

The prevalence and clinical spectrum of post-Covid syndrome in patients with rheumatic diseases: a single-center experience

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SUMMARY

Post-coronavirus disease (COVID) syndrome (PCS) is a term used to describe the clinical condition of patients who have recovered from COVID-19 but are still experiencing prolonged effects of infection or persistent symptoms for longer than expected. Although PCS has been previously studied in the general population, it has not been investigated in a specific population of patients with inflammatory rheumatic disease (IRD). This study aims to evaluate the presence and frequency of PCS among our rheumatology outpatients.

This is a cross-sectional study of patients with IRD whose symptoms persisted for 12 weeks after the detection of COVID-19 infection. The patients were assessed with a survey form during their routine clinic follow-up or by contacting them by phone. Patients' demographics, diagnosis, medication, comorbidities, outcome of COVID-19, and symptoms related to PCS were collected.

Fifty-three patients with IRD and COVID (mean age: 48.5±13.99 years, 71.7% women) were included. PCS was observed in 36 (67.9%) patients. Twenty-two (41.5%) of them had three or more symptoms; 14 (26.4%) had one or two symptoms. Although more than 30 symptoms were detected, the most frequent were fatigue and weakness. No significant relationship was detected between the development of PCS and gender, age, disease duration, presence of COVID-related complications, and the need for oxygen support, except for smoking which showed a protective effect ($p=0.008$).

PCS was detected in more than half of the patients. There was no independent risk factor for the development of PCS, except smoking.

Key words: COVID-19; post COVID-19 syndrome; rheumatology; long COVID; inflammatory rheumatic disease.

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INTRODUCTION

In February 2020, the World Health Organization reported that the median time from onset to clinical recovery for mild COVID-19 was approximately 2 weeks, and for patients with severe or critical COVID-19, this period varied from 3 to 6 weeks (1). However, over time, it was discovered that a proportion of COVID-19 related symptoms persisted for weeks or even months in some patients. As experience and clinical evidence increased about COVID-19, new terms, such as 'long COVID', 'post-acute COVID-19', and 'post-COVID syndrome' (PCS) have been

added to the literature (2-4). Persistent symptoms of SARS-CoV-2 infection can be associated with many health problems, such as fatigue, dyspnea, chest pain, cough, headache, cognitive impairment (brain fog), arthralgia, myalgia, sleep disturbance, depression, or anxiety (5). These symptoms can be one or more, permanent, temporary, or can modify over time and impair the quality of life.

There are several different definitions of prolonged COVID-19 in the recent literature. The National Institute for Health and Care Excellence guideline defines three categories based on the duration of symptoms: acute COVID-19 infection (0-4

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weeks), ongoing symptomatic COVID-19 (4-12 weeks), and PCS (>12 weeks and exclusion of alternative diagnoses) (6).

The present data investigating the incidence of persistent symptoms after COVID-19 infection are highly heterogeneous. Accepted definitions and symptom durations are variable, and patient characteristics include a wide spectrum, such as outpatients, inpatients in the ward, or in the intensive care unit. As a result, the definitions of the investigated symptoms and signs are different in each study. Additionally, it is unclear why prolonged symptoms develop. Moreno-Pérez *et al.* reported that baseline clinical features and development of PCS were unrelated (7). The majority of the studies investigating the incidence of PCS focus on the general patient population, while, to our knowledge, no studies investigating patients with inflammatory rheumatic disease (IRD) have been published in the literature. Prolonged COVID and IRD symptoms are quite similar, and it is essential to distinguish between the two conditions to plan the treatment properly. This study aims to investigate the presence and frequency of post-COVID symptoms among our rheumatology outpatients.

■ MATERIALS AND METHODS

This study is a cross-sectional study conducted in the Division of Rheumatology, Department of Physical Medicine and Rehabilitation of Gazi University Hospital and approved by Clinic Research Ethical Committee of the university and General Directorate of Health Services of Turkey. The participants were informed about the research and gave written informed consent.

Among 320 patients followed up with IRD in our rheumatology outpatient clinic, we have detected 53 patients with COVID-19 infection between July 2020 and February 2021. COVID-19 infection was determined by: i) a positive real-time polymerase chain reaction (RT-PCR) test result in the previous 3 months; ii) clinical history suggestive of COVID-19 infection; and/or iii) chest computed tomography (CT) findings com-

patible with COVID-19. We have further assessed these 53 patients for a possible post-COVID syndrome with a survey form either during their routine clinic follow-up or by contacting them by phone between April to July 2021.

Demographic characteristics of the patients (age, gender, body mass index, occupation, educational status, smoking, diagnosis, duration of disease, medications, and comorbidities) were recorded.

The time of COVID-19 infection, its symptoms, the results of the RT-PCR/antibody test/rapid antigen test, the results of chest CT, treatments for COVID-19, the length of hospitalization if required, the presence of COVID-19-related complications, oxygen support, and noninvasive mechanical ventilation/intensive care support were recorded.

Symptoms, such as fatigue, weakness, arthralgia, myalgia, headache, fever, hot flashes, dyspnea, palpitations, sore throat, runny nose, cough, diarrhea, nausea/vomiting, weight loss, loss of smell or taste, vision or hearing problems, chest pain, exercise intolerance, hair loss, rash, depression, anxiety, and sleep problems were investigated for 12 weeks after the onset of COVID-19. The diagnosis of an exacerbation of the rheumatic disease after the first three months from COVID-19 infection was based on symptoms, physical examination, imaging, and test results used in routine clinical care.

For the descriptive analysis, the mean, median, standard deviation, interquartile range and frequency were used. The Kolmogorov-Smirnov test was used to determine normal distribution. Mann-Whitney U test and independent *t*-test were used to compare continuous variables. The Chi-square test was used to compare categorical variables. All statistical analyses were performed using IBM SPSS Statistics 21 software, and *p*-values <0.05 were considered significant.

■ RESULTS

In this study, 53 patients with COVID-19 (38 women) with a mean age of 48.5±13.99

Table I - Demographic characteristics, diagnoses, and treatments of the patients with rheumatic diseases recruited for the survey on post-COVID syndrome.

Number of patients	53
Female, n (%)	38 (71.7)
Male, n (%)	15 (28.3)
Age (years) (mean±sd)	48.5±13.99
Education (years) (median) (min-max)	8 (0-16)
BMI (kg/m ²) (mean±sd)	28.1±5.63
Smoking, n (%)	
- Active	10 (18.9)
- Non-smoker	43 (81.1)
Occupation n (%)	
- Officer	7 (13.2)
- Retired	4 (7.5)
- Private sector	10 (18.9)
- Self-employment	3 (5.7)
- Housewife	27 (50.9)
- Student	2 (3.8)
Comorbidities n (%)	
- Hypertension	18 (33.9)
- Diabetes	6 (11.3)
- Cardiovascular disease	4 (7.5)
- Pulmonary disease	11 (20.7)
- Malignancy	1 (1.9)
- Liver disease	1 (1.9)
- Renal disease	2 (3.8)
Rheumatological diagnosis n (%)	
- Rheumatoid arthritis	10 (18.9)
- Spondyloarthropathy	16 (30.2)
- Connective tissue diseases	10 (18.9)
- Familial Mediterranean fever	8 (15.1)
- Vasculitis	7 (13.2)
- Gout	1 (1.9)
- Sarcoidosis	1 (1.9)
Disease duration (months) (median) (min-max)	84 (6-372)
Medications	
csDMARD	
- MTX/LEF/SSZ monotherapy	12 (22.6)
- Combination therapy	3 (5.7)
- Hydroxychloroquine	8 (15.1)
Corticosteroid	14 (26.4)
Azathioprine	5 (9.4)
Mycophenolate mofetil	1 (1.9)
tsDMARD	1 (1.9)
Biologic DMARDs n (%)	
- Adalimumab	1 (1.9)
- Infliximab	2 (3.8)
- Golimumab	2 (3.8)
- Etanercept	2 (3.8)
- Rituximab	1 (1.9)
Non-steroidal anti-inflammatory drugs	13 (24.5)
Colchicine	13 (24.7)

years were analyzed. There were ten cases of rheumatoid arthritis (RA); sixteen of spondyloarthropathy (SpA); ten of connective tissue disease; eight of familial Mediterranean fever (FMF); seven of vasculitis; one of gout, and one of sarcoidosis. The median disease duration was 84 months. A total of 15 (28.3%) patients were on conventional synthetic disease-modifying antirheumatic drugs (DMARDs; methotrexate, leflunomide, sulfasalazine); eight (15.1%) patients were on biological DMARDs; 14 (26.4%) patients were on glucocorticoids; eight (15.1%) patients received hydroxychloroquine; five patients were on azathioprine; one patient was on targeted synthetic DMARD; and one patient was on mycophenolate mofetil treatment. Twenty-seven (51%) patients had at least one comorbid disease. Table I shows the clinical and demographic characteristics of the patients. Forty-nine (92.5%) patients had symptomatic COVID-19, and 12 (22.6%) patients required hospitalization due to COVID-19. There were no patients requiring intensive care admission. The majority (81.1%) of patients received antiviral therapy. Six (11.3%) patients received antibiotic therapy for secondary bacterial infection. Oxygen support was required in seven (13.2%) patients. In 36 (67.9%) patients, at least one symptom associated with PCS was detected 3 months after the onset of COVID-19. Twenty-two (41.5%) patients had three or more symptoms, whereas 14 (26.4%) had one or two symptoms. The most common symptoms were fatigue and weakness. Table II shows the characteristics of patients with COVID-19, and Figure 1 shows the distribution of PCS-related symptoms. Rheumatological disease flare was observed in 14 (26.4%) patients within 12 weeks of COVID-19 diagnosis, in four patients with rheumatoid arthritis, namely FMF attack in two patients, exacerbation of SpA in two patients, newly diagnosed interstitial lung disease in one patient with RA, arthritis flare-up in two patients with psoriatic arthritis and one with undifferentiated connective tissue disease, acute anterior uveitis in one patient with SpA, and exacerbation of polymyalgia rheumatica in

one patient already diagnosed with giant cell arteritis.

Smoking habit was significantly less frequent in patients developing PCS (p=0.008). There was no difference in terms of gender, age, disease duration, ongoing treatments, presence of COVID-related complications, nor the need for oxygen support in the groups with and without PCS. Table III shows the characteristics of patients with or without PCS.

DISCUSSION

In this study, we investigated the frequency of PCS and associated symptoms in patients with IRD. Approximately, 68% of our patients had at least one symptom suggestive of PCS. The most common symptoms were weakness and fatigue. A rheumatological disease flare was observed in about a quarter of patients after COVID-19. While some of these exacerbations occurred after discontinuation of their rheumatological treatment during COVID-19, others were spontaneous exacerbations.

In a systematic review and meta-analysis evaluating the long-term effects of COVID-19, at least one effect persisted in 80% of patients for 2 weeks following acute infection, and 55 different features including symptoms, signs, and laboratory parameters have been reported (5). The most common symptoms reported were fatigue, headache, attention disorder, hair loss, and dyspnea (5). In a post-acute COVID-19

Table II - Characteristics of patients with COVID-19 infection.

COVID-19 infection n (%)	
- Symptomatic	49 (92.5)
- Asymptomatic	4 (7.5)
PCR + n (%)	51 (96.2)
COVID-19 distribution by months	
July 2020	1
August 2020	1
September 2020	12
October 2020	11
November 2020	6
December 2020	5
January 2021	9
February 2021	8
Pneumonia	12 (22.6)
Hospitalization	12 (22.6)
Hospitalization time (day) (median)(min-max)	7 (2-17)
Antiviral therapy	43 (81.1)
Secondary bacterial infection	6 (11.3)
Oxygen supplementation	7 (13.2)
Rheumatological treatment status	
- Continue	36 (67.9)
- Interrupt	13 (24.5)
Post-COVID syndrome	
1 symptom	4 (7.5)
2-3 symptoms	10 (18.9)
>3 symptoms	22 (41.5)
Flare of inflammatory rheumatic disease	14 (26.4)

study conducted in Italy, it was reported that at least one symptom, especially fatigue or dyspnea, persisted in 87.4% of hospitalized patients at a mean follow-up of 60 days from the onset of COVID-19 (8). Another single-center study showed that most patients had persistent symptoms

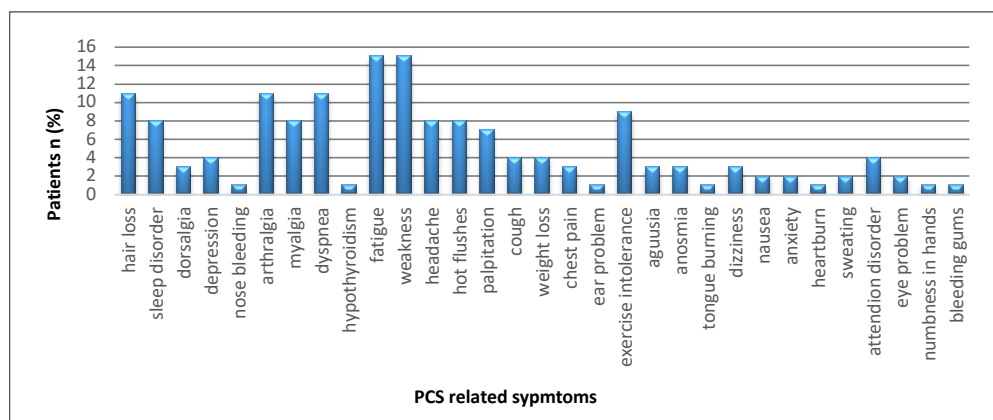


Figure 1 - Distribution of post-COVID syndrome related symptoms.

Table III - Comparison of demographics and clinical features between patients with and without post-COVID syndrome.

	PCS+ (n: 36)	PCS- (n: 17)	p value
Sex, female, n (%)	29 (80.6)	9 (53)	0.053
Age, years (mean±sd)	50.8±12.7	43.6±15.7	0.180
Smoking	3 (8.3)	7 (41.2)	0.008
Disease duration (months) (mean±sd)	115.9±94.7	71.1±52.5	0.127
COVID-19 related complication	6 (16.7)	0	0.085
Oxygen supplementation	7 (19.4)	0	0.082
Corticosteroids	11 (30.6)	3 (17.6)	0.259
csDMARD	13 (36.1)	2 (11.8)	0.103
bDMARD	3 (8.3)	5 (29.4)	0.094

PCS+, patients with post-COVID syndrome; PCS-, patients without PCS; sd, standard deviation.

even 110 days after they were discharged from the hospital. In addition, no statistically significant differences regarding symptoms were reported in a study comparing hospitalized patients who needed intensive care vs. those who did not (9). We detected at least one PCS-related symptom in approximately 68% of patients who were followed up in our rheumatology outpatient clinic. This rate does not seem to be higher than the frequency of PCS in the general population. The most frequent symptoms were fatigue, weakness, hair loss, arthralgia, myalgia, dyspnea, and exercise intolerance. These symptoms are quite similar to the symptoms in many patients followed up with IRD in the rheumatology outpatient clinic, and it is challenging to distinguish whether it is related to PCS or to a possible flare of the underlying rheumatic disease (10).

A multistate health care systems network reported that patients with severe COVID-19, as well as those with mild COVID-19 who were followed in outpatient clinics, took weeks to return to their usual health within 2–3 weeks of testing (11). Furthermore, it was shown that older age, presence of multiple chronic medical conditions, and underlying chronic psychiatric conditions were associated with a delayed return to normal health (11). In a prospective cohort study, 277 patients who had mild or severe COVID-19 were evaluated 10–14 weeks after the onset of COVID-19.

Post-acute COVID-19 syndrome was detected in 50.9% of the patients. No correlation was found between the persistence of symptoms and the patients' baseline clinical features or COVID-19 features in the global cohort including patients with severe or mild pneumonia and without pneumonia. However, the extension of pulmonary involvement and high heart rate at admission were found as risk factors in the severe pneumonia group (7). Similarly, in our study there was no association between the development of PCS and age, gender, duration of rheumatic disease, presence of COVID-19-related complications, or the need for oxygen support, while PCS was found to be significantly less common in smokers. Contrary to our study Mahmoud et al reported that smoking significantly correlated with the occurrence of PCS (12). The reason why PCS was less common in smokers may be a type 1 error due to our small sample size. Eventually, it is still unclear who may develop PCS and which conditions are risk factors for PCS development.

Aside from the variety of symptoms associated with PCS, it appears to affect multiple organ systems, which is thought to be associated with multiple factors. Potential mechanisms might be viral and host factors. Several studies show that some patients infected with COVID-19 fail to clear the virus successfully for a long time (13–14). In a study involving 203 patients, it

was found that after 90 days, 5.3% of those tested remained positive for SARS-CoV-2 via RT-PCR nasopharyngeal testing (14). Several studies have found that the development of mutations in the virus conferring resistance to neutralizing antibodies or spike protein mutations that evade HLA-restricted cellular immunity facilitate the development of persistent SARS-CoV-2 in non-immunocompetent individuals (15-17). Another factor is that the virus may dysregulate the host immune response, causing reactivation of previously encountered pathogens and leading to new clinical symptoms as a result of infecting new body areas (18). Immunosuppression in the host, impaired interferon response, microbiome/virome dysbiosis, long-term production of autoantibodies targeting vascular cell types, central nervous system compartments, connective tissue and extracellular matrix, and genetic variation in innate immune components are other factors that may cause persistent symptoms (18). In summary, many biological factors can contribute to the development of PCS. It has never been explored before whether having IRD is a risk factor for the development of PCS. According to our results, IRD does not seem to be a risk factor for PCS, since the prevalence of PCS found in our study was not different from that found in other populations.

The limitation of this study is that we could not evaluate the duration of PCS-related symptoms and their long-term results, as we evaluated patients cross-sectionally. Another limitation might be the small sample size. In future studies, there is a need to investigate the long-term follow-up results of PCS and whether having a rheumatological disease contributes to its pathogenesis.

■ CONCLUSIONS

PCS was observed in 68% of patients with IRD in our study, no significant risk factor for PCS was found except smoking, which showed a protective effect. As a result, while evaluating the symptoms of patients followed up in the rheumatology outpatient

clinic, it should be kept in mind that this condition may be associated with PCS besides disease flare.

Ethical statement

Ethics approval for this study was obtained from the Ethics Committee of Gazi University (approval number: 355). Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The material has not been published anywhere. The author of the manuscript has no financial ties to disclose and has met the ethical adherence.

Declaration of authorship

The authors have directly participated in the planning, execution, analysis, or reporting of this research paper. They have read and approved the final version of the manuscript.

Conflict of interest

The authors declare no competing interests.

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