Could Chest Computed Tomography Scores Assess the Inflammatory Markers and Disease Severity of Coronavirus Disease-2019 Patients?

Korovirus Hastalığı-2019 Hastalarında Toraks Bilgisayarlı Tomografi Skoru Enflamatuvar Belirteçleri ve Hastalığın Şiddetini Yansıtabilir Mi?

Objective: This study aimed to investigate the relationship between chest computed tomography (CT) scores and inflammatory markers in patients with coronavirus disease-2019 (COVID-19).

Methods: A total of 259 patients who were confirmed to be COVID-19 positive with polymerase chain reaction test and CT findings, between 20 March and 30 May 2020, were included in our study. The patients were divided into two groups as critical and moderate according to their clinical conditions. CT findings, complete blood account and C-reactive protein (CRP) were recorded and statistically analysed. Receiver operating characteristic (ROC) curves were plotted in terms of CT scores, white blood cells, neutrophil/lymphocyte ratio (NLR) and CRP for the patients in the moderate and critical groups.

Results: CT scores (p<0.001), neutrophil counts (p<0.001), NLR (p<0.001) and CRP values (p<0.001) were significantly higher in the critical group than in the moderate group, whereas the lymphocyte count (p<0.001) and haemoglobin values (p=0.003) were significantly lower. In the ROC curve analysis, when the cut-off value was set at 6.5 to differentiate the moderate and critical groups, the CT score sensitivity was 0.86, specificity 0.809, area under the curve 0.899 and accuracy 0.81.

Conclusion: There is a correlation between CT scores and NLR. It is crucial to differentiate patients in critical and moderate conditions for the treatment planning of COVID-19. In addition to clinical findings and inflammatory markers, radiological imaging is an effective method to identify patients and determine the prognosis.

Keywords: Chest computed tomography, COVID-19, neutrophil/lymphocyte ratio, CT score

ABSTRACT

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Received Date/Geliş Tarihi: 01.10.2020 Accepted Date/Kabul Tarihi: 16.02.2021

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**INTRODUCTION**

The World Health Organization (WHO) China Country Office first reported cases of pneumonia with unknown origin in Wuhan, China, on 31 December 2019. In the following days, it was announced that the cause of pneumonia is a new coronavirus that has not been previously detected in humans, and the disease was named as coronavirus disease-2019 (COVID-19) (1-3). Because of its rapid transmission from person to person, COVID-19 has crossed the borders of China and caused a pandemic, and according to WHO’s COVID-19 epidemiologic update in January 2021, it has infected 96 million people worldwide and caused 2 million deaths.

The factor of COVID-19 mostly affects the respiratory system in humans, and the spectrum of the illness severity ranges from a simple cold to severe respiratory failure (2,4-6). It has been reported that it may involve enteric, hepatic, nephrotic and neurological systems as well as the respiratory system (4-6).

The diagnostic reference of COVID-19 is the examination of the obtained respiratory tract samples by reverse-transcription polymerase chain reaction (PCR) (2,3). However, insufficient sampling, sampling too early or in the late phase of infection and sampling with inappropriate method may cause false-negative results (6). In possible/definite COVID-19 cases, chest computed tomography (CT) is used to support diagnosis, demonstrate lung involvement and evaluate the extent of lung infection (7-10). The most frequent CT findings of patients are peripherally located ground-glass density and vascular thickening, and their CT findings may be positive, although the PCR test results are negative (4,8,10,11). In a recent study, the sensitivity of chest CT (98%) was higher than that of the PCR test (10).

There are four clinical stages of the disease [early stage (days: 0-4)], progression period (days: 5-8), peak stage (days: 9-13) and resolution phase (after day: 14). Radiological findings may vary according to these stages (11-13). The distinction of the critical group from the non-critical group according to the patients’ clinical manifestations is important for treatment choice and prognosis (14-16). There are publications examining the role of laboratory markers in distinguishing between the moderate and critical groups of patients and to assess which laboratory markers are correlated with the chest CT involvement score.

METHODS

This retrospective study was approved by the Local Ethics Committee University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (approval number: 89, approval date: 28.05.2020) and the Republic of Turkey Ministry of Health, COVID-19 Scientific Research Committee. Written informed consent was obtained from the patients enrolled. Between 20 March and 30 May 2020, 330 patients between 18 and 90 years old who were admitted to our hospital with suspicion of COVID-19 pneumonia and underwent chest CT were retrospectively reviewed using picture archiving communication systems. Of these patients, those with positive COVID-19 PCR test results and positive COVID-19 CT images with appropriate imaging protocol (n=259) were included in the study. Those who had negative PCR test results and had no evidence of typical COVID-19 pneumonia (n=71) were excluded from the study. A total of 259 patients were included in the study. Laboratory findings, complete blood count (number/μL) and CRP (mg/dL), presence of comorbidities [hypertension, diabetes mellitus (DM), heart failure, renal failure, malignancy history and chronic respiratory diseases] at the first hospital admission and clinical findings of the patients were obtained from the hospital archive. Care was taken to ensure that the laboratory data and CT images were acquired on the same day at the time of admission.

In terms of their clinical features at the time of hospital admission, patients were divided into two groups: moderate and critical [according to the guideline on COVID-19 (trial version 5) issued by the China National Health Commission] (19). The moderate group was composed of patients with fever, cough or shortness of breath only, whereas the critical group comprised those with Tachypnea (>30 breaths per minute), with less than 93% oxygen saturation at room environment or with \( \text{PaO}_2/\text{FiO}_2 <300 \text{mmHg} \) and with mechanical ventilation and intensive care requirement.

All images were acquired using a multidetector scanner (GE Optima CT660, 64 slices; General Electric, USA, 5 mm collimation) with the following parameters: 120 kVp, 40 mm beam collimation, 5 mm image thickness, 500 mm reconstruction field of view, 500 mA (maximum), 10 mA (minimum) and 1 s rotation time. Images were evaluated by two radiologists, “Yasemin Kayadibi and Neşe Uçar” with 9 and 11 years of chest radiology experiences, respectively. Image examination parameters such as ground-glass opacity, consolidation, vascular thickening, interlobular septal thickening, mediastinal lymphadenopathy, pleural effusion, subpleural bands and pericardial effusion were evaluated. CT images were scored from 1 to 4 (1: 0%-25%; 2: 26%-50%; 3: 51%-75%; 4: 76%-100%).
for each lobe according to the semiquantitative scoring system described in the literature (9,10,14,15). Scores determined for all lobes were summed, and the total CT score (from 0 to 20) was determined by the consensus of the two radiologists (Yasemin Kayadibi and Neşe Uçar).

Statistical Analysis
The statistical software SPSS version 22.0 IBM was used for data analysis. As descriptive analyses, frequency rates and percentages were described for the categorical variables and means and standard deviations for the continuous variables. Normality was checked using the Shapiro-Wilk test. The Mann-Whitney U and Student's t-tests were used for non-normally and normally distributed variables, respectively. Receiver operating characteristic (ROC) was used to determine the cut-off values, sensitivity and specificity. The chi-square test was used to test relationships between categorical variables. A p-value of <0.05 was considered statistically significant. For the correlation analysis, the Spearman test was used as a non-parametric test.

RESULTS

Patients Analysis
Table 1 presents patient analysis details. A total of 259 patients were included in the study. Patients whose clinical and laboratory findings could not be reached, who had negative PCR results and those with tomography images having artefacts were excluded in the study. Of patients, 122 (80 moderate and 57 critical) were men and 137 (93 moderate and 29 critical) women. Men dominated the study. Of patients, 122 (80 moderate and 57 critical) were men and 137 (93 moderate and 29 critical) women. Men dominated the moderate group (p=0.02), whereas no gender dominated the moderate group. The mean ages of patients were 53.2 and 63.18 years in moderate and critical groups, respectively. Comorbidity was present in 208 of 259 patients.

Radiological Findings
All CT images were obtained at the time of patients' first hospital admission. The summary of radiological and laboratory findings of the patients is presented in Table 2. Considering the radiological findings, a comparison of the two groups revealed that the lower lobes were statistically significantly higher in the severe group in which the disease affected more than one lobe. There was no significant difference in terms of right and left lung involvement in both groups (p=0.684). The right lower lobe was the most commonly involved lobe (93%). There was no significant difference between the number of lobes involved in both groups (p=0.152). The detection rate of ground-glass opacity was similar in both groups (p=0.792); however, the prevalence of consolidation and crazy paving were higher in the critical group (p<0.001 for both). Central involvement between the two groups was significantly higher in the critical group (p<0.001). Pleural effusion and subpleural band formation were observed significantly higher in the critical group (p<0.001 and p=0.005, respectively). The total mean CT score of the moderate and critical groups were 4.8 and 10.8, respectively. The CT score in the critical group was significantly higher than in the moderate group according to the Mann-Whitney U test (p<0.001). ROC curve analysis revealed that for a cut-off value of 6.5, the CT score had a sensitivity of 0.86, specificity 0.809, area under the curve (AUC) 0.899 and accuracy 0.81 (with 95% confidence interval: 0.854-0.944; Figure 1, 2).

Laboratory Findings
Table 3 presents the curves obtained from laboratory findings. The mean white blood cell (WBC) value was 6,845 in the total patient group, 6,335 in the moderate group and 8,335 in the critical group. WBC values were statistically significant (p<0.001) between the critical and moderate groups according to the Mann-Whitney U test after normality evaluation using the Shapiro-Wilk test (p<0.001). Increased neutrophil count, decreased lymphocyte count and increased CRP amount were statistically significantly higher in the critical group (p<0.001) according to the chi-square test. There was no significant difference in haemoglobin and platelet levels between the groups (p=0.003 and 0.265, respectively). Neutrophil/lymphocyte ratio (NLR) was statistically significantly higher in the critical group than in the moderate group (p<0.001) according to the Mann-Whitney U test.

Evaluation of the Relation between CT Scores and Laboratory Findings
When the correlation between CT scores and laboratory findings was compared, it was found that there was a positive correlation between WBC (r=0.341), neutrophil count (r=0.457), NLR (r=0.496), CRP (r=0.750) and CT scores, whereas there was a negative correlation between CT scores and lymphocyte counts (r=-0.315). The highest correlation was found between CRP and CT scores (Figure 3, Table 4). Spearman test was used for correlation analysis because of the value of p<0.001 obtained as a result of the normality calculation performed using the Shapiro-Wilk test.

DISCUSSION
Chest CT plays an important role in the diagnosis and follow-up of COVID-19 treatment (10). Many studies examine the relationship between the CT findings of the disease and its clinical manifestation...
**Table 2. Summary of chest CT and laboratory findings**

| Chest CT findings                          | Moderate (n=173) | Critical (n=86) | Total (n=259) | p        |
|--------------------------------------------|-----------------|-----------------|--------------|----------|
| Right upper lobe (n, %)                    | 131 (76)        | 82 (95)         | 213 (82)     | <0.001** |
| Right middle lobe (n, %)                   | 109 (63)        | 81 (94)         | 190 (73)     | <0.001** |
| Right lower lobe (n, %)                    | 160 (93)        | 82 (95)         | 242 (93)     | 0.439    |
| Left upper lobe (n, %)                     | 132 (76)        | 79 (92)         | 211 (82)     | 0.002**  |
| Left lower lobe (n, %)                     | 145 (84)        | 84 (98)         | 229 (88.4)   | 0.001**  |
| Single lobe (n, %)                         | 12 (6.9)        | 2 (2)           | 14 (5.4)     | 0.152    |
| Multiple lobes (n, %)                      | 161 (93)        | 84 (98)         | 245 (95)     | 0.152    |
| Total CT score (mean ± SD)                 | 4.8±0.17        | 10.8±0.45       | 6.8±4.12     | <0.001** |
| GGD (n, %)                                 | 168 (97)        | 84 (98)         | 252 (97)     | 0.792    |
| Consolidation (n, %)                       | 65 (38)         | 57 (66)         | 122 (47)     | <0.001** |
| Crazy-paving pattern (n, %)                | 39 (23)         | 46 (54)         | 85 (33)      | <0.001** |
| Round (n, %)                               | 131 (76)        | 64 (74)         | 195 (75)     | 0.879    |
| Patchy (n, %)                              | 104 (60)        | 76 (88)         | 180 (70)     | 0.001**  |
| Peripheric distribution (n, %)             | 153 (88.4)      | 86 (100)        | 239 (92)     | 0.001**  |
| Central distribution (n, %)                | 64 (37)         | 67 (78)         | 131 (51)     | 0.001**  |
| Peripheral + central (n %)                 | 60 (35)         | 67 (78)         | 127 (49)     | 0.001**  |
| Single focus (n, %)                        | 12 (7)          | 0 (0)           | 12 (4.6)     | 0.01*    |
| Multiple foci (n, %)                       | 161 (93)        | 86 (100)        | 247 (95.4)   | 0.01*    |
| Halo sign (n, %)                           | 38 (22)         | 19 (22)         | 57 (22)      | 0.981    |
| Reverse halo sign (n, %)                   | 14 (8)          | 9 (10.5)        | 23 (9)       | 0.643    |
| Vascular thickening (n, %)                 | 51 (29.5)       | 34 (40)         | 85 (34)      | 0.123    |
| Pleural effusion (n, %)                    | 1 (0.6)         | 12 (14)         | 13 (5)       | 0.001**  |
| Lymph node enlargements (n, %)             | 7 (4)           | 7 (8)           | 14 (5.4)     | 0.241    |
| Subpleural bants (n, %)                    | 37 (21.4)       | 33 (38)         | 70 (27)      | 0.005*   |
| Three in bud appearance (n, %)             | 7 (4)           | 6 (7)           | 13 (5)       | 0.367    |
| Dilatation of peripheral airways (n, %)    | 20 (12)         | 15 (17.4)       | 35 (14)      | 0.246    |
| Fibrous stripe (n, %)                      | 31 (18)         | 22 (25.6)       | 53 (21)      | 0.190    |

**Laboratory findings**

|                                  | Moderate (n=173) | Critical (n=86) | Total (n=259) | p        |
|----------------------------------|-----------------|-----------------|--------------|----------|
| WBC count (mean ± SD)            | 6.1±0.21        | 8.3±0.39        | 6.85±3.22    | <0.001** |
| Increased WBC (n, %)             | 7 (4)           | 19 (22)         | 26 (10)      | <0.001** |
| Neutrophil count (mean ± SD)     | 4.14±0.18       | 6.84±0.38       | 5.04±3.09    | <0.001** |
| Increased neutrophil (n, %)      | 8 (4.6)         | 25 (29)         | 33 (13)      | <0.001** |
| Lymp count (mean ± SD)           | 1.41±0.05       | 1.6±0.39        | 1.5±2.1      | <0.001** |
| Decreased lymp (n, %)            | 45 (26)         | 47 (55)         | 92 (36)      | <0.001** |
| NLR                              | 3.53±0.21       | 8.74±0.94       | 5.3±6.02     | <0.001** |
| Platelet count (mean ± SD)       | 197.59±5.47     | 212.57±9.99     | 202.56±79.39 | 0.256    |
| Increased platelet (n, %)        | 2 (1.2%)        | 2 (2%)          | 4 (1.5%)     | 0.602    |
| Hb (mean ± SD)                   | 133.65±1.32     | 126.93±1.82     | 131.42±17.48 | 0.003*   |
| Decreased Hb (n, %)              | 12 (7)          | 12 (14)         | 24 (9)       | 0.073    |
| CRP (mean ± SD)                  | 58.74±10.97     | 135±13.49       | 84.07±142.53 | <0.001** |
| Increased CRP (n, %)             | 146 (84.4)      | 86 (100)        | 232 (90)     | <0.001** |

The p-values for CT scores and WBC were calculated using the Mann-Whitney U test. The p-values for other parameters were calculated using the Pearson chi-square test. *P<0.05, **P<0.001.

CT: computed tomography, GGD: ground-glass appearance, WBC: white blood cells, NLR: neutrophil/lymphocyte ratio, CRP: C-reactive protein, Lymp: lymphocyte, Hb: haemoglobin, SD: standard deviation.
In the literature, areas of ground-glass density, crazy-paving pattern and vascular congestion, which are the most common findings observed in COVID-19 pneumonia, are predicted to reflect the virus-related septal and alveolar damage, the less frequently observed consolidations reflect the exudate in alveoli and hyaline membrane formation. A limited number of autopsy studies also support these findings (13,20-22). Similarly, in our study, the most common finding observed in the whole patient population was ground-glass density areas involving more than one lobe, but consolidations were statistically significantly higher in the critical group.

In COVID-19 pneumonia, a better prognosis is expected in the moderate group, whereas worse prognosis is likely in the critical group. It has been shown that early distinction between the two groups and early treatment has increased the survival rates significantly. CT scoring systems were developed to calculate the radiological involvement of the disease, and a significant correlation was found between the high score, clinical conditions and laboratory findings (8,12,15,17,18,20). In our study, we aimed to investigate the relationship between lung involvement severity and inflammatory markers in patients diagnosed with COVID-19 and the role of CT score in differentiating clinical severity. Li et al. (20), Liu et al. (15) and Francone et al. (17) reported the cut-off values for CT scores at 7, 4 and 18, respectively, to distinguish the moderate and critical groups. In our study (n=259), this value was 6.5 (AUC: 0.899, specificity: 0.809, sensitivity: 0.86 and accuracy: 0.81). In addition to the clinical and laboratory data of the patient, this study has demonstrated that chest CT findings are also useful in the distinction of disease severity.

Many alterations occur in the immune and haematopoietic systems of patients diagnosed with COVID-19. In the literature, various laboratory findings including lymphopenia and elevated liver enzymes, lactate dehydrogenase, inflammatory markers (e.g. CRP and ferritin), D-dimer (>1 mcg/mL), prothrombin time, troponin and creatine phosphokinase have been associated with poor prognosis in COVID-19 (14,15,17,20). Immune cell destruction, impaired immune cell function, decreased lymphocyte level as a result of bone marrow involvement and simultaneous neutrophil dominance are the most striking findings in the haematological system in COVID-19 (22-25). NLR, as a marker of inflammatory response, has been associated with poor prognosis in sepsis,

![Figure 1. Chest computed tomography (CT) example of the moderate group: a 30-year-old man (CT score: 1, neutrophil/lymphocyte ratio: 2.5, C-reactive protein: 3.5). The axial CT image revealed a single focus of ground-glass opacity with adjacent dilated bronchus](image)

![Figure 2. Chest computed tomography (CT) example of the critical group: A 79-year-old man (CT score: 19, neutrophil/lymphocyte ratio: 12.5, C-reactive protein: 190). Axial CT image revealed bilateral diffuse ground-glass opacities and consolidations with dilated bronchi and air bubbles](image)

| Table 3. Cut-off values and statistical analysis in distinguishing the moderate and critical groups |
|-------------------------------------------------|----------------|----------------|----------------|----------------|
| Cut-off value | AUC (CI: lower-upper) | Specificity | Sensitivity | Accuracy |
| Total CT Score | 6.5 | 0.899 (0.854-0.944) | 0.809 | 0.86 | 0.81 |
| WBC (n/μL) | 6.13 | 0.712 (0.646-0.779) | 0.601 | 0.686 | 0.629 |
| Neu (n/μL) | 4.38 | 0.773 (0.712-0.834) | 0.659 | 0.709 | 0.675 |
| Lymp (n/μL) | 1.04 | 0.683 (0.613-0.752) | 0.593 | 0.699 | 0.664 |
| NLR | 3.74 | 0.792 (0.729-0.855) | 0.74 | 0.802 | 0.76 |
| CRP | 47.9 | 0.812 (0.758-0.866) | 0.682 | 0.802 | 0.722 |

CT: computed tomography, WBC: white blood cells, Neu: neutrophil, NLR: neutrophil/lymphocyte ratio, CRP: C-reactive protein, Lymp: lymphocyte, AUC: areas under the curve, CI: confidence interval
cardiovascular diseases and malignancies (4,14,23-25). Fu et al. (26) found a significant difference between the mild/moderate and severe groups in terms of WBC, NLR, lymphocyte counts, D-dimer levels and fibrinogen levels. Among these parameters, the highest AUC was 0.88, which was the most significant parameter for NLR. They also argued that the change in haematological parameters is an earlier and more reliable change than inflammatory markers (26). The study by Lagunas-Rangel (27) also supported the statistically significant increase in NLR in severe patients. In our study, the CRP level, neutrophil count and NLR in the critical group increased statistically significantly than in the moderate group (p<0.001 for all), whereas the lymphocyte count decreased statistically significantly (p<0.001). In the ROC curve analysis, it was calculated as 47.9 mg/dL (AUC: 0.812) for CRP, 6.13 n/μL (AUC: 0.777) for WBC, 4.38 n/μL (AUC: 0.757) for neutrophil count, 1.04 n/μL (AUC: 0.683) for lymphocyte count and 3.75 (AUC: 0.792) for NLR. In addition, a positive correlation was noted between CT scores and CRP, WBC, neutrophil count and NLR and a negative correlation with lymphocyte count (correlation coefficients: 0.496, 0.341, 0.457, 0.496 and -0.315, respectively). Our study showed that the CT score in patients’ initial tomography was significantly related to the patient’s inflammatory response and NLR. Our study is also compatible with studies in the literature that reveal the correlation between CRP, D-dimer, NLR and decreased lymphocyte count and CT scores (17,18,25-27).

Although COVID-19 is known to cause infection in completely healthy adults, more serious involvement is observed in adults with advanced age and comorbidities such as cardiovascular diseases, DM, hypertension, chronic lung diseases, cancer and chronic kidney disease (15,17,18,21,23). In our study, the comorbidity rate was higher in the critical group than in the moderate group, and the most common comorbidity was hypertension, followed by DM.

**Study Limitations**

Our study has some limitations. Our study was single-centred and retrospective. There are four clinical stages of the disease [early stage (days: 0-4), progression period (days: 5-8), peak stage (days: 9-13) and resolution phase (after day: 14)], and radiological findings may vary according to these stages. However, in our study, it was impossible to obtain the information from the patients’ records about which date the patients were admitted to the hospital after the onset of the disease and at which stage of the disease the chest CT was obtained. Except for patients who did not worsen, control follow-up CT was not requested, and follow-up was generally conducted by chest radiography. Patients who have positive PCR with no radiological findings, have negative PCR with positive radiological findings and did not require hospitalisation were excluded in the study, and therefore, we may have caused bias in patient selection in our study.

**CONCLUSION**

The demographic data of our study are compatible with other studies investigating the correlation between CT scores and NLR among the studies conducted to date are limited in number. Many clinical parameters are used to determine the critical patient group in COVID-19 pneumonia. In our study, we showed that the findings observed in chest CT reflect the severity of the disease at the time of admission. We found a positive correlation between CT scores and NLR, which has a prognostic side, and a determined cut-off score of 6.5 to distinguish the moderate and critical groups. We think that it can guide clinicians to determine the severity of involvement and choose an effective treatment according to the severity of the disease.

**Ethics Committee Approval:** This retrospective study was approved by the Local Ethics Committee University of Health Sciences Turkey, Gaziosmanpaşa Training and Research Hospital (approval number: 89, approval date: 28.05.2020).

**Informed Consent:** Written informed consent was obtained from the patients enrolled.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Surgical and Medical Practices - B.D.; Concept - N.U.; Design - Y.K.; Data Collection and/or Processing - N.U., M.F.K., O.G.;

| Table 4. Statistical analysis of the correlation between laboratory findings and CT scores |
|-----------------------------------------------|
| **CT scores** | **r** | **p** |
|----------------|------|------|
| WBC            | 0.341| <0.001 |
| Neu            | 0.457| <0.001 |
| NLR            | 0.496| <0.001 |
| CRP            | 0.750| <0.001 |
| Lymph          | -0.315| <0.001 |

Spearman test (r) was used for correlation analysis. CT: computed tomography, WBC: white blood cells, Neu: neutrophil, NLR: neutrophil/lymphocyte ratio, CRP: C-reactive protein, Lymp: lymphocyte
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