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ARAŞTIRMA / RESEARCH

Post-COVID corticosteroid use and pulmonary fibrosis: 1 year follow-up

Post-COVID kortikosteroid kullanımı ve pulmoner fibrozis: 1 yıllık izlem

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Abstract

Purpose: Depending on the prevalence and severity of COVID-19 disease, pulmonary sequelae and fibrotic lung disease continue to pose significant problems for patients in the post-COVID period. In our study, we aimed to determine the risk factors for pulmonary sequelae and fibrosis with post-COVID patient management.

Materials and Methods: The study comprised 67 post-COVID patients who were released from the hospital after receiving low-dose corticosteroids (0.5 mg/kg daily methylprednisolone) as a result of COVID-19. Socio-demographic data, radiological and laboratory findings of the patients were recorded. All patients were followed up at 3, 6, and 12 months after discharge, and the diagnosis of pulmonary fibrosis was made according to high resolution computed tomography (HRCT) findings, by evaluating with detailed biochemical blood tests and HRCT.

Results: Thirtyfour (50.7%) of the 67 patients were male and the mean age was 57±16.33 (min.19–max.90). At 3 months, there were 59 patients (88.1%) with aberrant thoracic computed tomography (CT) findings, 28 (41.8%) at 6 months, and 21 (31.3%) at 12 months. In the 12th month follow-up, pulmonary fibrosis was detected in a total of 9 (13.4%) patients according to thorax CT findings.

Conclusion: In our study, the most important risk factors for the development of post-COVID pulmonary fibrosis were intensive care unit (ICU) follow-up, lymphocyte count <500 and ferritin ≥300. For this reason, patients who are treated in the ICU, especially in the hospital, should be followed up regularly and frequently after discharge.

Keywords:. Corticosteroid, COVID-19, post-COVID, pulmonary fibrosis, radiological findings, risk factors

Öz

Amaç: COVID-19 hastalığının yaygınlığı ve ağırlığına bağlı olarak post-COVID dönemde pulmoner sekeller ve fibrotik akciğer hastalığı hastalar için önemli problemler oluşturmaya devam etmektedir. Biz de çalışmamızda post-COVID hasta yönetimi ile pulmoner sekel ve fibrozis için risk faktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: COVID-19 nedeni ile hastaneden düşük doz kortikosteroid (0,5 mg/kg/gün metilprednisolon) ile taburcu edilen 67 post-COVID hasta çalışmaya dahil edildi. Hastaların sosyo-demografik verileri, radyolojik ve laboratuvar bulguları kayıt altına alındı. Taburculuk sonrası tüm hastalar 3,6 ve 12. ayda takipleri yapılarak ayrıntılı biyokimyasal kan tetkikleri ve yüksek rezolüsyonlu bilgisayarlı tomografi (HRCT) ile değerlendirilerek pulmoner fibrozis tanısı HRCT bulgularına göre konuldu.

Bulgular: Altmış yedi hastanın 34 (50,7%)'ü erkek ve yaş ortalaması 57±16,33 yıl (min.19–max.90) idi. Üçüncü ayda 59 (%88,1), 6. ayda 28 (%41,8) ve 12. ayda 21 (%31,3) hastada anormal toraks bilgisayarlı tomografi (BT) bulguları vardı. On ikinci ay takibinde toraks BT bulgularına göre toplam 9 (%13,4) hastada pulmoner fibrozis saptandı.

Sonuç: Araştırmamızda post-COVID pulmoner fibrosis gelişimi için en önemli risk faktörleri yoğun bakım ünitesi (YBÜ) takibi, lenfosit sayısının <500, ferritinin ≥300 olması şeklinde tespit edildi. Bu nedenle özellikle hastanede YBÜ'de tedavi gören hastaların taburculuk sonrası düzenli ve sık aralıklarla takibi gerekmektedir.

Anahtar kelimeler: Kortikosteroid, COVID-19, post-COVID, pulmoner fibrozis, radyolojik bulgular, risk faktörleri.

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INTRODUCTION

While the devastating effects of the COVID-19 pandemic, which affects the whole world and millions of people, are decreasing, many new patients who survived the acute period but continue to live with the long-term symptoms of the disease continue to emerge. Discomforts in these patients occur in a wide perspective, ranging from mild malaise to permanent pulmonary fibrosis. For the first four weeks of the COVID-19 disease, the phrases acute COVID-19, continuing or protracted COVID-19, and post-COVID-19 syndrome terminology are used to define the disease[1].

Clinical signs involving the respiratory, cardiovascular, gastrointestinal and neuropsychiatric systems are among the multiorgan effects of COVID-19, albeit it is unknown how long they will last. The typical pulmonary sequelae seen in patients with post-acute COVID-19 syndrome include dyspnea, cough, dependency on oxygen, difficulties weaning off mechanical ventilation or NIV, fibrotic lung alterations, decreased diffusion capacity, and reduced endurance[2].

There is little information analyzing the effectiveness of steroids in post-acute COVID-19 patients, and their significance in this condition is uncertain[2]. A small research analyzing COVID-19 patients four weeks after discharge found that early steroid induction resulted in a rapid and considerable recovery[3]. Therefore, it is clear that more work is needed on this subject.

Pulmonary fibrosis is the long-term consequence that is most feared in the lungs, one of the most often damaged organs in the post-COVID process[4]. In a recent study, the prevalence of post-COVID pulmonary fibrosis was 9.3 percent[5] for the post-COVID period, 20 percent[6] after acute H7N9 infection with a similar course, and 45 percent[7] after SARS was identified. The prevalence of post-COVID pulmonary fibrosis will be better understood over time.

Numerous lung damage pathways, including viral and immune-mediated ones, have been discovered in COVID-19[8]. Pulmonary fibrosis may start and worsen due to a cytokine storm brought on by an aberrant immune system[9]. Once more, it was discovered that 20% of ARDS cases in COVID-19 patients were severe and that 40% of patients acquired ARDS[10]. It is characterized by an initial acute inflammatory exudative phase with a hyaline membrane, followed by an organized phase, and lastly a fibrotic phase that results in fibrosis. Diffuse alveolar injury and the development of this damage are the pathological features of ARDS[11]. Long-term use of antiviral, anti-inflammatory, and antifibrotic medications in the treatment of postcovid pulmonary fibrosis may lessen the risk of lung fibrosis. According to a recent theory that takes into account the profit-loss ratio, corticosteroid therapy can avoid remodeling and pulmonary fibrosis[12].

For the time being, there are no effective confirmed treatments for post-inflammatory COVID-19 pulmonary fibrosis. Therefore, in our study, we evaluated the efficacy of low-dose steroid therapy (0.5 mg/kg/day methylprednisolone), which is currently accepted in the treatment of post-COVID pulmonary fibrosis, by observing the changes in the clinical features and after 3, 6 and 12 months of follow-up and to determine the risk factors for the development of pulmonary fibrosis.

MATERIALS AND METHODS

This is a cross-sectional study that was approved by the local institutional ethics committee of Cukurova University, Adana, Turkey (approval no 106/2020). An informed consent statement was required to assigned by the participants. All procedures performed in the study involving human participants were in accordance with the ethical standards of the Hospital, National research committe and the 1964 Helsinki declaration. This cross-sectional study was conducted at Cukurova University Faculty of Medicine Balcali Hospital, Department of Chest Diseases between December 2020 and May 2022. There is limited data in the literature for postviral fibrotic lung disease. While the mean rate of fibrotic lung development was 40%[3-6,8] and our expectation was approximately 20%, we needed a minimum of 54 cases with 90% power analysis and 0.5% error.

Sample

Inclusion criteria were patients treated in Çukurova University Hospital COVID-19 department, patients discharged with low dose (0.5 mg/kg daily methylprednisolone) corticosteroid and patients with lung involvement due to COVID-19. Exclusion criteria were patients without lung involvement, patients who did not receive corticosteroid treatment at discharge and patients who did not accept to

participate in the study 76 patients were evaluated for the study. 2 of them were excluded from the study because they had no lung involvement, 3 of them did not use corticosteroids, and 4 of them did not agree to participate in the study. 67 patients were included in the study. The individuals participating in the study were examined at the 3, 6 and 12. months by the specialist physicians in charge of the chest diseases outpatient clinic and evaluated with their clinical, radiological and laboratory findings, and the findings were recorded.

Measures

The data collection forms were used to record sociodemographic characteristics, previous history of post-COVID symptoms, momentary history and physical examination signs, previous and novel laboratory and radiographic findings, medical therapies employed during the acute infection and in post-COVID period. Patients were evaluated clinically at each visit with vital signs (fever, heart rate, respiratory rate, systolic/diastolic blood pressure), oxygen saturation (SaO2), and symptom questioning.

Extensive biochemical tests including routine complete blood count, CRP, procalcitonin, ferritin, liver and kidney function tests were documented. Imaging of the lungs was performed with Computed Tomography (CT) of the Thorax and High Resolution Computed Tomography (HRCT) within the radiology department of our hospital. The decision for fibrosis on CT was made as a result of the evaluation of experts in the radiology department of the tertiary university hospital. The evaluations in the follow-ups were also carried out with the same team.

Implementation

The first data of the patients who were hospitalized due to acute COVID-19 were obtained from the patients' epicrisis and the hospital database. During the first visit at the 3rd month, 67 patients selected for the study underwent detailed anamnesis, physical examination, clinical evaluation, as well as detailed laboratory examinations and thorax CT-HRCT imaging. At the 6th and 12th months, the patients were re-evaluated clinically, laboratory and radiologically with the same tests. The findings were recorded with the hospital data processing management system database.

Primary outcomes were positive effects of low-dose corticosteroids on the development of fibrosis in the lungs, to identify risk factors for the development of post-COVID lung fibrosis. Secondary outcomes were to determine the prevalence of post-COVID lung fibrosis and evaluation of symptoms, clinical and radiological aspects in the post-COVID period of patients hospitalized with acute COVID-19 and started on steroid therapy.

Statistical analysis

SPSS-22 program was used in the analysis of the data. Descriptive statistics for continuous variables are given as mean±standard deviation while for categorical variables it is given as frequency and percentages. Kolmogorov-Smirnov test was used as the normal distribution test. T-test, Mann-Whitney U test, One Way ANOVA test, Kruskal-Wallis test, Chi-square test were used in the analysis. In addition, for variables considered significant in similar studies for post-COVID fibrosis, a single-variable logistic regression analysis was performed first and a multivariate logistic regression analysis was performed according to its results. A value of $p<0.05$ was considered statistically significant.

RESULTS

The study included 67 individuals who had COVID-19 infections and were examined in an outpatient clinic after being discharged from an inpatient facility or critical care unit. Thirty-four (50.7%) of our patients were male and the mean age was 57±16.33 years (min.19–max.90). While 17 (25.4%) patients did not have an additional disease, 33 (49.3%) patients had 2 or more comorbidities. Thirtyfive (52.2%) of our patients had at least one dose of COVID-19 vaccine. 39 (58.2%) patients were followed up in the inpatient service and 28 (41.8%) patients were followed up in the ICU.

At 3 months, there were 59 patients (88.1%) with aberrant thoracic CT findings, 28 (41.8%) at 6 months, and 21 (31.3%) at 12 months. It was shown that the patient's existing cardiovascular illness and hematological malignancy may be connected to the CT abnormality that appeared in the third and sixth months, respectively, in the study of risk factors for the emergence of abnormal findings on CT (p values; 0.028 and 0.067, respectively). Among the symptoms, myalgia ($p=0.048$) and loss of taste and smell ($p=0.085$) were associated with abnormal CT images in the first 3 months, while cough was be associated

with abnormal CT images in both 6th and 12th months, and this situation was statistically significant (p values were 0.004 and 0.002, respectively). In addition, it was determined that being followed in the intensive care unit, independent of the time of admission, was associated with abnormal CT images and this was statistically significant (p values were 0.009, 0.002 and 0.000, respectively). It was determined that among the laboratory parameters, especially CRP in the first 3 months of follow-up and d-Dimer in the 12th month may be associated with abnormal CT findings, but this situation did not have statistical significance. The features related to thorax CT findings at the 3rd, 6th and 12th months follow-up are given in Table 2.

In the 12th month follow-up, pulmonary fibrosis was detected in a total of 9 (13.4%) patients according to thorax CT findings. In the risk factor analysis for the development of pulmonary fibrosis in post-COVID patients, male gender (p value 0.082) may lead to the development of pulmonary fibrosis, but it was statistically low-significant, ICU follow-up (p value 0.000), lymphocyte count <500 (p value 0.017) and ferritin ≥300 (p value 0.037) could lead to the development of pulmonary fibrosis and these factors were statistically significant. Risk factors for pulmonary fibrosis in post-COVID patients are given in Table 3. We conducted multivariate logistic regression analysis for the risk factors that we identified significant for the development of pulmonary fibrosis, including gender, low lymphocyte count, and high ferritin level. We found that people with a lymphocyte count below 500 had a 5.9-fold increased risk of developing pulmonary fibrosis, and people with ferritin levels above 300 had a 9.6-fold increased risk. However, gender had no statistically significant effect on the development of pulmonary fibrosis (Table 4).

Table 1. Sociodemographic characteristics of Post-COVID patients

Characteristics	**n (%) or X±S.D. (min–max)**
Age (years)	57±16.33 (19–90)
Sex (male/female)	34(50.7) / 33(49.3)
Active smoker (No/Yes)	19(28.4) / 48(71.6)
Number of Comorbidities (0/1/2 and more)	17(25.4) / 17(25.4) / 33(49.3)
Charlson Comorbidity Index (Low / Medium / High / Very High)	17(25.4) / 26(38.8)/ 15(22.4) / 9(13.4)
COVID-19 vaccine (No/Yes)	32(48.8) / 35(52.2)
Hospitalization (Inpatient Service / Intensive Care Unit)	39(58.2) / 28(41.8)
Steroid use at the first visit at 3 months (No/Yes)	9(13.4) / 58(86.6)
Symptoms	
Dyspnea (No/Yes)	16(23.9) / 51(76.1)
Cough (No/Yes)	39(58.2) / 28(41.8)
Fatigue (No/Yes)	37(55.2) / 30(44.8)
Myalgia (No/Yes)	59(88.1) / 8(11.9)
Loss of taste and smell (No/Yes)	51(76.1) / 16(23.9)
Sleeping Disorders (No/Yes)	61(91) / 6(9)
Hair loss and skin problems (No/Yes)	58(86.6) / 9(13.4)

Table 2. Thorax CT findings at 3,6 and 12. months follow-up

		Normal CT Findings at 3/6/12 months n(%)	Abnormal CT Findings at 3/6/12 months n(%)	p (3/6/12 months)
Age (years)	≥65	1(12.5) / 11(28.2) / 13(28.3)	20(66.1) / 10(35.7) / 8(38.1)	0.212 / 0.348 / 0.298
	<65	7(87.5) / 28(71.8) / 33(71.7)	39(33.9) / 18(64.3) / 13(61.9)	
Sex	Male	5(62.5) / 17(43.6) / 21(45.7)	29 (49.2) / 17(60.7) / 13(61.9)	0.372 / 0.128 / 0.166
	Female	3 (37.5) / 22(56.4) /25(54.3)	30 (50.8) / 11(39.3) /8(38.1)	
Smoker	Yes	2 (25) / 10(25.6) / 12(26.1)	17 (28.8) / 9(32.1) / 7(33.3)	0.594 / 0.377 / 0.370
	No	6 (75) / 29(74.4) / 34(73.9)	42 (71.2) / 19(67.9) / 14(66.7)	
HT	Yes	3 (37.5) / 15 (38.5) / 18(39.1)	25 (42.4) / 13(46.4) / 10(47.6)	0.554 / 0.344 /0.348
	No	5 (62.5) / 24(61.5) / 28(60.9)	34 (57.6) / 15(53.6) / 11(52.4)	
DM	Yes	4 (50) / 16(41) / 19(41.3)	24 (40.7) / 12(42.9) /9(42.9)	0.446 / 0.539 / 0.556
	No	4 (50) / 23(59) / 27(58.7)	35 (59.3) / 16(57.1) /12(57.1)	
Cardiovascular Disease	Yes	0 (0) / 4(10.3) / 7(15.2)	13 (22) / 9 (32.1) / 6(28.6)	0.160 / 0.028 / 0.171
	No	8 (100) / 35(89.7) / 39(84.8)	46 (78) / 19(67.9) / 15(71.4)	
Chronic Respiratory Diseases	Yes	0 (0) / 7(17.9) / 8(17.4)	12 (20.3) / 5(17.9) / 4(19)	0.187 / 0.626 / 0.560
	No	8 (100) / 32(82.1) / 38(82.6)	47 (79.7) / 23(82.1) / 17(81)	
Solid Organ Malignancies	Yes	2 (25) / 4(10.3) / 5(10.9)	4 (6.8) / 2(7.1) / 1(4.8)	0.147 / 0.506 / 0.382
	No	6 (75) / 35(89.7) / 41(89.1)	55 (93.2) / 26(92.9) / 20(95.2)	
Hematological Malignancies	Yes	2 (25) / 2(5.1) / 4(8.7)	2 (3.4) / 2(7.1) / 0(0)	0.067 / 0.559 / 0.213
	No	6 (75) / 37(94.9) / 42(91.3)	57 (96.6) / 26(92.9) / 21(100)	
Dyspnea	Yes	6 (75) /29(74.4) / 34(73.9)	45 (76.3) / 22(78.6) /17(81)	0.618 / 0.460 /0.383
	No	2 (25) / 10(25.6) / 12(26.1)	14 (23.7) / 6(21.4) /4(19)	
Cough	Yes	4 (50) / 22(56.4) / 25(54.3)	24 (40.7) / 6(21.4) / 3(14.3)	0.446 / 0.004 / 0.002
	No	4 (50) / 17(43.6) / 21(45.7)	35 (59.3) / 22(78.6) / 18(85.7)	
Fatigue	Yes	4 (50) / 19(48.7) / 22(47.8)	26 (44.1) / 11(39.3) / 8(38.1)	0.520 /0.303 / 0.318
	No	4 (50) / 20(51.3) / 24(52.2)	33 (55.9) / 17(60.7) / 13(61.9)	
Myalgia	Yes	3 (37.5) / 6(15.4) / 6(13)	5 (8.5) / 2(7.1) / 2(9.5)	0.048 / 0.265 / 0.514
	No	5 (62.5) / 33(84.6) / 40(87)	54 (61.5) / 26(92.9) / 19(90.5)	
Loss of taste and smell	Yes	4 (50) / 10(25.6) / 12(26.1)	12 (20.3) / 6(21.4) / 4(19)	0.085 / 0.460 / 0.383
	No	4 (50) / 29(74.4) / 34(73.9)	47 (79.7) / 22(78.6) / 17(81)	
COVID-19 vaccine	Yes	3 (37.5) / 19(48.7) / 25(54.3)	32 (54.2) / 16(57.1) / 10(47.6)	0.304 / 0.333 / 0.402
	No	5 (62.5) / 20(51.3) / 21(45.7)	27 (45.8) / 12(42.9) / 11(52.4)	
Hospitalization	Inpatient Service	8 (100) / 29(74.4) / 35(76.1)	31 (52.5) / 10(35.7) / 4(19)	0.009 / 0.002 / 0.000
	Intensive Care Unit	0 (0) / 10 (25.6) / 11(23.9)	28 (47.5) / 18(64.3) / 17(81)	
Steroid use	Yes	6 (75) / 32(82.1) / 39(84.8)	52 (88.1) / 26(92.9) / 19(90.5)	0.291 / 0.181 / 0.417
	No	2 (25) / 7(17.9) / 7(15.2)	7 (11.9) / 2(7.1) / 2(9.5)	
PLT	<150000	2 (25) / 10(25.6) / 12(26.1)	17 (28.8) / 9(32.1) / 7(33.3)	0.594 / 0.377 / 0.370
	≥150000	6 (75) / 29(74.4) / 34(73.9)	42 (71.2) / 19(67.9) / 14(66.7)	
Lymphocyte (/mm^3)	<500	1 (12.5) / 10(25.6) / 11(23.9)	19 (32.2) / 10(35.7) / 9(42.9)	0.241 / 0.267 / 0.101
	≥500	7 (87.5) / 29(74.4) / 35(76.1)	40 (67.8) / 18(64.3) / 12(57.1)	
CRP	<50	5 (62.5) / 12(30.8) / 14(30.4)	17 (28.8) / 10(35.7) / 8(38.1)	0.070 / 0.434 / 0.364
	≥50	3 (37.5) / 27(69.2) / 32(69.6)	42 (71.2) / 18(64.3) / 13(61.9)	
Ferritin	<300	2 (25) / 17(43.6) / 19(41.3)	28 (47.5) / 13(46.4) / 11(52.4)	0.208 / 0.507 / 0.280
	≥300	6 (75) / 22(56.4) / 27(58.7)	31 (52.5) / 15(53.6) / 10(47.6)	
d-Dimer	<0.55	3 (37.5) / 16(41) / 21(45.7)	23 (39) / 10(35.7) / 5(23.8)	0.627 / 0.428 / 0.074
	≥0.55	5 (62.5) / 23(59) / 25 (54.3)	36 (61) / 18(64.3) / 16(76.2)	
Creatinin	<1.2	8 (100) / 33(84.6) / 37(80.4)	44 (74.6) / 19(67.9) / 15(71.4)	0.115 / 0.093 / 0.302
	≥1.2	0 (0) / 6(15.4) / 9(19.6)	15 (25.4) / 9(32.1) / 6(28.6)	
LDH	<300	0 (0) / 9(23.1) / 10(21.7)	13 (22) / 4(14.3) / 3(14.3)	0.160 / 0.283 / 0.306
	≥300	8 (100) / 30(76.9) / 36(78.3)	46 (78) / 24(85.7) / 18(85.7)	

CRP: C-reactive protein, DM: Diabetes Mellitus, HT: Hypertension, LDH: Lactate dehydrogenase, PLT: Platelet

Table 3. Risk factors for pulmonary fibrosis in post-COVID patients.

		Pulmonary Fibrosis		p
		Yes n (%)	No n (%)	
Age (years)	≥65	4 (44.4)	17 (29.3)	0.292
	<65	5 (55.6)	41 (70.7)	
Sex	Male	7 (77.8)	27 (46.6)	**0.082**
	Female	2 (22.2)	31 (53.4)	
Steroid use	Yes	9 (100)	49 (84.5)	0.249
	No	0 (0)	9 (15.5)	
Cardiovascular Disease	Yes	1 (11.1)	12 (20.7)	0.441
	No	8 (88.9)	46 (79.3)	
Hematological Malignancies	Yes	0 (0)	4 (6.9)	0.554
	No	9 (100)	54 (93.1)	
Dyspnea	Yes	7 (77.8)	44 (75.9)	0.634
	No	2 (22.2)	14 (24.1)	
Cough	Yes	2 (22.2)	26 (44.8)	0.181
	No	7 (77.8)	32 (55.2)	
Myalgia	Yes	1 (11.1)	7 (12.1)	0.709
	No	8 (88.9)	51 (87.9)	
Loss of taste and smell	Yes	1 (11.1)	15 (25.9)	0.309
	No	8 (88.9)	43 (74.1)	
Hospitalization	Inpatient Service	0 (0)	39 (67.2)	**0.000**
	Intensive Care Unit	9 (100)	19 (32.8)	
PLT	<150000	4 (44.4)	15 (25.9)	0.221
	≥150000	5 (55.6)	43 (74.1)	
Lymphocyte (/mm³)	<500	6 (66.7)	14 (24.1)	**0.017**
	≥500	3 (33.3)	44 (75.9)	
CRP	<50	3 (33.3)	19 (32.8)	0.623
	≥50	6 (66.7)	39 (67.2)	
Ferritin	<300	7 (77.8)	23 (39.7)	**0.037**
	≥300	2 (22.2)	35 (60.3)	
d-Dimer	<0.55	2 (22.2)	24 (41.4)	0.237
	≥0.55	7(77.8)	34 (58.6)	
Creatinin	<1.2	7 (77.8)	45 (77.6)	0.679
	≥1.2	2 (22.2)	13 (22.4)	
LDH	<300	1 (11.1)	12 (20.7)	0.441
	≥300	8 (88.9)	46 (79.3)	

Abbrevations: CRP: C-reactive protein, LDH: Lactate dehydrogenase, PLT: Platelet

Table 4. Multivariate Logistic Regression Analysis for Pulmonary Fibrosis Risk Factors

Variables in the Equation					
				95% C.I.for OR	
	B	p	OR	Lower	Upper
Sex	1.855	0.056	6.394	0.952	42.925
Lymphocyte	1.777	0.039	5.909	1.097	31.819
Ferritin	2.269	0.020	9.673	1.431	65.375
Constant	-4.060	0.000	0.017		

DISCUSSION

Dyspnea and cough, as well as weakness and fatigue, were the symptoms that were most frequently found in our research during the third month of follow-up. No beneficial effect on thorax CT improvement or fibrosis development was discovered in the 1-year follow-up findings of steroid usage. It was believed

that a significant portion of the patients who took part in our study and contributed to this circumstance by using steroids. The presence of myalgia symptoms for patients admitted within the first three months, cardiovascular disease and cough for patients admitted within the sixth month, and cough and the need for intensive care for patients admitted within the 12th month were all found to increase the risk of developing thoracic CT abnormalities. It was also determined that a low lymphocyte count, a high ferritin level, and ICU follow-up might all be risk factors for post-COVID fibrosis.

The most prevalent symptoms were fatigue (58%), headache (44%), attention deficit (27%), hair loss (25%), and shortness of breath in a meta-analysis with 14–118 days of follow-up (24%)[13]. According to a cohort study from January to May 2020 with an average follow-up of 186 days, the most common disorders were fatigue, weakness (63%), sleep issues (26%), and anxiety or sadness (23%)[14]. Only 18.6% of participants in a multicenter study of patients in the first wave of the pandemic in Spain were found to be completely free of any post-COVID symptoms when they were evaluated an average of seven months after hospital discharge. The most prevalent symptoms were fatigue (60.8%), hair loss (26.3%), and shortness of breath (23.5%)[15]. The prevalence of cough, chest pain, dyspnea, and fatigue in the same group was 2.5%, 6.5%, 23.3%, and 61.2%, respectively, at the end of a one-year follow-up[16]. The overall symptom frequency in our findings was consistent with the literature.

In our study, the rate of patients with post-COVID 3, 6 and 12 months abnormal thorax CT findings was 88.1%, 41.8% and 31.3%, respectively, while the rate of pulmonary fibrosis was 13.4%. Even a modest percentage of post-COVID lung fibrosis is concerning since there are millions of COVID-19 cases globally. Some authors claimed that at a three-month follow-up a higher incidence of fibrosis was linked to previous coronavirus-related epidemic infections, such as the Middle East respiratory syndrome (MERS) and the severe acute respiratory syndrome (SARS), in 33% and 38% of patients, respectively[17]. In a research, during a 4-week follow-up, the lung lesions of 64.7% of patients who were discharged were completely absorbed[18]. Another one indicated that, on average, after almost two months of follow-up, 62% of radiographs were normal, 27% showed a considerable improvement, and the remaining 9% showed a major deterioration[19]. In a research, interstitial thickness was observed in 27% of participants three months after discharge, and at least one radiological abnormality was found in 70.91% of patients[20]. One study with severe COVID-19 cases revealed that at 4 months, 20% of non-mechanically ventilated patients and 72% of mechanically ventilated patients exhibited radiographic abnormalities that resembled fibrosis[21]. In a comprehensive 6-month follow-up research, a total of 353 patients were declared suitable for lung computed tomography; nearly 50% of them had at least one abnormality, the most frequent of which were ground glass opacities and irregular lines. 1% of individuals had interlobular septal thickening[22].

In a research examining post-COVID pulmonary sequelae, risk variables for the emergence of interstitial lung disease, including ICU follow-up, invasive MV support, and bacterial superinfections, were identified[23]. According to published research, 70% of ARDS patients who recover have aberrant imaging findings at 6 months, regardless of the underlying reason, and in some cases may experience sequelae such fibrosis and pulmonary hypertension[24]. Age, BMI, and inflammatory markers (procalcitonin) were found to be the main risk factors for post-COVID-19 pulmonary fibrosis that was diagnosed between 90 and 150 days[25]. Our findings are consistent with the few studies that have been published. In our investigation, it was discovered that the development of post-COVID fibrosis was influenced by factors such as ICU follow-up, high ferritin, low lymphocyte count. Since there are few studies on radiological follow-up and pulmonary fibrosis in the post-COVID period in the literature, we believe that our work is important.

Our study has some limitations, including the limited number of participants, lack of pre-COVID-19 radiological images of patients, the single-center design, and the impossibility of obtaining a control group because practically all of our patients used corticosteroids both during their hospitalization and at the time of release. For a better knowledge of the topic, multicenter, prospective randomized controlled trials are required.

In conclusion, the most feared long-term complication of SARS-CoV-2 is the development of fibrosis in the lungs, which is the most common organ. Obviously, although there are no clear data on the prevalence in the literature, it is likely that the disease will reach a frightening size due to its prevalence. The most important risk factor seems to

be disease severity and ICU follow-up. For this reason, it is of great importance to follow these patients more carefully and to make diagnosis and follow-up-treatment management in the early period.

In our study, we observed that steroid therapy was not effective enough to prevent the development of postcovid pulmonary fibrosis. However, since our study was single-centered and did not have a control group, it is clear that there is a need for multicenter and randomized controlled studies on this subject.

Yazar Katkıları: Çalışma konsepti/Tasarımı: EG, OBT; Veri toplama: EG, OBT; Veri analizi ve yorumlama: EG, OBT; Yazı taslağı: EG, OBT; İçeriğin eleştirel incelenmesi: EG, OBT; Son onay ve sorumluluk: EG, OBT; Teknik ve malzeme desteği: EG; Süpervizyon: EG; Fon sağlama (mevcut ise): yok.
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