Original Article

Long-COVID syndrome in hospitalized patients after 2 years of follow-up

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Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic affected many leading to higher mortality and morbidity worldwide. The post-COVID syndrome (PCS) is characterized by heterogeneous group of clinical manifestations which can frequently lead to a significant worsening in everyday life, working and social conditions.

Methods: We prospectively examined in a cohort of patients discharged from our hospital "Saint Andrea", Vercelli, Italy, from 10th March 2020 to 15th January 2021, with COVID-19 diagnosis during the first wave of pandemic the prevalence and characteristics of PCS after 2 years of follow-up.

Results: Overall included patients were 306; prevalence of PCS after 2 years was 43.8%; the fatigue assessment scale (FAS) evidenced that only 8.5% of patients suffered from a severe fatigue with important limitations. Most frequently observed symptoms/conditions were: fatigue (38.2%), breathlessness (19.3%), "brain fog" (29.7%), sleeping disorders (28.8%), post-traumatic stress disorder (29.4%), anxiety (39.9%); only 7.2% of patients resumed the work without limitations or rest period. In multivariate analysis intensive care unit (ICU) admission [odds ratio (OR) =3.950; 95% confidence interval (CI): 2.466–8.112; P=0.002], length of hospitalization (OR =1.855; 95% CI: 1.248–5.223; P=0.004) and nosocomial infections (OR =2.556; 95% CI: 1.443–5.292; P<0.001) were predictive of PCS at 2 years in the study population.

Conclusions: After 2 years of follow-up, the 43.8% of enrolled subjects suffered from the PCS, but only the 8.5% with severe limitations in everyday life. We expect these data to highlight the importance of clinical and non-clinical aspect following the PCS in hospitalized patients.

Keywords: Coronavirus disease 2019 (COVID-19); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); post-COVID syndrome (PCS)

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Introduction

Coronaviruses are a group of RNA viruses currently classified in the order *Nidovirales*. All the coronaviruses responsible for respiratory syndrome are β-coronaviruses (1,2). The coronavirus disease 2019 (COVID-19) due to the novel severe acute respiratory syndrome coronavirus

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2 (SARS-CoV-2) emerged as global pandemic as reported by the World Health Organization (WHO) on the 11th March 2020 and quickly become a global health emergency (3). Main clinical manifestations in the acute phase of viral infections were respiratory, cardiovascular and multi-organ involvement (4); however, in the last two years, several studies highlighted persistence of multiorgan dysfunction after hospital discharge in patients with acute COVID-19 (5). Post-viral systemic sequelae were observed also after other coronavirus diseases such as the Middle East respiratory syndrome coronavirus (MERS) and the severe acute respiratory syndrome coronavirus (SARS) (6), and acute COVID-19 (7-10). As reported in these studies, the most frequent symptoms were: fever, fatigue, breathlessness, headaches, cough, cognitive blunting ("brain fog"), anxiety and depression, muscle pains, arthralgias, paraesthesias, etc. (7,11). Risk factors, severity grade of presentation and duration of the post-COVID-19 syndrome (PCS) are currently subjects for discussion; in some studies the symptoms' severity and duration were related to the patients' clinical characteristics or hospitalization course: admission in the intensive care unit (ICU), need of mechanical ventilation, comorbidities, older age, etc. (12), but with variables findings in different populations (13); this may depend by the higher heterogeneity among the various studies involving subjects with different illness severity and follow-up period. Because of this, a novel definition of PCS according to the time of follow-up and the duration of symptoms was recently proposed: acute-PCS, within 12 weeks after hospital discharge, long-PCS between 12–24 weeks and persistent-PCS after 24 weeks (14). This approach maybe interesting because could allow to distinguish the real PCS from non-specific symptoms mainly related to the hospitalization and more frequent in the first time of follow-up; the persistence of PCS after 12–24 weeks, on the other hand, can be more correlated with the immunological consequence due to the "viral trigger" of SARS-CoV-2 infection (15).

The main purpose of this study was the analysis of prevalence and the risk factors of PCS in a cohort of hospitalized patients with a long-term follow-up (2 years) after hospital discharge. We present this article in accordance with the STROBE reporting checklist (available at https://jphe.amegroups.com/article/view/10.21037/jphe-22-66/rc).

Highlight box

Key findings

- COVID-19; SARS-CoV-2; post-COVID syndrome; antiviral therapy.

What is known and what is new?

- Post-Covid syndrome affects about 20–40% of infected subjects, but clinical data at longer time of follow-up are not currently reported.
- At 2 years of follow-up, about 40% of enrolled subjects was affected by the post-COVID syndrome; only 8.5% had severe limitations in everyday life.

What is the implication, and what should change now?

- Long-COVID is a clinical challenge also after 2 years of follow-up. Early intervention and treatment of viral infection should be the optimal approach.

Methods

Study design and definitions

We conducted a prospective study including all patients with diagnosis of COVID-19 hospitalized from 10th March 2020 to 15th January 2021 at our center of infectious diseases at "Saint Andrea Hospital", Vercelli, Italy, and followed in our "post-COVID ambulatory" for at least 2 years after discharge. At the follow-up visit a structured interview was done to register global health status and clinical scores; demographic, clinical, laboratory and radiological data were obtained. All patients were included in this study after acceptance of study protocol and informed consent. The study protocol was approved by the local Ethics Committee: 'Comitato Etico Interaziendale ASL VC' (4/8/2020; Protocol number: 0026301). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all individual participants included in this study.

Study endpoints

The primary outcome of this study was the assessment of prevalence and severity of PCS in the enrolled patients after 6 months of follow-up period. The level of functional status and the severity of PCS were reported using the "post-COVID-19 functional status scale (PCFS)" defining the presence of significant PCS for values >2. Grade 0–1 was referred to the absence of limitations or presence of negligible limitations; grade 2 is related to mild limitations that do not affect the everyday life; grade 3–4 were referred to significant limitations in everyday life with important functional limitations (16). The Fatigue Assessment Scale

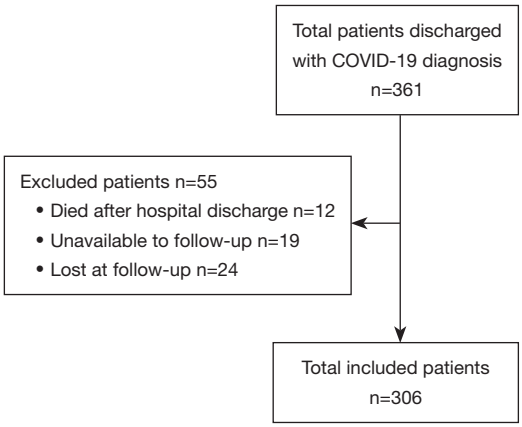

Figure 1 Flow-chart of the study. COVID-19, coronavirus disease 2019.

(FAS) was used to quantify the level of fatigue reported in the follow-up: the total score ranges from 10 to 50 points; 0–21: no fatigue; 22–34: mild/moderate fatigue; ≥35: severe fatigue (17). The Hospital Anxiety and Depression Scale (HADS) was used to identify patients with significant anxiety or depression disorders (cut-off ≥8) (18).

Statistical analysis

In descriptive statistics continuous variables were summarized as median [interquartile range (IQR): 25th to 75th percentiles]. Categorical variables were described as frequency and percentage. All data were assessed for normality using a Shapiro-Wilk test and categorical data were compared using a Mann Whitney or Kruskal-Wallis statistical test. To investigate continuous data, a Spearman Rank correlation was utilized. The association was calculated using the χ^2-test. Multivariate logistic regression analysis with stepwise forward selection was performed to evaluate the factors associated with the PCS presence, with P values of less than 0.05 as the criteria for model inclusion. All P values were two-tailed. P<0.05 was considered statistically significant. Statistical analyses were conducted by using SPSS software package ver. 28.0 (Chicago, IL, USA).

Results

Patients' selection and baseline characteristics

A total of 361 patients were discharged after hospital admission due to COVID-19 in the study period. Excluded subjects were 55 for the following reasons: 12 died after hospital discharge, 19 were unavailable to follow-up and 24 were lost at follow-up. Finally, 306 patients were included in the analysis (*Figure 1*). In the *Table 1* were described the baseline characteristics of the study population. Median age was 66.5 years; male patients were 225 (73.5%); obesity was observed in 44 subjects (14.4%); the most frequent comorbidities were cardiovascular diseases (27.1%), diabetes (49.3%), neurological diseases (16.7%) and chronic obstructive pulmonary diseases (COPD) (11.8%). Median time from the onset of symptoms and the hospital admission was 11.5 days; the median time of follow-up was 25.5 months. 178 subjects received continuous positive airway pressure (CPAP)/non-invasive ventilation (NIV) (58.2%), 81 needed of ICU admission (26.5%); median time of hospitalization was 14.5 days. Sepsis was observed in 54 (17.6%), nosocomial infections in 112 (36.6%); 169 were discharged at home (55.2%), 137 in long-term care facilities (44.8%). 14 patients (4.6%) were further re-hospitalized due to other clinical conditions.

Clinical outcomes

In the *Table 2* was described the overall follow-up evaluation in the study population; the PCS was diagnosed in 134 subjects (43.8%); according to the PCFS scale we observed 188 patients with score 0–1, 78 with score 2 and 40 with score 3–4. According to FAS we observed 189 subjects with no fatigue (61.8%), 91 (29.7%) with mild/moderate fatigue and 26 (8.5%) with severe fatigue.

The follow-up evaluation of clinical condition revealed that the most common symptoms were: fatigue (38.2%), headache (25.2%), breathlessness (19.3%), "brain fog" (29.7%), sleeping disorders (28.8%), anxiety (39.9%), stress disorders (29.4%), memory impairment (20.9%). Interstitial lung abnormalities were present in 38 patients (12.4%). In baseline working status of enrolled patients, we reported that 71 of them (23.2%) were employed at the time of hospital admission. At the follow-up visit 22 patients resumed the work without limitations (31%), 13 were jobless after hospital admission (18%), 19 had a reduced working ability (27%), 11 were retired after hospital discharge (16%) and 6 were late resumption of work (8%) (*Figure 2*). According to FAS and HADS score we reported in *Figure 3* the different values observed in patients with hospitalization time longer than 10 days, need of CPAP/NIV, need of ICU, presence of sepsis and nosocomial infections.

Table 1 Baseline characteristics of the study population

Characteristics	Values (N=306 patients)
Demographics	
Age (years), median (IQR)	66.5 (58.5–78.5)
Male, n (%)	225 (73.5)
BMI (kg/m^2), n (%)	
<25	71 (23.2)
25–30	191 (62.4)
>30	44 (14.4)
Ethnicity, n (%)	
Italian	281 (91.8)
East Europe	8 (2.6)
Asian	4 (1.3)
African	13 (4.2)
Smoking status, n (%)	
Current	81 (26.5)
Former	78 (25.5)
Never	147 (48.0)
Working status, n (%)	
Employed	71 (23.2)
Retired	181 (59.2)
Unemployed	54 (17.6)
Comorbidities, n (%)	
Cardiovascular disease	83 (27.1)
COPD	36 (11.8)
Chronic kidney disease	14 (4.6)
Diabetes	151 (49.3)
Neurological chronic disease	51 (16.7)
Psychiatric disease	31 (10.1)
Neoplastic disease	18 (5.9)
Immunological disease	8 (2.6)
Chronic liver disease	32 (10.5)
Days from the onset of symptoms to hospital admission, median (IQR)	11.5 (8.4–16.8)
Time of follow-up (months), median (IQR)	25.5 (21.0–30.5)
Outcomes and clinical features	
Days of hospitalization, median (IQR)	14.5 (9.6–31.8)
Need of CPAP/NIV, n (%)	178 (58.2)
Need of ICU admission, n (%)	81 (26.5)
Sepsis, n (%)	54 (17.6)
Nosocomial infections, n (%)	112 (36.6)
Discharged at home, n (%)	169 (55.2)
Discharged at long-term care facilities, n (%)	137 (44.8)
Need of oxygen at home, n (%)	227 (74.2)
Need of rehabilitation after discharge, n (%)	183 (59.8)
Need of rehospitalization after discharge, n (%)	14 (4.6)

IQR, interquartile range; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; ICU, intensive care unit.

Analysis of risk factors for the presence of PCS in the study population

Descriptive clinical variables were assessed in the univariate logistic regression: age, sex, BMI, ethnicity, smoking status, comorbidities, days from the onset of symptoms to hospital admission, length of hospitalization, presence of sepsis, nosocomial infection, need of ICU, need of CPAP/NIV. All variables with P<0.20 were evaluated in the multivariate logistic regression.

After multivariate adjustment the following parameters resulted independent predictors of PCS: ICU admission (OR =3.950; 95% CI: 2.466–8.112; P=0.002), length of hospitalization (OR =1.855; 95% CI: 1.248–5.223; P=0.004) and nosocomial infections (OR =2.556; 95% CI: 1.443–5.292; P<0.001).

Discussion

After 2 years of follow-up, a significant proportion of patients discharged after hospital admission due to

Table 2 Follow-up evaluation according to clinical and non-clinical conditions of enrolled patients

Follow-up evaluation	Subcategory	N (%) (n=306)
Overall PCS	–	134 (43.8)
Systemic symptoms	Fatigue	117 (38.2)
	Myalgias/arthralgias	14 (4.6)
	Fever	2 (0.7)
	Headache	77 (25.2)
Pneumological symptoms	Dyspnea/breathlessness	59 (19.3)
	Cough	21 (6.9)
	Chest pain	6 (2.0)
Neurological symptoms	“Brain fog”	91 (29.7)
	Dizziness	11 (3.6)
	Memory impairment	64 (20.9)
	Anosmia	44 (14.4)
	Ageusia/dysgeusia	24 (7.8)
	Peripheral neuropathy	23 (7.5)
Cardiovascular symptoms	Arrhythmias	49 (16.0)
	Pericarditis/myocarditis	9 (2.9)
	Myocardial infarction	4 (1.3)
Psychiatric symptoms	Sleeping disorders	88 (28.8)
	Post-traumatic stress disorder	90 (29.4)
	Anxiety	122 (39.9)
	Major depression	31 (10.1)
	Psychosis	4 (1.3)
	Behavior disorder	2 (0.7)
Other clinical conditions	Weight loss	24 (7.8)
	Hair loss	31 (10.1)
	Diabetes	40 (13.1)
	Hypertension	36 (11.8)
	Psoriasis	11 (3.6)
	Venous thromboembolism	10 (3.3)
	Thyroid dysfunction	17 (5.5)
Radiological characteristics	Interstitial lung abnormalities	38 (12.4)
Post-COVID-19 functional status scale	0–1	188 (61.4)
	2	78 (25.5)
	3–4	40 (13.1)
Fatigue assessment scale	10–21 (no fatigue)	189 (61.8)
	22–34 (mild/moderate fatigue)	91 (29.7)
	≥35 (severe fatigue)	26 (8.5)
Working status	Jobless after hospital admission	13 (4.2)
	Reduced working ability	19 (6.2)
	Retired after hospital admission	11 (3.6)
	Late resumption of work (>6 months)	6 (2.0)
	Normal resumption of work	22 (7.2)

PCS, post-COVID syndrome; COVID-19, coronavirus disease 2019.

COVID-19 in the first wave of pandemic was still affected by PCS. In facts, 43.8% of enrolled subjects suffered of PCS after 2 years of follow-up; in our previous study we reported that PCS was observed in 71% of patients at the first follow-up visit (1 month) and 45% at the second visit (6 months) (19). These data confirmed the main findings observed in other studies, with some different due to patient's enrollment, time of follow-up and PCS definition (20,21). However, the severity of different clinical symptoms was significantly lower at 2 years of follow-up as compared to 6 months and 1 year: only 13.1% of patients had a PCFS score >3, and 8.5% with severe fatigue assessment. Mild fatigue, "brain fog" and memory loss, anxiety and sleep disorders were finally the most prevalent observed symptoms. An interesting debatable point is the lack of agreement in the definition of PCS. Although several proposals were available, the most common description was the presence of COVID-19 related symptoms for more than three months after the diagnosis of SARS-CoV-2 infection or symptoms' onset (22). Different proposals as "chronic COVID syndrome, long-COVID, post-COVID, post-acute COVID" were based on symptoms' timing and their magnitude, with a relevant difference between PCS observed in hospitalized or non-hospitalized patients (14). In outpatients the diagnosis could be difficult due to the asymptomatic phase of infection or the lack of diagnosis by PCR. Furthermore, in the early phase of follow-up (within 6 months after discharge) most subjects suffered from an "acute-post-COVID syndrome", with higher prevalence of signs and symptoms mainly related to hospitalization: weight loss, myalgias, polyneuropathies, dysphonia, trouble walking, sleep disorders and psychiatric symptoms such as anxiety, depression and post-traumatic stress disorder that were frequently related to prolonged

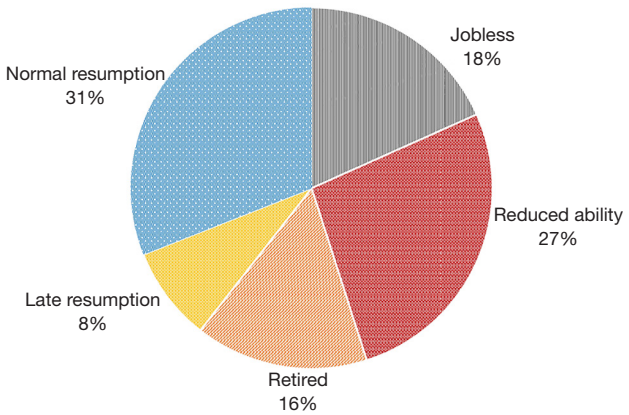

Figure 2 Working conditions in the follow-up.

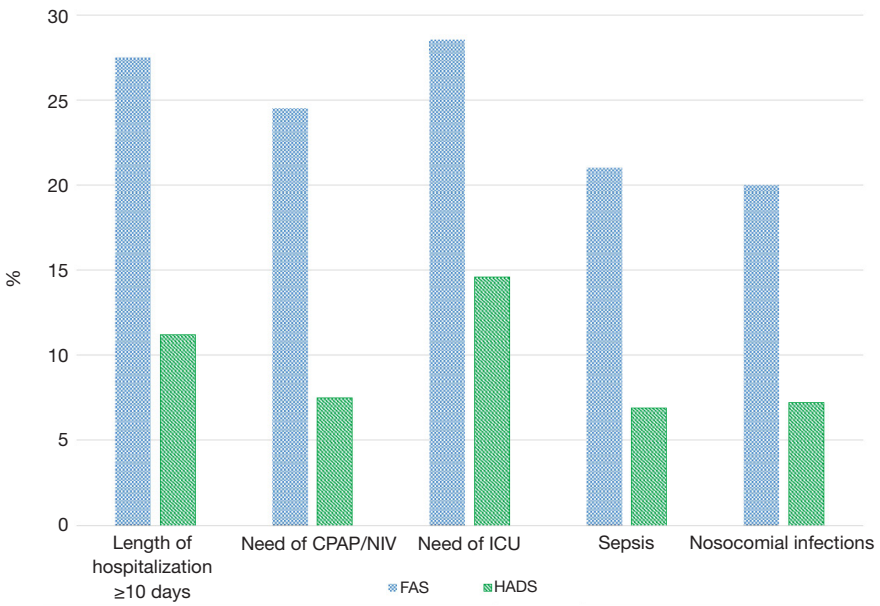

Figure 3 PCFS and HADS scores in patients with PCS. CPAP, continuous positive airway pressure; NIV, non-invasive ventilation; ICU, intensive care unit; FAS, fatigue assessment scale; HADS, Hospital Anxiety and Depression Scale; PCFS, post-COVID-19 functional status scale; COVID-19, coronavirus disease-2019; PCS, post-COVID syndrome.

isolation period and the "fear of death" experienced during the hospitalization. Other clinical manifestations as diabetes or hypertension were often consequent to the use of high dose of corticosteroids and CPAP/NIV. Although the frequency and duration of follow-up is currently not defined, a real "long-COVID or persistent-COVID" was referred to a longer time of follow-up (>1 year) and this condition was relevant both in clinical and non-clinical conditions in the overall limitation and worsening of everyday life. The pathophysiology was still unknown, involving a possible post-viral syndrome, especially for hearth (tachycardia, myocarditis, pericarditis), lung (dyspnea, cough, chest pain, breathlessness) and central nervous system ("brain fog", anosmia, ageusia, psychosis) or prolonged inflammation syndrome determinant in "fatigue syndrome", headache, autoimmune diseases, dizziness, fever, etc. In our study we observe that after 2 years of follow up fatigue (38.2%), breathlessness (19.3%), "brain fog" (29.7%), sleeping disorders (28.8%), post-traumatic stress disorder (29.4%) and anxiety (39.9%) were the most frequent clinical manifestations of PCS. Despite a severe limitation in everyday life was documented in only 8.5% of the patients, some of these symptoms had a negative impact on the quality of life mainly in non-clinical setting. Our analysis revealed that a condition of general and psychological distress due to viral infection, hospitalization and emotional consequences have a negative impact on the quality of life and related psychiatric symptoms such as anxiety, depression, and post-traumatic stress disorders; furthermore, the "brain fog" condition was mainly related to worsening in working ability, social relations and other activities. The working status at follow-up, surprisingly, revealed that only 7.2% of patients resumed the work after hospital discharge without reduced ability or need of rest period. This is a new data that we believe should focus the attention on this topic still little known and studied.

Our logistic regression showed that the ICU admission, nosocomial infection and the hospitalization time were the most important factor related to the PCS; interestingly, age and comorbidities were not predictive of PCS, that follows from the SARS-CoV-2 infection also in younger patients without other illness. Treatment of PCS was based on the symptoms management and rehabilitation (physical, psychological, and psychiatric) with a multidisciplinary approach including appropriate specialistic support. No specific pharmacology treatment is available for "brain fog" syndrome with cognitive impairment and more studies are needed to better understand the management of these conditions.

This study presents some strengths: follow-up time longer than most of previous studies, real-life intervention with clinical evaluation, blood test, radiographs and other relevant tests, analysis of both clinical and non-clinical aspects of PCS.

Main limitations of this study are: patients' selection based on the hospitalization, with a 26.5% of ICU admission, could represent a population with greater incidence of PCS than non-hospitalized subjects; the evaluation period of the first follow-up at 2 years included patients in the first wave of pandemic, with consequent more aggressive disease and less effective treatment and management: for these reasons the prevalence of PCS could be higher than in other waves.

Conclusions

Although the long-term follow-up of PCS is relatively new medical condition, after 2 years a significant rate of patients suffers from this syndrome, even if a small part of them is characterized by a severe limitation in everyday life. Working/social condition of patients and the "brain fog" syndrome required more attention in further studies.

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Footnote

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Conflicts of Interest: All authors have completed the

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study protocol was approved by the local Ethics Committee: 'Comitato Etico Interaziendale ASL VC' (4/8/2020; Protocol number: 0026301). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from all individual participants included in this study.

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