expected to recover within weeks after initial symptoms, at 1–1.5 months after discharge, a high proportion of individuals (87.4%) reported persistence of at least 1 symptom, particularly fatigue and dyspnea and worsened quality of life (Carfi, Bernabei, Landi, & Gemelli Against, 2020) and 34.3% referred persistent cognitive complaints (Almeria, Cejudo, Sotoca, Deus, & Krupinski, 2020).

The variability of sequelae and persistent symptoms requires a comprehensive screening and evaluation process by a multidisciplinary expert team and a range of tailored rehabilitation intervention (Wade, 2020). Early detection of persistent symptoms and sequelae in post COVID-19 patients and their inclusion in rehabilitation programs are imperative to reduce disability and to improve patients' quality of life and community reintegration.

In the current study we characterize persistent symptoms, physical, neurological and respiratory sequelae and their impact on daily life activities and quality of life in post COVID-19 patients included in an outpatient rehabilitation program. In addition, we evaluate the relationship between demographic characteristics, preexisting comorbidities, acute COVID-19 severity (ICU vs non-ICU) and the spectrum of persistent symptoms and sequelae in this cohort. We hypothesize that both ICU and non-ICU patients will present multiple physical, neurological and respiratory persistent symptoms. We also expect that ICU patient will present with more severe symptoms,

lower functional independency and quality of life and will initiate rehabilitation earlier after discharge compared to non-ICU patients.

2. Methods

This is a single center cross-sectional observational study on patients with persistent symptoms and/or sequelae of COVID-19 referred by a primary care physician or a specialist for outpatient rehabilitation at Institute Guttmann (Badalona, Barcelona, Spain).

Inclusion criteria were: adults >18 years with persistent symptoms or sequelae of COVID-19 infection confirmed by either PCR or serology.

Exclusion criteria were: previous neurological, psychiatric or severe medical condition; persistent symptoms of confirmed COVID-19 without indications for rehabilitation interventions (e.g. anosmia, dysgeusia, pain symptoms), clinically diagnosed COVID-19 with non-specific symptoms and negative PCR or serology.

A total of 41 individuals (16 post-ICU and 25 non-ICU) were evaluated in the outpatient department by a multidisciplinary COVID-19 team which included physicians (physical rehabilitation and neurology specialists), neuropsychologists and physical therapists. All recruited patients signed a written informed consent for participation in this research study. The study protocol was approved by the local Research Ethics Committee of and was carried out in accordance with the Declaration of Helsinki.

2.1. Medical evaluation

Before inclusion in the rehabilitation program, a structured medical evaluation gathered: demographic data; preexisting comorbidities; current smoking habits; acute COVID-19 symptoms and current respiratory, neurological and cognitive-affective symptoms from a checklist; duration of hospitalization and duration of ICU stay; required oxygen supplementation and ventilation support; acute COVID-19 treatment and complications.

Participants were asked to answer questionnaires evaluating the impact of the experienced physical, cognitive and social fatigue on daily life activities (Modified Fatigue Impact Scale, MFIS) (Larson, 2013), their sleep habits and perceived sleep quality (The Pittsburgh Sleep Quality Index) (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and perceived quality of life (WHOQOL-BREF questionnaire) (WHO, 1996).

2.2. Physical and respiratory evaluation

Respiratory function was evaluated using a portable spirometer (Conter® SP10). The following parameters were measured: forced vital capacity (FVC); forced expiratory volume in 1 second (FEV₁); FEV₁/FVC ratio; and the peak expiratory flow (PEF). Data were expressed as % of the expected value according to their age, gender and height. A FVC and FEV₁ >80%, a FEV₁/FVC ratio >0.7 and a PEF >80% of the expected value were considered normal (Garcia-Rio et al., 2013).

Maximal handgrip strength (MHS) was measured on the dominant non-affected hand or on the less affected hand using a hand dynamometer (Biometrics). MHS was recorded as the maximum value obtained from three consecutive trials and results were compared to normative values according to individual's age and gender (Massy-Westropp, Gill, Taylor, Bohannon, & Hill, 2011).

The Short Physical Performance Test (SPPT) assessed lower extremity physical performance status based on gait speed, chair stand and balance tests (Bergland & Strand, 2019).

The Functional Independence Measure (FIM) scale was used to assess measures of independence for self-care, including sphincter control, transfers, locomotion, communication, and social cognition (Mackintosh, 2009).

2.3. Neuropsychological evaluation

All patients underwent a baseline neuropsychological evaluation regardless of the presence of subjective cognitive complaints. A set of neuropsychological tests was selected to cover the most representative aspects of cognitive functions.

Orientation in person, place and time was measured using the Barcelona Test which is based on the Benton Temporal Orientation Test (Benton, Hamsher, Varney, & Spreen, 1983; Peña-Casanova, 1991). Immediate attention was assessed by means of Digit Span forward subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1997). Verbal memory was assessed using the Rey Auditory Verbal Learning Test (RAVLT) that include three domains of verbal learning, long-term verbal memory, and verbal recognition (Schmidt, 1996). Working memory was evaluated employing the Digit Span backward subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1997). Executive control was evaluated using the PMR task (a Spanish version of the FAS letter fluency

task) (Benton et al., 1983; Fortuny, 1999). In addition, patients were screened for symptoms of anxiety and depression (Hospital Anxiety and Depression Scale, HADS) (Herrero et al., 2003).

2.4. Data analysis

Statistical analyses were conducted with a commercial software package (SPSS, version 13.0; SPSS Inc., Chicago, IL, USA). Descriptive statistics characterized basic demographic and clinical characteristics of the patients enrolled in the study. The Chi-square test for independence was used to assess associations between categorical variables. The Shapiro-Wilk's test was used to examine the normality of distribution. The Mann-Whitney U test was used to compare differences between subgroups on age, respiratory function variables, MHS and sleep quality parameters. Quade's test for non-parametric ANCOVAs was conducted on FIM and SPPT as dependent variables and age and gender as covariables. General linear models were conducted to study between group differences in anxiety, depression, impact of fatigue and quality of life measures as dependent variables and age and gender as covariables. A Bonferroni correction was used for multiple comparisons. Spearman's correlation analyses were run to study relationships between continuous variables. Variables are presented as a median value with interquartile range (25–75%). A two-tailed test with an alpha level of 0.05 was used for all analyses.

3. Results

Thirty individuals (16 post-ICU and 14 non-ICU) met the inclusion criteria and were recruited for

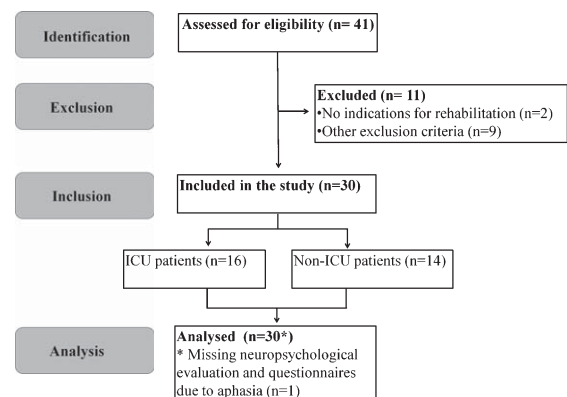


Fig. 1. STROBE flow diagram.

the study. Three patients with clinically diagnosed COVID-19 with non-specific symptoms and negative PCR or serology and 1 patient with persistent symptoms of COVID-19 confirmed by positive PCR and previously known cognitive decline were included in a rehabilitation program but not enrolled in the current study. Other non-enrolled individuals were 4 patients who presented exacerbated symptoms of previously known affective disorders and had a negative PCR and serology for COVID-19; 2 patients with persistent symptoms (e.g. anosmia, dysgeusia, pain symptoms) of COVID-19 confirmed by positive PCR and/or serology with no indications for rehabilitation; and 1 patient with symptoms of substance use disorders with negative PCR and serology for COVID-19 (Fig. 1).

3.1. Baseline demographic and clinical characteristics

The selected cohort of patients selected for the study consisted of: (I) the ICU subgroup which included 16 patients who developed severe COVID-19 and required admission to ICU and (II) the non-ICU subgroup included 14 patients of which 7 patients required admission to a conventional hospital unit (non-ICU) and 7 patients who were home confined (Table 1).

Compared to the non-ICU group, patients in the ICU subgroups were older ($p=0.001$), predominantly male ($p=0.03$) with preexisting obesity ($p=0.003$) and hypertension ($p=0.01$).

In the acute phase, bilateral pneumonia was the main reason for hospitalization in the ICU subgroup (16 patients) compared to bilateral or unilateral pneumonia (6 patients) and transitory loss of consciousness (1 patient) in the non-ICU subgroup. Acute COVID-19 medical and neurological complications were identified only in the ICU subgroup, which required a longer hospital stay and more aggressive oxygen supplementation and pharmacological treatment.

3.2. Reason for referral to rehabilitation

The main reasons for rehabilitation referred by patients during the baseline clinical evaluation, were: fatigue (86.6%), dyspnea (66.7%), cognitive impairment (46.7%) and neurological sequelae (33.3%) (Fig. 2).

On average, patients in the non-ICU subgroup started the rehabilitation 110.5 (89–124) days from

the beginning of acute COVID-19 symptoms and 79 (64–90) days after discharge from conventional hospital unit, whereas in the ICU subgroup patients started the rehabilitation at 98 (95–112) days from the beginning of symptoms and 42 (8–64) days after hospital discharge. The time of rehabilitation start after beginning of symptoms and after hospital discharge were not statistically significant sub-groups ($p=0.26$ and $p=0.45$ respectively).

3.3. Respiratory function

Prevalence of alterations in spirometry varied among patients in the ICU vs non-ICU subgroup: low FVC (<80%) was found in 31.25% vs 0%; low FEV₁ (<80%) in 35.71% vs 37.5%; low FEV₁/FVC ratio (<0.7) in 7.1% vs 12.5%; and low PEF (<80%) in 81.25% vs 50% of patients in each subgroup. The FVC was significantly lower in the ICU subgroup compared to the non-ICU subgroup ($p=0.02$), but there were no statistically significant differences between subgroups in the FEV₁ ($p=0.26$), FEV₁/FVC ($p=0.20$) or PEF ($p=0.80$) (Table 2, Fig. 3).

3.4. Physical functioning and disability

We did not find significant differences between subgroups for SPPT score [$F(1,23)=0.88$; $p=0.36$], FIM total score [$F(1,25)=1.41$; $p=0.25$], FIM motor sub-score [$F(1,25)=1.99$; $p=0.17$], FIM cognitive sub-score [$F(1,25)=0.57$; $p=0.46$] or MHS [$F(1,25)=0.99$; $p=0.33$] (Table 2). Furthermore, MHS correlated with SPPT ($R^2=0.52$; $p=0.01$) and FIM score ($R^2=0.43$; $p=0.025$) and PEF ($R^2=0.45$, $p=0.02$) (Table 3).

3.5. Neuropsychological characteristics

Results of the neuropsychological evaluation and answers to questionnaires were missing in one patient in the UCI subgroup due to communication limitations (non-fluent aphasia).

Overall, 12 of 14 patients reporting subjective cognitive complains (e.g. difficulties with focusing attention, concentration and short memory problems) and 13 of 15 patients without cognitive complains scored lower than expected by age and education in at least one cognitive test. However, reporting subjective cognitive complains was unrelated to altered cognitive tests [$X^2(1)=0.17$, $p=0.68$]. Furthermore,

Table 1
Health-related characteristics, clinical course and outcomes of acute infection in post COVID-19 patients

Characteristics	Total	ICU sub-group	Non-ICU subgroup	P value
Number of patients	30	16	14	
Gender (M/F)	19/11	13/3	6/8	0.03
Age (years)	54 (43.8–262)	61.5 (54–64.75)	43.5 (37.5–53.25)	0.001
Coexisting conditions				
Active smoking	0	0	0	NP
Obesity	13	9	4	0.13
BMI before COVID-19	27.52 (23.74–31.47)	30.28 (26.9–33.50)	23.80 (22.10–30.32)	0.003
BMI after COVID-19	24.30 (21.88–28.05)	25.57 (23.04–29.39)	23.20 (21.09–28.05)	0.15
Arterial Hypertension	9	8	1	0.01
COPD	3	2	1	0.63
Asthma	3	1	2	0.47
Coronary heart disease	3	2	1	0.63
Cerebrovascular disease	2	1	1	0.92
Diabetes Mellitus type 1	0	0	0	NP
Diabetes Mellitus type 2	2	2	0	0.17
Immune disorders	2	1	1	0.92
Kidney disease	0	0	0	NP
Active Cancer	0	0	0	NP
Acute COVID-19 course				
Required hospital admission	23	16	7	0.01
Required admission to ICU	16	16	0	0.001
Length of hospital stay (days)	37 (15–69)	57 (36–86)	11 (4–15)	0.001
Length of ICU stay (days)	26 (12–44)	26 (12–44)	0	0.001
Time from beginning of symptoms to rehabilitation (days)	103 (93–116)	98 (95–112)	110.5 (89–124)	0.26
Time from hospital discharge to rehabilitation (days)	50 (12–74)	42 (8–64)	79 (64–90)	0.45
Clinical presentation and medical complications				
Pneumonia	24	16	8	0.002
ARDS	6	6	0	0.01
Pulmonary embolism	4	4	0	0.04
Cardiac injury or arrhythmia	3	3	0	0.09
Septic shock	5	5	0	0.02
Acute kidney injury	8	8	0	0.002
Weight loss >10 kg	11	11	0	0.001
Neurological complications				
CIP/CIM only	3	3	0	0.04
CIP/CIM +Brain stroke	3	3	0	0.04
CIP/CIM + Spinal epidural hematoma	1	1	0	0.28
Brain stroke only	1	1	0	0.28
Encephalopathy	2	2	0	0.17
O2 Supplementation and Pharmacological treatments				
O2 support/NIV/IMV	1/2/14	0/1/14	1/1/0	0.28/0.92/0.001
Antiretroviral	12	12	0	0.001
Hydroxychloroquine	17	12	5	0.03
Azithromycin	15	10	5	0.14
Ceftriaxone	12	10	2	0.007
Anti-IL-6 drug (Tocilizumab)	7	7	0	0.005
Systemic glucocorticoids	11	8	3	0.28

Legend: ARDS: Acute Respiratory Distress Syndrome; COPD: Chronic obstructive pulmonary disease; CIP/CIM: Critical illness polyneuropathy/ Critical illness polyneuropathy myopathy; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation. Variables are presented as absolute values and median value with interquartile range (25–75%). The Chi-square test was used for categorical variables and the Mann-Whitney U test for continuous variables, to compare ICU vs non-ICU subgroups.

318 there was no significant association between previous
319 admission to ICU and low scores on orienta-
320 tion [X2(1)=0.97, $p=0.33$], attention [X2(1)=1.01,

$p=0.32$], verbal learning [X2(1)=1.77, $p=0.18$],
long-term verbal memory [X2(1)=0.28, $p=0.60$],
verbal recognition [X2(1)=1.44, $p=0.23$], working

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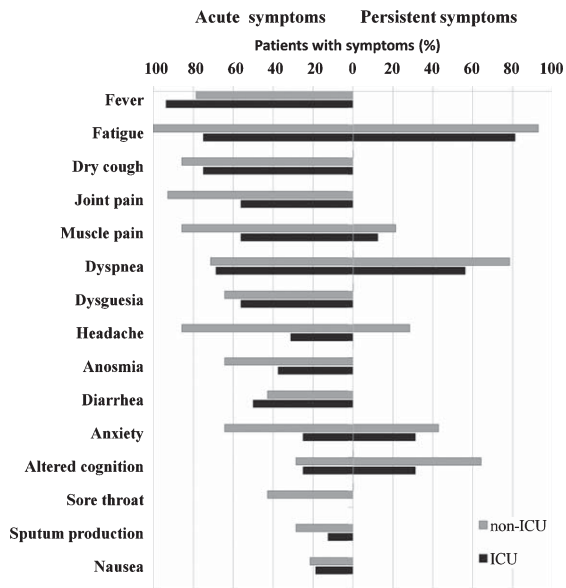


Fig. 2. Acute phase and persistent COVID-19 symptoms.

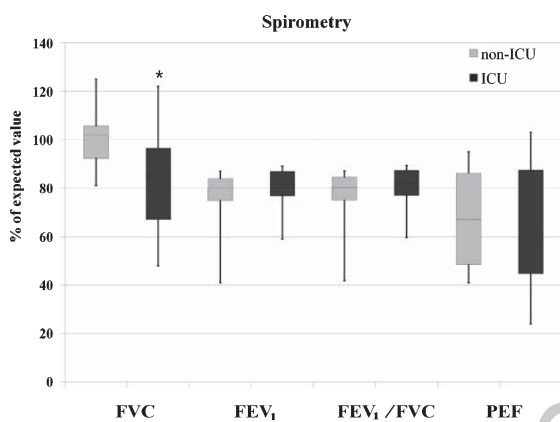


Fig. 3. Respiratory function. Legend: The upper, mid, and lower box edges represent the 75th, 50th, and 25th percentiles, respectively. The whiskers represent maximum and minimum observed values. * $p < 0.05$, Mann Whitney U test for ICU vs non-ICU subgroups comparison.

memory [$X^2(1) = 1.45, p = 0.50$] or executive control [$X^2(1) = 0.18, p = 0.89$] (Table 2, Fig. 4).

At cohort level, 11 patients had high anxiety and depression sub-scores ($>8 p$) and 4 patients had increased depression score only (Table 2). Furthermore, we found no significant differences in anxiety [$F(1,25) = 2.91, p = 0.10$] or depression score [$F(1, 25) = 3.77, p = 0.06$] between subgroups (Table 3).

At cohort level, reporting subjective emotional distress was not associated with altered anxiety [$X^2(1) = 0.86, p = 0.36$] or depression scores [$X^2(1) = 1.68,$

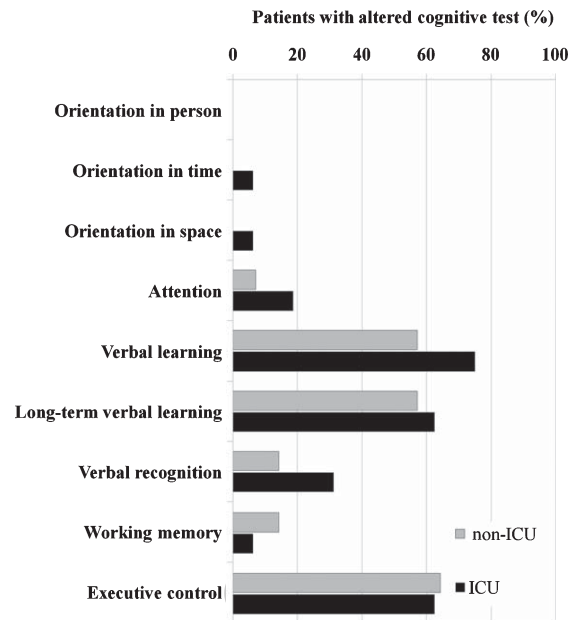


Fig. 4. Alterations in specific cognitive domains.

$p = 0.19$]. However, patients presenting depression were more likely to have altered attention [$X^2(1) = 4.97, p = 0.026$] and verbal recognition functions [$X^2(1) = 5.18, p = 0.023$].

3.6. Sleep quality, impact of fatigue and quality of life

Sleep quality was reported as being “fairly bad” or “bad” by 10 individuals in the non-ICU subgroup, and 2 patients were taking daily sleep medication. In the ICU subgroup, 2 patients reported “fairly bad” or “bad” sleep quality and 8 patients were taking sleep medication. Patients in the non-ICU subgroup had lower sleep quality ($p = 0.01$) and higher daytime dysfunction ($p = 0.046$) compared to the ICU subgroups but there were no significant differences in PSQI sub-scores for sleep latency, duration, efficacy, disturbance or medication use between subgroups ($p > 0.05$ for all comparisons) (Table 2).

At cohort level, most patients reported high impact of fatigue on physical and cognitive activities (Fig. 5), but we found no significant differences between subgroups on measures of impact of fatigue on physical [$F(1, 26) = 1.22, p = 0.28$], cognitive [$F(1, 26) = 1.22, p = 0.28$] or psychosocial activities [$F(1, 26) = 0.75, p = 0.40$] (Table 2).

Overall, patients reported low quality of physical: 38 (19–50)%; psychological: 50 (31–66) %; social: 56 (44–75)%; and environmental health: 56

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Table 2
Results of respiratory, physical and neuropsychological evaluation

Characteristics	Total	ICU sub-group	Non-ICU sub-group	P value
Respiratory function				
FVC	91.5 (81–104.5)	85 (67–96.5)	102 (92.25–105.75)	0.02
FEV1	81.0 (76.25–85.75)	81.5 (76.75–87)	80 (74.75–84)	0.26
FEV1/FCV	81.4 (76.4–85.75)	82.0 (76.9–87.4)	80.2 (74.9–84.6)	0.20
PEF	65.5 (47.75–86.25)	63.5 (44.75–87.5)	67 (48.5–86.25)	0.80
Physical functioning				
FIM total	123 (114–125)	121.5 (104–124.75)	124 (122–125)	0.25
FIM motor	89 (81–91)	88.5 (76.76–89.75)	90 (89–91)	0.17
FIM cognitive	34 (33–35)	34 (33–35)	34 (32–35)	0.46
MHS	24 (18–30)	22.5 (18–29.5)	24 (17–35)	0.33
SPPT	10.5 (7.75–12)	10 (5–11)	12 (8–12)	0.36
Neuropsychological				
Orientation	35 (35–35)	35 (35–35)	35 (35–35)	0.33
Attention	6 (5–6)	5.5 (5–6)	6 (5–7)	0.32
Verbal learning	44 (36.5–50.75)	40 (33.75–44.75)	47.5 (40.75–54.5)	0.18
Long-term verbal memory	8.5 (6–9.75)	6 (5.75–9)	9 (7.75–12)	0.60
Verbal recognition	12.5 (11–14.75)	12 (10–14.25)	13.5 (11–15)	0.23
Working memory	4 (4–5)	4 (4–5)	4 (4–5)	0.50
Executive control	40.5 (27.5–47)	29.5 (21.75–47)	44.5 (34.5–50)	0.89
HADS				
Anxiety	6 (4–10)	5 (3–7)	8.5 (5.75–11.25)	0.10
Depression	8 (3–9)	4 (3–9)	9 (6.5–10)	0.06
Sleep quality				
Quality	1 (0.5–2)	1 (0–1)	2 (1–3)	0.012
Latency	1 (0–2)	1 (0–2)	1 (0–3)	0.31
Duration	1 (0–1)	1 (0–1)	1 (0–2.25)	0.45
Efficacy	1 (0–2)	1 (0–2)	1 (0–2)	0.68
Disturbance	1 (1–2)	1 (1–1)	1.5 (1–2)	0.06
Medication Use	0 (0–3)	3 (0–3)	0 (0–1.25)	0.25
Daytime dysfunction	1 (0.5–2)	1 (0–2)	2 (1–2.25)	0.046
Impact of fatigue				
Physical	80.55 (66.7–94.4)	80.55 (63.9–94.4)	81.9 (68.75–95.1)	0.28
Cognitive	72.5 (60–85)	72.5 (57.5–85)	73.75 (61.9–85.6)	0.28
Social	30 (38.5–69.5)	20 (10–35)	35 (25–40)	0.40
Quality of life				
Physical	38 (19–50)	38 (31–63)	25 (19–45.5)	0.30
Psychological	50 (31–66)	56 (38–69)	44 (23.5–57.75)	0.46
Social	56 (44–75)	69 (44–75)	50 (25–70.5)	0.14
Environmental	56 (50–63)	56 (50–75)	56 (50–63)	0.48

Variables are presented as absolute values and median value with interquartile range (25–75%). The Chi-square test was used for categorical variables and the Mann-Whitney U test and the Quade's test for continuous variables, to compare ICU vs non-ICU subgroups.

(50–63)%. However, the reported quality of physical health [$F(1, 25) = 1.12, p = 0.30$], psychological health [$F(1, 25) = 0.56, p = 0.46$], social relationship [$F(1, 25) = 2.31, p = 0.14$] or environmental [$F(1, 25) = 0.53, p = 0.48$] did not differ between the ICU and non-ICU subgroups (Table 2). Measures of impact of fatigue correlated with aspects of affective impairment, sleep quality and quality of live (Table 3).

4. Discussion

The current cross-sectional study describes sequelae and persistent symptoms at more than 3 months

after acute COVID-19 and their impact on activities of daily living, sleep and quality of life in patients in an outpatient rehabilitation program. Our main findings reveal that multiple persistent symptoms of COVID-19, such as fatigue, dyspnea and cognitive impairment, were main reasons for inclusion in the outpatient rehabilitation program irrespective the acute COVID-19 severity. Patients in the ICU subgroup were older, mostly male, and with obesity and arterial hypertension. Similarly, they more often presented with restrictive ventilatory impairment, single or multiple neurological sequelae of severe acute COVID-19 and were also more likely to be on treatment for sleep alterations. However, in contradiction to our hypothesis post-ICU patients did not

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Table 3
Correlations between impact of fatigue, anxiety and depression symptoms with quality of life

	Impact of fatigue					HADS			Quality of life			Sleep Quality
	Physical	Cognitive	Social	Anxiety	Depression	Physical	Psychological	Social	Environmental	Total score		
Impact of fatigue	1	1.00**	0.68**	0.27	0.49**	-0.55**	-0.33	-0.38*	-0.01	0.64**		
HADS	1.0**	1	0.68**	0.27	0.49**	-0.55**	-0.33	-0.38*	-0.01	0.64**		
Quality of life	0.68**	0.68**	1	0.34	0.54**	-0.65**	-0.51**	-0.62**	-0.30	0.62**		
	0.27	0.27	0.34	1	0.73**	-0.62**	-0.60**	-0.50**	-0.28	0.61**		
	0.49**	0.49**	0.54**	0.73**	1	-0.70**	-0.45*	-0.63**	-0.31	0.63**		
	-0.55**	-0.55**	-0.65**	-0.62**	-0.70**	1	0.67**	0.75**	0.54**	-0.70**		
	-0.33	-0.33	-0.51**	-0.45*	0.67**	1	0.71**	0.53**	0.46*	-0.53**		
	-0.38*	-0.38*	-0.62**	-0.50**	-0.63**	0.71**	1	0.46*	0.46*	-0.60**		
	-0.01	-0.01	-0.30	-0.31	-0.31	0.53**	0.46*	1	1	-0.16		
	0.64**	0.64**	0.62**	0.63**	0.63**	-0.53**	-0.60**	-0.16	-0.16	1		

* $p < 0.05$; ** $p < 0.001$; Spearman Correlation coefficient.

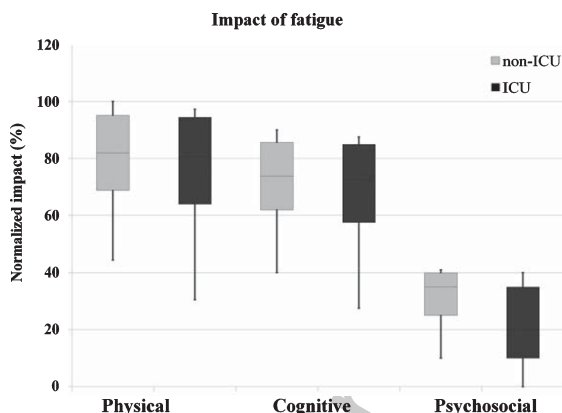


Fig. 5. Impact of fatigue on daily life activities. Legend: The upper, mid, and lower box edges represent the 75th, 50th, and 25th percentiles, respectively. The whiskers represent maximum and minimum observed values.

start rehabilitation earlier than non-ICU patients and their functional independence measures, cognitive-affective state and quality of life were similar to the non-ICU sub-group.

4.1. COVID-19-related alterations in respiratory function

COVID-19 is considered primarily a respiratory disease with increased risk of residual lung damage and long-term alteration of pulmonary function. Although longitudinal studies are needed, recent research reveals abnormal lung function characterized by impairment of diffusion capacity and restrictive ventilatory defects at the moment of discharge in patients with non-critical COVID-19 (Mo et al., 2020). This may still be detected in more than 50% of patients at 1 month after COVID-19 infection (Frijia-Masson et al., 2020). Furthermore, respiratory impairment were found in 25.45% of COVID-19 survivors who were free of respiratory symptoms at 3 months after discharge (Zhao et al., 2020). In our study, dyspnea was the second most prevalent reason of referral to rehabilitation in both subgroups. However, only patients in the ICU subgroup (31.25%) showed altered spirometry with low FVC, suggesting restrictive pulmonary function. Data from SARS survivors indicate that severe pneumonia may determine long-term restrictive ventilatory dysfunction and impaired diffusion capacity for carbon monoxide in 28% of patients at 1 year (Hui et al., 2005) and 23.7% of patients at 2-year follow-up (Ngai et al., 2010). However, although fibrotic irreversible interstitial lung disease is central to severe ARDS, with

422 higher risk in people of advanced age, more severe
423 illness, longer ICU stay with need of mechanical ven-
424 tilation (Gentile et al., 2020; Ojo, Balogun, Williams,
425 & Ojo, 2020), irreversible fibrotic interstitial lung
426 disease in COVID-19 survivors remains speculative.
427 Restrictive chest wall mobility in people with obesity
428 and neuromuscular disorders such as critical illness
429 myopathy and deconditioning may also contribute to
430 ventilatory dysfunction (Melo, Silva, & Calles, 2014;
431 Nusair, 2020).

432 4.2. COVID-19-related physical and 433 neurological impairment

434 Persistent fatigue was the most prevalent symptom
435 of COVID-19 affecting 53.1% of patients discharged
436 from the hospital after recovery from acute COVID-
437 19 (Carfi et al., 2020). Persistent fatigue is commonly
438 reported by ARDS survivors at 1-year (Neufeld et al.,
439 2020) and 4-year follow up (Lam et al., 2009). Main
440 determinants of persistent fatigue may include ARDS
441 severity, cytokine storm in the acute phase and the
442 use of cortisol (Lam et al., 2009). Other studies sug-
443 gest that ARDS severity and the length of ICU stay
444 had little association with persistent fatigue, which
445 seems to be conditioned by worse physical, cogni-
446 tive, and mental health symptoms (Neufeld et al.,
447 2020), in line with our findings. In our study, 81.25%
448 patients in the ICU subgroup and 92.86% in the non-
449 ICU subgroup reported persistent fatigue at more than
450 3 months after acute COVID-19, and its prevalence
451 and impact on daily life activities were independent
452 of acute COVID-19 severity. Furthermore, the impact
453 of physical fatigue correlated with higher depression
454 score and low quality of physical and social life.

455 Severe COVID-19 patients referred for rehabilita-
456 tion are characterized by older age, high prevalence
457 of sequelae of multiple medical and neurological
458 complications, preexisting comorbidities, long ICU
459 stay and prolonged mechanical ventilation, consis-
460 tent with studies (Argenziano et al., 2020; Jurado
461 et al., 2020; Petrilli et al., 2020; Richardson et al.,
462 2020; Suleyman et al., 2020; Varatharaj et al.,
463 2020; Wendel Garcia et al., 2020). In our study,
464 62.5% of patients who required admission to ICU
465 presented single or multiple neurological complica-
466 tions. The diffuse and symmetrical muscle weakness
467 due to CIP/CIM was the most prevalent neurologi-
468 cal complication affecting 43.75% of patients in
469 the ICU subgroup. Potential mechanisms of CIP/CIM
470 include microcirculatory changes associated with

471 systemic inflammation, increased vascular perme-
472 ability, metabolic alterations, denervated muscles
473 exposed to high-dose corticosteroids (Shepherd,
474 Batra, & Lerner, 2017), low-grade myotoxicity in
475 patients with prolonged periods of mechanical ven-
476 tilation and use of sedative drugs (Lonnqvist et al.,
477 2020). Surprisingly, although CIP/CIM is the most
478 common cause of neuromuscular weakness in the
479 intensive care settings, affecting approximately 25%
480 to 45% of patients admitted to the ICU (Lacomis,
481 2011), there are a few case reports of CIP/CIM
482 in patients with COVID-19 (Bagnato et al., 2020;
483 Tankisi et al., 2020). Furthermore, 25% of patients in
484 the ICU subgroup presented sequelae of cerebral or
485 spinal stroke in addition to CIP/CIM, probably due to
486 preexisting vascular risk factors and complications of
487 the critically ill settings (e.g., hypercoagulable state,
488 shock, heart failure, arrhythmogenic cardiomyopa-
489 thy, etc.), which increase the risk of stroke (Fifi &
490 Mocco, 2020; Montalvan, Toledo, & Nugent, 2020).
491 Although the presence of multiple neurological and
492 medical complications determines longer hospital
493 stays and increases the disability rates in the subacute
494 COVID-19 phase, we found no differences in func-
495 tional independence measures and lower extremity
496 functioning between the ICU and non-ICU subgroups
497 at >3 months after acute COVID-19.

498 4.3. Neuropsychological functioning, sleep 499 quality and quality of life

500 During the acute COVID-19, patients may present
501 alteration in personality, behavior, cognition and con-
502 sciousness resulting from cerebrovascular events,
503 encephalopathy and other complications such as sep-
504 sis and hypoxia and the use of sedative drugs (Helms
505 et al., 2020; Rogers et al., 2020; Troyer, Kohn, &
506 Hong, 2020; Varatharaj et al., 2020). Zhou et al.
507 (Zhou et al., 2020) report cognitive dysfunction in
508 sustained attention in recovered COVID-19 patients
509 as compared to healthy controls, which correlated
510 with the level of inflammatory markers. Another
511 study reported specific decline in attention, memory,
512 language and praxis abilities in severe COVID-19
513 patients entering in the post-acute phase, which
514 seemed to be associated with the length of ICU stay
515 (Negrini et al., 2020). During the first months after
516 hospital discharge and 34.3% of patients referred per-
517 sistent cognitive complaints and neuropsychological
518 evaluation revealed alterations in memory domains,
519 attention and semantic fluency, working memory and
520 mental and phonetic fluency as well as high anxiety

and depression scores (Almeria et al., 2020). In our study, patients in the ICU and non-ICU subgroup reported persistent subjective cognitive and affective symptoms (difficulties focusing attention, altered concentration, short term memory impairment and anxiety) beyond the considered recovery, constituting the third most prevalent reason for rehabilitation referral. However, their perception was not related with altered cognitive performance or clinically relevant anxiety or depression symptoms in clinical evaluation. Furthermore, whereas patients with more severe COVID-19 and longer ICU stay would be expected to have more severe cognitive impairment (Rogers et al., 2020) we did not observe any significant differences in the cognitive domains and affective measures between subgroups.

The COVID-19 pandemic can impact the mental health of people in the general population with higher rates of depression, anxiety and sleep disorders (Stanton et al., 2020). In our study, patients in the non-ICU subgroup more frequently reported untreated sleep alterations with lower sleep quality and higher daytime dysfunction compared to ICU patients, whereas higher anxiety and depression score correlated significantly with low physical, psychological and social quality of life at cohort level. Furthermore, at the cohort level, patients presenting with depression were more likely to have altered attention and verbal recognition functions. Subjective cognitive impairment is commonly seen in patients with sleep alterations (Bubbico et al., 2019) and affective symptoms (Hill et al., 2016; Zlata et al., 2018), supporting the relevance of screening for sleep alterations and affective symptoms in post COVID-19 patients with subjective cognitive impairment.

4.4. Implication for rehabilitation

Our study showed that post COVID-19 patients may present multiple physical, neuropsychological and respiratory sequelae and persistent symptoms months after acute infection. The prevalence and severity of fatigue, cognitive-affective impairment and low quality of life, irrespective of the acute infection severity (ICU vs non-ICU patients) advocate complex evaluation and design of multidisciplinary rehabilitation. The European Respiratory Society and American Thoracic Society-coordinated International Task Force recommend the screening for treatable traits and more comprehensive assessment of rehabilitation needs, including physical as well as mental aspects, at 6–8 weeks after discharge (Spruit

et al., 2020). The high prevalence of dyspnea, physical and cognitive fatigue could be important limiting factors for rehabilitation therefore should be considered when designing rehabilitation interventions to improve patients' tolerance and adherence to treatment.

4.5. Limitations

Our study has several limitations. We describe the profile of a specific subgroup of patients with post COVID-19 sequelae and persistent symptoms in individuals included in an outpatient rehabilitation program >3 months after acute phase therefore their clinical characteristic cannot be generalized to the broad population of COVID-19 patients. The study was conducted in a small population of post ICU and non-ICU COVID-19 patients therefore there is a possibility that comparisons between sub-groups were underpowered. We did not include patients with clinically diagnosed COVID-19 with criteria for physical and cognitive rehabilitation as we could not rule out other infective/non-infective etiology of symptoms. The study has a cross-sectional design therefore we do not have baseline (before COVID-19 infection) clinical measures and we cannot discard potential for preexisting respiratory, physical and cognitive-affective alterations. In addition, despite the high prevalence of dyspnea among post COVID-19 patients, we did not evaluate its severity and impact on daily life activities.

5. Conclusions

Following acute COVID-19 infection, patients may present multiple physical, cognitive-affective and respiratory impairments. The high impact of persistent symptoms on daily life activities and quality of life advocate for a multidisciplinary evaluation and clinical profiling of post COVID-19 patients before rehabilitation interventions, regardless of the severity of acute infection.

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615 **Conflict of interest**

616 The authors declare no conflicts of interest.

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