Journal of Izmir Chest Hospital 2023;37(2):75–83
DOI: 10.14744/IGH.2023.80664

RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

Finding Predictors of Radiological Regression for COVID-19 Pneumonia

COVID-19 Pnömonisinde Radyolojik Regresyona Etki Eden Faktörler

[1]Sezgi ŞAHİN DUYAR
[1]Özlem SÖNMEZ
[1]Dicle KAYMAZ
[2]Hakan ERTÜRK

[1]Deparment of Pulmonology, Atatürk Sanatory Training and Research Hospital, Ankara, Türkiye

[2]Deparment of Radiology, Atatürk Sanatory Training and Research Hospital, Ankara, Türkiye

ORCID ID
SŞD : 0000-0001-5004-4077
ÖS : 0000-0003-1551-2845
DK : 0000-0001-7951-2065
HE : 0000-0002-5730-9215

ABSTRACT

Objective: The factors associated with post-COVID sequela need to be revealed for a better follow-up. This study is conducted to reveal the parameters associated with radiological regression in non-intubated patients hospitalized for COVID pneumonia.

Material and Methods: The demographic and clinical characteristics of the coronavirus disease 2019 (COVID-19) pneumonia patients hospitalized in August 2020 were reviewed retrospectively. The data of patients who had radiological complete regression in the 1st month according to chest X-ray and/or computed tomography of the thorax were compared with the others.

Results: The patients (n=42) who were followed up in our clinic for COVID-19 pneumonia between August 1 and September 1, 2020, and had undergone radiological control examinations at least 4 weeks after discharge, were included in the study. It was observed that a complete radiological response could not be achieved in 38% (n=16) of the patients in the 1st month. The data of patients with and without complete radiological regression were found to be similar in terms of mean age, gender distribution, comorbidities, smoking rate, length of hospital stay, duration of radiological follow-up, and oxygen values at admission. The rates of use of hydroxychloroquine, inhaled corticosteroid, non-specific antibiotics, and vitamin C during hospitalization were the same in both groups. However, the rate of IV steroid administration and antipseudomonal antibiotic use was lower in the group with complete radiological response (p=0.021 and p=0.038, respectively), and the C-reactive protein (CRP) value was statistically higher in the group without complete radiological response (33.2 mg/L–78.9 mg/L, p=0.020). Regression analysis showed that CRP at admission was independently associated with delayed radiological regression (p=0.011, RR: 1.02, CI: 1.004–1.033).

Conclusion: Our results revealed that patients with CRP ≥60 mg/L and who had received IV steroids and antipseudomonal antibiotic therapy can be regarded as candidates for prolonged radiological response in the post-COVID period.

Keywords: COVID-19, CRP, hypoxia, radiologic sequel.

Cite this article as: Şahin Duyar S, Sönmez Ö, Kaymaz D, Ertürk H. Finding Predictors of Radiological Regression for COVID-19 Pneumonia. Journal of Izmir Chest Hospital 2023;37(2):75–83.

Received (Geliş): March 31, 2023 **Revised (Revize):** July 13, 2023 **Accepted (Kabul):** July 14, 2023 **Online (Çevrimiçi):** August 10, 2023
Correspondence author (Sorumlu yazar): Sezgi ŞAHİN DUYAR, MD. Atatürk Sanatoryum Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Ankara, Türkiye.
Tel: +90 312 355 21 10 **e-mail:** drsezgisahin@gmail.com

ÖZ

Amaç: Koronavirüs hastalığı (COVID-19) sonrası dönemde görülen sekel lezyonlar ile ilişkili faktörlerin ortaya konulması hasta takibi açısından önemlidir. Bu çalışma, COVID-19 pnömonisi nedeniyle servise yatırılan entübe olmayan hastalarda radyolojik gerileme ile ilişkili parametreleri belirlemek amacıyla yapıldı.

Gereç ve Yöntemler: Çalışmada, Ağustos 2020 tarihinde hastaneye yatırılan COVID-19 pnömonisi hastalarının demografik ve klinik özellikleri retrospektif olarak incelendi. Akciğer grafisi ve/veya bilgisayarlı toraks tomografisine göre birinci ayda radyolojik olarak tam gerileme olan hastaların verileri diğer hastalarla karşılaştırıldı.

Bulgular: 01 Ağustos 2020–01 Eylül 2020 tarihleri arasında kliniğimizde COVID-19 pnömonisi nedeniyle takip edilen en az dört hafta sonraya ait kontrol radyolojik tetkikleri olan 42 hasta çalışmaya alındı. Tam radyolojik cevabın birinci ayda hastaların %38'inde (n=16) sağlanamadığı görüldü. Radyolojik olarak tam gerileme olan hastaların verileri diğerleri ile karşılaştırıldığında ortalama yaş, cinsiyet dağılımı, ek hastalıklar, sigara içme oranı, hastanede kalış süresi, radyolojik izlem süresi ve başvuru anındaki oksijen değerleri açısından benzer bulundu. Hastanede yatış sırasında hidroksiklorokin, inhale kortikosteroid, spesifik olmayan antibiyotik ve C vitamini kullanım oranları da her iki grupta aynı bulundu. Ancak tam radyolojik cevabı olan grupta intravenöz steroid uygulama ve antipsödomonal antibiyotik kullanma oranı daha düşüktü (sırasıyla p=0,021 ve p=0,038) ve C-reaktif protein (CRP) değeri tam radyolojik cevap göstermeyen grupta istatistiksel olarak yüksek bulundu (33,2mg/L–78,9 mg/L, p=0,020). Regresyon analizi başvuru anındaki CRP değerinin gecikmiş radyolojik regresyon ile bağımsız olarak ilişkili olduğunu gösterdi (p=0,011, RR=1,02, CI=1,004–1,033).

Sonuç: CRP düzeyi ≥60 mg/L olan, intravenöz steroid ve antipsödomonal antibiyotik tedavisi alan hastalarda COVID-19 sonrası dönemde uzamış radyolojik cevap olduğu tespit edildi.

Anahtar kelimeler: COVID-19, CRP, hipoksi, radyolojik sekel.

INTRODUCTION

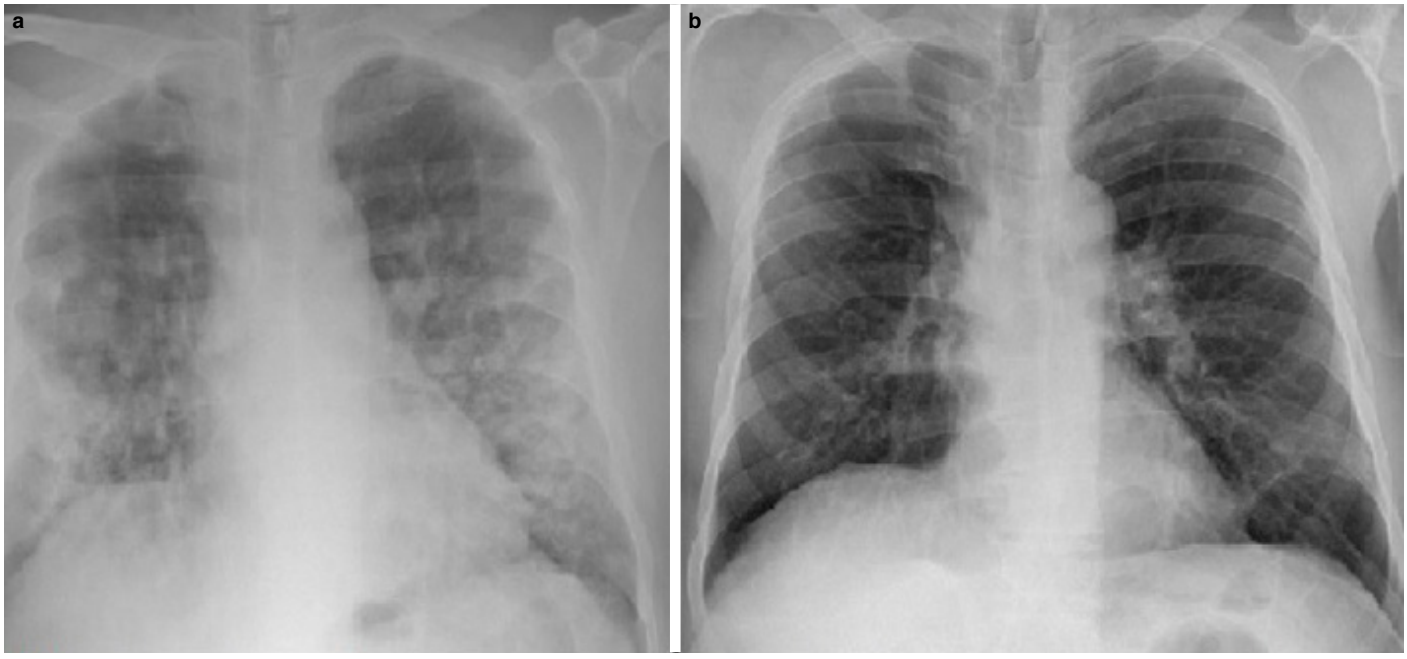
The coronavirus disease 2019 (COVID-19) continues to affect the globe in all aspects of health and socioeconomic issues. After many overwhelming waves, in addition to the worries about upcoming variants, the long-lasting symptoms in the COVID-19 survivors also stand at our door as an important problem. Long-COVID can be defined as chronic symptoms of any system lasting more than 12 weeks in the lack of another alternative diagnosis.[1] However, the clinical features of COVID survivors suffering from long-lasting symptoms and having radiological sequelae have not been fully understood yet. A 15-year follow-up study showed that after the 2003 epidemic caused by severe acute respiratory syndrome virus from the same virus family, radiological changes including band-like consolidations and ground-glass opacities might be permanent.[2] For COVID-19 pneumonia, the sequential radiologic changes on thorax computed tomography (CT) begin with ground-glass opacities and progressive consolidation in the early, progressive, and peak stages covering the first 13 days after the symptom onset. The radiologic lesions subside through the late stage (after 2 weeks of the symptom onset) and faint ill-defined ground-glass areas and linear opacities may take the stage afterward.[3,4] It was reported that 1 year after moderate COVID nearly one-third of the patients present with severe DLCO impairment and fibrotic changes. The estimated incidence of post-COVID lung fibrosis after moderate illness is 2–6%.[5] Undoubtedly, pulmonary fibrosis will affect many people as an important part of the post-COVID syndrome, considering the pandemic scale.[6] Pulmonary fibrosis related to COVID-19 has been reported mostly in patients discharged from the intensive care unit.[1] A recent meta-analysis revealed that CT score of ≥18, ICU admission, mechanical ventilation, longer hospitalization, and steroid, antibiotic and immunoglobulin treatments, chronic obstructive pulmonary disease, and persistent symptoms may be regarded as risk factors for post-COVID pulmonary fibrosis.[7]

On the other hand, it was reported that 53.0% of patients with mild COVID-19 recovered with no radiological sequelae within 3 weeks after discharge.[8] However, nearly half of the patients with mild disease present with prolonged radiologic recovery for which risk factors and follow-up protocols should be addressed. In this study, we aimed to reveal the clinical factors associated with prolonged radiological recovery (over 4 weeks) in non-intubated patients and to provide scientific proof for organizing the follow-up protocols for the non-intubated patients.

MATERIAL AND METHODS

This study includes patients (age >18 years) with COVID-19 pneumonia who were hospitalized between August 1 and September 1, 2020, in our clinic. This retrospective and cross-sectional study was approved by the Local Ethics Committee (2012-15/2457) and was performed in line with the principles of the Declaration of Helsinki. Informed consent was obtained from the patients for the usage of their medical data during hospitalization.

All patients had been confirmed as COVID-19 positive by reverse-transcription polymerase chain reaction test applied on the throat and nasopharyngeal swab samples obtained at the admission to the hospital. The hospitalization criteria of the Turkish Ministry of Health were applied. The patients with respiratory rate >24–30/min, SpO_2 <93%, blood lymphocyte count <800/μL, C-reactive protein (CRP) >10 mg/L, ferritin >500 ng/mL, or D-dimer >1000 ng/mL were interned in a conventional service unless they needed intubation. In line with the recommendations of the Turkish Ministry of Health, the patients with dyspnea, respiratory rate >24/min, SpO_2 <93%, or abnormal findings in physical examination of the respiratory system underwent thorax CT. The CT findings of all the patients were reported as typical for COVID-19 pneumonia based on the criteria of the Radiological Society of North America consensus by a radiologist who had 20 years



Initial chest X-ray Post-COVID control chest X-ray on the 426th day

Figure 1: An example of a chest X-ray for a patient without complete regression showing reticular and band-like opacities **(a)** chest X-ray on the admission to hospital and **(b)** chest X-ray during the follow-up.

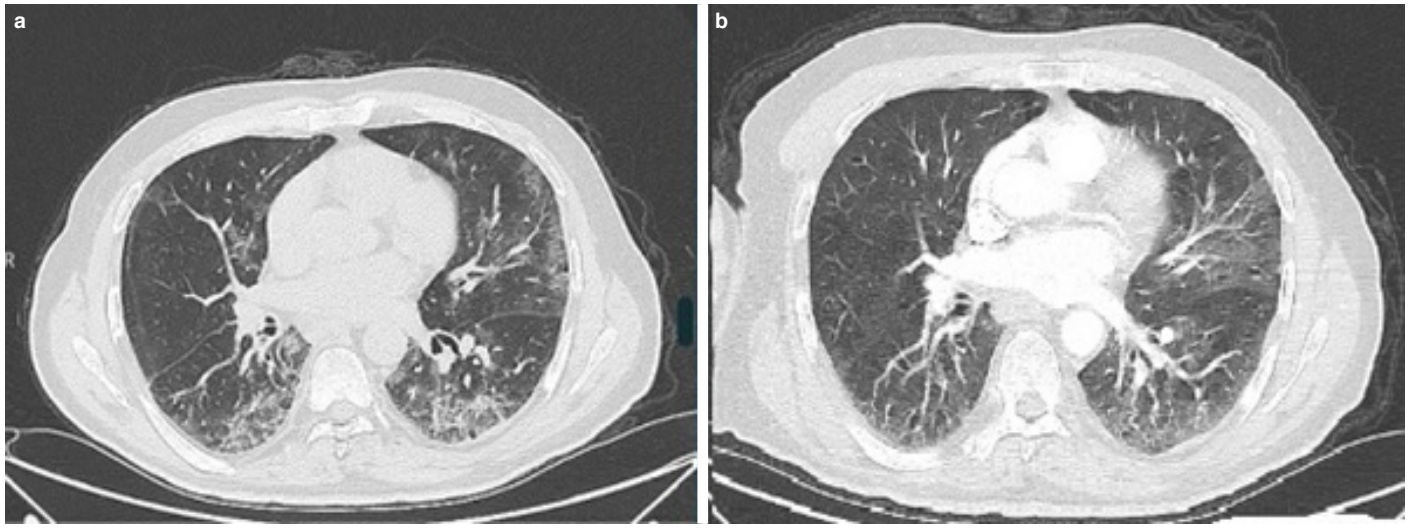
of experience.[9] Radiologic findings other than ground-glass opacities including mediastinal lymphadenopathy, nodules, pleural effusion, bronchiectasis, and consolidation were also reported. In addition, the proportion of lung parenchyma involved was visualized in the axial, coronal, and sagittal planes and categorized as ≤50% or >50%, subjectively. A follow-up CT was scheduled for the patients who were admitted to the outpatient clinic after discharge with persistent symptoms of dyspnea, chest pain, cough, and/or abnormal radiologic findings on chest X-ray. High-resolution CT (HRCT) examinations were performed in the supine position and deep inspiration using Siemens Emotion 6 (Siemens AG, Erlangen, Germany) and Toshiba Alexion 16 (Nasu, Japan). No contrast medium was injected. Parameters were each set to 80–135kV, 50–300 mA with dose modulation, a 1 mm and –1.25 mm thickness, and reconstruction. All axial and reconstructed CT images were reviewed in the PACS using mediastinal (width, 340 HU; level, 50 HU), lung (width, 1500 HU; level, –500/–600 HU) window settings.

The patient's medical files, nursing, and electronic records were reviewed retrospectively. The demographic characteristics including age gender, comorbidities, and smoking history were extracted. The length of hospital stay and the radiological follow-up period was calculated. The clinical and radiological findings were collected for this study as follows: fever and oxygen saturation (by pulse oximetry or arterial blood gas) values at admission, treatment protocols (hydroxychloroquine, favipiravir, inhaled or intravenous (IV) steroids, antibiotics, vitamin C, and anticoagulants), the presence of severe pneumonia (lung parenchyma involvement >50% by visual quantification), radiologic abnormalities in thorax CT (mediastinal lymphadenopathy, nodules, pleural effusion, bronchiectasis, and consolidation), and laboratory findings at admission (white blood cell, neutrophil, lymphocyte eosinophil, and platelet counts, hemoglobin, mean corpuscular volume, red cell distribution width, mean platelet volume, blood urea nitrogen, creatine, aspartate aminotransferase, alanine aminotransferase, D-dimer, CRP ferritin, and troponin values). The prolonged treatment with low-molecular-weight heparin (LMWH) after the discharge was also recorded. It was evaluated whether the D-dimer value was higher than the age-adjusted cutoff (>age×10), or twice the normal value (>1 mg/L). In addition, systemic inflammatory index (SII) and platelet mean volume/platelet count ratio (MPR) were calculated. MPR was defined as (mean platelet volume (fL)/platelet count)×10^3. SII was calculated as (neutrophil count × platelet count/lymphocyte count)/10^3.

Among the patients who recovered from COVID-19 pneumonia without the need for intubation, the ones who had radiological control with chest X-ray and/or HRCT at least 4 weeks after hospitalization were evaluated by two pulmonologists and a radiologist. The patients with the complete regression were determined as the complete response group, and the others with the residual radiological sequelae (residual ground glass, reticular, and/or band-like opacities) as the prolonged regression group (Fig. 1). In addition to the parameters mentioned above, these two groups were compared in terms of follow-up times and laboratory findings during the control. A subgroup analysis was also performed for the data of the patients who underwent HRCT for radiological controls (Fig. 2).

Statistical Analysis

The SPSS Statistics 21 for Windows package program (IBM, New York/USA) was used for the analysis of the data. Descriptive statistics were shown as mean±standard deviation for normally distributed variables, median (25–75th percentile) for the other variables, and the number of cases and percentages for nominal variables. The significance of the difference between the groups in terms of means was evaluated with the "t-test," the significance of the difference in terms of median values



Initial thorax CT

Post-COVID thorax CT control on the 133rd day

Figure 2: An example of thorax CT for the patients without complete regression showing reticular and ground-glass opacities **(a)** initial thorax CT and **(b)** post-COVID thorax CT control on the 133rd day.

CT: Computed tomography.

was evaluated with the "Mann–Whitney U-test," and nominal variables were evaluated with the "Pearson Chi-square or Fisher Exact test." ROC analysis was performed to calculate the cutoff values. Logistic regression analysis was applied to identify independent risk factors. P<0.05 was considered statistically significant.

RESULTS

The data of 97 COVID PCR-positive patients who were hospitalized and followed up by our clinic between August 1 and September 1, 2020, were reviewed retrospectively. To determine the clinical factors affecting the radiological regression, the analysis was performed for 42 patients whose radiological data at least 4 weeks after hospitalization due to COVID-19 pneumonia were available. It was observed that 38% (n=16) of the patients could not reach a complete regression in the 1st month. The patients with the radiologic sequela presented with residual ground glass, reticular, and/or band-like opacities. New-onset traction bronchiectasis or honeycombing was not seen in any of the patients. The data of the patients with complete regression were compared with the others. The rate of radiologic follow-up with thorax CT was similar between the groups. Radiologic sequelae were observed in seven out of 21 patients who were controlled by thorax CT. These data were also compared in a subgroup analysis. The groups were similar in terms of mean age, gender distribution, comorbidities, smoking rate, length of hospital stay, duration of radiological follow-up, and radiological findings. The median control time was 64.5 days; the median length of hospital stay was 8 days. The groups were not statistically different in terms of oxygenation value at the time of admission. The rates of using hydroxychloroquine, an inhaled corticosteroid, non-specific antibiotics, and vitamin C during hospitalization were similar in both groups. Hydroxychloroquine was solely used for 7.1% of the patients while 31% took only favipiravir, and 61.9% were given both drugs together or consecutively. It was observed that LMWH treatment was continued after discharge in approximately one-third of the patients in both groups (p=1.00). However, the rate of IV steroid administration and antipseudomonal antibiotic use was lower in the group with complete regression (p=0.021 and p=0.038, respectively) (Table 1). Among the laboratory results obtained both on the day of admission and on the day of follow-up, only the CRP value at admission was found to be statistically higher in the group without complete regression (33.2 mg/L vs. 78.9 mg/L, p=0.020). In the statistical analysis performed after the exclusion of three patients with PTE, the rate of D-dimer higher than 2 times the normal and higher than the age-adjusted cutoff were similar between the groups (Tables 2, 3).

When subgroup analysis was performed using data from 21 patients who underwent radiologic follow-up with thorax CT, the parameters showing statistical significance were similar to the previous results. CRP value at admission was higher in the group with radiologic sequelae after 4 weeks (19 mg/L vs. 73.9 mg/L, p=0.002). The rate of IV steroid and antipseudomonal antibiotic use was also higher in this group (p=0.017 and p=0.049, respectively) (Table 1). It was found that out of 18 patients with radiologic follow-up data after the 3rd month, six patients had sequelae lesions. The rate of radiologic sequela after 3 months was 33.3%. When the group with sequelae lesions in the 3rd month was compared with the remaining 12 patients, no statistically significant difference was found between the groups in terms of parameters included in our study. According to the results of the regression analysis in which parameters with statistically significant differences in univariate analysis (IV steroid use, antipseudomonal antibiotic use, and CRP value), the CRP value at the time of admission was independently associated with delayed radiological regression (p=0.011, RR: 1.02, CI: 1.004–1.033).

With ROC analysis, it was determined that a CRP value of ≥60 mg/L at the time of application could predict the delay of radiological resolution with 68.8% sensitivity and 69.2% specificity (AUC: 0.716, p: 0.020, CI: 0.56–0.88) (Fig. 3).

Table 1: Comparisons of demographic and clinical features for factors affecting radiological regression

	Patients followed up with chest X-ray and/or thorax CT					Patients followed up with thorax CT				
	Complete regression + (n=26)		Complete regression - (n=16)		p	Complete regression + (n=14)		Complete regression - (n=7)		p
	n	%	n	%		n	%	n	%	
Age	55.7±14		59.9±12.8		0.33	53.4±14.2		63.9±16.1		0.143
Gender (male)	76.9	20	75	12	1	78.4	11	71.4	5	1
Hospitalization (days)	8 (6–10)		10 (5.3–12.8)		0.267	6 (5–9.3)		10 (5–12)		0.289
Follow-up period (days)	79.5 (50.8–199.3)		56 (45.8–206.5)		0.727	90 (51.5–204.5)		93 (51–303)		0.551
SO_2 (in room air)	93 (90–96) (n=23)		93 (91.3–94.8) (n=12)		0.78	94 (90–97) (n=13)		93 (91–94.5) (n=5)		0.804
Hypoxemia (SO_2<90%)	33.3 (n=24)	8	26.7 (n=15)	49	0.734	35.7	5	28.6	29	1
Fever	36.7 (36.4–37)		36.7(36.4–37)		1	36.8 (36.6–37.2)		36.4(36.2–36.8)		0.176
Follow-up with thorax CT	53.8	14	43.8	7	0.751					
Comorbidities										
HT	30.8	8	31.3	5	1	50	7	14.3	1	0.174
CAD/CHF	7.7	2	0	0	0.256	7.1	1	0	0	0.469
DM	30.8	8	31.3	5	1	42.9	6	42.9	3	1
Asthma/COPD	11.5	39	35.7	6	0.063	14.3	2	28.6	2	0.432
Treatment										
Hydroxychloroquine	73.1	19	62.5	10	0.51	85.7	12	42.9	3	0.12
ICS	23.1	6	50	8	0.098	21.4	3	42.9	3	0.306
IV steroid	23.1	6	62.5	10	0.021	14.3	2	71.4	5	0.017
IV vitamin C	23.1	6	18.8	3	1	14.3	2	28.6	2	0.432
Non-specific Ab	57.7	15	68.8	11	0.53	42.9	6	85.7	6	0.159
Antipseudomonal Ab	7.7	2	37.5	6	0.038	7.1	1	42.9	3	0.049
LMWH after discharge	31.3 (n=16)	5	40 (n=10)	4	0.692	20 (n=10)	2	33.3 (n=4)	1	0.631
Tomographic findings										
Severe involvement*	8	2	13.3	2	0.586	14.3	2	0	0	0.293
Nodule	12	3	6.7	1	0.586	14.3	2	0	0	0.293
Consolidation	4	1	6.7	1	0.708	7.1	1	0	0	0.469
Pleural effusion	0	0	13.3	2	0.061	0	0	14.3	1	0.147
Bronchiectasis	12	3	6.7	1	0.586	21.4	3	0	0	0.186
Mediastinal LAP	40	10	33.3	5	0.746	35.7	5	28.6	2	1

*: Lung parenchyma involvement >50% by visual quantification. CT: Computed tomography, SO_2: Oxygen saturation, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, ICS: Inhaled corticosteroids, IV: Intravenous, Ab: Antibiotics, LMWH: Low molecular weight heparin, LAP: Lymphadenopathy.

DISCUSSION

Recent studies have proven that overexuberant inflammatory response and coagulopathy are the main mechanisms responsible for pulmonary parenchymal lesions in severe COVID-19 cases.[10,11] COVID-19 pneumonia results in mortality in 2–3% of patients, depending on the degree of pulmonary lesions and the patient's cardiopulmonary reserve.[12–14] In line with our results, the previous studies proved that the parenchymal changes due to viral pneumonia disappear completely in two-thirds of patients within 2–4 weeks.[15,16] However, for COVID-19 survivors intubated due to acute respiratory distress syndrome, post-COVID fibrotic changes are observed in a wide range of 4–61% increasing with the duration of the disease.[17]

Table 2: Comparisons of laboratory findings at admission for factors affecting radiological regression

	Patients followed up with chest X-ray and/or thorax CT			Patients followed up with thorax CT		
	Complete regression + (n=26)	Complete regression - (n=16)	p	Complete regression + (n=14)	Complete regression - (n=7)	p
WBC#/mm^3	5085 (4239.8–6972.5)	6155 (4592.5-9957.5)	0.166	5085 (4272.5–5765)	6550 (4490–7130)	0.136
Neutrophil#/mm^3	3335 (2532.5–4880)	4435 3365–7037.5)	0.074	3230 (2450–4052.5)	4320 (3320–5350)	0.062
Lymphocyte#/mm^3	1250 (1050–1540)	1125 (962.5–1427.5)	0.517	1295 (1002.5–1690)	1260 1110–1420	0.911
Eosinophil#/mm^3	10 (0–30)	10 (0–27.5)	0.611	10(10–25	10(0–30)	0.507
Hemoglobin (gr/dl)	13.8±1.6	14.4±1.5	0.275	13.9±1.9	14.4±1.6	0.502
MCV (fl)	89.2 (87.1-92)	90 (86.6–92.8)	0.717	88.2 (84.5–91.5)	90.5 (88.7-92.8)	0.167
RDW (%)	13.5 (13.1–14.9)	13.1 (12.5–13.9)	0.108	14 (13.2–15.2)	12.9 (12.3–13.5)	0.057
Platelet#10^3/mm^3	198.5±55.7	205.6±60.6	0.699	204.3±50.3	185.9±47	0.429
MPV (fl)	9.6 (8.7-10.1)	9.2 (8.7–9.6)	0.243	9.8 (8.7–10.3)	9.6 (9.3–10.7)	0.601
SII	549 (350.4–839.5)	769.3 (517.1–1306.2)	0.133	590.1 (305–865.9)	743.1 (494.7–890.9)	0.502
MPR/Platelet#	5 (4–5.8)	4.5 (3.3–5.99	0.517	4.4 (4–5.7)	5.1 (4–6.2)	0.456
BUN (mg/dL)	15 (11.5–20.3)	13 (11.3–15)	0.269	15.5 (9.8–20.3)	14 (12–17)	0.68
Creatinine (mg/dL)	1.1 (0.91–1.19)	0.91 (0.78–1.1)	0.087	1.1 (0.79–1.16)	0.84 (0.75–1.06)	0.217
ALT (U/L)	26.5 (20.8–40.8)	18 (15.5–27.8)	0.068	22.5 (19.3–39.3)	23 (17–43)	0.911
AST (U/L)	33 (26–47)	25.5 (19.3–40.3)	0.1	26 (24–40)	35 (27–46)	0.217
CRP (mg/L)	13.2 (14.3–81.3)	78.9 (44.6–147.8)	0.02	19 (8.9–44.2)	73.9 (67.4–148.7)	0.003
D-dimer (mg/L)	0.48 (0.38–0.66)	o.44 (0.33–0.90)	0.86	0.45 (0.35–0.59)	0.65 (0.33–0.91)	0.483
D-dimer>2×n (n), %	(3) 12.5	(2) 13.3	0.94	(2) 16.7	0	0.289
Dimer>age-adjusted cutoff (n), %	(8) 33.3	(6) 40	0.74	(3) 25	(3) 50	0.289
Ferritin (ng/mL)	221.6 (132.1–509.5)	313.6 (117–594.3)	0.754	194.6 (86.4–357.5)	308.5 (158.6–510.7)	0.219
Troponin(mg/L)	3.8 (2.5–6.1)	4.1 (2.5–10)	0.57	3.1 (2.5–6.7)	6.6 (3.2–11.7)	0.206

CT: Computed tomography, WBC: White blood cells, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume, SII: Systemic inflammatory index, MPR: Platelet mean volume/platelet count ratio, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein

The results of our study contribute to the previous research by presenting the factors affecting radiological regression in non-intubated patients with COVID-19 pneumonia. Besides, the relationships between many parameters including SII, MPR, and RDW, and the radiologic regression were analyzed for the same clinic setting.

Our results show that the complete radiological regression was observed at the end of the 1st month in 62% of these patients who were discharged without the need for intensive care. In another study including intensive care patients, radiological complete regression in 6 months was reported in only 38% of patients with COVID-19 pneumonia.[13] In a study by Vural et al.,[18] it was stated that during the 3rd to 6th-month follow-ups with thorax CT, fibrotic changes were observed in 35% of the patients, depending on the presence of severe pneumonia and the length of hospital stay. In our study, when patients with and without complete regression were compared, the groups were statistically identical in terms of age, comorbidities, and oxygenation at admission. However, the proportion of patients who received IV steroids and antipseudomonal antibiotics during hospitalization was statistically higher in the group without complete regression. Steroids may prevent progression to post-COVID pulmonary remodeling and fibrosis in the lung.[19] On the other hand, as they may cause bacterial or fungal infections as well as prolonged radiological regression, steroid administration should be tailored to each patient considering comorbidities. The poor response to initial treatments can be caused by progressing COVID-19 illness and/or bacterial coinfection or superinfection. The difficulties in differential diagnosis between these two phenomena result in a higher rate of empiric use of wide-spectrum antibiotic treatments. Recent researches showed that empiric antibiotic use for COVID-19 pneumonia did not prevent deterioration or mortality and even is associated with post-COVID pulmonary fibrosis.[7,20]

According to our results, as well as dimer value and thorax CT findings at admission, the rate of vitamin C, hydroxychloroquine, and favipiravir administration during hospitalization was the same between the groups. Underlining that the rate of vitamin C and hydroxychloroquine administration was not different between the groups, this study contributes to the concrete evidence against the speculations about these drugs. The results from the Turkish National COVID-19 cohort including 1500 patients also show that antiviral agents and hydroxychloroquine do not affect mortality.[21] According to our results, the ratio of the prolonged treatment with LMWH after discharge does not differ

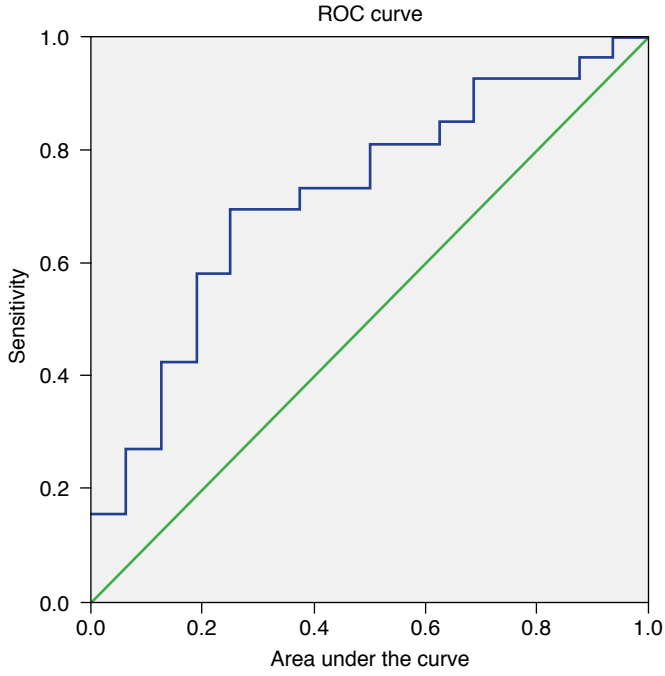
Table 3: Comparisons of laboratory findings at the follow-up visits for factors affecting radiological regression

	Patients followed up with chest X-ray and/or thorax CT			Patients followed up with thorax CT		
	Complete regression + (n=26)	Complete regression - (n=16)	p	Complete regression + (n=14)	Complete regression - (n=7)	p
WBC #/mm^3	7419.5±1614.1	7966.4±1233.4	0.29	7228±1693.2 (n=10)	7781.7±1076.2 (n=6)	0.487
Neutrophil#/mm^3	4370.5±1783.3	4762.9±989.9	0.46	4361±1184.8	4688.3±1080.5	0.59
Lymphocyte#/mm^3	2059.8±764.8	2501.4±799.2	0.11	2095±725.3	2376.7±624.8	0.444
Eosinophil#/mm^3	160 (100–225)	180 (97.5–340)	0.555	160 (97.5–240)	160 (90–257.5)	0.457
Hemoglobin (gr/dl)	14.4 (12.4–15.7) (n=21)	14.9 (13.8–15.8) (n=13)	0.366	14.6 (12.3–15.6)	14.8 (14.3–15.6)	0.55
MCV (fl)	91.3 (88.4–92.9)	89.2 (85.9–94.6)	0.366	88.8 (87.3–91.6)	86.9 (85.5–95.2)	0.664
RDW (%)	14.2 (13.3–15.1)	13.58 (12.9–14.3)	0.256	14.4 (12.8–16.2)	13 (12.6–14)	0.193
Platelet#10^3/mm^3	262.2±42.2	456.8±56	0.747	269.6±53.4	241.8±7.2	0.385
MPV (fl)	9.6 (9.1–9.9)	9 (8.6–9.6)	0.085	9.6 (9.2–10)	9.4 (9–9.8)	0.445
SII	420.6 (370.1–642.3)	444.5 (408.7–587.8)	0.814	478.3 (388.4–765.8)	443.1 (408.7–550.5)	1.00
MPR/Platelet#	3.4 (3.2–4.3)	3.7 (2.9–4.6)	0.736	3.4 (2.9–4.4)	4 (3.1–5.5)	0.588
BUN (mg/dL)	12.5 (11–16.1) (n=24)	14.5 (11–17) (n=11)	0.708	16 (12–32) (n=11)	21.3 (13.4–34) (n=4)	0.794
Creatinine (mg/dL)	0.9 (0.8–0.99)	0.87 (0.74–1.1)	0.876	0.9 (0.83–1.1)	0.73 (0.66–1)	0.281
ALT (U/L)	20.5 (13.8–34.3) (n=22)	19.5 (15.5–28.8) (n=12)	0.942	18.1 (15–35) (n=11)	21 (16–40.5) (n=5)	0.733
AST (U/L)	21 (15.8–30.8)	23 (15–259	0.674	19 (14–33)	21.5 (14.3–30.3)	0.48
CRP (mg/L)	3.6 (2.1–11.8) (n=19)	4.3 (1.5–8.9) (n=14)	0.716	3.9 (1.3–12) (n=10)	3.7 (1–7) (n=6)	0.588
D-dimer (mg/L)	0.21 (0.19–0.73) (n=19)	0.39 (0.2–0.65) (n=11)	0.25	0.22 (0.19–0.83) (n=9)	0.39 (0.24–1.4) (n=5)	0.257
D-dimer>2xn (n), %	(3) (n=24) 12.5	(2) n=15 13.3	0.94	(2) 16.7	0	0.289
Dimer>age-adjusted cutoff (n), %	(8) (n=24) 33.3	(6) (n=15) 40	0.74	(3) (n=12) 25	(3) (n=6) 50	0.344
Ferritin (ng/ml)	72.5 (32.3–139.6) (n=12)	107.5 (62.5–197.4) (n=79)	0.554	74 (37.8–40.8) (n=7)	76.2 (42.4–107.7) (n=4)	0.571

CT: Computed tomography, WBC: White blood cells, MCV: Mean corpuscular volume, RDW: Red cell distribution width, MPV: Mean platelet volume, SII: Systemic inflammatory index, MPR: Platelet mean volume/platelet count ratio, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP:C-reactive protein

between the groups of radiologic regression. We could not show any statistically significant difference between the laboratory values at the time of control, either. However, the initial CRP value was significantly higher in the group without complete regression. In regression analysis, CRP value also emerged as an independent factor for complete radiologic regression. According to the results of the ROC analysis, it was seen that for the patients with initial CRP<60 mg/L, the complete radiological resolution can be observed in 4 weeks, with a sensitivity and specificity of 70%, approximately. In another study about the radiological findings in the 3rd month after COVID-19 pneumonia, the increase in the initial BUN value was reported as an independent risk factor for residual radiological abnormalities.[22] Similarly, Han et al.[13] showed that the initial CRP value was higher in patients with fibrotic changes in thorax CT during post-COVID follow-up in 6 months. Nevertheless, by multivariate analysis, they concluded that there is a correlation between post-COVID fibrotic changes and older age, acute respiratory distress syndrome, longer hospital stays, tachycardia, non-invasive mechanical ventilation, and higher initial thorax CT score.

The biomarkers which can be used in identifying severe COVID-19 patients have been a focus of scientific interest since the beginning of the pandemic. These studies showed that elevated levels of CRP, ferritin, serum amyloid A, procalcitonin, lactate dehydrogenase, uric acid, D-dimer, and lower levels of hemoglobin, oxygen saturation, lymphocyte, and platelet count can be regarded as indicators of severe patients.[21,23–25] Besides these classical biomarkers, some researchers have focused on the clinical importance of RDW, MPV, SII, and MPR in COVID-19. These orphan parameters which can be easily derived from complete blood count have already been offered as markers of



Test result variable(s): CRP				
Area	Standard error	p	95% confidence interval	
			Lover bound	Upper bound
0.716	0.082	0.020	0.557	0.876

Figure 3: ROC curve analysis for a cutoff value of CRP in predicting complete radiologic regression in 4 weeks.

ROC: Receiver operating characteristic, CRP: C-reactive protein.

inflammation for a broad spectrum of diseases, including cardiovascular diseases, renal diseases, cancer, and ARDS.[25–27] The studies investigating the role of these parameters in COVID-19 pneumonia have shown that high RDW at admission is associated with mortality, and high MPR and SII are associated with severe pneumonia.[26,28,29] In this study, the values RDW, MPV, SII, and MPR were found statistically the same for the group of patients with and without complete radiologic regression. In addition, when the D-dimer value was analyzed both numerically and according to different cutoff values (1 mg/L and cutoff according to age), it was found to be statistically the same between the study groups. The results of a follow-up study about the pulmonary functions in COVID-19 survivors pointed out that an elevated level of D-dimer is associated with a decrease in post-COVID diffusion capacity.[22] However, this may be due to coagulopathy in the microvascular area rather than radiological sequelae at the macro-level.

The fact that the follow-up laboratory test results were similar between the groups with and without complete regression raises the hypothesis that it may be more cost-effective to request tests according to the severity of the symptoms in the control visits of these patients. The subgroup analysis of the patients who underwent radiologic follow-up with thorax CT yielded the same results as the group including the patients who followed up with a Chest X-ray. However, since we could not reach sufficient data on the severity of the residual symptoms or could not perform CT for all the patients in our retrospective study, it would not be correct to make a judgment on these subjects with the results of this study. The correlations between CT and chest X-ray findings must be investigated in larger series. We found that one-third of our non-intubated group of patients with residual symptoms and available follow-up data presented with radiologic sequela after 3 months. We recommend that the effects of these radiologic lesions including residual ground glass, reticular, and/or band-like opacities on pulmonary functions and quality of life as a focus for the studies in the future.

Based on the results for predicting radiological responses in the post-COVID period for non-intubated patients with COVID-19 pneumonia, complete radiological regression at the end of the 1st month may not be achieved in the ones who are given IV steroids and antipseudomonal antibiotics and who have high initial CRP levels. There is a need for studies that reveal the effects of these sequelae on quality of life and respiratory functions in the long term. Most studies on this subject include intubated patients in the post-COVID survivor group. We think that the results of this study, in which the factors affecting the radiological regression in patients who were followed up outside the intensive care unit, will contribute to the post-COVID follow-up processes.

Disclosures

Ethics Committee Approval: The study was approved by The University of Health Sciences Ankara Keçiören Training and Research Hospital Clinical Research Ethics Committee (date: 25.01.2022, number: 2012-15/2457).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Ş.D., H.E.; Design – S.Ş.D., H.E., D.K., Ö.S.; Supervision – H.E., D.K.; Fundings – S.Ş.D., H.E., D.K., Ö.S.; Materials – S.Ş.D., H.E., D.K., Ö.S.; Data Collection and/or Processing – S.Ş.D., H.E., D.K., Ö.S.; Analysis and/or Interpretation – S.Ş.D.; Literature Search – S.Ş.D., D.K.; Writing – S.Ş.D., H.E., D.K., Ö.S.; Critical Reviews – D.K., H.E..

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Esendağli D, Yilmaz A, Akçay Ş, Özlü T. Post-COVID syndrome: Pulmonary complications. Turk J Med Sci 2021;51:3359–71.
2. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: A 15-year follow-up from a prospective cohort study. Bone Res 2020;8:8.
3. Hemraj SK, Jacob MJ, Kotian V, K SD, G GR, Veliath LB. Chest CT findings and their temporal evolution in COVID-19 pneumonia. Cureus 2022;14:e26021.
4. Larici AR, Cicchetti G, Marano R, Merlino B, Elia L, Calandriello L, et al. Multimodality imaging of COVID-19 pneumonia: From diagnosis to follow-up. A comprehensive review. Eur J Radiol 2020;131:109217.
5. Bazdyrev E, Rusina P, Panova M, Novikov F, Grishagin I, Nebolsin V. Lung Fibrosis after COVID-19: Treatment prospects. Pharmaceuticals (Basel) 2021;14:807.

6. Udwadia ZF, Koul PA, Richeldi L. Post-COVID lung fibrosis: The tsunami that will follow the earthquake. Lung India 2021;38(Supplement):S41–7.
7. Hama Amin BJ, Kakamad FH, Ahmed GS, Ahmed SF, Abdulla BA, Mohammed SH, et al. Post COVID-19 pulmonary fibrosis; a meta-analysis study. Ann Med Surg (Lond) 2022;77:103590.
8. Liu D, Zhang W, Pan F, Li L, Yang L, Zheng D, et al. The pulmonary sequalae in discharged patients with COVID-19: A short-term observational study. Respir Res 2020;21:125.
9. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America expert consensus statement on reporting Chest CT findings related to COVID-19. Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA - secondary publication. J Thorac Imaging 2020;35:219–27.
10. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: The potential role for antifibrotic therapy. Lancet Respir Med 2020;8:807–15.
11. Helms J, Tacquard C, Severac F, Leonard-Lorant I, Ohana M, Delabranche X, et al. High risk of thrombosis in patients with severe SARS-CoV-2 infection: A multicenter prospective cohort study. Intensive Care Med 2020;46:1089–98.
12. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese center for disease control and prevention. JAMA 2020;323:1239–42.
13. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month Follow-up Chest CT findings after severe COVID-19 pneumonia. Radiology 2021;299:E177–86.
14. Singhal T. A review of Coronavirus disease-2019 (COVID-19). Indian J Pediatr 2020;87:281–6.
15. Gündüz Y, Öztürk MH, Tomak Y. The usual course of thorax CT findings of COVID-19 infection and when to perform control thorax CT scan. Turk J Med Sci 2020;50:684–6.
16. Liu C, Ye L, Xia R, Zheng X, Yuan C, Wang Z, et al. Chest computed tomography and clinical follow-up of discharged patients with COVID-19 in Wenzhou City, Zhejiang, China. Ann Am Thorac Soc 2020;17:1231–7.
17. Rai DK, Sharma P, Kumar R. Post covid 19 pulmonary fibrosis. Is it real threat? Indian J Tuberc 2021;68:330–3.
18. Vural A, Kahraman AN. Pulmonary fibrotic-like changes on follow-up chest CT exam in patients recovering from COVID-19 pneumonia. Tuberk Toraks 2021;69:492–8.
19. Gentile F, Aimo A, Forfori F, Catapano G, Clemente A, Cademartiri F, et al. COVID-19 and risk of pulmonary fibrosis: The importance of planning ahead. Eur J Prev Cardiol 2020;27:1442–6.
20. Ng TM, Ong SWX, Loo AYX, Tan SH, Tay HL, Yap MY, et al. Antibiotic therapy in the treatment of COVID-19 Pneumonia: Who and when? Antibiotics (Basel) 2022;11:184.
21. Kokturk N, Babayigit C, Kul S, Duru Cetinkaya P, Atis Nayci S, Argun Baris S, et al. The predictors of COVID-19 mortality in a nationwide cohort of Turkish patients. Respir Med 2021;183:106433.
22. Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. EClinicalMedicine 2020;25:100463.
23. Alkan S, Akça A, Şener A, Doğan E, Gönlügür U, Şimşek T, et al. Evaluation of the hospitalized coronavirus disease 2019 patients in first 3 months of the pandemic. Turk Thorac J 2022;23:52–7.
24. Tjendra Y, Al Mana AF, Espejo AP, Akgun Y, Millan NC, Gomez-Fernandez C, et al. Predicting disease severity and outcome in COVID-19 patients: A review of multiple biomarkers. Arch Pathol Lab Med 2020;144:1465–74.
25. Gallo Marin B, Aghagoli G, Lavine K, Yang L, Siff EJ, Chiang SS, et al. Predictors of COVID-19 severity: A literature review. Rev Med Virol 2021;31:1–10.
26. Sarkar S, Kannan S, Khanna P, Singh AK. Role of red blood cell distribution width, as a prognostic indicator in COVID-19: A systematic review and meta-analysis. Rev Med Virol 2022;32:e2264.
27. Djordjevic D, Rondovic G, Surbatovic M, Stanojevic I, Udovicic I, Andjelic T, et al. Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymphocyte Ratio, Platelet-to-Lymphocyte Ratio, and Mean Platelet Volume-to-Platelet Count Ratio as Biomarkers in Critically Ill and Injured patients: Which ratio to choose to predict outcome and nature of bacteremia? Mediators Inflamm 2018;2018:3758068.
28. Zhong Q, Peng J. Mean platelet volume/platelet count ratio predicts severe pneumonia of COVID-19. J Clin Lab Anal 2021;35:e23607.
29. Nalbant A, Demirci T, Kaya T, Aydın A, Altındiş M, Güçlü E. Can prognostic nutritional index and systemic immune-inflammatory index predict disease severity in COVID-19? Int J Clin Pract 2021;75:e14544.