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Factors associated with post-covid syndrome 3 months after covid-19 diagnosis

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Abstract

Factors associated with post-covid syndrome 3 months after covid-19 diagnosis

Objective: Post-COVID Syndrome has been defined as a syndrome with chronic fatigue and psychiatric problems continue after COVID-19. In this study, it was aimed to evaluate patients' health-related quality of life standards 3 months after COVID-19 diagnosis.
Method: In this study, the psychosocial status and quality of life standards of patients, who were older than 18 years old and followed up due to COVID-19 in the outpatient clinic, ward, or intensive care unit of a university hospital, were assesed by the short form-36 scoring system.
Results: Of 67 patients, 57 were followed up and treated at home, nine were admitted to the ward, and one was admitted to the the intensive care unit. Short form-36 test scores of women patients, patients aged over 65, had at least one comorbid disease, and inpatient treatments during acute infection were found to be statistically significantly lower.
Conclusion: Gender, advanced age, presence of comorbidity, and history of hospitalization were determined as risk factors for Post-COVID Syndrome.
Keywords: COVID-19, Health-related quality of life, Long COVID, Post-acute COVID-19 syndrome, Symptom assessment.

INTRODUCTION

Even most of the patients experience symptoms such as fever, cough, and weakness in COVID-19, it may be fatal for some patients due to acute respiratory distress syndrome and multiple organ dysfunction syndrome (1). Post-COVID Syndrome (PCS) has been defined as a syndrome in which chronic physical and mental problems continue after COVID-19 (2). In many studies, it has been proven that symptoms observed in this syndrome can range from mild to severe enough to be unable to work and reducing the quality of life (QOL) (3,4). These symptoms include fatigue, headache, muscle and joint pain, shortness of breath, depression, sleep disorders, and anxiety disorders (5). In a review of eighteen studies, the most common symptom was found as fatigue in PCS. Depression was observed in 23% and anxiety in 22% of the patients. These symptoms were followed by memory and sleep problems (6). In a study conducted in Italy, in which patients were evaluated 7 weeks after discharge, it was observed that 97% of the patients had at least one symptom. The most common symptom was fatigue, and followed by shortness of breath and joint pain (1).

According to the literature, PCS is an extremely common problem. The mechanism behind PCS is not well understood, but it is assumed to be secondary to virus-specific pathophysiological changes, prolonged inflammatory response to acute infection, and sequelae of Post-Intensive Care Syndrome (3). We evaluated PCS with Short Form-36 (SF-36) questionnaire, which is widely acknowledged as the gold standard generic measure of health related QOL. SF-36 form is shown in Figure 1.

In this study, it was aimed to evaluate factors associated with PCS of patients, who were followed in the outpatient clinic, inpatient service, or intensive care unit of a university hospital 3 months after COVID-19 diagnosis.

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SF-36 Questionnaire

INSTRUCTIONS: Please answer every question. Some questions may look like others, but each one is different. Please take the time to read and answer each question carefully by circling the number that best represents your response.

1. In general, would you say your health is?

Excellent (1)	Very Good (2)	Good (3)	Fair (4)	Poor (5)

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago (1)	Somewhat better now than one year ago (2)	About the same as one year ago (3)	Somewhat worse now than one year ago (4)	Much worse now than one year ago (5)

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much: (circle one number on each line)

	Yes, Limited A Lot	Yes, Limited A Little	No, Not Limited At All
A. **Vigorous activities**, such as running, lifting heavy objects participating in strenuous sports	1	2	3
B. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
C. Lifting or carrying groceries	1	2	3
D. Climbing **several** flights of stairs	1	2	3
E. Climbing **one** flight of stairs	1	2	3
F. Bending, kneeling, or stooping	1	2	3
G. Walking **more than a mile**	1	2	3
H. Walking **several hundred yards**	1	2	3
I. Walking **one hundred yards**	1	2	3
J. Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health? (Circle one number on each line)

	Yes	No
A. Cut down on the **amount of time** you spend on work or other activities		
B. **Accomplished less** than you would like		
C. Were limited in the **kind** of work or other activities		
D. Had **difficulty** performing the work or other activities (for example, it took extra effort)		

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? (Circle one number on each line)

	Yes	No
A. Cut down on the **amount of time** you spend on work or other activities		
B. **Accomplished less** than you would like		
C. Did work or activities **less carefully than usual**		

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your social activities with family, friends, neighbours, or groups? (Circle one)

Not at all (1)	Slightly (2)	Moderately (3)	Quite a bit (4)	Extremely (5)

7. How much bodily pain have you had during the past 4 weeks? (Circle one)

None (1)	Very Mild (2)	Mild (3)	Moderate (4)	Severe (5)	Very Severe (6)

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Circle one)

Not at all (1)	Slightly (2)	Moderately (3)	Quite a bit (4)	Extremely (5)

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks… (Circle one number on each line)

	All the time	**Most** of the time	**Some** of the time	**A little** of the time	**None** of the time
A. did you feel full of life?	1	2	3	4	5
B. have you been very nervous?	1	2	3	4	5
C. have you felt so down in the dumps nothing could cheer you up?	1	2	3	4	5
D. have you felt calm and peaceful?	1	2	3	4	5
E. did you have a lot of energy?	1	2	3	4	5
F. have you felt downhearted and depressed?	1	2	3	4	5
G. did you feel worn out?	1	2	3	4	5
H. have you been happy?	1	2	3	4	5
I. did you feel tired?	1	2	3	4	5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the Time (1)	Most of the Time (2)	Some of the Time (3)	A Little of the Time (4)	None of the Time (5)

11. How TRUE or FALSE is each of the following statements for you? (Circle one number on each line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
A. I seem to get sick a little easier than other people	1	2	3	4	5
B. I am as healthy as anybody I know	1	2	3	4	5
C. I expect my health to get worse	1	2	3	4	5
D. My health is excellent	1	2	3	4	5

Figure 1: SF-36 Form

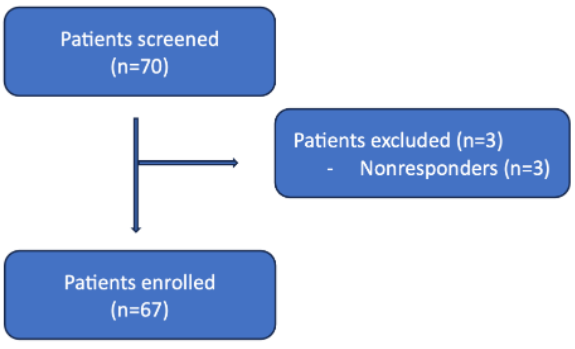

Figure 2:Flow chart

METHOD

Ethical permission was obtained from the Istanbul Okan University, Medical Faculty Ethics Committee for this study with date 20.20.2021 and number 20, and Helsinki Declaration rules were followed to conduct this study. Patients' consents were obtained via telephone. The study included cross-sectional retrospective data analyze and prospective questionnaire, which was conducted by applying the questionnaire via telephone to the patients 3 months after COVID-19 diagnosis, on November 2021. All patients enrolled in this study fullfilled the following criteria: being older than 18 years old and the disease confirmed by real time polymerase chain reaction (RT-PCR). Patients, who were under 18 years old, did not want to participate to the survey, died during this period, and diagnosis was not confirmed by RT-PCR were excluded from the study. Patients' age, gender, smoking status, comorbidities (diabetes mellitus (DM), hypertension (HT), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), and obesity, hospitalization status, and received COVID-19 treatments were recorded. Patients were contacted by telephone to evaluate with SF-36 questionnaire, which consists of eight main topics with a total of 36 questions, and provides the measurement of health related QOL. Eight main topics includes: physical functions (10 items), pain (2 items), limitations due to physical problems (4 items), limitations due to emotional problems (4 items), emotional well-being (5 items), social functions (2 items), fatigue (4 items), and general perception of health (5 items). Scores for each main topics range from 0 to 100, with a higher score defining a more favorable health state. First, we assessed factors associated with health related QOL. Second, we analyzed patients according to their ages, comorbidities, hospitalization statuses, and COVID-19 treatments.

Statistical analysis

All statistical analyses were performed using SPSS 25.0 (IBM SPSS Statistics 25 software (Armonk, NY: IBM Corp.)). Continuous variables were defined by the mean ± standard deviation, median (IQR: 25th and 75th percentiles) and categorical variables were defined by number and percent. Kolmogorov Smirnov and Shapiro Wilk tests were used for determination of normal distribution. For independent groups comparisons, we used Independent samples t test and One Way Analysis of Variance (post hoc: Tukey method) when parametric test assumptions were provided, Mann Whitney U test and Kruskal Wallis Variance Analysis (post hoc: Mann Whitney U test with Bonferroni Correction) were used when parametric test assumptions were not provided. Chi-square test was used to compare the categorical variables. To investigate the effects of independent variables on Quality of Life Total Scores (SF-36 Total Scores), we used univariate and multivariate linear regression models. Statistical significance was determined as $p<0,05$. The level of statistical significance was set at $p \leq 0.05$.

RESULTS

We anaylzed the data of 70 patients retrospectively, and 67 patients accepted to participate the questionnaire (Figure 2). Median (IQR 25-75) age of all patients was 37 (30-47) years. Other demographic variables of patients presented in Table 1.

Table 1. Demographic variables of patients

Variables	Number	%
Gender		
Male	44	66
Smoking	19	28
Comorbidity		
DM	10	15
HT	6	9
CAD	3	5
COPD	2	3
Obesity	6	9
None	40	59
Hospitalization	9	13
COVID-19 treatment		
No treatment	11	16
Favipravir	48	72
Favipravir+steroid	8	12

DM: diabetes mellitus, HT: hypertension, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease

First, we analyzed the eight main factors' (physical function, pain, limitation due to physical problems, limitation due to emotional problems, emotional well-being, social function, fatigue, and general perception of health) association with age (young (18-40 years old)/ middle aged (41-64 years old)/ old (65 years and over)), gender (male/ female), smoking status (smoker/ nonsmoker), comorbidity (with/ without any comorbidity including DM, HT, CAD, COPD, and obesity), hospitalization (hospitalized/ nonhospitalized) and COVID-19 treatment (no treatment/ favipravir/ favipravir+steroid) (Table 2). There was a significant difference between SF-36 eight main topics and four variables including age, gender, comorbidity and hospitalization status. In addition, we analyzed SF-36 eight main topics association with these four variables.

We divided patients into three groups according to their ages; young (18-40 years old), middle (41-64 years old), and old (65 years old and over). Pain, limitation due to physical problems, emotional well-being, social function and general perception of health were significantly different between age groups (Table 3).

Table 2. Variables Associated with SF-36

Variables	Physical function	Pain	Limitation due to physical problems	Limitation due to emotional problems	Emotional well-being	Social function	Fatigue	General perception of health
Age	-0.301	-0.121	-0.353	-0.214	-0.073	-0.251	-0.192	-0.213
p values	0.013*	0.329	0.003*	0.082	0.559	0.04*	0.12	0.083
Gender	0.234	0.349	0.139	0.207	0.237	0.193	0.217	0.324
p values	0.056	0.004*	0.261	0.092	0.053	0.117	0.077	0.008*
Smoking	0.094	0.106	0.073	0.097	-0.014	0.168	-0.03	0.075
p values	0.45	0.393	0.555	0.434	0.913	0.174	0.811	0.549
Comorbidity	-0.482	-0.382	-0.42	-0.409	-0.419	-0.419	-0.42	-0.543
p values	0.0001*	0.001*	0.0001*	0.001*	0.0001*	0.0001*	0.0001*	0.0001*
Hospitalization	-0.564	-0.248	-0.52	-0.317	-0.293	-0.434	-0.258	-0.276
p values	0.0001*	0.043*	0.0001*	0.009*	0.016*	0.0001*	0.035*	0.024*
COVID-19 treatment	-0.162	0.075	-0.163	-0.033	0.109	-0.149	-0.043	-0.018
p values	0.189	0.546	0.188	0.792	0.381	0.227	0.73	0.883

All results represented with Standardized Beta Coefficient (p value); *p<0.05 statistically significant

Table 3. SF-36 Results according to age

Variables	18-40 years	41-64 years	≥ 65 years	P value			
	Number	Med IQR (25-75)	Number	Med IQR (25-75)	Number	Med IQR(25-75)	
SF-36 scores							
Physical function	41	100 (87-100)	20	100 (90-100)	6	75 (17-100)	0.122 [kw]
Pain	41	100 (68-100)	20	100 (82-100)	6	55 (17-83)	0.031* [kw, c]
Limitation due to physical problems	41	100 (87-100)	20	100 (56-100)	6	50 (0-81)	0.009* [kw, b]
Limitation due to emotional problems	41	100 (67-100)	20	100 (42-100)	6	67 (25-100)	0.432 [kw]
Emotional well-being	41	64 (54-88)	20	86 (58-100)	6	50 (35-68)	0.05* [kw, c]
Social function	41	100 (75-100)	20	100 (100-100)	6	31 (22-66)	0.0001* [kw, b, c]
Fatigue	41	50 (35-75)	20	57 (26-84)	6	20 (7-45)	0.056[F]
General perception of health	41	75 (45-87)	20	75 (65-85)	6	37 (20-49)	0.019* [kw, b, c]

*p<0.05 statistically significant, [kw]: Kruskal Wallis Variance Analysis, [F]: One Way ANOVA, [a]: Significant difference between 18-40 years and 41-64 years groups, [b]:Significant difference between 18-40 years and ≥ 65 years groups; [c]:Significant difference between 41-64 years and ≥ 65 years groups

In gender, only pain (p=0.004) and general health perception (p=0.008) scores were lower in women. When the SF-36 scores were compared according the comorbidities, there was a statistically significant difference between patients without and with comorbidity. The mean SF-36 scores of patients with one or more comorbidities were found to be lower than patients without comorbidity in all eight main topics (Table 4). When we analyze comorbidities individually; patients with DM had significantly lower scores in limitation due to emotional problems (p=0.036) and fatigue (p=0.049). Patients with HT had significantly lower results in limitation due to physical problems (p=0.030), emotional well-being (p=0.035), social function (p=0.003), fatigue (p=0.025), and general perception of health(p=0.027). Patients with CAD had significantly lower results in pain (p=0.03), limitation due to physical problems (p=0.004), limitation due to emotional problems (p=0.038), emotional well-being (p=0.01), social function (p<0.001), and fatigue (p=0.017). Patients with COPD had significantly lower results in limitation due to physical problems (p=0.037) and general perception of health (p=0.006). There was no significant difference in SF-36 scores of patients with and without obesity.

Table 4. SF-36 results according to presence of comorbidity

Variables	With comorbidity	Without comorbidity	P value		
	Number	Med IQR (25-75)	Number	Med IQR (25-75)	
SF-36 scores					
Physical function	27	75 (60-100)	20	100 (95-100)	0.001* z
Pain	27	73 (30-100)	20	100 (90-100)	0.001* z
Limitation due to physical problems	27	75 (18-100)	40	100 (87-100)	0.005* z
Limitation due to emotional problems	27	67 (33-100)	40	100 (67-100)	0.004* z
Emotional well-being	27	52 (43-68)	40	80 (60-100)	0.002* z
Social function	27	75 (34-100)	40	100 (100-100)	0.001* z
Fatigue	27	32 (19-51)	40	60 (37-82)	0.0001* t
General perception of health	27	42 (29-75)	40	80 (65-90)	0.0001* z

*p<0.05 statistically significant, z: Mann Whitney U Test, t: Independent Samples

Table 5. SF-36 results according to hospitalization

Variables	Hospitalized	Unhospitalized	P value		
	Number	Med IQR (25-75)	Number	Med IQR (25-75)	
SF-36 scores					
Physical function	10	60 (30-95)	57	100 (94-100)	0.001* z
Pain	10	77 (16-100)	57	100 (76-100)	0.069 z
Limitation due to physical problems	10	25 (0-87)	57	100 (75-100)	0.001* z
Limitation due to emotional problems	10	67 (0-100)	57	100 (67-100)	0.077 z
Emotional well-being	10	48 (26-68)	57	72 (56-96)	0.016* z
Social function	10	50 (25-87)	57	100 (75-100)	0.001* z
Fatigue	10	20 (12-50)	57	50 (34-80)	0.035* t
General perception of health	10	40 (32-75)	57	75 (50-85)	0.022* z

*p<0.05 statistically significant, z: Mann Whitney U Test, t: Independent Samples

In the comparison of hospitalization, 57 patients (85%) were followed up and treated at home and 10 and 1 (1%) patient in the intensive care unit). Patients, who were treated at home did not receive any oxygen treatment; patients, who were treated at ward, received only oxygen support; and patients, who were treated in the ICU, received non-invasive mechanical ventilator. Except pain and limitation due to emotional problems, all six main topics were significantly different between hospitalized and unhopitalized patients (Table 5).

DISCUSSION

Age, gender, comorbidity, and hospitalization status of patients were found to be the factors associated with health related quality of life 3 months after COVID-19 diagnosis. In the current study, SF-36 scores of patients, who were aged 65 and over, were found to be lower in pain, limitation due to physical problems emotional well-being, and general perception of health. Our data are consistent with the literature review, which showed advanced age and presence of comorbidity increased the severity of both COVID-19 symptoms and PCS (3).

In this study, patients with comorbidity had lower scores in all eight main topics. Supporting this result, literature showed patients with comorbidity had worse COVID-19 symptoms and PCS (3) Contrary this result, Huang et al. (7) showed no significant association between comorbidity and PCS.

Our findings on DM agree with those reported by Su et al. (8), who found that diabetes poses a risk for PCS in patients who

have had COVID infection. In contrast, in a study conducted in Spain in which 144 diabetic patients were compared with healthy controls, it was found that diabetes was not a risk factor for PCS (9). In HT evaluation, a systematic review of 45 studies showed HT was a risk factor for PCS. It has been observed that one of the most common comorbid diseases in patients with PCS was hypertension. (10) Also, Tleyjeh et al. (11) found that patients diagnosed with hypertension were at a higher risk for PCS. However, a study in India showed that the most common comorbid disease among patients diagnosed with PCS was hypertension, but it was observed that hypertension was not a risk factor for PCS. (12). In COPD evaluation, likewise our results, Subramanian et al. (13) found that COPD was the most common risk factor for PCS. Our data differ from a study conducted in the USA showed that chronic lung diseases are not a risk factor for PCS (14). In CAD evaluation, a study, which compared healthy volunteers with people diagnosed with PCS, it has been determined that cardiovascular disease was not a risk factor for PCS. This situation can be explained by all the mechanisms that impair clinical outcomes in the acute phase of COVID-19, including obesity-related hyperinflammation, cytokine release, immune dysfunction, and comorbidities (16, 17). It was thought that the results of this study were inconsistent with the literature, because the number of obese patients (9%) was insufficient and 4 of 6 patients with obesity were under the age of 40.

Hospitalized patients had lower scores in physical function, limitation due to physical problem, emotional well-being, social function, fatigue, and general perception of health. Our data are consistent with Maestre-Muniz et al. (18), who showed hospitalized patients had more complaints than nonhospitalized patients 1 year after COVID-19 diagnosis.

Our findings on smoking agree with those reported by Huang et al. (7), who did not show any association between smoking and PCS. In the comparison of SF-36 scores between genders, women had significantly lower scores in pain and general health perception. In the literature review, the risk of ongoing symptoms after COVID-19 was found to be higher in women, which is consistent with this study (7, 19). Unlike Huang et al. (7), we observed no significant difference between COVID-19 treatments in SF-36 scores. They showed corticosteroid treatment during acute infection was a risk factor for ongoing fatigue and muscle weakness after 12 months. The reason for this is thought to be related with corticosteroid myopathy.

Limitations of the study

This study has some limitations. First, this study was a single-centered study with a small number of patients. Secondly, the inability to conduct face-to-face interviews with patients was also seen as a limitation. In addition, the decrease in the incidence of other viral infections due to COVID-19 caused us to form a control group.

CONCLUSION

Advanced age, gender, presence of comorbidity, and history of hospitalization were determined as risk factors for PCS. To evaluate other risk factors, more studies should be conducted on this subject. Identifying the risk factors is crucial in terms of predicting such a commonly encountered condition observed after COVID-19.

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Peer-Review

Both externally and internally peer reviewed.

Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article.

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Ethical Declaration

Ethical permission was obtained from the Istanbul Okan University, Medical Faculty Ethics Committee for this study with date 20.20.2021 and number 20, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept: HA, GA, Design: HA, Supervising: HA, GA, Data collection and entry: HA, GA, Analysis and interpretation: HA, GA, Literature search: HA, Writing: HA, GA, Critical review: HA, GA

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