“Long COVID” follow-up pathway: results of longitudinal cohort study to investigate 6- and 12-month outcomes after hospitalization for SARS-CoV-2 infection

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Abstract

Long-term sequelae of symptomatic infection caused by SARS-CoV-2 are largely undiscovered. We performed a prospective cohort study on consecutively hospitalized Sars-CoV-2 patients (March-May 2020) for evaluating COVID-19 outcomes at 6 and 12 months. After hospital discharge, patients were addressed to two follow-up pathways based on respiratory support needed during hospitalization. Outcomes were assessed by telephone consultation or ambulatory visit. Among 471 patients, 81.6% received no respiratory support during hospitalization; 8.2% received non-invasive ventilation; 0.2% required invasive mechanical ventilation (IMV). 64 patients died during hospitalization, therefore 407 were enrolled for follow-up. At 6 months, among 355patients, the 27.0% had any symptoms, 19.4% dyspnea, 5.4% neurological symptoms. Fifty-two out of 104 had major damages in interstitial Computed Tomography images. IMV patients had higher probability to suffer of neurological symptoms (OR=4.12, p=0.01). At 12 months, among 344, the 24.4% suffered on any symptoms, 14.0% dyspnea, 10.0% neurological symptoms. Severe interstitial lesions were present in 37 out of 47 investigated patients. IMV patients in respect to no respiratory support, had higher probability of experiencing symptoms (OR=3.51, p<0.01), dyspnea (OR=3.08, p<0.01), neurological symptoms (OR= 11.50, p<0.01). COVID-19 patients showed prolonged sequelae up to 12 months, highlighting the need of follow-up pathways for post-COVID-19 syndrome.

Introduction

Coronavirus disease 2019 (COVID-19) is a severe acute respiratory infection caused by the emergent coronavirus, SARS-CoV-2. Though most infected individuals are asymptomatic, SARS-CoV-2 infection may cause symptoms ranging from mild to severe acute respiratory distress, with a substantial fraction of patients requiring hospitalization (estimated to be around 10%) and many patients experiencing prolonged symptoms and complications for weeks or months after the initial period of acute illness [1–6].

The long COVID-19 phase or post-acute sequelae (signs and symptoms that continue or develop after acute COVID-19) includes both ongoing symptomatic COVID-19 (from 4 to 12 weeks) and post-COVID-19 syndrome (12 weeks or more) [6,7] and are not explained by an alternative diagnosis. Therefore, patients should be followed up to detect and manage sequelae and functional impairment [8,9].

Since COVID-19 has spread globally, and long COVID became a burgeoning health concern [10], a growing number of studies has been focused on “long-term effects of COVID-19” [11–18]. However, to date only a few studies [19–24] really addressed long term (up to 12 months) sequelae for hospitalized patient populations, as well as temporal trends and longstanding health consequences for “long-haulers” with a whole patient pathway perspective in different populations, timepoints, settings and countries. The full range of long-term health consequences of COVID-19 in patients who were discharged from hospital is largely unclear [25].

We implemented a stratified follow-up pathway and performed a prospective observational cohort study in patients who survived hospitalization for acute COVID-19 with the aim to:

- Investigate the prevalence of COVID-related symptoms and additional clinical findings at 6 and 12 months after hospital discharge;
- Identify the association of hospital respiratory support needed to help deal with the long-term effects of COVID-19.

Methods

Study design and participants

We conducted a prospective observational cohort study in adult patients with COVID-19 who had been admitted to the Internal Medicine ward of the Santa Maria del Carmine Hospital of Rovereto (Italy), between March 1, 2020, and May 31, 2020. The setting was a public general hospital with 300 beds that was identified in the first phase of the Italian COVID-19 outbreak as a regional hub hospital for COVID patients in the Autonomous Province of Trento (northeastern Italy, around 543,000 inhabitants).

All COVID diagnoses were confirmed using molecular diagnostic tests for SARS-CoV-2 (Reverse Transcription Polymerase Chain Reaction, RT-PCR) performed with a nasopharyngeal swab, oropharyngeal swab, or bronchoalveolar lavage using the standard protocols determined by the Italian Health Ministry, consistent with the World Health Organization's interim guidance diagnostic criteria for adults with severe COVID-19 pneumonia [26,27].

We set up a long-term stratified follow-up pathway supported by a telehealth solution (a structured and recorded call) that enabled patient monitoring and evaluation and the recording of long-lasting symptoms and clinical findings in patients hospitalized with COVID-19.

We implemented two different follow-up routes targeting two different patient groups on the basis of the severity of COVID disease assessed during hospitalization through the Brescia-COVID Respiratory Severity Scale (BCRSS), a scoring system developed in Italy during the early phase of the COVID-19 pandemic to aid the assessment and management of patients with COVID-19 pneumonia [28]. The score was calculated for each patient at the time of admission and in the case of clinical worsening during hospital stay; for patient stratification, we used the worst score recorded.

We further categorized and routed patients as follows:

- cohort 1: patients with mild COVID-19, treated without oxygen or with nasal cannula or mask to administer supplemental low flow oxygen-therapy < 6 l/minute (BCRSS 0–1); independently of the severity of COVID-19 during hospitalization, patients with severe cognitive or motor disabilities, residents of long-term care facilities and those refusing (i.e. because living far away from the hospital) the ambulatory follow up were included in this group;

- cohort 2: patients with moderate to severe disease requiring oxygen-therapy > 6 l/min, High-Flow Nasal Cannula (HFNC), Non-Invasive Ventilation (NIV) including Continuous positive airway pressure (CPAP), or invasive mechanical ventilation (IMV) (BCRSS ≥ 2). All patients in IMV previously failed to recover on HFNC or NIV.

The time frames for the follow-up visits were as follows: 6 months (25–27 weeks post symptom onset), and 12 months (50–54 weeks post symptom onset).

Procedures

All patients pertaining to cohort 1 and 2 were assessed at 6 months and 12 months after discharge and were investigated for serum levels of SARS-CoV-2 IgG antibodies (6 and 12 months) and status of vaccination anti-SARS-CoV-2 (fully vaccinated individuals) at 12-months, when vaccination was available and indicated for infected individuals according to Italian guidance on vaccination of COVID survivors [29].

Patients enrolled in route one (cohort 1) have been phone interviewed by physicians of the general medicine ward following a structured questionnaire (Table 1S Supplementary material) conceived similarly to other published tools [30] investigating clinical recovery and presence of COVID related symptoms. Additionally, all patients were assessed with the modified British Medical Research Council (mMRC) dyspnea scale, a five-category scale to characterize the level of dyspnea with physical activity in which higher scores correspond with increased dyspnea (from 0 to 4) [31]. In case of mMRC scale ≥ 1 the patient was shifted to ambulatory follow up at the same timepoint. For people with disabilities or long-term care facilities residents the interview was supported by caregiver or treating physician.

Patients enrolled in route two (cohort 2) have been evaluated with follow-up in person. We performed a complete ambulatory visit where patients were interviewed with the same questionnaire used at distance and undertaken the mMRC score. In addition, the same day of the visit, patients performed a functional assessment carried out with Six-Minute-Walking test (6MWT) [32] which was performed on all patients at 6 months and at 12 months only on patients showing altered 6MWT test at 6 months; as part of the pathway, patients with altered 6MWT were referred to pneumological specialistic consultation to perform additional lung tests. In addition, we performed a chest non-contrast high resolution Computed Tomography (CT) scan on all patients at 6 months and only on survivors with interstitial abnormalities of degree 3 and 4 (see below) at 6 months for the 12-month follow-up.

The focus was whether lesions identified on the CT, involved one or both lungs and several lung lobes. The evaluation of the imaging appearance included: lesion density (ground-glass opacity, consolidation), distribution (unilateral, bilateral), interlobular septa thickening, crazy-paving patterns, bronchiolectasis and bronchiectasis. The degree of chest imaging changes of the lung parenchyma and lung interstitium were graded on a 5-point scale based on the severity of the abnormal finding and the extent of lung involvement.

For parenchymal CT the score was categorized as follows:

- 0 normal;
- 1 unilateral ground-glass opacity (GGO);
- 2 bilateral GGO;
- 3 bilateral GGO and unilateral consolidations;
- 4 bilateral GGO and bilateral consolidations.

For interstitial CT the score was categorized as follows:

- 0 normal;
- 1 unilateral thickening of the subpleural perilobular septa;
- 2 bilateral thickening of the subpleural perilobular septa;
- 3 bilateral thickening of the subpleural perilobular septa and subpleural bronchiolectasis;
- 4 bilateral thickening of the subpleural perilobular septa and subpleural bronchiolectasis and bronchiectasis.

All chest CT scans were performed by the hospital radiology unit using a GE Revolution Evo CT scanner (GE Medical System, Boston, Massachusetts, USA). Scanning parameters were tube voltage (100 kV), tube current (10–240 mA), slice thickness (5mm), interval between slices (5 mm), consecutive 1,25 mm slices for high-resolution reconstruction scan and scanning time (< 5 s). A senior radiologist evaluated the scanned images to identify CT characteristics of each patient. People were placed in a supine position with feet first.

Immunoglobulin G test for SARS-CoV-2 was performed by adopting a fully automated chemiluminescence immunoassay (CLIA) for the quantitative detection of anti-SARS-CoV-2 IgG antibodies [33]. SARS-CoV-2 antibodies IgG CLIA kits were from Shenzhen YHLO Biotech Co, Ltd China) with two antigens of SARS-CoV-2 coated on the magnetic beads of the CLIA (nucleocapsid protein or N protein and spike protein or S protein). All antibody tests were performed by iFlash1800 CLIA fully automatic analyzer from YHLO biotech Co. The cut-off value proposed by manufacturer for a positive result was 10 AU/mL, samples with values more than or equal to 10 AU/mL were considerate as positive results.

Data Sources, Variables, and Outcomes

All demographic and clinical data were prospectively collected in an ad hoc file. The sources of data and information were clinical records including all available information sources (i.e., medical and nursing assessments, administration records, operative checklists, laboratory examinations…), and data from the hospital information system.

The outcomes we assessed were: symptoms, mMRC dyspnea scale, neurological symptoms, overall mortality, COVID-related re-hospitalization, IgG antibody presence, 6 minutes walking test, and CT images' scores.

The study was approved by the Ethics Committee of the Autonomous Province of Trento (reference number 4659) and followed the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Informed consent was obtained from all individual participants.

Statistical analyses

Dichotomous variables or scores were expressed as frequencies and percentages of occurrence. Continuous variables were checked for normality using Shapiro–Wilk test and, since their distribution was non-normal, they were expressed by median and first and third quartiles (q1-q3). Differences among groups were tested using the Fisher's exact test. We performed univariate logistic regression models to assess whether patients with greater respiratory needs during hospitalization had higher risk of having symptoms at the follow-up. Therefore, for each outcome we calculated the Odds Ratio (OR) for IMV patients in respect to no therapy of low flow oxygen, and the OR for HFNC/NIV patients in respect to no therapy of low flow oxygen. A P-value < 0.05 was considered to be statistically significant. Statistical analyses were performed using the Stata software, (StataCorp, College Station, Texas USA).

Results

The demographic and clinical characteristics of the 471 eligible hospitalized patients who were admitted to hospital with COVID-19 are shown in Table 1.

Table 1
Characteristics of hospitalized patients.

Characteristics	**471 patients**
Male, n (%)	300/471 (63.7)
Female, n (%)	171/471 (36.3)
Age, median (Q1-Q3) years	71 (58–81)
Age male, median (Q1-Q3) years	68 (56–78)
Age female, median (Q1-Q3) years	76 (61–85)
BCRSS at admission 0, n (%)	227/471 (48.2)
BCRSS at admission 1, n (%)	112/471 (23.8)
BCRSS at admission 2, n (%)	47/471 (10.0)
BCRSS at admission 3, n (%)	45/471 (9.5)
BCRSS at admission 4, n (%)	38/471 (8.1)
BCRSS at admission 5, n (%)	2/471 (0.4)
P/F ratio at admission, median (q1-q3)	310 (191–368)
P/F ratio < 300, n (%)	218/469 (46.5)
NEWS2 at admission, median (q1-q3)	4 (2–7)
NEWS2 0–4, n (%)	258/471 (54.9)
NEWS2 5–6, n (%)	83/471 (17.7)
NEWS2 ≥ 7, n (%)	129/471 (27.4)
Comorbidities:	
Cardiovascular (including hypertension), n (%)	289/471 (61.4)
Diabetes, n (%)	82/471 (17.4)
Gastrointestinal, n (%)	73/471 (15.5)
Autoimmune, n (%)	63/471 (13.4)
Obesity, n (%)	55/471 (11.7)
Pulmonary, n (%)	58/471 (12.3)
Renal, n (%)	51/471 (10.8)

Legend: BCRSS = Brescia COVID Respiratory Severity Scale; HFNC = High-Flow Nasal Cannula; IMV = Invasive Mechanical Ventilation; NEWS2 = National Early Warning Score 2; NIV = Non-invasive Ventilation; P/F ratio = PiO2/FiO2 ratio; Q1 = first quartile; Q3 = third quartile; TI = tracheal intubation.

Characteristics	471 patients
Cancer, n (%)	56/471 (11.9)
Received respiratory support:	
No supplemental oxygen or low-flow oxygen, n (%)	385/471 (81.6)
HFNC or NIV, n (%)	39/471 (8.2)
IMV, n (%)	48/471 (10.2)
Outcomes:	
Intra-hospital mortality, n (%)	64/471 (13.6)
Length of stay, median (Q1-Q3)	10 (6–16)
Complications:	
Venous thromboembolism (pulmonary embolism – Deep vein thrombosis), n (%)	28/468 (6.0)
Acute coronary syndrome, n (%)	9/468 (1.9)
Sepsis, n (%)	24/468 (5.1)
Guillian-Barrè syndrome, n (%)	1/468 (0.2)
Pneumothorax, n (%)	4/468 (0.9)
Pneumomediastinum, n (%)	6/468 (1.3)

Legend: BCRSS = Brescia COVID Respiratory Severity Scale; HFNC = High-Flow Nasal Cannula; IMV = Invasive Mechanical Ventilation; NEWS2 = National Early Warning Score 2; NIV = Non-invasive Ventilation; P/F ratio = PiO2/FiO2 ratio; Q1 = first quartile; Q3 = third quartile; TI = tracheal intubation.

In total, 63.7% (300) were male, 36.3% (171) were female, and the median age was 71 (first and third quartiles 58–81) years. During hospitalization, 81.6% (385 patients) had received no respiratory support or supplemental low-flow oxygen via a nasal tube or mask; 8.2% (39 patients) had received HFNC or NIV; and 10.2% (48 patients) had required IMV. Among the patients hospitalized, 13.6% (64 patients) died during their hospital stay, therefore 407 patients were prospectively enrolled after discharge for the follow-up. The patients' flow diagrams are shown in Fig. 1.

Six-month follow-up results

Out of 407 discharged patients, 30 patients died and 22 were lost to follow-up. In total, 250 patients completed remote follow-up and 105 patients completed ambulatory follow-up (Fig. 1). Outcomes at 6-month were summarized in Table 2a, moreover outcomes were stratified according to received hospital respiratory support in Table 2b. Six months after discharge, 27.0% of patients suffered of any symptoms (displayed in Fig. 2, and analytically reported in Table 2S - Supplementary material). Furthermore, 19.4% of patients felt dyspnea and 20.5% had altered or abnormal results on the mMRC scale (Table 2a). A total

of 5.4% of patients experienced neurological symptoms (see Fig. 2 and Table 2S for details). Globally, 20 different general symptoms/neurological symptoms were reported by patients. The COVID-related 6-month re-hospitalization was 2.8%, and overall mortality was 20.9%. The IgG were found in the 95.3% of the tested patients, while 13.4% of patients showed an altered or scarce walking test. At 6 months 86.5% of 104 patients investigated showed different degrees of chest imaging abnormalities of the lung: including parenchymal GGO in 61.5% of patients (with bilateral damage in 50.0% of cases and 2.9% with consolidation). The interstitium abnormalities recorded included thickening of the subpleural perilobular septa in 86.5% of patients, bilateral thickening was present in 78.8% of cases, 33.6% also with bilateral subpleural bronchiolectasis and 16.3% with bronchiectasis in addition to brochiolectasis.

Table 2
a. Outcomes at 6 months.

Outcomes	n (%)
Symptoms	96/355 (27.0)
Dyspnea	69/355 (19.4)
mMRC scale 0	282/355 (79.5)
mMRC scale 1	59/355 (16.6)
mMRC scale 2	9/355 (2.5)
mMRC scale 3	4/355 (1.1)
mMRC scale 4	1/355 (0.3)
Neurological symptoms	19/355 (5.4)
COVID-related re-hospitalization	10/355 (2.8)
Overall 6-month mortality	94/449 (20.9)
IgG	163/171 (95.3)
Walking test 0	90/104 (86.6)
Walking test 1	12/104 (11.5)
Walking test 2	2/104 (1.9)
Parenchymal CT 0	40/104 (38.5)
Parenchymal CT 1	9/104 (8.6)
Parenchymal CT 2	52/104 (50.0)
Parenchymal CT 3	1/104 (1.0)
Parenchymal CT 4	2/104 (1.9)
Interstitial CT 0	14/104 (13.5)
Interstitial CT 1	8/104 (7.7)
Interstitial CT 2	30/104 (28.9)
Interstitial CT 3	35/104 (33.6)
Interstitial CT 4	17/104 (16.3)

Legend: CT = computed tomography; IgG = Immunoglobulin G; mMRC = Modified Medical Research Council.

As far as outcomes stratified by received respiratory support during hospitalization are concerned (Table 2b), patients treated with IMV had higher percentage of neurological symptoms (15.1%) in comparison to

HFNC/NIV (6.2%) and to no therapy or low-flow oxygen (4.1%), p = 0.03 (Odds Ratio IMV versus no therapy = 4.12 (1.35–12.55), p = 0.01, Odds Ratio HFNC/NIV versus no therapy = 1.54 (0.33–7.20), p = 0.58). No statistical differences in the CT scores based on patients' respiratory support were noted.

Table 2
b. Outcomes at 6 months stratified by received respiratory support.

	No therapy or low-flow oxygen, n (%)	HFNC/NIV, n (%)	IMV, n (%)	p-value
Outcomes				
Symptoms	74/290 (25.5)	10/32 (31.2)	12/33 (36.4)	0.34
Dyspnea	53/290 (18.3)	8/32 (25.0)	8/33 (24.2)	0.44
mMRC scale 0	236/290 (81.4)	22/32 (68.8)	24/33 (72.7)	0.24
mMRC scale 1	42/290 (14.5)	10/32 (31.2)	7/33 (21.2)	
mMRC scale 2	7/290 (2.4)	0/32 (0.0)	2/33 (6.1)	
mMRC scale 3	4/290 (1.4)	0/32 (0.0)	0/33 (0.0)	
mMRC scale 4	1/290 (0.3)	0/32 (0.0)	0/33 (0.0)	
Neurological symptoms	12/289 (4.1)	2/32 (6.2)	5/33 (15.1)	0.03
Walking test 0	70/78 (89.7)	9/11 (81.8)	11/15 (73.3)	0.05
Walking test 1	8/78 (10.3)	2/11 (18.2)	2/15 (13.3)	
Walking test 2	0/78 (0.0)	0/11 (0.0)	2/15 (13.3)	
Parenchymal CT 0	32/78 (41.0)	5/12 (41.7)	4/15 (26.7)	0.37
Parenchymal CT 1	4/78 (5.1)	3/12 (25.0)	2/15 (13.3)	
Parenchymal CT 2	39/78 (50.0)	4/12 (33.3)	9/15 (60.0)	
Parenchymal CT 3	1/78 (1.3)	0/12 (0.0)	0/15 (0.0)	
Parenchymal CT 4	2/78 (2.6)	0/12 (0.0)	0/15 (0.0)	
Interstitial CT 0	12/78 (15.6)	1/12 (8.3)	1/15 (6.7)	0.42
Interstitial CT 1	7/78 (9.1)	0/12 (0.0)	1/15 (6.7)	
Interstitial CT 2	20/78 (26.0)	4/12 (33.3)	6/15 (40.0)	
Interstitial CT 3	28/78 (36.4)	5/12 (41.7)	2/15 (13.3)	
Interstitial CT 4	10/78 (13.0)	2/12 (16.7)	5/15 (33.3)	

Legend: HFNC = High-Flow Nasal Cannula; IgG = Immunoglobulin G; IMV = Invasive Mechanical Ventilation; mMRC = Modified Medical Research Council; NIV = Non-invasive Mechanical Ventilation; TC = Computed Tomography.

Twelve-month follow-up results

By the 12-month follow-up, 5 more patients died, 237 patients performed a phone follow-up, 107 patients performed an ambulatory follow-up, and 6 more patients were lost to follow-up (Fig. 1). Outcomes at 12 months were summarized in Table 3a, moreover outcomes were stratified according to received hospital respiratory support in Table 3b. Twelve months after discharge, 24.4% of patients suffered of any symptoms (see Fig. 2, and Table 2S for details); 14.0% of patients felt dyspnea, and 14.5% of patients had altered or abnormal results on the mMRC scale (Table 3a). In total, the 10.0% of patients experienced neurological symptoms (see Fig. 2, and Table 2S for details). Globally, 23 different symptoms/neurological symptoms were reported by patients. The COVID-related 12-month re-hospitalization was 1.4%, and overall mortality was 22.3%. IgG antibodies were found in the 85.7% of the patients tested and 41.0% of the patients followed up had been vaccinated. Among the patients investigated with CT images at 12 months (47), GGO was still present in 51.0% of patients (with bilateral damage in 46.8 % of cases), while 2.1% continued to show consolidation (score > 2). Interstitium abnormalities in this group of patients included thickening of the subpleural perilobular septa in 95.8% of patients, bilateral thickening was found in 12.8 % of cases, 51.1% also with bilateral subpleural bronchiolectasis and 27.2% with bronchiectasis in addition to brochiolectasis. Among patients followed up with CT at 6 months, it could be estimated that any form of GGO was found in 23.1% of cases, while interstitial severe damages (score > 2) were still present in 35.6% of patients followed up with CT at 6 months.

Table 3
a. Outcomes at 12 months.

Outcomes	n (%)
Symptoms	84/344 (24.4)
Dyspnea	48/344 (14.0)
mMRC scale 0	294/344 (85.5)
mMRC scale 1	38/344 (11.0)
mMRC scale 2	7/344 (2.0)
mMRC scale 3	4/344 (1.2)
mMRC scale 4	1/344 (0.3)
Neurological symptoms	34/341 (10.0)
COVID-related re-hospitalization	5/344 (1.4)
Overall 12-month mortality	99/443 (22.3)
IgG	192/224 (85.7)
Vaccinated	132/322 (41.0)
Walking test 0	7/11 (63.6)
Walking test 1	4/11 (36.4)
Walking test 2	0/11 (0.0)
Parenchymal CT 0	23/47 (49.0)
Parenchymal CT 1	1/47 (2.1)
Parenchymal CT 2	22/47 (46.8)
Parenchymal CT 3	1/47 (2.1)
Parenchymal CT 4	0/47 (0.0)
Interstitial CT 0	2/47 (4.2)
Interstitial CT 1	2/47 (4.2)
Interstitial CT 2	6/47 (12.8)
Interstitial CT 3	24/47 (51.1)
Interstitial CT 4	13/47 (27.7)

Legend: CT = computed tomography; IgG = Immunoglobulin G; mMRC = Modified Medical Research Council.

As far as outcomes stratified by received respiratory support during hospitalization are concerned (Table 3b), patients treated with IMV and HFNC/NIV had higher probability of experiencing symptoms in respect to no therapy (Odds Ratio IMV versus no therapy = 3.51 (1.68–7.31), $p < 0.01$, Odds Ratio HFNC/NIV versus no therapy = 2.25 (1.05–4.86), $p = 0.04$). Similarly, patients treated with IMV and HFNC/NIV had higher probability of experiencing dyspnea in respect to no therapy (Odds Ratio IMV versus no therapy = 3.08 (1.35–7.01), $p < 0.01$; Odds Ratio HFNC/NIV versus no therapy = 1.32 (0.48–3.66), $p = 0.59$). Indeed, mMRC scale showed worst score for IMV in respect to HFNC/NIV and no therapy, $p = 0.02$ (Table 3b). Moreover, patients treated with IMV and HFNC/NIV had higher probability of experiencing neurological symptoms in comparison to no therapy or low-flow oxygen (Odds Ratio IMV versus no therapy = 11.50 (4.79–27.61), $p < 0.01$; Odds Ratio HFNC/NIV versus no therapy = 5.00 (1.85–13.49), $p < 0.01$). No statistical differences were noted in CT scores based on patients' respiratory support.

Table 3
b. Outcomes at 12 months stratified by received respiratory support.

	No therapy or low-flow oxygen, n (%)	HFNC/NIV, n (%)	IMV, n (%)	p-value
Outcomes				
Symptoms	56/277 (20.2)	12/33 (36.4)	16/34 (47.1)	< 0.01
Dyspnea	33/277 (11.9)	5/33 (15.2)	10/34 (29.4)	0.03
mMRC scale 0	243/277 (87.7)	28/33 (84.9)	23/34 (67.7)	0.02
mMRC scale 1	26/277 (9.4)	4/33 (12.1)	8/34 (23.5)	
mMRC scale 2	5/277 (1.8)	0/33 (0.0)	2/34 (5.9)	
mMRC scale 3	3/277 (1.1)	1/33 (3.0)	0/34 (0.0)	
mMRC scale 4	0/277 (0.0)	0/33 (0.0)	1/34 (2.9)	
Neurological symptoms	14/274 (5.1)	7/33 (21.2)	13/34 (38.2)	< 0.01
Walking test 0	6/8 (75.0)	0/0 (0.0)	1/3 (33.3)	0.49
Walking test 1	2/8 (25.0)	0/0 (0.0)	2/3 (66.7)	
Walking test 2	0/8 (0.0)	0/0 (0.0)	0/3 (0.0)	
Parenchymal CT 0	6/13 (46.1)	9/14 (64.3)	8/20 (40.0)	0.38
Parenchymal CT 1	0/13 (0.0)	1/14 (7.1)	0/20 (0.0)	
Parenchymal CT 2	7/13 (53.9)	4/14 (28.6)	11/20 (55.0)	
Parenchymal CT 3	0/13 (0.0)	0/14 (0.0)	1/20 (5.0)	
Parenchymal CT 4	0/13 (0.0)	0/14 (0.0)	0/20 (0.0)	
Interstitial CT 0	0/13 (0.0)	2/14 (14.3)	0/20 (0.0)	0.15
Interstitial CT 1	2/13 (15.4)	0/14 (0.0)	0/20 (0.0)	
Interstitial CT 2	2/13 (15.4)	3/14 (21.4)	1/20 (5.0)	
Interstitial CT 3	5/13 (38.4)	6/14 (42.9)	13/20 (65.0)	

Legend: CT = computed tomography; HFNC = High-Flow Nasal Cannula; IgG = Immunoglobulin G; IMV = Invasive Mechanical Ventilation; mMRC = Modified Medical Research Council; NIV = Non-invasive ventilation; TI = tracheal intubation.

	No therapy or low-flow oxygen, n (%)	HFNC/NIV, n (%)	IMV, n (%)	p-value
Interstitial CT 4	4/13 (30.8)	3/14 (21.4)	6/20 (30.0)	

Legend: CT = computed tomography; HFNC = High-Flow Nasal Cannula; IgG = Immunoglobulin G; IMV = Invasive Mechanical Ventilation; mMRC = Modified Medical Research Council; NIV = Non-invasive ventilation; TI = tracheal intubation.

Discussion

We implemented a long-term stratified follow-up path that adhered to the international proposed clinical guidance for the assessment and management of COVID-19 patients [7,8,34,35], in the context of the limited availability of resources and the operational pressure faced by hospitals during the pandemic. This project was part of a broad set of strategies and paths implemented within the Healthcare Trust of the Autonomous Province of Trento for reorganizing care and managing patients at a distance, including routine services and the continuation of care after hospital discharge [36], as well assessing the impact of pandemic burden and related change in practice [37]. In our study, we targeted the same cohort of patients (excluding six patients with multiple admissions) to investigate in-hospital outcomes during the COVID-19 pandemic [38].

Overall, in our study any long COVID symptoms were reported at 6 months in 27.0% of patients and at 12 months in 24.4%, but we noted an increased number of different symptoms at 12 months. Alterations in the mMRC scale were reported in almost 20.5% of patients at 6 months and in 14.5% of patients at 12 months. The frequency of neurocognitive symptoms increased from 5.4–10.0% from the 6-month to the 12-month timepoints. At both 6 and 12 months, neurocognitive symptoms were markedly more common in patients who had been treated with mechanical ventilation during hospital admission. Furthermore, patients who had been treated with tracheal intubation in comparison to HFNC or NIV and who had received no therapy or low-flow oxygen reported a significantly higher prevalence of experiencing any symptom and having dyspnea at 12 months.

Published studies investigating the highly heterogeneous and poorly understood post-COVID-19 syndrome show the relevance of medical and psychological sequelae for several months after active infection, with more than 50 long-term effects of COVID-19 having been reported [39]. Pooled prevalence data show that the 10 most prevalent symptoms are fatigue, shortness of breath, muscle pain, joint pain, headache, cough, chest pain, altered smell, altered taste, and diarrhea [40]. The increasingly evident long-term neurological effects include the impact of the virus on cognition, autonomic function, and mental wellbeing [41]. Patients with long COVID present with prolonged multisystem involvement and significant disability [13]. The development of long COVID symptoms may be linked to symptomatic COVID-19 infection, hospitalization (with mechanical ventilation being required), severity of illness, and sex (women may have a higher incidence) [42–44]. However, any patient with COVID-19 may develop long COVID, regardless of the severity of their infection and the intensity of the treatment they received [43].

The few published prospective studies using a 12-month timepoint providing an overview of the clinical symptoms and quality of life of adult patients show that, although decreasing over time, a meaningful portion of patients still report persistent symptoms one year after infection [20,22–25]. Overall, our findings are in line with such results, although with a lower proportion of patients experiencing persistent symptoms, with a meaningful proportion of patients of experiencing dyspnea and patterns of neurologic symptoms. Clinical impairment can persist at least until one year after COVID-19 symptom onset and reduce patients' quality of life significantly [22]. The persistence of neuropsychiatric long COVID symptoms (which can reduce quality of life significantly) one year after COVID-19 symptom onset may be partially explained by the influence of the extended pandemic situation and consequent psychological impact [22].

Our findings seem consistent with the literature showing the persistence of chest imaging manifestations months after hospitalization for COVID-19 pneumonia [12,45–47] and the persistence (although decreasing over time) of pulmonary alterations up to 12 months later [21,25]. However, we did not find any association between lung structural abnormalities and the severity of the disease during hospital stay. Lung imaging patterns at 12 months may be associated with lung diffusion impairment, although further studies are needed to explore the effect of these persistent abnormalities on physical function and quality of life [25].In our study, we found a decreased detection of IgG antibodies in SARS-CoV-2-infected patients, dropping from 95.3% at six months to 85.7% at 12 months. The detectability of antibodies 1 year after infection, although with different temporal trends and magnitudes, seems to confirm the findings of other studies that have carried out comparable long-term follow-ups [48–50]. The relationship between the antibody level and protection against COVID-19 is still unclear; however, the one-year follow-up data show that patients who have recovered from COVID-19 have a very low risk of reinfection. Natural immunity to SARS-CoV-2 appears to confer a protective effect for at least a year [51]. The rate of full vaccine coverage at 12 months seem to mirror the progress of the Italian vaccination campaign, which is still underway at the timeframe of the writing, reflecting the need of specific logistic organization [52–54].

All in all, our study shows the high clinical burden of long COVID-19 12 months after acute infection and affirms the importance of understanding the natural course of long COVID as a long-term chronic condition with symptoms persisting beyond 12 months after the onset of illness. Identifying patients at major risk of sequelae from the early post-acute phase; setting up appropriate and patient-centered pathways supported by online support tools; and the implementation of surveillance systems and specialized multidisciplinary care, including rehabilitation, are critical in order to understand and treat patients suffering from long COVID [40,55–58].

The development and implementation of clinical guidelines [59] as well as use of tools and methods for Health Technology Assessment [60,61] in order to evaluate the effects of decisions and actions related to resource allocation, models of care, professional practice, drugs, and medical devices in response to the complex and evolving challenges of long COVID may enable value-based decisions to be made [62].

Strenghts And Limitations

To the best of our knowledge, our research represents one of the few 12-month follow-up studies on COVID-19 reported to date, addressing a unique mix of symptoms and clinical findings and including the investigation of a broad range of clinical symptoms, serum antibodies titers, pulmonary functions, and CT imaging and vaccination statuses.

The strength of our study is its long-term follow-up of a well-characterized patient population from the first peak of the pandemic in Italy (with almost no missing data and no risk of any selection bias) within a real world standardized pathway in which we prioritized instrumental assessments and investigations directed at survivors by exploiting telehealth solution to reduce ambulatory burden and patient risk. Following appropriateness principle, in deep diagnosis as CT at 12 months was performed only on survivors who had had interstitial abnormalities of degree 3 and 4 at 6 months, and the Six-Minute Walking test at 12 months was performed only on patients who had had altered test results at 6 months. Considering the diversity of the initial target population and the duration of the pathway, we believe that our drop-out rate was very low, which may be attributable to the benefit of engaging patients within a structured and patient-oriented follow-up path.

We acknowledge the potential bias caused by not performing the same investigations on all patients prospectively followed by either comparing cohort one and two as well as within cohort two (see above). In addition, our findings apply to a population selected in the early phase of the pandemic, in which we did not have a clinical assessment for use before acute infection. Both presenting patient characteristics and clinical management have evolved since. The generalizability of our results may be limited by the potential patient population selection bias, lack of standardized validated questionnaires for reporting the prevalence of COVID-19 symptoms at the international level and the self-reporting of symptoms based on a remote interview (19) as well as the study's single-center, not-blinded, and not-randomized design.

Conclusions

Our study may provide valuable information enabling relevant professionals to understand the clinical needs of long COVID patients and identify practical and feasible approaches for the routine follow-up and management of patients with long-term COVID-19 complications. Large and long-ranging observational studies and clinical trials for investigating long-term sequelae, as well as follow-up pathways for looking after people with long-term complications after acute COVID-19, should be considered.

Declarations

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ETHICS STATEMENT

The study protocol was approved by the ethic committee of the Autonomous Province of Trento (reference number 4659) and followed the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Informed consent was obtained from all individual participants for whom identifying information is included in this article.

COMPETING INTERESTS STATEMENT

The authors declare no competing interests.

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AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to all of the following: (1) the conception and design of the study (SC, LDD, GN, MR and ET), or acquisition of data (LL, SR, LDD, and AF), or analysis and interpretation of data (MR, GN, and ET), (2) drafting the article or revising it critically for important intellectual content (ET, MR, GN, LDD, and SC), (3) final approval of the version to be submitted (all authors).

DATA AVAILABILITY STATEMENT

Data are available on reasonable requests.

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Figures

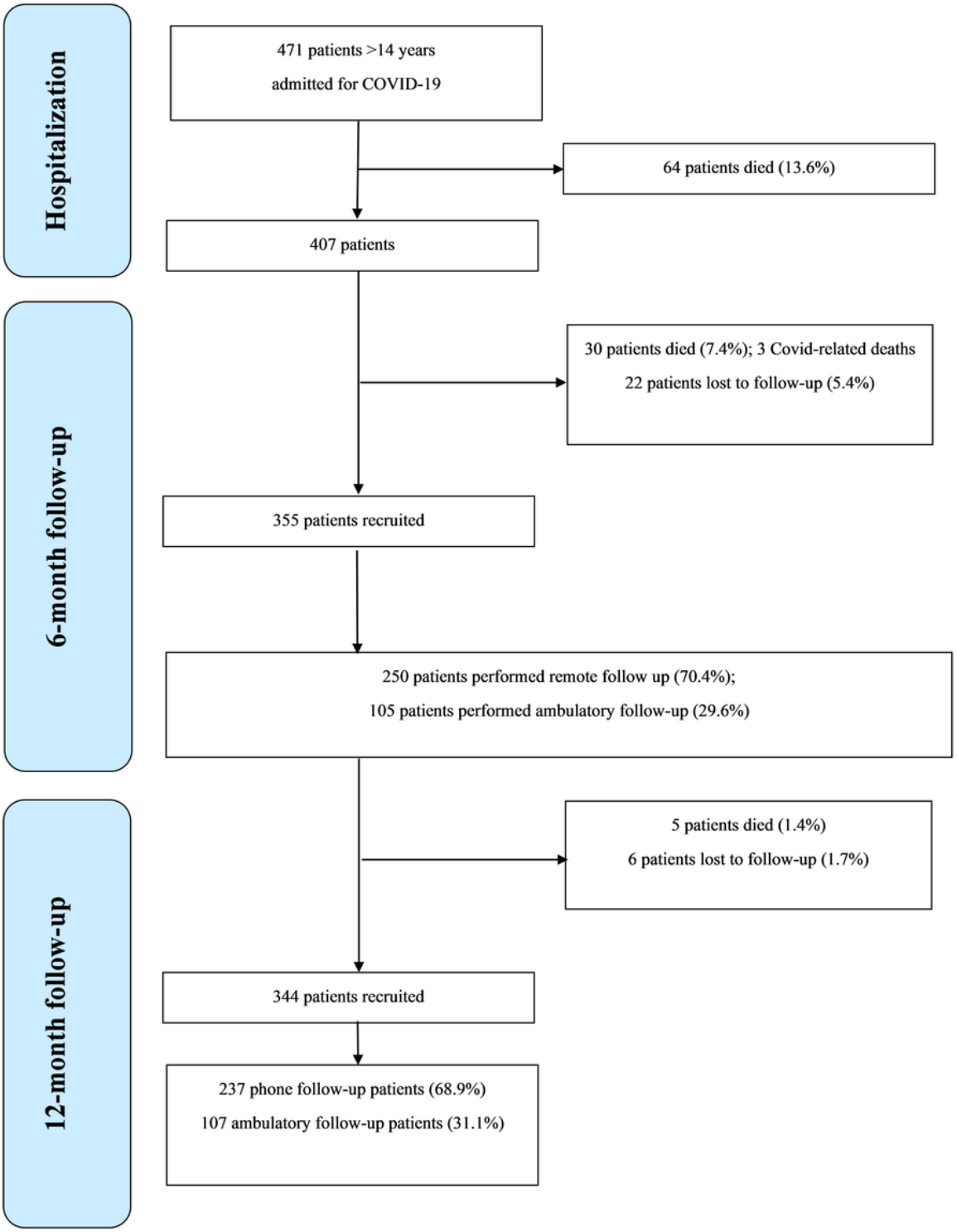

Figure 1

Patients' flow diagram.

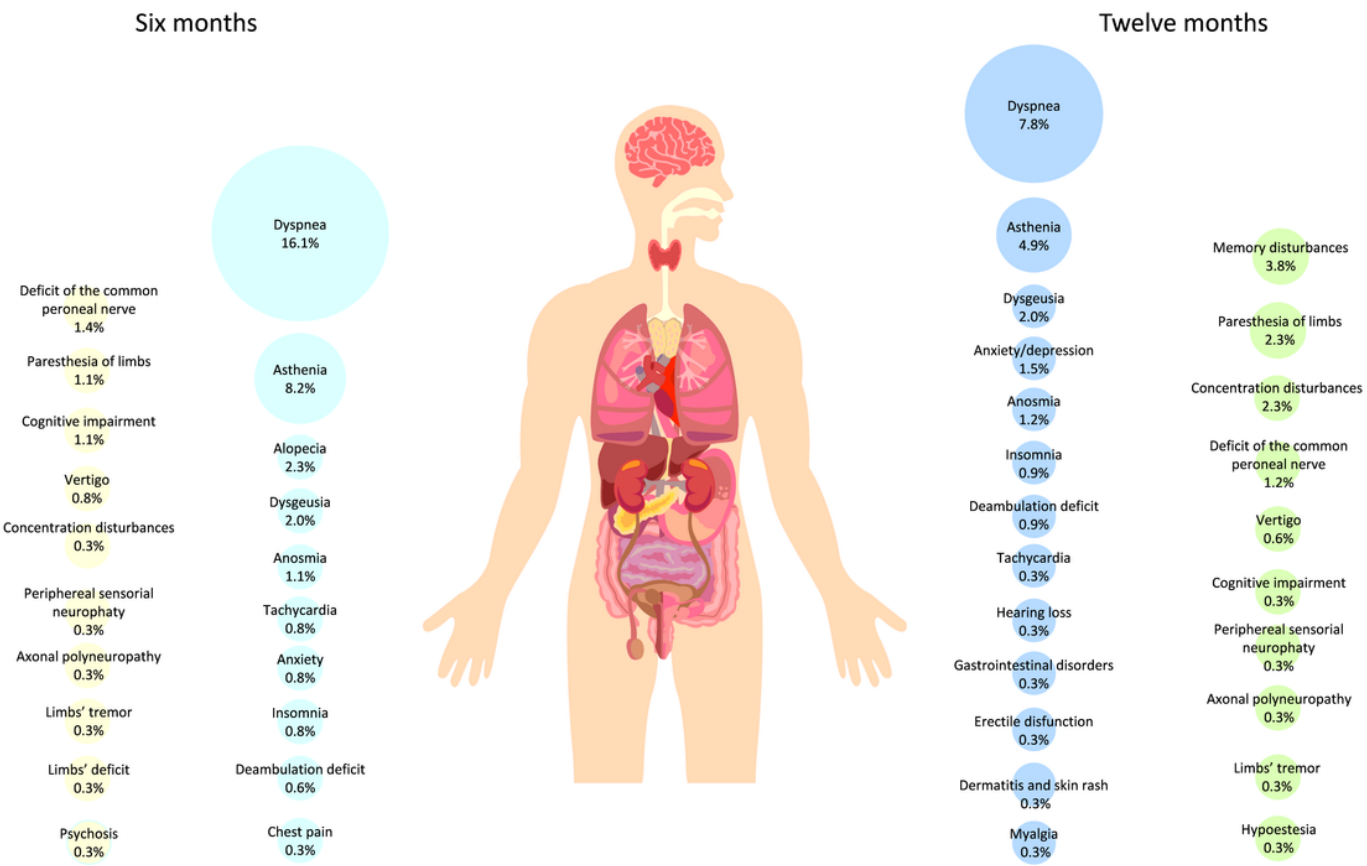

Figure 2

General (blue color) and neurological symptoms (green color) at 6 (left) and 12 months (right) after discharge for hospitalized SARS-CoV-2 patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytables.docx