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The impact of post-COVID syndrome across a multitude of health domains: a comparative analysis in previously hospitalized *versus* non-hospitalized COVID-19 survivors

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Abstract

This study aimed to evaluate the impact of post-COVID syndrome across a multitude of health domains among COVID-19 survivors *via* comparative analysis in previously hospitalized *vs.* non-hospitalized patients. A total of 158 adult COVID survivors who had symptoms that continued during post-COVID recovery were included in this prospective observational study. Data on handgrip strength, the 1-minute sit-to-stand test (1-MSTST), radiological scoring (CXR), Medical Research Council (MRC) dyspnea, Fatigue Assessment Scale (FAS), International Physical Activity Questionnaire, Post-COVID-19 Functional Status, Hospital Anxiety-Depression Scale, and Short Form Health Survey 36 (SF-36) health-related quality of life (SF-36 HRQoL) were recorded. Post-COVID 1st-month data revealed dyspnea (MRC scale 2 in 57.0% of patients) and fatigue (FAS scores 22 in 55.7%), a decrease in handgrip strength (60.0%) and physical activity (60.0%), poor HRQoL (SF-36 general health score 50 in 61.4%), and radiological disease progression (CXR score 3 in 56.8%) in at least half of patients, along with depression (34.8%) or anxiety (43.7%). Post-COVID 6th-month values for fat-free mass index (p=0.008, respectively), 1-MSTST recovery time (p=0.012), and 3rd-month CXR scores (p=0.024) were significantly higher, and 3rd-month SF-36 social functioning domain scores (p=0.026) were significantly lower in previously hospitalized *vs.* non-admitted patients. In conclusion, our findings indicate a diverse range of impairments in several health domains in COVID-19 survivors, while radiological disease progression and functional limitations were more remarkable in those with previous hospitalization. A comprehensive assessment of health status and persisting rehabilitation needs is necessary in COVID-19 survivors, regardless of disease severity.

Key words: COVID-19 survivors, long-term health outcomes, functional status, quality of life, outpatient, inpatient.

Introduction

The vast majority of people worldwide have recovered from global outbreak of COVID-19, and the clinical characteristics and health outcomes of COVID-19 at acute phase have been extensively documented [1,2].

However, despite the evolving evidence regarding the post-COVID syndrome (PCS) causing long-lasting morbidity with persisting dyspnea, fatigue, exercise intolerance, lung function impairment, residual pulmonary parenchymal abnormalities and worsened health-related quality of life (HRQL) in a considerable proportion of COVID-19 survivors, the full spectrum of long-term health consequences of disease among survivors at different stages of post-discharge recovery remain largely unknown [3-5].

Moreover, most studies have focused on hospitalized or post-discharge patients with COVID-19 rather than the COVID-19 survivors who were managed in the outpatient setting despite they account for at least 80% of cases [6-8].

This prospective 6-month follow up study aimed to comprehensively assess the long-term consequences of COVID-19 in several health domains including persisting symptoms, muscle weakness, exercise capacity, functional status, psychological and cognitive state, pulmonary disease progression and QoL, via objective and self-reported tools, in COVID-19 survivors previously treated in the outpatient vs. inpatient setting.

Materials and Methods

Study population

A total of 158 COVID-19 survivors who had symptoms continued after the treatment of acute infection were included in this prospective observational 6-month follow up study conducted at a tertiary care post-COVID outpatient clinic between March 2021 and September 2021. Patients who had symptoms continued during post-COVID recovery following treatment of acute infection either via hospitalization or on an outpatient basis were included. Advanced age (>75 years old), intensive care unit admission during the hospital stay for COVID-19, the presence of auditory, visual or orthopedic impairment, cognitive disorder, acute myocarditis, myopathy or neurological deficit, newly detected active pulmonary embolus treated with anticoagulants, pregnancy or breastfeeding, acute comorbidity and ongoing anticancer treatment within the last year were the exclusion criteria of the study. Of 348 patients admitted to our post-COVID outpatient clinic within the study period, 190 patients were excluded due to advanced age (>75 years old, n=38), concomitant pulmonary emboli (n=81), failure in Mini-mental test (n=32), orthopedic disorders challenging the physical functional

assessment (n=39) and the study population subjected to final analysis was composed of 158 patients (Figure 1).

Written informed consent was obtained from each subject. The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the institutional ethics committee (Protocol No: 2017-KAEK-101).

Assessments

Patients were assessed at three consecutive visits during post-COVID recovery including 1st month, 3rd month visit and 6th month visits. Data on patient demographics and management of previous COVID-19 (outpatient or inpatient) were recorded at baseline. Body mass index (BMI, kg/m^2), fat free mass index (FFMI), handgrip strength (kg), Visual Analogue Scale (VAS) pain scores, 1-min sit-to-stand test (1-MSTST) repetitions and the radiological scoring were recorded in each visit. The study questionnaires evaluated at each visit included Medical Research Council (MRC) dyspnea scale, Fatigue Assessment Scale (FAS), International Physical Activity Questionnaire-Short Form (IPAQ-SF), Post-COVID-19 Functional Status (PCFS) scale, Hospital Anxiety-Depression Scale (HADS) and SF-36 health-related QoL (SF-36 HRQoL) questionnaire. Study parameters were evaluated with respect to study visit in the post-COVID recovery period (1st to 6th month visits) and previous COVID-19 management (outpatient vs. inpatient).

1-min sit-to-stand test (1-MSTST)

1-MSTST was applied to quantify exercise capacity as an indicator of functional status, as previously described [9]. The number of complete sit-to-stand cycles (repetitions) completed in 1 min was recorded as the test score with consideration of less than 20 repetitions as a decrease in the lower extremity muscle power [9].

Radiological (CXR) scoring

Radiological scoring was performed by two chest diseases specialists and one radiology specialist, using a chest X-ray scoring system for quantifying and monitoring disease progression [10]. Each of the six lung zones were scored (from 0 to 3) based on the lung abnormalities detected on frontal chest projection including no lung abnormalities (Score 0), interstitial infiltrates (Score 1), interstitial and alveolar infiltrates (interstitial predominance, score 2) and interstitial and alveolar infiltrates (alveolar predominance, score 3). The scores of the six lung zones are then added to obtain an overall "CXR Score" ranging from 0 to 18.

Fatigue Assessment Scale (FAS)

The FAS is a 10-item self-report tool evaluating symptoms of chronic (physical and mental) fatigue based on a 5-point Likert-type scale ranging from 1 (“never”) to 5 (“always”). Total scores can range from 10 (lowest level of fatigue) to 50 (highest level), while a total FAS score < 22 indicates no fatigue and a score 22 indicates the presence of fatigue [11,12].

International Physical Activity Questionnaire - Short Form (IPAQ-SF)

IPAQ-SF is a 7-item self-report questionnaire that addresses the number of days and time spent on physical activity in moderate intensity, vigorous intensity and walking of at least 10-min duration the last 7 days [13,14].

Post-COVID-19 Functional Status (PCFS) scale

PCFS is used to assess full range of functional limitations to capture the heterogeneity of post-COVID-19 outcomes based on the final PCFS grade that ranges from grade 0 (no limitation) to grade 4 (severe functional limitation) [15,16].

Hospital Anxiety-Depression Scale (HADS)

The HADS is a fourteen item [seven relate to anxiety (HADS-A) and seven relate to depression (HADS-D)] scale used to screen anxiety and depression in medical outpatient settings [17]. Each item on the questionnaire is scored from 0-3 leading overall score to range between 0 and 21 for either anxiety or depression as categorized into normal (scores 0-7), borderline abnormal (scores 8-10) and abnormal (scores 11-21) status [17,18].

SF-36 HRQoL

SF-36 is a self-administered questionnaire that measures HRQoL across eight domains including physical functioning, physical and emotional role limitations, bodily pain, general health perception, vitality, social functioning and mental health Total scores range from 0 to 100 with higher transformed scores indicating better health status [19].

Statistical analysis

Statistical analysis was made using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). Shapiro Wilks test was used to investigate normal distribution. Friedman test with post Hoc Bonferroni corrected Wilcoxon Signed Rank test was used to compare two dependent non-normally distributed variables. Repeated Measures ANOVA was used for analysis of two dependent normally

distributed variables. Data were expressed as "mean ± standard deviation (SD), median (min-max) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

Results

Sociodemographic characteristics

The mean±SD age of patients was 54.3± 10.6 years (range, 27 to 75 years) and 113 (71.5%) of 158 patients were males. Acute infection was treated in outpatient and inpatient setting in 96(60.8%) and 62(39.2%) patients, respectively. Comorbid lung diseases were evident in 92(58.2) patients (COPD in 34.8%).

Poor health outcomes at 1 month after acute infection

According to post-COVID 1st month data, dyspnea (MRC scale 2 in 57.0% of patients) and fatigue (FAS scores 22 in 55.7%), decrease in handgrip strength (<40 kg in males/ <24 kg in females in 60.0%) and physical activity (median IPAQ-SF score < 150 MVPA-minutes per week in 60.0%), poor HRQoL (SF-36 general health score 50 in 61.4%) and radiological disease progression (CXR score 3 in 56.8%) were evident in at least half of patients. Also, there was decrease in lower extremity muscle power (1-MSTST <20 repetitions in 32.3%) and the presence of depression (34.8%) or anxiety (43.7%) and functional limitations (PCFS score 3 in 10.8%) in a considerable proportion of patients (Table 1 and Figure 2).

Post-COVID 1st to 6th month data on functional status and quality of life parameters

The parameters that showed significant increase from 1st month to 3rd and 6th months of post-COVID recovery involved the FFMI ($p<0.001$ for each), handgrip strength ($p<0.001$ for each), 1-MSTST repetitions ($p<0.001$ for each), IPAQ-SF MVPA MET-minutes per week ($p<0.001$ for each) and SF-36 HRQoL ($p<0.001$ for each domain) (Table 2). The increase was also significant from 3rd month to 6th month for all these parameters (p values ranged 0.003 to <0.001) (Table 2). These findings were also consistent across outpatient and inpatient treatment groups (Tables 3 and 4).

The parameters that showed significant decrease from 1st month to 3rd and 6th months of post-COVID recovery involved VAS pain intensity ($p<0.01$ and $p<0.001$, respectively), 1-MSTST recovery time ($p<0.001$ for each), CXR score ($p<0.001$ for each), MRC dyspnea scale ($p<0.001$ for each), FAS score ($p<0.001$ for each, both mental and physical domains), PCFS scale ($p<0.001$ for each), HADS-D score ($p<0.001$ for each) and HADS-A score ($p<0.001$ for each). The decrease was also significant from 3rd month to 6th month for all these parameters (p values ranged 0.003 to <0.001), except for 1-min MSTST recovery time (Table 2). These

findings were also consistent across outpatient and inpatient treatment groups (Tables 3 and 4).

Clinical data in inpatient vs. outpatient COVID-19 treatment groups

Post-COVID 1st month, 3rd month and 6th month values for FFMI (p=0.039, p=0.020 and p=0.008, respectively), 1-min MSTST recovery time (p=0.006, p<0.001 and p=0.012, respectively), 1st month and 3rd month values for CXR scores (p<0.001 and p=0.024, respectively) and 1st month PCFS scale scores (p=0.023) were significantly higher in previously hospitalized vs. non-admitted patients. The 1st and 3rd month SF-36 social functioning domain scores (p<0.001 and p=0.026, respectively) were significantly lower in the inpatient group (Tables 3 and 4).

No significant difference was noted between outpatient vs. inpatient management of COVID-19 in terms of post-COVID data on VAS pain scores, 1-MSTST repetitions, MRC dyspnea scale, FAS, IPAQ-SF and HADS scores and SF-36 HRQoL (except for the social functioning domain) (Tables 3 and 4).

Discussion

Our findings revealed that most of COVID-19 survivors, even those previously treated in outpatient setting, still suffer from persisting symptoms, and functional and pulmonary limitations at first month after recovery. The main post-COVID health effects included reduced handgrip strength, decrease in exercise capacity (1-MSTST) and physical activity (IPAQ-SF), impaired HRQoL (SF-36) along with chronic fatigue (FAS), dyspnea (MRC), depression or anxiety, functional limitations (PCFS) and radiological disease progression (CXR scores). These effects have gradually ameliorated during the 3rd and 6th months of the post-COVID recovery period. The radiological disease progression (CXR scores) and functional limitations (PCFS) were more remarkable and 1-MSTST recovery time were longer during post-COVID recovery period in those previously had inpatient vs. outpatient treatment.

Similarly, in a large cohort study assessing the post-discharge 6-month health consequences in 1733 COVID-19 survivors discharged from hospital, most patients were reported to suffer from fatigue, muscle weakness and anxiety or depression at 6 months after acute infection, along with higher rate of pulmonary diffusion abnormality and a higher CT score (ground glass opacity and irregular lines) during follow-up in those with more severe disease at acute phase [3]. Also, in a study on the long-term functional status of COVID-19 survivors at 3-11 months after hospital discharge, most of patients were found to suffer from limited daily

activities (70.9%), pain and discomfort (64.5%), breathlessness (64.7%) and anxiety and depression (57.3%) [7].

Other studies in previously hospitalized COVID-19 survivors also identified the fatigue, muscle weakness, dyspnea, limited exercise capacity, physical impairment, functional limitation, anxiety and depression, cognitive deficits and poor HRQoL amongst the important post-acute sequelae of COVID-19 after hospital discharge [5,20-23]. Indeed, the likelihood of developing long COVID-19 is suggested to be lower in non-hospitalized patients after COVID-19 than in those admitted to hospital with COVID-19 [24,25].

Our findings support the consideration of muscle weakness, reduced exercise capacity, fatigue, dyspnea, anxiety or depression amongst the most prevalent long-term conditions compromising the functional status of previously hospitalized COVID-19 survivors [3,5,7,21-23] but also emphasize the likelihood of COVID-19 survivors who were previously treated in an outpatient setting to be similarly affected from these adverse health effects.

In a study with 102 non-hospitalized COVID-19 survivors, more than 60% of patients were reported to have impaired physical function at 3 months, while 40%-56% had post-traumatic stress disorder (PTSD), anxiety or depression, cognitive dysfunction and dyspnea [8]. The authors also noted that HRQoL was impaired (except for mobility and pain/discomfort domains) in 60% of patients at 3 months and remained impaired at 6-7 months, while only a slight improvement occurred in dyspnea and physical and cognitive function at 6-7 months [8].

In a 3-6 months follow-up study of 239 COVID-19 survivors, while significant improvements were reported in work productivity, self-reported good health, functional status and HRQoL during recovery period, a need for improved management of long-term impacts of COVID-19 has been suggested given that a large proportion of survivors still experienced persistent symptoms, moderate-to-poor health, functional limitations, and/or an impaired QoL approximately 6 months after the onset of COVID-19-related symptoms [26].

In our study, while the long-term repercussions of COVID-19 were evident even among the previously non-hospitalized patients, there was a trend of change in the functional status and QoL with a gradual improvement during 3-to-6-month recovery period. Indeed, the QoL of patients with COVID-19 is considered to be as affected as that of patients with chronic respiratory diseases such as asthma [8,27], while the long-term persistence of symptoms of anxiety/depression in COVID-19 survivors is suggested to play a key role in poor QoL [8]. In addition, the presence of muscle fatigue/muscle weakness (OR 5.7), PTSD (OR 6.0) and impaired HRQoL (OR 11.7) at 3 months after acute infection was reported to predict the risk of having impaired HRQoL at 6-7 months in COVID-19 survivors [8].

In a study with 124 COVID-19 survivors including hospitalized and non-admitted patients, at 3 months after recovery from COVID-19, majority of discharged patients had residual pulmonary parenchymal abnormalities (ground-glass opacification on repeat CT imaging), particularly those with severe disease, as correlated with reduced lung diffusion capacity [6]. However, majority of non-admitted patients with mild disease had normal chest X-rays (93%) but more frequent problems related to physical functioning, fatigue, and QoL despite lack of major radiological, lung function, inflammatory, or exercise capacity abnormalities [6]. Nonetheless, while the increased chance of preserved lung function in the long-term is suggested in non-hospitalized COVID-19 survivors, a reduction in respiratory muscle strength seems to persist in nearly half of these patients at 6–7 months after acute infection [8]. Thus, pulmonary rehabilitation is considered likely to be of high relevance for both hospitalized and non-admitted COVID-19 survivors [9,28,29].

In the current study, previously hospitalized vs. non-admitted patients had significantly longer 1-MSTST recovery time during the entire 6-month recovery period along with a more marked radiological disease progression (CXR scores) and functional limitations (PCFS) within 3 months of recovery. Although these findings support the association of the disease severity in the acute phase with pulmonary diffusion abnormality and percentage change of CT score among COVID-19 survivors [3], the presence of radiological and physiological pulmonary abnormalities has been noted in a considerable proportion of even noncritical COVID-19 cases at 3 months after discharge and persistent restrictive ventilatory deficits is considered likely in COVID-19 survivors, regardless of their disease severity [30,31].

Accordingly, our findings emphasize the need for quantitative pulmonary assessments as well as the assessment of muscle weakness, functional capacities and QoL in COVID-19 survivors, regardless of the previous hospitalization, and support that COVID-19 survivors with functional and muscular performance impairment, dyspnea, and poor perceived health status can benefit from pulmonary rehabilitation [32-34].

Data from the Linköping COVID-19 Study (LinCoS) on rehabilitation needs in 158 COVID-19 survivors confirmed that most of the participants who had reported concerning problems suffered persisting dyspnea and other residual respiratory symptoms, persisting fatigue, weakness in extremities, pathological results in 6MWT and spirometry as well as persisting sensorimotor impairments and cognitive dysfunction at 5 months after acute illness [32]. Also, 44% of patients (16% of total cohort of survivors) required further rehabilitative interventions at the five-month assessment, particularly those with severe disease [32].

Also, in a systematic review of 36 studies regarding the limitations of functioning of rehabilitation interest suffered by COVID-19 patients, the authors concluded the severe

impact of the disease in terms of rehabilitation needs and the likelihood of persistent restrictive ventilatory defect and even lung hypoperfusion or delayed lung thromboembolic complications among COVID-19 survivors after discharge, regardless of disease severity [31]. Hence, a long-term follow-up of COVID-19 survivors via use of instrumentalized measures and self-reported tools is suggested to be important to capture the functional impairments, cognitive problems and the individual rehabilitation needs after COVID-19 [8,28,32,33]. The therapeutic interventions in COVID-19 survivors are suggested to be targeted primarily towards improving fatigue, muscle weakness and cognitive symptoms, while the respiratory impairment is considered a key target with implications for functional ability [32,35].

The major strength of this study is the comprehensive assessment of long-term health outcomes in COVID-19 survivors, with use of instrumentalized measures in addition to self-reported tools and consecutively during 6-month recover period, and both in hospitalized and non-admitted groups of patients during acute infection management. Also, functional assessments were performed by two experienced physiotherapists. However, certain limitations to this study should be considered. First, due to observational nature, selection bias and confounding is possible. Second, single-center design and relatively small number of patients is another limitation. Third, lack of data on 12^{th} month assessment is another limitation in terms of evaluating the percentage of full recovery (if present) overall and in each cohort, which was related to the fact that patients were reluctant to visit hospitals during the pandemic in fear of contracting the disease. Fourth, lack of data on standardized baseline measurements before the acute phase as well as the likelihood of potential confounders not to be considered due to unknown aspects of COVID-19 are other limitations.

Conclusions

In conclusion, our findings revealed that considerable proportion of previously hospitalized or non-hospitalized COVID-19 survivors, still suffer from persisted symptoms of fatigue, dyspnea, anxiety or depression, along with muscle weakness, reduced exercise capacity, poor QoL and radiological disease progression at first month after acute infection. While these effects have gradually ameliorated during later stages of the post-COVID recovery period, radiological disease progression and functional limitations were more remarkable in previously hospitalized vs. non-hospitalized COVID-19 survivors. Comprehensive multidisciplinary assessment of health status and persisting rehabilitation needs is needed among COVID-19 survivors with all degrees of disease severity, given the diverse range of impairments in several health domains after recovering from the acute phase. Larger scale high-quality evidence studies with longer follow-up are necessary to understand the natural

trajectories of COVID-19 recovery and the predictors of long-term sequelae to develop strategies to decrease long-term morbidity and increase quality of life.

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Table 1. Poor health outcomes at 1-month after acute infection.

Poor health outcomes at 1st month	Patients with abnormal findings, n(%)
Fat free mass index (kg/m^2)	
< 16.7 kg/m^2 in males, <14.6 kg/m^2 in females	2(1.3)
Handgrip strength (kg)	
<40 kg in males (left: 2 kg lesser) <24 kg in females (left: 1.5-2 kg lesser)	90 (60.0)
1-min MSTST	
Less than 20 repetitions	51(32.3)
CXR	
Score >3	83(56.8)
MRC dyspnoea scale	
Score 2	90(57.0)
FAS	
Score 22	88(55.7)
IPAQ-SF	
< 150 MVPA-minutes, per week	109(69.0)
PCFS scale	
Grade 3	17(10.8)
HADS-D	
Score 8	55(34.8)
HADS-A	
Score 8	69(43.7)
SF-36 HRQoL- general health	
Score 50	97(61.4)

1-MSTST, 1-min sit-to-stand test; CXR, chest X-ray; MRC, Medical Research Council; FAS, Fatigue Assessment Scale; IPAQ-SF, International Physical Activity Questionnaire - Short Form; MPVA, moderate and vigorous physical activity; PCFS, Post-COVID-19 Functional Status; HADS, Hospital Anxiety-Depression Scale; A, anxiety; D, depression; HRQoL, health-related quality of life.

Table 2. Post-COVID 1st to 6th month data on functional status and quality of life parameters

Variables,		Post-COVID 1st month (A)	Post-COVID 3rd month (B)	Post-COVID 6th month (C)	p value[1]	Post hoc comparisons[3] A-B	A-C	B-C
FFMI (kg/m²), median(min-max)		20.5(14.8-30.2)	20.8(15-30.2)	21(15.9-30.8)	**<0.001**	**<0.001**	**<0.001**	**0.001**
Handgrip strength (kg), median(min-max)		33.5(8-60.2)	34.9(12-62.6)	36.3(12.2-58.6)	**<0.001**	**<0.001**	**<0.001**	**0.003**
VAS pain		1(0-8)	0(0-7)	0(0-10)	**<0.001**	**0.004**	**<0.001**	0.408
1-min repetitions, mean±SD		21.6±5.3	23.1±5.2	25.4±5.2	**<0.001[2]**	**<0.001**	**<0.001**	**<0.001**
MSTST recovery time (sec), median(min-max)		92(20-300)	83.5(30-240)	88(35-248)	**<0.001[1]**	**<0.001**	**<0.001**	1.0
CXR Score, median(min-max)		3(0-14)	2(0-10)	0(0-6)	**<0.001**	**<0.001**	**<0.001**	**0.003**
MRC dyspnoea scale, median(min-max)		2(0-4)	1(0-3)	1(0-3)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
FAS score, median(min-max)	Total	24(10-44)	20(10-47)	17(10-44)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Physical	14(5-24)	11(5-23)	10(5-23)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
	Mental	10(5-23)	9(5-25)	7(5-21)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
IPAQ-SF MVPA MET-minutes, per week, median(min-max)		338.5(0-6330)	990(0-7497)	1626(0-8172)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PCFS scale, median(min-max)		1(0-3)	1(0-3)	0(0-3)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
HADS-D score, median(min-max)		6(0-16)	5(0-16)	4(0-15)	**<0.001**	**0.001**	**<0.001**	0.016
HADS-A score, median(min-max)		6(0-18)	5(0-17)	4(0-15)	**<0.001**	**<0.001**	**<0.001**	**0.007**
SF-36 HRQoL Scores, median(min-max)								
Physical functioning score		60(0-100)	75(10-100)	85(10-100)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Bodily pain score		57.5(0-100)	77.5(0-100)	79(0-100)	**<0.001**	**<0.001**	**<0.001**	0.016
General health score		50(5-100)	60(15-100)	70(15-100)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Vitality score		50(5-95)	60(10-100)	70(0-100)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Social functioning score		57.5(0-100)	70(0-100)	78.8(0-100)	**<0.001**	**<0.001**	**<0.001**	**0.001**

FFMI, Fat-Free Mass Index; VAS, Visual Analogue Scale;1-MSTST, 1-min sit-to-stand test; CXR, chest X-ray; MRC, Medical Research Council; FAS, Fatigue Assessment Scale; IPAQ-SF, International Physical Activity Questionnaire-Short Form; MPVA, moderate-vigorous physical activity; PCFS, Post-COVID-19 Functional Status; HADS, Hospital Anxiety-Depression Scale; A, anxiety; D, depression; HRQoL: health-related quality of life. [1]Friedman Test, [2]Repeated Measures ANOVA, [3]Bonferroni corrected Wilcoxon Signed Rank test (critical p value for significance: p<0.0166).

Table 3. Post-COVID 1st to 6th month data on muscular strength, pain, physical and clinical functional status parameters with respect to initial COVID-19 treatment (outpatient *vs.* inpatient).

Variables, median(min-max)	Post-COVID 1st month (A)	Post-COVID 3rd month (B)	Post-COVID 6th month (C)	p value[1]	Post hoc comparisons[5] A-B	A-C	B-C
FFMI (kg/m²)							
Outpatient	20.3(16-27.2)	20.5(16.3-26.2)	20.6(16.3-26.8)	**<0.001[1]**	**0.007**	**<0.001**	**0.020**
Inpatient	21(14.8-30.2)	21.4(15-30.2)	21.6(15.9-30.8)	**<0.001[1]**	**0.002**	**<0.001**	0.066
p value (outpatient vs. inpatient)	**0.039[2]**	**0.020[2]**	**0.008[2]**				
Handgrip strength (kg)							
Outpatient	33.3(10.1-60.2)	35(12-62.6)	34.7(12.2-58)	**<0.001[1]**	**<0.001**	**<0.001**	**0.001**
Inpatient	34(8-58.1)	34.9(12-58.6)	38.1(15-58.6)	**<0.001[1]**	**<0.001**	**<0.001**	**0.001**
p value (outpatient vs. inpatient)	0.573[3]	**0.001[4]**	0.237[2]				
VAS pain							
Outpatient	1(0-8)	1(0-7)	0(0-10)	**<0.001[1]**	**0.012**	**<0.001**	0.886
Inpatient	0(0-7)	0(0-7)	0(0-8)	**<0.001[1]**	0.415	**0.031**	0.844
p value (outpatient vs. inpatient)	0.060[2]	0.152[2]	0.086[2]				
1-MSTST repetitions, mean±SD							
Outpatient	21(12-40)	23(14-35)	25(14-44)	**<0.001[1]**	**<0.001**	**<0.001**	**0.001**
Inpatient	20(8-36)	22.5(7-35)	25.5(14-36)	**<0.001[1]**	**<0.001**	**<0.001**	**<0.001**
p value (outpatient vs. inpatient)	0.086[2]	0.281[2]	0.846[2]				
1-MSTST recovery time (sec)							
Outpatient	88(20-195)	74(30-180)	80(35-248)	**0.003[1]**	**0.006**	**0.025**	1.000
Inpatient	106(45-300)	100(44-240)	100(46-240)	**0.001[1]**	**0.046**	**0.001**	0.844
p value (outpatient vs. inpatient)	**0.006[2]**	**<0.001[2]**	**0.012[2]**				
MRC dyspnoea scale							
Outpatient	2(0-4)	1(0-3)	1(0-2)	**<0.001[1]**	**0.001**	**<0.001**	**0.002**
Inpatient	2(0-4)	1(0-3)	1(0-3)	**<0.001[1]**	**<0.001**	**<0.001**	**0.002**
p value (outpatient vs. inpatient)	0.118[2]	0.283[2]	0.880[2]				
PCFS scale							
Outpatient	1(0-3)	1(0-3)	0(0-3)	**<0.001[1]**	**<0.001**	**<0.001**	**0.001**
Inpatient	2(0-3)	1(0-3)	0(0-3)	**<0.001[1]**	**0.001**	**<0.001**	**<0.001**
p value (outpatient vs. inpatient)	**0.023[2]**	0.147[2]	0.373[2]				
Radiological assessment- CXR score							
Outpatient	2(0-14)	2(0-5)	0(0-5)^{**,qq}	**<0.001[1]**	0.191	**<0.001**	**<0.001**
Inpatient	4(0-12)	2(0-10)*	1(0-6)^{**,qq}	**<0.001[1]**	**0.004**	**<0.001**	**<0.001**
p value (outpatient vs. inpatient)	**<0.001[2]**	**0.024[2]**	0.171[2]				

FFMI, Fat-Free Mass Index; VAS,Visual Analogue Scale;1-MSTST, 1-min sit-to-stand test; MRC, Medical Research Council; PCFS, Post-COVID-19 Functional Status; CXR, chest X-ray. [1]Friedman Test, [2]Mann-Whitney U,[3]Between-Subjects Effects, [4]Tests of Within-Subjects Effects Factor, [5]Bonferroni corrected p values (values in bold indicate statistical significance).

Table 4. Post-COVID 1st to 6th month data on fatigue, physical activity, negative emotional states and quality-of-life parameters with respect to initial COVID-19 treatment (outpatient vs. inpatient).

Variables, median(min-max)	Post-COVID 1st month (A)	Post-COVID 3rd month (B)	Post-COVID 6th month (C)	p value[1]	Post hoc comparisons[3] A-B	A-C	B-C
FAS score							
Total							
Outpatient	24(10-44)	20(10-47)	16.5(10-44)	**<0.001**[1]	**<0.001**	**<0.001**	**<0.001**
Inpatient	25(10-44)	20(10-42)	18(10-37)	**<0.001**[1]	**<0.001**	**<0.001**	1.000
p value (outpatient vs. inpatient)	0.468[2]	0.996[2]	0.441[2]				
Physical							
Outpatient	13.5(5-24)	11(5-23)	10(5-23)	**<0.001**[1]	**<0.001**	**<0.001**	**0.002**
Inpatient	14(5-23)	12(5-22)	10(5-19)	**<0.001**[1]	**<0.001**	**<0.001**	0.117
p value (outpatient vs. inpatient)	0.617[2]	0.804[2]	0.663[2]				
Mental							
Outpatient	10(5-23)	9(5-25)	7(5-21)	**<0.001**[1]	**0.023**	**<0.001**	**<0.001**
Inpatient	10(5-22)	9(5-20)	7(5-18)	**<0.001**[1]	**<0.001**	**<0.001**	0.348
p value (outpatient vs. inpatient)	0.311[2]	0.700[2]	0.304[2]				
IPAQ-SF MVPA MET-minutes, per week							
Outpatient	354.5(0-6330)	1066-5(0-7497)	1735.5(0-8172)	**<0.001**[1]	**<0.001**	**<0.001**	**<0.001**
Inpatient	198(0-5358)	976.5(0-5358)	1556(0-6048)	**<0.001**[1]	**<0.001**	**<0.001**	**<0.001**
p value (outpatient vs. inpatient)	0.156[2]	0.199[2]	0.185[2]				
HADS-D score							
Outpatient	6(0-16)	4 (0-16)	4(0-14)	**<0.001**[1]	**0.006**	**<0.001**	0.291
Inpatient	6(0-15)	5(0-14)	4(0-15)	**<0.001**[1]	0.145	**<0.001**	0.052
p value (outpatient vs. inpatient)	0.939[2]	0.420[2]	0.949[2]				
HADS-A score							
Outpatient	7(0-18)	5(0-17)	4(0-15)	**<0.001**[1]	**0.001**	**<0.001**	**0.042**
Inpatient	6(0-18)	5(0-17)	4(0-12)	**<0.001**[1]	0.381	**0.003**	0.217
p value (outpatient vs. inpatient)	0.104[2]	0.399[2]	0.598[2]				
SF-36 HRQoL Scores							
Physical functioning score							
Outpatient	65(0-100)	75(15-100)	85(15-100)	**<0.001**[1]	**<0.001**	**<0.001**	**0.001**
Inpatient	50(0-100)	72.5(10-100)	85(10-100)	**<0.001**[1]	**<0.001**	**<0.001**	**0.004**
p value (outpatient vs. inpatient)	0.347[2]	0.687[2]	0.326[2]				
Bodily pain score							
Outpatient	57.5(0-100)	77.5 (22.5-100)	77.5(0-100)	**<0.001**[1]	**<0.001**	**<0.001**	0.582
Inpatient	57.5(0-100)	73.8(0-100)	85(0-100)	**<0.001**[1]	0.093	**<0.001**	**0.014**

p value (outpatient vs. inpatient)	0.970[2]	0.617[2]	0.242[2]				
General health score							
Outpatient	50(10-95)	25(0-75)	50(0-100)	**<0.001[1]**	**<0.001**	**<0.001**	**0.042**
Inpatient	45(5-100)	25(0-75)	50(0-100)	**<0.001[1]**	**0.003**	**<0.001**	**0.001**
p value (outpatient vs. inpatient)	0.347[2]	0.124[2]	0.490[2]				
Vitality score							
Outpatient	55(5-95)	62.5(10-95)	70(20-100)	**<0.001[1]**	**<0.001**	**<0.001**	**0.042**
Inpatient	45(10-90)	60(10-100)	70 (0-100)	**<0.001[1]**	**<0.001**	**<0.001**	**0.007**
p value (outpatient vs. inpatient)	0.151[2]	0.510[2]	0.641[2]				
Social functioning score							
Outpatient	62.5(0-100)	72.5(0-100)	77.5(0-100)	**<0.001[1]**	**<0.001**	**<0.001**	0.052
Inpatient	50(0-100)	62.5(12.5-100)	78.8(0-100)	**<0.001[1]**	**<0.001**	**<0.001**	**0.018**
p value (outpatient vs. inpatient)	**<0.001[2]**	**0.026[2]**	0.704[2]				

FAS, Fatigue Assessment Scale; IPAQ-SF, International Physical Activity Questionnaire - Short Form; MPVA, moderate and vigorous physical activity; HADS, Hospital Anxiety-Depression Scale; A, anxiety; D, depression; HRQoL, Health-related Quality of Life. [1]Friedman Test, [2]Mann-Whitney U, [3]Bonferroni corrected p values (values in bold indicate statistical significance)

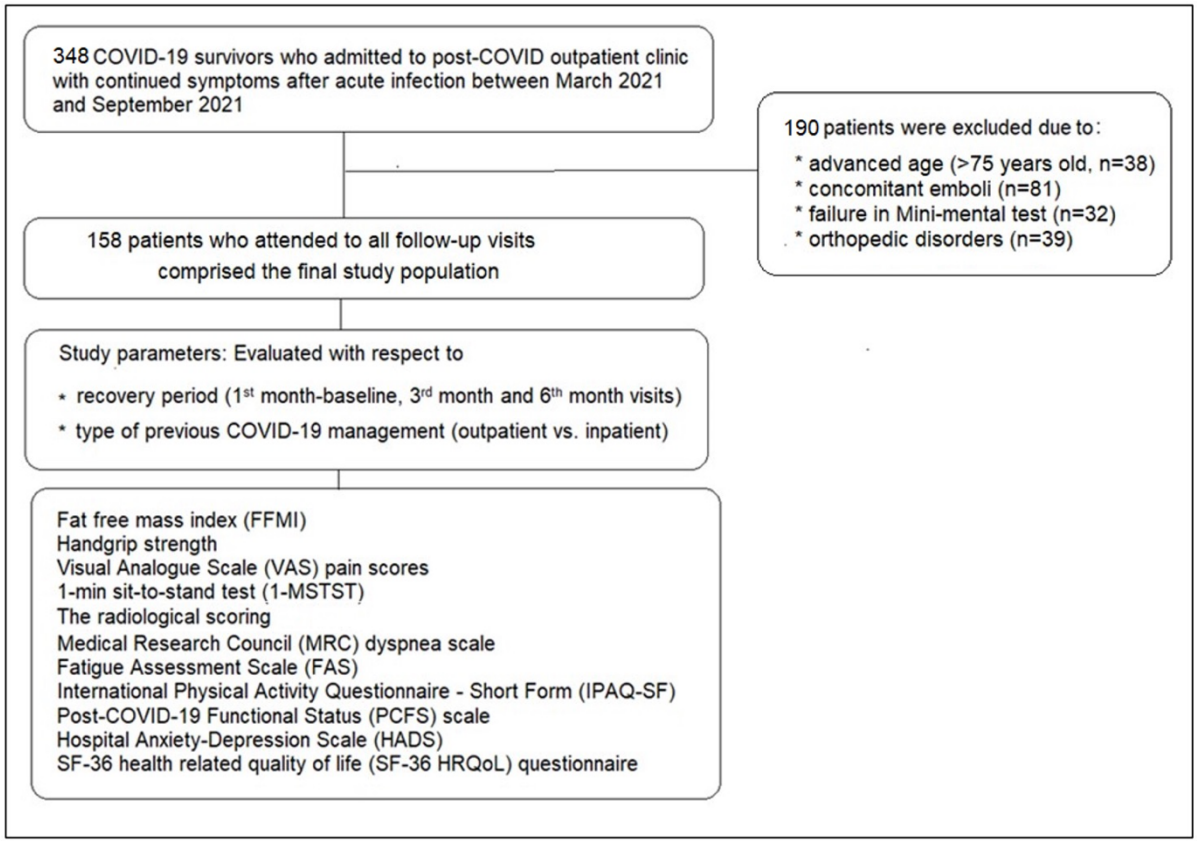

Figure 1. Study flowchart.

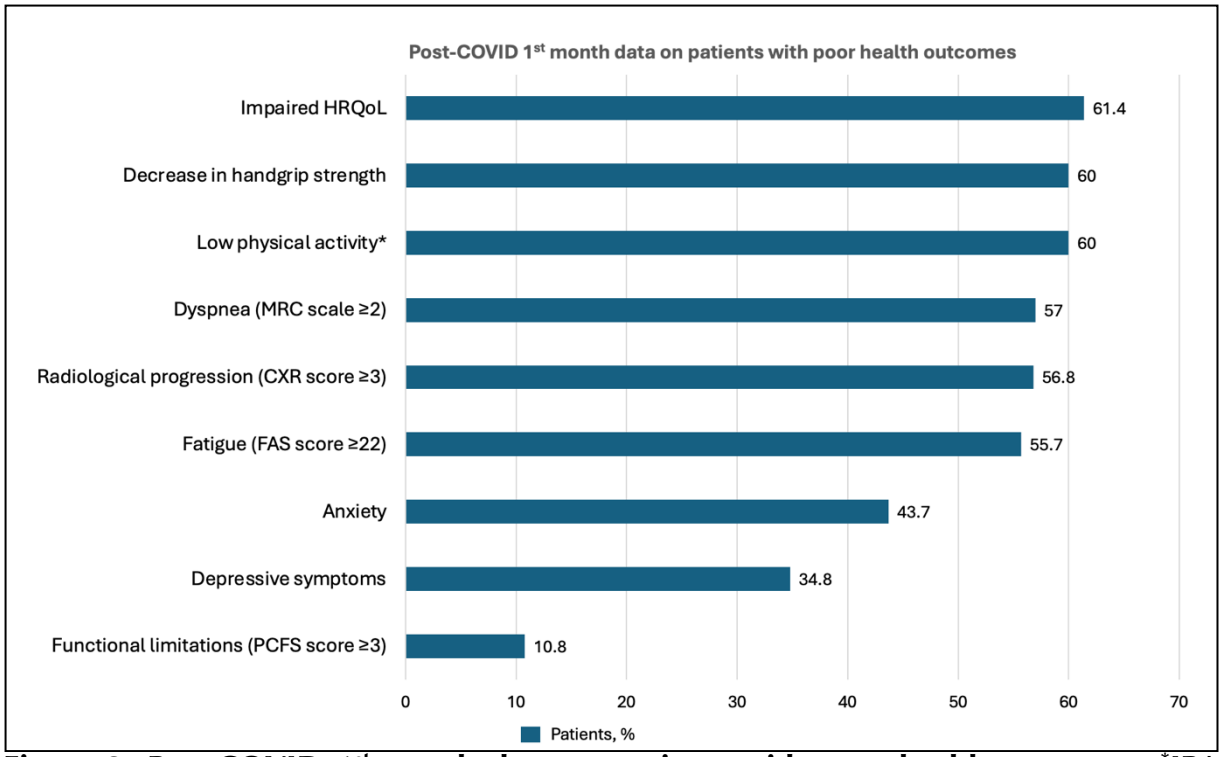

Figure 2. Post-COVID 1st month data on patients with poor health outcomes. *IPAQ-SF MVPA MET-minutes per week scores were divided by 10.