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The Impact of Morphological Shapes in Chest Computed Tomography on Disease Severity in COVID-19 Pneumonia: A Descriptive Study

COVID-19 Pnömonisinde Toraks Bilgisayarlı Tomografideki Morfolojik Şekillerin Hastalık Şiddeti Üzerindeki Etkisi: Tanımlayıcı Bir Çalışma

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ABSTRACT Objective: This study aimed to evaluate the relationship between the shapes of lung lesions on computed tomography (CT) scans of patients with coronavirus disease-2019 (COVID-19) pneumonia and course of the disease based on laboratory data. Material and Methods: A total of 500 patients with COVID-19 pneumonia were included in the study, and were divided into four groups based on the shapes of the lung lesions in their CT scans: Group A (round-shaped), Group B (patchy-shaped), Group C (halo sign/reverse halo), and Group D (diffuse). Laboratory data, including lymphocyte, C-reactive protein, lactate dehydrogenase, ferritin and D-dimer tests, were collected for all patients, and the 4 groups were compared with the laboratory results to evaluate their association with disease severity. Results: The results showed that patchy-shaped lesions were the most common (44.6%), whereas halo sign/reverse halo sign were rare, with only 15 patients (3%) in Group C. Patients with round lesions were found to have milder disease severity, with stable laboratory results. Conversely, patients in Group B with patchy shape exhibited less favorable disease severity compared to Group A. Those with halo/reversed halo signs had minimal lung involvement but higher inflammatory markers. Patients with diffuse spread showed the highest disease severity and poorest laboratory findings. Conclusion: Describing and evaluating lung lesion shapes on CT scans of COVID-19 pneumonia patients can guide clinicians in managing the disease and hospitalization decisions. Our findings suggest that in predicting the course of COVID-19 pneumonia, the shapes of lung lesions on CT scans may be a more critical determinant than their extent.

ÖZET Amaç: Bu çalışma, koronavirüs hastalığı-2019 [coronavirus disease-2019 (COVID-19)] pnömonili hastaların toraks bilgisayarlı tomografi (BT) taramalarındaki akciğer lezyonlarının morfolojik şekilleri ile laboratuvar verilerine dayalı hastalığın seyrini değerlendirmeyi amaçlamıştır. Gereç ve Yöntemler: Toplam 500 COVID-19 pnömonili hasta çalışmaya dâhil edildi ve toraks BT taramalarındaki akciğer lezyonlarının şekline göre 4 gruba ayrıldı: A grubu (yuvarlak şekilli), B grubu (yamasal şekilli), C grubu (halo/ters halo işareti), ve D grubu (diffüz yayılma). Tüm hastaların lenfosit sayıları, C-reaktif protein, laktat dehidrogenaz, ferritin ve D-dimer testleri dâhil olmak üzere laboratuvar verileri toplandı ve 4 grup, hastalık şiddeti üzerine etkisi değerlendirilmek amacıyla laboratuvar test sonuçları ile karşılaştırıldı. Bulgular: Sonuçlar, yamasal şekilli lezyonların en yaygın olduğunu (%44,6), halo /ters halo işaretli lezyonların ise nadir olduğunu, sadece C grubunda 15 hastada (%3) bulunduğunu gösterdi. Yuvarlak lezyonlara sahip hastaların (A Grubu), daha hafif hastalık siddetine ve stabil laboratuvar sonuclarına sahip olduğu bulundu. Buna karşılık, yamalı şekilli olan B grubundaki hastalar, A grubuna göre daha az olumlu hastalık şiddeti göstermiştir. Halo veya ters halo işareti olanlar minimal akciğer tutulumuna sahipti ancak daha yüksek inflamatuar belirteçlere sahipti. Lezyonların yayılma gösterdiği D grubundaki hastalar en yüksek hastalık şiddeti ve en kötü laboratuvar bulgularına sahipti. Sonuç: COVID-19 pnömonisi olan hastalar hastaneye başvurduğunda alınan toraks BT taramalarında gözlenen akciğer lezyonlarının morfolojik şekillerini tanımlamak ve bunların hastalık şiddeti üzerindeki etkisini değerlendirmek, klinisyenlere hastalığın yönetimi ve hastaneye yatış kararlarında değerli bir rehberlik sağlayabilir. Bulgularımız, COVID-19 pnömonisinin seyrini tahmin etmede, toraks BT taramalarındaki akciğer lezyonlarının şekillerinin, yayılım ve dağılımlarından daha kritik bir belirleyici olabileceğini önermektedir.

Keywords: COVID-19; viral pneumonia; multislice computed tomography; disease severity; biomarkers Anahtar Kelimeler: COVID 19; viral pnömoni; çok kesitli bilgisayarlı tomografi; hastalık şiddeti; biyobelirteçler

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The emergence of the coronavirus disease-2019 (COVID-19) pandemic in December 2019 in Wuhan, China has rapidly spread throughout the world, leading to a global health emergency declaration by the World Health Organization on January 30, 2020. The disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), primarily affecting the respiratory system.¹ Symptoms of a SARS-CoV-2 infection include fever, cough, respiratory illness, and radiologic abnormalities, with diagnosis primarily conducted using the real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) test.^{2,3} However, initial tests may yield negative due to sampling and laboratory analysis issues.⁴ Chest computed tomography (CT) scans have proven to be more sensitive in the early stages of the disease and have played a critical role in diagnosis management, and tracking disease progression.^{5,6} Various scoring systems are used to predict the prognosis of COVID-19 pneumonia based on clinical, radiological, and laboratory parameters.7 Studies have associated higher scores with increased risk of mortality in COVID-19 pneumonia patients. Many studies have demonstrated that laboratory abnormalities in COVID-19 pneumonia patients serve as important predictors of disease severity, prognosis, and even mortality, either independently or in conjunction with other factors.⁸ Some of these include: in previous studies high lactate dehydrogenase (LDH) levels are associated with increased disease severity in COVID-19 and may serve as an indicator of respiratory failure due to its potential relationship with lung injury, so it is a significant, independent risk factor for disease severity and mortality; high C-reactive protein (CRP) levels, alone or combined with other biomarkers, have been suggested as predictors of COVID-19 severity; in cases with COVID-19, it was found that elevated ferritin level is a marker for hemophagocytic lymphohistiocytosis and associated with severe clinical course.⁹⁻¹⁴ In a meta-analysis evaluating effects of patient characteristics on mortality in COVID-19, presence of elevated CRP and D-dimer levels at presentation were found to be associated with mortality and in another study, it was shown that D-dimer level>2 µg/mL was predictive for in-hospital mortality.15-17 Evidence from multiple studies suggests that

patients with severe COVID-19 have lower lymphocyte counts compared to those with mild disease, indicating an inverse correlation between the severity of COVID-19 and the degree of lymphopenia, impacting prognosis.^{18,19} As evidenced by all these studies, it is recommended that these markers, which may serve as clinical determinants of severe and fatal COVID-19, be considered as a possible indication of critical disease development in patients hospitalized with respiratory distress. Therefore, in our study, we focused on laboratory markers to interpret disease severity. As far as we know, despite numerous studies on various chest CT characteristics associated with COVID-19 pneumonia, the relationship between the morphology of lung lesions and disease severity has not been investigated.^{6,20,21} This retrospective study aims to determine the morphological shapes of lesions seen in chest CT scans of COVID-19 pneumonia patients and to examine their potential connection with disease severity.

MATERIAL AND METHODS

STUDY POPULATION

This retrospective study protocol was conducted in accordance with the principles of the Helsinki Declaration and received approval from the Ethical Review Committee of Bursa City Hospital Clinical Research (date: January 6, 2021; no: 2021-1/7). Five hundred seventeen patients diagnosed with COVID-19 pneumonia in our hospital from March 18, 2020, to December 31, 2020 were evaluated. Patients meeting these criteria were included in the study as COVID-19 pneumonia cases if they; 1) presented clinical findings suggestive of COVID-19 disease, 2) had a positive rRT-PCR detection of SARS-CoV-2 nucleic acid in throat swabs or lower respiratory tract, and 3) had at least one CT scan confirming COVID-19 pneumonia [The mean time between the initial CT scan and symptom onset was 5.0 days (range, 2-15 days)].

The exclusion criteria for the study were patients under 18 years of age, pregnant individuals, and those with insufficient data to pool. All virus tests were conducted at the clinical laboratory. The clinical parameters including age, sex, and laboratory findings were collected and evaluated.

CT TECHNIQUE

Because this study is retrospective, a standardized CT protocol was not employed. CT scans and/or CT pulmonary angiography (CTPA) were utilized to identify pulmonary lesions. All images were obtained through a CT scan (Siemens Somatom.go. Now 16, Germany) with patients positioned supine during end-inspiration. Scans were reviewed using both standard mediastinal and lung windows in the axial plane, with reconstructed coronal images also obtained. Parameters for CT scans included 130 kV, auto-modulated mA, 5 mm slice thickness, and a 512×512 matrix. CTPA parameters were 110 kV, auto-modulated mA, 1.5 mm slice thickness, and a 512×512 matrix. A radiologist with six years of experience in chest CT interpretation reviewed each examination while being blinded to all clinical and laboratory patient information.

IMAGE ANALYSIS

The CT images were assessed for pulmonary parenchymal abnormalities, including (1) morphological abnormalities (nodular, patchy, halo/ reverse halo sign, and diffuse spread), (2) extent of pneumonia in the entire lung, and (3) course of lesions determined by follow-up radiographs. The anatomical side of the lung involvement was also examined (i.e., whether lesions were unilateral or bilateral).

There were basic morphological shapes in the CT scans of the lungs of patients with COVID-19 pneumonia. Based on the morphology of these lung lesions, patients were divided into four groups named A, B, C, and D. In the first group (A), lung lesions were round-shaped of ground-glass opacity (GGO) or had consolidation with well-defined borders. In the second group (B) lesions were patchy with ill-defined, amorphous, and irregularly circumscribed areas. In the third group (C) lung lesions had a halo or reverse halo sign. The halo sign is defined as nodules surrounded by GGO. The reversed halo sign, also known as atoll sign, refers to a focal round GGO surrounded by a complete or incomplete ring-like consolidation.²¹ In the fourth group (D) lesions merged with each other and spread diffusely. We investigated the impact of these shapes on the severity of the disease.

Scoring lung involvement on CT in COVID-19 helps improve patient triage at the outset, thus aiding in better clinical management and mitigating the adverse effects of the disease. At least 6 different CT severity scoring systems have been proposed in the literature.²² We employed a system that divides the lung into 5 anatomical lobes and scores based on the percentage of involvement.^{6,23} Accordingly, each of the lung lobes were categorized as Score 1 for 1-25% involvement, Score 2 for 26-50% involvement, Score 3 for 51-75% involvement, and Score 4 for 76-100% involvement. The course of the lesions was also evaluated by examining the follow-up CT/CTPA or Xray images of all patients in the subsequent days (mean 8.5 days after the initial CT scan). Changes in the lung lesions were evaluated as no change, disease progression, or change of morphology. Seventeen of 517 patients exhibited a change in their initial morphologic shape on follow-up images (e.g., while it was round in shape on the initial CT, it evolved into a patchy shape on the follow-up image), and they were subsequently excluded from the study. Therefore, the remaining 500 patients were included in the analysis.

LABORATORY TESTS

Laboratory data of all patients who underwent lung CT scans were collected retrospectively. This data included lymphocyte counts, CRP, LDH, ferritin, and D-dimer tests conducted within three days after admission. Laboratory values obtained beyond three days after the patient's initial admission were disregarded, as complications that may develop after this period (e.g., superimposed bacterial infection, vascular thrombus, etc.) could affect the laboratory results. Subsequently, we compared the laboratory test results across all 4 groups and evaluated their association with disease severity.

STATISTICAL ANALYSIS

The findings of the study were analyzed using the IBM SPSS Statistics software (version 21; IBM, ABD). Descriptive statistics, including mean±standard deviation, were employed. The CT lung patterns were analyzed using scatter diagrams for each group, and a quadratic function was fitted using SPSS to generate the corresponding curve. Comparison of parameters was performed using an analysis of variance test for three or more independent groups. A correlation coefficient (r) greater than 0.75 was considered indicative of a strong correlation. The significance threshold was set at p<0.05.

RESULTS

PATIENT CHARACTERISTICS

The age distribution of the patients ranged from 24 to 92 years, with a mean age of 60.69 ± 11.98 years. Males comprised a larger proportion (269; 53.8%) within our sample compared to females (231; 46.2%), with no statistically significant difference in their ages. The mean age was 60.7 ± 11.62 years for males and 60.66 ± 12.4 years for females.

CHEST CT CHARACTERISTICS

All lung CT scans of the enrolled patients underwent thorough evaluation. Analysis of the chest CT examinations revealed that the majority of lesions were bilateral, accounting for 96.2% (481 patients), whereas unilateral lesions were observed in a minority of cases, constituting 3.8% (19 patients). The predominant morphological shape observed was patchy, with Group B comprising the largest proportion of patients (224; 44.8% of the cohort). Following this, the second most prevalent morphological shape identified was the diffuse lesion, observed in Group D, encompassing 166 patients (33.2%). Conversely, Group C exhibited a considerably lowest representation, with only 15 patients (3%) demonstrating this morphological shape. Approximately three-quarters of the patients exhibited less than 50% involvement of lung parenchyma. Specifically, 188 patients (37.6% of the cohort) were assigned a lung score of 1, while 180 patients (36%) received a lung score of 2. Only a small fraction, comprising 5.8% of all patients, attained a lung score of 4. Notably, all patients except one with a lung score of 4 were categorized under Group D. Detailed CT characteristics are delineated in Table 1.

LABORATORY PARAMETERS

A progressive decline in lymphocyte count and a corresponding increase in mean values of CRP, ferritin, and D-dimer were observed from Group A to Group D. LDH values were lowest in Group A and highest in Group D, with Group B exhibiting higher values compared to Group C, albeit without reaching statistical significance. The mean values of all laboratory measures displayed statistically significant differences among the groups (p<0.05), as summarized in Table 2.

CT FINDINGS AND LABORATORY DATA AMONG GROUPS AND DISEASE SEVERITY EVALUATION

The chest CT scans of all patients in group A depicted round or nodular lesions, with 91.5% of patients presenting a lung Score of 1 (Figure 1). None of the patients in group A exhibited a lung score of 3 or 4, indicating a relatively low extent of lung involvement within this cohort. Furthermore, Group A displayed the highest lymphocyte count and the lowest levels of CRP, ferritin, D-dimer, and LDH. Moreover, no

Characteristics	All patients	Group A	Group B	Group C	Group D
No.	500	95 (19.8%)	224 (44.8%)	15 (3%)	166 (33.2%)
Score of 1*	188 (37.6%)	87 (91.5%)	83 (37%)	11 (73.3%)	7 (4.2%)
Score of 2*	180 (36%)	8 (8.4%)	101 (45%)	4 (26.6%)	67 (40.3%)
Score of 3*	103 (20.6%)	0	39 (17.4%)	0	64 (38.5%)
Score of 4*	29 (5.8%)	0	1 (0.4%)	0	28 (16.8%)
Lung region distribution					
Unilateral	19 (3.8%)				
Bilateral	481 (96.2%)				

*The percentages of lung involvement were evaluated using a score based on the extent of lung involvement (Score 1 for 1-25% involvement, Score 2 for 26-50% involvement, Score 3 for 51-75% involvement, and Score 4 for 76-100% involvement).

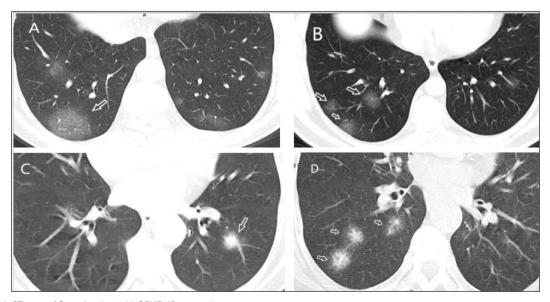
TABLE 2: Laboratory findings for patient groups with COVID-19 pneumonia.							
	Group A	Group B	Group C	Group D	p value		
Lymphocytes (10^3/L)	1.68±0.69	1.45±1.43	1.14±0.41	0.93±0.44	<0.001		
C-reactive protein (mg/L)	16.47±17.74	50.86±46.06	50.58±34.14	131.70±84.24	< 0.001		
Ferritin (ug/L)	143.98±179.03	261.13±218.06	311.0±402.88	661.53±456.92	< 0.001		
D-dimer (mg/dL)	0.48±0.42	0.57±0.40	0.55±0.28	1.32±1.22	< 0.001		
LDH (U/L)	236.18±61.96	304.49±100.82	271.31±81.74	436,35±153.47	<0.001		

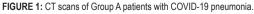
LDH: Lactate dehydrogenase.

significant differences were observed in laboratory results over the following three days, and there was no progression of lesions on subsequent CT scans or X-rays. Consequently, this pattern was associated with a mild disease severity.

The chest CT scans of all patients in group B revealed the presence of amorphous, patchy, and irregular lesions (Figure 2). Approximately half (45%) of the patients exhibited a lung score of 2, indicating a higher degree of lung involvement compared to Group A. Upon subsequent CT or X-ray imaging, the lesions remained stable without any signs of spreading or progression. Additionally, the mean lymphocyte count was lower, while inflammation markers were higher in Group B compared to Group A. Consequently, the severity for patients in Group B was deemed less favorable than that for those in Group A.

The chest CT scans of all patients in Group C revealed a halo or reverse halo sign (Figure 3). Eleven out of 15 patients (73.3%) had a lung score of 1, and none had a score of 3 or 4, indicating minimal lung involvement compared to other groups. Surprisingly, the mean lymphocyte levels were lower in Group C compared to Groups A and B, while the levels of other inflammation markers (excluding LDH) were higher than those observed in Groups A and B. LDH





Axial lung CT scans are shown, displaying a single large lesion (A) and multiple small lesions (B) with well-circumscribed and round-shaped pure ground-glass opacity in the right lower lobe, a single lesion (C) and multiple lesions (D) with well-circumscribed and round-shaped consolidation in the lower lobes (white arrows); CT: Computed tomograph

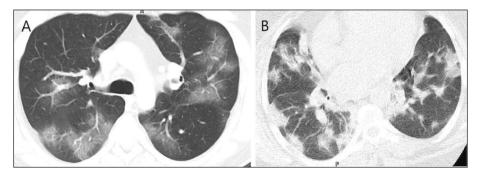


FIGURE 2: CT scans of Group B patients with COVID-19 pneumonia.

Axial lung CT scans are shown, displaying bilateral multifocal irregular and ill-defined patchy ground-glass opacity (A) and consolidation (B) areas in both central and peripheral areas of both lungs; CT: Computed tomography.

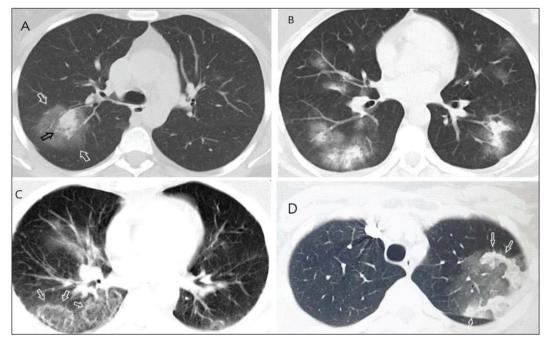


FIGURE 3: CT scans of Group C patients with COVID-19 pneumonia.

Axial lung CT scans are shown, displaying a single lesion with a halo sign, defined as a solid nodule (black arrow) with a ground-glass opacity surrounding it (white arrow in **A**) and multiple lesions with "halo sign" (**B**). Lesions with "reversed halo sign" are also shown, displaying a rounded ground-glass opacity surrounded by complete (**C**) or incomplete (**D**) consolidation (white arrows); CT: Computed tomography.

values in Group C were intermediate between Groups A and B, likely due to the small sample size in this group.

In Group D, the lesions extended across multiple segments and exhibited diffuse spread (Figure 4). Among the patients, 28 out of 29 (96.5%) with a score of 4 and 64 out of 103 (62.1%) with a score of 3 belonged to Group D, indicating the highest extent score in this group. Additionally, Group D exhibited the lowest mean lymphocyte level and the

highest mean CRP, ferritin, D-dimer, and LDH values. These findings are indicative of severe disease for Group D.

DISCUSSION

The exact mechanism underlying the development of pneumonia in COVID-19 disease is not yet fully understood, although some insights are available. The most widely accepted mechanism is related to the angiotensin-converting enzyme II, a key molecule im-

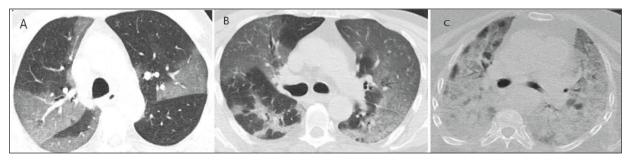


FIGURE 4: CT scans of Group D patients with COVID-19 pneumonia.

Axial lung CT scans are shown, displaying ground-glass opacity that tend to merge with each other with a multi-segment distribution (A), diffuse ground-glass opacity in both lungs (B), and bilateral diffuse consolidations in the entire lung (C); CT: Computed tomography.

plicated in the pathogenesis of diffuse alveolar damage and acute lung failure.²⁴ The CT characteristics and shapes are believed to be a consequence of this pathological basis, stemming from pulmonary injury caused by fluid exudation into the alveoli and interstitium. Our study also identified four main shapes of lung lesions including round, patchy, halo/reverse halo, diffuse.

Recent studies have reported the sensitivity and specificity of CT scans in diagnosing COVID-19 pneumonia to range from 60% to 98% and 25% to 53%, respectively.^{5,25} While numerous studies have investigated the characteristics of lung lesions observed in CT scans of patients with COVID-19 pneumonia, to the best of our knowledge, there is either a lack of research on the impact of lung lesion morphology on prognosis and its correlation with disease severity, or it remains poorly studied.^{6,20,21}

Round lesions have been reported as relatively more specific to this disease and have been observed in 11% to 54% of patients in previous studies.^{6,26,27} In our study, 19.5% of patients exhibited round-shaped lesions (Group A). We observed that round lesions did not exhibit spread or progression according to follow-up images obtained from control CT scans or Xrays. Laboratory results of this group were consistent with the mild severity of the disease and did not deteriorate. Consequently, we infer that this rounded morphology indicate a favorable disease course and thus conclude that outpatient treatment may be sufficient for these patients without necessitating hospitalization.

Consolidations in COVID-19 pneumonia were typically patchy, with multifocal, patchy, or segmental consolidations reported in 2% to 64% of patients in previous studies, indicating their prevalence over other patterns.^{28,29} Similarly, a predominant patchy pattern was observed in most patients in our study (Group B; 44.6%). Patients with patchy-shaped CTs have higher lung involvement scores and worse laboratory results than those with round-shaped lesions. However, patients with patchy-shaped CTs did not show radiological or laboratory deterioration during follow-ups; thus, this pattern may indicate moderate disease. Therefore, we suggest that clinical findings and other parameters (age, comorbidities, etc.) should be considered when deciding on hospitalization for patients with this pattern.

Recent studies have indicated that a halo sign may be evident in COVID-19 patients, suggesting an absorption within the lesion.³⁰ Previous studies have reported the halo and reversed halo signs as less frequent findings in patients with COVID-19 with the halo sign observed in 13.8% of cases and the reversed halo sign observed in 4.6% of cases.^{6,31} Similarly, this pattern was notably rare in our study, identified in only 15 (3.2%) of the patients. These lesions were localized in one or a few segments of the lung, resulting in a very low involvement score. Nevertheless, the laboratory results of this group were worse compared to those of groups A and B, suggesting that this pattern may indicate a poorer prognosis than the nodular and patchy patterns. Therefore, we emphasize that it should be recognized as an alarming pattern for clinicians.

According to the study by Yuan et al., a widespread distribution is more commonly seen in lung CT scans of severe and critical patients.³² In our study, 28 out of 29 patients in Group D (96.5%) had a lung score of 4, indicating involvement of 75% to 100% of the lung, and follow-up images frequently showed progression in the extent and distribution of lesions. The laboratory results of patients in Group D were also the worst. These findings indicate the most severe form of the disease among the groups. Therefore, we emphasize the importance of recognizing this pattern in the initial CT scan of a patient with COVID-19 pneumonia as a warning to clinicians that the disease will worsen and hospitalization will be required.

Recent studies have shown that the extent of parenchymal involvement on CT is associated with the clinical severity of the disease and the need for intensive care.^{6,23} However, in our study, we found that the shape of lung lesions may be more predictive than the extent of the lesion. We reached this assumption based on the following findings; despite the lower lung involvement score in Group C compared to groups A and B, it had worse laboratory results. Additionally, despite the majority of patients in Group D (40.3%) having less than 50% lung involvement, their laboratory results were very poor. These findings underscore the importance of considering the shape of lesions regardless of their extent.

It is well known that various laboratory parameters provide valuable clues about the severity of the disease in many infectious diseases. In several studies, the most common laboratory findings in severe COVID-19 cases have been reported as lymphopenia, increased inflammatory markers, and elevated Ddimer levels.9,19 In our study, we also evaluated lymphocyte counts along with CRP, LDH, ferritin, and D-dimer levels to assess disease severity. We observed a progressively increasing positive correlation in the inflammatory response from Group A to D, while there was a negative correlation in lymphocyte counts. Canovi et al. found an association between high inflammatory response and lung parenchymal involvement, but our study suggests an association with the morphological patterns observed in lung parenchyma.29

The primary limitation of our study was its retrospective nature, which resulted in a lack of detailed patient clinical information, comorbidities, or other factors (e.g., viral load) that could influence the severity of the disease and the extent of COVID-19 pneumonia. Prognostic assessments were made based on laboratory results and follow-up imaging. Additionally, the study was limited by the small number of patients in Group C, as this pattern was exceedingly rare. More comprehensive studies are warranted to explore the impact of this pattern on clinical outcomes.

CONCLUSION

Our study underscores the significance of recognizing the morphological patterns of lung lesions in CT scans of COVID-19 pneumonia patients and their correlation with disease prognosis. Understanding the shapes of lung lesions and their link to adverse prognosis can offer crucial insights to clinicians in disease management, guiding decisions on the need for vigilant monitoring and hospitalization. Clinicians should incorporate the assessment of lung lesion morphology in CT scans as a routine part of clinical evaluation upon admission, as it may aid in early identification of patients with poor prognosis and facilitate timely intervention.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Bilge Sezin Akhan; Design: Bilge Sezin Akhan; Control/Supervision: Bilge Sezin Akhan, Nigar Yılmaz; Data Collection and/or Processing: Bilge Sezin Akhan, Nigar Yılmaz; Analysis and/or Interpretation: Bilge Sezin Akhan, Nigar Yılmaz; Literature Review: Bilge Sezin Akhan; Writing the Article: Bilge Sezin Akhan, Nigar Yılmaz; Critical Review: Bilge Sezin Akhan, Nigar Yılmaz; Materials: Bilge Sezin Akhan, Nigar Yılmaz.

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