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Title page

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 hospitalized for COVID-19 according to the ICF domains of impairments, limitations in activity, and participation restrictions.

Design: Cross-sectional study consisting in a telephone interview three 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: hospitalization 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**:** dyspnea (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 ICU while hospitalized. Three months after hospital discharge, almost half of the participants still suffered from dyspnea and fatigue. Individuals 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: This independent observational study was registered on ClinicalTrials.com (NCT04438239).

Key Words: COVID-19, rehabilitation medicine, respiratory infections.

Article Summary

- 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 post-acute sequelae of SARS-COV2 infection, individuals with acute or chronic concomitant conditions causing disability and with previous complete dependence in activities of daily living (ADLs) 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-related hospital care and long-term health outcomes were collected.

Introduction

Background

The onset of the coronavirus disease 2019 (COVID-19) pandemic in early 2020 had a tremendous impact on the world population and on healthcare systems, with more than 140.332.386 total confirmed cases worldwide as of April 18, 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 categorization 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 (WHO 2021),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, dyspnea, 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 post-acute sequelae of SARS-CoV-2 infection (PASC) characterized by fatigue, dyspnea, brain fog, headache, mood disturbances, and atypical chest pain.[5] These symptoms can last several weeks after the acute phase of the disease[6-12] and may impact an individual's functional status and quality of life. Further, in the presence of comorbidities, they may lead to deconditioning, fatigue, and social isolation.[13]

To our knowledge, no clinical trial has comprehensively assessed the persistent impact of COVID-19 according to the International Classification of Functioning, Disability and Health (ICF),[14] which 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 hospitalized 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 hospitalization for COVID-19. It investigated the associations between sociodemographic characteristics, health status prior to COVID-19, COVID-related clinical manifestations and symptoms, and hospital care pathway up to discharge and health outcomes assessed three months after hospital discharge.

Methods

Study design and population

This cross-sectional study is reported according to the STROBE guidelines.[15] The study consisted in a telephone interview of patients hospitalized 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 of the Province of Reggio Emilia (Italy) between April and June 2020, were screened for eligibility by medical documentation. Excluded were individuals hospitalized for reasons other than COVID-19, unable to participate in the study procedures (e.g., dementia, psychiatric disorders, linguistic barriers, etc.), with acute or chronic concomitant conditions causing disability (e.g., recent stroke, surgical interventions, heart failure, etc.), and individuals with previous complete dependence in activities of daily living (ADLs). The study was approved by the local Ethics Committee (prot. 2020/0133, April 21, 2020).

All eligible individuals were sent a letter of invitation to participate in this study, written information about the study, and a consent form. The letter included the principal investigator's request for permission for a researcher affiliated with the study (physician, physiotherapist, or occupational therapist) 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 requested, 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.

The medical records of each consenting participant were retrospectively reviewed to collect data on potential exposures, i.e., sociodemographic characteristics (age, sex, household composition) and health status prior to COVID-19 (comorbidities, use of aids, and level of independence prior to hospitalization). We also collected data regarding COVID-related hospital care, the symptoms and clinical manifestation of COVID-19 (e.g., cough, fever, diarrhea, asthenia, localization of pneumonia, respiratory failure), admission to the intensive care unit (ICU) and its duration, any rehabilitation treatment during hospitalization (e.g., mobilization, chest physiotherapy), and length of stay (LOS).

Three months after hospital discharge, data regarding long-term health outcomes were collected through a telephone interview, which consisted in the assessment of persistent symptoms and impairments: dyspnea was assessed through the Medical Research Council (MRC) scale,[16] fatigue through the Fatigue Severity Scale (FSS),[17] and mood disturbances were assessed through the Hospital Anxiety and Depression Scale (HADS).[18] Data were also collected on limitations in basic activities of daily living (B-ADL) using the Barthel Index (BI)[19] and on restrictions in participation using the Italian version of the Reintegration to Normal Living Index (RNLI).[20] 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.
Furthermore, qualitative data were explored through open-ended questions on the patient's recovery from COVID-19. The reporting of these qualitative data is currently underway.

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-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 standard deviation for symmetric quantitative variables, and median and IQR for skewed variables.

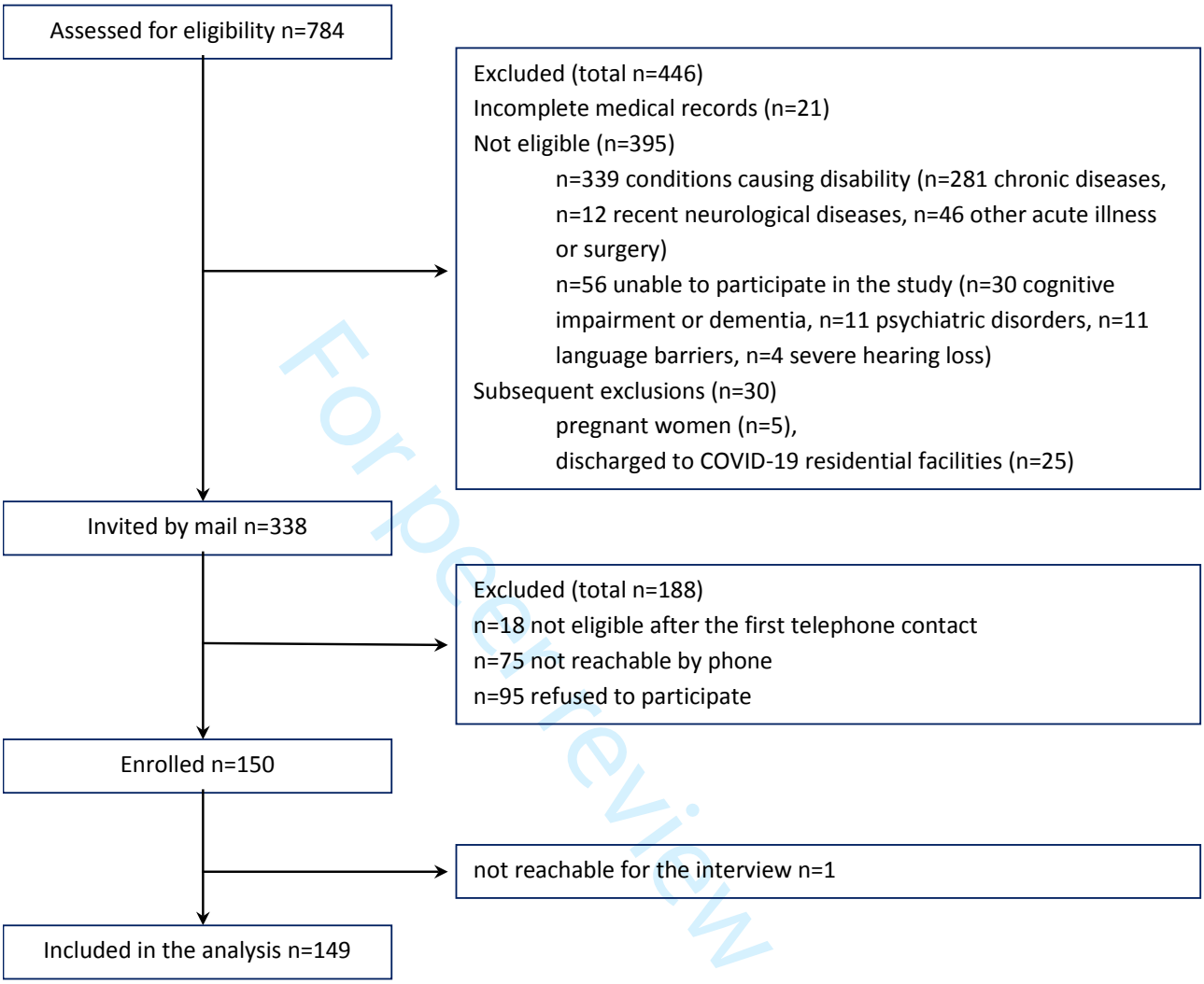
Proportions between groups were compared using the chi-square test or the Fisher's exact test. Associations between potential exposures and long-term outcomes were investigated using logistic regression models. Similarly, associations between the presence of long-term outcomes of COVID-19 and rehabilitation interventions, accidental falls/fractures, emergency room accesses, and/ or any hospital admission in the three months following hospital discharge were investigated. Unless otherwise specified, confidence intervals 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 3.5.2 R Core Team 2020.[21]

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 having recovered from COVID-19. Overall, 446 of these patients were excluded for the following reasons: incomplete medical records, thus not permitting the eligibility screening (21), presence of acute or chronic conditions causing disability other than COVID-19 (339), and inability to participate in the study (56). Five pregnant women were also excluded, as were 25 individuals who were discharged to a COVID-19 residential facility. Thus, 338 invitations to participate in the study were mailed to potentially eligible individuals, who were contacted by telephone two weeks later; 18 more individuals were excluded in this phase for inability to participate in the interview (language barrier, cognitive impairment, severe hearing loss, aphasia). Ninety-five individuals refused to participate and 75 could not be reached by phone, despite repeated attempts. 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.

Table 1. Socio-demographic characteristics and health status of the cohort

Socio-demographic characteristics and health status	**TOTAL (N=149)**
Age, mean (SD)	62(±11.5)
Gender, 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 (dyslipidemia, 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)
Hematological diseases	8 (3.0)
Rheumatological diseases	8 (3.0)
Others	45(17.1)
Independence before hospital admission, N (%)	
Yes	148 (99.3)
Need little help for ADL	1 (0.7)
Use of aids before hospital admission, N (%)	
Yes	9 (6.0)
No	140 (94.0)

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%). Other comorbidities included diseases of the digestive or respiratory systems (6.1% and 3.8%, respectively), hematological or rheumatological diseases (3% each); less frequent comorbidities included cancer, musculoskeletal diseases, and urogenital diseases (2.7% each), kidney and neurological diseases and psychiatric disorders (2.3% each), immune deficiencies (0.4%), and other (1.9%).

Before hospitalization for COVID-19, all participants were independent in B-ADL, and only 6% used walking aids for mobility.

Table 2 reports data regarding the hospital care of participants, showing intensive care unit (ICU) admissions and sex-disaggregated data.

Table 2. Hospital care of participants and post-discharge period.

Information about patients' hospital care and post-discharge				**Sex-disaggregated data**	
	TOTAL	ICU[a]	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)
LOS TOT, mean (SD)	18 (±14)	33 (±20)	14 (±8)	18.7 (±13.9)	17.4 (±15.4)
LOS[b] 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[C]-NIV[d]-intubation)	56 (37.6)	35 (100)	21 (18.4)	43 (46.2)	13 (23.2)
Severe COVID-19 (HF[e] oxygen devices)	61 (40.9)	0 (0)	61 (53.6)	33 (35.5)	28 (50.0)
Moderate COVID-19 (LF[f] 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 hospitalization, 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)

Legend: [a] ICU = Intensive Care Unit; [b] LOS= Length Of Stay; [c] CPAP = Continuous Positive Airway Pressure; [d] NIV = Non-Invasive Ventilation; [e] HF = High Flow; [f] LF = Low Flow.

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. Accordingly, 37.6% of participants were in critical condition and needed respiratory assistance by means of continuous positive airway pressure, non-invasive ventilation, or

intubation, while 40.9% needed high-flow oxygen therapy. Only 10.7% needed low-flow oxygen support, and an equal proportion did not need any respiratory support at all.

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. Similarly, outpatient rehabilitation after hospital discharge was attended by 21 individuals (14.1%), several of whom had been admitted to the ICU (40.0%). In most cases, rehabilitation programs included pulmonary rehabilitation, mobilization, counselling, and exercises.

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 three months after hospital discharge.

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

Outcome	Male (=93)	Female (=56)	Total (=149)
Dyspnea, 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[(a)]	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[(a)]	1 (1.1)	1 (1.8)	2 (1.3)
Anxiety, N (%)			
No (HADS-a score<8)	76 (81.7)	35 (62,5)	111 (74.5)
Yes (HADS-a score≥8)	16 (17.2)	21 (37.5)	37 (24.8)
Data missing[(a)]	1 (1.1)	0 (0.0)	1 (0.7)
Depression, N (%)			
No (HADS-d score<8)	84 (90.3)	40 (71.4)	124 (83.2)
Yes (HADS-d score≥8)	8 (8.6)	16 (28.6)	24 (16.1)
Data missing[(a)]	1 (1.1)	0 (0.0)	1 (0.7)
Limitation in B-ADL[(b)], N (%)			
Independent (BI score=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[(a)]	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(a)	1 (1.1)	0 (0.0)	1 (0.7)

Legend: [(a)] impossibility of administering the assessments due to difficulties in understanding the questions during the phone call on behalf of the participant; [(b)] B-ADL = Basic Activities of Daily Living.

Fatigue and dyspnea were the most prevalent persistent symptoms in the cohort investigated: 87.9% of participants experienced fatigue and 43% suffered from mild to severe dyspnea. 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, three 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 odds ratios (OR) of the associations between potential exposures and outcomes three months after discharge.

Table 4. Associations between potential exposures and outcomes three months after discharge.

Risk factors	**Dyspnea** OR[(a)][CI][(b)]	**Fatigue** OR (P-value)	**Anxiety** OR (P-value)	**Depression** OR (P-value)	**Dependence in B-ADL**[(c)] OR (P-value)	**Reintegration** OR (p-value)
Age	1.00 [0.96-1.05] p=0.806	0.97 [0.93-1.00] p=0.087	0.94 [0.90-0.98] p=0.006*	0.95 [0.90-0.99] p=0.036*	1.05 [0.99-1.12] p=(0.119)	0.95 [0.88-1.00] p=0.102
Female sex	3.61 [1.26-11.26] p=0.019*	3.75 [1.75-8.26] p<0.001*	3.26 [1.40-7.81] p= 0.007*	3.71 [1.39-10.69] p=0.011*	3.18 [0.90-12.79] p=0.078	2.59 [0.70-10.66] p=0.157
Several comorbidities (>3)	1.03 [0.20-4.26] p=0.970	0.92 [0.29-1.47] p=0.883	1.26 [0.34-4.34] p= 0.709	0.30 [0.01-1.89] p=0.281	0.57 [0.02-4.24] p=0.630	2.66 [0.45-15.85] p=0.260
Diabetes	1.57 [0.40-5.09] p=0.471	0.98 [0.37-2.48] p=0.965	0.88 [0.26-2.49] p=0.823	0.45 [0.06-1.76] p=0.317	3.12 [0-75-11.57] p=0.094	0.48 [0.02-2.77] p=0.499
Cardiovascular diseases	1.80 [0.54-8.23] p=0.380	0.73 [0.32-1.66] p=0.458	0.62 [0.25-1.58] p=0.311	0.79 [0.28-2.44] p=0.675	0.60 [0.16-2.42] p=0.438	1.46 [0.34-10.06] p=0.642
Obesity	1.57 [0.40-	1.36 [0.52-	0.67 [0.18-	0.82 [1.17-	1.06 [0.15-	2.23 [0.45-

(BMI[(d)]≥30)	5.09] p=0.471	3.53] p=0.520	2.03] p=0.519	2.78] p=0.775	4.55] p=0.940	8.91] p=0.274
Critical or severe COVID-19	0.80 [0.26-2.28] p=0.691	0.70 [0.32-1.48] p=0.360	0.29 [0.10-0.75] p=0.016*	0.33 [0.90-0.97] p=0.062	1.29 [0.35-4.56] p=0.681	1.03 [0.25-3.81] p=0.965
Use of walking aids after discharge	3.52 [0.97-11.62] p=0.042*	2.38 [0.79-7.56] p=0.124	2.05 [0.64-6.12] p=0.205	0.69 [0.10-2.79] p=0.653	2.79 [0.56-11.14] p=0.164	0.71 [0.03-4.24] p=0.762
Accidental falls after discharge	5.02 [1.16-20.10] p=0.023*	2.28 [0.61-9.37] p=0.220	3.48 [0.90-13.46] p=0.063	2.39 [0.48-9.58] p=0.237	5.51 [1.04-24.56] p=0.029*	1.27 [0.06-8.00] p=0.829
Rehabilitation during hospitalization	3.01 [0.59-13.69] p=0.158	3.40 [0.97-13.89] p=0.064	0.43 [0.07-1.86] p=0.298	0.64 [0.07-3.40] p=0.639	4.12 [0.64-22.75] p=0.114	0.66 [0.02-5.60] p=0.751

Legend: [(a)] OR = Odds Ratio; [(b)] CI = Confidence interval; [(c)] B-ADL = Basic Activities of Daily Living; [(d)] BMI = Body Mass Index; *statistically significance.

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: three months after hospital discharge, women showed a three to four times higher risk of suffering from dyspnea (OR 3.61, P = 0.019), fatigue (OR 3.75, P < 0.001), anxiety (OR 3.26, P = 0.007), and depression (3.71, P = 0.011) than men; albeit not significantly, limitations in B-ADL were also more reported in females (OR 3.18, P = 0.078).

Surprisingly, comorbidities were not associated with worse outcomes.

Dyspnea 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 dyspnea (OR 5.02, P = 0.032) and dependence in B-ADL (OR 5.51, P = 0.029).

Discussion

Statement of principal findings

This study aimed to focus the long-term impact of COVID-19 on functional status of patients after hospital discharge. The results confirm that individuals hospitalized experience persistent symptoms, and adds insight into the impact of COVID-19 on limitations in activities and participation.

As millions of individuals are recovering from the infection, it may be appropriate to recognize 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[22,23] or on the implications for health care organizations.[24,25] More recently, a rapid guideline on the management of the long-term outcomes of COVID-19 has been published and is now available to clinicians.[26] This guideline recommends 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 .

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 post-COVID-19 syndrome is not linked to the severity of disease, and also confirm that the most persistent symptoms are fatigue and dyspnea, as previously detected.[8,9,27]

Moreover, in the cohort investigated, clinically relevant anxiety and depression characterized 25% and 16% of participants respectively, which are proportions very close to those reported in a similar French cohort.12 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.[28] Thus, regardless of their triggers, the prevalence of anxiety and depression during the pandemic seems higher than the usual estimate (10-11%).[29]

Interestingly, despite the large number of patients who claimed complete post-discharge independence in B-ADL (91.3%), 76% did not recover full social participation three months after hospital discharge. This finding should not be underestimated, given that social participation is a domain of health and an indicator of successful aging. In fact, where post-COVD-19 clinics have been activated, the accurate assessment of limitations in B-ADL and social participation is considered important by clinicians.[30]

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, inpatient rehabilitation was mainly provided to patients admitted to an ICU. This is reasonable, 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 post-intensive care syndromes, which affect up to 50% of ICU patients.[31]

This may explain why our data do not show a significant association between rehabilitation interventions and any of the health outcomes assessed three 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.

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,[32,33,34] and the role of sex in the early immune response after SARS-CoV-2 infection and in mortality has been highlighted.[35,36] While mortality rate for COVID-19 seems higher in men with comorbidities,[37] our results suggest that women may be more frail several weeks after hospital discharge.

Strengths and weaknesses of the study AND Strengths and weaknesses in relation to other studies

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%). Moreover, since this study was uncontrolled, we cannot exclude that some of the persistent symptoms and manifestations might also affect the general population (e.g., anxiety, participation restrictions) due to the containment measures imposed by the Italian government. Causal inferencing and generalization 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. To our knowledge, this is the first study using this approach. Moreover, a valid assessment of outcomes allowed us to bring out differences between the sexes in post-COVID-19 syndrome, and, although further exploration is required, these data suggest that female COVID-19 survivors may need specific follow-up.

Meaning of the study

A current and very lively debate concerns the sequelae of COVID-19 and the most appropriate definition for this syndrome.[38,39,40] We believe that our data contribute to this debate, as they highlight that COVID-19 can also affect the social activities of recovered patients, putting their global health at risk.

To our knowledge, this is the first research study highlighting sex differences in post-COVID-19 recover, differences which has been noticed in clinics.[30] These apparent differences merit further investigation to identify specific rehabilitation needs and to ensure appropriate, tailored interventions.[34]

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 post-COVID-19 syndrome. 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.

What is already known on this topic

- Early reports about the presenting features of SARS-COV-2 infection, the diffusion patterns and prevention strategies have been well described and updated regularly.
- To date, no clinical trial has comprehensively assessed the long-term impact of COVID-19 on functional status of patients after hospital discharge;
- The International Classification of Functioning, Disability and Health (ICF) has been recommended to explore the long-term impairments, limitations in activity and participation restrictions caused by SARS-CoV-2 infection.

What this study adds

- Three months after hospital discharge for COVID-19, individuals still reported moderate to severe fatigue (88%) and dyspnea (44%). They recovered a good level of independence in basic activities of daily living, but 76% still suffered participation restrictions and females showed higher levels of fatigue, dyspnea, anxiety, and depression.
- Our study noticed that differences between the sexes emerged in the long-term impact of COVID-19 and these should be considered when offering tailored rehabilitation and equity in access to care.

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Competing Interests: all authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Contributor and guarantor information: as dictated by the Authorship guidelines of the International Committee of Medical Journal Editors, all the authors of this manuscript gave substantial contributions to the conception or design of the work or to the acquisition, analysis, or interpretation of data for the work; AND gave substantial contributions to the drafting the work or to its critical revision for important intellectual content; AND approved the final version to be published. All the authors agree to be accountable for all aspects of the work and ensure that

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SF had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LB conducted and is responsible for the data analysis.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval: This independent study was approved by Provincial Ethics Committee of Reggio Emilia on 21/04/2020 (ID 2020/0133). All participants provided written informed consent to participate in the trial.

Transparency statement: the lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing: Reasonable requests for all of the individual participant data collected during the trial, after deidentification, should be made to the corresponding author and will be considered by the REACT lead author. The presented data are anonymised and risk of identification is low.

Patient and public involvement: it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research, due to the circumstances of COVID-19 emergency.

Dissemination declaration: we planned to disseminate the results to study participants who will specifically request them via e-mail.

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	NA
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 1, p.7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	8-9

Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12; Table 4.
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Primary Subject Heading:	Rehabilitation medicine
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Title page

Sex Differences and Rehabilitation Needs after Hospital Discharge for COVID-19: An Italian Cross-sectional Study

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19) can result in persistent symptoms leaving potential rehabilitation needs unmet. This study aims to describe persistent symptoms and health status of individuals hospitalized for COVID-19 according to the International Classification of Functioning, Disability and Health (ICF) domains of impairments, limitations in activity, and participation restrictions.

Design: Cross-sectional study consisting in a telephone interview three 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: hospitalization 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**:** dyspnea (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 ICU while hospitalized. Three months after hospital discharge, nearly half of the participants still suffered from dyspnea (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: This independent observational study was registered on ClinicalTrials.com (NCT04438239).

Key Words: COVID-19, rehabilitation medicine, respiratory infections.

Article Summary

- 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 post-acute sequelae of SARS-COV2 infection, individuals with acute or chronic concomitant conditions causing disability and with previous complete dependence in activities of daily living (ADLs) 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-related hospital care and long-term health outcomes were collected.

Introduction

Background

The onset of the coronavirus disease 2019 (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 December 19, 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 categorization 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 (WHO 2021),[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, dyspnea, 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 post-acute sequelae of SARS-CoV-2 infection (PACS) characterized by fatigue, dyspnea, 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 hospitalized 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 hospitalization for COVID-19. It investigated the associations between sociodemographic characteristics, health status prior to COVID-19, COVID-related clinical manifestations and symptoms, and hospital care pathway up to discharge and health outcomes assessed three months after hospital discharge.

Methods

Study design and population

This cross-sectional study is reported according to the STROBE guidelines.[16] The study consisted in a telephone interview of patients hospitalized 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 a) were hospitalized for reasons other than COVID-19; b) were unable to participate in the study procedures (e.g., dementia, psychiatric disorders, linguistic barriers, etc.); c) had acute or chronic concomitant conditions causing disability (e.g., recent stroke, surgical interventions, heart failure, etc.); d) 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 dyspnea. The study was approved by the local Ethics Committee (prot. 2020/0133, April 21, 2020). 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 hospitalization)
- data regarding COVID-related hospital care
- symptoms and clinical manifestation of COVID-19 (e.g., cough, fever, diarrhea, asthenia, localization of pneumonia, respiratory failure)
- admission to the intensive care unit (ICU) and its duration
- any rehabilitation treatment during hospitalization (e.g., mobilization, 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:

- dyspnea, assessed by the Medical Research Council (MRC)[17]
- fatigue, assessed by the Fatigue Severity Scale (FSS)[18]
- mood disturbances, assessed by the Hospital Anxiety and Depression Scale (HADS)[19]
- limitations in basic activities of daily living (B-ADL), assessed by the Barthel Index (BI)[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-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 standard deviation 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 three months following hospital discharge were investigated. Unless otherwise specified, confidence intervals 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 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 two 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.

Insert Figure 1 near here

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 hospitalization for COVID-19, all but one participant were independent in B-ADL, and only 6% used walking aids for mobility.

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 (dyslipidemia, 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)
Hematological 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)

Legend: SD = Standard Deviation; N = Number; BMI = Body Mass Index; ADL = Activities of Daily Living

Table 2 reports data regarding the hospital care of participants, showing intensive care unit (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 mobilization was offered to patients in the ICU and to patients hospitalized in acute wards, if they presented severe risk of functional limitations due to frailty or mobility limitations. Inpatient rehabilitation was performed six days per week and included pulmonary rehabilitation, mobilization, exercises, and counseling. Also, as soon as patients could self-manage a program 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, PEP-bottle exercises, and incentive spirometer. Patients were advised to continue the exercises at home, with individualized 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.

Table 2. Hospital care of participants and post-discharge period.

Information about patients' hospital care and post-discharge				**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 hospitalization, 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)

Legend: ICU = Intensive Care Unit; LOS= Length Of Stay; CPAP = Continuous Positive Airway Pressure; NIV = Non-Invasive Ventilation; HF = High Flow; LF = Low Flow.

Outcome data

Table 3 describes the persistent symptoms, limitations in activity, and restrictions in participation three months after hospital discharge. Fatigue and dyspnea were the most prevalent persistent symptoms in the cohort investigated: 87.9% of participants experienced fatigue and 43% suffered from mild to severe dyspnea. 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, three 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 3. Persistent symptoms, limitations in activity and restrictions in participation three months after hospital discharge

Outcome	Male (=93)	Female (=56)	Total (=149)
Dyspnea, 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[(a)]	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[(a)]	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[(a)]	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[(a)]	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[(a)]	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[(a)]	1 (1.1)	0 (0.0)	1 (0.7)

Legend: MRC=Medical Research Council; FSS= Fatigue Severity Scale; HADS-a= Hospital Anxiety and Depression Scale – anxiety; HADS-d= Hospital Anxiety and Depression Scale – depression; B-ADL = Basic Activities of Daily Living; BI= Barthel Index; RNLI=Reintegration to Normal Living Index.[(a)] impossibility of administering the assessments due to difficulties in understanding the questions during the phone call on behalf of the participant;

Table 4 shows the odds ratios (OR) of the associations between potential exposures and outcomes three 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: three months after hospital discharge, 25% of females versus 7.5% of males suffered from dyspnea (OR 3.61, p = 0.019), 59% of females versus 27% of males suffered from fatigue (OR 3.75, p < 0.001), 37.5% of females versus 17% of males suffered from anxiety (OR 3.26, p = 0.007), and 28.5% of females versus 8.6% of males suffered from depression (3.71, p = 0.011); albeit not significantly, limitations in B-ADL were also more reported in females (14% versus 5.3%; OR 3.18, p = 0.078).

Surprisingly, comorbidities were not associated with worse outcomes.

Dyspnea 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 dyspnea (OR 5.02, p = 0.032) and dependence in B-ADL (OR 5.51, p = 0.029).

Table 4. Associations between potential exposures and outcomes three months after discharge.

Risk factors	**Dyspnea** 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 [0.96-1.05] p=0.806	0.97 [0.93-1.00] p=0.087	0.94 [0.90-0.98] **p=0.006***	0.95 [0.90-0.99] **p=0.036***	1.05 [0.99-1.12] p=(0.119)	0.95 [0.88-1.00] p=0.102
Female sex	3.61 [1.26-11.26] **p=0.019***	3.75 [1.75-8.26] **p<0.001***	3.26 [1.40-7.81] **p= 0.007***	3.71 [1.39-10.69] **p=0.011***	3.18 [0.90-12.79] p=0.078	2.59 [0.70-10.66] p=0.157
Several comorbidities (>3)	1.03 [0.20-4.26] p=0.970	0.92 [0.29-1.47] p=0.883	1.26 [0.34-4.34] p= 0.709	0.30 [0.01-1.89] p=0.281	0.57 [0.02-4.24] p=0.630	2.66 [0.45-15.85] p=0.260
Diabetes	1.57 [0.40-5.09] p=0.471	0.98 [0.37-2.48] p=0.965	0.88 [0.26-2.49] p=0.823	0.45 [0.06-1.76] p=0.317	3.12 [0-75-11.57] p=0.094	0.48 [0.02-2.77] p=0.499
Cardiovascular diseases	1.80 [0.54-8.23] p=0.380	0.73 [0.32-1.66] p=0.458	0.62 [0.25-1.58] p=0.311	0.79 [0.28-2.44] p=0.675	0.60 [0.16-2.42] p=0.438	1.46 [0.34-10.06] p=0.642
Obesity (BMI ≥30)	1.57 [0.40-5.09] p=0.471	1.36 [0.52-3.53] p=0.520	0.67 [0.18-2.03] p=0.519	0.82 [1.17-2.78] p=0.775	1.06 [0.15-4.55] p=0.940	2.23 [0.45-8.91] p=0.274

Critical or severe COVID-19	0.80 [0.26-2.28] p=0.691	0.70 [0.32-1.48] p=0.360	0.29 [0.10-0.75] **p=0.016***	0.33 [0.90-0.97] p=0.062	1.29 [0.35-4.56] p=0.681	1.03 [0.25-3.81] p=0.965
Use of walking aids after discharge	3.52 [0.97-11.62] **p=0.042***	2.38 [0.79-7.56] p=0.124	2.05 [0.64-6.12] p=0.205	0.69 [0.10-2.79] p=0.653	2.79 [0.56-11.14] p=0.164	0.71 [0.03-4.24] p=0.762
Accidental falls after discharge	5.02 [1.16-20.10] **p=0.023***	2.28 [0.61-9.37] p=0.220	3.48 [0.90-13.46] p=0.063	2.39 [0.48-9.58] p=0.237	5.51 [1.04-24.56] **p=0.029***	1.27 [0.06-8.00] p=0.829
Rehabilitation during hospitalization	3.01 [0.59-13.69] p=0.158	3.40 [0.97-13.89] p=0.064	0.43 [0.07-1.86] p=0.298	0.64 [0.07-3.40] p=0.639	4.12 [0.64-22.75] p=0.114	0.66 [0.02-5.60] p=0.751

Legend: OR = Odds Ratio; CI = Confidence interval; B-ADL = Basic Activities of Daily Living; BMI = Body Mass Index; *statistically significant.

Discussion

Statement of principal findings

This study focused on the long-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 dyspnea (44%). They recovered a good level of independence in basic activities of daily living, but 76% still suffered participation restrictions. Females showed higher levels of fatigue, dyspnea, anxiety, and depression. Thus, these results confirm that individuals hospitalized experience persistent symptoms, adding insight into the impact of COVID-19 on limitations in activities and participation.

As millions of individuals are recovering from the infection, it may be appropriate to recognize 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 health care organizations.[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 three months from the onset of COVID-19, with symptoms lasting for at least two months, that 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]

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 PACS is not linked to the severity of disease, and also confirm that fatigue and dyspnea 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 characterized 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 Lemhofer.[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 post-discharge independence in B-ADL (91.3%), 76% did not recover full social participation three 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 aging. 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 post-intensive 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 three 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 dyspnea 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 German survey,[37] and it is extremely important to expand outpatient therapeutic options to alleviate PACS 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,[38,39,40] 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,[44,45]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 hypothesized that the higher representation of women in autoimmune diseases may explain the sex differences in the immunological response to the acute and post-acute manifestations of COVID-19.[35,46]

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 PACS (dyspnea 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 hospitalization or to post-ICU syndrome, or that they might also affect the general population (e.g., anxiety, participation restrictions) due to the containment measures imposed by the Italian government. Causal inferencing and generalization 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 post-COVID-19 syndrome, 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 post-COVID-19 syndrome. 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.

Figure 1. Flow diagram of the study participants.

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SF had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LB conducted and is responsible for the data analysis.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval: This independent study was approved by Provincial Ethics Committee of Reggio Emilia on 21/04/2020 (ID 2020/0133). All participants provided written informed consent to participate in the trial.

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Transparency statement: the lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing: Reasonable requests for all of the individual participant data collected during the trial, after deidentification, should be made to the corresponding author and will be considered by the REACT lead author. The presented data are anonymized and risk of identification is low.

Dissemination declaration: we planned to disseminate the results to study participants who will specifically request them via e-mail.

License for publication

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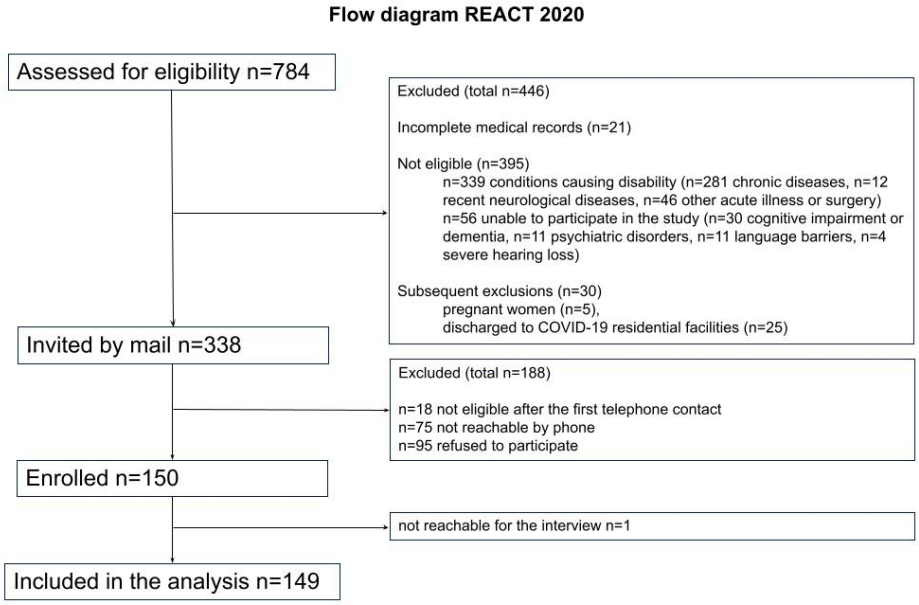

Figure 1. Flow diagram of the study participants

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Title page

Sex Differences and Rehabilitation Needs after Hospital Discharge for COVID-19: An Italian Cross-sectional Study

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19) can result in persistent symptoms leaving potential rehabilitation needs unmet. This study aims to describe persistent symptoms and health status of individuals hospitalized for COVID-19 according to the International Classification of Functioning, Disability and Health (ICF) domains of impairments, limitations in activity, and participation restrictions.

Design: Cross-sectional study consisting in a telephone interview three 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: hospitalization 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**:** dyspnea (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 ICU while hospitalized. Three months after hospital discharge, ~~Almost~~ nearly half of the participants still suffered from dyspnea (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: This independent observational study was registered on ClinicalTrials.com (NCT04438239).

Key Words: COVID-19, rehabilitation medicine, respiratory infections.

Article Summary

- 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 post-acute sequelae of SARS-COV2 infection, individuals with acute or chronic concomitant conditions causing disability and with previous complete dependence in activities of daily living (ADLs) 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-related hospital care and long-term health outcomes were collected.

Introduction

Background

The onset of the coronavirus disease 2019 (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 December 19, 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 categorization 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 (WHO 2021),[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, dyspnea, 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 post-acute sequelae of SARS-CoV-2 infection (PACS) characterized by fatigue, dyspnea, 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 hospitalized 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 hospitalization for COVID-19. It investigated the associations between sociodemographic characteristics, health status prior to COVID-19, COVID-related clinical manifestations and symptoms, and hospital care pathway up to discharge and health outcomes assessed three months after hospital discharge.

Methods

Study design and population

This cross-sectional study is reported according to the STROBE guidelines.[16] The study consisted in a telephone interview of patients hospitalized 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 a) were hospitalized for reasons other than COVID-19; b) were unable to participate in the study procedures (e.g., dementia, psychiatric disorders, linguistic barriers, etc.); c) had acute or chronic concomitant conditions causing disability (e.g., recent stroke, surgical interventions, heart failure, etc.); d) 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 dyspnea. The study was approved by the local Ethics Committee (prot. 2020/0133, April 21, 2020).

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 (~~physician, physiotherapist, or occupational therapist)~~ 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 ~~requested~~, 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 hospitalization)
- data regarding COVID-related hospital care
- symptoms and clinical manifestation of COVID-19 (e.g., cough, fever, diarrhea, asthenia, localization of pneumonia, respiratory failure)
- admission to the intensive care unit (ICU) and its duration
- any rehabilitation treatment during hospitalization (e.g., mobilization, chest physiotherapy)
- length of stay (LOS)

~~The medical records of each consenting participant were retrospectively reviewed to collect data on potential exposures, i.e., sociodemographic characteristics (age, sex, household composition) and health status prior to COVID-19 (comorbidities, use of aids, and level of independence prior to hospitalization). We also collected data regarding COVID-related hospital care, the symptoms and clinical manifestation of COVID-19 (e.g., cough, fever, diarrhea, asthenia, localization of pneumonia, respiratory failure), admission to the intensive care unit (ICU) and its duration, any rehabilitation treatment during hospitalization (e.g., mobilization, chest physiotherapy), and 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:

- dyspnea, assessed by the Medical Research Council (MRC)[17]

- fatigue, assessed by the Fatigue Severity Scale (FSS)[18]
- mood disturbances, assessed by the Hospital Anxiety and Depression Scale (HADS)[19]
- limitations in basic activities of daily living (B-ADL), assessed by the Barthel Index (BI)[20]
- restrictions in participation, assessed by the Reintegration to Normal Living Index (RNLI)[21] (Italian version)

~~Three months after hospital discharge, data regarding long-term health outcomes were collected through a telephone interview, which consisted in the assessment of persistent symptoms and impairments: dyspnea was assessed through the Medical Research Council (MRC) scale,[16] fatigue through the Fatigue Severity Scale (FSS),[17] and mood disturbances were assessed through the Hospital Anxiety and Depression Scale (HADS).[18] Data were also collected on limitations in basic activities of daily living (B-ADL) using the Barthel Index (BI)[19] and on restrictions in participation using the Italian version of the Reintegration to Normal Living Index (RNLI).[20]~~ 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.

~~Furthermore, qualitative data were explored through open-ended questions on the patient's recovery from COVID-19. The reporting of these qualitative data is currently underway.~~

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-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 standard deviation 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 three months following hospital discharge were investigated. Unless otherwise specified, confidence intervals 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 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 ~~having recovered~~ from the acute phase of COVID-19. Overall, 446 ~~of these patients~~ individuals were excluded for the reasons listed in Figure 1 ~~for the following reasons: incomplete medical records, thus not permitting the eligibility screening (21), presence of acute or chronic conditions causing disability other than COVID-19 (339), and inability to participate in the study (56). Five pregnant women were also excluded, as were 25 individuals who were discharged to a COVID-19 residential facility. Thus~~; 338 invitations to participate in the study were mailed to potentially eligible individuals, who were contacted by telephone two weeks later. ~~; 18 more individuals were excluded in this phase for inability to participate in the interview (language barrier, cognitive impairment, severe hearing loss, aphasia). Ninety-five individuals refused to participate and 75 could not be reached by phone, despite repeated attempts.~~ 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.

Insert Figure 1 near here

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%). ~~Other comorbidities included diseases of the digestive or respiratory systems (6.1% and 3.8%, respectively), hematological or rheumatological diseases (3% each); less frequent comorbidities included cancer, musculoskeletal diseases, and urogenital diseases (2.7% each), kidney and neurological diseases and psychiatric disorders (2.3% each), immune deficiencies (0.4%), and other (1.9%).~~Before hospitalization for COVID-19, all but one participant were independent in B-ADL, and only 6% used walking aids for mobility.

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 (dyslipidemia, 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)
Hematological diseases	8 (3.0)
Rheumatological diseases	8 (3.0)
Others	45 (17.1)
Independence before hospital admission, N (%)	
Yes	148 (99.3)
Minimal assistance ~~Need little help~~ for ADL	1 (0.7)
Use of aids before hospital admission, N (%)	
Yes	9 (6.0)
No	140 (94.0)

Legend: SD = Standard Deviation; N = Number; BMI = Body Mass Index; ADL = Activities of Daily Living

Table 2 reports data regarding the hospital care of participants, showing intensive care unit (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. ~~Accordingly, 37.6% of participants were in critical condition and needed respiratory assistance by means of continuous positive airway pressure, non-invasive ventilation, or intubation, while 40.9% needed high-flow oxygen therapy. Only 10.7% needed low-flow oxygen support, and an equal proportion did not need any respiratory support at all.~~ 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 mobilization was offered to patients in the ICU and to patients hospitalized in acute wards, if they presented severe risk of functional limitations due to frailty or mobility limitations. Inpatient rehabilitation was performed six days per week and included pulmonary rehabilitation, mobilization, exercises, and counseling. Also, as soon as patients could self-manage a program 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, PEP-bottle exercises, and incentive spirometer. Patients were advised to continue the exercises at home, with individualized 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.

Table 2. Hospital care of participants and post-discharge period.

Information about patients' hospital care and post-discharge				**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 hospitalization, 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)

Legend: ICU = Intensive Care Unit; LOS= Length Of Stay; CPAP = Continuous Positive Airway Pressure; NIV = Non-Invasive Ventilation; HF = High Flow; LF = Low Flow.

Outcome data

Table 3 describes the persistent symptoms, limitations in activity, and restrictions in participation three months after hospital discharge. Fatigue and dyspnea were the most prevalent persistent symptoms in the cohort investigated: 87.9% of participants experienced fatigue and 43% suffered from mild to severe dyspnea. 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, three 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 3. Persistent symptoms, limitations in activity and restrictions in participation three months after hospital discharge

Outcome	**Male (=93)**	**Female (=56)**	**Total (=149)**
Dyspnea, 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[a]	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[a]	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[a]	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[a]	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[a]	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[a]	1 (1.1)	0 (0.0)	1 (0.7)

Legend: MRC=Medical Research Council; FSS= Fatigue Severity Scale; HADS-a= Hospital Anxiety and Depression Scale – anxiety; HADS-d= Hospital Anxiety and Depression Scale – depression; B-ADL = Basic Activities of Daily Living; BI= Barthel Index; RNLI=Reintegration to Normal Living Index.[a] impossibility of administering the assessments due to difficulties in understanding the questions during the phone call on behalf of the participant;

Table 4 shows the odds ratios (OR) of the associations between potential exposures and outcomes three 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: three months after hospital discharge, 25% of females versus 7.5% of males suffered ~~howed a three to four times higher risk of suffering~~ from dyspnea (OR 3.61, p = 0.019), 59% of females versus 27% of males suffered from fatigue (OR 3.75, p < 0.001), 37.5% of females versus 17% of males suffered from anxiety (OR 3.26, p = 0.007), and 28.5% of females versus 8.6% of males suffered from depression (3.71, p = 0.011); albeit not significantly, limitations in B-ADL were also more reported in females (14% versus 5.3%; OR 3.18, p = 0.078).

Surprisingly, comorbidities were not associated with worse outcomes.

Dyspnea 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 dyspnea (OR 5.02, p = 0.032) and dependence in B-ADL (OR 5.51, p = 0.029).

Table 4. Associations between potential exposures and outcomes three months after discharge.

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

Legend: OR = Odds Ratio; CI = Confidence interval; B-ADL = Basic Activities of Daily Living; BMI = Body Mass Index; *statistically significant.

Discussion

Statement of principal findings

This study focused on the long-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 dyspnea (44%). They recovered a good level of independence in basic activities of daily living, but 76% still suffered participation restrictions. Females showed higher levels of fatigue, dyspnea, anxiety, and depression. Thus, these results confirm that individuals hospitalized experience persistent symptoms, adding insight into the impact of COVID-19 on limitations in activities and participation.

As millions of individuals are recovering from the infection, it may be appropriate to recognize 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 health care organizations.[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 ~~and is now available to clinicians.[26] This guideline and~~ 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 three months from the onset of COVID-19, with symptoms lasting for at least two months, that 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]

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 PACS~~post-COVID-19 syndrome~~ is not linked to the severity of disease, and also confirm that fatigue and dyspnea 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 characterized 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 Lemhofer.[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 post-discharge independence in B-ADL (91.3%), 76% did not recover full social participation three 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 aging. 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 post-intensive 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 three 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 dyspnea 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 German survey,[37] and it is extremely important to expand outpatient therapeutic options to alleviate PACS 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,[38,39,40] 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,[44,45]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 hypothesized that the higher representation of women in autoimmune diseases may explain the sex differences in the immunological response to the acute and post-acute manifestations of COVID-19.[35,46]

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 PACS (dyspnea 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 hospitalization or to post-ICU syndrome, or that they might also affect the general population (e.g., anxiety, participation restrictions) due to the containment measures imposed by the Italian government. Causal inferencing and generalization 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. ~~To our knowledge, this is the first study using this approach.~~ Moreover, a valid assessment of outcomes allowed us to confirm~~bring out~~ differences between the sexes in post-COVID-19 syndrome, 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.

~~*Meaning of the study*~~

~~A current and very lively debate concerns the sequelae of COVID-19 and the most appropriate definition for this syndrome.[38,39,40] We believe that our data contribute to this debate, as they highlight that COVID-19 can also affect the social activities of recovered patients, putting their global health at risk.~~

~~This study confirmed sex differences in post-COVID-19 recovery, that has already been noticed both in clinics[30] and in previous studies. These apparent differences merit further investigation to identify specific rehabilitation needs and 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 post-COVID-19 syndrome. 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.

Figure 1. Flow diagram of the study participants.

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~~**Contributor and guarantor information**~~**Contributorship statement:** as dictated by the Authorship guidelines of the International Committee of Medical Journal Editors, SF, MD, CM, MAA, GB, DG, AB, OE, CG, MS, LB and SC ~~all the authors of this manuscript~~ gave substantial contributions to the conception or design of the work or to the acquisition, analysis, or interpretation of data for the work; AND gave substantial contributions to the drafting the work or to its critical revision for important intellectual content; AND approved the final version to be published. All the authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This manuscript was completely written by its authors and reviewed in kind contribution for English language by an editor. The authors did not make use of medical writers.
SF had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LB conducted and is responsible for the data analysis.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethical approval: This independent study was approved by Provincial Ethics Committee of Reggio Emilia on 21/04/2020 (ID 2020/0133). All participants provided written informed consent to participate in the trial.

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Transparency statement: the lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing: Reasonable requests for all of the individual participant data collected during the trial, after deidentification, should be made to the corresponding author and will be considered by the REACT lead author. The presented data are anonymized and risk of identification is low.

Dissemination declaration: we planned to disseminate the results to study participants who will specifically request them via e-mail.

License for publication

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STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	NA
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 1, p.7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	8-9

Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12; Table 4.
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Keywords:	COVID-19, REHABILITATION MEDICINE, Respiratory infections < THORACIC MEDICINE

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Title page

Sex Differences and Rehabilitation Needs after Hospital Discharge for COVID-19: An Italian Cross-sectional Study

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Abstract

Objectives: Coronavirus disease 2019 (COVID-19) can result in persistent symptoms leaving potential rehabilitation needs unmet. This study aims to describe persistent symptoms and health status of individuals hospitalized for COVID-19 according to the International Classification of Functioning, Disability and Health (ICF) domains of impairments, limitations in activity, and participation restrictions.

Design: Cross-sectional study consisting in a telephone interview three 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: hospitalization 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**:** dyspnea (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 ICU while hospitalized. Three months after hospital discharge, nearly half of the participants still suffered from dyspnea (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: This independent observational study was registered on ClinicalTrials.com (NCT04438239).

Key Words: COVID-19, rehabilitation medicine, respiratory infections.

Article Summary

- 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 post-acute sequelae of SARS-COV2 infection, individuals with acute or chronic concomitant conditions causing disability and with previous complete dependence in activities of daily living (ADLs) 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-related hospital care and long-term health outcomes were collected.

Introduction

Background

The onset of the coronavirus disease 2019 (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 December 19, 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 Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-COV-2) infection have been well described, with a widely accepted categorization of acute COVID-19 published by the World Health Organization (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, dyspnea, 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 post-acute sequelae of SARS-CoV-2 infection (PASC) characterized by fatigue, dyspnea, 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 hospitalized 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 hospitalization for COVID-19. It investigated the associations between sociodemographic characteristics, health status prior to COVID-19, COVID-related clinical manifestations and symptoms, and hospital care pathway up to discharge and health outcomes assessed three 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 (STROBE) guidelines.[16] The study consisted in a telephone interview of patients hospitalized 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 a) were hospitalized for reasons other than COVID-19; b) were unable to participate in the study procedures (e.g., dementia, psychiatric disorders, linguistic barriers, etc.); c) had acute or chronic concomitant conditions causing disability (e.g., recent stroke, surgical interventions, heart failure, etc.); d) 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 dyspnea. The study was approved by the local Ethics Committee (prot. 2020/0133, April 21, 2020). 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 hospitalization)
- data regarding COVID-related hospital care
- symptoms and clinical manifestation of COVID-19 (e.g., cough, fever, diarrhea, asthenia, localization of pneumonia, respiratory failure)
- admission to the intensive care unit (ICU) and its duration
- any rehabilitation treatment during hospitalization (e.g., mobilization, 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:

- dyspnea, assessed by the Medical Research Council (MRC)[17]
- fatigue, assessed by the Fatigue Severity Scale (FSS)[18]
- mood disturbances, assessed by the Hospital Anxiety and Depression Scale (HADS)[19]
- limitations in basic activities of daily living (B-ADL), assessed by the Barthel Index (BI)[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-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 standard deviation for symmetric quantitative variables, and median and interquartile range (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 three months following hospital discharge were investigated. Unless otherwise specified, confidence intervals 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 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 two 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.

Insert Figure 1 near here

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 hospitalization for COVID-19, all but one participant were independent in B-ADL, and only 6% used walking aids for mobility.

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 (dyslipidemia, 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)

Hematological 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)

Legend: SD = Standard Deviation; N = Number; BMI = Body Mass Index; ADL = Activities of Daily Living

Table 2 reports data regarding the hospital care of participants, showing intensive care unit (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 mobilization was offered to patients in the ICU and to patients hospitalized in acute wards, if they presented severe risk of functional limitations due to frailty or mobility limitations. Inpatient rehabilitation was performed six days per week and included pulmonary rehabilitation, mobilization, exercises, and counseling. Also, as soon as patients could self-manage a program 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 (PEP)-bottle exercises, and incentive spirometer. Patients were advised to continue the exercises at home, with individualized 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.

Table 2. Hospital care of participants and post-discharge period.

Information about patients' hospital care and post-discharge				**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)	ICU 9 (16.1)

				Not-ICU 67 (72.0)	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 hospitalization, 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)

Legend: ICU = Intensive Care Unit; LOS= Length Of Stay; CPAP = Continuous Positive Airway Pressure; NIV = Non-Invasive Ventilation; HF = High Flow; LF = Low Flow.

Outcome data

Table 3 describes the persistent symptoms, limitations in activity, and restrictions in participation three months after hospital discharge. Fatigue and dyspnea were the most prevalent persistent symptoms in the cohort investigated: 87.9% of participants experienced fatigue and 43% suffered from mild to severe dyspnea. 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, three 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 3. Persistent symptoms, limitations in activity and restrictions in participation three months after hospital discharge

Outcome	Male (=93)	Female (=56)	Total (=149)
Dyspnea, 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[(a)]	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[(a)]	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[(a)]	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[(a)]	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[(a)]	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[(a)]	1 (1.1)	0 (0.0)	1 (0.7)

Legend: MRC=Medical Research Council; FSS= Fatigue Severity Scale; HADS-a= Hospital Anxiety and Depression Scale – anxiety; HADS-d= Hospital Anxiety and Depression Scale – depression; B-ADL = Basic Activities of Daily Living; BI= Barthel Index; RNLI=Reintegration to Normal Living Index.[(a)] impossibility of administering the assessments due to difficulties in understanding the questions during the phone call on behalf of the participant;

Table 4 shows the odds ratios (OR) of the associations between potential exposures and outcomes three 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: three months after hospital discharge, 25% of females versus 7.5% of males suffered from dyspnea (OR 3.61, p = 0.019), 59% of females versus 27% of males suffered from fatigue (OR 3.75, p < 0.001), 37.5% of females versus 17% of males suffered from anxiety (OR 3.26, p = 0.007), and 28.5% of females versus 8.6% of males suffered from depression (3.71, p = 0.011); albeit not significantly, limitations in B-ADL were also more reported in females (14% versus 5.3%; OR 3.18, p = 0.078).

Surprisingly, comorbidities were not associated with worse outcomes.

Dyspnea 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 dyspnea (OR 5.02, p = 0.032) and dependence in B-ADL (OR 5.51, p = 0.029).

Table 4. Associations between potential exposures and outcomes three months after discharge.

Risk factors	**Dyspnea** 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 [0.96-1.05] p=0.806	0.97 [0.93-1.00] p=0.087	0.94 [0.90-0.98] **p=0.006***	0.95 [0.90-0.99] **p=0.036***	1.05 [0.99-1.12] p=(0.119)	0.95 [0.88-1.00] p=0.102
Female sex	3.61 [1.26-11.26] **p=0.019***	3.75 [1.75-8.26] **p<0.001***	3.26 [1.40-7.81] **p= 0.007***	3.71 [1.39-10.69] **p=0.011***	3.18 [0.90-12.79] p=0.078	2.59 [0.70-10.66] p=0.157
Several comorbidities (>3)	1.03 [0.20-4.26] p=0.970	0.92 [0.29-1.47] p=0.883	1.26 [0.34-4.34] p= 0.709	0.30 [0.01-1.89] p=0.281	0.57 [0.02-4.24] p=0.630	2.66 [0.45-15.85] p=0.260
Diabetes	1.57 [0.40-5.09] p=0.471	0.98 [0.37-2.48] p=0.965	0.88 [0.26-2.49] p=0.823	0.45 [0.06-1.76] p=0.317	3.12 [0-75-11.57] p=0.094	0.48 [0.02-2.77] p=0.499
Cardiovascular diseases	1.80 [0.54-8.23] p=0.380	0.73 [0.32-1.66] p=0.458	0.62 [0.25-1.58] p=0.311	0.79 [0.28-2.44] p=0.675	0.60 [0.16-2.42] p=0.438	1.46 [0.34-10.06] p=0.642
Obesity (BMI ≥30)	1.57 [0.40-5.09] p=0.471	1.36 [0.52-3.53] p=0.520	0.67 [0.18-2.03] p=0.519	0.82 [1.17-2.78] p=0.775	1.06 [0.15-4.55] p=0.940	2.23 [0.45-8.91] p=0.274
Critical or severe COVID-19	0.80 [0.26-2.28] p=0.691	0.70 [0.32-1.48] p=0.360	0.29 [0.10-0.75] **p=0.016***	0.33 [0.90-0.97] p=0.062	1.29 [0.35-4.56] p=0.681	1.03 [0.25-3.81] p=0.965
Use of walking aids after discharge	3.52 [0.97-11.62] **p=0.042***	2.38 [0.79-7.56] p=0.124	2.05 [0.64-6.12] p=0.205	0.69 [0.10-2.79] p=0.653	2.79 [0.56-11.14] p=0.164	0.71 [0.03-4.24] p=0.762

Accidental falls after discharge	5.02 [1.16-20.10] **p=0.023***	2.28 [0.61-9.37] p=0.220	3.48 [0.90-13.46] p=0.063	2.39 [0.48-9.58] p=0.237	5.51 [1.04-24.56] **p=0.029***	1.27 [0.06-8.00] p=0.829
Rehabilitation during hospitalization	3.01 [0.59-13.69] p=0.158	3.40 [0.97-13.89] p=0.064	0.43 [0.07-1.86] p=0.298	0.64 [0.07-3.40] p=0.639	4.12 [0.64-22.75] p=0.114	0.66 [0.02-5.60] p=0.751

Legend: OR = Odds Ratio; CI = Confidence interval; B-ADL = Basic Activities of Daily Living; BMI = Body Mass Index; *statistically significant.

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 dyspnea (44%). They recovered a good level of independence in basic ADL, but 76% still suffered participation restrictions. Females showed higher levels of fatigue, dyspnea, anxiety, and depression. Thus, these results confirm that individuals hospitalized experience persistent symptoms, adding insight into the impact of COVID-19 on limitations in activities and participation.

As millions of individuals are recovering from the infection, it may be appropriate to recognize 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 health care organizations.[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 three months from the onset of COVID-19, with symptoms lasting for at least two months, that 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]

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 dyspnea 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 characterized 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 Lemhofer.[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 post-discharge independence in B-ADL (91.3%), 76% did not recover full social participation three 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 aging. 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 post-intensive 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 three 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 dyspnea 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 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,[38,39,40] 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,[44,45]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 hypothesized that the higher representation of women in autoimmune diseases may explain the sex differences in the immunological response to the acute and post-acute manifestations of COVID-19.[35,46]

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 ~~PACS~~ (dyspnea 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 hospitalization or to post-ICU syndrome, or that they might also affect the general population (e.g., anxiety, participation restrictions) due to the containment measures imposed by the Italian government. Causal inferencing and generalization 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.

Figure 1. Flow diagram of the study participants.

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SF had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. LB conducted and is responsible for the data analysis.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Transparency statement: the lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted; any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.

Data sharing: Reasonable requests for all of the individual participant data collected during the trial, after deidentification, should be made to the corresponding author and will be considered by the REACT lead author. The presented data are anonymized and risk of identification is low.

Dissemination declaration: we planned to disseminate the results to study participants who will specifically request them via e-mail.

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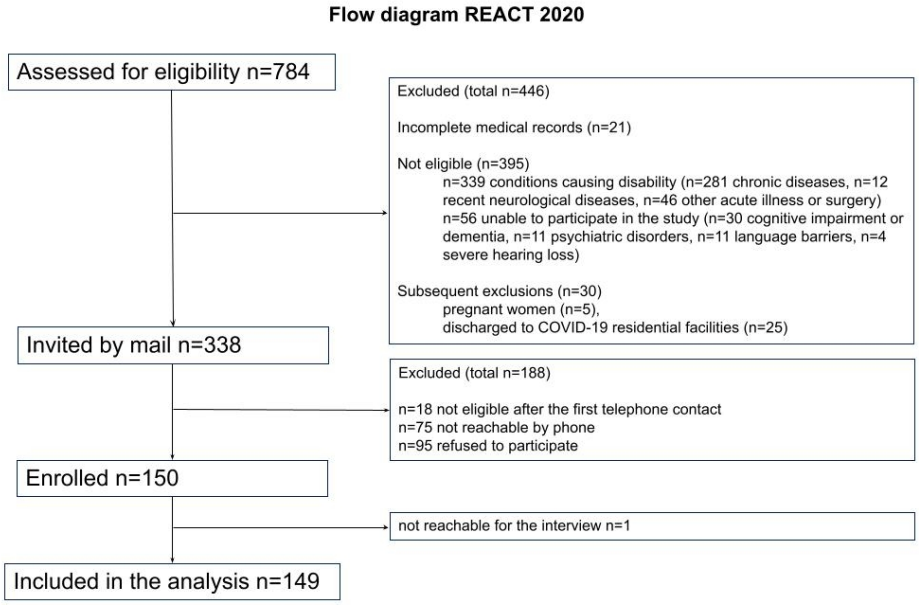

Figure 1. Flow diagram of the study participants

372x287mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	NA
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	NA
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	Figure 1, p.7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-8
		(b) Indicate number of participants with missing data for each variable of interest	8-9

Outcome data	15*	Report numbers of outcome events or summary measures	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-12; Table 4.
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11-12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12-13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.