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Original Article *Özgün Araştırma*

COMPARISON OF INFECTED LUNG VOLUME OF COVID-19 PATIENTS AND THEIR CLINIC AND LABORATORY DATA

Covıd-19 Hastalarında Enfekte Akciğer Volümü ile Klinik ve Laboratuvar Bulguların Karşılaştırılması

Murathan KÖKSAL[1], Erdem ÖZKAN[1], Mutlu GÜLBAY[1], Yeşim AYBAR BİLİR[2], Esragül AKINCI[2], Adalet AYPAK[2], Hatice Rahmet GÜNER[2]

[1]Ankara Şehir Hastanesi, Radyoloji Kliniği, ANKARA, TÜRKİYE
[2] Ankara Şehir Hastanesi, Enfeksiyon Hastalıkları Kliniği, ANKARA, TÜRKİYE

ABSTRACT

Objective: In this study, it was aimed to evaluate the healthy and infected area volumes and elementary lesion characteristics in thorax computed tomography examinations of mild-moderate and severe patient groups according to the clinical severity scoring determined by the World Health Organization, and to compare the obtained findings with laboratory and clinical data.

Material and Methods: A total of 100 cases (59 males, 41 females; age range 18-95 years) were retrospectively and randomly selected from the patients who had non-contrast thoracic computed tomography scan and were diagnosed with Covid-19 pneumonia by reverse transcription polymerase chain reaction test. According to clinical severity scoring, patients were classified as mild-moderate and severe groups. Volumetric measurements were made in the lungs using quantitative analyses. In addition, lesion characteristics (ground glass opacity, consolidation, air bronchogram) in the infiltration areas were recorded. The relationship between radiological findings and clinical-laboratory data was statistically evaluated.

Results: The age of the patients ranged between 58.80±14.74 years; 52% of the cases were in the severe category, 48% of them were in the mild-moderate category. Lung volumes did not differ significantly between disease groups. According to computed tomography findings, there was a statistically significant correlation between subpleural reticulations and air bronchogram and disease groups. IL-6, D-dimer, ferritin, neutrophil lymphocyte ratio and C-Reactive Protein values were higher in the severe disease group than in the mild-moderate group.

Conclusion: Volumetric values associated with laboratory parameters are thought to be an important indicator of the immune response that determines the course of the disease.

***Keywords**: COVID-19, computed tomography, volumetry*

ÖZ

Amaç: Bu çalışmada, Dünya Sağlık Örgütü'nün belirlediği klinik şiddet skorlamasına göre hafif-orta grup ile ağır hasta gruplarının toraks bilgisayarlı tomografi tetkiklerinde sağlıklı ve enfekte alan volümleri ile elementer lezyon özelliklerinin değerlendirilmesi, elde edilen bulguların laboratuvar ve klinik verilerle karşılaştırılması amaçlanmıştır.

Gereç ve Yöntemler: Hastaneye kabul sırasında kontrastsız toraks bilgisayarlı tomografisi çekilen ve ters transkripsiyon polimeraz zincir reaksiyonu testi ile Covid-19 pnömonisi tanısı alan hastalar arasından geriye dönük ve rastgele olarak toplam 100 olgu (59 erkek, 41 kadın; yaş aralığı 18-95) toplandı. Klinik şiddet skorlamasına göre hastalar hafif-orta ve ağır grup olarak sınıflandırıldı. Kantitatif analizler kullanılarak akciğerlerde volümetrik ölçümler yapıldı. Ayrıca infiltrasyon alanlarındaki lezyon özellikleri (buzlu cam opasitesi, konsolidasyon, hava bronkogramı vb.) kaydedildi. Radyolojik bulgular ve klinik-laboratuvar veriler arasındaki ilişki istatistiksel olarak değerlendirildi.

Bulgular: Hastaların yaşları 58.80±14.74/yıl arasında değişmekte olup; olguların %52'si ağır kategoride, %48'i hafif-orta kategorideydi. Akciğer hacimleri, hastalık grupları arasında anlamlı farklılık göstermiyordu. Bilgisayarlı tomografi bulgularına göre subplevral retikülasyonlar ile hava bronkogramı ve hastalık grupları arasında istatistiksel olarak anlamlı bir ilişki mevcuttu. IL-6, D-dimer, ferritin, nötrofil lenfosit oranı ve C-Reaktif Protein değerleri ağır hastalık grubunda, hafif-orta gruba göre daha yüksekti.

Sonuç: Laboratuvar parametreleriyle ilişkilendirilen hacimsel değerlerin, hastalığın seyrini belirleyen immün yanıtının önemli bir göstergesi olduğu düşünülmektedir.

***Anahtar Kelimeler**: COVID-19, bilgisayarlı tomografi, volümetri*

Correspondence / Yazışma Adresi: **Dr. Murathan KÖKSAL**
Ankara Şehir Hastanesi, Radyoloji Kliniği ANKARA, TÜRKİYE
Phone / Tel: +90 505 6888729 **E-mail** / E-posta: murathankoksal@gmail.com
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INTRODUCTION

Covid-19 infections are very similar to seasonal flu with symptoms such as fever, cough, exhaustion, and muscle pain (1). The lungs are the primary involvement site of this disease, and the severity of the disease causes viral pneumonia (2). There are still unexplained parts about the immune pathogenesis of the disease. Current scientific data indicate many possible mechanisms that may affect the pathogenesis such as antibody-dependent enhancement, systemic inflammatory response, and T cell over-activation and angiotensin-converting enzyme 2 receptor down-regulation, antibody cross-reaction against pneumocytes (3).

Some studies have shown a significant correlation between disease severity and pro-inflammatory cytokine levels and immunity cell groups (4). Serum C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, serum creatinine, creatine kinase (CK), and IL-6 and D-dimer levels were found to be increased in these patients (5,6).

According to the treatment guideline of WHO dated 27 May 2020, symptomatic patients without hypoxia or viral pneumonia are classified as moderate. The moderate category includes patients with signs of pneumonia such as fever, cough, dyspnea, and rapid breathing, but normal saturation. Severe category includes at least one of the findings among the following in addition to pneumonia findings such as fever, cough, dyspnea, and rapid breathing: respiratory rate above 30 per minute, prominent respiratory distress, or low saturation. Critical diseases are known to have conditions such as ARDS, sepsis, and septic shock together with severe pneumonia (7,8).

The main imaging method, which is used extensively for the diagnosis of Covid-19, and whose effectiveness has been stated in many studies, is thorax computed tomography (CT). Thorax CT findings are mostly bilateral, peripheral, and basal ground-glass opacities, consolidations, or a combination of these (9,10).

The purpose of this study is to compare the infected lung site with thorax CT findings and with laboratory data for moderate and severe-critical patient groups. Thus, it was aimed to reveal the correlation between the severity of the disease and CT findings and laboratory data. It was also aimed to understand the implications of the damage caused by this disease in the lungs on clinical and laboratory data.

MATERIALS AND METHODS

The study was carried out observationally and retrospectively in Ankara City Hospital, and the necessary permission was obtained from the ethics committee of the hospital (Ankara City Hospital-01 Clinical Research Ethics Committee, date: 14.05.2020; issue number: E1/594/2020) and the Ministry of Health of the Republic of Turkey.

Cases

This study included 100 patients chosen among those who applied to Ankara City Hospital between June and November 2020 with the symptoms of pneumonia such as fever, cough, and shortness of breath, who were diagnosed with Covid-19 pneumonia, who had a positive RT-PCR test, and whose thorax computed tomography was taken during the admission were registered in the system. Patients with signs of pneumonia but negative repetitive RT-PCR tests, patients who did not have a thorax computed tomography taken during the admission, and patients who had intense motion artifacts that distorted volume measurements of tomography were excluded from the study. Epidemiological characteristics and laboratory data of the patients such as age and gender were recorded. The clinical results of the patients were classified as moderate and severe- critical.

Imaging Technique

The technique was standard for all patients. Non-contrast thorax CT was applied upon the suspicion of Covid-19 pneumonia (GE Healthcare, USA). Scannings were performed in supine position during the inspiration

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phase. Scanning parameters were 100kV tube voltage, 50-399 mAs, 1.3mm section thickness.

Imaging Interpretation

Thoracic computed tomographies of the patients obtained at the time of admission were uploaded to the AW Volume Share 7 workstation with thoracic VCAR software for quantitative analysis and volume measurement.

For CT, attenuation was measured as Hounsfield Unit (HU). The density of water is accepted to be 0 HU, and the density of air is -1000 HU. Naturally ventilated lung parenchyma was measured as -900 to -500/-700 HU values in various studies (11,12). In line with precedent studies and software recommendations, HU units between -1024 to -725 were accepted as pneumatic lung parenchyma and -725 to 0 were accepted as consolidation and ground-glass opacities (Figure 1). In our study, infected lung volume was measured by determining non-pneumatized and weakly pneumatized lung regions.

The software calculates non-pneumatic and poorly pneumatic parenchyma sites based on attenuation values and defines the infected percentage and volumes compared to the full lung volume. Infected lung volumes were calculated separately for the right and left lungs (Figure 2). In addition, elemental lesions (ground glass opacity, consolidation, subpleural reticulations, etc.) in the infiltration areas were also recorded.

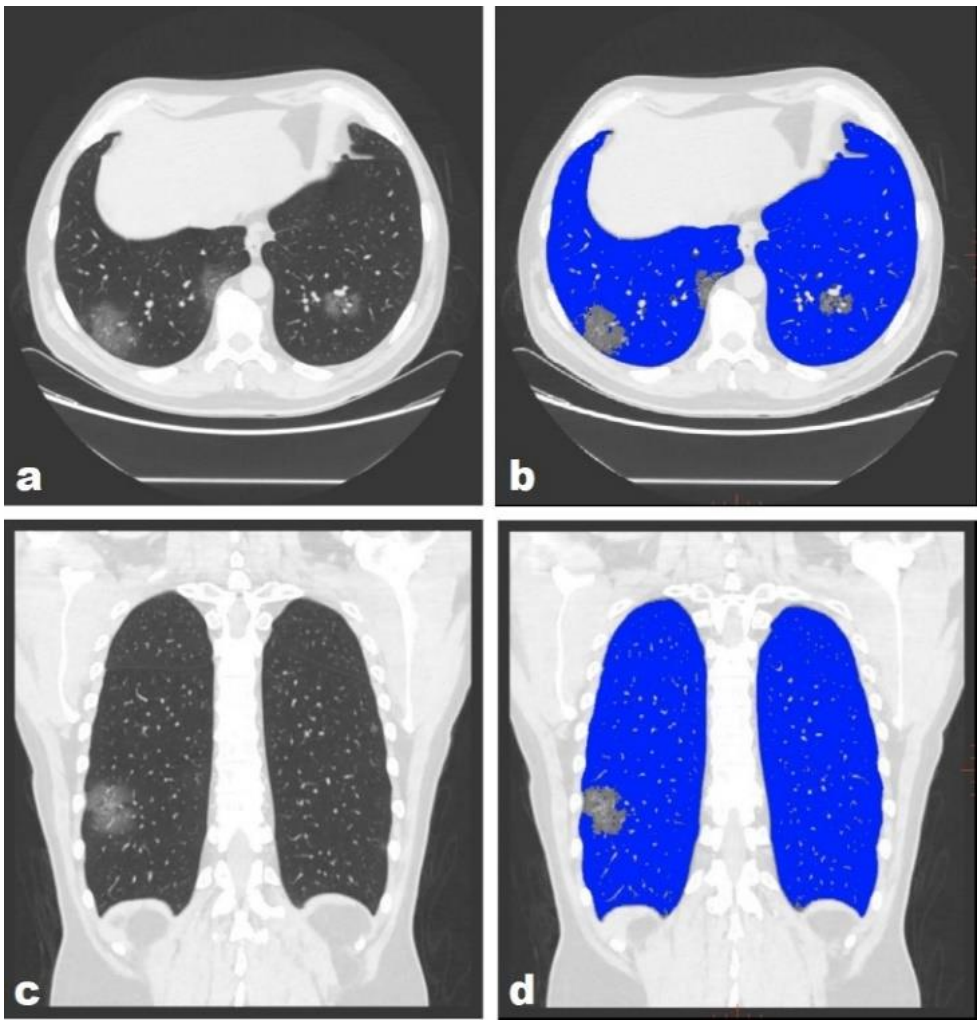

Figure 1: Example of lung analysis in a COVID-19 patient with the Thoracic VCAR software in axial (a, b) and coronal (c, d) planes

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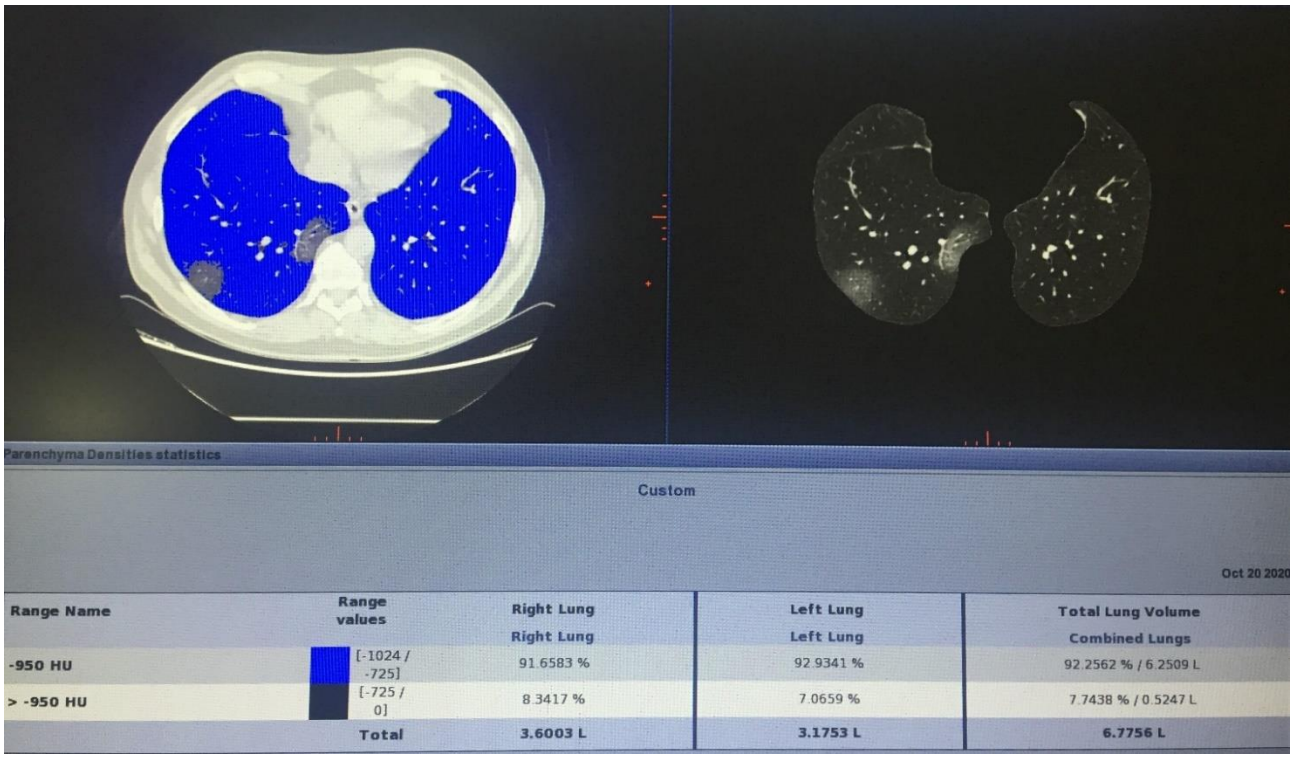

Range Name	Range values	Right Lung Right Lung	Left Lung Left Lung	Total Lung Volume Combined Lungs
-950 HU	[-1024 / -725]	91.6583 %	92.9341 %	92.2562 % / 6.2509 L
> -950 HU	[-725 / 0]	8.3417 %	7.0659 %	7.7438 % / 0.5247 L
	Total	3.6003 L	3.1753 L	6.7756 L

Figure 2: Volumetric scale of infected and healthy lung areas. Image shows an example of the automatic analysis of highlighted (blue) pneumatized lung parenchyma areas using a colorimetric map. The remaining area (denser than -725 HU) represents the infiltration area.

Statistical Analysis

SPPS 25 (IBM Corporation Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) statistical package program was used to evaluate the data. To evaluate the differences between the two groups, "Student's t Test" was used when the prerequisites of the parametric test were met, and the "Mann Whitney–U test" was used if not. Correlations between categorical variables were analyzed through Fisher's Exact Test and Pearson Chi-Square Test. The correlation between two continuous variables was evaluated with the Pearson Correlation Coefficient, but if the prerequisites for the parametric test were not met, the Spearman Correlation Coefficient was used. $P<0.05$ was considered statistically significant.

RESULTS

The age of the patients varied between 58.80±14.74 /years; 52% of the patients in the clinical category were in the severe category, and 48% were in the mild-moderate category; also 41% of the patients were female and 59% were male.

For both lung volumetry, the mean percentage of total involvement is 22.33±12.88 (%), the total volume was 3.86±1.41 liters, and the total involvement volume was 0.83±0.60 liters. Laboratory and CT findings are summarized in Table 1.

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Table 1: Clinical, laboratory and CT findings (n=100)

			Mean±SD-n (%)
Right lung volumetry	percentage of involvement		22.32±13.69
	total volume		2.08±0.75
Left lung volumetry	percentage of involvement		22.55±12.53
	total volume		1.79±0.65
Both lungs total volumetry	percentage of total involvement		22.33±12.88
	total volume		3.86±1.41
	total involvement volume		0.83±0.60
Laboratory findings	IL-6		226.29±380.07
	D-dimer		4.11±7.61
	Ferritin		1098.48±1971.06
	NLR		11.95±10.28
	Procalcitonin		1.25±4.85
	CRP (g/L)		0.14±0.17
CT findings	GGO	(-)	11 (11)
		(+)	89 (89)
	Consolidation	(-)	59 (59)
		(+)	41 (41)
	Crazy-Paving pattern	(-)	41 (41)
		(+)	59 (59)
	Pleural effusion	(-)	96 (96)
		(+)	4 (4)
	Subpleural reticulation	(-)	67 (67)
		(+)	33 (33)
	Air bronchogram	(-)	83 (83)
		(+)	17 (17)

[1] "(-)" means absent, "(+)" means present.

*CT: Computed Tomography, IL-6: Interleukin-6, NLR: Neutrophile / Lymphocyte Ratio, GGO: Ground-glass opacity, CRP: c-reactive protein

According to Table 2, lung volumetrics did not differ significantly among disease groups. However; all laboratory findings indicated statistically significant difference based on the disease groups. According to the results of IL-6, d-dimer, ferritin, NLR and CRP (g/L) measurements, the severe group had a higher mean than the mild-moderate group. In terms of procalcitonin results, a higher mean was measured for the mild-moderate group compared to the severe group.

According to CT findings, there was a statistically significant correlation among subpleural reticulations (SR) and air bronchogram (AB) and disease groups. CT findings are summarized in Table 3.

Table 2: Evaluation of measurements of the study according to disease groups (n=100)

		Severe category (n=52) Mean±SD Median (Min.-Max.)	**Mild-moderate category** (n=48) Mean±SD Median (Min.-Max.)	**Critical value** (p)
Right lung volumetry	percentage of involvement	23.59±14.73 20.74 (0.00-58.70)	20.94±12.49 18.35 (1.47-52.69)	-0.686 (0.492) [2]
	total volume	2.08±0.83 1.94 (1.00-3.97)	2.08±0.67 2.05 (0.79-3.68)	-0.383 (0.702) [2]
Both lungs total volumetry	percentage of total involvement	23.67±13.84 21.26 (1.50-56.90)	20.88±11.72 18.77 (1.56-49.43)	-0.862 (0.388) [2]
	total volume	3.86±1.60 3.52 (0.77-7.73)	3.85±1.19 3.72 (1.51-6.55)	0.011 (0.991) [1]
	total involvement volume	0.93±0.73 0.79 (0.14-4.88)	0.72±0.39 0.61 (0.08-1.99)	-1.653 (0.098) [2]
Left lung volumetry	percentage of involvement	24.20±13.36 21.45 (0.00-58.60)	20.75±11.43 19.07 (1.66-45.80)	-1.180 (0.238) [2]
	total volume	1.82±0.74 1.68 (0.53-3.73)	1.77±0.54 1.69 (0.67-3.12)	-0.097 (0.923) [2]
Laboratory findings	IL-6	367.19±464.92 137 (9.88-2241)	73.64±154.77 30.05 (4.39-1000)	-5.501 (0.001) [2**]
	D-dimer	5.60±9.05 1.52 (0.37-39.50)	2.51±5.29 0.90 (0.21-33.54)	-3.546 (0.001) [2**]
	Ferritin	1611.85±2543.02 1424.75 (74.60-18915)	542.33±747.42 366.90 (28.60-4746.5)	-6.168 (0.001) [2**]
	NLR	15.46±10.27 12.24 (2.29-42.26)	8.14±8.93 5.02 (1.13-45.48)	-4.567 (0.001) [2**]
	Procalcitonin	0.53±1.06 0.18 (0.03-6.04)	2.03±6.86 0.08 (0.03-31.08)	-3.395 (0.001) [2**]
	CRP (g/L)	0.20±0.22 0.16 (0.02-1.47)	0.09±0.06 0.08 (0.00-0.22)	-4.574 (0.001) [2**]

*p<0.05 **p<0.01. [1] Student t test, [2]Mann Whitney U test

***IL-6: Interleukin-6, NLR: Neutrophile / Lymphocyte Ratio, CRP: c-reactive protein

In terms of the correlation between the laboratory findings and lung volumetry measurements of all the patients evaluated in this study, there was a weak positive correlation between IL-6 and the percentage of total involvement of both lungs (r=0.278, p=0.005) (Table 4).

In terms of the correlations between the laboratory findings of the participants in the mild-moderate group and lung volumetry; there was a moderate positive correlation between IL-6 and both lungs total involvement percentage (r=0.413, p=0.004). There was a weak positive correlation between ferritin and both lung total involvement volume (r=0.352, p=0.014). Other findings are summarized in Table 5.

In terms of the correlations between the laboratory findings of the participants in the severe group and lung volumetry; there was a weak positive correlation between d-dimer and both lungs total involvement percentage (r=0.314, p=0.023) (Table 6).

Table 4: Relationships between laboratory findings and lung volumes for all cases regardless of clinical groups (n=100)

		Right lung (percentage of involvement)	**Right lung (total volume)**	**Both lungs (percentage of total involvement)**	**Both lungs (total volume)**	**Both lungs (total involvement volume)**	**Left lung (percentage of involvement)**	**Left lung (total volume)**
IL-6	r (p)	0.270 (0.007) **	-0.174 (0.084)	0.278 (0.005) **	-0.157 (0.118)	0.249 (0.013) *	0.289 (0.004) **	-0.133 (0.188)
D-dimer	r (p)	0.263 (0.008) **	-0.174 (0.083)	0.281 (0.005) **	-0.187 (0.063)	0.181 (0.071)	0.296 (0.003) **	-0.174 (0.084)
Ferritin	r (p)	0.117 (0.245)	0.021 (0.835)	0.138 (0.172)	0.008 (0.934)	0.240 (0.016) *	0.188 (0.060)	0.018 (0.861)
NLR	r (p)	0.252 (0.011) *	-0.214 (0.032) *	0.274 (0.006) **	-0.230 (0.021) *	0.176 (0.079)	0.303 (0.002) **	-0.220 (0.028) *
Procalcitonin	r (p)	0.313 (0.002) **	-0.172 (0.088)	0.330 (0.001) **	-0.183 (0.069)	0.288 (0.004) **	0.344 (0.001) **	-0.195 (0.052)
CRP (g/L)	r (p)	0.249 (0.013) *	-0.150 (0.137)	0.255 (0.010) *	-0.160 (0.112)	0.259 (0.009) **	0.271 (0.006) **	-0.144 (0.152)

Table 5: Relationships between laboratory findings and lung volumetry for mild-moderate cases (n=48)

		Right lung (percentage of involvement)	**Right lung (total volume)**	**Both lungs (percentage of total involvement)**	**Both lungs (total volume)**	**Both lungs (total involvement volume)**	**Left lung (percentage of involvement)**	**Left lung (total volume)**
IL-6	r (p)	0.371 (0.009) **	-0.069 (0.643)	0.413 (0.004) **	-0.091 (0.537)	0.446 (0.001) **	0.406 (0.004) **	-0.110 (0.458)
D-dimer	r (p)	0.182 (0.216)	-0.007 (0.961)	0.215 (0.143)	-0.045 (0.763)	0.161 (0.274)	0.211 (0.150)	-0.078 (0.597)
Ferritin	r (p)	0.074 (0.618)	0.192 (0.191)	0.151 (0.307)	0.146 (0.323)	0.352 (0.014) *	0.219 (0.135)	0.109 (0.462)
NLR	r (p)	0.315 (0.029) *	-0.115 (0.437)	0.364 (0.011) *	-0.178 (0.227)	0.365 (0.011) *	0.369 (0.010) **	-0.209 (0.154)
Procalcitonin	r (p)	0.304 (0.035) *	-0.021 (0.887)	0342 (0018) *	-0.054 (0.717)	0.386 (0.007) **	0.356 (0.013) *	-0.081 (0.585)
CRP (g/L)	r (p)	0.320 (0.027) *	-0.050 (0.736)	0.352 (0.014) *	-0.097 (0.510)	0.429 (0.002) **	0.356 (0.013) *	-0.117 (0.428)

Table 6: Relationships between laboratory findings and lung volumetry for severe cases (n=52)

		Right lung (percentage of involvement)	**Right lung (total volume)**	**Both lungs (percentage of total involvement)**	**Both lungs (total volume)**	**Both lungs (total involvement volume)**	**Left lung (percentage of involvement)**	**Left lung (total volume)**
IL-6	r (p)	0.209 (0.137)	-0.263 (0.060)	0.173 (0.219)	-0.221 (0.115)	-0.049 (0.730)	0.145 (0.306)	-0.169 (0.232)
D-dimer	r (p)	0.335 (0.015) *	-0.307 (0.027) *	0.314 (0.023) *	-0.326 (0.018) *	0.093 (0.513)	0.309 (0.026) *	-0.301 (0.030) *
Ferritin	r (p)	0.125 (0.375)	0.027 (0.851)	0.103 (0.469)	0.022 (0.879)	0.082 (0.565)	0.115 (0.417)	0.056 (0.695)
NLR	r (p)	0.208 (0.140)	-0.306 (0.027) *	0.177 (0.209)	-0.303 (0.029) *	-0.090 (0.525)	0.190 (0.178)	-0.274 (0.049) *
Procalcitonin	r (p)	0.315 (0.023)	-0.313 (0.024) *	0.322 (0.020) *	-0.295 (0.034) *	0.147 (0.299)	0.324 (0.019)	-0.314 (0.023) *
CRP (g/L)	r (p)	0.217 (0.123)	-0.264 (0.059)	0.193 (0.171)	-0.258 (0.065)	0.044 (0.756)	0.180 (0.201)	-0.221 (0.116)

*p<0.05; **p<0.01; [1]Spearman correlation coefficient; ***IL-6: Interleukin-6; NLR: Neutrophile / Lymphocyte Ratio; CRP: c-reactive protein

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Table 3: Distribution of CT findings by disease groups (n=100)

		Severe n (%)	**Moderate** n (%)	**Critical value** (p)	**Cramer's V**
GGO	(-)	6 (11.53)	5 (10.42)	0.032 (0.858)	0.018
	(+)	46 (88.47)	43 (89.58)		
Consolidation	(-)	29 (55.77)	30 (62.5)	0.467 (0.494)	0.068
	(+)	23 (44.23)	18 (37.5)		
Crazy-Paving Pattern	(-)	23 (44.23)	18 (37.5)	0.467 (0.494)	0.068
	(+)	29 (55.77)	30 (62.5)		
Pleural effusion	(-)	51 (98.08)	45 (93.75)	1.217 (0.270)	0.110
	(+)	1 (1.92)	3 (6.25)		
Subpleural reticulation	(-)	29 (55.77)	38 (79.17)	6.18 (0.013) *	0.249
	(+)	23 (44.23)	10 (20.83)		
Air bronchogram	(-)	38 (73.08)	45 (93.75)	7.56 (0.006) **	0.275
	(+)	14 (26.92)	3 (6.25)		

*p<0.05 **p<0.01. [1] "(-)" means absent, "(+)" means present. *** GGO: Ground-glass opacity

DISCUSSION

There are many studies on lung CT scan findings of Covid-19 pneumonia. These findings are bilateral involvement, ground glass opacities, consolidations, with the accompanying crazy-paving appearance (13,14). In a study carried out by Sana Salahi et al. ground-glass opacity was reported for 88% of the patients (15). This rate was 89% in our study.

In the study of Cheng et al., which included 38 patients, a slight positive correlation was observed between the pneumonia severity index (PSI) score and the total infected lung site, but no significant statistical variance was found. This was explained by the small number of patients and the lack of equal distribution between clinical groups (16). Colombi et al. found a significant correlation between well pneumatic lung volume (WAL%,-950, -700 HU) during Covid-19, intensive care need, and death. However, as stated, a significant limitation of this study was that the need for intensive care was not always correlated with bad results, and deaths could occur among patients not requiring intensive care as well (17). In a study by Lanza et al., which included 220 people, a moderate negative correlation was found between the infected lung volume and PaO_2/FiO_2. It was also found that lung functions are damaged as the infected volume increases. The infected lung volume was found to be a predictive value in terms of hospital mortality, together with age and cancer parallel to it (18). In our study, we did not find a significant difference between the severe and mild-moderate patients and the infected lung volume. This indicates that factors other than the involved lung volume such as patient immune response and other comorbidities may be effective due to a clinical situation.

In terms of correlation between volumetric measurements and laboratory data in infected lungs; we found correlations in both the severe group and the mild-moderate group. The correlation between infected lung volume and laboratory values may be an indicator of the effectiveness of immune modulators that are thought to play a role in the pathogenesis of the disease and the increased acute phase reactants accordingly. Therefore, these laboratory data are expected to increase as the volume of infected lung increases. This supports that the more areas of the lung that are affected, the more immune response will be produced against the disease.

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The significant correlation between laboratory data and the mild-moderate group suggests that the volume-laboratory data correlation alone may not be sufficient to differentiate clinically severe or mild-moderate disease. Since very few of the patients included in the study had follow-up CT scans, the relationship between lung volume and clinical severity in the disease process could not be investigated. This was the main limitation of our study. In addition, since the clinical parameters used in the classification of mild and moderate patient groups may be insufficient to differentiate these two groups, we had to consider these patient groups as a single group in our study. Different results can be obtained with clinical classifications with better standardization.

We could not detect a significant correlation between infected volume measurements in the lungs and patient clinical severity. However, different results can be obtained if more comprehensive studies are conducted with a larger number of patients and more homogeneous patient groups, or if artificial intelligence-designed studies are added to existing studies. Finally, it is considered that the volumetric values correlated to laboratory parameters may be an indicator of the immune system response that determines the course of the disease.

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