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Sex differences and rehabilitation needs after hospital discharge for COVID-19: an Italian cross-sectional study

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ABSTRACT

Objectives COVID-19 can result in persistent symptoms leaving potential rehabilitation needs unmet. This study aims to describe persistent symptoms and health status of individuals hospitalised for COVID-19 according to the International Classification of Functioning, Disability and Health domains of impairments, limitations in activity, and participation restrictions.

Design Cross-sectional study consisting in a telephone interview 3 months after hospital discharge.

Setting This study was conducted during the first peak of the COVID-19 pandemic by the Local Health Authority of Reggio Emilia (Italy).

Participants Adult individuals discharged from hospital between April and June 2020 after COVID-19. Exclusion criteria: hospitalisation for reasons other than COVID-19, inability to participate in the study, concomitant acute or chronic conditions causing disability.

Primary and secondary outcome measures We assessed: dyspnoea (Medical Research Council), fatigue (Fatigue Severity Scale), mood disturbances (Hospital Anxiety and Depression Scale), limitations in activity (Barthel Index) and participation restrictions (Reintegration to Normal Living Index). We also collected data on sociodemographic characteristics, health status prior to COVID-19, COVID-related clinical manifestations and hospital care pathway up to discharge, rehabilitation interventions, accidental falls and emergency room access.

Results 149 participants (men, 62%; average age 62 (±11) years) were enrolled, 35 of which (23%) were admitted to the intensive care unit (ICU) while hospitalised. Three months after hospital discharge, nearly half of the participants still suffered from dyspnoea (44%) or fatigue (39%). Almost all individuals (91.2%) recovered a good level of independence in activity of daily living, but 76% still suffered participation restrictions. Female sex was significantly associated with worse outcomes for all symptoms.

Conclusions Individuals who had moderate or severe COVID-19 may perceive persistent symptoms which may result in reduced social participation. Sex differences should be monitored, as women may recover more slowly than men.

Trial registration number NCT04438239.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This cross-sectional study investigated the long-term impact of COVID-19 on functional status of patients after hospital discharge.
⇒ The telephone interviews collected data of patients discharged from the hospitals of the Local Health Authority of the Province of Reggio Emilia (Italy) only.
⇒ To catch postacute sequelae of SARS-COV2 infection, individuals with acute or chronic concomitant conditions causing disability and with previous complete dependence in activities of daily living were excluded.
⇒ Eligible individuals were contacted by a letter of invitation and, if necessary, also by phone.
⇒ Sociodemographic characteristics, health status prior to COVID-19, data regarding COVID-19-related hospital care and long-term health outcomes were collected.

INTRODUCTION

Background

The onset of the COVID-19 pandemic in early 2020 had a tremendous impact on the world population and on healthcare systems, with over 273 million cases worldwide as of 19 December 2021.[1] Early reports about surveillance were promptly released, and a tremendous effort was made to increase knowledge of diffusion patterns and prevention strategies. The presenting features of SARS-COV-2 infection have been well described, with a widely accepted categorisation of acute COVID-19 published by the WHO[2] and updated regularly. According to the WHO classification of COVID-19, which includes asymptomatic, mild, moderate, severe and critical disease,[2] 14%–15% of cases have been severe and 5% critical.[3] However, for the first months of the pandemic, the long-term impact of the disease remained underexplored.

COVID-19 patients admitted to hospital experience fever, cough, dyspnoea, muscle soreness and/or acute respiratory distress

syndrome, but also fatigue, gastrointestinal symptoms and headache.[4] While most patients recover quickly, a growing number of studies have highlighted that several survivors of COVID-19 experience a multisystem condition termed postacute sequelae of SARS-CoV-2 infection (PASC) characterised by fatigue, dyspnoea, brain fog, headache, mood disturbances and atypical chest pain.[5] These symptoms can last several weeks after the acute phase of the disease and may worsen functioning and quality of life and hinder participation.[6–13] Furthermore, in the presence of comorbidities, they may lead to deconditioning, fatigue and social isolation.[14]

The International Classification of Functioning, Disability and Health (ICF) is a classification of health and health-related domains which measures health and disability at both the individual and population levels.[15] To our knowledge, no clinical trial has comprehensively assessed the persistent impact of COVID-19 according to the ICF,[15] although this assessment has been recommended to explore the long-term impairments but also limitations in activity and participation restrictions caused by SARS-CoV-2 infection.[6] This study aimed to verify whether individuals who had been hospitalised for COVID-19 had unmet rehabilitation needs lasting long beyond recovery.

Objective

This study describes the persistent symptoms and impairments, limitations in activity and restrictions in participation in social activities of those individuals who required hospitalisation for COVID-19. It investigated the associations between sociodemographic characteristics, health status prior to COVID-19, COVID-19-related clinical manifestations and symptoms, and hospital care pathway up to discharge and health outcomes assessed 3 months after hospital discharge.

METHODS

Study design and population

This cross-sectional study is reported according to the Strengthening The Reporting of OBservational studies in Epidemiology guidelines.[16] The study consisted in a telephone interview of patients hospitalised for COVID-19 during the first peak of the pandemic to collect current and retrospective data. All adult symptomatic individuals, discharged from the hospitals of the Local Health Authority (LHA) of the Province of Reggio Emilia (Italy) between April and June 2020, were screened for eligibility by medical documentation. We excluded individuals who (1) were hospitalised for reasons other than COVID-19; (2) were unable to participate in the study procedures (eg, dementia, psychiatric disorders, linguistic barriers); (3) had acute or chronic concomitant conditions causing disability (eg, recent stroke, surgical interventions, heart failure); (4) had previous complete dependence in activities of daily living (ADLs). We also excluded pregnant women to avoid a confounding effect of pregnancy on symptoms like fatigue or dyspnoea. Due to the concomitant pandemic, it was not possible to involve patients or the public in the design, conduction, reporting or dissemination of this study.

All eligible individuals were sent a letter of invitation to participate in this study, written information about the study, a consent form and the principal investigator's request for permission for a researcher affiliated with the study to contact the individual by phone. Two weeks after the letter was sent, the potentially eligible individuals were contacted by a researcher, who gave them any further information, and asked that they return the written informed consent to participate in the interview. Individuals who did not answer the phone after three attempts and those who explicitly stated they did not intend to participate in the study were deleted from the list.

We retrospectively collected the following data of each participant:

- Sociodemographic characteristics (age, sex, household composition).
- Health status prior to COVID-19 (comorbidities, use of aids and level of independence prior to hospitalisation).
- Data regarding COVID-19-related hospital care.
- Symptoms and clinical manifestation of COVID-19 (eg, cough, fever, diarrhoea, asthenia, localization of pneumonia, respiratory failure).
- Admission to the ICU and its duration.
- Any rehabilitation treatment during hospitalisation (eg, mobilisation, chest physiotherapy).
- Length of stay (LOS).

Three months from hospital discharge, participants were interviewed by telephone to collect data on the persistency of the following symptoms and limitations:

- Dyspnoea, assessed by the Medical Research Council.[17]
- Fatigue, assessed by the Fatigue Severity Scale.[18]
- Mood disturbances, assessed by the Hospital Anxiety and Depression Scale (HADS).[19]
- Limitations in basic-ADL (B-ADL), assessed by the Barthel Index.[20]
- Restrictions in participation, assessed by the Reintegration to Normal Living Index (RNLI)[21] (Italian version).

Data on any rehabilitation intervention implemented after hospital discharge (type, duration, frequency) and on any accidental falls and related consequences, emergency room access, or any further hospital admissions after hospital discharge were also collected.

Statistical analysis

In absence of an a priori hypothesis, given the exploratory nature of the study, no formal sample size calculation was performed; all eligible individuals who agreed to participate in the study were recruited. Sociodemographic characteristics, health status prior to COVID-19, COVID-19-related clinical manifestations and symptoms, and hospital care pathway up to discharge are reported,

as are the data on long-term outcomes of COVID-19. Data are reported as frequency and percentage for categorical variables, mean and SD for symmetric quantitative variables, and median and IQR for skewed variables.

Proportions between groups were compared using the chi-square test or the Fisher's exact test. Associations between potential exposures and long-term outcomes were investigated using logistic regression models. Similarly, associations between the presence of long-term outcomes of COVID-19 and rehabilitation interventions, accidental falls/fractures, emergency room accesses and/or any hospital admission in the 3 months following hospital discharge were investigated. Unless otherwise specified, CIs are two tailed and calculated at the 0.95 confidence level. Tests were considered statistically significant when the p value was <0.05. Statistical analysis was performed using R V.3.5.2 R Core Team 2020.[22]

Patient and public involvement

Due to the concomitant pandemic, it was not possible to involve patients or the public in the design, conduction, reporting or dissemination of this study.

RESULTS

Participants

Between April and June 2020, 784 patients were discharged from the hospitals of the LHA of Reggio Emilia (Italy), which serves a population of 533 158 residents, after being healed from the acute phase of COVID-19. Overall, 446 individuals were excluded for the reasons listed in figure 1; 338 invitations to participate in the study were mailed to potentially eligible individuals, who were contacted by telephone 2 weeks later. Overall, 150 individuals consented to participate, and a telephone appointment for the interview was set up. One individual could not be reached for the interview, and his data were excluded from the analysis. Thus, 149 participants were interviewed between June and September 2020, at an average of 104 days (±18.5) from hospital discharge. Figure 1 reports the flow diagram of the study participants.

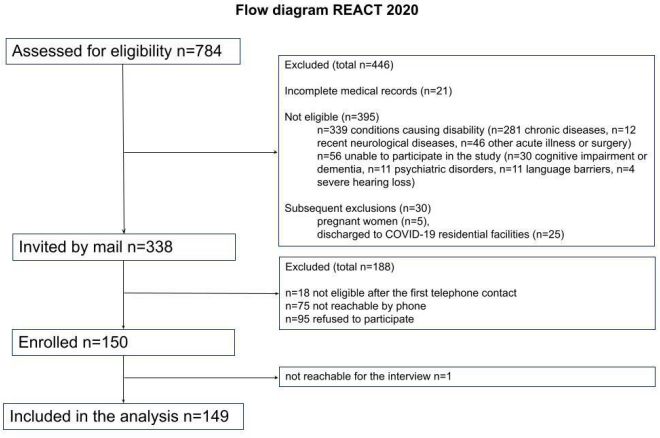

Figure 1 Flow diagram of the study participants.

Descriptive data

The sociodemographic characteristics and health status of study participants are reported in table 1. The average age of the study cohort was 62 (±11) years. Males accounted for 62.4% of the sample, and 51% were employed. Most participants lived with family members (89.3%) and had one or more comorbidities (82.6%), the most frequent being cardiovascular diseases (34.6%), metabolic diseases (15.6%), diabetes (8.7%) and obesity (8%). Before hospitalisation for COVID-19, all but one participant were independent in B-ADL, and only 6% used walking aids for mobility.

Table 2 reports data regarding the hospital care of participants, showing ICU admissions and sex-disaggregated data. Thirty-five individuals (23.5%) were admitted to the ICU. Overall, the average LOS was 18 (±14) days, with a higher average LOS for individuals admitted to the ICU (33±20 days). Most participants experienced respiratory failure (83.9%), with 12.1% having documented bilateral pneumonia.

Inpatient rehabilitation was delivered to 21 individuals, corresponding to 14.1% of the total sample and to 51.4% of participants admitted to the ICU. Early mobilisation was offered to patients in the ICU and to patients hospitalised in acute wards, if they presented severe risk of functional limitations due to frailty or mobility limitations. Inpatient rehabilitation was performed 6 days per week and included pulmonary rehabilitation, mobilisation, exercises and counselling. Also, as soon as patients could self-manage a programme of simple exercise, the physiotherapist gave them instructions and written information to guide them in the execution of breathing exercises, active range of motion exercises and strength training while lying supine or sitting.

Outpatient rehabilitation after hospital discharge was attended by 21 individuals (14.1%), several of whom had been admitted to the ICU (40.0%). Outpatient rehabilitation was provided three times per week at the physical therapy department and consisted in comprehensive pulmonary rehabilitation to improve persistent fatigue, exercise capacity and breathlessness. It included breathing techniques such as pursed lip breathing, positive expiratory pressure-bottle exercises and incentive spirometer. Patients were advised to continue the exercises at home, with individualised home sessions based on their needs (repeating breathing techniques, performing aerobic exercise, balance exercises or resistance training).

Seventeen participants (11.4%) reported using a walking aid for mobility after hospital discharge (wheelchair, walker, stick, crutches). Moreover, accidental falls after hospital discharge were reported by 6.7% of participants, but only one resulted in emergency room access.

Outcome data

Table 3 describes the persistent symptoms, limitations in activity and restrictions in participation 3 months after hospital discharge. Fatigue and dyspnoea were the most prevalent persistent symptoms in the cohort investigated:

Table 1 Sociodemographic characteristics and health status of the cohort

Sociodemographic characteristics and health status	Total (N=149)
Age, mean (SD)	62 (±11.5)
Sex, N (%)	
Male	93 (62.4)
Female	56 (37.6)
Household conditions, N (%)	
Alone	15 (10.0)
With others	133 (89.3)
Data missing	1 (0.7)
Occupation, N (%)	
Employed	76 (51.0)
Retired	66 (44.3)
Unemployed	7 (4.7)
Smoker, N (%)	
Yes	11 (7.4)
No	92 (61.7)
Ex-smoker	46 (30.9)
Comorbidities, N (%)	
No	26 (17.4)
Yes	123 (82.6)
N of comorbidities per patient, N (%)	
0	26 (17.4)
1	43 (28.9)
2	39 (26.2)
3	23 (15.4)
>3	18 (12.1)
Type of comorbidities, N (%), (Total N=263)	
Cardiovascular diseases	91 (34.6)
Metabolic diseases (dyslipidaemia, gout, fatty liver disease, etc)	41 (15.6)
Diabetes	23 (8.7)
Obesity (BMI ≥30)	21 (8.0)
Digestive system diseases	16 (6.1)
Respiratory diseases	10 (3.8)
Haematological diseases	8 (3.0)
Rheumatological diseases	8 (3.0)
Others	45 (17.1)
Independence before hospital admission, N (%)	
Yes	148 (99.3)
Minimal assistance for ADL	1 (0.7)
Use of aids before hospital admission, N (%)	
Yes	9 (6.0)
No	140 (94.0)

ADL, activities of daily living; BMI, body mass index; N, Number.

87.9% of participants experienced fatigue and 43% suffered from mild to severe dyspnoea. Clinically relevant anxiety and depression scores (HADS ≥8) were detected in 24.8% and 16.1% of participants, respectively.

Most of the sample (91.3%) was completely independent, with only a few individuals (11) reporting need for assistance in B-ADL. Nevertheless, 3 months after discharge, only 24.2% of participants were completely reintegrated, while 75.1% reported moderate (RNLI 60–99) or even severe (RNLI <60) restrictions in participation (67.1% and 8.0%, respectively).

Table 4 shows the ORs of the associations between potential exposures and outcomes 3 months after discharge. Increasing age seemed to be associated with less anxiety (OR 0.94, p=0.006), as each year of age seemed to reduce the risk by about 5%. Similar results were detected for depression (OR 0.95, p=0.036).

Being female was associated with persistent symptoms after COVID-19: 3 months after hospital discharge, 25% of females vs 7.5% of males suffered from dyspnoea (OR 3.61, p=0.019), 59% of females vs 27% of males suffered from fatigue (OR 3.75, p<0.001), 37.5% of females vs 17% of males suffered from anxiety (OR 3.26, p=0.007), and 28.5% of females vs 8.6% of males suffered from depression (3.71, p=0.011); although not significantly, limitations in B-ADL were also more reported in females (14% vs 5.3%; OR 3.18, p=0.078).

Surprisingly, comorbidities were not associated with worse outcomes.

Dyspnoea was more frequently reported by participants who used walking aids for mobility after discharge (OR 3.52, p=0.042) and by those who experienced an accidental fall (OR 5.02, p=0.023).

Moreover, having had critical or severe COVID-19 was associated with a 70% reduction in the risk of anxiety (OR 0.29, p=0.016) and in the risk of depression, bordering on significance (OR 0.33, p=0.062).

Finally, accidental falls occurring after hospital discharge were associated with a fivefold increase in the risk of dyspnoea (OR 5.02, p=0.032) and dependence in B-ADL (OR 5.51, p=0.029).

DISCUSSION

Statement of principal findings

This study focused on the medium-term impact of COVID-19 on functional status of those individuals who were severely affected by this disease. Three months after hospital discharge for COVID-19, individuals still reported moderate to severe fatigue (88%) and dyspnoea (44%). They recovered a good level of independence in basic ADL, but 76% still suffered participation restrictions. Females showed higher levels of fatigue, dyspnoea, anxiety and depression. Thus, these results confirm that individuals hospitalised experience persistent symptoms, adding insight into the impact of COVID-19 on limitations in activities and participation.

Table 2 Hospital care of participants and postdischarge period

Information about patients' hospital care and postdischarge				Sex-disaggregated data	
	Total	ICU	Not-ICU	Male (N=93)	Female (N=56)
Hospital care, N (%)	149 (100%)	35 (23.5%)	114 (76.5%)	ICU 26 (28.0) Not-ICU 67 (72.0)	ICU 9 (16.1) Not-ICU 47 (83.9)
Total LOS, mean (SD)	18 (±14)	33 (±20)	14 (±8)	18.7 (±13.9)	17.4 (±15.4)
LOS in ICU, mean (SD)		14 (±11)		13.2 (±10.8)	16.1 (±13.8)
Symptoms at admission, N (%)					
Respiratory failure	125 (83.9)	35 (100)	90 (78.9)	80 (86.0)	46 (82.1)
Bilateral pneumonia	18 (12.1)	0 (0)	18 (15.8)	11 (11.8)	7 (12.5)
Mild symptoms	4 (2.7)	0 (0)	4 (3.5)	2 (2.2)	2 (3.6)
Other (pulmonary embolism)	2 (1.3)	0 (0)	2 (1.8)	0 (0)	1 (1.8)
Clinical Category of COVID-19 and type of oxygen support, N (%)					
Critical COVID-19 (CPAP-NIV-intubation)	56 (37.6)	35 (100)	21 (18.4)	43 (46.2)	13 (23.2)
Severe COVID-19 (HF oxygen devices)	61 (40.9)	0 (0)	61 (53.6)	33 (35.5)	28 (50.0)
Moderate COVID-19 (LF oxygen devices)	16 (10.7)	0 (0)	16 (14.0)	9 (9.7)	7 (12.5)
Mild COVID-19 (no oxygen support)	16 (10.7)	0 (0)	16 (14.0)	8 (8.6)	8 (14.3)
Rehabilitation during hospitalisation, N (%)					
No	128 (85.9)	17 (48.6)	111 (97.4)	81 (87.1)	47 (83.9)
Yes	21 (14.1)	18 (51.4)	3 (2.6)	12 (12.9)	9 (16.1)
Rehabilitation after discharge, N (%)					
No	128 (85.9)	21 (60.0)	107 (93.9)	80 (86.0)	48 (85.7)
Yes	21 (14.1)	14 (40.0)	7 (6.1)	13 (14.0)	8 (14.3)
Use of aids after discharge, N (%)					
No	132 (88.6)	26 (74.3)	106 (93.0)	85 (91.4)	47 (83.9)
Yes	17 (11.4)	9 (25.7)	8 (7.0)	8 (8.6)	9 (16.1)
Accidental falls after discharge, N (%)					
No	139 (93.3)	32 (91.4)	107 (93.9)	88 (94.6)	51 (91.1)
Yes	10 (6,7)	3 (8.6)	7 (6.1)	5 (5.4)	5 (8.9)

CPAP, continuous positive airway pressure; HF, high flow; ICU, intensive care unit; LF, low flow; LOS, length of stay; NIV, non-invasive ventilation.

As millions of individuals are recovering from the infection, it may be appropriate to recognise those in need of rehabilitation, to help them to recover complete function and previous levels of participation.

Accordingly, the WHO recommends screening COVID-19 patients before hospital discharge to detect any rehabilitation needs they may have.[2] Reasonably, in the first few months after the outbreak of the pandemic, the very few studies published on the rehabilitation of patients with COVID-19 focused on treatment during the acute phase[23 24] or on the implications for healthcare organisations.[14 25] In December 2020, a rapid guideline on the management of the long-term outcomes of COVID-19 was published by the National Institute for Health and Care Excellence, which recommended a careful evaluation of symptoms, but also an overall assessment of the impact of the disease on daily life, including B-ADL, occupations and social activities.[26] Recently, the WHO has published a new version of a living clinical guidance,[2] updating both the symptoms persisting after COVID-19 and the recommendations for rehabilitation needs assessment.[27] Moreover, in October 2021, the WHO coined the definition of 'post COVID-19 condition' to describe the condition of 'individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms lasting for at least 2 months, which cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction among other and generally have an impact on everyday functioning'.[28]

Table 3 Persistent symptoms, limitations in activity and restrictions in participation 3 months after hospital discharge

Outcome	Male (=93)	Female (=56)	Total (=149)
Dyspnoea, N (%)			
Absent (MRC=0)	59 (63.4)	24 (42.9)	83 (55.7)
Mild (MRC=1)	26 (28.0)	17 (30.3)	43 (28.9)
Moderate (MRC 2–3)	6 (6.4)	13 (23.2)	19 (12.8)
Severe (MRC=4)	1 (1.1)	1 (1.8)	2 (1.3)
Data missing*	1 (1.1)	1 (1.8)	2 (1.3)
Fatigue, n (%)			
Absent (FSS=9)	13 (14.0)	3 (5.4)	16 (10.7)
Mild-moderate (FSS 10–36)	54 (58.0)	19 (33.9)	73 (49.0)
Severe (FSS >36)	25 (26.9)	33 (58.9)	58 (38.9)
Data missing*	1 (1.1)	1 (1.8)	2 (1.3)
Anxiety, N (%)			
No (HADS-a <8)	76 (81.7)	35 (62,5)	111 (74.5)
Yes (HADS-a ≥8)	16 (17.2)	21 (37.5)	37 (24.8)
Data missing*	1 (1.1)	0 (0.0)	1 (0.7)
Depression, N (%)			
No (HADS-d <8)	84 (90.3)	40 (71.4)	124 (83.2)
Yes (HADS-d ≥8)	8 (8.6)	16 (28.6)	24 (16.1)
Data missing*	1 (1.1)	0 (0.0)	1 (0.7)
Limitation in B-ADL, N (%)			
Independent (BI=100)	88 (94.6)	48 (85.7)	136 (91.3)
Mild dependence (BI 91–99)	2 (2.2)	5 (8.9)	7 (4.7)
Moderate dependence (BI 61–90)	2 (2.2)	2 (3.6)	4 (2.7)
Severe dependence (BI 21–60)	0 (0.0)	0 (0.0)	0 (0.0)
Complete dependence (BI 0–20)	0 (0.0)	0 (0.0)	0 (0.0)
Data missing*	1 (1.1)	1 (1.8)	2 (1.3)
Participation, N (%)			
Complete reintegration (RNLI=100)	32 (34.4)	4 (7.1)	36 (24.2)
Reduced reintegration (RNLI 60–99)	55 (59.1)	45 (80.4)	100 (67.1)
Poor reintegration (RNLI <60)	5 (5.4)	7 (12.5)	12 (8.0)
Data missing*	1 (1.1)	0 (0.0)	1 (0.7)

*Impossibility of administering the assessments due to difficulties in understanding the questions during the phone call on behalf of the participant.
B-ADL, basic activities of daily living; BI, Barthel Index; FSS, Fatigue Severity Scale; HADS-a, Hospital Anxiety and Depression Scale-anxiety; HADS-d, Hospital Anxiety and Depression Scale-depression; MRC, Medical Research Council; RNLI, Reintegration to Normal Living Index.

Our study explored all the dimensions of health status by means of valid tools to assess symptoms, independence in B-ADL and reintegration to normal living. The data collected seem to confirm that the likelihood of developing PASC is not linked to the severity of disease, and also confirm that fatigue and dyspnoea are among the most frequent and persistent symptoms, as reported by some authors in the last months of 2020,[8 9] but also by more recent studies.[29–35]

Moreover, in the cohort investigated, clinically relevant anxiety and depression characterised 25% and 16% of participants, respectively, which are proportions very close to those reported in a similar French cohort[12] and in a German cross-sectional study by Lemhöfer *et al*.[13] Certainly, mood disorders can also be caused by the extraordinary nature of the pandemic, which has literally affected the entire planet. In fact, a study conducted on the healthy population living in the same area as the cohort investigated showed that, during the first peak of pandemic, mood disturbances were present in 13.6%–54.5% of individuals.[30] Thus, regardless of their triggers, the prevalence of anxiety and depression during the pandemic seems higher than the usual estimate (10%–11%).[31]

Interestingly, despite the large number of patients who claimed complete postdischarge independence in B-ADL (91.3%), 76% did not recover full social participation 3 months after hospital discharge. Although data were collected during the summer, when the SARS-CoV-2 contagion was low and the restrictions imposed were minimal, we cannot exclude that at least part of those limitations in social participation may have been due to the remaining restrictions or to the fear of contracting the disease again. Whatever the cause or the mix of causes, this finding should not be underestimated, given that social participation is a domain of health and an indicator of successful ageing. In fact, where post-COVID-19 clinics have been activated, the accurate assessment of limitations in B-ADL and social participation is considered important by clinicians.[32]

Social participation is one of the goals of rehabilitation interventions. However, during the first pandemic peak, rehabilitation was delivered to a limited number of COVID-19 patients, and, in our cohort, daily inpatient rehabilitation was mainly provided to patients admitted to an ICU; outpatient rehabilitation was offered to a small number of individuals. Focusing inpatient rehabilitation mainly on ICU patients was reasonable during the first wave of the pandemic, given that the long-term impact of COVID-19 was not known at the time, and directing all resources to the care of individuals struggling with severe or critical COVID-19 seemed appropriate, in the attempt to prevent the onset of postintensive care syndromes, which affect up to 50% of ICU patients.[36]

This may explain why our data do not show a significant association between rehabilitation interventions and any of the health outcomes assessed 3 months after hospital discharge. Rehabilitation was delivered to more severe patients, supporting them in recovering a level of activity and participation similar to that of individuals with mild or moderate COVID-19, who were generally not referred to rehabilitation. Moreover, outpatient rehabilitation was offered three times per week only to patients with severe persistent dyspnoea or fatigue, as rearranging health pathways during the early months of the pandemic in Italy was extremely complex.[14]

Taking into account the growing number of people affected by long-lasting consequences of COVID-19, outpatient rehabilitation is likely to represent a key element to support their recovery, as reported in a recent

Table 4 Associations between potential exposures and outcomes 3 months after discharge

Risk factors	Dyspnoea OR (CI) (p value)	Fatigue OR (CI) (p value)	Anxiety OR (CI) (p value)	Depression OR (CI) (p value)	Dependence in B-ADL OR (CI) (p value)	Reintegration OR (CI) (p value)
Age	1.00 (0.96 to 1.05) p=0.806	0.97 (0.93 to 1.00) p=0.087	0.94 (0.90 to 0.98) **p=0.006***	0.95 (0.90 to 0.99) **p=0.036***	1.05 (0.99 to 1.12) p=(0.119)	0.95 (0.88 to 1.00) p=0.102
Female sex	3.61 (1.26 to 11.26) **p=0.019***	3.75 (1.75 to 8.26) **p<0.001***	3.26 (1.40 to 7.81) **p=0.007***	3.71 (1.39 to 10.69) **p=0.011***	3.18 (0.90 to 12.79) p=0.078	2.59 (0.70 to 10.66) p=0.157
Several comorbidities (>3)	1.03 (0.20 to 4.26) p=0.970	0.92 (0.29 to 1.47) p=0.883	1.26 (0.34 to 4.34) p=0.709	0.30 (0.01 to 1.89) p=0.281	0.57 (0.02 to 4.24) p=0.630	2.66 (0.45 to 15.85) p=0.260
Diabetes	1.57 (0.40 to 5.09) p=0.471	0.98 (0.37 to 2.48) p=0.965	0.88 (0.26 to 2.49) p=0.823	0.45 (0.06 to 1.76) p=0.317	3.12(0-75-11.57)p=0.094	0.48 (0.02 to 2.77) p=0.499
Cardiovascular diseases	1.80 (0.54 to 8.23) p=0.380	0.73 (0.32 to 1.66) p=0.458	0.62 (0.25 to 1.58) p=0.311	0.79 (0.28 to 2.44) p=0.675	0.60 (0.16 to 2.42) p=0.438	1.46 (0.34 to 10.06) p=0.642
Obesity (BMI ≥30)	1.57 (0.40 to 5.09) p=0.471	1.36 (0.52 to 3.53) p=0.520	0.67 (0.18 to 2.03) p=0.519	0.82 (1.17 to 2.78) p=0.775	1.06 (0.15 to 4.55) p=0.940	2.23 (0.45 to 8.91) p=0.274
Critical or severe COVID-19	0.80 (0.26 to 2.28) p=0.691	0.70 (0.32 to 1.48) p=0.360	0.29 (0.10 to 0.75) **p=0.016***	0.33 (0.90 to 0.97) p=0.062	1.29 (0.35 to 4.56) p=0.681	1.03 (0.25 to 3.81) p=0.965
Use of walking aids after discharge	3.52 (0.97 to 11.62) **p=0.042***	2.38 (0.79 to 7.56) p=0.124	2.05 (0.64 to 6.12) p=0.205	0.69 (0.10 to 2.79) p=0.653	2.79 (0.56 to 11.14) p=0.164	0.71 (0.03 to 4.24) p=0.762
Accidental falls after discharge	5.02 (1.16 to 20.10) **p=0.023***	2.28 (0.61 to 9.37) p=0.220	3.48 (0.90 to 13.46) p=0.063	2.39 (0.48 to 9.58) p=0.237	5.51 (1.04 to 24.56) **p=0.029***	1.27 (0.06 to 8.00) p=0.829
Rehabilitation during hospitalisation	3.01 (0.59 to 13.69) p=0.158	3.40 (0.97 to 13.89) p=0.064	0.43 (0.07 to 1.86) p=0.298	0.64 (0.07 to 3.40) p=0.639	4.12 (0.64 to 22.75) p=0.114	0.66 (0.02 to 5.60) p=0.751

*Statistically significant.
B-ADL, basic activities of daily living; BMI, body mass index.

German survey,[37] and it is extremely important to expand outpatient therapeutic options to alleviate PASC and to hasten the return to normal life and working capacity.

The most interesting finding of this study is that it seems that the long-term impact of COVID-19 is worse on women. Since the very first months of the pandemic, the need for sex-disaggregated data was advocated by researchers,[38–40] and the role of sex in the early immune response after SARS-CoV-2 infection and in mortality has been highlighted.[41 42] While mortality rate for COVID-19 seems higher in men with comorbidities,[43] our results, consistent with those of other research studies,[33 44]suggest that women may be more affected by COVID-19 sequelae several weeks after hospital discharge. Although no clear pathophysiology can explain this phenomenon, it has been hypothesised that the higher representation of women in autoimmune diseases may explain the sex differences in the immunological response to the acute and postacute manifestations of COVID-19.[35 45]

Strengths and weaknesses of the study

The results of this cross-sectional study should be interpreted with caution, since they originate from a single Italian province. Recruitment bias cannot be ruled out, as several individuals who were invited to participate did not adhere to the study (23% of those eligible) or could never be reached by phone (29%). Thus, it may be that individuals who were asymptomatic or those who still felt too unwell declined to participate. Moreover, for feasibility reasons, we chose to investigate only the most frequent persistent symptoms associated with PASC (dyspnoea and fatigue). Nevertheless, several others, including musculoskeletal pain, mood disturbances and cognitive deficits, among others, may also lead to the need for rehabilitation. Since this study was uncontrolled, we cannot exclude that some of the persistent symptoms and manifestations may have been due to the prolonged hospitalisation or to post-ICU syndrome, or that they might also affect the general population (eg, anxiety, participation restrictions) due to the containment measures imposed by the Italian government. Causal inferencing and generalisation of the conclusions are therefore challenging.

One strength of this study is that the ICF framework was used to guide data collection, and the assessment of health status extended beyond impairment. Moreover, a valid assessment of outcomes allowed us to confirm differences between the sexes in PASC, and, although further exploration is required, these data suggest that female COVID-19 survivors may need specific follow-up to ensure appropriate interventions[34] and equity in access to care.

Unanswered questions and future research

After hospital discharge, differences between the sexes emerged in the long-term impact of COVID-19 in this Italian study. These differences should be searched and considered in future research. Future studies should investigate if tailored rehabilitation is offered and if equity is warranted in access to care.

CONCLUSIONS

Examining the long-term impact of COVID-19 is essential, given that the number of recovering individuals is growing daily. Healthcare services must implement the

best-practice standards of care for individuals with PASC. The results of this study indicate that women may recover more slowly than men. If confirmed, this information may prevent gender inequalities in accessing health services and facilitate appropriate referral to tailored rehabilitation.

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