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Long Term Respiratory Follow up Findings of COVID-19 Cases

COVID-19 Olgularının Uzun Dönem Solunumsal Takip Bulguları

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Long Term Respiratory Follow up Findings of COVID-19 Cases

ABSTRACT

Objective: The aim of this study was to determine the long-term clinical, laboratory and radiologic findings, long-term follow-up findings after acute infection and complications in patients who recovered from COVID-19 infection, especially in patients with insufficient data on long-term effects.

Material and Method: Patients who were admitted to the pulmonology outpatient clinic of our hospital and recovered from COVID-19 infection were included in the study. Demographic data, peripheral oxygen saturation, mMRC score, 6-minute walk test data, ongoing symptoms, laboratory data, radiologic findings and complications during follow-up were recorded. Patients admitted up to the first 4 weeks from the time of diagnosis were grouped as visit 1, patients admitted between 4 and 12 weeks were grouped as visit 2, and patients admitted after 12 weeks were grouped as visit 3.

Results: A total of 520 patients were evaluated, including 190 patients at the first visit interval, 203 patients at the second visit interval and 127 patients at the third visit interval, including duplicate patients. 54% of the participants were female, 46% were male and the mean age was 54 years. Patients had at least one ongoing symptom in 96.3%, 90.6% and 89.8% of the visits, respectively. The most common symptoms were exertional dyspnea, fatigue and cough. The most common pathologic radiographic findings were ground glass opacities in the early period and linear/reticular opacities in the late period. The rates of complications during follow-up were 4.7%, 23.2%, 24.4% according to the visit intervals, respectively and the most common complication was pulmonary fibrosis.

Conclusion: COVID-19 patients; while struggling with the problems associated with the acute disease in the early period, they also have to struggle with persistent symptoms and newly developing complications in the long term. In this context, we think that our study will form a basis for the data of our country and contribute to the literature.

Keywords: COVID-19, long-COVID, post-COVID.

ÖZET

Amaç: Bu çalışmayla özellikle uzun dönem etkileri hakkında yeterli veri olmayan COVID-19 enfeksiyonunu geçirip iyileşen hastaların; uzun dönem klinik, laboratuvar ve radyolojik bulgularının, akut enfeksiyon sonrası uzun vadeli takip bulgularının ve komplikasyonların ortaya konması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya hastanemiz göğüs hastalıkları polikliniğine başvuran, COVID-19 enfeksiyonu geçirip iyileşen hastalar dahil edildi. Hastaların demografik verileri, periferik oksijen satürasyonu, mMRC skoru, 6 dakika yürüme testi verileri, devam eden semptomları, laboratuvar verileri, radyolojik bulguları ve takipte gelişen komplikasyonlar kaydedildi. Tanı anından itibaren ilk 4 haftaya kadar olan sürede başvuran hastalar 1. vizit, 4 ila 12. hafta arasında başvuran hastalar 2. vizit, 12. haftadan sonra başvuran hastalar 3. vizit aralığı olarak gruplandırıldı.

Bulgular: İlk vizit aralığında 190, 2. vizit aralığında 203 ve 3. vizit aralığında 127 olmak üzere mükerrer hastalarla birlikte toplam 520 hasta değerlendirildi. Katılımcıların %54'ü kadın, %46'sı erkek ve ortalama yaş 54'tü. Hastaların, vizit aralıklarına göre sırasıyla %96,3, %90,6, %89,8 oranında devam eden en az bir semptomu mevcuttu. En sık izlenen semptomlar; efor dispnesi, halsizlik, öksürük şeklinde sıralandı. En sık patolojik grafi bulgusu erken dönemlerde buzlu cam opasiteleri iken geç dönemde çizgisel/retikuler opasiteler olarak görüldü. Takipte komplikasyon izlenme oranları vizit aralıklarına göre sırasıyla %4,7, %23,2, %24,4 olarak izlendi ve en sık izlenen komplikasyonun akciğer fibrozisi olduğu görüldü.

Sonuç: COVID-19 hastaları; erken dönemde akut hastalıkla ilişkili sorunlarla mücadele ederken, uzun dönemde de sebat eden semptomlar ve yeni gelişen komplikasyonlarla mücadele etmek zorunda kalmaktadır. Bu bağlamda, çalışmamızın ülkemiz verilerine dayanak oluşturacağını ve literatüre katkı sağlayacağını düşünmekteyiz.

Anahtar Sözcükler: COVID-19, long-COVID, post-COVID.

Introduction

At the end of 2019 in Wuhan city, Hubei province of China; pneumonia cases of unknown cause began to be reported. As a result of the examination of the patients' lower respiratory tract samples, it was understood that the causative agent was a new type of coronavirus and was named 2019 new coronavirus (2019-nCoV) (1). The World Health Organization (WHO) defined the disease COVID-19, which stands for Coronavirus Disease 2019, on February 12, 2020 (2). A pandemic was declared by WHO on March 11, 2020 and as of April 7, 2024, 775,293,630 confirmed cases and 7,044,637 deaths were reported worldwide (3).

While discussions about the follow-up and treatment of acute infection continue, long-term follow-up of patients who have recovered from the disease and the management of complications are also an important problem. Although the literature on the subject is limited, in a comprehensive study Huang et al. shared data as a result of 1-year follow-up of 1276 patients who received inpatient treatment in the hospital with a diagnosis of COVID-19; It was observed that 68% of the participants continued to have at least one complaint after 6 months and 49% after 1 year (4). The most common symptoms were reported respectively as weakness, muscle pain, sleep disturbance and hair loss and it was found to be more common in patients requiring oxygen support and intensive care hospitalization (4). In addition, although multisystemic complications such as lung fibrosis, thromboembolic events, diabetes, hypertension, chronic kidney disease are observed in patients in the long term, the frequency and risk factors of these complications have not been fully elucidated (5).

With this study, patients who have recovered from COVID-19, especially for whom there is not enough data about its long-term effects; It is aimed to reveal long-term clinical, laboratory and radiological findings, long-term follow-up findings and complications after acute infection. Again, during the period when diagnosed with COVID-19, it can be determined whether long-term symptoms and complications develop depending on variables such as age, gender, chronic disease history, severity of the disease and laboratory findings. We aim to use our findings as a reference for the development of long-term follow-up algorithms for COVID-19 patients and recommendations for patient management in the acute period to reduce permanent damage.

Material and Method

Study Design

Our study was conducted between February 2021 and September 2021 after obtaining the approval of the ethics committee. Patients who recovered from COVID-19 infection and applied to our outpatient clinic were included in the study prospectively. This study was obtained from the medical specialty thesis titled 'Long Term Follow up Findings of Covid-19 Cases and Determination of Permanent Disability Status' with ethics committee number 2021/9. Patients over the age of 18 who were diagnosed with SARS-CoV-2 PCR test or with computed tomography and clinical findings and gave written consent to participate in the study were included to this research. Patients who did not meet the inclusion criteria and did not give written informed consent were excluded from the study. When the study was designed, as a result of the evaluations made with the statistical unit in terms of sample size, it was concluded that the number obtained during the study would constitute the final sample since the study was prospective and therefore a standard sample size could not be determined. Demographic data of the patients, peripheral oxygen saturation, mMRC score, 6-minute walking test data, ongoing symptoms, laboratory data, radiological findings (x-ray and computed tomography), complications during follow-up were recorded. Patients who applied within the first 4 weeks from the time of diagnosis were grouped as the 1st visit, patients who applied between 4 and 12 weeks were grouped as the 2nd visit and patients who applied after 12 weeks were grouped as the 3rd visit interval. At the time of admission to the outpatient clinic, patients were admitted to the study at the interval of the visit, taking into account the time elapsed since the time of diagnosis.

Endpoints of the Study

The primary endpoint of our study was determined as the presentation of long-term clinical, laboratory and radiological findings, long-term follow-up findings after acute infection and complications of patients

who had COVID-19 disease and recovered.

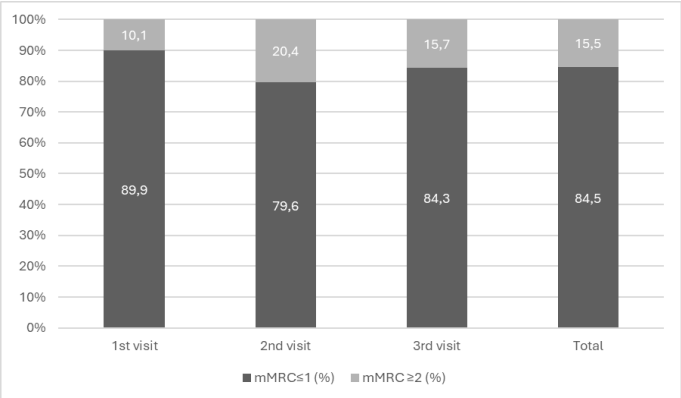
Statistical Analysis

The analysis of the data obtained in the study was performed with the SPSS 23.0 package program. Descriptive statistics were given as arithmetic mean (Mean/Percentage) for measurement variables, standard deviation (SD) and number (n) and percentage (%) for qualitative variables. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to evaluate the suitability of the data for normal distribution. Comparisons of measurement variables between three independent groups were evaluated with the Kruskal Wallis test in data that did not meet the normal distribution condition. Chi-square test was used to compare qualitative variables in independent groups. Statistical significance level was accepted as $p<0.05$.

Results

A total of 520 patients were included in the study, including 190 patients at the first visit interval, 203 patients at the second visit interval and 127 patients at the third visit interval, including duplicates. The mean admission time from the time of diagnosis was calculated as 25.4(±9.9) days for the first visit interval, 71.1(±18.7) days for the second visit interval and 171(±59.3) days for the third visit interval. The comparison of the demographic data of the patients by groups is given in Table I. No statistically significant difference was observed in the demographic distribution between the groups except for age.

Figure I. mMRC Distribution According to Visit Intervals



mMRC: Modified Medical Research Council

At least 1 symptom was still present in 181 (96.3%) patients who applied to our outpatient clinic at the first visit interval, 184 (90.6%) patients at the second visit interval and 114 (89.8%) patients at the third visit interval. The most frequently described symptoms were exertional dyspnea, fatigue and cough, respectively. The detailed distribution of the frequency of symptoms by visit intervals is given in Table II. At the visits, the patients' Modified medical Research Council Respiratory Scale (mMRC) scores were also evaluated. The mMRC score was classified as 1 and below, 2 and above (Figure I).

Table I. Demographic Data

	1st visit	2nd visit	3rd visit	Total	*p*
Age (Year)	52.4 (±13.4)	54 (±12.9)	56.3 (±14.6)	54 (±13.6)	*0.017*
Gender Female Male	105 (55.3%) 85 (44.7%)	108 (53.2%) 95 (46.8%)	68 (53.5%) 59 (46.5%)	281 (54%) 239 (46%)	0.912
Comorbidities Hypertension Diabetes Mellitus Asthma Thyroid dysfunction Coronary artery disease Heart failure Arrhythmia COPD	 83 (43.7%) 34 (17.9%) 29 (15.3%) 26 (13.7%) 18 (9.5%) 11 (5.8%) 5 (2.6%) 4 (2.1%)	 87 (42.9%) 44 (21.7%) 39 (19.2%) 25 (12.3%) 23 (11.3%) 9 (4.4%) 12 (5.9%) 11 (5.4%)	 56 (44.1%) 16 (12.6%) 16 (12.6%) 12 (9.4%) 19 (15.0%) 5 (3.9%) 7 (5.5%) 7 (5.5%)	226 (43.5%) 94 (18.1%) 84 (16.2%) 63 (12.1%) 60 (11.5%) 25 (4.8%) 24 (4.6%) 22 (4.2%)	
BMI (kg/m²) <30 ≥30	 96 (56.5%) 74 (43.5%)	 104 (56.8%) 79 (43.2%)	 64 (57.1%) 48 (42.9%)	 264 (56.8%) 201 (43.2%)	0.994
Marital status Married Single	 164 (87.2%) 24 (12.8%)	 182 (90.1%) 20 (9.9%)	 117 (92.9%) 9 (7.1%)	 463 (89.7%) 53 (10.3%)	*0.267*
Smoking status Never used Active smoker Quit smoking Passive exposure	 109 (57.4%) 18 (9.5%) 51 (26.8%) 12 (6.3%)	 129 (63.5%) 16 (7.9%) 53 (26.1%) 5 (2.5%)	 73 (57.5%) 12 (9.4%) 38 (29.9%) 4 (3.1%)	 311 (59.8%) 46 (8.8%) 142 (27.3%) 21 (4%)	0.481
Vocation Not working Working Health worker	 131 (68.9%) 59 (31.1%) 22 (11.6%)	 139 (68.5%) 64 (31.5%) 9 (4.4%)	 100 (78.7%) 27 (21.3%) 13 (10.2%)	 370 (71.2%) 150 (28.8%) 44 (8.5%)	*0.94*
Form of diagnosis PCR test CT and clinical	 171 (90.5%) 18 (9.5%)	 195 (96.1%) 8 (3.9%)	 114 (89.8%) 13 (10.2%)	480 (92.5%) 39 (7.5%)	0.132
Previous vaccination Annual flu vaccination Pneumococcal vaccine	 23 (12.6%) 29 (15.8%)	 25 (12.3%) 42 (20.7%)	 9 (7.1%) 25 (19.7%)	 57 (11.1%) 96 (18.7%)	 0.250 0.452
Immunosuppression	14 (7.4%)	12 (5.9%)	5 (3.9%)	31 (6%)	0.449

COPD: Chronic Obstructive Pulmonary Disease, **BMI:** Body Mass Index, **PCR:** Polymerase Chain Reaction, **CT:** Computed Tomography

Within the scope of our study, fingertip oxygen saturations (SpO2) of the patients who applied to our outpatient clinic were measured and grouped by taking a 93% cut-off limit. Accordingly, patients were divided into 94% and above, and 93% and below. 11 (5.9%) of the 185 patients who underwent

SpO_2 evaluation during the first visitwere 93% and below and 174 patients (94.1%) were 94% and above in saturation. In the second visit interval, the number of patients with 93% and below were 24 (12%), 94% and above were 176 (88%); in the third visit interval they were 8 (6.3%) and 119 (93.7%), respectively (*p=0.062*).

Table II. Ongoing Symptoms

	1st visit	2nd visit	3rd visit	Total
Symptom				
Exertional dyspnea	99 (52.4%)	131 (64.5%)	76 (59.8%)	306 (59.0%)
Fatigue	104 (55.0%)	92 (45.3%)	43 (33.9%)	239 (46.1%)
Cough	87 (46.0%)	74 (36.5%)	39 (30.7%)	200 (38.5%)
Chest-back pain	67 (35.4%)	61 (30.0%)	38 (29.9%)	166 (32.0%)
Muscle-joint Pain	31 (16.4%)	31 (15.3%)	6 (4.7%)	68 (13.1%)
Sleep Disturbance	27 (14.3%)	27 (13.3%)	13(10.2%)	67 (12.9%)
Memory Problems	11 (5.8%)	19 (9.4%)	28 (22.0%)	58 (11.2%)
Loss of Taste and Smell	24 (12.7%)	13 (6.4%)	12 (9.4%)	49 (9.4%)
Dyspnea (at rest)	19 (10.1%)	20 (%9.9)	8 (%6.3)	47 (%9.1)
Sputum	15 (7.9%)	17 (8.4%)	10 (7.9%)	42 (8.1%)
Nausea and Vomiting	14 (7.4%)	6 (3.0%)	3 (2.4%)	23 (4.4%)
Loss of Appetite	12 (6.3%)	7 (3.4%)	2 (1.6%)	21 (4.0%)
Excessive Sweating	13 (6.8%)	5 (2.5%)	4 (3.1%)	22 (4.2%)
Headache	11 (5.8%)	7 (3.4%)	1 (0.8%)	19 (3.7%)
Vertigo	6 (3.2%)	6 (3.0%)	2 (1.6%)	14 (2.7%)
Hair loss	3 (1.6%)	4 (2.0%)	6 (4.7%)	13 (2.5%)

Six-minute walking test (6-MWT) was performed on selected patient groups who applied to our outpatient clinic. Start and end saturations (%) and total walking distances (m) were measured. Total walking distances were 397m (±83.2) at visit 1, 363m (±95.5) at visit 2, and 404m (±71.5) at visit 3 and a statistically significant difference was found (*p=0.03*) (Table III).

Another data evaluated in the patients was whether there was weight loss. Weight loss was observed in 76 (51.1%) patients during the first visit, 115 (71.4%) patients during the second visit and 59 (60.2%) patients during the third visit (*p=0.028*). The average weight loss amount was calculated as 3.2kg (±3.6), 7.5kg (± 5.0), 8.6kg (±6.4), respectively, according to the visit intervals (*p=0.00*).

The time to return to normal life, which questioned the time to do daily work or return to the active profession, was 14 days (±7.5), 20.7 days (±15.2), 26.9 days (±26.3), respectively (p<0.05). At the time of the evaluation, 24 (12.6%) patients stated that they could not return to normal life in the first visit interval when the patients were evaluated on the 25.4th day on average, 24 (11.8%) patients in the second visit interval when they were evaluated on the 71.1 th day and 13 (11.2%) patients in the third visit interval when they were evaluated on the 171 st day.

Table III. Six-Minute Walk Test Data

	Start SpO_2 (%)	End SpO_2 (%)	Distance (m)
1st Visit			
93% and below	4 (7.5%)	9 (17%)	397 (±83.2)
94% and above	49 (92.5%)	44 (83%)	
2nd Visit			
93% and below	3 (5.1%)	14 (23.7%)	363 (±95.5)
94% and above	56 (94.9%)	45 (76,3%)	
3rd Visit			
93% and below	4 (6.3%)	11 (17.2%)	404 (±71.5)
94% and above	60 (93.7%)	53 (82.8%)	
Total			
93% and below	11 (6.2%)	34 (19.3%)	388 (±85.1)
94% and above	165 (93.8%)	142 (80.7%)	
p	*0.551*	*0.557*	*0.03*

Intergroup comparisons were made by evaluating the biochemical and radiological findings of the patients at three visit intervals. Among the biochemical parameters, the differences between mean Lymphocyte, Neutrophil, CRP, Procalcitonin, Ferritin, ALT and Creatine kinase (CK) levels were found to be statistically significant. The mean lymphocyte counts according to the groups were calculated as 2215/µl (±1097), 2460/µl (±1072), 2625/µl (±1688) (*p=0.01*). The distribution of neutrophil counts by groups were 5443/µl(±2578), 5177/µl(±4278),4355/µl(±1771) (*p*=0.00). Intergroup CRP levels were 8.1mg/L (±13.3), 7.9mg/L (±14), and 12.1mg/L (±66.2), respectively(*p=0.018*). Procalcitonin levels were calculated as 0.04µg/L (±0.03), 0.18µg/L (±1.03), 0.03µg/L (±0.02) (p=0.044). According to the groups, ferritin levels were 158.8µg/L (±178.9), 167.8µg/L (±261.8), 75.5µg/L(±70.1) (*p=0.001*). According to the visit intervals, ALT levels were 36U/L (±28.3), 32U/L (±41.6), 24.5U/L (±21.1) (*p=0.00*), while CK levels were 71.7U/L (±63.3), 80.7U/L (±72.0), 102.6U/L (±59.0) (*p=0.00*) (Table IV).

Table IV. Laboratory Results by Visit Intervals

	1st visit	2nd visit	3rd visit	Total	Normal range	*p*
Laboratory						
Leucocyte	8439	8199	7133	8223	3710-10190 /µl	*0.452*
Hemoglobin	13.6	13.6	13.9	13.7	12.89-16.73 g/dL	*0.225*
Platelets	282	265	259	271	130-400 103/µl	*0.258*
Neutrophil	5443	5177	4355	5074	1910-7080 /µl	*0.000*
Lymphocyte	2215	2460	2625	2410	1200-3600 /µl	*0.001*
CRP	8.1	7.9	12.1	9.0	< 5 mg/L	*0.018*
Procalcitonin	0.04	0.18	0.03	0.1	< 0.5 µg/L	*0.044*
Glucose	108	114	101	109	70-100 mg/dL	*0.159*
Creatinine	0.79	0.79	0.82	0.8	0.67-1.17 mg/dL	*0.237*
BUN	16.8	16.3	16.5	16.5	6-20 mg/dL	*0.474*
ALT	36	32	24.5	31.7	0-45 U/L	*0.000*
AST	24.5	23.1	21.6	23.2	0-35 U/L	*0.107*
GGT	42.4	55.8	25.1	42.8	0-55 U/L	*0.000*
LDH	223	230	205	222	<248 U/L	*0.075*
CK	71.7	80.7	102.6	82.4	20-200 U/L	*0.000*
D-Dimer	0.7	1.3	0.8	0.9	0-0.55mg/L	*0.555*
Ferritin	158.8	167.8	75.5	140.8	23.9-336.2 µg/L	*0.001*
TSH	1.8	2.5	2.1	2.2	0.34-5.6 µIU/mL	*0.864*

CRP: C-Reactive Protein, **BUN:** Blood Urea Nitrogen, **ALT:** Alanine Aminotransferase, **AST:**Aspartate Aminotransferase**, GGT:** Gamma Glutamyl Transferase**, LDH:** Lactate Dehydrogenase, **CK:** Creatinin Kinase, **TSH:** Thyroid Stimulating Hormone

Patients who applied to our outpatient clinic were evaluated radiologically by chest radiography and if clinically necessary computed lung tomography (CT). Pathological x-ray findings were detected in 74 (41.6%) patients at the first visit, pathological x-ray findings were observed in 65 (35.3%) patients at the second visit and 26 (21.8%) patients at the third visit (p=0.02).

Table V. Chest X-Ray Findings

	1st visit	2nd visit	3rd visit	Total	*p*
Pathological Finding	74 (41.6%)	65 (35.3%)	26 (21.8%)	165 (34.3%)	*0.02*
Ground Glass Opacity	52 (29.2%)	50 (27.2%)	7 (5.9%)	109 (22.7%)	*<0.01*
Consolidation	13 (7.3%)	8 (4.3%)	1 (0.8%)	22 (4.6%)	*0.032*
Linear/Reticular Opacity	33 (18.5%)	44 (23.9%)	22 (18.5%)	99 (20.6%)	*0.364*
Atelectasis	21 (11.8%)	18 (9.8%)	13 (10.9%)	52 (10.8%)	*0.826*
Bronchiectasis	4 (2.2%)	2 (1.1%)	4 (3.4%)	10 (2.1%)	*
Peripheral Localization	54 (30.3%)	55 (29.9%)	23 (19.3%)	132 (27.4%)	*0.073*
Central Localization	2 (1.1%)	17 (9.2%)	1 (0.8%)	20 (4.2%)	*
Bilateral Distribution	48 (27.0%)	60 (32.6%)	23 (19.3%)	131 (27.2%)	*0.04*
Multilobar Distribution	26 (14.6%)	31 (16.8%)	19 (16.0%)	76 (15.8%)	*0.84*
Subpleural Distribution	18 (10.1%)	37 (20.1%)	12 (10.1%)	67 (13.9%)	*0.009*

*: p value could not be given

While the most common pathological x-ray finding in the first visit interval was ground- glass opacities (n=52, 29.2%), similarly, ground-glass opacities were the most common in the second visit interval (n=50, 27.2%). The most common pathological radiographic finding in the third visit interval was linear/reticular opacities (n=22, 18.5%) (Table V).

The distribution of ground-glass opacities, which is the most common CT finding, according to visit intervals was 11 (61.1%), 13 (54.2%), and 9 (40.9%). The distribution of linear-reticular opacities was 7 (38.9%),9 (37.5%) and 14 (63.6%) patients. The distribution of other findings by visit intervals is detailed in Table VI.

Table VI. Distribution of CT Findings

	1st Visit	2nd Visit	3rd Visit	Total
Pathological Finding	16 (88.9%)	17 (70.8%)	20 (90.9%)	53 (82.8%)
Ground Glass Opacity	11 (61.1%)	13 (54.2%)	9 (40.9%)	33 (51.6%)
Linear/Reticular Op.	7 (38.9%)	9 (37.5%)	14 (63.6%)	30 (46.9%)
Atelectasis	6 (33.3%)	7 (29.2%)	6 (27.3%)	19 (29.7%)
Bronchiectasis	3 (16.7%)	6 (25.0%)	6 (27.3%)	15 (23.4%)
Interlobular Septal Thickening	-	4 (16.7%)	7 (31.8%)	11 (17.2%)
Crazy Paving Sign	-	-	5 (22.7%)	5 (7.8%)
Pulmonary Nodule	-	7 (29.2%)	5 (22.7%)	12 (18.8%)
Lymphadenopathy (LAP)	-	2 (8.3%)	2 (9.1%)	4 (6.3%)
Consolidation	1 (5.6%)	1 (4.2%)	-	2 (3.1%)
Pleural Effusion	1 (5.6%)	-	1 (4.5%)	2 (3.1%)
Honey Comb	-	-	2 (9.1%)	2 (0.4%)
Peripheral Localization	11 (61.1%)	14 (58.3%)	18 (81.8%)	43 (67.2%)
Bilateral Distribution	10 (55.6%)	14 (58.3%)	17 (77.3%)	41 (64.1%)
Multilobar Distribution	10 (55.6%)	13 (54.2%)	12 (54.5%)	35 (54.7%)
Subpleural Distribution	1 (5.6%)	11 (45.8%)	8 (36.4%)	20 (31.3%)

Different rates of pulmonary and extrapulmonary complications were observed in the patient groups included in the study. Complications were observed in 9 (4.7%) of the participants evaluated in the first visit interval, 47 (23.2%) in the second visit interval and 31 (24.4%) in the third visit interval (*p<0.005*). The most common complication was lung fibrosis and it was detected in 38 (18.7%) patients in the second visit interval and 20 (15.7%) patients in the third visit interval. DM was observed at a rate of 6(3.2%) in the first visit interval, 11 (5.4%) in the second visit interval and 7 (5.5%) in the last visit interval. Pulmonary thromboembolism (PTE) and venous thromboembolism (VTE) were observed in 1 (0.5%) patient at the first visit interval, 4 (2.0%) patients at the second visit interval and 7 (5.5%) patients at the third visit interval (Table VII).

Table VII. Disturbution of Complications

	1st visit	2nd visit	3rd visit	Total
Complication	9 (4.7%)	47 (23.2%)	31 (24.4%)	68 (13.1%)
Pulmonary Fibrosis	-	38 (18.7%)	20 (15.7%)	58 (11.2%)
Diabetes Mellitus (DM)	6 (3.2%)	11 (5.4%)	7 (5.5%)	24 (4.6%)
PTE/VTE	1 (0.5%)	4 (2%)	7 (5.5%)	12 (2.3%)
Hypertension	2 (1.1%)	1 (0.5%)	2 (1.6%)	5 (1.0%)
CRF	-	-	1 (0.8%)	1 (0.2%)
GI Bleeding	-	1 (0.5%)	-	1 (0.2%)
Avascular Necrosis	-	-	1 (0.8%)	1 (0.2%)
Proteinuria	1 (0.5%)	-	-	1 (0.2%)
Hypothyroidism	-	-	1 (0.8%)	1 (0.2%)

PTE: Pulmonary Thromboembolism, **VTE:** Venous Thromboembolism, **CRF:** Chronic Renal Failure,

GI: Gastrointestinal

Discussion

Although the severity of the COVID-19 pandemic,

which causes significant mortality and morbidity worldwide, has been greatly reduced, we may still encounter patients with SARS-CoV-2. Knowing the long-term effects of this infection on the lungs in patients who have had the infection and recovered is important for both pandemic period patients and follow-up of new cases. For this purpose, in our study, we tried to define the demographic data, comorbidities, ongoing symptoms, laboratory and radiological findings and developing complications of patients who had acute infection and recovered and applied to our outpatient clinic.

In the study conducted by Huang et al. with discharged COVID-19 patients, in which 1733 patients were evaluated at an average of 6 months after symptom onset; 68% of the patients stated that they still had an ongoing symptom and this rate was even higher in those with severe illness. Ongoing symptoms were, in order of frequency, fatigue and muscle pain, sleep disturbance, hair loss and inability to smell (6).

In another study by Carfi et al., patients were evaluated at an average of 60.3 days from the onset of symptoms after discharge and symptom questioning was performed. In this study, which included a total of 143 participants, only 12.6% of patients reported that all symptoms disappeared, 32% reported that 1 or 2 symptoms persisted and 55% reported that 3 or more symptoms persisted. The most common symptoms were weakness, shortness of breath, joint pain and chest pain, respectively (7). In a meta-analysis evaluating long-term COVID symptoms, the most common symptoms were pain, fatigue, neurocognitive symptoms, shortness of breath and palpitations (8).

In our study, 96.3%, 90.6% and 89.8% of the patients admitted to the outpatient clinic had ongoing symptoms according to the visit intervals. The most common symptoms were exertional dyspnea, fatigue, cough, chest and back pain, fatigue, muscle and joint pain. The fact that symptoms such as shortness of breath, exertional dyspnea and fatigue were observed more frequently in the last visit interval was thought to be related to the fact that patients who had a more severe illness in the 3rd visit interval and whose respiratory complaints still persisted presented to the outpatient clinic more frequently. Forgetfulness and memory problems were observed in 5.8% at the first visit and increased to 9.4% and 22.0% at subsequent visits, respectively. It was also found that sleep problems, muscle joint pain, taste and smell complaints were also common. In a review evaluating the neurological and neurocognitive outcomes of Long Covid, fatigue, headache, sleep disturbances, muscle weakness and muscle pain were the most common symptoms (9). The persistence of muscle and joint pain, sleep disturbances, forgetfulness and memory blurring symptoms at approximately 6 months from the time of diagnosis were considered as components of Post Covid-19 Neurologic Syndrome (PCNS), on which studies are ongoing (10).

In our study, mean lymphocyte and neutrophil counts, CRP, procalcitonin, ferritin, ALT and creatine kinase (CK) levels were found to be statistically significant according to the visit intervals of patients admitted to our outpatient clinic. In a systematic review of 34 relevant studies, it was observed that serum C-reactive protein (CRP), interleukin-6 (IL-6), lactate dehydrogenase (LDH), D-dimer levels were more elevated in critically ill patients (11). In addition, increased total white blood cell count was observed as a poor prognostic factor, while a decrease in the agranulocytic series, including lymphocytes and monocytes, was associated with poor disease prognosis. LDH levels were found to be higher in patients followed up in intensive care unit (11). In a case-control study by Gameil et al. in which patients' laboratory findings were evaluated at least 3 months after PCR negativity, erythrocyte sedimentation rate, CRP, D-dimer, ALT, AST, GGT and ALP levels were significantly higher in the case group (12). D-dimer is a biomarker of fibrinolytic system and coagulation activation. In a French review of 71 studies, increased D-dimer levels (3-4 times the upper limit of normal) were associated with poor prognosis and mortality in COVID-19 (13). No statistically significant difference was observed between the mean D-dimer levels of the patients included in our study. However, the fact that D-dimer levels were still above the upper limit of normal at all visit intervals and especially at the 3rd visit interval when the patients were evaluated at approximately 6 months suggests that the coagulation and fibrinolytic system has not yet reached physiologic limits in patients.

The mean CRP levels of the patients evaluated in our study were found to be higher than the upper normal limit of 5 mg/L in all visit intervals and it was observed to be higher especially in the 3rd visit interval. This was thought to be related to the fact that patients who applied to our outpatient clinic in the 3rd visit interval, in which the participants were evaluated at an average of approximately 6. months, had more severe illnesses and had higher hospitalization rates.

In a review comparing 70 studies evaluating ferritin levels in Covid-19 patients, it was observed that ferritin levels were higher in severe disease [(95% CI 306.51-489.02), *p <.001*], and significantly higher in patients who died compared to those who survived [(95% CI 391.01-963.33), *p <.001*] (14). In addition, a systematic review comparing inflammatory markers of COVID-19 patients with and without Post Covid syndrome showed no significant difference in ferritin levels between the two groups (15). In our study, although mean serum ferritin levels were normal at all visit intervals, a statistically significant decrease was observed at later visit intervals, suggesting that it may be associated with disease severity in the early period.

In a study in which a total of 384 patients were evaluated at an average of 8 weeks after discharge, 333 (87%) patients had chest radiographs and 85% had pathologic radiographic findings. 56% of the radiographs were typical for Covid-19 and 29% were indeterminate (16). In an another study in which patients were evaluated radiologically at the time of diagnosis and 3 months later, the most common radiologic findings in the early period were ground-glass opacities and consolidation, while reticular opacities were observed much more frequently at 3 months (17). In our study, the rates of pathological radiography according to the visit intervals were 41.6%, 35.3% and 21.8%, respectively. While ground glass opacities were dominant in the first visit interval, it was observed that they were replaced by linear/reticular opacities and atelectasis in the following visit intervals.

In a study conducted in China in which long-term CT findings were also evaluated, HRCT was performed in 353 patients evaluated at 6 months from symptom onset and 186 (53%) patients had at least one pathologic CT finding (6). In a systematic review evaluating the radiological findings of Long COVID patients, the most common tomography finding was ground-glass opacities, followed by fibrotic/interstitial abnormalities (18). In our study, a relatively limited number of CT scans were performed within clinical necessity. The most common pathologic CT findings are ground-glass opacities, linear/reticular opacities and atelectasis. While ground glass opacities are more common in the early period, linear/reticular opacities are more common CT findings in the later period.

Especially in severe COVID-19 patients, respiratory complications and lung fibrosis are observed due to diffuse lung involvement, macrophage activation syndrome, excessive immune response and subsequent ARDS, advanced age, intensive care follow-up and mechanical ventilation (19). This suggests that patients with severe disease and survivors are at risk for pulmonary fibrosis in the future. In a meta-analysis of 69 studies from 15 different countries, shortness of breath, cough, lung dysfunction and pulmonary fibrosis were the most common complications after COVID-19 (20). In a study by Stewart et al. in which patients were evaluated at a mean of 240 days after discharge, residual lung anomalies were found in 166 (79.4%) of 209 patients, with ground glass opacities in 25.5% and reticulation in 15.1% (21). In the patients we evaluated in our study, respiratory distress and pulmonary fibrosis were commonly seen. In the follow-up of the patients, patients who were still ongoing after the 12 th week and thought to be associated with lung fibrosis and whose radiological findings such as linear, reticular opacities, traction bronchiectasis and honeycomb were observed, were evaluated as post-COVID lung fibrosis. In this context, lung fibrosis was considered in 38 (18.7%) patients in the second visit interval and 20 (15.7%) patients in the third visit interval. Although it is observed to be relatively less at the last visit interval, it is thought that the level of persistence of respiratory symptoms and fibrosis needs to be evaluated with longer follow-up.

Stress hyperglycemia, impaired glucose tolerance and the use of drugs that impair glycemic control, especially corticosteroids, stand out as facilitating factors for the development of Diabetes Mellitus (DM)

in COVID-19 patients (22). In our patients we followed up, DM was observed to develop in 6(3.2%) patients in the first visit interval, 11 (5.4%) in the second visit interval and 7 (5.5%) in the last visit interval. It is thought that DM developed in our patients due to frequent use of corticosteroids, possibly impaired fasting glucose, and stress-related factors.

COVID-19 patients are at risk for increased thromboembolic events, macrovascular and microvascular thromboses (23). In a meta-analysis, it was found that venous thromboembolism (VTE) was approximately 30%, deep vein thrombosis (DVT) was 20% and pulmonary thromboembolism (PTE) was 18% in COVID 19 patients (24). In our study, PTE/VTE was observed in 0.5%, 2% and 5.5% according to the visit intervals, while gastrointestinal bleeding was observed in 1 (0.5%) patient in the 2nd visit interval. It is thought that seasonal influenza vaccine and pneumococcal vaccines will provide a milder course of Covid-19, a shorter length of stay in the intensive care unit and a decrease in the need for mechanical ventilation, especially by preventing secondary respiratory infections, but there is not enough evidence in this regard (25,26). In our study, a statistically significant difference was found between those who were vaccinated with pneumococcal or annual influenza vaccines and those who were not vaccinated in terms of service hospitalization rates in the total population (49.2% vs. 38.8%, *p=0.042*). Although no significant difference was observed in other subgroups in this respect, it was observed that the hospitalization rates were generally higher in the vaccinated groups. This was thought to be related to the fact that the vaccinated population was generally over 65 years of age and had higher additional comorbidities and high overall hospitalization rates. At the beginning of the study, it was planned to evaluate the patients included in the first visit interval at other visit intervals with ongoing follow-ups. However, we had patients who could not come to the next visits due to reasons such as patients avoiding coming to the hospital due to the pandemic and patients whose complaints regressed did not want to reapply. Our study was conducted as a cross-sectional study, not a follow-up study.

Since our study was planned prospectively, the risk of data loss was minimized. However, in the follow-up data of patients who were followed up in external centers and then applied to our outpatient clinic (despite the use of platforms such as e-nabız etc.), sometimes deficiencies were observed, especially in the data related to the acute disease period.

References

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet 2020 Feb 15;395(10223).
2. https://apps.who.int/iris/handle/10665/330992. (accessed on 2021 Oct 6).
3. https://data.who.int/dashboards/covid19. (accessed on 2024 Apr 7).
4. Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study [published correction appears in Lancet 2022 May 7;399(10337).
5. Gorna R, MacDermott N, Rayner C, et al. Long COVID guidelines need to reflect lived experience. Lancet 2021;397(10273):455-457.
6. Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2023;401(10393):e21-e33.
7. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020;324(6):603-605.
8. Natarajan A, Shetty A, Delanerolle G, et al. A systematic review and meta-analysis of long COVID symptoms. Syst Rev 2023;12(1):88.
9. Stefanou MI, Palaiodimou L, Bakola E, et al. Neurological manifestations of long-COVID syndrome: a narrative review. Ther Adv Chronic Dis 2022;13
10. Wijeratne T, Crewther S. Post-COVID 19 Neurological Syndrome (PCNS); a novel syndrome with challenges for the global neurology community. J Neurol Sci 2020;419
11. Kermali M, Khalsa RK, Pillai K, Ismail Z, Harky A. The role of biomarkers in diagnosis of COVID-19 - A systematic review. Life Sci 2020;254
12. Gameil MA, Marzouk RE, Elsebaie AH, Rozaik SE. Long-term clinical and biochemical residue after COVID-19 recovery. Egypt Liver J 2021;11(1):74.
13. Rostami M, Mansouritorghabeh H. D-dimer level in COVID-19 infection: a systematic review. Expert Rev Hematol 2020;13(11):1265-1275.
14. Cheng L, Li H, Li L, et al. Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. J Clin Lab Anal 2020;34(10).
15. Yong SJ, Halim A, Halim M, et al. Inflammatory and vascular biomarkers in post-COVID-19 syndrome: A systematic review and meta-analysis of over 20 biomarkers. Rev Med Virol 2023;33(2).
16. Mandal S, Barnett J, Brill SE, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax 2021;76(4):396-398.
17. Gao Y, Liang WQ, Li YR, He JX, Guan WJ. The Short- and Long-Term Clinical, Radiological and Functional Consequences of COVID-19. Arch Bronconeumol 2022;58:32-38.
18. Bazdar S, Kwee AKAL, Houweling L, et al. A Systematic Review of Chest Imaging Findings in Long COVID Patients J Pers Med. 2023;13(2):282.
19. McDonald LT. Healing after COVID-19: are survivors at risk for pulmonary fibrosis?. Am J Physiol Lung Cell Mol Physiol 2021;320(2):L257-L265.
20. Elhiny R, Al-Jumaili AA, Yawuz MJ. An overview of post-COVID-19 complications. Int J Clin Pract 2021;75(10)
21. Stewart I, Jacob J, George PM, et al. Residual Lung Abnormalities after COVID-19 Hospitalization: Interim Analysis of the UKILD Post-COVID-19 Study. Am J Respir Crit Care Med 2023;207(6):693-703.
22. Pal R, Bhadada SK. COVID-19 and diabetes mellitus: An unholy interaction of two pandemics. Diabetes Metab Syndr 2020;14(4):513-517.
23. Gąsecka A, Borovac JA, Guerreiro RA, et al. Thrombotic Complications in Patients with COVID-19: Pathophysiological Mechanisms, Diagnosis, and Treatment. Cardiovasc Drugs Ther 2021;35(2):215-229.
24. Di Minno A, Ambrosino P, Calcaterra I, Di Minno MND. COVID-19 and Venous Thromboembolism: A Meta-analysis of Literature Studies. Semin Thromb Hemost 2020;46(7):763-771.
25. Sultana J, Mazzaglia G, Luxi N, et al. Potential effects of vaccinations on the prevention of COVID-19: rationale, clinical evidence, risks, and public health considerations. Expert Rev Vaccines 2020;19(10):919-936.
26. Thindwa D, Garcia Quesada M, Liu Y, et al. Use of seasonal influenza and pneumococcal polysaccharide vaccines in older adults to reduce COVID-19 mortality. Vaccine 2020;38(34):5398-5401.