Longitudinal study of changes observed in quality of life, psychological state cognition, and pulmonary and functiona capacity after COVID-19 infection: A 6–7-month prospectiv cohort

Journal:	*Journal of Clinical Nursing*
Manuscript ID	Draft
Manuscript Type:	Special Issue Article
Search Terms:	Quality of Life, Psychological Well-Being, Physical Skills, Long-Term Care, Infectious Diseases Nursing

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Abstract

Aims To investigate the health-related quality of life (HRQoL), symptoms, psychological and cognitive state, and pulmonary and physical function of nonhospitalized COVID-19 survivors at long-term, and to identify factors to predict a poor HRQoL in this follow-up.

Background Most studies have focused on persistent symptoms of hospitalized patients with COVID-19 in the medium term. Thus, long-term studies on the persistent symptoms of nonhospitalized survivors are urgently required.

Design A longitudinal cohort study.

Methods 102 nonhospitalized COVID-19 survivors were recruited. We collected symptoms at 3 months (baseline) and at 6–7 months (follow-up) from the COVID-19 diagnosis (dyspnea, fatigue/muscle weakness, chest/joint pain), HRQoL, psychological state, cognitive function, pulmonary and physical function.

Results HRQoL was impaired in almost 60% of the sample and remained impaired 6–7 months. At 3 months, more than 60% of the participants had impaired physical function (fatigue/muscle weakness, as well as reduced lower limb and inspiratory muscle strength). In addition, 40-56% of the sample showed an altered psychological state (post-traumatic stress disorder (PTSD), anxiety/depression), cognitive function impairment and dyspnea. At 6–7-months, only a slight improvement in dyspnea and physical and cognitive function was observed, with a very high proportion of the sample (29-55%) remained impaired. Impaired HRQoL at 6–7 months was predicted with 82.4% accuracy (86.7% sensitivity and 83.3% specificity) by the presence at 3 months of muscle fatigue/muscle weakness (OR=5.66 (1.77-18.05), PTSD (OR=6.0 (1.74-20.71) and impaired HRQoL (OR=11.67 (3.71-36.77).

Conclusion A high proportion of nonhospitalized COVID-19 survivors experience an impaired HRQoL, cognitive and psychological function at long-term. HRQoL, PTSD and dyspnea at 3 months can identify the majority of COVID-19 survivors who will have a long-term impaired quality of life.

Relevance to clinical practice To improve the psychological state and to reduce the fatigue/muscle weakness of post-COVID-19 survivors is necessary to improve their HRQoL.

Keywords: COVID-19; health-related quality of life; psychological status; pulmonary function; physical function; long-term.

Introduction

In December 2019, a novel pneumonia infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a member of the betacoronavirus genus, spread in the Hubei province of China, causing the coronavirus disease 2019 (COVID-19) (Esakandari et al., 2020). Currently, COVID-19 has caused a worldwide pandemic and has had a huge impact on human health, daily life, and the economy.

The acute coronavirus infection is very similar to seasonal influenza, with the most common symptoms being fever, headache, shortness of breath, cough, myalgia, and fatigue (Disser et al., 2020; Esakandari et al., 2020; Mao et al., 2020; Pascarella et al., 2020). The clinical presentation begins within 14 days of exposure, presenting symptoms after approximately 5 days (Lauer et al., 2020). The course of the infection is mild or asymptomatic in approximately 80%–90% of cases (Pascarella et al., 2020), although some patients develop severe symptoms such as difficulty breathing, chest pain and/or pressure, and loss of speech and/or movement, which can be associated with pneumonia, sepsis, lung failure, and cardiac injury, requiring urgent medical attention (Esakandari et al., 2020).

The epidemiological and clinical characteristics, pathogenesis, and complications of patients with COVID-19 in the acute phase have been explicitly described; however, the long-term consequences of the illness remain largely unclear. To the best of our knowledge, only a few studies with 3-month follow-ups after discharge have been published (Bellan et al., 2021; González et al., 2021; Meys et al., 2020; Qu et al., 2021; Raman et al., 2021; Rass et al., 2021; Wong, Shah, Johnston, Carlsten, & Ryerson, 2020). These studies have reported certain persistent symptoms, such as extreme fatigue, breathlessness, coughing, limited exercise capacity, depression, cognitive deficits, neurological symptoms, smelling disorders, and impaired lung function, as well as poor health-related quality of life (Anastasio et al., 2021; Bellan et al., 2021; González et al., 2021; Meys et al., 2020; Miskowiak et al., 2021; Qu et al., 2021; Raman et al., 2021; Rass et al., 2021). Thus, the medium-term changes in health-related quality of life and functional status and the cognitive and psychological consequences of COVID-19 infection are apparent. Only 2 studies have reported the health consequences 6 months after a COVID-19 infection, one in a Chinese cohort (C. Huang et al., 2021) that observed fatigue, muscle weakness, anxiety, and depression, and the other in a Norwegian population that reported a decline in health-related quality of life and function (Walle-Hansen et al., 2021). However, no study to date has followed the same patient cohort over time to monitor the progression of these symptoms.

Since the beginning of the COVID-19 pandemic, most studies have focused on the health-related quality of life and persistent symptoms of hospitalized or post-discharge patients with COVID-19 in the medium term; however, few have reported on the clinical characteristics of post-COVID-19 survivors who can manage their symptoms at home without needing hospitalization due to their relatively mild symptoms, who account for 80%–90% of cases (Pascarella et al., 2020). For the diagnosis of a post-COVID syndrome, a post-infection period of at least 6 months is required (Lamprecht, 2020). Thus, long-term follow-up studies on the persistent symptoms of nonhospitalized COVID-19 survivors are urgently required because they can provide more comprehensive information for observing the changes in patient health and determining the long-term impact of COVID-19.

This longitudinal study was conducted to investigate the health-related quality of life, symptoms, psychological and cognitive state, and pulmonary and physical function of a cohort of nonhospitalized COVID-19 survivors. The study sought to identify factors to predict a poor health-related quality of life over 6–7 months of follow-up.

Methods

Study design

This cohort study was approved by the local ethics committee (registration number: XXX), was conducted in accordance with the Declaration of Helsinki, and reported its findings following the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies (von Elm et al., 2008). We obtained written informed consent from all participants.

Study population

The COVID-19 diagnosis was based on a typical clinical presentation coupled with a positive reverse-transcription–polymerase chain reaction (RT-PCR) SARS-CoV-2 test from a nasopharyngeal or oropharyngeal swab or serological tests positive for SARS-CoV-2 antibodies. The general inclusion criteria consisted of (1) confirmed SARS-CoV-2 infection; (2) non-hospital management; (3) age ≥18 years; and (4) no more than 3 months since the infection. Participants were excluded if they met any of the following criteria: (1) clinically evident cognitive impairment or active mental disorders; (2) difficulty understanding the language or visual, abstraction, or orientation impairment precluding the ability to complete the questionnaires; (3) presence of any concomitant condition that might affect the respiratory and/or functional state; and (4) living outside the XXX.

Study procedures

The participants were recruited via bulletin advertisements by e-mail and flyer distribution, using convenience sampling. All participants underwent an evaluation of symptoms at 3 months after the confirmed diagnosis and 6–7 months of follow-up in their homes by trained clinical evaluators between July 2020 and February 2021. We collected data by interviewing the participants as to their demographic characteristics, current symptoms at 3 months and at 6–7 months of follow-up from the COVID-19 diagnosis, including dyspnea, fatigue/muscle weakness, and chest and joint pain, and assessed the participants through a physical examination and questionnaires.

1. *Health-related quality of life.* To assess the participant' quality of life, we employed the EQ-5D-3L life, which consists of 5 dimensions (1, mobility; 2, self-care; 3, usual activities; 4, pain/discomfort; 5, anxiety/depression) with 3 response options based on severity level (1, no problems; 2, some problems; and 3, extreme problems/unable to) (Badia et al., 1999). Based on these 5-dimension codes, an index score is provided, ranging from −0.059 (poorest quality of life) to 1 (best quality of life) (Badia et al., 1999). We used the reference values to calculate the proportion of participants with an EQ-5D index below the 25th percentile of the mean age-based and sex-based reference values (König et al., 2009). Additionally, the participants had to rate their current overall health on a visual analogue scale (EQ-VAS) ranging from 0 (worst imaginable health) to 100 (best imaginable health).
2. *Psychological status*
    a. *Post-traumatic stress disorder (PTSD)*. We used the 17-item self-rating PTSD Checklist-Civilian Version (PCL-C) questionnaire to assess this outcome (Miles et al., 2008). The participants rated the degree to which they were bothered by each symptom on a 5-point Likert scale ranging

from 1 (not at all) to 5 (extremely). The cutoff score of 34 suggests a clinically relevant PTSD (Yeager et al., 2007).

3. *Anxiety and depression levels*. We used the Hospital Anxiety and Depression Scale (HADS) (Herrero et al., 2003), which consists of 14 items divided into 2 subscales for anxiety and depression. The subscales include 7 items each, and the scores range from 0 to 42. We used the HADS optimal cut-off score of ≥13 (Singer et al., 2009).
4. *Cognitive function*. We used the Montreal Cognitive Assessment (MoCA) (www.mocatest.org) as a screening test to estimate the severity of global cognitive impairment, with subcategories reflecting the following cognitive domains: visuospatial-executive, naming, memory, attention, and language (Delgado et al., 2019). We classified participants scoring below 26 points as having impairment.
5. *Pulmonary function.* The forced spirometry measurements included forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), and their ratio (FEV_1/FVC), assessed using a portable spirometer (Spirobank II USB, MIR, Rome, Italy) according to the American Thoracic Society/European Respiratory Society guidelines for standardizing spirometry (Miller et al., 2005). The measurements are expressed as percentages of the predicted values.
6. *Physical function/strength*
    a. Inspiratory muscle strength was evaluated by measuring maximum inspiratory pressure (MIP) using a Powerbreath Kinetic KH1 device (POWERbreathe International Ltd) according to American Thoracic Society/European Respiratory Society guidelines ("ATS/ERS Statement on respiratory muscle testing.," 2002). The estimated inspiratory muscle

strength values were established following the reference equation for MIP for the adult population (Morales et al., 1997).

b. To test the participants' isometric hand and forearm strength, we employed a hand dynamometer (JAMAR®, Patterson Medical, IL, USA) (Peolsson et al., 2001). We used the predicted hand strength values in the adult population to predict impairment (Mateo Lázaro et al., 2008).

c. We used the 1-min sit-to-stand (1 min STS) test to assess lower muscle strength (Núñez-Cortés et al., 2021). We used the reference values to identify the participants with decreased lower body muscle strength (Strassmann et al., 2013).

Data analysis

The data analysis was performed with SPSS version 21.0 (SPSS Inc., Chicago, IL, USA), establishing a significance level of 5%. The data are presented as mean ± standard deviation for the continuous variables and as n (%) for the categorical variables. The continuous variables were converted into categorical variables according to the criteria proposed for the different study variables (<25th percentile, <80% of predicted, or less than the cut-off from the questionnaires/scales) (Szende et al., 2014). In addition, we dichotomized the EQ-VAS on the basis of a receiver operating characteristic (ROC) curve analysis and considered scores ≤70 as "impaired". Differences between the assessment at 3 months and at 6–7 months after the COVID-19 diagnosis were examined using McNemar's test for the categorical variables and Student's t-test for related samples for the continuous variables. In the latter case, we calculated the effect size using Cohen's d as follows: small (0.20–0.49), medium (0.50–0.79), or large (≥0.8) (Cohen, 1988).

We performed a univariate logistic regression analysis to determine the relationship of the various dichotomized potential predictor variables (examined at 3 months), with impaired quality of life at 6–7 months after the COVID-19 diagnosis. Variables with a significance level of $p<0.05$ were retained as potential predictors for a backward stepwise multiple logistic regression. We examined the model's discriminant validity by means of an ROC analysis, determining (according to Youden's index) the optimal cut-off for the probability set by the model to identify the participants with impaired quality of life at 6–7 months after the COVID-19 diagnosis, with its corresponding sensitivity and specificity. We evaluated the diagnostic precision according to the area under the ROC curve (AUC), with values >0.7 being considered acceptable (Swets, 1988) and when at least 70% sensitivity and 50% specificity were obtained (Turner et al., 2009).

Results

The final sample consisted of 102 participants (38 men and 64 women), with a mean age of 46.62 ± 14.11 years, who had a confirmed diagnosis of COVID-19 (**Figure 1**). None of the participants required hospital admission, although 11 underwent a rehabilitation program before entering the study. In terms of their anthropometric characteristics, the participants' weight increased slightly but significantly during the 3–4 months of follow-up. **Table 1** presents the participants' anthropometric characteristics and lifestyle habits.

Health-related quality of life

The health-related quality of life was impaired in almost 60% of the sample and remained impaired 6–7 months after their COVID-19 diagnosis (**Table 2**). In fact, the participants who presented with impaired health-related quality of life remained practically the same in the various dimensions assessed in the EQ-5D-3L, except for mobility and pain/discomfort (**Figure 2)**.

In terms of the differences between the participants with impaired health-related quality of life and those with preserved health-related quality of life, the dimensions that mainly determined the deterioration in health-related quality of life were pain/discomfort, anxiety/depression and usual activities, as shown in the radar plot in **Figure 2**. The differences remained virtually unchanged at 6–7 months in all dimensions, except for anxiety/depression, which increased.

Symptoms, psychological state, and cognitive, pulmonary, and physical function

Table 2 indicates the percentage of participants with symptoms and/or impaired psychological and cognitive states and reduced pulmonary and physical function at 3 and 6–7 months after the COVID-19 diagnosis, as well as the changes during this time. Dyspnea and fatigue/muscle weakness were the most prevalent symptoms at 6–7 months, with significant improvements in the number of participants reporting these symptoms at 6–7 months after the COVID-19 diagnosis. However, almost 30% of the sample experienced dyspnea and fatigue/muscle weakness at 6–7 months, with no improvement in the other symptoms.

The psychological state and cognitive function were impaired in almost half of the participants, with slight improvement at 6–7 months (approximately 40% were still impaired in some of these variables). In fact, the mean scores on the various instruments employed to examine these variables were above or very close to the cut-off point for being considered as experiencing cognitive deficits, anxiety/depression and/or PTSD.

Pulmonary function was preserved in virtually the entire sample, with the lowest parameter being the FEV_1/FVC ratio, with less than 15% of the sample reflecting values below 70% at 6–7 months after the COVID-19 diagnosis. In terms of physical function, approximately 60% of the participants showed loss of lower limb and inspiratory muscle strength at 3 months, which improved significantly at 6–7 months, although the improvement was slight, with 50% of participants still showing values below the 25th percentile of their baseline values for age and sex.

Prediction of impaired health-related quality of life at 6–7 months

The results of the univariate logistic regression analysis showed that the presence at 3 months after the COVID-19 diagnosis of chest pain, dyspnea, anxiety/depression, PTSD, fatigue/muscle weakness, and/or impaired health-related quality of life (index score <25th percentile or EQ-VAS ≤70) were significant predictors of health-related quality of life impairment at 6–7 months after the COVID-19 diagnosis. The remaining variables examined were not predictive, given that their relationship with the dependent variable was not statistically significant. **Figure 3** shows the results of the univariate logistic regression analysis.

According to the backward stepwise multiple logistic regression, the presence at 3 months of "impaired health-related quality of life" (EQ-5D index score <25th percentile), "PTSD" (PCL-C ≥ 35), and "fatigue/muscle weakness" were positively associated with health-related quality of life impairment at 6–7 months after the COVID-19 diagnosis (**Table 3**). This model correctly predicted 82.4% of those with persistent health-related quality of life impairment. Furthermore, the ROC analysis supported the model's adequate discriminant validity (AUC, 0.90 [0.84–0.96]; p<0.001), presenting a sensitivity of 86.7% and a specificity of 83.3% (Youden index, 0.70) for identifying individuals whose health-related quality of life will be impaired at

6–7 months post-COVID-19 when the probability proposed by the model (P [impaired QoL at 6–7 months]) is ≥0.57 (**Table 3**).

Discussion

To our knowledge, this is the first study to investigate the influence of COVID-19 on the long-term outcomes of nonhospitalized COVID-19 survivors and to follow them over time to track the progression of their symptoms. The most striking finding is the high proportion (60%) of the participants with health-related quality-of-life impairment 6–7 months after the first symptoms. We also observed a high level of self-reported symptoms, such as dyspnea, fatigue/muscle weakness, PTSD, anxiety, depression, cognitive deficits, and a decrease in physical function among survivors. The univariate regression analysis indicated that chest pain, dyspnea, anxiety/depression, PTSD, and/or fatigue/muscle weakness were risk factors for developing impaired health-related quality of life. This study therefore confirms the long-term repercussions of COVID-19 on nonhospitalized patients, suggesting that many of these deficits are likely ongoing consequences of COVID-19 due to them not returning to normal over time. Increased knowledge regarding the significant predictors of health-related quality-of-life impairment in the long term due to COVID-19 is imperative to develop preventive measures for patients at risk.

Health-related quality of life

In our cohort, 60% of the participants who had not been admitted to the hospital demonstrated an EQ-5D index below the 25^{th} percentile of normative values, indicating that their health-related quality of life did not return to normal, even long after the infection. The participants with impaired health-related quality of life reported problems in all EQ dimensions that remained virtually unchanged 6–7 months after the COVID-19 infection, except for mobility and pain/discomfort. In addition, the dimensions that mainly conditioned the deterioration in health-related quality of life were pain/discomfort, anxiety/depression, and usual activities. Comparing our data with a representative sample of the general population, the frequency with which the coronavirus survivors reported certain quality-of-life problems was substantially higher than the Spanish norm (König et al., 2009). For the mean EQ-VAS scores, there were significant differences at 6–7 months when the values increase; however, the gross value (74.38) was similar to that of the heathy Spanish population (75) (Szende et al., 2014), a finding that could be explained by the large sample size, given that any small change would show statistically significant gains. These findings were consistent with previous studies of medium-term outcomes of patients with COVID-19 after hospital discharge (Meys et al., 2020; Qu et al., 2021; Rass et al., 2021; van der Sar - van der Brugge et al., 2021; Willi et al., 2021; Wong et al., 2020) and at 6 months of follow-up (Walle-Hansen et al., 2021). The quality of life of nonhospitalized Belgian patients after 3 months was affected in 40% of the cases, with a mean EQ-5D index and EQ-VAS score of 0.62 and 51, respectively, results lower than those of our cohort, perhaps due to the 5th percentile of normative values used as the cut-off (Meys et al., 2020). Even in the long term, the quality of life of participants is as affected as that of patients with chronic respiratory diseases such as asthma (mean EQ-5D index, 0.77–0.88) (Hernandez et al., 2019; Szentes et al., 2020), which permanently detracts from their quality of life, due possibly to the incomplete recovery of pulmonary function (Zheng, Yao, Wu, & Zheng, 2020) or psychological problems (Yuan et al., 2020). It is therefore important for health professionals to be aware of the relationships between the psychological factors and health-related quality of life, given these relationships can identify possible targets for interventions to improve the health-related quality of life.

Symptoms and psychological state

At 6–7 months after the COVID-19 infection, the nonhospitalized patients were mainly troubled by dyspnea and fatigue/muscle weakness. In the medium term, 41% and 63% reported dyspnea and muscle fatigue, respectively, which agrees with other studies on hospitalized patients (Carfì et al., 2020; González et al., 2021; Qi et al., 2020; Raman et al., 2021; Willi et al., 2021; Wong et al., 2020). In the long term, Huang et al. (C. Huang et al., 2021) observed a prevalence of muscle fatigue of 63%, which is higher than in our report; however, their sample consisted of hospitalized patients who were severely ill, who might have had more severe muscle weakness due to immobilization during their hospital stay (Aarden et al., 2019). The assessment of the psychological state revealed PTSD and symptoms of anxiety/depression in 34% and 45%, respectively, in the long term, with the post-traumatic stress slightly improving over time but the anxiety and depression remaining constant. PTSD in the medium term was considerably more prevalent in our cohort than those in other studies (Bellan et al., 2021; Bonazza et al., 2020; Mazza et al., 2020; Qi et al., 2020; Rass et al., 2021; Tarsitani et al., 2021), as was anxiety and depression in the long term (C. Huang et al., 2021; Qi et al., 2020; Taquet et al., 2021). These differences might be due to sample size, methodology (e.g., assessment tools and cut-offs) and management of the pandemic (e.g., health system collapse and prolonged confinement). Close attention should therefore be paid to subject' mental health after a COVID-19 infection due to the negative psychosocial consequences of their isolation.

Cognitive, pulmonary, and physical function

Cognitive and physical function are among the most important factors for health-related quality of life and the patients' perception of the impact of the disease and their disability (Fusco et al., 2012; Saraçli et al., 2015). In our study, long-term cognitive deficits were frequent (41%) after the COVID-19 diagnosis, which is in line with other study (Miskowiak et al., 2021), although the deficits slightly improved over time. Impaired lung function was observed in a small proportion of the sample in the long term, indicating that the preserved pulmonary function of the nonhospitalized patients with COVID-19 might be due to the critical illness showing a higher incidence of major long-term sequelae in the lungs (Anastasio et al., 2021; Bellan et al., 2021; González et al., 2021; C. Huang et al., 2021; Y. Huang et al., 2020; van der Sar - van der Brugge et al., 2021). However, more than half of the participants experienced a reduction in respiratory muscle strength in the long term, a finding in line with other studies (Anastasio et al., 2021; Y. Huang et al., 2020). Lower limb strength showed the same tendency consistent with the evidence (Bellan et al., 2021; Belli et al., 2020; Núñez-Cortés et al., 2021; Raman et al., 2021), although it slightly improved over time. The main reasons for the reduction in physical function might lie in the fact that the lockdowns heavily limited people's exercise possibilities, promoting sedentary lifestyles due to the hesitation to go outside (Constandt et al., 2020); in fact, most of the participants in our sample gained weight in the long term. The result from our study highlights a clear need for rehabilitative interventions after a COVID-19 infection.

Prediction of impaired health-related quality of life at 6–7 months

The results of the univariate logistical regression indicated that the health-related quality of life at 6–7 months after the COVID-19 diagnosis was affected by certain factors, such as chest pain, dyspnea, anxiety/depression, PTSD and/or fatigue/muscle weakness and, especially, the quality of life at 3 months. The proposed model for calculating the probability of impaired health-related quality of life in the long term predicted 82.4% of the cases based on an EQ-5D index score less than the 25th percentile, PTSD, and fatigue/muscle weakness. These results are in line with emerging evidence showing that PTSD leads to a higher risk of developing serious events and poorer outcomes in COVID-19 (Chang & Park, 2020; Tarsitani et al., 2021). Physical symptoms are closely related to an increased psychological burden, as well as impaired physical function, ultimately impacting on the quality of life (Nunes et al., 2017; Storm van's Gravesande et al., 2019). The quality of life 3 months after the COVID infection appears to be the most important predictor of the subject's quality of life at 6–7 months, which is consistent with the predictive models of disability established in other diseases in which the assessment of medium-term disability itself is the best indicator of the degree of disability in the long term (Ritchie et al., 2015, 2013). Future studies are warranted to examine the multidisciplinary interventions aimed at improving the psychological and physical state, which will presumably lead to an increase in the quality of life for post-COVID-19 infection.

Limitations

The first limitation of the current study is its limited external validity due to the fact that our sample was limited to a single geographic location. Although a larger sample size from different areas would be ideal for this type of study, ours is a diverse cohort from a catchment area that represents the diversity of XXX and is located in the early epicenter of the COVID-19 outbreak (XXX). Thus, the generalization of our results is facilitated by the well-characterized and prospective nature of our cohort. Although this probably overestimates the actual impact on the quality of life of general nonhospitalized COVID-19 survivors, it might also be a reliable representation of the current population of nonhospitalized COVID-19 survivors with persistent symptoms. Lastly, we only recorded the relevant clinical findings that were self-reported by the participants or by their physicians through a physical examination during medium and long-term follow-up periods.

Clinical implications

Our findings highlight the long-term impact of COVID-19, even after their reported recovery from the acute manifestations of this disease. Our results emphasize the need for a comprehensive multidisciplinary approach that is aligned with patient needs to deliver the most appropriate care to these patients. It is important that health practitioners focus on improving the psychological state and reducing the fatigue/muscle weakness of post-COVID-19 survivors to improve the patients' health-related quality of life. More longitudinal studies with larger samples are needed to determine the causal relationships and identify the effects of time. Long-term follow-up of COVID-19 survivors is needed to determine the dynamic recovery of their health-related quality of life.

Conclusion

In conclusion, a considerable number of nonhospitalized COVID-19 survivors experience an impaired health-related quality of life and symptoms such as dyspnea, fatigue/muscle weakness, PTSD, anxiety, depression, cognitive deficits, and reduced physical function at long-term after the COVID-19 diagnosis. Poor health-related quality of life was significantly associated with chest pain, dyspnea, anxiety/depression, PTSD and/or fatigue/muscle weakness in the long term. This adds further evidence that patients who have not been admitted to the hospital with COVID-19 continue to struggle after recovering from the acute phase of this disease, with a diverse range of impairments.

What does this paper contribute to the wider global clinical community?

- A considerable number of nonhospitalized COVID-19 survivors experience an impaired health-related quality of life and symptoms such as dyspnea, fatigue/muscle weakness, PTSD, anxiety, depression, cognitive deficits, and reduced physical function at long-term after the COVID-19 diagnosis.

- Our findings highlight the long-term impact of COVID-19, even after their reported recovery from the acute manifestations of this disease.

- It is important that health practitioners focus on improving the psychological state and reducing the fatigue/muscle weakness of post-COVID-19 survivors to improve the patients' health-related quality of life.

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Table 1. Anthropometric characteristics and lifestyle habits of the sample.

	Post COVID-19 infection		Changes occurred
	3 months	6–7 months	McNemar's test P-value AND/OR Mean difference (95%CI); Cohen's *d*
Age (years)	46.62 ± 14.11	—	
Height (cm)	168.92 ± 9.88	—	
Weight (Kg)	75.36 ± 15.93	76.18 ± 15.57	–0.81 (–1.30 to –.31)**; *d* = 0.05
BMI (Kg/cm^2)	26.37 ± 4.84	26.68 ± 4.69	–0.31 (–.50 to –.12)**; *d* = 0.07
Current Smoking			
Current smoker	23 (22.55 %)	—	
Former smoker	32 (31.37 %)	—	
Never smoker	47 (46.08 %)	—	
Performed Rehabilitation			
Yes	11 (10.78 %)	—	
No	91 (89.22 %)	—	
Physical Activity (IPAQ)			
Low	23 (22.55 %)	19 (18.63 %)	
Moderate	57 (55.88 %)	62 (60.78 %)	P = .787
High	22 (21.57 %)	21 (20.59 %)	
Total IPAQ Score (Mets)	2074.35 ± 1995.12	2291.16 ± 2418.41	–216.82 (–691.07 to 257.44); *d*=0.10

COVID-19: coronavirus disease-19; IPAQ: International Physical Activity Questionnaire; Mets: Metabolic Equivalent of Task

Table 2. Symptoms and/or deterioration of psychological state and cognitive, pulmonary and physical function at 3 and 6–7 months after COVID-19 diagnosis, as well as the changes occurred during this time.

	Post COVID-19 infection		**Changes occurred**
	3 months	6–7 months	McNemar's test P-value AND/OR Mean difference (95%CI); Cohen's *d*
Health-related quality of life (EQ-5D-3L)			
Index score			
Impaired (< 25th percentile)	60 (58.82 %)	60 (58.82 %)	P-value = 1.00
Total score	0.82 ± 0.22	0.83 ± 10.2	-0.011 (-.048 to 0.027); *d* = 0.001
EQ-Visual analogue scale (0-100)	70.41 ± 18.37	74.38 ± 17.91	-3.97 (-6.46 to -1.48)**; *d* = 0.22
Symptoms			
Dyspnoea	42 (41.18 %)	30 (29.41 %)	P-value = .002
Fatigue/muscle weakness	64 (62.75 %)	36 (35.29 %)	P-value < .001
Chest pain	21 (20.59 %)	17 (16.67 %)	P-value = .344
Joint pain	13 (13.75 %)	11 (10.78 %)	P-value = .754
Psychological status			
Post-traumatic stress disorder (PCL-C)			
Impaired (score ≥ 35)	41 (40.2 %)	35 (34.31 %)	P-value = .263
Total score	34.16 ± 14.81	32.27 ± 14.18	1.88 (.25 to 3.52)*; *d* = 0.13
Anxiety and Depression (HADS)			
Moderate/Severe (score ≥ 13)	47 (46.08 %)	46 (45.1 %)	P-value = 1.00
Total score	13.15 ± 5.77	13.25 ± 6.01	-0.10 (-.96 to 0.76); *d* = 0.02
Cognitive function (MoCA)			
Impaired (score < 26)	57 (55.88 %)	42 (41.18 %)	P-value = .004
Total score	24.72 ± 3.03	25.81 ± 2.65	-1.10 (-1.49 to -0.70)**; *d* = 0.38
Pulmonary function			
FVC (% of predicted)			
Impaired (<80 %)	4 (3.92 %)	2 (1.96 %)	P-value = .625
Total score	114 ± 18.21	116.16 ± 18.02	-2.16 (-3.98 to -0.33)*; *d*= 0.12
FEV_1 (% of predicted)			
Impaired (<80 %)	9 (8.82 %)	6 (5.88 %)	P-value = .687
Total score	101.17 ± 20.36	104.99 ± 19.18	-3.82 (-6.58 to -1.07)**; *d* = 0.19
FEV_1/FVC (%)			
Impaired (<70 %)	20 (19.61 %)	15 (14.71 %)	P-value = .227
Total score	74.02 ± 9.68	75.46 ± 9.06	-1.44 (-2.99 to 0.10); *d* = 0.15
Physical function/strength			
Inspiratory strength (MIP, % of predicted)			
Impaired (<80 %)	68 (66.67%)	56 (54.90%)	P-value = .017
Total score	74.75±22.64	77.24±22.52	-2.49 (-5.20 to 0.21); *d* = 0.11
Right handgrip strength (kg)			
Decreased (< 25th percentile)	7 (6.86%)	2 (1.96%)	P-value = .063
Total score	32.40±11.84	33.66±11.88	-1.26 (-2.11 to -0.40)**; *d* = 0.11
Left handgrip strength (kg)			
Decreased (< 25th percentile)	7 (6.86%)	3 (2.94%)	P-value = .219
Total score	30.85±11.63	31.37±12.15	0.52 (-1.60 to 0.56); *d* = 0.04
Lower limb strength (1 min STS)			
Decreased (< 25th percentile)	61 (59.80%)	46 (45.10%)	P-value = .001
Total score	31.67±9.67	34.69±11.93	-3.02 (-4.42 to -1.62)**; *d* = 0.28

Abbreviatures: EQ, EuroQol; FEV_1, Forced Expiratory Volume at the first second; FVC, Forced Vital Capacity; HADS, Hospital Anxiety and Depression Scale; MIP, Maximal Inspiratory Pressure; MoCA, Montreal Cognitive Assessment; PCL-C, Post-Traumatic Stress Disorder Checklist – Civilian version.

* P < .05

Table 3. Results of backwards stepwise multiple logistic regression analysis showing factors associated with presence of impaired health-related quality of life at 6–7 months after COVID-19 diagnosis.

Outcomes at 3 months	B	SE	Wald test	P-value	OR (95% CI)
Impaired QoL (EQ-5D-3L < 25th percentile)	2.457	.585	17.612	< .001	11.67 (3.71 to 36.77)
Post-traumatic stress disorder (PCL-C ≥ 35)	1.791	.632	8.024	.005	6.00 (1.74 to 20.71)
Fatigue/muscle weakness	1.733	.592	8.570	.003	5.66 (1.77 to 18.05)

Formula proposed by the model for calculating the probability of the presence of impaired quality of life:

$$\text{Probability (impaired QoL at 6–7months)} = \frac{1}{1 + e^{-(2.457*[\text{Impaired QoL}]+1.791*[\text{Posttraumatic stress disorder}]+1.733*[\text{Fatigue/muscle weakness}] -2.676)}}$$

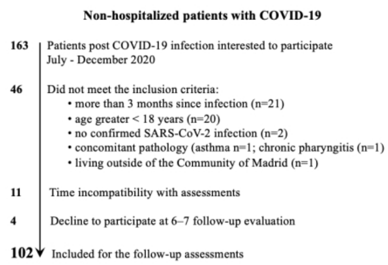
Abbreviatures: CI, Confidence Interval; EQ, EuroQol; OR, Odds Ratio; PCL-C, Post-Traumatic Stress Disorder Checklist – Civilian version; QoL, Quality of Life; SE, Standard Error.

Figure 1. Flow-chart for recruitment of patients in post COVID-19 long-term follow-up assessments.

Figure 2. Change in EQ-5D-3L dimensions in participants with and without impaired health-related quality of life.

Figure 3. Results of univariate logistic regression analysis showing factors associated with presence of impaired health-related quality of life at 6–7 months after COVID-19 diagnosis.

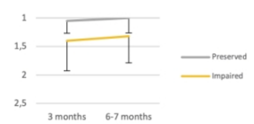
CI, Confidence Interval; EQ, EuroQol; FEV_1, Forced Expiratory Volume at the first second; FVC, Forced Vital Capacity; HADS, Hospital Anxiety and Depression Scale; MIP, Maximal Inspiratory Pressure; MoCA, Montreal Cognitive Assessment; OR, Odds Ratio; PCL-C, Post-Traumatic Stress Disorder Checklist – Civilian version; VAS, Visual Analogue Scale.



Flow-chart for recruitment of patients in post COVID-19 long-term follow-up assessments.

296x209mm (150 x 150 DPI)

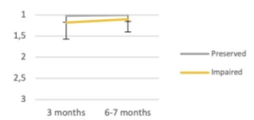
MOBILITY



	3 months	
No problems	Some problems	Unable to
77 (75.49%)	24 (23.53%)	1 (0.98%)

	6–7 months	
No problems	Some problems	Unable to
80 (78.43%)	22 (21.57%)	—

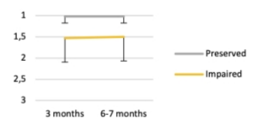
SELF-CARE



	3 months	
No problems	Some problems	Unable to
90 (88.24%)	12 (11.76%)	—

	6–7 months	
No problems	Some problems	Unable to
95 (93.14%)	7 (6.96%)	—

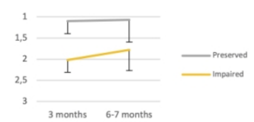
USUAL ACTIVITIES



	3 months	
No problems	Some problems	Unable to
71 (69.61%)	29 (28.43%)	2 (1.96%)

	6–7 months	
No problems	Some problems	Unable to
73 (71.57%)	27 (26.47%)	2 (1.96%)

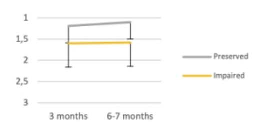
PAIN / DISCOMFORT



	3 months	
No problems	Some problems	Unable to
40 (39.22%)	59 (57.84%)	3 (2.94%)

	6–7 months	
No problems	Some problems	Unable to
44 (43.14%)	55 (53.92%)	3 (2.94%)

ANXIETY / DEPRESSION

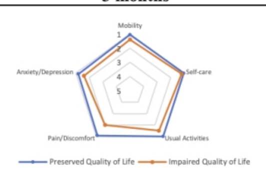


	3 months	
No problems	Some problems	Unable to
60 (58.82%)	40 (39.22%)	2 (1.96%)

	6–7 months	
No problems	Some problems	Unable to
61 (59.80%)	39 (38.24%)	2 (1.96%)

EQ-5D-3L DESCRIPTIVE SYSTEM

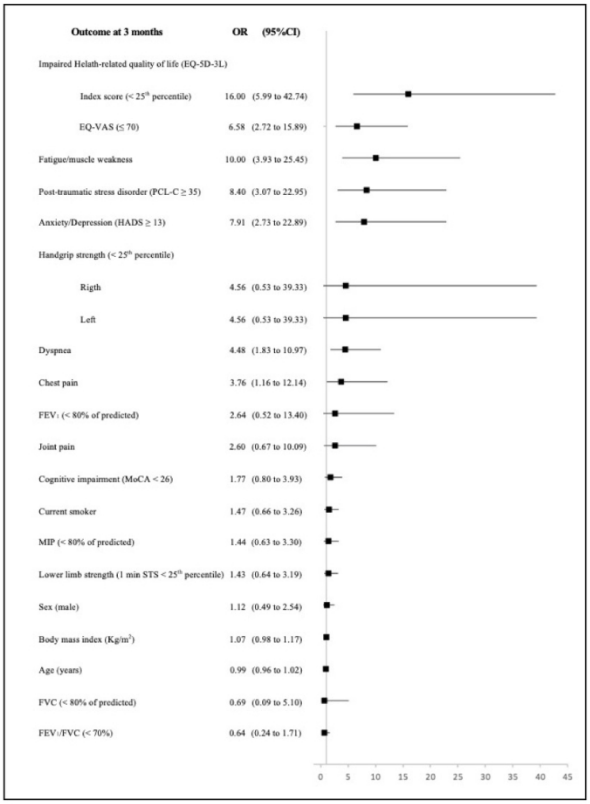
3 months



6–7 months

Change in EQ-5D-3L dimensions in participants with and without impaired health-related quality of life.

209x296mm (150 x 150 DPI)



Results of univariate logistic regression analysis showing factors associated with presence of impaired health-related quality of life at 6–7 months after COVID-19 diagnosis.
CI, Confidence Interval; EQ, EuroQol; FEV1, Forced Expiratory Volume at the first second; FVC, Forced Vital Capacity; HADS, Hospital Anxiety and Depression Scale; MIP, Maximal Inspiratory Pressure; MoCA, Montreal Cognitive Assessment; OR, Odds Ratio; PCL-C, Post-Traumatic Stress Disorder Checklist – Civilian version; VAS, Visual Analogue Scale.

419x594mm (72 x 72 DPI)