

First insights from patients presenting with long/post-COVID syndrome in primary care: an exploratory report

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Abstract

Background: Following the global pandemic of coronavirus disease 2019 (COVID-19), the long COVID or post-COVID syndrome refers to a relatively complex novel clinical entity. We conducted this study to assess the primary epidemiological features, main symptoms, and comorbidities probably related to this syndrome in patients referred to our long/post-COVID primary care unit during the initial months of its operation.

Methods and Material: This single-center prospective observational study was conducted between April 2022 and December 2022 and enrolled 71 patients (33 men, 38 women) who were examined due to persisting symptoms after recovering from COVID-19 infection, with the mean time of the first visit estimated at 3.12 ± 2.41 months from their acute COVID-19 illness. A thorough medical history, clinical examination, laboratory, and any other tests were performed on all patients when necessary.

Results: The most common symptoms of long/post-COVID reported were fatigue (63.4 %), a persistent cough (45.1 %), stress manifestations (42.3 %), arthralgia or myalgia (33.8 %), tachycardia (32.4 %), depression manifestations (29.6 %), exertional dyspnea (28.2 %), and sleep disorders (25.4 %). Hypertension (in about 40 %) and the presence of five or more symptoms during the acute COVID-19 illness (in approximately 52 %) could be regarded as factors increasing the long/post-COVID appearance. The long/post-COVID syndrome affects even patients not experiencing severe COVID-19 illness. Unvaccinated patients are at higher risk of severe COVID-19 ($p=0.014$), higher risk of hospitalization ($p=0.002$), and in higher need of respiratory support with high flow ($p=0.017$) when compared to vaccinated ones. Hospitalized patients appear to be older than outpatients (59 ± 12.42 vs 52.78 ± 11.48 years of age; $p=0.032$).

Conclusion: The long/post-COVID syndrome is an established clinical entity, and several clinical features, symptoms, and patient profiles have to be assessed from the initial medical contact in primary care to exclude early any other clinical conditions and offer guided therapeutic strategies to those patients. HIPPOKRATIA 2022, 26 (4):138-142.

Keywords: Primary care, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, coronavirus disease 2019, COVID-19, long COVID syndrome, post-COVID syndrome

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Introduction

Following the global pandemic of coronavirus disease 2019 (COVID-19), a novel clinical entity, the long COVID or post-COVID syndrome, was introduced, referring to a clinical condition characterized by a list of persisting or novel symptoms such as cough, shortness of breath, chest discomfort, cognitive disorders, fatigue, etc. which are manifested after the acute phase of COVID-19 and are not attributed to any other disease or clinical disorder¹. More specifically, two definitions according to time passed from the onset of illness have been proposed: i) the ongoing symptomatic COVID-19 for patients who are still symptomatic between four and 12 weeks after the acute phase of COVID-19, and ii) the long/post-COVID syndrome for people who still have symptoms for

more than three months after having been diagnosed with COVID-19^{2,3}.

The syndrome shows diversity among patients and cannot always be easily assessed. The significance of the involvement of primary care lies in the early diagnosis of this syndrome, patients' support, exclusion of other diseases, guided and personalized treatment, and, what is more, the prevention of potential socioeconomic consequences provoked by long COVID⁴⁻⁶. Therefore, the 3rd Health Regional Authority of Greece initiated the provision of post-COVID services in all health centers of its jurisdiction in March 2022. We conducted this study to register and assess the primary epidemiological features, main symptoms, and comorbidities probably associated with the manifestation of long/post-COVID syndrome in

patients referred in our long/post-COVID primary care special unit during the initial months of its operation.

Methods and Materials

This single-center observational study was designed as an open study to include all patients suffering from ongoing or new symptoms of COVID-19 at least four weeks after the initial infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The study was prospectively conducted between April 2022 and December 2022 and enrolled 71 patients (33 men, 38 women) who attended our long/post-COVID primary care unit and were examined for persisting symptoms after recovering from acute COVID-19 infection. All included patients fulfilled the appropriate criteria for enrollment, and the mean time of the first visit was estimated at 3.12 ± 2.41 months from their acute COVID-19 illness.

Per standard protocol, we obtained a detailed medical history by completing a designated questionnaire the 3rd Greek Regional Health Care Authority provided. Patients were questioned regarding the date of initial infection, their COVID-19 vaccination status, symptoms they suffered during infection, their illness's severity, and the need for hospitalization or high-flow respiratory support. All epidemiological markers and comorbidities synthesizing patients' profiles were recorded. According to the questionnaire, each patient provided information concerning their long/post-COVID symptoms. The intensity of those long/post-COVID symptoms was subjective and reported on a graded scale from zero to four.

All patients underwent a thorough and systematic clinical examination. Laboratory tests and imaging were utilized to exclude other clinical conditions except for COVID-19, which could be accountable for patients' symptoms, according to guidelines^{2,5}. When more precise testing or specialized consultation was required, patients were referred to the referral centers established by the 3rd Greek Regional Health Care Authority for this reason.

All patients provided written informed consent. The study was approved by the Scientific Committee of Primary Care of the 3rd Greek Regional Health Care Authority (decision No 8/2022, dated 23/08/2022) and was performed according to the Declaration of Helsinki guidelines.

Statistical analyses

Continuous variables are estimated and expressed as means with standard error, while categorical variables are presented as absolute values and percentages. We checked the normality of data distribution for those variables using the Shapiro-Wilk test. Accordingly, the Student's t-test, the Mann-Whitney U-test, Pearson's chi-square, and Fisher's exact test were utilized for the appropriate comparisons and associations of variables. The level of statistical significance was set at $p < 0.05$ with a corresponding 95 % confidence interval. The statistical analysis was performed with IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA),

and charts were constructed with Microsoft Excel 2010 (Microsoft Corp., Redmond, WA, USA).

Results

We prospectively enrolled and analyzed 71 patients with a mean age of 55.76 ± 12.26 (33 men, mean age: 58.91 ± 12.24 years; 38 women, mean age: 53.03 ± 11.77) years. Regarding the severity of the preceding acute COVID-19 infection, nine patients recovered from severe or very severe COVID-19 illness with arterial oxygen saturation (SaO_2) below 90 %, and 14 were hospitalized at the acute phase (six supported with high flow non-invasive ventilation).

Long/post-COVID syndrome symptoms at first medical attendance have been checked and reported per system according to the above-described questionnaire. Concerning general symptoms, none had a fever; 63.4 % of patients reported fatigue, 29.6 % pain, and 19.7 % weight loss. Respiratory system symptoms were frequently observed, as 45.1 % of patients reported cough, 19.7 % dyspnea, and 28.2 % exertional dyspnea. Cardiovascular symptoms included thoracic pain or chest discomfort in 15.5 % of patients and tachycardia/palpitations or postural tachycardia in 32.4 % and 22.5 %, respectively. Neurological or psychological symptoms included numbness, headache, brain fog, sleep disorders, memory disorders, depression, and stress manifestations (16.9 %, 16.9 %, 16.9 %, 25.4 %, 18.5 %, 29.6 %, and 42.3 %, respectively). Regarding musculoskeletal symptoms, apart from pain in general, 33.8 % complained about arthralgia or myalgia. Gastrointestinal symptoms included diarrhea in 5.6 % of patients, while nausea was not reported. Changes or loss of taste or smell were reported in 11.3 % and 7 %, whereas nobody reported nasal congestion. Skin disorders were expressed mainly by hair loss in 14.1 % of the patients, while itching was observed in a smaller percentage of 4.2 %, and nobody presented with skin rash. A decrescendo presentation of more frequent to less frequent symptoms is shown in Figure 1.

Regarding patients' profiles and comorbidities presumably related to the syndrome's occurrence, 52.1 % of patients reported more than five symptoms during the acute illness, such as cough, fever, shortness of breath, sore throat, myalgia, arthralgia, smell or taste disorders, etc. Approximately 7% of patients in our study's population were smokers, 39.4 % suffered from hypertension, and 7% from other cardiovascular diseases. Hyperlipidemia was reported by 43.7 % of the patients; 8.5% have been diagnosed with diabetes mellitus, 11.3 % with depression, and 5.6 % with chronic obstructive lung disease. Thyroid function disorders were reported by 15.5 %, rheumatic disorders by 5.6 %, and other comorbidities by 23.6 % of the patients (Figure 2). Moreover, the whole population was overweight, with a body mass index of $28.29 \pm 5.64 \text{ kg/m}^2$ ($28.29 \pm 5.64 \text{ kg/m}^2$ in men and $28.46 \pm 5.17 \text{ kg/m}^2$ in women).

Thirty-nine of the patients enrolled in the study had been vaccinated before the infection (two to three doses),

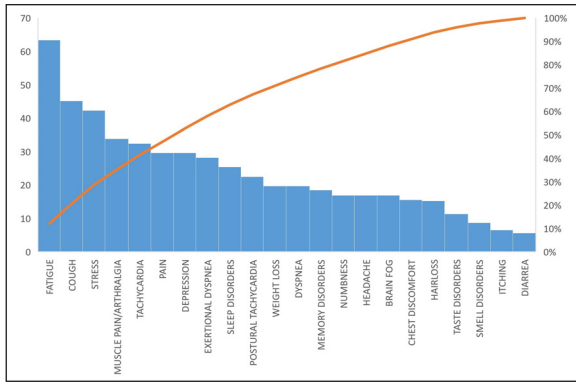


Figure 1: In a decrescendo presentation, the percentage of patients' long/post-COVID symptoms at first medical attendance in the primary care long/post-COVID special unit.

while 32 received zero to one dose of the COVID-19 vaccine. The unvaccinated patients appeared to be at higher risk of severe illness during the acute phase of COVID-19 ($p = 0.014$), higher risk of hospitalization ($p = 0.002$), and a higher need for respiratory support with high flow ($p = 0.017$) when compared to vaccinated patients. Hospitalized patients tended to be older than outpatients, 59 ± 12.42 vs 52.78 ± 11.48 years, respectively ($p = 0.032$).

Discussion

The long/post-COVID syndrome affects not only patients who have been hospitalized but also outpatients, even those who have not suffered from a severe disease from SARS-CoV-2 in the acute phase^{3,7-9}. A similar observation was made in our study as out of the 71 patients referred to our unit, $3.12 (\pm 2.41)$ months after acute COVID-19, only nine recovered from severe or very severe illness (as indicated by arterial oxygen saturation levels, presence of lung disease, or need for hospitalization) and only 14 were ultimately hospitalized. The remainder of the patients recovered from mild or moderate disease; more specifically, they were neither hospitalized nor experienced desaturation during acute illness.

A multisystem involvement with a great variety of symptoms, with different duration, persisting or first appearing, at least four weeks after COVID-19 infection, probably with outbreaks and recessions and even in the absence of specific laboratory or radiological findings, could contribute to the manifestation of syndrome^{3,10,11}. Most of these symptoms are usually attributed to immunologic and inflammatory mechanisms persisting after recovery from COVID-19 infection¹². Before establishing the diagnosis of long/post-COVID, attending physicians should always exclude other medical conditions potentially responsible for those symptoms. Moreover, symptoms should be carefully investigated and not be attributed to anxiety easily as such effortless diagnosis may not be accurate nor helpful to the patients¹³.

The most common symptoms described in recent research in this field are fatigue¹⁴, cough, dyspnea or exer-

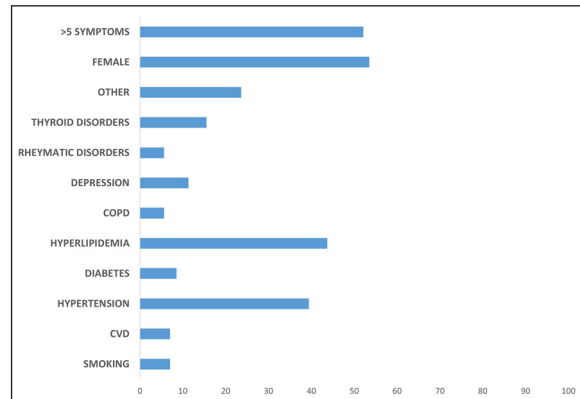


Figure 2: Patients' profile and percentage of comorbidities probably related to long/post-COVID syndrome. CVD: cardiovascular disease, COPD: chronic obstructive lung disease.

tional dyspnea, arthralgia or myalgia, tachycardia, cognitive disorders¹⁴, loss of smell or taste, depression manifestations¹⁵, gastrointestinal malfunctions, skin disorders, etc.^{1,2,5,9,13,16}. In agreement with existing literature^{14,17,18}, the most common symptoms reported in our study were fatigue (63.4 %) and persistent cough (45.1 %). We herein report in high percentages the presence of stress manifestations (42.3 %), arthralgia or myalgia (33.8 %), tachycardia (32.4 %), depression manifestations (29.6 %), exertional dyspnea (28.2 %), and sleep disorders (25.4 %) (Figure 1), as also described in large studies, reviews or meta-analyses in this field^{19,20}.

Other cardiopulmonary, gastrointestinal, neuromuscular, or neurological symptoms, as well as from the sensory organs, have been reported^{1,20}. Concerning the cardiopulmonary system, in our small sample, we did not detect any pulmonary fibrosis, pulmonary hypertension, pericarditis, or myocarditis¹⁷ as appropriately investigated with computed tomography, echocardiography, or clinical and functional tests performed in our long/post-COVID primary care unit or at the referral centers. It must be noted, though, that in cases of severe respiratory disorders or psychiatric manifestations, patients were referred to relevant medical specialties not readily available in our primary care facility for the appropriate evaluation and treatment needed.

Taste or smell disorders (sensory loss or diminution) were recorded in a small percentage of our long/post-COVID patients, 11.3 % and 7 %, respectively (Figure 1). That could be attributed to the widespread prevalence of specific SARS-CoV-2 variants, reported being less related to such disorders, during our study's patient enrollment period. What is more, no patient in our sample complained about nasal congestion.

Many factors are potentially related to the manifestation of long/post-COVID syndrome¹². It is considered that older age, female gender, obesity, pre-existing comorbidities, and most frequently hypertension or diabetes mellitus, as well as the number of initial symptoms during COVID-19, are related to an increased risk of long/post-COVID syndrome^{16,21}. Moreover, hypercho-

lesterolemia and its effect on endothelial dysfunction are important factors to manage²². In our study, hypertension was reported in approximately 40 % of patients with long/post-COVID, while hyperlipidemia in 44 %, followed by other comorbidities. A crucial risk factor seems to be the number of symptoms during the acute phase of COVID-19²¹. Five or more symptoms during acute COVID-19 illness were reported by 52.1 % of our patients, and such a finding could serve as an independent risk factor that could predict the probability of long covid-19 syndrome after even a mild illness from SARS-CoV-2 (Figure 2).

Finally, an important finding of the current study concerns the value of vaccination before COVID-19 onset. Relevant research has noted that vaccination with an mRNA COVID-19 vaccine is correlated to a lesser degree to COVID-19 hospitalization, disease severity, and progression to mechanical ventilation need or death²³. Interestingly, in our study, 39 of the 71 enrolled long/post-COVID patients were fully COVID-19 vaccinated, and this high percentage could be attributed to the fact that fully vaccinated patients are more likely to seek medical assistance when presenting with symptoms as those patients generally adopt a more responsible and careful attitude in health care issues. This recorded benefit of COVID-19 vaccination in our study is in agreement with recent relevant research²³, as complete vaccination with two or three doses of the SARS-CoV-2 vaccine seems to protect vaccinated compared to unvaccinated patients from severe disease ($p = 0.014$), hospitalization during acute COVID-19 infection ($p = 0.002$), and need of respiratory support with high flow ($p = 0.017$). These vaccination benefits could be of interest, especially to older patients. Age seems to be an independent risk factor of disease severity⁷; we found that hospitalized patients appear to be older than outpatients (59 ± 12.42 vs 52.78 ± 11.48 years; $p = 0.032$).

Limitations

Even though the 3rd Greek Regional Health Care Authority initiated in March 2022 the provision of post-COVID services in all health facilities of its jurisdiction and provided appropriate instructions to healthcare professionals, the various units and referral centers varied regarding the commencement of this service and involved medical specialties. Moreover, many doctors were not aware of the definition of the long/post-COVID syndrome, patients were not properly informed regarding its symptoms, and only a portion of them attended/were referred to the long/post-COVID units. Therefore, our study was designed as a single-center, and our sample was limited.

This small sample does not allow further subgroup analysis (age, gender). The small number of events within subgroups could probably result in misleading information or effects attributed to chance. For the same reason, reported symptoms have been counted in terms of their existence, as analysis by quantification could lead to a

great distribution of results in too small groups.

Pre-consultation selection bias might occur due to existing comorbidity, which leads patients to be more aware and seek medical care. Furthermore, the SARS-CoV-2 variants that infected our study's patients have not been verified with laboratory tests, and symptoms related to different variants could display remarkable diversity in long/post-COVID syndrome expression. Nonetheless, during the study period, the sub-variants of the omicron dominated, probably leading to similar symptoms and consequences.

In conclusion, the long/post-COVID syndrome remains challenging for clinical physicians to assess. Clinical features, symptoms, and the patient's profile or comorbidities must be considered carefully to recognize the syndrome's presence, exclude any other causal factors and offer guided therapeutic options to patients¹⁹. All these should be precisely performed even at first medical attendance, and there lies the critical role of primary health care^{24,25} in the early recognition and diagnosis of the syndrome, in patients' guided advice and treatment, and in referring them to more specialized centers when required.

Summarizing primary health care's objectives towards long/post-COVID syndrome, those would be the following²⁶: i) COVID-19 requires in-hospital care, continuing care, and community-based care; primary care physicians ii) have to use specific tools for thorough screening and assessment of symptoms related to long/post-COVID syndrome; iii) organize patients' rehabilitation strategy and guide their transition between care units; iv) provide the appropriate educational resources and self-management advice to patients and health care providers. All those could commence from the first medical attendance to primary care. Undoubtedly, a greater vigilance among primary care healthcare professionals, better public awareness, and faithful adherence to established protocols by all long/post-COVID centers could lead to more representative data, cooperation among all units, and the conduction of multicenter studies that are favorable to health care systems and patients' treatment^{25,26}.

Conflict of Interest

Authors declare no conflicts of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgment

In the electronic version of the paper, the designated questionnaire supplied by the 3rd Greek Regional Health Care Authority is provided as supplementary material.

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