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The Association Between Chest CT Severity Scores, CO-RADS, Vitamin D Levels and Other Laboratory Parameters of COVID-19 Patients

COVID-19 Hastalarında Toraks BT Şiddet Skorları, CO-RADS, D Vitamini Düzeyleri ve Diğer Laboratuvar Parametreleri Arasındaki İlişki

Kaan Alişar, Dilek Çetinkaya Alişar*, Gonca Sağlam**, Serdar Karakullukçu**

University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital, Clinic of Radiology, Erzurum, Turkey
**University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital, Clinic of Physical Medicine and Rehabilitation, Erzurum, Turkey*
***Karadeniz Technical University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Trabzon, Turkey*
****Bayburt Community Health Center, Clinic of Public Health, Bayburt, Turkey*

Abstract

Objective: This study determined the correlation between several laboratory variables, chest computed tomography severity score (CTSS), and coronavirus disease-2019 (COVID-19) Reporting and Data System (CO-RADS) in COVID-19 patients.

Materials and Methods: Ninety-one patients with COVID-19 infection verified by polymerase chain reaction test, presented to the emergency department with COVID-19 symptoms, and had a thoracic computed tomography (CT) scan at the time of admission were included in this retrospective study. 25-hydroxyvitamin D [25(OH)D] levels, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer, glucose, ferritin, creatinine, alanine aminotransferase, aspartate aminotransferase, phosphorous, and calcium levels recorded and CO-RADS and CTSS data. The correlation of laboratory parameters with radiological findings was analyzed.

Results: A positive correlation was found between CTSS and age, ESR, CRP, D-dimer while a negative correlation was found between CTSS and lymphocyte count. Patients with high CTSS levels had higher ESR, CRP, D-dimer, ferritin values and lower lymphocyte count, and lower calcium levels. Patients with typical CO-RADS involvement had higher sedimentation, CRP, glucose, and ferritin levels and lower lymphocyte count. No significant correlation was determined between the 25(OH)D level, CO-RADS, and CTSS.

Conclusion: The results of this study highlight that the reduced lymphocyte count, high D-dimer, sedimentation, ferritin, and CRP levels are predictors of severe lung involvement in COVID-19 patients. Hypocalcemia can also be considered a marker of severe lung involvement evaluated by CT in COVID-19 patients. the association between vitamin D deficiency and COVID-19 pneumonia should be investigated in future studies.

Keywords: COVID-19, CO-RADS, CTSS, real-time reverse transcription-polymerase chain reaction, vitamin D deficiency, hypocalcemia

Öz

Amaç: Bu çalışma, koronavirüs hastalığı-2019 (COVID-19) hastalarında laboratuvar parametreleri, toraks bilgisayarlı tomografisi (BT) şiddet skoru (CTSS) ve COVID-19 Raporlama ve Veri Sistemi (CO-RADS) arasındaki ilişkiyi belirlemeyi amaçlamaktadır.

Gereç ve Yöntem: COVID-19 semptomları ile acil servise başvuran ve başvuru anında toraks BT çekilmiş olan, polimeraz zincir reaksiyon testi ile COVID-19 olduğu doğrulanan 91 hasta çalışmaya dahil edildi. Hastaların 25-hydroksivitamin D [25(OH)D] seviyeleri, eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP), D-dimer, glikoz, ferritin, kreatinin, alanin aminotransferaz, aspartat aminotransferaz, fosfor ve kalsiyum seviyeleri ile birlikte CO-RADS ve CTSS verileri retrospektif olarak kaydedildi. Laboratuvar parametrelerinin radyolojik bulgularla korelasyonu incelendi.

Bulgular: CTSS ile yaş, ESR, CRP, D-dimer arasında pozitif korelasyon bulunurken, CTSS ile lenfosit sayısı arasında negatif korelasyon bulundu. Yüksek CTSS seviyeleri olan hastalarda daha yüksek ESR, CRP, D-dimer, ferritin değerleri ve daha düşük lenfosit sayısı ile kalsiyum seviyeleri vardı. Tipik CO-RADS tutulumu olan hastalar daha yüksek sedimantasyon, CRP, glikoz ve ferritin seviyelerine ve daha düşük lenfosit sayısına sahipti. 25(OH)D düzeyi ile CO-RADS ve CTSS arasında anlamlı bir ilişki saptanmadı.

Sonuç: Bu çalışmanın sonuçları, düşük lenfosit sayısı, yüksek D-dimer, sedimantasyon, ferritin ve CRP düzeylerinin COVID-19 hastalarında şiddetli akciğer tutulumunun belirleyicileri olduğunu düşündürmektedir. Hipokalsemi, BT ile değerlendirilen COVID-19 hastalarında ciddi akciğer tutulumunun bir belirteci olarak da düşünülebilir. D vitamini eksikliği ve COVID-19 pnömonisinin ilişkisi ileri çalışmalarda araştırılmalıdır.

Anahtar kelimeler: COVID-19, CO-RADS, CTSS, gerçek zamanlı polimeraz zincir reaksiyonu, vitamin D eksikliği, hipokalsemi

Address for Correspondence/Yazışma Adresi: Kaan Alişar MD, University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital, Clinic of Radiology, Erzurum, Turkey
Phone: +90 533 310 94 44 **E-mail:** kaan_alisar@hotmail.com **ORCID ID:** orcid.org/0000-0002-4351-2458
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Introduction

In December 2019, several patients with pneumonia and no recognized etiology were reported in Wuhan, China. Molecular analysis of the lower respiratory system samples taken from the patients showed that the disease-causing organism is a virus from the coronavirus family. On February 11, 2020, this virus was identified as a coronavirus disease-2019 (COVID-19) by the World Health Organization (1). Worldwide, more than 2.5 million fatalities and more than 116.3 million confirmed cases had been reported as of March 5, 2021 (2).

Previously, a decrease in leukocyte count and an increase in C-reactive protein (CRP) levels are observed in COVID-19 with several other abnormalities in some of the laboratory tests (3). Furthermore, a number of risk factors for COVID-19 disease have been discovered, including advanced age, ethnicity, type 2 diabetes, hypertension, obesity, renal dysfunction, and cardiovascular disorders (4). It is well recognized that each of these factors has some connection to vitamin D insufficiency. This has led to the question of whether low vitamin D levels can alter the development or even prognosis of COVID-19 disease (5). On the other hand, hypocalcemia is a frequent in-hospital consequence that happens in tandem with other clinical problems including an imbalance in the secretion of parathyroid hormone (PTH) and vitamin D (6).

The most accurate method for determining if a person has COVID-19 infection is real-time reverse transcriptase-polymerase chain reaction (RT-PCR) and chest computed tomography (CT) has been reported to be predictive in case of false-negative results of RT-PCR. CT is not only a diagnostic tool but also has great importance in monitoring the progression of the disease and evaluating the treatment outcomes (7). In COVID-19, pneumonia is the most frequent cause of morbidity and death. PCR test is not found to be a predictive factor for the severity of pulmonary involvement (8,9). On the other hand, chest imaging plays an important role in both diagnosis and classification of disease severity in COVID-19 triage (10,11). Conventional chest radiography is the first step of imaging in emergency services due to its easy accessibility and cheapness. However, the sensitivity of chest radiography is quite low in the diagnosis of COVID-19 pneumonia. The sensitivity of chest CT in the diagnosis of COVID-19 pneumonia is quite high compared to the PCR tests (12,13).

We aimed to determine the correlation between various laboratory parameters including vitamin D, chest CT severity scores (CTSS), and COVID-19 Reporting and Data System (CO-RADS) in COVID-19 patients in this study.

Materials and Methods

Study Protocol and Design

This study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (decision no: 2021/02-21, date: 18.01.2021). This study was conducted in January-February 2021 after ethical approval, using patient recorded data of 2020. Ninety-one patients who were admitted to the emergency department with suspected COVID-19 infection, screened with chest CT and had positive COVID-19 RT-PCR results, were included in this retrospective study. Age, gender, laboratory data, chest CT images and RT-PCR results of the patients were retrospectively scanned from the hospital database. The laboratory data and chest CT images at the first admission to the emergency department were recorded. Laboratory investigations included erythrocyte sedimentation rate (ESR), white blood cell, lymphocyte and platelet counts, 25-hydroxyvitamin D [25(OH)D] levels evaluated in the last three months, CRP, D-dimer, glucose, ferritin, creatinine, alanine aminotransferase, aspartate aminotransferase, phosphorus and calcium levels.

CO-RADS and CTSS

The CO-RADS, a procedure mostly based on the suggestions of the North American Radiology Association, was published by the Netherlands Radiology Association (NVvR) in 2020. From the lowest degree of suspicion (CO-RADS 1) to the highest level of suspicion (CO-RADS 5), this method employs a scoring system from 0 to 5 to classify COVID-19 pulmonary involvement on CT (14). Two additional categories denote a technically deficient review (CO-RADS 0) and COVID-19 infection that was verified at the time of the research by RT-PCR (CO-RADS 6). In the diagnosis of COVID-19 pneumonia, CO-RADS 2 corresponds to "Atypical", CO-RADS 3 "Low Probability, Suspicious", CO-RADS 4 "High Probability, Suspicious" (Table 1). The inter-observer variation of CO-RADS 2, 3, and 4 classifications can be high. Since a

Table 1. CO-RADS, COVID-19 infection suspicion level, CT findings

CO-RADS	COVID-19 infection suspect level	CT findings
CO-RADS 0	-	Technically inadequate
CO-RADS 1	Highly unlikely	Normal or non-infectious anomalies
CO-RADS 2	Unlikely	Abnormalities consistent with infections other than COVID-19
CO-RADS 3	Equivocal	Unclear whether COVID-19 is present
CO-RADS 4	Probable	Abnormalities suspicious for COVID-19
CO-RADS 5	Highly likely	Typical COVID-19
CO-RADS 6	PCR proven	

CO-RADS: COVID-19 reporting and data system, CT: Computed tomography, COVID-19: Coronavirus disease-2019, PCR: Polymerase chain reaction

mild infection may have a negative CT scan in the first few days, CT findings should be interpreted together with clinical symptoms and duration of symptoms (15). The CTSS, which was determined using a semi-quantitative scoring approach, has been shown to be related to the severity of the disease and can be used as a prognostic indicator (16-21). With CTSS, each of the five lobes of the lung is evaluated. Involvement in each lobe is scored between 0 and 5. Each lobe's overall scores might vary from 0 (without involvement) to 25 (maximum involvement) (Table 2).

CO-RADS classification and CTSS data were recorded by a six-year experienced radiologist according to chest CT of the patients. CO-RADS was classified from 1 to 5. The CTSS was scored between 0 and 5 for each five lobes of the lung. The chest CT was evaluated by a radiologist who was blinded to the other features of the patients.

Statistical Analysis

SPSS (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.) program was used for data analysis. Results of evaluations are documented using descriptive statistics, including mean and standard deviation for numerical variables and number and percentage for categorical variables. The one-sample Kolmogorov-Smirnov test was used to examine if the groups' distributions were normal. Comparison of numerical variables between two independent groups; the Mann-Whitney U test was used to assess it because the normal distribution requirement was not satisfied. Since the normal distribution requirement was not satisfied, Spearman test was utilized in correlation analysis. The statistical significance level of alpha was accepted as $p<0.05$.

Results

The research involved 91 patients in total. Among the patients, 71 (78.0%) were men and 20 (22.0%) were women 71. The average age of the patients is 57.8±16.4. Table 3 provides an overview of the patients' demographics and laboratory results. The CTSS score was recorded as the lowest 0 and the highest 24. Correlation analyses were performed by evaluating CTSS scores into two groups as below 10 and above 10 and also CO-RADS scores into two groups as 1-3 and 4-5.

Table 2. CTSS in each lung lobe

Score	Pulmonary lobe involvement rate
0	No involvement
1	<5% involvement
2	5%-25% involvement
3	26%-49% involvement
4	50%-75% involvement
5	>75% involvement

CTSS: Computed tomography severity score

The correlation of age, gender, and laboratory parameters with CTSS and CO-RADS classification is shown in Table 4. CTSS was correlated with age, sedimentation, CRP, D-dimer, and CO-RADS classification positively while it was and correlated with lymphocyte, platelet counts, and calcium levels negatively. The CO-RADS classification was correlated with age, sedimentation, CRP, D-dimer, glucose, ferritin levels, and CTSS positively and was correlated with lymphocyte count negatively. Comparison of the laboratory parameters, CTSS, and CO-RADS classification are summarized in Table 5. While sedimentation, CRP, D-dimer, and ferritin levels were higher in CTSS 10-24 group than CTSS 0-9 group, lymphocyte count and calcium levels were significantly lower ($p<0.05$). Compared to the CO-RADS 1-3 group, the CO-RADS 4-5 group had considerably greater sedimentation, CRP, glucose, and ferritin levels, but the lymphocyte count was much lower ($p<0.05$).

Discussion

COVID-19 is still a cause of significant viral disease and death around the world and continues to spread rapidly. In this study, we hypothesized that the severity of lung involvement on chest CT may be correlated with laboratory findings. CTSS and CO-RADS classification based on chest CT findings obtained at the first admission to the hospital can be predictive for COVID-19 prognosis disease and this can guide physicians to

Table 3. Demographics and clinical characteristics of patients with COVID-19 on admission

	All patients (n=91) mean ± SD
Age (years)	57.8±16.4
Gender, male (n, %)	71 (78.0)
25(OH)D (ng/mL)	17.3±10.5
Lymphocyte (10^9/L)	1645.7±1033.0
WBC (10^9/L)	9003.8±4356.0
Platelet (10^9/L)	243736.5±79500.9
ESR	20.5±18.4
CRP (mg/L)	33.3±48.7
D-dimer (ng/mL FEU)	15407±4431.3
Glucose (mg/dL)	127.3±61.7
Ferritin (ng/mL)	446.3±444.4
Creatinine (mg/dL)	1.0±0.4
ALT (IU/L)	33.1±22.7
AST (IU/L)	31.4±21.5
Phosphorus (mg/dL)	3.3±0.8
Calcium (mg/dL)	8.9±0.7

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, COVID-19: Coronavirus disease-2019, 25(OH)D: 25-hydroxyvitamin D, SD: Standard deviation

Table 4. Summary of the relationship between chest CT scores. CO-RADS classification and clinical characteristics in COVID-19

	Chest CT scores		CO-RADS
	Correlation coefficient	p-value	Correlation coefficient
Age (years)	0.485	<0.001	0.211
25(OH)D (ng/mL)	-0.058	0.585	-0.082
Lymphocyte (10^9/L)	-0.725	<0.001	-0.437
WBC (10^9/L)	0.080	0.451	-0.095
Platelet (10^9/L)	-0.217	0.038	0.053
ESR	0.460	<0.001	0.347
CRP (mg/L)	0.601	<0.001	0.463
D-dimer (ng/mL FEU)	0.552	<0.001	0.253
Glucose (mg/dL)	0.333	0.001	0.335
Ferritin (ng/mL)	0.395	<0.001	0.441
Creatinine (mg/dL)	0.253	0.016	0.066
ALT (IU/L)	-0.055	0.605	0.155
AST (IU/L)	-0.007	0.951	0.078
Phosphorus (mg/dL)	-0.052	0.622	-0.035
Calcium (mg/dL)	-0.236	0.024	-0.197
CO-RADS classification	0.510	<0.001	-
Chest CT scores	-	-	0.510

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CO-RADS: COVID-19 reporting and data system, 25(OH)D: 25-hydroxyvitamin D, CT: Computed tomography, COVID-19: Coronavirus disease-2019

establish proper treatment promptly. We compared laboratory parameters with CTSS to determine the poor prognosis risk factors [Decrease in calcium and 25(OH)D levels, lymphocyte, white blood cell and platelet count and increase in liver-kidney function tests, glucose, D-dimer, CRP, ferritin levels, ESR] for COVID-19 disease. Additionally, we investigated the relationship between these laboratory variables and CO-RADS to define the difference between patients with typical lung involvement and those who did not present with typical lung involvement.

Vitamin D levels are frequently measured using serum total 25(OH)D, which is the active form of vitamin D3 and a key regulator of innate and adaptive immunity. Low vitamin D levels have been linked to a number of clinical disorders, including a higher risk of contracting infectious diseases, although its underlying cause is still debatable (22). Retrospective research have shown how vitamin D works to prevent the spread of viruses, lower the incidence of pneumonia and acute viral respiratory tract infections, and reduce inflammation (23). Low vitamin D levels have been linked to an increased risk of developing severe pneumonia through increasing the production of inflammatory cytokines. It has been discovered that thrombotic attacks, which are frequent in COVID-19, are also linked to vitamin D insufficiency (24).

A meta-analysis of 25 randomized controlled trials (RCT) found that vitamin D supplementation helps individuals with very low vitamin D status [25(OH)D:<10 ng/mL] from developing acute respiratory tract infections. Recently, this finding has attracted considerable interest regarding the potential effects of vitamin D status on severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection mortality and vitamin D supplementation as a potential COVID-19 treatment strategy (25). However, data on vitamin D status in relation to the clinical results of SARS-CoV-2 infection are few. Only a few research on vitamin D levels in COVID-19 patients have been reported. Patients having positive PCR results for SARS-CoV-2 had decreased 25(OH)D concentrations, according to research by D'Avolio et al. (26). The supplementation of vitamin D is suggested as a helpful approach to lower the risk of infection. A prognostic influence of vitamin D insufficiency was shown in a newly published meta-analysis by Munshi et al. (27) in determining the likelihood of developing severe COVID-19. The fact that our study was done in the winter, when sun exposure is at a minimum, and in a region where vitamin D insufficiency is endemic can be used to explain why we were unable to discover a correlation between vitamin D deficit and the severity of COVID-19 pneumonia in our study. RCTs and cohort studies on this topic should be conducted as there is insufficient data to demonstrate a relationship between vitamin D levels and the severity of lung involvement and mortality.

Hypocalcemia is a common condition observed in viral infections and pneumonia (28). It was identified as a poor prognostic factor related with the clinical severity of COVID-19 in earlier research

Table 5. Comparison of between CTSS and CO-RADS groups and laboratory findings

	Chest CT scores		p-value	CO-RADS		p-value
	0-9	10-24		1-3	4-5	
25(OH)D (ng/mL)	17.9±11.0	15.4±8.6	0.476	17.3±8.8	17.2±12.0	0.497
Lymphocyte (10^9/L)	1973.8±972.0	675.6±414.0	<0.001	2018.7±1028.1	1264.4±898.6	<0.001
WBC (10^9/L)	8820.5±4229±0	9545.7±4769.4	0.361	9265.5±3179.4	8736.2±5322.6	0.145
Platelet (10^9/L)	249602.9±86536.2	226391.3±51277.1	0.473	236217.4±58707±9	251422.2±96351.5	0.487
ESR	17.2±16.2	30.2±21.3	0.005	14.0±11.5	27.1±21.6	0.002
CRP (mg/L)	24.3±42.3	60.0±57.0	<0.001	23.2±41.1	43.6±54.0	0.001
D-dimer (ng/mL FEU)	778.7±1243.1	3793.3±8278.1	<0.001	1831.6±6083.1	1243.2±1463.9	0.086
Glucose (mg/dL)	124.7±65.2	135.1±50.6	0.087	117.7±58.1	137.1±64.3	0.012
Ferritin (ng/mL)	352.9±395.7	722.3±473.7	0.001	286.3±385.4	609.7±444.9	<0.001
Creatinine (mg/dL)	1.0±0.3	1.2±0.5	0.114	1.0±0.5	1.0±0.4	0.576
ALT (IU/L)	33.4±24.2	32.1±18.2	0.891	29.1±14.8	37.2±28.3	0.221
AST (IU/L)	30.7±22.1	33.4±20.2	0.508	28.7±15.3	34.1±26.3	0.905
Phosphorus (mg/dL)	3.3±0.8	3.1±0.7	0.272	3.2±0.6	3.3±0.9	0.911
Calcium (mg/dL)	9.0±0.6	8.7±0.8	0.049	9.1±0.6	8.8±0.7	0.054

WBC: White blood cell, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CO-RADS: COVID-19 reporting and data system, CT: Computed tomography, COVID-19: Coronavirus disease-2019, 25(OH)D: 25-hydroxyvitamin D, CTSS: Computed tomography severity score

(29). There are a number of potential processes that might explain why people with severe COVID-19 experience hypocalcemia. One of them is the possibility that poor diet and advanced age might result in hypocalcemia and vitamin D insufficiency (30). Cell membrane disruption brought on by tissue and organ hypoxia allows calcium to enter the cell. Proinflammatory cytokines interfere with the response to PTH by preventing its release, which may result in an imbalance of calcium (31). Neuromuscular excitability, shown as muscle twitching, spasms, tingling, and numbness, is one of the most well-known signs of hypocalcemia. Severe hypocalcemia will raise mortality by resulting in major neuroendocrine and cardiovascular consequences if it is not treated over time. It should be kept in mind that individuals with more severe lung involvement may have lower calcium levels at the time of hospital admission. Similarly, our study revealed that CTSS was negatively correlated with calcium levels indicating the relationship between lung disease severity and hypocalcemia.

Inflammatory activation and coagulopathy have been reported to often raise serum CRP and D-dimer levels in COVID-19 patients, and these elevated levels are closely related with the disease's more severe manifestations (32,33). Additionally, it has been shown that the levels of CRP, ESR, ferritin, and procalcitonin increase in response to inflammation, particularly in patients receiving intensive care. These parameters may have increased as a result of both a secondary bacterial infection and an intensifying inflammatory response, which is frequently referred to as a cytokine storm brought on by COVID-19 infection (34).

Previous studies have reported that as the severity of COVID-19 disease increased, CRP, PCT, IL-6, and ESR increased proportionally (35,36). High fasting blood sugar levels may independently predict mortality in non-diabetic people, according to certain studies (37). In our investigation, there was a positive association between age, sedimentation, CRP, D-dimer, glucose, ferritin, and creatinine as well as the CTSS. Similarly, it was discovered that the CO-RADS 4-5 group had statistically substantially higher ESR, CRP, hyperglycemia, and ferritin levels. Accordingly, typical lung involvement may not be visible on a CT scan in individuals whose sedimentation, CRP, glucose, and ferritin levels are not high as well as lymphocyte count is not low for those who applied to the emergency room with the suspicion of COVID-19. According to earlier research, lymphopenia is a common symptom in COVID-19 patients and is a crucial and accurate

sign of the severity of the disease (1,38,39). Lymphopenia may result from the virus suppressing lymphocyte production directly (such as cells with ACE2 receptors being the target of the virus) or indirectly, or shortening the half-life of lymphocytes (40,41). In our study, as the blood lymphocyte count of the patients decreased, more typical and severe CT findings were observed. For COVID-19 patients, thrombocytopenia has been linked to an elevated risk of severe disease and mortality (42). A possible cause of thrombocytopenia may be that damaged lung tissue and pulmonary endothelial cells increase platelet consumption by activating platelets in the lungs, causing microthrombin aggregation and formation (43). Hypocalcemia, thrombocytopenia, and lymphopenia during admission to the hospital may lead to the conclusion that the lung involvement may be more severe.

In the scientific community, there is still debate concerning the diagnostic value of chest CT. Despite some research opposing the use of CT as a first-line diagnostic test (7), our study's findings suggest that combining a highly sensitive imaging technique like CT with laboratory measurements may aid in quick diagnosis and therapy. According to Orsi et al. (44), CT can be utilized to discharge patients without waiting for the results of the swab test who have clinical stability and are not at risk based on laboratory parameters, especially in the presence of negative radiographic findings.

This study has some limitations. First, we conducted a retrospective and single-center study among a limited sample of patients. We assessed the relationship between the severity of lung involvement and laboratory parameters, however we could not demonstrate this relationship including patients' clinical condition, hospitalization status, survival, or death. The direct effect of CT on the clinical decision has not been evaluated.

Conclusion

To date, several clinical laboratory variables were found to be related with COVID-19 severity across various studies without consistency. Lymphocyte count and calcium D-dimer, sedimentation, ferritin, and CRP levels may serve as markers of severe or critical COVID-19. Although vitamin D deficiency is thought to be a risk factor for COVID-19 pneumonia, the degree of lung involvement may not be reflected by this risk factor. To clarify the probable link between vitamin D deficiency and COVID-19 pneumonia, more research should be performed.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee of Erzurum Regional Training and Research Hospital (decision no: 2021/02-21, date: 18.01.2021).
Informed Consent: Retrospective study.
Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.A., Concept: K.A., Design: K.A., G.S., Data Collection or Processing: D.Ç.A., Analysis or Interpretation: D.Ç.A., S.K., Literature Search: G.S., Writing: K.A., G.S.

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