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Can we Predict Lung Involvement by Laboratory Markers in Covid-19 Patients

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ABSTRACT

When the COVID-19 pandemic started, we had insufficient knowledge of clinical clues. The flu-like presentation of COVID-19 makes the management of patients presenting to the emergency service challenging. Our study retrospectively investigated the parameters of neutrophil, lymphocyte, platelet R in 349 moderately and severely COVID-19 PCR+ patients, with or without HR-CT findings. As a result, the CRP, D-dimer, troponin, ferritin, and NLR values were determined to be significantly higher, and the lymphocyte count was significantly lower in the patients with CT involvement, consistent with the literature. Our study aimed to give an idea regarding possible tomographic involvement with the blood tests we performed in COVID-19 PCR+ patients during their first presentation to the emergency service, thus contributing to both the cost-effectivity and the literature on behalf of our district and serving as a guide for the outcome.

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Introduction

In December 2019, an outbreak of a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) started in Wuhan, China, and following the rapid increase throughout the world, the WHO declared COVID-19 infections as a 'pandemic' on March 11, 2020 [1-3]. The disease's most common symptoms were high-grade fever, weakness, dry cough, shortness of breath, chest pain, and viral pneumonia with radiological evidence of bilateral, interstitial, ground-glass opacities, and peripheral lung consolidation [2, 4]. Especially in winter and spring, it is not easy to distinguish the early stages of COVID-19 infection due to the wide variety of flu-like presentations. Any misdiagnosis will lead to severe problems in controlling the outbreak. Even though most patients present mild symptoms, Covid-19 causes significant problems regarding the global healthcare system [2,5,6]. Therefore, it is necessary to determine the clinical laboratory biomarkers that will help predict the differential diagnosis of COVID-19 infection and the severity of the disease [7]. In the studies conducted, it was found that the values of D-dimer, CRP, Troponin IH, and ferritin increased, and the lymphocyte count decreased regarding the laboratory markers associated with severe COVID-19. Such results obtained by meta-analysis have also entered the literature [2, 8-12].

At the time of conducting our study, clinical and laboratory studies on COVID-19 were insufficient regarding the local population in our country, and the first case was detected on March 11, 2020, while several clinical and laboratory studies

on COVID-19 had already been published. With this study, we aimed to contribute to the literature on behalf of our region and guide the outcome.

This study compared clinical and laboratory biomarkers of 349 mild and severe COVID-19 patients with or without high-resolution computed tomography (HR-CT) findings.

Material and Method

Our study was a retrospective and descriptive study conducted at Isparta City Hospital, where approximately 300.000 patients are referred per year. Permissions for COVID-19 studies were granted by the Ministry of Health of the Republic of Turkey and the Isparta City Hospital's Chief Physician. The local ethics committee approval was obtained from The Ethics Committee for Clinical Research in Suleyman Demirel University Medical Faculty (date July 4, 2020, and protocol # 110). Three hundred forty-nine patients who had presented to the adult emergency service between April 1, 2020, and May 2020, and were investigated according to the Turkish Ministry of Health's COVID-19 guideline, were included in the study after verification with Rt-PCR. The age, gender, platelet, neutrophil, lymphocyte counts, neutrophil/lymphocyte ratio, C-reactive protein, ferritin, troponin I, and D-dimer values of the patients were recorded on the case report forms.

Statistical Analysis

Statistical Package for Social Sciences (SPSS) for Windows (version 22.0; IBM, Chicago, USA) software was used for statistical analysis of the data. The Kolmogorov-Smirnov test tested the conformity of quantitative data with a normal distribution. Mann-Whitney U test was used for statistical analysis of quantitative data not conforming to a normal

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distribution, Student-T test for analysis of normally distributed data, and Chi-Square test for analyzing categorical variables. Descriptive statistics of quantitative variables were presented as mean \pm standard deviation and those of categorical variables as the number of cases (%). Determination of the data's sensitivity-specificity was made on the ROC curve. $p < 0.05$ was considered statistically significant.

Results

Among all patients who had presented to our hospital's emergency service between April 2020 and May 2020, investigated as suspicious COVID-19 cases, and combined nasal-oral swab samples were obtained, those with a positive SARS-CoV2 RT-PCR result were included in our study. In our study, the age, gender, the admission CT, primary acute-phase reactants, the fibrin degradation product (D-dimer), and the cardiac-specific enzyme (troponin I) were investigated. In our study, among the SARS-CoV2 RT-PCR+ patients with a mean age of 55.8 ± 16.7 years, 165 (47.3%) were male, and 184 (52.7%) were female. No inter-gender difference was present regarding the mean age ($p=0.76$). In 251 of the patients, computed tomography (CT) detected an appearance that might be compatible with COVID-19 pneumonia. No inter-gender difference was determined regarding pulmonary involvement in CT ($p=0.131$). On the other hand, the mean age of patients with CT involvement was higher ($p=0.00$).

The parameters such as the platelet, neutrophil, lymphocyte counts, neutrophil/lymphocyte ratio, C-reactive protein, ferritin, troponin, and D-dimer values of the patients were scanned retrospectively. The CRP, D-dimer, troponin, NLR, and ferritin levels were significantly high, whereas the lymphocyte count was significantly low in the patients with CT involvement. A ROC curve of these values was prepared according to the cases with CT involvement (Figure 1), and the sensitivity and specificity were shown together with the p values according to the Area Under the Curve and the confidence interval of 0.05 (Table 1).

Discussion

COVID-19 first appeared in December 2019 in Wuhan-China, then spread worldwide and declared a pandemic in March

2019 by the WHO [1]. The first case in Turkey was detected on March 11, 2019, and while preparing this manuscript, there were about 7.583.200 cases reported in Turkey [13]. To determine Covid-19 patients who might become severely ill at an early stage of the disease is vital to take the pandemic under control, improve patients' outcomes, and use limited medical re-sources effectively.

A meta-analysis study calculated the optimum limit as $3.65 \times 10^9/L$ (sensitivity = 75%, specificity = 81.2%) for the neutrophil count, $0.83 \times 10^9/L$ for the lymphocyte count (sensitivity = 72%, specificity = 96%), $5.3 \times 10^9/L$ for the leucocyte count (sensitivity = 66.6%, specificity=79.1%) and $170.8 \times 10^9/L$ for the platelet count (sensitivity = 66.6%, specificity = 80%) [14]. In our study, we investigated the laboratory parameters of the COVID-19 RTPCR+ patients admitted to the emergency service for the first time and the clinical clues that led us to the indication for HR-CT and the outcome.

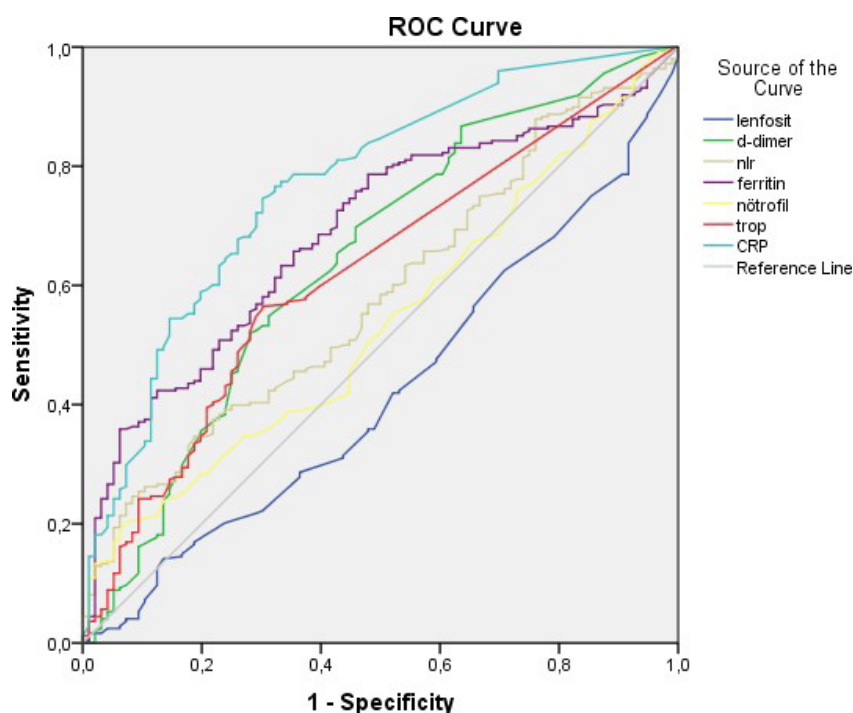
In a study by Sumer et al. conducted with 149 patients with an average age of 49.3 ± 17.6 years, 55% were female, and 45% were male [15]. In our study, 165 (47.3%) were male, and 184 (52.7%) were female, consistent with the literature, and the mean age was calculated as 55.8 ± 16.7 years. We think that the female population's higher average age in our district and women preferring to socialize in their house environments under the pandemic's restrictive circumstances played roles regarding the more common occurrence of COVID-19 infections in women.

The average age being under 65 years, the young, productive population staying more in social settings because of their active role in the community, and the wrong prejudice regarding its more common occurrence in the elderly show that individuals from all age groups should pay the same attention to protection. With our study, the importance of paying attention by every gender and age group to the rules of social distancing, hygiene, and using a mask were well-understood.

In the study conducted by Zhang et al., 31.6% of patients had a neutrophil count above $710 \times 10^3 / \mu L$, 44.2% between $210 \times 10^3 / \mu L$ and $710 \times 10^3 / \mu L$, and 24.2% under $210 \times 10^3 / \mu L$. In patients with disseminated COVID infection, these values were

Table 1: Comparison of the patients' laboratory parameters.

	CT Involvement		P-value	Sensitivity	Specificity	EAA: (ROC) P: (ROC)
	Absent	Present				
Neutrophil	3.45 ± 1.69 $10^3/\mu L$	3.60 ± 2.67 $10^3/\mu L$	0.25	-	-	-
Lymphocyte	1.52 ± 0.6 $10^3/\mu L$	1.30 ± 0.5 $10^3/\mu L$	0.021	56	57	0.57 0.021
Platelet	237.1 ± 57.6 $10^3/\mu L$	215.0 ± 94.5 $10^3/\mu L$	0.33	-	-	-
CRP	3.15 ± 22.7 mg/L	16.0 ± 48.9 mg/L	0.000	65	75	0.768 0.000
Troponin	8.1 ± 21.5 ng/L	24.45 ± 180.5 ng/L	0.000	45	75	0.622 0.000
D-Dimer	0.3 ± 1.25 mg/L	0.5 ± 0.9 mg/L	0.000	62	58	0.643 0.000
Ferritin	51.7 ± 530.6 μL	140.2 ± 1422.6 μL	0.000	68	60	0.689 0.000
NLR	2.24 ± 1.8	2.57 ± 5.9	0.013	50	56	0.583 0.018



Diagonal segments are produced by ties.

Figure 1: The appearance of the laboratory parameters in the ROC curve.

found to be lower than those in patients in whom the disease was not disseminated ($p < 0.0001$) [16]. In the same study, 44.2% of the patients had a lymphocyte count over $0.8 \times 10^3 / \mu\text{L}$, 44.2% between $0.8 \times 10^3 / \mu\text{L}$ and $0.4 \times 10^3 / \mu\text{L}$, and 11.6% of the patients had lymphocyte counts under $0.4 \times 10^3 / \mu\text{L}$. Lymphopenia was reported to be more prominent in the diffuse disease than the non-diffuse disease. ($p < 0.0001$) [16].

Wu et al. determined higher neutrophil counts and lower lymphocyte counts in ARDS patients than those without ARDS and found no significant difference regarding the platelet count ($p=0.25$). In the same study, among patients who progressed to ARDS, the neutrophil counts were similar in the deceased and surviving patients, whereas lymphopenia in the deceased was more profound than the survivors. The regression analysis performed in the same study showed that the low neutrophil and lymphocyte counts adversely affected the outcomes of patients significantly who had progressed to ARDS or deceased [17]. In Meta-analyses, similar results were present; the leucocyte count was significantly higher in mild disease and higher in the deceased than in the survivors [18].

Regarding the platelet count, meta-analyses have been performed showing that significant reductions were present in deceased patients compared to survivors [19]. However, whether poor prognosis is related to lymphopenia under the reference range or the absolute count is not clear. In our study, in COVID-19 PCR + patients with an involvement compatible with pneumonia, the lymphocyte count was significantly lower, and the neutrophil counts of the two groups were similar, like the literature. In our study also, no significant difference was present between the two groups regarding platelet count. Our results' consistency with the literature enlightens us more about emergency service patient management and helps us to evaluate the investigation results and plan the treatment.

In the evaluation of Mardani et al. in suspect COVID-19 cases, the C-reactive protein (CRP) level was statistically significantly high in RTPCR+ patients [20]. In our study also, the CRP levels were significantly high in patients with CT involvement, consistent with the literature.

In the COVID-19 infection, D-dimer level also increases [6]. In the study of Sümer et al., the D-dimer level was reported to increase with increasing severity of pneumonia [15]. Gao et al. compared the laboratory parameters of the patients with mild and severe clinical features and found that the D-dimer level was statistically significantly higher in seriously ill patients [7]. In the study conducted by Zhou et al., the D-dimer value was approximately nine-fold increase in the deceased patients [8]. In our study, D-dimer values were significantly higher in COVID-19 patients with CT involvement than those without, similar to the literature.

Tests for cardiac-specific troponin I and T are widely used as diagnostic and prognostic indicators in managing myocardial infarct and acute coronary syndrome. Elevated troponin levels might indicate myocardial involvement in COVID-19 infection and might play a significant role in mortality. In Zhou et al.'s study, troponin values were seven-fold increase in deceased patients [8]. Troponin appears to be a powerful prognostic indicator of mortality [21]. In our study, consistent with the literature, troponin values were significantly higher in patients with CT involvement and guided the patients' ward-intensive care unit hospitalizations and the outpatient follow-ups.

Even though widely used as a marker for the iron store, ferritin is also an acute-phase reactant. In the study conducted by Wu et al., the ferritin level was elevated in patients trending toward ARDS ($p < 0.0001$), and among their ARDS patients, no significant difference was present between those who died and survived regarding the ferritin level ($p=0.34$) [17]. In the survival study

conducted by Zhou et al., the ferritin level increased three-fold in their deceased patients [9]. In our study, consistent with the literature, the ferritin level was significantly higher in the patients with CT involvement, and ferritin was determined as an indicator of poor prognosis.

Neutrophil/lymphocyte ratio (NLR), calculated from a routinely performed blood test, has been reported to have great importance in revealing patients' general inflammatory status [22]. In the study conducted by Liu et al., increased NLR was reported to increase the mortality rate in all COVID-19 cases, particularly in men [23]. In our study, this ratio was higher in COVID-19 patients with CT involvement. New studies should further clarify whether NLR can be an independent predictor of mortality in hospitalized COVID-19 patients.

The literature and our study results show that monitoring inflammatory markers is a correct approach to identifying the progression of and treating COVID-19 as soon as possible [18]. The diagnosis of COVID-19 should be based on the clinical and epidemiological history, the etiological diagnostic tests, and tests supporting the identification of infection and/or complications [24]. Our study tried to show that alterations in laboratory parameters supported viral pneumonia in patients with the verified diagnosis. The compatibility of our study's results with the world population contributed to the literature that the laboratory results of COVID-19 patients do not have any differences regarding racial characteristics.

When evaluating the patient at the first presentation to the emergency service, it would be meaningful regarding cost-effectivity to interpret the laboratory results first, and then, based on this interpretation, to decide for CT, which we usually prefer for getting the results faster. This situation attracts our attention once again during the pandemic, involving crowded patient admissions and economic losses. Because patients' clinical features were not standardized, we showed that low lymphocyte count and elevations of CRP, D-dimer, troponin, and ferritin levels increased the risk for the presence of severe disease, and thus, patients should be evaluated regarding medications and hospitalization without waiting for the PCR result. More studies investigating the effects of laboratory results at first admission on diagnosis, prognosis, and mortality are required. The most significant limiting factors of our study were its retrospective nature and being a single-center study. Within the specified timeframe, and with the data gathered through our institution's information processing system and the Public Health Management System, the present study's sample size was considered enough to contribute to the literature. The difficulty in standardizing the methods used during the pandemic, observed in studies on disease course and severity, was also limiting for our study.

In conclusion, many issues about the COVID-19 pandemic, which has become a significant problem in our country and worldwide, have not yet been identified. Confusion in definitions such as probable case, suspect case, and confirmed case, and the RTPCR tests' reliability and speed are the speed-limiting steps in diagnosing COVID-19. Evaluating the patients at the time of diagnosis, identifying the indications regarding hospitalization and discharge, determining the intensive care unit requirement clearly, and standardizing the clinical

practices worldwide will contribute to taking the pandemic under control.

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