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Post-COVID Syndrome: From the Perspective of Physiatrists

ABSTRACT

Objectives: The presence of various symptoms with a duration that exceeds the acute phase of coronavirus disease 2019 (COVID-19) is called post-COVID syndrome (PCS). This study aimed to evaluate the patients with PCS who applied to outpatient clinics of Physical Medicine and Rehabilitation (PMR).

Methods: This study included 70 patients who developed PCS after COVID-19 infection and 45 patients who recovered completely from the infection without ongoing symptoms related to the disease as a control group. The patients' demographic and clinical features were recorded. The signs in the acute phase of COVID-19 infection, the treatment content, location, duration, and persistent symptoms were recorded. The patients' kinesiophobia, anxiety-depression levels, and quality of life were evaluated.

Results: The study population consisted of 78 (67.8%) women and 37 (32.2%) men, with an average age of 48.88±12.89. The frequency of females was significantly higher in the PCS group than in the control group (p=0.024). The most common complaints reported by PCS patients were fatigue (64.3%), weakness (44.3%), myalgia (35.7%), and back pain (31.4%). PCS was significantly higher in patients hospitalized during the acute infection, those with COVID-19 pneumonia, and those with chronic diseases, especially hypertension. The kinesiophobia scores of patients in the PCS group were considerably higher than those of patients in the control group (p<0.001).

Conclusion: PCS appears to be related to the female gender and the severity of the acute disease. In this study, the most frequently reported persistent symptom by patients with PCS was fatigue, and back pain was the most common reason for admission to the PMR outpatient clinics.

Keywords: Anxiety, depression, long COVID, kinesiophobia, physical medicine and rehabilitation, post-COVID-19 syndrome

In 2020, the world faced an extraordinary and devastating experience due to the pandemic coronavirus disease 2019 (COVID-19). Millions of people have been infected, and more will continue to be infected in the protracted pandemic. Although most COVID-19 patients recover completely, some experience persistent symptoms months after recovery, and some may even develop new symptoms. This clinical condition that occurs after acute infection is defined as post-COVID-19 syndrome (PCS) (1). Acute COVID-19 was described as the presence of signs and symptoms of COVID-19 lasting up to four weeks, while ongoing symptomatic COVID-19 was described as the persistence of signs and symptoms lasting between four and twelve weeks; the presence of persistent symptoms and signs during or following acute infection lasting more than twelve weeks and not explained by another diagnosis was called PCS by the United Kingdom (UK) National Institute for Health and Care Excellence guidelines (2). Various terminologies have been proposed throughout the pandemic, including post-COVID-19 condition, long COVID, and long-haul COVID. Although different descriptions have been proposed, PCS is accepted as symptoms that persist for three months from the onset of COVID-19 infection, or the beginning of new symptoms or fluctuations after the acute infection, and cannot be explained by another diagnosis (3). The estimated prevalence of PCS ranges from 9% to 63% (4). The most commonly reported PCS symptoms include fatigue, headache, dyspnea, musculoskeletal pain, sleep disturbances, and cognitive impairment (5). PCS mainly requires at least one of the symptoms listed above. Among the most frequently reported musculoskeletal symptoms and signs are fatigue, myalgia, arthralgia, back pain, energy loss, muscle weakness, sarcopenia, impaired exercise capacity, and low physical performance (6). Dyspnea, reduced exercise capacity, and lower limb strength lead to poor quality of life in post-COVID-19 individuals (7). The adverse effects of COVID-19 on

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health, including psychological and physical deterioration, continue to be reported during the prolonged COVID-19 pandemic. However, the available knowledge of PCS, especially musculoskeletal manifestations, is still insufficient. Therefore, this study aimed to describe the frequent clinical characteristics of PCS from the perspective of physiatrists regarding musculoskeletal system problems and evaluate measures of kinesiophobia, depression, anxiety, and quality of life in individuals after experiencing COVID-19.

METHODS

Study Design and Patients

This study was designed as a cross-sectional study and was carried out between November 2021 and May 2022 in the outpatient clinics of a state hospital's PMR Department. The study protocol followed the principles of the Declaration of Helsinki, and the local ethics committee approved the study (decision no: 2021.06.15, date: 16.09.2021). Inclusion criteria were patients admitted to the PMR outpatient clinics with PCS symptoms after recovering from COVID-19, whose diagnosis was confirmed by positive nasopharyngeal reverse transcriptase-polymerase chain reaction (RT-PCR) test results, or who had a thorax computed tomography scan showing features of COVID-19 pneumonia although with negative PCR testing; they had to be older than 18 and volunteer to participate in the research. Exclusion criteria included being newly diagnosed with COVID-19 and therefore in quarantine at home or hospitalized for treatment; having suspected COVID-19; being pregnant. Inclusion criteria for non-PCS controls included having recovered completely from COVID-19 without any residual symptoms, being at least three months post-COVID-19 infection, being older than 18, and volunteering to participate in the research. Exclusion criteria for controls were physical or mental disability, acute or chronic infection, other health problems, or being in quarantine for acute COVID-19. Sociodemographic characteristics of the patients and clinical features, details of acute COVID-19 infection, content, location, and duration of the treatment, and persistent symptoms at follow-up were recorded.

Kinesiophobia

To evaluate the patients' fear of movement, known as kinesiophobia, the Tampa Scale of Kinesiophobia (TSK) was used. The scale includes 17 items concerning injury or re-injury in work-related activities, anxiety, and avoidance. Each item is scored on a 4-point Likert-type scale, from 1 (strongly disagree) to 4 (totally agree). The total score ranges from 17 to 68, with higher scores indicating an increased level of kinesiophobia. A cut-off score for a high degree of kinesiophobia is defined as >37 points by Vlaeyen et al. (8). The reliability and validity studies of the Turkish version of the scale were conducted by Tunca Yilmaz et al. (9).

Anxiety and Depression

To determine the patients' levels of anxiety and depression, the Hospital Anxiety and Depression Scale (HADS) was employed. The scale consists of 14 items with two subscales, seven for anxiety and seven for depression. Each item is scored from 0-3, and each subscale is scored from 0 to 21. A score of ⩾8 defines anxiety and depression. The validity and reliability studies of the Turkish version of the scale were carried out by Aydemir et al. (10).

Quality of Life

To assess the patients' quality of life, the Short Form-12 (SF-12) was utilized. This questionnaire contains 12 items across eight subdimensions: physical functioning (2 items), role-physical (2 items), bodily pain (1 item), general health status (1 item), vitality (1 item), social functioning (1 item), role-emotional (2 items), and mental health (2 items). Each item is scored on a 0-4 Likert-type scale. The total Physical Component Summary (PCS-12) score is calculated by summing the scores of general health, physical functioning, role-physical, and bodily pain subdimensions, and the total Mental Component Summary (MCS-12) score is calculated by summing the scores of social functioning, role-emotional, mental health, and vitality subdimensions. The PCS-12 and MCS-12 subscales are scored from 0 to 100, with higher scores indicating a better health status. The validity and reliability studies of the Turkish version of the questionnaire were performed by Kütük and Soylu (11).

Statistical Analysis

The sample size was calculated using the G * Power (v3.1.7) program, with at least 45 patients required for each group with $\alpha = 0.05$, 95% power, and an effect size (d) of 0.701. All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0 software (IBM Corporation, Chicago, IL). The Shapiro-Wilk test was used for data distribution analysis. The collected data were expressed as frequency (%) for nominal and categorical variables, median (min-max) for non-normally distributed variables, and mean ± standard deviation (SD) for normally distributed variables. The independent sample t-test and Mann-Whitney U test were used to compare continuous and discrete variables, respectively. The Pearson chi-square and Fisher's exact tests were used to compare categorical variables. The Spearman correlation coefficient (r) was used to determine the correlation between kinesiophobia scores and anxiety-depression and quality of life scores. Correlation coefficients were interpreted as follows: 0-0.25 indicated a weak correlation, 0.25 to 0.50 a weak-to-moderate correlation, 0.50-0.75 a strong correlation, and 0.75-1 a very strong correlation. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Overall, during the study period, 115 patients with a mean age of 46.88±12.89 were included in this study. Patients were divided into two groups according to the presence or absence of PCS. The PCS group comprised 53 (75.7%) women and 17 (24.3%) men. The control group included 25 (55.6%) women and 20 (44.4%) men. The female frequency was significantly higher in the PCS group than in the control group (p=0.024), as seen in Figure 1. The general characteristics of the patients are summarized in Table 1. The admis-

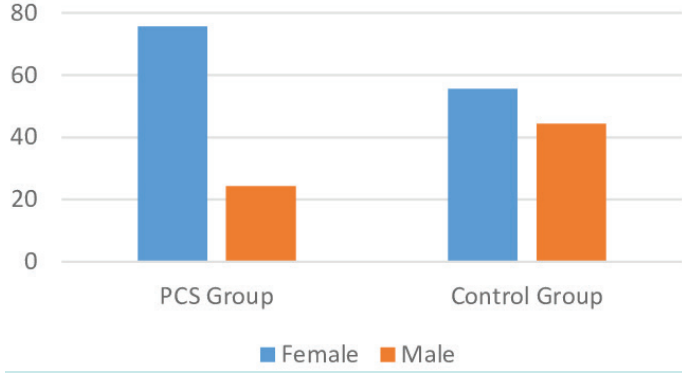

Figure 1. Gender distribution of the PCS and control group.

Table 1. General characteristics of patients

	Total (n=115)	PCS group (n=70)	Control group (n=45)	p
Age (years)	46.88±12.89	48.25±13.25	44.75±12.13	0.156
Gender				
Female	78 (67.8)	53 (67.9)	25 (32.1)	**0.024***
Male	37 (32.2)	17 (45.9)	20 (54.1)	
Education level				
Unschooled	4 (3.5)	4 (100)	0	0.306
Primary school	53 (46.1)	34 (64.2)	19 (35.8)	
High school	24 (20.9)	13 (54.2)	11 (45.8)	
University	34 (29.6)	19 (55.9)	15 (44.1)	
Occupation				
Student	2 (1.7)	1 (50)	1 (50)	0.432
White collar	26 (22.6)	15 (57.7)	11 (42.3)	
Blue collar	13 (11.3)	5 (38.5)	8 (61.5)	
Housewife	61 (53)	42 (68.9)	19 (31.1)	
Self-employment	2 (1.7)	1 (50)	1 (50)	
Retired	11 (9.6)	6 (54.5)	5 (45.5)	
Height (cm)	163 (145-181)	163 (145-181)	165 (149-176)	0.716
Weight (kg)	75 (49-120)	75 (49-120)	73 (50-114)	0.733
BMI (kg/m²)	26.9 (17-45.3)	27.65 (17.4-45.3)	26.3 (17.2-40)	0.068

Values are mean±SD (standard deviation), median (min-max), or percentage (n,%). *p values are statistically significant (p<0.05) and are shown in bold. PCS: Post-COVID-19 syndrome, BMI: Body mass index.

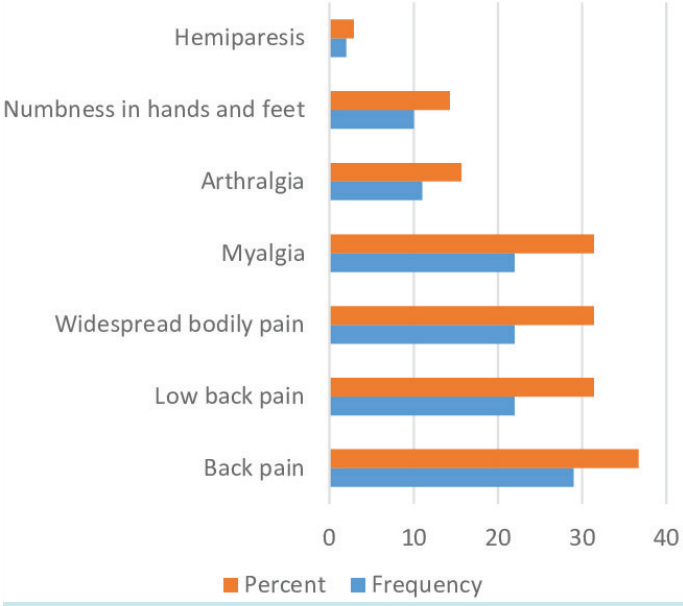

Figure 2. Admission reasons of the patients to the PMR outpatient clinics.

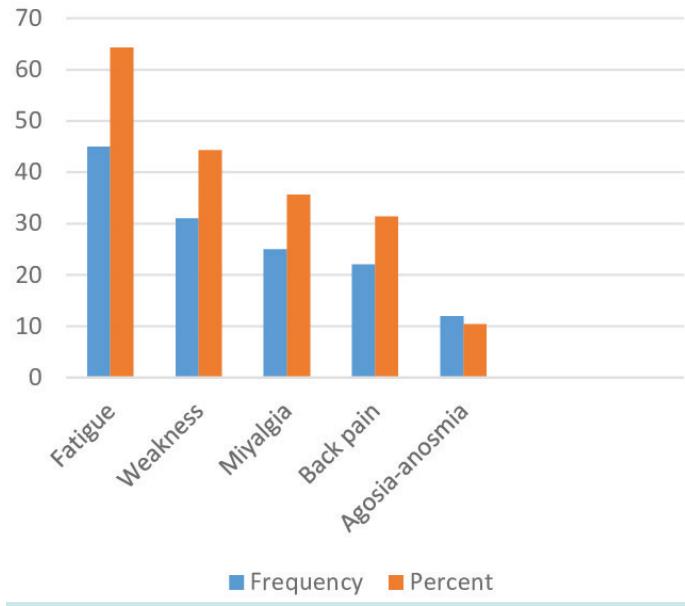

Figure 3. Frequency of most common persistent symptoms in patient with PCS.

sion reasons of patients with PCS to the PMR outpatient clinic were back pain (36.7%), widespread bodily pain (31.4%), low back pain (31.4%), myalgia (21.4%), arthralgia (15.7%), numbness in the hands and feet (14.3%), and hemiparesis (2.9%), as seen in Figure 2. The most common persistent symptoms in patients with PCS were fatigue (64.3%), weakness (44.3%), myalgia (35.7%), and back pain (31.4%), as seen in Figure 3. COVID-19-related features, including symptoms in the acute phase of SARS-CoV-2 infection (fever, cough, dyspnea, myalgia, anosmia, ageusia), the treatment content, location, duration, comorbidities, need for respiratory support, and mechanical ventilation are shown in Table 2. It was observed that the incidence of pneumonia and hospitalization was significantly higher in patients with PCS during the acute infection period than in the control group (p=0.002 and p=0.033, respectively). Among the symptoms seen during the acute COVID-19 infection period, shortness of breath and fatigue were observed significantly more frequently in the PCS group, while the duration of symptoms was longer in the PCS group (p=0.040, p=0.033, and p=0.020, respec-

Table 2. COVID-19-related features of the patients

n (%), Med (Min-Max)	Total (n=115)	PCS Group (n=70)	Control Group (n=45)	p
Symptomatology				
Throat ache	107 (93)	41 (59.4)	28 (40.6)	0.697
Headache	61 (53)	38 (62.3)	23 (37.7)	0.739
Rhinorrhea	57 (49.6)	35 (61.4)	22 (38.6)	0.907
Cough	90 (78.3)	56 (62.2)	34 (37.8)	0.573
Shortness of breath	27 (23.5)	21 (77.8)	6 (22.2)	**0.040***
Fever	55 (47.8)	34 (61.8)	21 (38.2)	0.842
Diarrhea	11 (9.6)	6 (54.5)	5 (45.5)	0.749
Anosmia-agnosia	43 (37.4)	29 (67.4)	14 (32.6)	0.264
Back pain	60 (52.2)	37 (61.7)	23 (38.3)	0.855
Myalgia	107 (93)	68 (63.6)	39 (36.4)	0.055
Arthralgia	39 (33.9)	26 (66.7)	13 (33.3)	0.362
Fatigue	109 (94.8)	69 (63.3)	40 (36.7)	**0.033***
Duration of symptoms (days)	10 (5-50)	10 (5-50)	10 (5-15)	**0.020***
Chronic disease				
Yes	52 (45.2)	41 (78.8)	11 (21.2)	**<0.001***
No	63 (54.8)	29 (46)	34 (54)	
Comorbidities				
Hypertension	17 (14.8)	15 (88.2)	2 (11.8)	**0.012***
Diabetes mellitus	19 (16.5)	14 (73.7)	5 (26.3)	0.210
Coronary heart disease	8 (7)	5 (62.5)	3 (37.5)	0.922
Hyperlipidemia	8 (7)	5 (62.5)	3 (37.5)	1.000
Thyroid dysfunction	8 (7)	7 (87.5)	1 (12.5)	0.146
COPD	1 (0.9)	1 (100)	0	1.000
CKD	1 (0.9)	1 (100)	0	1.000
Fibromyalgia	5 (4.3)	5 (100)	0	0.155
Smoking habits				
Smoker	16 (13.9)	11 (68.8)	5 (31.2)	0.586
Non-smoker	86 (74.8)	50 (58.1)	36 (41.9)	
Ex-smoker	13 (11.3)	9 (69.2)	4 (30.8)	
Time since COVID-19 (months)	5 (3-18)	5 (3-15)	6 (3-18)	0.684
SARS-CoV-2 RT-PCR test				
Positive	107 (93)	64 (59.8)	43 (40.2)	
Negative	8 (7)	6 (4.9)	2 (25)	0.479
Pneumonia				
Yes	37 (32.2)	30 (81.1)	7 (18.9)	**0.002***
No	78 (67.8)	40 (51.3)	38 (48.7)	
Treatment place				
Home	97 (84.3)	55 (56.7)	42 (43.3)	**0.033***
Hospital	18 (15.7)	15 (83.3)	3 (16.7)	
Treatment time (days)	5 (5-30)	5 (5-30)	5 (5-10)	0.279
Treatment agents				
Hydroxychloroquin	31 (27)	19 (61.3)	12 (38.7)	0.955
Favipiravir	71 (61.7)	45 (63.4)	26 (36.6)	0.483
Moxifloxacin	23 (20)	16 (69.6)	7 (30.4)	0.339
LMWH	20 (17.4)	17 (85)	3 (15)	**0.015***
Mechanical ventilation				
Yes	3 (2.6)	3 (100)	0 (0)	
No	112 (97.4)	67 (59.8)	45 (40.2)	0.279
Need of intensive care unit				
Yes	4 (3.5	4 (100)	0 (0)	
No	111 (96.5)	66 (59.5)	45 (40.5)	0.154

Values are mean±SD, median (minimum-maximum), or percentage (n, %) *p values are statistically significant (p<0.05) and are shown in bold. COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease.

Table 3. Kinesiophobia, anxiety-depression, and quality of life scores of patients

n (%), Med (Min-Max), Mean±SD	Total (n=115)	PCS Group (n=70)	Control Group (n=45)	p
HADS-Anxiety	7 (1-19)	8 (1-19)	6 (2-14)	0.119
HADS-Depression	6 (0-19)	6 (0-19)	5(1-10)	0.054
SF-12 PCS	38.44±9.16	38.50±9.29	38.33±9.08	0.921
SF-12 MCS	48.85 (20.47-63.27)	48.94 (20.47-63.27)	48.85 (22.75-63.27)	0.733
TKS	35.54±8.46	38.02±8.80	31.68±7.06	**<0.001***
TKS				
<37	64 (55.7)	30 (46.9)	34 (53.1)	**0.001***
>37	51 (44.3)	40 (78.4)	11 (21.6)	

Values are mean±SD, median (minimum-maximum), or percentage (n, %) *p values are statistically significant (p<0.05) and are shown in bold. HADS: Hospital anxiety and depression scale, SF-12: Short Form-12, PCS: Physical component score, MCS: Mental component score, TKS: Tampa kinesiophobia scale.

tively). In addition, the frequency of accompanying chronic diseases, especially hypertension (p=0.012), was significantly higher in the PCS group (p<0.001). The kinesiophobia scores of patients with PCS were significantly higher than those in the control group (p<0.001). There was no significant difference between the patients with and without PCS regarding anxiety and depression levels and quality of life scores, as shown in Table 3. Kinesiophobia levels showed a weak to moderate positive correlation with anxiety levels (r=0.258, p=0.005) and depression levels (r=0.397, p<0.001). Kinesiophobia levels also exhibited a weak but significant negative correlation with quality of life scores (for PCS r=-0.259, p=0.005; for MCS r=-0.231, p=0.013).

DISCUSSION

Findings from this study suggest that female gender, disease severity, hospitalization, pneumonia in acute infection, and comorbidities, especially hypertension, may be risk factors for PCS. The most frequent persistent symptom in patients with PCS was fatigue, and back pain was the most common admission reason to the PMR outpatient clinics. A high degree of kinesiophobia was observed in patients with PCS. However, quality of life and anxiety-depression levels were similar in patients with and without PCS.

COVID-19 infection has been reported to have equal prevalence in men and women, but male gender is a risk factor for higher disease severity and mortality (12). This study found a higher frequency of females in the PCS group than males. Peghin et al. (3) identified female gender as an independent risk factor for PCS six months after COVID-19 infection. Sudre et al. (13) reported that long-term COVID was associated with female gender, advanced age, and high body mass index. Poyraz et al. (14) found female sex and previous psychiatric disorders as related risk factors for PCS. Some studies have indicated that women have higher rates of long-term COVID-19 symptoms than men after hospital discharge (14-16).

Although a few studies reported that men are as likely to experience long COVID symptoms as women (17,18), female gender seems to have a higher risk for PCS manifestations. Immunological differences based on gender are thought to play a role in this disparity (19).

Fatigue was the most common persistent symptom in patients with PCS, and back pain was the most common admission reason to the PMR outpatient clinics. Fatigue is a common symptom during both the acute COVID-19 infection and the post-COVID period. Persistent fatigue has been reported in a significant minority of COVID-19 patients 16-20 weeks after symptom onset, ranging from 13% to 33% (20). Self-reported fatigue was the most typical complaint among a large group of long-COVID patients in a COVID symptom study (13). Cares-Marambio et al. (21) noted that fatigue and dyspnea were the most frequent symptoms of long-term COVID-19. Patients with back pain during the acute COVID-19 infection often had higher rates of pneumonia (22). The severity of acute COVID-19 infection, older age, smoking, and lower physical activity levels have been identified as risk factors for persistent musculoskeletal symptoms in patients recovered from COVID-19 (23).

PCS prevalence was significantly higher in patients hospitalized during the acute COVID-19 infection, in those with COVID-19 pneumonia, and in those with chronic diseases, particularly hypertension. Chen et al. (24) reported that around 34% of non-hospitalized and 54% of hospitalized patients experienced symptoms post-acute phase of COVID-19. Muñoz-Corona et al. (25) observed that at least one symptom persisted 12 weeks after hospital discharge in 75.9% of patients. Among these patients, 6.38% had one symptom, 19.22% had two symptoms, and 60.28% had three or more. Román-Montes, et al. (26) reported a 76% prevalence of PCS in hospitalized Mexican patients with severe or critical COVID-19. Nasserie T, et al. (27) found that 72.5% of hospitalized patients experienced at least one ongoing symptom post-acute infection. Previous studies identified female gender, high body mass index, older age, hospitalization, prolonged immobilization, need for mechanical ventilation, and comorbid disorders such as hypertension as risk factors for PCS (4,27-29). Smoking, severe COVID-19, lower oxygen saturation upon admission, and extensive lung involvement were also linked to an increased frequency of PCS (26).

The mechanisms underlying the development of PCS and PCS-related musculoskeletal signs are not yet fully understood. In the literature, one hypothesis is that changes in viral load and prolonged inflammatory responses of the human immune system may contribute (3,30). A positive outcome indicates the eradication of infection by the immune response while providing resistance to re-infection. Conversely, a weak immune response with the persistence of viral triggers may promote a chronic phase of

the disease (31). However, current data on the immune response to SARS-CoV-2 infection and its relationship with PCS need further clarification. Huang et al. (15) observed decreased seropositivity and median titers of neutralizing antibodies compared to the acute phase in patients six months after hospital discharge, but they could not establish a connection to PCS due to limited serological data. Additionally, some studies have suggested that SARS-CoV-2 variants may pose an additional risk for PCS after COVID-19. One such study by Antonelli et al. (32) found that individuals infected with the delta variant had a higher risk of PCS than those with the omicron variant.

This study found that kinesiophobia scores in patients with PCS were significantly higher than in the control group. Kinesiophobia levels had a weak but significant positive correlation with anxiety (r=0.258, p=0.005) and depression (r=0.397, p<0.001) levels. They also had a weak but significant negative correlation with quality of life scores (for PCS r=-0.259, p=0.005; for MCS r=-0.231, p=0.013). Kinesiophobia, the fear of movement, contributes to the chronicity, persistence, and exacerbation of pain (33). Herrero-Montes et al. (34) reported that nearly 57% of patients with post-COVID pain exhibited potential kinesiophobic behavior. Higher kinesiophobia levels are associated with decreased physical activity (35). Studies have also shown that older men with post-COVID-19 sarcopenia experienced kinesiophobia (36,37).

This study observed poor quality of life scores, especially in the physical component subdimensions in the SF-12, in all patients with and without PCS. However, there was no significant difference in quality of life scores between the patients with and without PCS. Muñoz-Corona et al. (25) studied patients 90 days after discharge and reported that 75.9% of PCS patients had poor scores, especially in the physical and general health subdimensions in SF-36. The authors also reported that patients with joint pain, fatigue, and dyspnea had lower scores than patients without those symptoms. A recent meta-analysis showed that 58% of the post-COVID-19 patients had reported poor quality of life. In the same analysis, the poor quality of life was considerably higher among post-COVID-19 patients with ICU admission and fatigue (30). In many patients, persistent symptoms may result in them reducing their work hours or quitting altogether, which can increase their financial distress (38).

Limitations

This study has several limitations. First, it was a single-center study with a small sample size, introducing potential selection bias; it relied on self-reported patient symptoms and cross-sectional surveys, which may introduce information bias. Secondly, the cross-sectional design does not allow for follow-up data at different times. Thirdly, kinesiophobia, anxiety, and depression levels may interact and possibly affect other body systems. Further research is required to understand the risk factors causing PCS.

CONCLUSION

In conclusion, PCS appears to be associated with the female gender, the severity of the acute illness, and comorbidities, especially hypertension. In this study, the most frequently reported persistent symptom in patients with PCS was fatigue, and back pain was the most common reason for admission to the PMR outpatient clinics. Kinesiophobia levels were higher in patients with PCS than in those without. Future research is necessary to clarify the risk factors that contribute to PCS and to develop the best treatment strategies.

Ethics Committee Approval: This study was conducted with the permission of the Kırıkkale University Faculty of Medicine Local Ethics Committee (decision no: 2021.06.15, date: 16.09.2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Z.T.B., C.U., E.Ü.A.; Design – F.B.U., Z.T.B., Z.K.Ü.; Supervision – E.Ü.A., Z.T.B.; Data Collection and/or Processing – Z.T.B., F.B.U., C.U., Z.K.Ü; Analysis and/or Interpretation – F.B.U., Z.T.B., E.Ü.A.; Literature Search – Z.T.B., C.U., F.B.U.; Writing – Z.T.B.; Critical Review – E.Ü.A.

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