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ORIGINAL ARTICLE

Midterm functional sequelae and implications in rehabilitation after COVID-19: a cross-sectional study

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ABSTRACT

BACKGROUND: COVID-19 has been mainly investigated concerning the acute and subacute phase implications and management. Meanwhile, few studies focused on the midterm sequelae, which still remain largely unknown.
AIM: To assess the physical performance of COVID-19 survivors at 3 to 6 months from Hospital discharge.
DESIGN: A cross-sectional study focused on mid-term functional outcomes evaluation in COVID-19 survivors.
SETTING: Outpatients who had been previously hospitalized due to COVID-19 from March to May 2020 at the University Hospital of Novara, Italy.
POPULATION: We enrolled 204 patients, of which 60% were men, with the mean age of 57.9 years.
METHODS: Patients firstly underwent the short physical performance battery test (SPPB), which is composed of a series of physical tests assessing the lower limb function and the functional status of the subjects. Subsequently, based on SPPB results, patients' cardiorespiratory fitness performance was further investigated. Patients with normal SPPB score (SPPB>10) underwent the 2-minute walking test (2MWT) whereas, in order to safely test the cardiorespiratory function, in patients with abnormal SPPB score (SPPB≤10) the 1-minute sit-to-stand test (1MSTST) was performed. It should be noted that the 1MSTST can be safely performed even by subjects with compromised walking ability.
RESULTS: Overall, 66 patients (32% of our sample) showed an impaired physical performance at 3 to 6 months after hospital discharge. In particular, 29 patients presented an SPPB score ≤10, and the 1MSTST confirmed this status in the whole group (100%) compared to the reference values for age and sex. Besides, among patients with a normal SPPB score, 37 showed a lower sex- and age-matched 2MWT score. Finally, a significant association between Intensive Care Unit hospitalization or mechanical ventilation and physical impairment was observed together with a significant association between the walking ability (measured with SPPB and 2MWT) and the number of comorbidities.
CONCLUSIONS: A residual physical and functional impairment was observed in COVID-19 survivors at mid-term evaluation after hospitalization.
CLINICAL REHABILITATION IMPACT: Considering the current COVID-19 epidemiology, we might expect a tremendous burden of disability in the next future. Thus, an appropriate clinical rehabilitation pathway must be implemented.

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KEY WORDS: Coronavirus; Rehabilitation; Patient outcome assessment; COVID-19; Disability evaluation; Outpatients.

In late 2019, a new highly infectious pathogenetic coronavirus (CoV-2) responsible for severe acute respiratory syndrome (SARS-CoV-2) appeared in Wuhan, China and rapidly spread throughout the world.[1] On March 11, 2020, the World Health Organization (WHO), after assessing the levels of severity and spread of CoV-2 infection, declared the state of pandemic.[2]

Although the first organ to be involved is usually the lungs, causing bilateral interstitial pneumonia, SARS-CoV-2 can damage many organs, not only by direct viral damage, but also by the general inflammatory state that the virus generates in the host.[3]

Coronavirus disease 19 (COVID-19) could appear with a wide range of clinical manifestations, from asymptomatic infection to acute respiratory distress syndrome (ARDS) and even death.[4] Usually, COVID-19 starts with such symptoms as fever, myalgia, cough and fatigue. Less common beginning symptoms include lymphopenia, hemoptysis, headache and diarrhea.[5] Other acute-phase symptoms like sore throat, rhinorrhea and sneezing represent important clinical features as they express the lower airways involvement, which is a specific CoV-2 target.[6] Among complications, the most frequently reported are sepsis, respiratory failure, ARDS, heart failure and septic shock.[7]

What remains still mysterious and debated are the midterm and long-term sequelae of COVID-19. Evidence from previous Coronavirus (CoV) outbreaks reported impaired pulmonary and physical function, reduced quality of life, and emotional distress.[8] At state of the art, sequelae of COVID-19 remain largely unknown, but some preliminary observations strongly suggest a similar profile to those of other CoV previously described.[9]

As far as we know, medical sequelae of COVID-19 determine a multiorgan engagement. A French expert opinion lists all possible medical sequelae, including interstitial pulmonary fibrosis, inflammatory myocarditis, renal damage, sarcopenia and psychic illness.[10]

As regards COVID-19 neurological sequelae, they are only partially known. Because of the virus-specific neuro-tropism, SARS-CoV-2 can cause both peripheral and central nervous system manifestations (PNS and CNS, respectively). More in detail, PNS symptoms could include skeletal and muscular pain, paresthesia, areflexia, ataxia, muscle and facial weakness, or paralysis, whereas main CNS symptoms could be headache and vertigo.[11] Moreover, critical illness polyneuropathy (CIP), a mixed sensorimotor neuropathy that leads to axonal degeneration, and critical illness myopathy (CIM), a non-necrotizing diffuse myopathy with fatty degeneration, fiber atrophy, and fibrosis, may occur after COVID-19.[12]

An Italian study declared fatigue as the most frequent long-term symptom in patients discharged from Hospital after recovery from COVID-19. Other persistent symptoms reported were dyspnea, joint pain, chest pain, cough, and anosmia. However, details on fatigue severity and, where appropriate, rehabilitation need in previously hospitalized patients are still lacking.[13] On the other hand, Vaes *et al*. described a significant decrease in health status in non-hospitalized patients after 79±17 (mean±SD) days from the beginning of the infection symptoms. More in detail, they found that almost all of the patients studied (98%) experienced fatigue, (90%) muscle weakness, (88%) sleeping problems and (87%) pain.[14]

Thus, to date, we are only aware that COVID-19 could determine many different sequelae, including remarkable functional and physical impairment. However, there still is a gap in knowledge in literature: we are not even completely aware of how the disease affects the physical fitness of patients, for how long these impairments will last, and what strategies could be implemented in the clinical practice to provide a full physical recovery.

With regard to the rehabilitation treatment, McWilliams *et al*. have recently published exciting results supporting the positive effects of acute rehabilitation during the ICU hospitalization over mobility levels of patients.[15] By contrast, level 1 and 2 studies about mid and long-term physical sequelae of COVID-19 and rehabilitation efficacy are still lacking, according to Negrini *et al*.[16] Consequently, these patients are only supposed to be eligible for an individualized and progressive treatment plan focusing on function, disability, and social life returning months after the acute illness.[17]

This study aimed to assess the physical and functional midterm sequelae in COVID-19 survivors. For this purpose, we assessed physical performance in these patients through a series of tests in order to find out the proportion of patients still affected by an impaired performance or low physical functioning at 3 to 6 months from Hospital discharge.

Materials and methods

We conducted a cross-sectional study on a subpopulation of previously independent walking patients already enrolled in a local multidisciplinary project focused on evaluating different outcomes in Coronavirus disease 19 survivors (No-more Covid Project).

STROBE checklist was followed for manuscript draft.

The eligibility criteria we used to select our subgroup of patients were the following: age 18-79 years, hospitalization for COVID-19 in the University Hospital of Novara (Italy) from March 1 to May 30, absence of significant disability value assessed by the modified rankin scale (mRS) before the viral infection (patients with an mRS score ≤3 were included). The mRS is a single-item, global outcomes rating scale that can support the clinician to categorize level of patient functional independence. An mRS level equal to 3 indicates a moderate disability, requiring some help, but letting the subject walk without assistance.[18]

All of the participants enrolled were outpatients and gave their written informed consent for participation in the study, carried out according to the Declaration of Helsinki and validated by the local Ethics Committee (CE 158/20, chair Dr. Gianfranco Zulian) and Competent Authority (Maggiore della Carità University Hospital, Novara, Italy Protocol IRB code CE 117/20, validated on June 12, 2020).

Patients were tested in an interval between 3 and 6 months after discharge from our Hospital with a confirmed diagnosis of SARS-CoV-2 infection.

Demographic and clinical data were collected through a detailed interview, during which patients were also asked to describe their premorbid functional independence status rated with the mRS. In addition, we also investigated the presence of comorbidities, defined as diseases the clinical implications of which were so relevant as to require chronic pharmacological treatment.

After the interview, patients underwent a series of proper tests focused on physical evaluation, as fully described below.

Our primary endpoint was the assessment of the midterm physical performance through the submission of the short physical performance battery (SPPB), that allows first line hierarchizing of patients based upon their functional status. It should be noted that SPPB showed a good predictivity on the disability level in daily activities.[19, 20] In particular, a score greater than ten is considered an expected value for healthy subjects, whereas an SPPB score ≤10 indicates a physical impairment.[21]

Additionally, in order to evaluate their residual aerobic capacity, patients with a high functional level showed at the SPPB (SPPB score >10) were then tested with the 2-minute walk test (2MWT).[22, 23] On the other hand, subjects who showed an SPPB score ≤10 underwent the 1-minute-sit-to-stand test (1-MSTST) to specifically assess their exercise tolerance and capacity.[24]

More in detail, the short physical performance battery (SPPB) is aimed to investigate both functional status and physical performance, and it is composed by a series of physical performance tests used to evaluate lower extremity function and mobility. It relies on three different components: walking speed, standing balance, and sit-to-stand performance.[25] A global score equal or lower than 10 indicates one or more mobility limitations. However, it should be noted that SPPB may not be able to distinguish the performance level in high functioning patients.[26] This is the reason why we used the SPPB as first-line test to assess the physical performance of patients, but subsequently this evaluation was completed with the aerobic resistance tests described below.

The 2-minute walking test (2-MWT) is an endurance measurement where patients are asked to walk and cover the longest distance possible over 2 minutes. Subjects must be able to ambulate without assistance while assistive devices are allowed but should be kept consistent from test to test. We submitted this test to patients with good mobility to deeply investigate their functional status and resistance. Reference data are available in literature based on population age and gender.[23]

Finally, the 1-minute sit-to-stand test (1-MSTST) was proposed to the patients with lower mobility. In order to complete the test, patients were asked to perform as many sit-to-stand actions as possible in 1 minute without using the upper limbs, sitting on an armless chair. Normative reference values are available, as presented by Strassmann *et al*.[27] 1-MSTST allows an evaluation of aerobic capacity also in people with a compromised walking ability or balance disturbances that may prevent them from walking. Interestingly, 1-MSTST is a validated test for assessing the impact of pulmonary rehabilitation in chronic obstructive pulmonary diseases.[24]

Statistical analysis

Descriptive statistics have been reported about the study sample. Continuous data are represented in terms of I, II (median), and III quartiles. The Mann-Whitney test was used to compare the medians of continuous variables. Categorical variables are summarized in terms of absolute and relative frequencies. Pearson's and Fisher's χ^2 were used, as appropriate, to test the association between categorical variables. A multivariable logistic regression model has been computed adjusting the ICU or OTI effect on the study outcomes by gender, age, and comorbidities.

The model adjusted odds ratios (OR) together with the 95% confidence intervals CI and P values have been reported. Nonlinear effects of age have been considered in the model *via* restricted cubic spline estimation. The Interquartile OR effect has been reported for the continuous variables. The significance level was assessed at 5%. Analyses have been performed with the R 3.4.2 (IBM; Armonk, NY, USA) with the rms package.

Results

Seven hundred sixty-seven patients discharged from the University Hospital of Novara (Novara, Italy) with a diagnosis of COVID-19 were contacted in accordance with the study protocol of No-more Covid Project. N.=494/767 (64.4%) declined, while 238 (31.0%) gave their informed consent and were enrolled in our study.

Based on inclusion and exclusion criteria, 204 patients, previously independent walkers, were finally included in our study (Figure 1).

Data will be reported below as mean±standard deviation (SD) for continuous variables.

As part of the No-more Covid Project, patients were tested from July 15, 2020 to September 15, 2020 after the mean time from Hospital discharge of 124.7 (17.5) days. The mean age of the sample was 57.9 (12.8) years, with the gender distribution of 60% (123) men and 40% (81) women. Comorbidities number had the mean of 1.6 (1.3). Specifically, considering comorbidities that might directly affect the patients' mobility and physical performance, 15 patients (7.4%) suffered from lung disease (9 patients from chronic obstructive pulmonary disease [COPD] and 6 from obstructive sleep apna syndrome [OSAS]), 21 patients (10.3%) were obese, 31 (15.2%) suffered from a cardiac disease, (11 suffered from atrial fibrillation [AF], 15 from ischemic cardiopathy, 3 from arrhythmias and 2 from structural cardiopathy), and, finally, 6 patients (2.9%) had a previous diagnosis of transitory ischemic attack (TIA) or stroke. The mean length of COVID-19 hospitalization was 12.9 (11.7) days. Moreover, 13% (27) of patients spent some days of their hospitalization in the Intensive Care Unit (ICU) and 10% (21) required invasive mechanical ventilation (Table I).

The SPPB score of the whole sample was analyzed, and we observed the median score of 12, with the mean value of 11.24 (1.39).

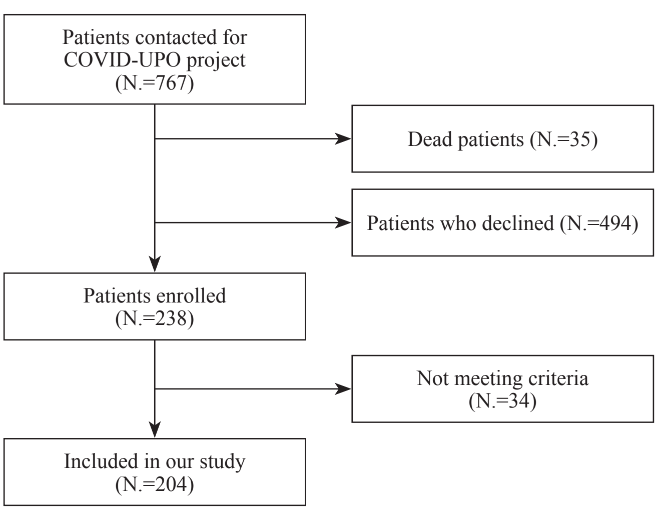

Figure 1.—CONSORT diagram.

More in detail, 175 patients of our sample (86%) obtained an SPPB score >10, revealing a good functional performance and mobility (group A). In contrast, 29 patients (14%) obtained an SPPB score ≤10, indicating physical impairment (group B) (Figure 2).

The baseline, anamnestic mRS value was not associated to an impairment of SPPB score (P=0.63); moreover, not even the time elapsed from hospital discharge differed between group A and group B (124 [112-132] *vs*. 130 [122-140] days; P=0.07, respectively). Interestingly, patients with physical impairment (group B) showed a longer median hospital in-stay (14 [8-23] *vs*. 8 [5-15] days; P=0.01).

Among the 29 patients from group B, the median value obtained at the SPPB tests was 9, with the mean score of 8.5 (1.8).

We also categorized the observed results depending on the specific SPPB sections.

In the balance section, 91% of patients reached the maximum score of 4, 6% reached the score of 3, 1% reached the score of 2, another 1% the score of 1 and 0.5% of patients obtained 0.

In the walking evaluation, 87% of patients obtained the maximum value of 4, 11% of them obtained the score of 3, 0.05% the score of 2, 1% the score of 1. No one got the score of 0 in the walking test.

In the lower limb strength and resistance section, tested through the repetition of 5 sit-to-stand, 68% of patients obtained the maximum score of 4, 23% of patients obtained the score of 3, 3% the score of 2 and 6% the score of 1. No one obtained the score of 0 in the sit-to-stand test.

Remarkably, it should be highlighted that, among all of the 204 patients included in our study, 66 of them (32%) showed physical impairment in one of our second line tests, the 2-MWT and 1-MSTST, respectively.

More in detail, all 29 patients (100%) of group B also showed at the 1-MSTST a lower score than the expectancy based upon gender and age, with the median number of repetitions of 18 and the mean value of 19.7 (7.3), supporting the presence of a reduction in aerobic capacity.

Additionally, among the 175 group A patients (86%), 37 of them (21%) obtained an inadequate 2-MWT score compared to that expected for age and sex, with the median value of 160 m and the mean value of 156 (16.4) m, revealing anyway a physical alteration (Table II).

Hence, overall 66 patients of the study (32%) had at least one test indicating physical impairment, 29 showing both an SPPB score ≤10 and 1-MSTST repetitions lower than expectancy, while 37 were deficient at the 2-MWT.

TABLE I.—*Demographic characteristics of patients.*

Parameters	Mean	q25	Median	q75	SD
Age (years)	57.9	50	59	68	12.8
Male, N. (%)	123 (60%)				
Female, N. (%)	81 (40%)				
Comorbidities, N.	1.6	1	1	2	1.3
COPD, N. (%)	9 (4.4%)				
OSAS, N. (%)	6 (2.9%)				
Obesity, N. (%)	21 (10.3%)				
AF, N. (%)	11 (5.4%)				
Ischemic cardiopathy, N. (%)	15 (7.4%)				
Arrhythmia, N. (%)	3 (1,5%)				
Structural cardiopathy, N. (%)	2 (1%)				
TIA, stroke, N. (%)	6 (2.9%)				
COVID-19 hospitalization (days)	12.9	5	9	16	11.7
Follow-up distance (days)	124.7	115	126	134	17.5
ICU hospitalization, N. of patients (%)	27 (13%)				
Mechanical ventilation, N. of patients (%)	21 (10%)				

COPD: chronic obstructive pulmonary disease; OSAS: obstructive sleep apnea syndrome; AF: atrial fibrillation; TIA: transitory ischemic attack; COVID-19: Coronavirus-disease 19; ICU: Intensive Care Unit; N.: number; q25: 25th percentile; q75: 75th percentile; SD: standard deviation.

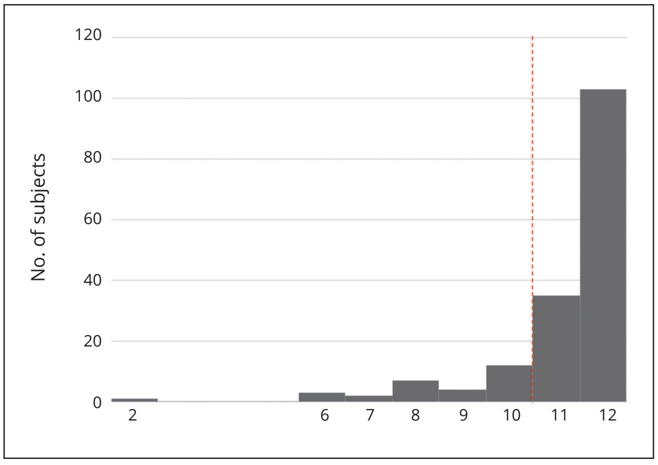

Figure 2.—SPPB score distribution.

TABLE II.—*Tests results.*

Parameters	Mean	q25	Median	q75	SD
SPPB (total score)	11.24	11	12	12	1.38
Balance (score)	3.86	4	4	4	0.52
Walking ability (score)	3.83	4	4	4	0.48
Sit to stand (score)	3.53	3	4	4	0.81
2MWT (meters)	182.83	165	180	201.5	27.80
1 MSTST (N. of repetitions)	19.72	14	18	24	7.33

SPPB: short physical performance battery; 2MWT: 2-minute walk test; 1 MSTST: 1-minute sit-to-stand test; q25: 25th percentile; q75: 75th percentile; SD: standard deviation.

Among these 66 patients with an impaired physical performance status, 13 (20%) spent part of their hospitalization in the ICU and 10 (15%) had been mechanically ventilated.

Moreover, as fully described in Table III, we also found that both hospitalization in ICU and orotracheal intubation (OTI) with mechanical ventilation are significantly associated with physical impairment ($P<0.01$). Regarding every single test analyzed, the walking ability section of the SPPB is associated with age ($P<0.02$) and number or comorbidities ($P<0.01$), while male gender is related with SPPB total score ($P<0.01$). Finally, our data showed that 2MWT is related to the number of comorbidities ($P<0.04$).

Discussion

Our aim was to evaluate the midterm functional and physical sequelae of COVID-19 hospitalized survivors, and our results showed that a considerable percentage (32%) of patients from our sample of hospitalized COVID-19 survivors were still showing an impaired physical performance up to three to six months after the SARS-CoV-2 infection.

To the best of our knowledge, this is one of firsts studies demonstrating a mid-term, persistent decline in functional tests in COVID-19 survivors.

A recently published paper aimed to investigate the functional level during subacute hospitalization for COVID-19. All of the patients were treated with medical therapies and mobilization/bedside physiotherapy. Researchers recorded a post-physiotherapy improvement in all functional areas investigated; however, it must be highlighted that a high percentage of patients were discharged home with impaired functional values.[28]

TABLE III.—*Variables correlations.*

Parameters	P value	OR	CI
Physical impairment			
Gender (male *vs.* female)	0.13	0.6	0.3-1.2
Age	0.41	0.8	0.5-1.3
Comorbidities (number)	0	1.9	1.4-2.5
ICU or OTI	0.01*	3.1	1.3-7.9
SPPB (walking ability section)			
Gender (male *vs.* female)	0	5.7	2.1-15.5
Age	0.02*	0.7	0.3-1.3
Comorbidities (number)	0.01*	0.6	0.4-0.9
ICU or OTI	0.21	0.5	0.1-1.6
SPPB (balance section)			
Gender (male *vs.* female)	0.38	1.6	0.6-4.5
Age	0.17	1.7	0.8-3.8
Comorbidities (number)	0	0.4	0.3-0.6
ICU or OTI	0.28	0.5	0.1-1.8
SPPB (sit to stand section)			
Gender (male *vs.* female)	0.05	1.9	1.0-3.4
Age	0.95	1.0	0.6-1.6
Comorbidities (number)	0	0.7	0.5-0.9
ICU or OTI	0.29	0.6	0.2-1.6
2MWT (when normal SPPB)			
Gender (male *vs.* female)	0.81	1.1	0.5-2.3
Age	0.14	0.6	0.3-1.3
Comorbidities (number)	0.04*	1.3	1.0-1.8
ICU or OTI	0.6	1.4	0.4-4.8
1MSTST (when pathological SPPB)			
Gender (male *vs.* female)	0.01*	0.3	0.1-0.8
Age	0.87	0.8	0.4-1.7
Comorbidities	0	2.0	1.4-2.8
ICU or OTI	0.24	2.3	0.6-9.4

*Statistically significant.
ICU: Intensive Care Unit; OTI: orotracheal intubation; SPPB: short physical performance battery; 2MWT: 2-minute walk test; 1 MSTST: 1-minute sit-to-stand test; d.f.: degrees of freedom; OR: odds ratio; CI: confidence interval.

Our data support the hypothesis that COVID-19 sequalae may persist even longer after hospitalization, suggesting that this disease may affect several aspects of functional independency of affected patients.

Several issues raised from these observations due to the paucity of data on long-term effects of the SARS-CoV-2 infection.

Firstly, it should be noted that a detrimental effect of hospitalization might be present in these patients. As experienced by Carda *et al.*,[29] the most important short-term sequelae of severe and critical forms of COVID-19 might involve respiratory, cognitive, central and peripheral nervous systems together with deconditioning, critical illness related myopathy and neuropathy, dysphagia, joint stiffness, pain and psychiatric issues.

However, based on previously published data, it is not clear how these aspects might be directly related to COVID-19 or, alternatively, caused by the hospitalization itself.

In particular, current evidence suggests that patients who underwent Intensive Care Unit (ICU) treatment, independently from COVID-19, revealed that they suffered from ICU-acquired weakness consisting of a marked disability affecting both physical and cognitive functions, lasting for years after ICU discharge.[30, 31]

Interestingly, it should be highlighted that evidence from previous CoV outbreaks reported impaired pulmonary and physical function, reduced quality of life and emotional distress.[8] Surviving ARDS is associated with a long-term substantial reduction in health-related quality of life, but this reduction does not differ from findings in patients surviving other critical illness.[32]

Our data only partially support this hypothesis.

We observed a significant association between ICU hospitalization and OTI with mechanical ventilation with physical performance, but only a small proportion (20%) of patients showing a persistent decline in physical function underwent ICU during the hospitalization.

These observations might suggest that a possible independent effect of SARS-CoV-2 infection may be directly involved in long-term evidence of physical decline in COVID-19 survivors.

Several mechanisms have been suggested as potentially involved in COVID-19 sequelae. Firstly, long-term respiratory consequences of SARS-CoV-2 infection are still debated. Based on previously published studies on SARS pandemic, it has been hypothesized that lung function might be affected also in COVID-19 patients.[33]

In a recently published review, Cagnazzo *et al.* reported that up to 21.3% of COVID-19 patients presented neurological symptoms. Among the most frequently reported neurological manifestations, skeletal muscle injury (5.1% of patients) and dizziness (1.3%) might also potentially affect the long-term physical performance.[34]

Additionally, cardiac involvement during COVID-19 is widely reported, mainly for the life-threatening consequences in the acute phase. The long-term consequences of these inflammatory changes are unknown, but accumulating data will provide insight regarding the longitudinal impact of COVID-19 infection on cardiovascular morbidity and mortality.[35]

Future studies should consider a focused evaluation in order to clarify the potential role of these specific issues on the patients' physical function in COVID-19 survivors.

Lastly, we should carefully consider that COVID-19 pandemic forced people to stay at home, thereby reducing their physical activity and causing an extremely sedentary lifestyle. This attitude can have a strong impact on musculoskeletal diseases also in people not directly affected by the virus.[36]

From a rehabilitation point of view, we must highlight that, due to the pandemic emergency, an appropriate rehabilitation paradigm was not applied after hospital discharge. As a consequence, we could not investigate a possible association between rehabilitation treatment and the physical outcomes we evaluated.

This aspect must be critically considered in order to interpret our data. Belli *et al.* observed that the majority of their patients had low (53.3%) or moderate (17.5%) SPPB scores when discharged home, but it must also be pointed out that these subjects showed a significant improvement after the rehabilitation interventions, compared to the admission scores.[28] The Authors did not report in detail the rehabilitation management of these patients but, as hypothesized by Carda *et al.*,[29] a multidisciplinary protocol should be considered based on patients' specific characteristics. Future studies must be focused on the specific, unmet needs of these patients, in order to provide an appropriate rehabilitation paradigm in all stages of disease.

Additionally, among the three areas investigated through the SPPB, the walking ability score appears to be statistically related to age and comorbidity, while balance and sit-to-stand data show no correlations with such variables. Furthermore, the 2-MWT (walking ability and aerobic capacity test) is significantly related to comorbidities of patients. These results highlight that age and number of comorbidities may affect the physical performance of patients, especially in their gait capacity.

It should be highlighted that the detrimental effect of aging on walking abilities could be associated with various causes, including a reduction in sensory capacity, weakness, decreased cognitive and neurological functioning, and an increased risk of comorbidities. These effects are the result of different pathogenetic mechanisms which might determine motor and cognitive dysfunction.[37] However, in order to reduce the potentially confounding impact represented by age, patients ≥80 years were excluded from our study.

Concerning comorbidities, many studies in literature investigate the effects of different pathologies on walking ability, especially in the form of neuromuscular, (*i.e.* Charcot-Marie-Tooth disease[38]), cognitive,[39] and cardiopulmonary diseases.[40] Additionally, it has been suggested that in COVID-19 course comorbidities are risk factors for severe, as compared with non-severe, patients.[41] Based on our results, we can hypothesize that comorbidities relate not only to acute COVID-19 course, but also to the midterm sequelae. Considering the specific involvement in the walking ability domain, we should also affirm that the rehabilitation program must be considered a cornerstone in COVID-19 patients' management.

All these considerations imply a deep reorganization of rehabilitation services, in order to guarantee an appropriate care in acute, subacute as well as long-term phases of hospitalization. Additionally, outpatient services must be involved in order to set an appropriate long-term management of COVID-19 patients, if required. In this context, it should be highlighted that a consensus statement has been recently proposed to provide guidance for rehabilitation.[42]

Limitations of the study

We are conscious that this study shows several limitations.

Firstly, we did not consider additional evaluations to clarify the specific role of each mechanism potentially involved in the physical decline in our patients. However, it must be pointed out that this is a preliminary study focused on the COVID-19 survivors' screening in order to analyze the unmet needs in this population. These results will help us in optimizing the future reorganization of rehabilitation services in our area. However, we are aware that future studies must be focused on a more specific assessment of included patients, which will be a significant contribution to the rehabilitation program design.

Additionally, we must consider that our sample was constituted by patients who voluntarily agreed to participate in the follow-up, representing only a small percentage of the source population. It might imply a possible non-representativeness compared to the whole patients' cohort of COVID-19 survivors discharged from our Hospital. On these bases, the real percentage of residual physical impairment might differ from our clinical observations. Future research might better clarify this crucial issue. Moreover, we did not consider the possible impact of different parameters, like heart rate and oxygen saturation, on the patient physical performance.

Future research must be focused on the long-term follow-up of these patients; ideally, clinical evaluations should include a systematic screening of sequalae potentially involved in the physical performance decline, such as respiratory, cardiac and neurological assessment. Moreover, the role of an appropriate rehabilitation treatment should be considered.

Conclusions

Our data suggest a possible persistence of mid-term sequelae on functional status and physical performance in COVID-19 survivors. Further studies are mandatory to confirm these critical observations, to improve the understanding of pathophysiologic mechanisms, and to clarify the possible role of rehabilitation treatment on the patients' outcome.

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