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## **Abstract**

We evaluated 100 post-acute COVID-19 patients, a median of 60 days (IQR 48-67) after discharge from the Careggi University Hospital, Italy. Eighty-four (84%) had at least one persistent symptom, irrespective of COVID-19 severity. A considerable number of hospital re-admission (10%) and/or infectious diseases (14%) during the post-discharge period was reported.

## **Keywords**

COVID-19; follow-up; sequelae, SARS-CoV-2; long-term

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## INTRODUCTION

On 31<sup>th</sup> December 2019, the world had the first notice of a cluster of atypical pneumonia due to a novel coronavirus, later named severe acute respiratory syndrome 2 (SARS-CoV-2) [1]. Twelve months later, nearly 90 million cases of Coronavirus disease 2019 (COVID-19) have been reported worldwide, with almost 2 million deaths [2].

Clinical presentation can be variable, ranging from SARS-CoV-2 asymptomatic carriers to life-threatening and fatal disease. Most common symptoms include fever, cough and shortness of breath. Musculoskeletal symptoms, such as myalgia, joint pain, headache, and fatigue were also reported, as well as enteric symptoms (abdominal pain, vomiting, and diarrhoea), anosmia and dysgeusia [3-4]. Critically ill patients often require prolonged hospital stay, mechanical ventilation and intensive level of treatments, being at higher risk of severe complications, such as septic shock, thromboembolic events and acute kidney injury [5]

Initial reports are emerging about persistence of a significant symptom burden in the aftermath of recovery from acute COVID-19, allowing the definition of the so-called 'Long-COVID' [6-8]. More insight about short- and long-term consequences of SARS-CoV-2 infection is essential, to properly inform the follow-up programs for patients who experienced symptoms of COVID-19[9]. An earlier clinical review within 4-8 weeks post-discharge has been recommended, at least in patients who experienced more severe symptoms [10]. In Tuscany Region, Italy, a comprehensive 12-months follow-up, including multidisciplinary evaluations according to disease severity and patient characteristics, is guaranteed to all individuals diagnosed with SARS-CoV-2 infection [11].

In this paper we report the results of the first step of the follow-up program for post-acute COVID-19 patients discharged from Careggi University Hospital, Florence, Italy, consisting of a clinical and biochemical assessment 8 weeks after hospital discharge.

## METHODS

Since 20<sup>th</sup> May 2020 - soon after the end of the epidemic phase - an outpatient service dedicated to the follow-up of post-discharge COVID-19 patients is active at the Careggi University Hospital, Florence, Italy, in accordance with the program of the Tuscany Region. Several specialists from different disciplines were involved into this program, including infectious diseases specialists, pulmonologists, cardiologists, immunologists and physiotherapists.

All patients discharged from the hospital were offered a clinical visit. Exclusion criteria were: (i) patients discharged for more than 10 weeks; (ii) patients unable to attend the visit, because hospitalized or residents in care facilities; (iii) patient's refusal. Data on subject's death after discharge were collected.

Data on previous hospital admission were retrieved from electronic medical records. Disease severity was classified in mild, moderate, severe and critical, according to World Health Organization (WHO) definition [12]. A detailed post-discharge clinical history was collected through a standardized questionnaire, focused on persistence of symptoms potentially related with the recent SARS-CoV-2 infection. Symptom count included any self-reported symptom, persisting at time of the follow-up visit. Post-discharge symptoms resolved before the visit were not considered in the count. Symptom inventory questionnaire used for the study is shown as Supplementary material 1. Moreover, hospital re-admissions and post-discharge infections were ascertained by medical record review or, alternatively, they were self-reported and supported by all available medical documentation. A full physical examination was performed.

Laboratory tests included complete blood count, coagulation profile, serum biochemical tests and serum inflammatory markers and arterial blood gas test.

Descriptive analysis was used to illustrate population characteristics. Categorical variables were evaluated with Pearson's chi-square/Fisher's exact test, as appropriated. Continuous variables with Mann-Whitney test. A multivariate logistic regression was performed, aiming to investigate the association between symptom persistence (categorical) and demographic

factors (age, gender), comorbidity burden (by Charlson comorbidity index) and clinical severity of COVID-19 (as per WHO classification).

### **Patient consent statement**

Data collection was approved by the local Ethics Committee (17104\_oss). Patients' consent was obtained. The study was performed in accordance with the ethical principles of the Declaration of Helsinki and with the International Conference on Harmonization Good Clinical Practice guidelines.

### **RESULTS**

Between 20<sup>th</sup> May and 26<sup>th</sup> August 2020, 178 patients were potentially eligible for the 8-week follow-up review, of whom 71 presented at least one exclusion criteria (41 residents of health care facilities, 7 patients re-admitted to hospital, 3 already followed in other outpatients' services, 20 refused or did not answer). In addition, seven patients died after discharge. One hundred patients (41% female, median age 67.5, IQR 56-78.5) consecutively performed the post-discharge follow-up visit. Baseline characteristics and data on COVID-19-related hospitalization of the 100 patients are reported in detail in Table 1. In brief, 12/100 (12%) and 47/100 (47%) experienced severe and critical COVID-19, respectively; median hospital stay was 16 days (IQR 8-27), being 31/100 (31%) admitted to ICU. Most of the evaluated subjects received antiretrovirals 76/100 (76%) and/or hydroxychloroquine 88/100 (88%). Immune-modulator drugs (such as tocilizumab and ruxolitinib) and high dose steroids (methylprednisolone equivalent  $\geq 1\text{mg/kg/day}$ ) were used in 48/100 (48%) and 26/100 (26%) cases, respectively; 90/100 (90%) required oxygen supplementation, including high flow nasal cannulae (7/100, 7%), non-invasive ventilation (26/100, 26%) and mechanical ventilation (21/100, 21%).

At the time of the follow-up visit, a median of 60 days (IQR 48-67) after hospital discharge, 84/100 (84%) had at least one persistent symptom, and 36/100 (36%) reported more than two symptoms. More frequent symptoms were fatigue (46%), dyspnea (30%), insomnia (26%), anosmia (20%), dysgeusia and palpitation (15%). Unusual symptoms, such as visual disorders (11%), hair loss (8%) and impaired hearing (6%) were also reported. Other

neurological disorders included mental confusion (10%), peripheral neuropathies (5%) and vertigo (3%). Furthermore, 4% of patients had psychological symptoms, such as anxiety and depression (Figure 1).

The persistence of symptoms was not associated with COVID-19 severity (83% vs 85% in patients with mild/moderate vs severe/critical disease, respectively,  $p=0.807$ ), nor with ICU admission (84% vs 84% in ICU vs non-ICU admitted patients, respectively,  $p=0.981$ ), nor with length of hospital stay (16 vs 13.5 days, in patients with or without persistent symptoms, respectively,  $p=0.559$ ) (Table 2).

Likewise, no statistical difference was observed between patients with or without symptom persistence, by gender, frequency of comorbidities (including hypertension, diabetes, chronic obstructive pulmonary disease, coronary heart disease, chronic kidney disease and obesity), and median Charlson comorbidity index. By multivariate analysis, only age was associated with an increased risk of symptom persistence (OR 1.09 for each one-year increase, 95% CI 1.02-1.16) (data not shown).

Some of them required hospital readmission (10/100, 10%). Causes for hospital readmission included cardiac disease, such as heart failure and myocardial infarction ( $n=5$ ), infectious diseases ( $n=2$ ), respiratory symptoms ( $n=1$ ) and neurologic disorders ( $n=2$ ). Overall, 14 patients (14%) experienced an infection during the post-discharge period, including urinary tract infections, skin and soft tissue infections and *Clostridioides difficile* colitis. Nineteen (18%) presented rectal colonization with multidrug resistant bacteria (vancomycin-resistant *Enterococcus* spp. and/or carbapenem-resistant *Enterobacterales*) during the hospital stay, with a higher risk in more severe patients (16/59, 27%) in comparison with milder cases (3/41, 7%,  $p=0.010$ ) and ICU admitted patients (11/31, 35%) in comparison with non-ICU patients (8/69, 12%,  $p=0.016$ ) (Table 2).

No significant alteration was observed in the median values of the blood test (Table 2). Among them, 22% (22/100) and 14% (14/100) showed persistence of elevated C-reactive protein and ferritin, respectively. Thirteen (13%) patients presented high D-dimer values ( $> 1000$  ng/mL). None presented respiratory failure ( $pO_2 < 60$  mmHg). Fifteen patients (15/100, 15%) were discharged with long-term oxygen therapy (LTOT), 5 of whom (5/100, 5%) were



still on LTOT at the time of the follow up visit (2 were already on LTOT before SARS-CoV-2 infection).

## DISCUSSION

We analysed clinical and laboratory results from the follow-up review of 100 COVID-19 patients, a median sixty-day after hospital discharge. At the time of the visit, a high percentage of patients (84%) complained one or more persistent symptom. Similar findings have been observed in recent studies, based on face-to-face reviews or telephone/web surveys, on both COVID-19 inpatient and outpatient populations [6-8, 13-14]. In our study, persistence of symptom was not related with COVID-19 severity, ICU admission, nor length of hospital stay. Among demographic and clinical characteristics, only increasing age resulted independently associated with a higher risk of SARS-CoV-2 infection sequelae. Moreover, in most cases symptoms were not accompanied by blood test abnormalities, since median values of lymphocyte count, D-dimer and inflammation markers resulted in range, and abnormal results occurred in a minority of patients. Fatigue was the most frequent self-reported symptom (46%). Persistent fatigue has been already reported as a common sequela following SARS-CoV-2 infection, raising concern that SARS-CoV-2 has the potential to trigger a post-viral chronic fatigue syndrome, similarly to other infectious diseases [15]. In the same study, post-viral fatigue was associated with female gender and a pre-existing diagnosis of depression/anxiety, while no correlation was observed with the severity of initial SARS-CoV-2 infection, nor with inflammatory biomarkers abnormalities.

Available data suggested that chronic sequelae are not limited to more severe COVID-19 cases. The results of a multistate telephone survey in US confirmed that return to baseline health after COVID-19 can take a long time, even in young adults with milder diseases and no chronic condition [13]. Age, female gender, obesity and burden of comorbidities have been variously identified as predictors of long-term symptom persistence during follow up assessment performed from few weeks to 6 months after the acute illness [7, 16-17].

Hospital readmission after an initial COVID-19 hospitalization was experienced in 10% of patients in our population. A large nationwide U.S. study, including more than 100 000 electronical records of COVID-19 patients' hospitalization, found a 9% of readmission to the same hospital within 2 months of discharge [18]. The odds of hospital readmission increased

with age, and in presence of chronic conditions, such as COPD, heart failure, diabetes, CKD and obesity. In our study, heart failure and other cardiac conditions accounted for half hospital re-admission within the 8-weeks post-discharge period, including an 82-year-old man diagnosed with heart failure and referred to the Emergency Room precisely during the follow-up visit. Moreover, at least one case of sudden death due to heart attack was recorded close to the follow-up visit in a 70-year-old man with previous history of CHD. Although it is hard to definitely establish whether these events are due to direct or indirect effects of COVID-19, rather than concurrent complications of underlying conditions, more information about burden and risk factors for COVID-19 patients' readmission are important to inform both clinical practice and public health decisions [19-20]. However, post-discharge cardiopulmonary manifestations, such as dyspnea, palpitations and chest pain, require a careful consideration, especially in elderly patients with multiple comorbidities. The wide range of reported symptoms reflects the multi-organ involvement of COVID-19, mediated by direct tissue damage, hyperinflammation condition and COVID-19 related coagulopathy. A number of symptoms reported in our study, like chemosensory dysfunction, insomnia, mental confusion, vertigo, belong to the neuropsychiatric sphere. SARS-CoV-2 tropism for central nervous system (CNS), likely due to the widespread angiotensin-converting enzyme 2 (ACE2) expression in the brain tissue, has been documented [21]. Long-term neurological sequelae in patients with previous SARS-CoV-2 infection will be fully understood only in the next months, when longitudinal assessments will be performed.

In addition, several patients complained unusual symptoms, like visual disorders, impaired hearing and hair loss. Vision and hearing impairment may be part of peripheral nervous system manifestations [22]. A high frequency of male pattern hair loss among patients hospitalized for COVID-19 patients has been observed in Spain, suggesting that androgen expression might be a clue to COVID-19 severity [23]. Albeit they are not life-threatening conditions, they can affect overall patients' well-being, and functional status.

Finally, 14% of patients had an infectious event after discharge. Immune system damage induced by SARS-CoV-2 infection, treatment with steroids and other immune-suppressant drugs and longstanding hospitalization exposed the patients to a high risk of infectious complications, which continues after hospital discharge. As a further element of concern, a significant rate of rectal colonization by MDR bacteria was detected in our population (19%),

especially those admitted to ICU. Considering that in 2019 the overall rate of rectal colonization by MDR bacteria in our hospital amounted to 14.4% (personal communication by Elisabetta Mantengoli, MD, Infectious and Tropical Diseases Unit, Careggi University and Hospital, Florence, Italy), it may be speculated that COVID-19 pandemic negatively influenced infection control practices.

Our study has some limitations. Only hospitalized patients were candidate for the follow-up review in our outpatient clinic, while no data were collected from COVID-19 outpatients. Moreover, due to the cross-sectional nature of the analysis, information about post-discharge symptoms resolved before the visit were missed. Finally, the study reflected an early follow-up review, limited to clinical and laboratory assessment. Further information, necessary to better characterize the burden and the pathogenesis of possible chronic sequelae, will be obtained from future radiological and functional testing, including chest radiograph, spirometry, exercise testing, echocardiogram, in addition to any other specialist evaluation, to be selected case-by-case. Future studies may also confirm the real frequency of unusual symptoms reported in our study, and may provide new insights into their pathogenesis.

## NOTES

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**Table 1.** Baseline characteristics and data on COVID-19-related hospitalization of the studied population (n=100 patients)

Baseline Characteristics	Total (n=100)
Gender female, No. (%)	41 (41%)
Age, years	
- median (IQR)	67.5 (56-78.5)
- range	24-90
Charlson comorbidity index, median (IQR)	3 (1-4)
- Hypertension, No. (%)	50 (50%)
- Diabetes	21 (21%)
- COPD	12 (12%)
- CHD	12 (12%)
- CKD	7 (7%)
- Obesity	25 (25%)
Length of hospital stay, median (IQR), days	16 (8-27)
Time for microbiological cure*	27 (14-44)
Treatments, No. (%)	
- antiretrovirals (LPV/r, DRV/c)	76 (76%)
- hydroxychloroquine	88 (88%)
- remdesivir	9 (9%)
- immune-modulators	48 (48%)
- high dose steroid ( $\geq 1$ mg/Kg 6-MP)	26 (26%)
- antibiotics	49 (49%)
ICU admission, No. (%)	31 (31%)



<b>Highest oxygen supplementation, No. (%)</b>	
- No support	<b>13 (13%)</b>
- Standard oxygen therapy	<b>33 (33%)</b>
- High flow nasal cannulae	<b>7 (7%)</b>
- Non-invasive ventilation	<b>26 (26%)</b>
- Mechanical ventilation	<b>21 (21%)</b>
<b>COVID-19 severity (WHO), No. (%)</b>	
- mild	<b>9 (9%)</b>
- moderate	<b>32 (32%)</b>
- severe	<b>12 (12%)</b>
- critical	<b>47 (47%)</b>
<b>Follow-up timing, median (IQR), d</b>	
- Days since symptoms onset	<b>82 (70-101)</b>
- Days since hospital discharge	<b>60 (48-67)</b>
- Days since microbiological cure	<b>50 (36-66)</b>

\* time from the first positive to the first negative nasopharyngeal swab  
 Legend: IQR: interquartile range, ICU: intensive care unit; WHO: World Health Organization; COPD: chronic obstructive pulmonary disease; CHD: coronary heart disease; CKD: chronic kidney disease.

**Table 2.** Clinical and laboratory findings at the follow-up review in the studied post-acute COVID-19 population (n=100 patients)

Persistent symptoms	Total (n=100)	Mild to moderate (n=41)	Severe to critical (n=59)	p- value	Non ICU (n=69)	ICU (n=31)	p- value
<b>No</b>	<b>16 (16%)</b>	7 (17%)	9 (15%)	0.807	11 (16%)	5 (16%)	0.981
<b>Yes</b>	<b>84 (84%)</b>	34 (83%)	50 (85%)		58 (84%)	26 (84%)	
<b>Symptoms No. (%):</b>							
- 0	<b>17 (17%)</b>	7 (17%)	10 (17%)	0.342	11 (16%)	5 (17%)	0.362
- 1- 2	<b>47 (47%)</b>	16 (39%)	31 (53%)		30 (43%)	17 (59%)	
- >2	<b>36 (36%)</b>	18 (44%)	18 (30%)		28 (41%)	7 (24%)	
<b>Post-discharge Infectious diseases</b>	<b>14 (14%)</b>	5 (12%)	9 (15%)	0.665	9 (13%)	5 (16%)	0.681
<b>Rectal colonization</b>	<b>19 (19%)</b>	3 (7%)	16 (27%)	<b>0.018</b>	8 (12%)	11 (35%)	<b>0.005</b>
<b>Blood test at follow up</b>	<b>Reference values</b>				<b>median values (IQR)</b>		
- White blood cell, 10 <sup>9</sup> cells per L	4.0-10.0				6.65 (5.38-7.72)		
- Neutrophil count, 10 <sup>9</sup> cells per L	1.5-7.5				3.98 (3.13-5.84)		
- Lymphocyte count, 10 <sup>9</sup> cells per L	0.5-5.0				1.84 (1.47-2.22)		
- Platelet count, 10 <sup>9</sup> cells per L	140-440				239 (194-290)		
- ALT, U/L	10-50				15 (12-21)		
- creatinine mg/dL	0.7-1.2				0.9 (0.8-1.1)		
- D-dimer, mg/L	<500				444 (302-816)		
- C-reactive protein, mg/L	0-5				4 (4-5)		
- Serum ferritin, µg/L	30-400				152 (69-276)		
- Lactate dehydrogenase, U/L	135-225				194 (174-219)		

**Figure 1.** Persistent symptoms reported among 100 post-acute COVID-19 patients a median of 60 days after hospital discharge.

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Figure 1

