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ATYPICAL CT FINDINGS AND CLINICAL CORRELATION OF COVID-19 PNEUMONIA

Covid -19 Pnömonisinin Atipik BT Bulguları ve Klinik Korelasyonu

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Our study was approved by our institutional Ethical Committee (2020.111.05.12).

Abstract

Aim: Our study aimed to evaluate the atypical CT findings and concomitant pathologies of COVID-19 pneumonia and clinical and laboratory findings and compare them with typical CT findings.

Materials and Methods: A total of 69 patients were diagnosed with COVID-19, 14 of which were atypical (20.2%), and 55 of which were typical (79%) chest computed tomography (CT) findings. CT images and clinical and laboratory data of patients with atypical findings were retrospectively analyzed. Lesions of the typical and atypical group and CT severity scores were compared.

Results: Atypical CT findings were centrilobular nodule, tree in bud, pleural effusion, lobar/segmental consolidation, bronchiectasis, pulmonary embolism, and mosaic attenuation by typical lesions with ground-glass opacity with/without consolidation. CT severity score was significantly higher in the atypical group ($p < 0.001$). CRP, procalcitonin, the neutrophil rate increased, and the lymphocyte count decreased in patients with a high CT severity score. Comorbidity was common in the atypical group (50%).

Conclusion: High CT severity score and widespread lung involvement of the patient group with atypical CT findings may be due to disease progression or other concomitant diseases. Atypical lesions accompanying typical lesions may cause false negativity in reporting. As radiologists' experience with COVID-19 pneumonia increases, it may improve that they categorize these images as typical or atypical.

Keywords: COVID-19, coronavirus disease, ground-glass opacity, chest CT Scan, atypical finding.

Öz

Amaç: Çalışmamızın amacı COVİD-19 pnömonisinin atipik BT bulgularını, eşlik eden ek patolojileri klinik ve laboratuar bulgularıyla birlikte değerlendirmek ve tipik BT bulguları ile karşılaştırmaktır.

Materyal ve Metot: Çalışmamıza 14'ü atipik (%20,2), 55'i tipik (%79) toraks bilgisayarlı tomografi (BT) bulguları olan COVID-19 tanısı almış toplam 69 hasta dahil edildi. Toraks BT görüntüleri, atipik bulguları olan hastaların klinik ve laboratuar verileri retrospektif incelendi. Tipik ve atipik grubun lezyonları ve BT şiddet skoru karşılaştırıldı.

Bulgular: Atipik BT bulguları sentrilobüler nodül, tomurcuklanmış ağaç, plevral effüzyon, lober/segmenter konsolidasyon, bronşiektazi, pulmoner emboli ve mozaik atenüasyon olup, periferik dağılım gösteren buzlu cam opasitesi ve/veya konsolidasyon gibi tipik lezyonlara eşlik etmekteydi. BT şiddet skoru atipik grupta belirgin yüksekti ($p<0,001$). BT şiddet skoru yüksek olguların CRP, prokalsitonin, nötrofil oranı artmış, lenfosit sayısı azalmıştı. Atipik grupta komorbidite daha sık görüldü (%50).

Sonuç: Atipik BT bulguları olan hasta grubunun yüksek BT şiddet skoru ve yaygın akciğer tutulumu hastalığın progresyonu ya da eşlik eden diğer hastalıklara bağlı olabilir. Tipik lezyonlara atipik lezyonların eşlik etmesi raporlamada yanlış negatifliğe neden olabilir. Radyologların COVID-19 pnömonisi ile deneyimi arttıkça bu görüntüleri tipik veya atipik olarak kategorize etmeleri gelişebilir.

Anahtar Kelimeler: COVID-19, koronavirüs hastalığı, buzlu cam opasitesi, toraks BT, atipik bulgu.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a highly contagious and progressive disease that primarily involved the respiratory system caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus[1]. COVID-19 emerged in Wuhan City, Hubei Province of China, in December 2019, declared by the World Health Organization (WHO) as a global health emergency on January 30,

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2020[2]. Computed tomography (CT) plays an essential role in diagnosing, managing, and following-up on COVID-19 pneumonia[3]. In several studies, typical chest CT findings of COVID-19 pneumonia were as follows; ground-glass opacity (GGO) with or without consolidation is more prominent in lower lobes and posterior peripheral areas. As the disease stage increase, usually, it progresses from the lower lobes to the upper lobes. GGO can also be seen in interlobular septal thickening, vascular enlargement, and crazy paving pattern[4-6]. Predominant perihilar ground-glass opacity, tree-in-bud, and centrilobular nodule, pleural thickening and effusion, lobar or segmental consolidation, lymphadenopathy have been reported as atypical findings because they are rare or absent in COVID-19 pneumonia[6-9]. However, in recent studies, typical and atypical chest CT findings are seen together in approximately 20% of patients with COVID-19. It suggests that there may be concomitant infections[8,9]. Reporting of atypical features by radiologists may result in false-negative cases, and the risk of missing COVID-19 can help spread the outbreak[9].

The available evidence is still limited concerning the appearance of COVID-19 that accompanying infectious and non-infectious diseases. This is one of the limitations of the previous studies[8]. Our study aims to evaluate atypical CT images of COVID-19 and accompanying diseases with their clinical and laboratory findings, compare atypical and typical CT images.

MATERIALS AND METHODS

Our study was approved by our institutional Ethical Committee (2020.111.05.12).

Study Populations

In this study, a total of 72 patients with both positive COVID-19 by Reverse transcription-polymerase chain reaction (RT-PCR) and chest CT images were identified from our hospital from March 25 to June 30, 2020. We retrospectively reviewed the non-contrast chest CT images by scanning the hospital PACS (Picture Archiving and Communications Systems). Clinical parameters and laboratory findings were reviewed from electronic medical records in the hospital information system. The inclusion criteria were as follows: positive RT-PCR test, having undergone non-contrast CT at least one time, typical or atypical findings in chest CT. Three patients were excluded from the study because their CTs were normal. A total of 69 patients were included in the study.

CT Protocol

All scans were obtained using a 16-row multidetector scanner (GE BrightSpeed 16, USA).

CT parameters: 120 kVp, 80-220 mAs, rotation time-0,8 second, 1,5 mm collimation, 1,37:1 pitch, matrix size 512x512, slice thickness 1,25 mm.

Experienced radiologists processed raw data in the Sectra PACS System, and multiplanar reconstruction (MPR) images were obtained.

CT Imaging Evaluation

Thorax CT images were evaluated independently by two radiologists with at least eight years of experience. The final decision was reached by consensus.

In our study, CT images were evaluated according to RSNA (Radiological Society of North America) expert opinion statement[8]. RSNA has been divided into four categories to standardize thorax CT images of COVID-19 pneumonia (Table 1).

Table 1. Thorax CT appearance of COVID-19 pneumonia

Typical CT appearance	Peripheral GGO bilateral with or without consolidation Inter / intralobular septal thickening (IST), crazy paving, reverse halo sign.
Indeterminate CT appearance	Multifocal, diffuse, perihilar, unilateral, non-round GGO
Atypical CT appearance	Segmental or isolated lobar consolidation, centrilobular nodules, tree-in-bud, cavitary nodule, pleural effusion or thickening
Negative pneumonia appearance	No pneumonia feature in CT

In our study, we determined patients with a typical appearance in CT as a typical group and patients with atypical appearance as an atypical group.

CT severity score (CT-SS)

We calculated the CT severity score (CT-SS) for assessing the extension of lesions on the initial scan obtained at admission. In this scoring, the percentage of opacities such as GGO, consolidation, and interstitial thickening in each lobe is scored. Bilateral lungs were divided into five lobes according to the anatomical structure. The scoring was as follows: score 0; 0 involvement, score 1; 1- 25%, score 2; 26-50%, score 3; 51-75%, score 4; 76 to 100%. The CT-SS was reached by summing the five lobe scores, which may range from 0-20 points[10].

Statistical Analysis

SPSS statistical software (version 25.0, IBM) was used in all statistical analyses. Continuous variables are described as a mean and standard deviation; categorical variables are described as frequency and percentage. Normalization of the distributions of continuous variables was evaluated with the Shapiro-Wilk test. According to normalization, the independent sample t-test or Mann-Whitney test were used in the data. Chi-square or Fisher's exact test was used for categorical variables. The statistical value of $p < 0.05$ was considered significant. Kappa test was used to compare the consistency of two observers in evaluating CT images.

RESULTS

There were 69 patients included in our study, 35 males (50.7%) and 34 females (49.3%), with a mean age of 45.1 (17.4%) years. 14 (20,2%) were atypical cases, and 55 (79,7%) were typical cases.

The kappa value for two observers was excellent (0,900), ($p<0.001$).

The most common symptoms in the two groups were fever, cough, and dyspnea. Hypertension (HT) and diabetes mellitus (DM) were the most common comorbidities in the typical group ($p> 0.05$). Seven of the patients in the atypical cases had comorbidities such as HT, DM, heart disease, malignity, and renal disease (Table 2).

Table 2. Comparison of the demographic and clinical features between the atypical group and typical group.

Parameter	Total (n=69)	Typical group (n=55)	Atypical group (n=14)	P
Age, y	45,1 (±17,4)	43,8 (±16,3)	50,2 (±21,3)	0,221
Sex				
Male	32 (46,4%)	24 (43,6%)	8 (57,1%)	0,547
Female	37(53,6%)	31 (56,4%)	6 (42,9%)	
Comorbidities	26 (37,7%)	19 (34,5%)	7 (50%)	0,306
Hypertension	9 (13%)	9 (16,3%)	0	0,055
Diabetes mellitus	5 (7,2%)	3 (5,4%)	2 (14,3%)	0,611
Heart disease	2 (2,9%)	1 (2%)	1 (7%)	0,478
Malign disease	5 (7,2%)	3 (5,5%)	2 (14,3%)	0,266
Renal disease	2 (2,9%)	0	2 (14,3%)	0,039
Symptoms				
Fever	34 (49,3%)	27 (54%)	7 (36,8)	0,203
Cough	25 (36,2%)	19 (38%)	6 (31,6%)	0,620
Dyspnea	13 (18,8%)	7 (14%)	6 (31,6%)	0,095
Fatigue	6 (8,7%)	6 (12%)	0	0,177
Nausea and vomiting	8 (11,6%)	7 (14%)	1 (5,3%)	0,429
Asymptomatic	6 (8,7%)	5 (10%)	1 (5,3%)	1,000

The right lower lobe involvement was common in both groups (65.5% typical, 85.7% atypical) (Table 3).

Table 3. Comparison of pulmonary lobe involvement between atypical and typical groups.

Parameter	Total (n= 69)	Typical group (n= 55)	Atypical group (n= 14)	p
Right upper lobe	37 (53,6%)	29 (52,7%)	8 (57,1%)	0,767
Right middle lobe	27 (39,1%)	20 (36,4%)	7 (50%)	0,351
Right lower lobe	48 (69,6%)	36 (65,5%)	12 (85,7%)	0,141
Left upper lobe	32 (46,4%)	27 (49,1%)	5 (35,7%)	0.370
Left lower lobe	41 (59,4%)	35 (63,6%)	6 (42,9%)	0,157
Bilateral lung	36 (52,2%)	24 (47,1%)	12 (66,7%)	0,152

Data are presented as n (%).

In addition to the atypical lesions in the atypical group, typical appearances such as GGO (50%), GGO with consolidation (50%), interlobular thickening (71%) and fibrotic band (22%) were accompanied (Table 4) (Figure 1).

Table 4. CT features between atypical and typical groups

Parameter	Atypical group (n= 14)	Typical group (n= 55)
GGO	7 (50%)	18 (32,7%)
GGO with consolidation	7 (50%)	22 (40%)
Interlobular septal thickening	10(71,4%)	21 (38%)
Fibrotic band	2 (15,4%)	13 (23,6%)
Reverse halo	1 (7,7%)	7 (12,7%)
Centrilobular nodul	5 (35,7%)*	0
Tree-in-bud	4 (21,1%)*	0
Pleural/pericard effusion	3 (23,1%)*	0
Lobar/segmental consolidation	2 (15,4%)*	0
Bronchiectasis	2 (15,4%)*	0
Mozaic attenuation	1 (7,7%)*	0
Pulmonary embolism	1 (7,7%)*	0

Data are presented as n (%). *: atypical CT findings. GGO: Ground-glass opacity.

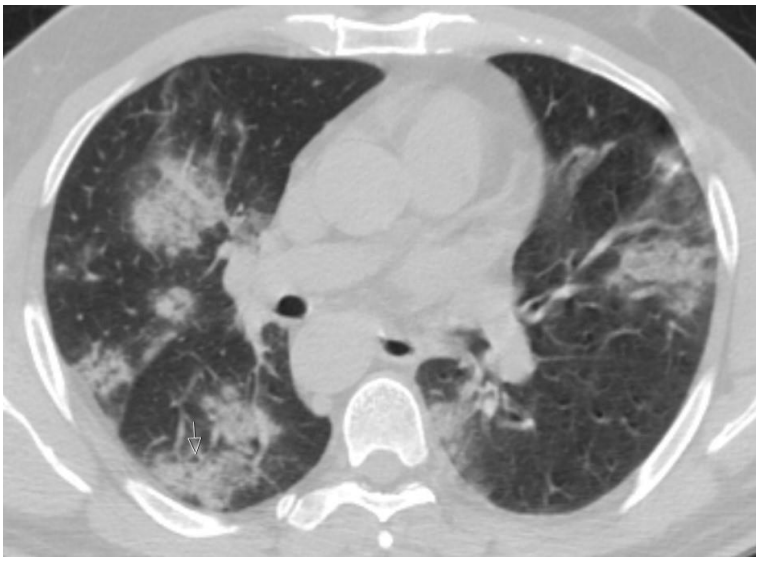

Figure 1. 57-year-old man with COVID-19. Axial chest CT image shows peripheral and peribronchovascular distributed focal ground-glass opacity in both lungs (arrow).

Correlation of atypical CT findings with clinical and laboratory findings

Centrilobular nodul: It was seen in five patients. One patient had kidney transplantation and had chronic kidney failure. GGO, consolidation and reverse halo findings accompanied atypical lesions in CT. C-reactive protein (CRP) increased, lymphocyte decreased. Extended spectrum Beta-lactamases (ESBL) were produced in sputum**.** One patient had renal cell cancer and metastasis. White blood cell (WBC), CRP, fibrinogen and d-dimer were increased. One patient had lobar consolidation and GGO, CRP increased. One patient's laboratory findings were normal and influenza was positive (Figure 2). One patient was no additional pathology and laboratory findings.

Figure 2. 34 year-old man with COVID-19 and influenza positive, in the atypical group. Axial CT image shows centrilobular nodules in ground-glass opacities in the right upper lobe (arrow).

Tree-in-bud: It was seen in four patients. There were no additional pathologies in two patients; laboratory findings were normal. One patient had tree-in-bud together with a centrilobular nodule, and influenza was positive (Figure 3). Lymphocyte decreased, WBC increased. One patient had decreased lymphocytes, increased CRP.

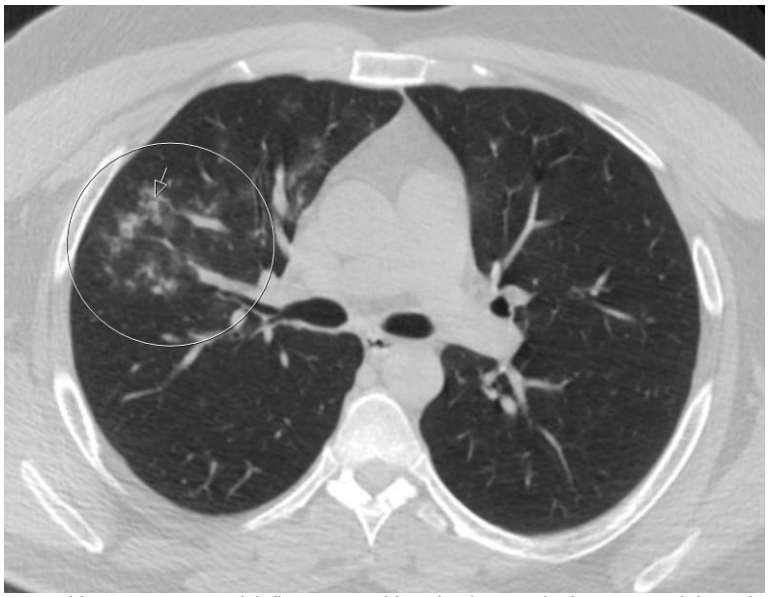

Figure 3. 42 year-old man with COVID-19 and influenza positive, in the atypical group. Axial CT image shows tree-in-bud opacities in the right upper lobe (circle and arrow).

Pleural/pericardial effusion: It was seen in three patients. One patient had breast cancer and liver, bone metastases. Pericardial effusion, GGO, consolidation were also accompanied (Figure 4). CRP increased, lymphocyte decreased, WBC normal, there was no reproduction in gram staining. She was accepted to the intensive care unit (ICU) on the 11th day. One patient had kidney failure and coronary artery disease (CAD) and was hospitalized in the intensive care unit due to general condition disorder. There was pleural effusion, GGO, with consolidation. CRP, WBC, procalcitonin were increased. Gr positive coc was produced in sputum. One patient was DM and intubated in intensive care unit. She had pleural and pericardial effusion, GGO, and crazy-paving pattern. PO2 was low, fasting blood sugar was high, CRP, WBC, fibrinogen, d-dimer were high.

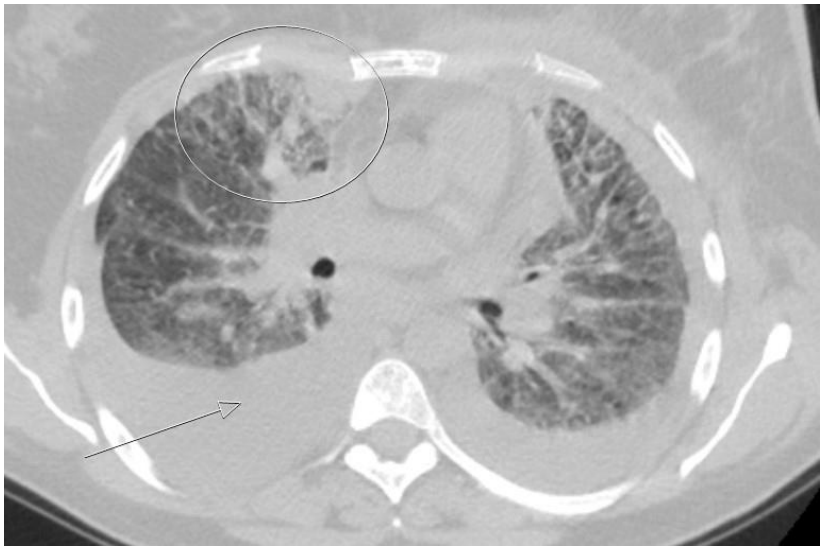

Figure 4. 35 year-old woman with COVID-19 and breast cancer, in the atypical group. Axial CT image shows mixed opacity (ground- glass opacity with consolidation) area and interlobular septal thickening in the right middle lobe (circle). Bilateral pleural effusion in both lungs (arrow).

Lobar/segmental consolidation: It was seen in two patients. One patient had lobar consolidation with GGO, centrilobular nodule (Figure 5). She had increased CRP. One patient also had GGO and bronchiectasis. He had increased CRP and WBC.

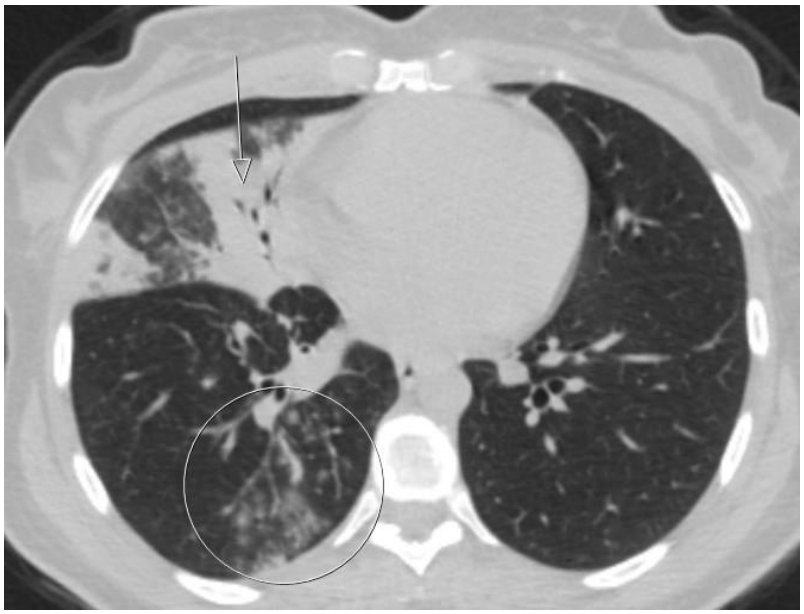

Figure 5. 35-year-old woman with COVID-19, in the atypical group. Axial CT image shows lober consolidation and ground-glass opacity in the right upper lobe (arrow), tree-in-bud in the posterior right lower lobe (circle).

Pulmonary embolism: One patient was performed pulmonary CT angiography. He was diagnosed with COVID-19 two weeks ago. Pulmonary embolism, pleural effusion, and GGO with consolidation were detected (Figures 6a and 6b). He had decreased PO2, increased CRP, d-dimer, and fibrinogen.

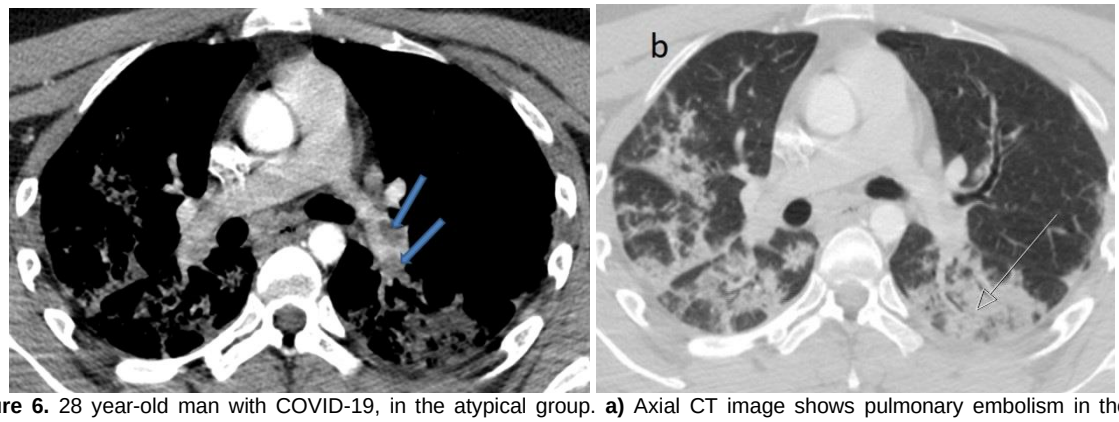

Figure 6. 28 year-old man with COVID-19, in the atypical group. **a)** Axial CT image shows pulmonary embolism in the left pulmonary artery (blue arrows). **b)** Axial image shows multiple subpleural consolidation and ground- glass opacity areas (arrow).

Mozaic attenuation: One patient had asthma. The mosaic appearance was accompanied by central distributed GGO. There was no additional pathology. Laboratory findings were normal**.**

Evaluation of Chest CT-SS

In our study, CT-SS in both lungs was reached by summing the score of five lobes (0 to 20)[10]. Kunwei et al. determined the cut-off value of CT-SS as 7,5. We accepted this value as cut-off in our study. In our study, CT-SS was significantly higher in the atypical group than in the typical group (p <0.001). (Table 4).

Table 4. Comparison of CT severity scores between typical and atypical groups

CT-SS	Total	Typical group (n=55)	Atypical group (n=14)	p
<7,5	56 (%81)	48 (%87,3)	8 (%57,1)	<0,001
>7,5	13 (%18,8)	7 (%12,7)	6 (%42,9)	<0,001

P values less than 0,05 were considered statistically significant. Note: cut-off value is 7,5. CT-SS: CT severity score.

DISCUSSION

Since the RT-PCR test's sensitivity is low in the early stage of COVID-19, thorax CT plays an essential role in the diagnosis and follow-up of the disease[3,11,12]. Diseases accompanying COVID-19 can cause an atypical appearance. Therefore, reporting of atypical CT findings can lead to false-negative cases[8]. Our study analyzed the relationship of atypical CT findings with the clinic and compared them with typical findings.

In our study, GGO was the most common finding in both groups. In the literature, it has been reported that GGO is the most common typical finding in the early stage of COVID-19 pneumonia[5,14]. It is reported that as the stage and severity of the disease increases, consolidation and interstitial thickening are indicative of interstitial edema and alveolar exudation[15]. In our study, in line with the literature, GGO with or without consolidation were the most common findings in 72.7% of typical cases and 100% of atypical cases. Four atypical patients had pleural effusion. In COVID-19 pneumonia, pleural effusion is indicated of poor prognosis due to pleural inflammation in the advanced stage of the disease, with less than 20% reported[15-18]. Since our cases are in the early stages of the disease, non-covid-19 diseases may cause pleural effusion. There were additional diseases with pleural effusion in our study, such as; metastatic breast cancer, DM, pulmonary embolism, chronic kidney failure, and bacterial infection. Recently studies reported the prevalence of pulmonary embolism 30% with COVID-19[19]. Higher d-dimer values may result from higher blood clotting activation in COVID-19 patients secondary to a systemic inflammatory response syndrome. In our case, we found high d-dimer values in addition to CT findings. The cause of pulmonary embolism may be COVID-19 since it was diagnosed with covid-19 two weeks ago. Some studies have reported that centrilobular nodule and tree-in-bud can be seen rarely in COVID-19 pneumonia and may occur secondary to community-acquired infection or aspiration[5,8]. In our study, additional patient findings were ESBL in sputum, influenza positivity, and bacterial pneumonia.

Our study performed a semi-quantitative CT-SS to evaluate the spread and severity of COVID-19 pneumonia in the lungs. Kunwei et al. found that the score was over 7,5 in the group, where the disease was serious[10]. In our study, in 42% of patients in the atypical group, we found a score above 7,5. Parenchymal changes caused by comorbidities accompanying atypical groups were effective in this.

In some studies, both lungs were divided into different regions, and the CT-SS was determined differently. For example, Yang R et al. divided the lungs into 20 segments, and parenchymal opacification involved 0%, less than %50, equal or more than 50% of each region; The CT-SS was 0, 1, and 2, respectively. The total severity score ranged from 0 to 40 points[20]. Chung et al.'s scoring was the same our study, but the CT-SS cut-off was 9,9[4] .

Previous studies have reported that COVID-19 pneumonia typically involves the lower lobes. Our study found the most common right lower lobe involvement in 85.7% of patients in the atypical group and 65.5% of patients in the typical group. In previous studies, it has been reported that the reduction of lymphocyte count is an essential criterion in assessing the severity of the disease and is caused by the destruction of many immune cells and impaired immune function[21]. It has been reported that the

ratio of C-reactive protein (CRP), procalcitonin, and neutrophils increase as a result of cytokine storm of bacterial superinfection and virus invasion, and poor prognosis with coagulation disorder with high d-dimer values[11,22]. In our study, CRP, procalcitonin, the neutrophil rate increased and lymphocyte count decreased in four patients with high CT-SS scores in the intensive care unit. The d-dimer value was increased in one patient with pulmonary embolism and one patient with kidney transplantation who received coronary artery disease and hemodialysis.

Our study has some limitations. The typical and atypical groups' data were not balanced, and the sample size of the atypical group was relatively small—further studies with more patients, especially atypical CT findings patients. For emerging imaging signs of pleural effusion after follow-up, it is necessary to evaluate the significance of the prognosis of COVID-19 in further studies. Since the study was retrospective, additional findings and new clinical data in the patients' follow-up could not be presented.

CONCLUSİONS

The atypical findings accompanying the typical findings of COVID-19 pneumonia will increase the awareness that the diagnosis of other diseases that may be directly related to COVID-19 pneumonia should be kept in mind, and if typical findings accompany the atypical findings COVID-19 pneumonia, false negativity rates will decrease by making it in the differential diagnosis.

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