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Research Article

Biochemical markers and NLR levels in COVID-19 infection: In cases with severe pulmonary involvement according to CT score

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Abstract

Objectives: Many studies have been conducted on ferritin, fibrinogen, D-dimer, and neutrophil-lymphocyte ratio (NLR), which are biochemical tests, to determine the severity and prognosis of the disease in the early period of coronavirus disease 2019 (COVID-19) infection. We aimed to determine the compatibility of these easily accessible and affordable tests with computed tomography (CT) in determining the severity of the disease at an early stage.

Methods: This study was carried out retrospectively on 79 patients. In all patients, nasal and pharyngeal swabs were collected and tested for SARS-CoV-2 RNA with reverse transcription-polymerase chain reaction assay. The severity of the disease was determined by computed tomography imaging. According to lung involvement, patients who were found to have a severe infection and divided into the severe group (n=26), and those with milder symptoms were divided into the non-severe group (n=53). The demographic information and laboratory parameters of the patients were obtained from the medical records of the hospital. Analyses were performed using the Statistical Package for the Social Sciencesversion 23.0 for Windows.

Results: NLR (8.36±2.45; 3.3±2.04 p<0.001), ferritin (ng/mL) (736.1±240.2; 374.7±248.4 p<0.001), fibrinogen (mg/mL) (725.7±84.9; 416.5±186.1 p<0.001), D-dimer (ug/mL) (3.68±1.42; 1.55±1.16 p<0.001), and C-reactive protein (CRP) (mg/dL) (81.1±11.9; 27.9±13.8 p<0.001) levels were found to be significantly higher in the severe group than the non-severe group. In addition, CRP (mg/mL) levelswere positively correlated with NLR (r=0.607 p<0.01). Receiver operator curve analyses were carried out to assess the efficacy of NLR, ferritin, fibrinogen, and D-dimer parameters.

Conclusion: These results suggest that NLR, ferritin, fibrinogen, and D-dimer may be useful biomarkers for the early detection of critical cases of COVID-19 infection, paralleling CT findings. These available tests can benefit clinicians in low-resource settings where access to complicated diagnostic methods may be limited.

Keywords: Coronavirus-19 disease, CT scan, D-dimer, ferritin, fibrinogen, neutrophil-lymphocyte ratio

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The novel coronavirus disease 2019 (COVID-19) pandemic, also called SARS-CoV-2, is recognized as a global health crisis. The infection first appeared in China in January 2020 [1]. The USA, South America, and Europe are reported as the most affected regions today. According to the World Health Organization (WHO) data, the total number of deaths from COVID-19

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toJune 19, 2022, is 6.3 million and the number of confirmed cases is over 536 million [2]. According to WHO interim guidelines, COVID-19 disease is a heterogeneous infection in clinical signs and symptoms, including severe and non-severe forms [3]. Therefore, the management of patients should be applied according to the severity of the clinical situation. According to recent experience, most infected people do not become seriously ill and can recover without medical treatment, but fewer cases require careful management, hospitalization, or even an intensive care unit (ICU) [4, 5]. Many articles propose protocols for disease management, according to the clinical, biological, and radiological features of COVID-19 infection. Biochemical analyses together with the radiological image gain importance in the diagnosis of severe forms [6, 7].

Many studies have shown that abnormal host immune response and cytokine storm may play an important role in the severity of COVID-19. Many prognostic factors seem to be associated with immune response However, the predictive power ofthese indicators in disease classification and prognosis has not yet been clearly defined [8, 9]. The early prediction of COVID-19 infection, evaluation of prognosis and response to treatment, C-reactive protein (CRP), neutrophil-lymphocyte ratio (NLR), fibrinogen, and D-dimer have been the parameters frequently investigated [10–12]. Tests that can be used as early biomarkers should be easily applicable, common, and inexpensive tests. In our study, we retrospectively analyzed the clinical, radiological, and biochemical features of patients infected with COVID-19 and investigated the value of D-dimer, ferritin, fibrinogen, and NLR measurements in predicting disease severity earlier [13].

Materials and Methods

Our study was conducted as a single center and retrospective. This research was carried out with a total of 79 patients who applied from July 2020 to October 2021. In all patients, nasal and pharyngeal swabs were collected and tested for SARS-CoV-2 RNA with reverse transcription-polymerase chain reaction assay. Patients who were positive for COVID-19 according to the PCR RNA test were included in the study. The severity of the disease was determined by computed tomography imaging. According to lung involvement, patients who were found to have a severe infection and were treated were divided into the severe group (n=26), and those with milder symptoms were divided into the non-severe (n=53) group. Most of the patients were health personnel working in the hospital. Demographic information and biochemical parameters of the patients were obtained from hospital and laboratory medical records. Patients with previously known systemic diseases (diabetes mellitus, systemic hypertension, immunodeficiency, metabolic syndromes, etc.) and patients who received any COVID-19 treatment were excluded from the study.

The enrolled patients had no known comorbidities. Initial hemogram (NLR), CRP, ferritin, fibrinogen, and D-dimer levels were recorded. PCR RNA tests were performed in Goztepe Prof. Dr. Süleyman Yalçın City Hospital İslab-2 laboratory. All other tests were performed in the laboratory of our hospital. Mindray BC 6800 device was used for hemogram measurement and NLR calculations. Ferritin was analyzed photometrically on the Cobas 6000 instrument. Fibrinogen was analyzed coagulometrically in the STA compact Stago device. D-dimer was analyzed bythe immunoturbidimetric method in the Siemens BCS xp device.

The method used in computed tomography (CT) scoring, especially in COVID-19, was obtained by giving 5 points according to the visual assessment of the involvement of each of the five lung lobes independently. 0 points, no participation; 1 point, <5% participation; 2 points, 25% participation; 3 points, 26–49% participation; 4 points, 50–75% participation; and 5 points, greater than 75% participation (Fig. 1). The total CT score was the sum of the scores of all lobes ranging from 0 to 25. According to these results, the cases were divided into two severe and non-severe involvements with a cutoff value of ≥7 [14].

This study was organized by the Declaration of Helsinki, the approval of the Turkish Ministry of Health, and the Ethics Committee of University of Health Sciences Fatih Sultan Mehmet Training and Research Hospital Ethics Committee (11.06.2020/11).

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0 for Windows (IBM-SPSS Inc, Armonk, NY, USA). The normal distribution of all data was determined using the Shapiro–WilkW Test. Student's t-test was used to compare normal distributions, but not normally distributed were compared using the Mann–Whitney U-test. Pearson correlation test was used for bivariate correlation analyses. Categorical variables were analyzed with the Chi-square (χ^2) test. Receiver operating characteristic (ROC) analysis was used to determine the diagnostic value and cut-off points of biochemical test results. The results of all the patients' parameters were given as follows: mean±standard deviation and median range. Probability values were bipolar and $p<0.05$ was considered significant.

Results

A total of 79 patients were recruited for this study. COVID-19 infection was confirmed by RNA PCR. According to lung involvement on CT imaging, 26 patients in the severe group15 (34.9%) were female and 11 (30.6%) were male. Likewise, the non-severe group included 53 patients and consisted of 28 (65.1%) male and 25 (69.4%) female patients. The mean age of the first group was 37.6±6.15, while the mean age of the second group was 34.70±8.29. The gender and age distribution of the study population is shown in (Table 1). No significant difference was found between the patient group and the control group in terms of gender and age ($p>0.05$). Fever (69.2%; 32.1%,

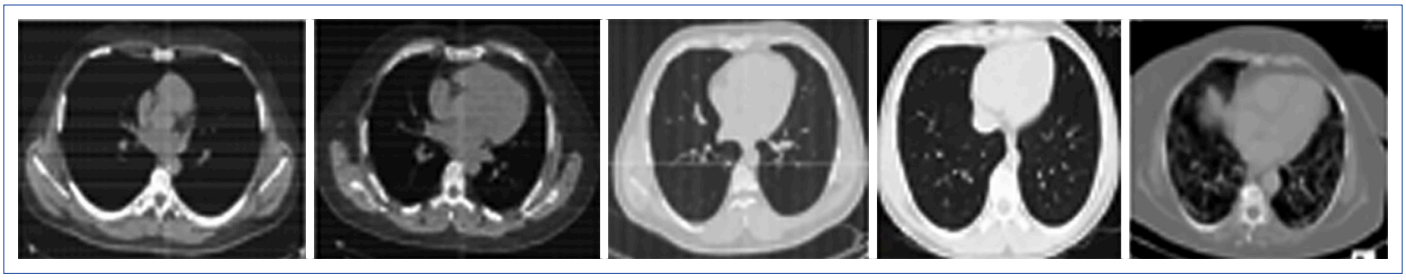

Figure 1. Lung CT image samples of cases.
CT: Computed tomography.

p<0.001), respiratory symptoms (80.8%; 30.2%, p<0.001), and general symptoms (fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, stuffy or runny nose, nausea, or vomiting 92.3%; 60.38% p<0.01)were more common in the severe group than in the non-severe group.

When the white blood cell count, platelet count, hemoglobin, LDH, ALT, AST, and creatinine serum levels were compared, no significant difference was found between the severe group and the non-severe group. There was a significant difference in neutrophil count, lymphocyte count, NLR and CRP, ferritin, fibrinogen, and D-dimer serum levels between severe and non-severe groups NLR (8.36±2.45; 3.3±2.04 p<0.001), ferritin (736.1±240.2; 374.7±248.4 p<0.001), fibrinogen (725.7±84.9; 416.5±186.1 p<0.001), D-dimer (3.68±1.42; 1.55±1.16 p<0.001) (Fig. 2). CRP levels were higher in the severe group than in the non-severe group (81.1±11.9; 27.9±13.8 p<0.001) and were positively correlated with NLR (r=0.607 p<0.01) (Fig. 3).

The cutoff value for serum D-dimer in predicting severe lung infiltration was calculated as 2.46 µg/mL andthe area under the curve (AUC) 0.815 (95% confidence interval [CI] 0.79–0.85, p<0.001) with 77.1% sensitivity and 70.5 specificities. The cutoff value for plasma fibrinogen was calculated as 766.13 ng/dL andthe AUC 0.766 (95% CI 0.72–0.85, p<0.001) with 82.1% sensitivity and 75%specificity. The cutoff value for serum ferritin was calculated as 523.4 ng/mL, AUC 0.801 (95% CI 0.74–0.81, p<0.001) with 79.2% sensitivity and 75 specificities, and the cutoff value for NLR was calculated as 4.76 AUC 0.751 (95% CI 0.75–0.82, p<0.001) with 79.2% sensitivity and 77.1 specificities (Fig. 4).

Table 1. Comparison of patients with demographic and clinical features on admission

Demographics	Severe (26)		Nonsevere (53)		p
	n	%	n	%	
Age, years	37.6 ±6.15		34.70±8.29		NS
Male	15	34.9	28	65.1	NS
Female	11	30.6	25	69.4	NS
Clinical symptoms					
Fever	18	69.2	17	32.1	0.00*
Respiratory symptoms	21	80.8	16	30.2	0.00*
General symptoms*	24	92.3	32	60.4	0.01*
Blood routines					
White bloodcell^{103µL} (N: 4.00-12.00)	7.48±1.70		6.9±1.79		NS
Neutrophils^{103µL} (N: 2.00-8.00)	9.4± 2.45		7.6±1.02		0.03*
Lymphocytes103µL (N: 0.80-7.00)	1.1±0.70		1.5±0.40		0.04*
NLR	8.36±2.45		3.3±2.04		0.00*
Hemoglobin g/dL (N: 12-16)	12.7±2.39		13.2±1.80		NS
Platelets^{103µL} (N: 100-400)	162.7±28.8		186.3±30.2		0.02*
ALT$^{aU/L}$ (N0: 5-34)	23.8±2.0		22.1±3.9		NS
AST$^{aU/L}$ (N: 0-33)	26.4±6.1		24.8±8.4		NS
Creatinin$^{mg/mL}$ (N: 0.32-0.59)	0.49±0.15		0.54±.0.34		NS
C-reactive protein$^{mg/dL}$ (N: 0-0.5)	81.1 ±11.9		27.9±13.8		0.00*
Ferritin$^{ng/mL}$ (N: 30-400)	736.1±240.2		374.7±248.4		0.00*
Fibrinogen$^{mg/dL}$ (N: 200-400)	725.7±84.9		416.5±186.1		0.01*
D-dimerµg/mL (N: 0-0.55)	3.68.±1.42		1.55±1.16		0.00*

*: General symptoms: Fatigue, muscle or body aches, headach, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting. *p<0.05 was considered significant. N: Normal reference laboratory value; NLR: Neutrophil-to-lymphocyte ratio; ALT: Alanin amino transferase; AST: Aspartame amino transferase; NS: Nosignificant.

Discussion

The global pandemic of SARS-COV-2 has created a major health crisis around the world, including in the most advanced healthcare systems. The most important achievement has been to take most cases under control in the shortest time with the available means. The primary goal is to improve the prognosis of patients with limited medical facilities and to identify COVID-19 patients who may become seriously ill at the onset of the disease.

In recent studies, it has been reported that easily accessible, inexpensive, and simply applicable laboratory tests and lymphocyte and neutrophil ratios are important in determining severe and mild COVID-19 cases in the early period. It is known that a decrease in the number of lymphocytes and an increase in the number of neutrophils may occur in almost all viral infections.

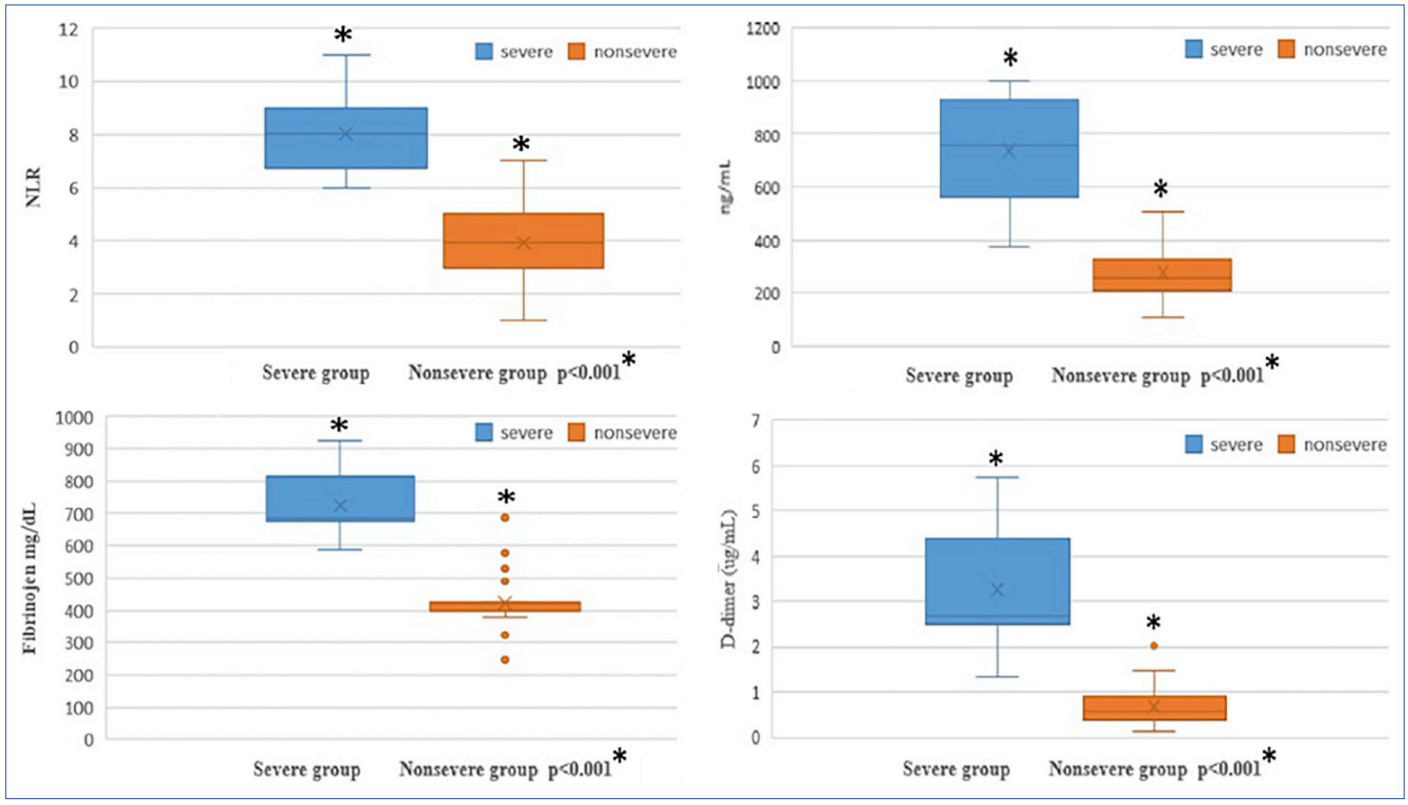

Figure 2. Biochemical markers and neutrophil-lymphocyte ratio values of severe and non-severe groups.

In general, it has been reported that neutrophil-derived cytokines are important in the immune response against viruses and cause effects that create symptoms and prognosis in a similar way to COVID-19 infection. It has also been reported that other regulated or unregulated cell death, such as apoptosis, may suppress lymphocyte count in viral infections [15, 16]. Many studies have revealed that neutrophil functions take on both pathological and protective functions in COVID-19 cases, as in all other viral infections [17]. Such prolonged activation of neutrophils can lead to the release of harmful proinflammatory mediators and toxins into the organism's cells, similar to viruses [18]. Several studies have revealed that lymphopenia depletes many immune elements against COVID-19, inactivating cellular immune function and resulting in reduced but hyper-activated peripheral T lymphocytes; this may be partly explained by the severe immune damage in SARS-COV-2 infection [19]. As a result of all this immune confusion, NLR can also be a useful diagnostic and prognostic indicator in determining the prognosis of COVID-19 patients. A significantly higher NLR measurement was also detected in after a few days compared to the early stage of COVID-19 infection. Accordance these findings NLR is accepted as a useful prognostic indicator in patients with severe course compared to non-severe patients [20, 21]. In our study, NLR values in the severe group were found to be significantly higher when compared to the non-severe group.

Ferritin is a protein whose serum level reflects the level of stored iron and helps diagnose iron deficiency anemia. It is known that circulating ferritin levels increase during viral infections. Secondary hemophagocytic lymphohistiocytosis (sHLH) activity increases in viral infections. Ferritin levels are also increase in severe COVID-19 patients due to cytokine storm and increasesHLH activity [22, 23]. The cytokine storm sequence in COVID-19 stimulates hepatocytes, Kupffer cells, and macrophages to secrete ferritin. This causes rapid produc-

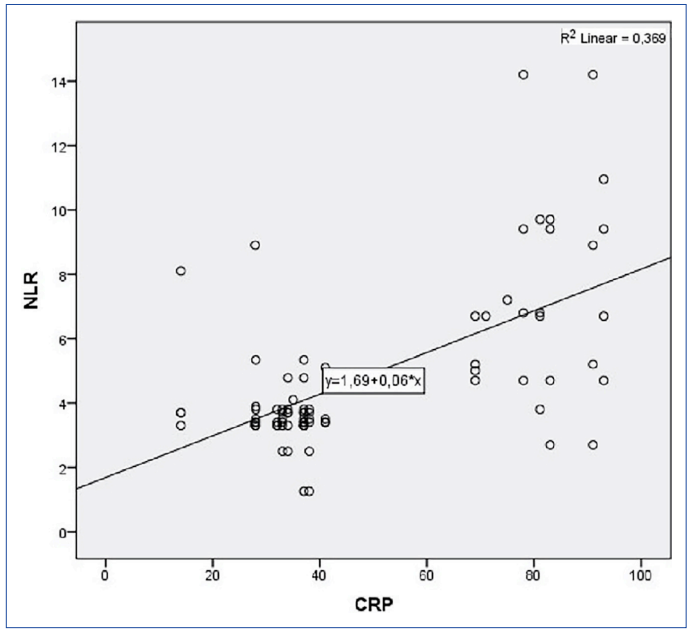

Figure 3. The relationship between neutrophil-lymphocyte ratio and the serum level of C-reactive protein.

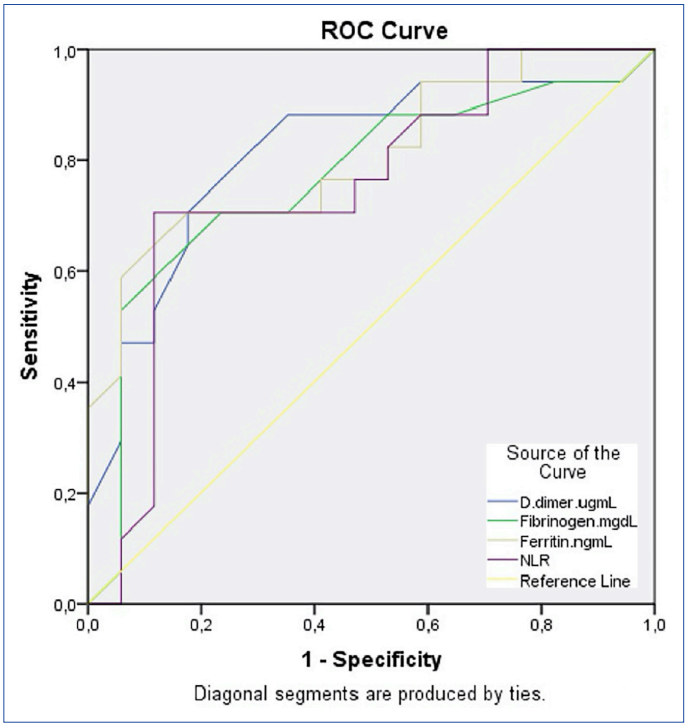

Figure 4. ROC curves of neutrophil-lymphocyte ratio, ferritin, fibrinogen, and D-dimer to predict severe lung infiltration at an early stage in COVID-19.

tion of many inflammatory cytokines such as IL-6, TNF-α, and IL-1β, uncontrolled and aimless immune response, increased macrophage activation, hyperferritinemia syndrome, and diffuse thrombosis. At the end of this process, multiple organ damage develops and a significant increase in mortality and morbidity is observed. Ferritin mediates the expression of multiple proinflammatory mediators both as a result of excessive inflammation and by binding with T-cell immunoglobulin-mucin domain 2. Moreover, ferritin has been shown to activate macrophages directly. It has been reported that hyperferritinemia in COVID-19 correlates with increased mortality, which increases the need for an ICU. The accepted cutoff value is that serum ferritin concentration higher than 500 ng/mL increases mortality by up to 58%. It has been reported that the worsening prognosis of patients is significantly associated with serum ferritin levels [24, 25]. Therefore, ferritin measurements are important both in monitoring hyperinflammation and in monitoring response to treatment [26]. In our findings, ferritin was found to be statistically higher in the severe group than in the non-severe group. This was evaluated as an immune marker rather than an increased iron load in severe cases.

The most important distinguishing symptom of patients with severe COVID infection is respiratory distress [4]. However, another cause of morbidity and mortality in COVID-19 is coagulopathy, which can progress to multi-organ failure [26, 27]. The finding accompanying the picture of diffuse coagulopathy is usually increased D-dimer levels. Increased D-dimer levels are frequently observed among COVID-19 patients at admission, and subsequent thromboembolic events are associated with an increased need for intensive care and mortality [28–30]. The most effective method of treatment to treat coagulopathy in COVID-19 has not yet been established. However, the International Society for Thrombosis and Hemostasis (ISTH) has published a guideline that recommends the evaluation of anticoagulant therapy in COVID-19 infection based on increasing evidence, though limited [31, 32]. Coagulopathy associated with COVID-19 is similar to disseminated intravascular coagulation (DIC). It is thought to be characterized by increased fibrinolysis rather than suppressed fibrinolysis as in other infectious DIC cases [33, 34]. In severe COVID-19 infection, it has been observed that fibrinogen initially increases rapidly and then begins to decrease rapidly [35, 36]. The clinical course suggests a transition from suppressed fibrinolysis to enhanced fibrinolysis. In general, it is observed that there is a significant decrease in fibrinogen levels with the first increase in D-dimer levels. These dynamic changes in fibrinogen and D-dimer are not separated by a clear boundary. According to the clinical conditions of the patients, the D-dimer peak is usually observed after the fibrinogen peak. It has been reported that D-dimer levels are useful in following the advanced stage of thromboembolism development and increased bleeding risk. Wichmann et al. [35] reported that 58% of the patients had deep vein thrombosis that could not be detected before death, with post-mortem findings. All these findings show the importance of monitoring the coagulation parameters of coagulopathy in COVID-19 infection. It has been reported that the D-dimer/fibrinogen ratio, expressed by a formula: (D-dimer [μg/ml]/fibrinogen [mg/dL])×100 is a specific calculation for embolism [35, 36] and the ratio above 1.0 has 94% specificity for diagnosing pulmonary embolism in patients without COVID-19. This ratio above 1.0 has 94% specificity for diagnosing pulmonary embolism other than COVID-19; also, this ratio, monitoring of fibrinogen, and d-dimer levels have been indicated to be useful in the prediction and management of coagulopathy in COVID-19 [35, 36]. In our study, both fibrinogen and D-dimer levels were found to be statistically significantly higher in the severe group compared to the non-sever group. This indicated that both fibrin formation and fibrinolysis were increased during acute infection.

The plausible cause of thrombocytopenia in COVID-19 appears to be the consumption of platelets to form a diffuse thrombus. In addition, although the bone marrow involvement of the virus in COVID-19 is thought to play a role in thrombocytopenia, this is not considered a reasonable cause. Because generally increased hemoglobin and white blood cell counts distract us from this process [34, 35]. In our study, when the hemogram and white blood cell results were compared in the severe and non-severe groups, no significant difference was found. In severe COVID-19 involvement, thrombus formation appears to be a non-effective process that cannot stop pathogen invasion into the bloodstream [35, 36]. On the contrary, a diffuse microthrombus has detrimental consequences for the host. It has been shown that increased platelet count

is inversely proportional to mortality and thrombotic process. Due to a similar mechanism, it has been reported that an improvement in the platelet count may mean a positive clinical indicator [34–36].

CRP serum levels are generally correlated with the severity of inflammation. CRP serum levels are independent of factors such as age, gender, and physiological conditions [37]. CRP levels may increase phagocytosis as a complementary activated immune response. CRP concentration can also be used for early detection and determination of the severity of COVID-19 infection. High CRP serum levels were detected in cases with severe lung involvement. It is an important indicator for the diagnosis and evaluation of diseases with severe pneumonia. In some publications, it has been reported that the diameter of the lung lesion is positively correlated with the CRP level [37–39]. According to our findings, CRP levels were positively correlated with lung infiltration and disease severity. In our study, we found that CRP levels increased significantly in the severe group compared to the non-severe group and showed a positive correlation with the NLR ratio. These results suggest that NLR, ferritin, fibrinogen, and D-dimer may be useful biomarkers for the early detection of critical cases of COVID-19 infection.

Conclusion

In light of the findings, it is thought that NLR, serum ferritin, fibrinogen, and D-dimer levels may show parallelism with CT scan scores for cases with severe lung involvement in COVID-19 infection. These tests may be valuable as biochemical diagnostic markers for severe cytokine elevation and severe and purposeless immune response.We believe that the laboratory facilities at hand can be a warning for cases that may have a serious course ofCOVID-19 infection. Based on these findings, we believe that it may benefit clinicians in low-resource settings, where access to laboratory testing may be limited in the follow-up of COVID-19 infection.

The study has some limitations. It is primarily a single-center retrospective observational study with a relatively small sample size. The biomarkers were measured only once at the time of initial application, so we do not know whether the kinetics of the respective tests could improve or worsen the observed results. Although viral presence is mainly confirmed by PCR assay, false-positives and false-negatives may be present. Finally, due to the nature of a retrospective observational study, there may be potential impacts of not being able to make a simultaneous evaluation.

Conflict of Interest: The authors declare that there is no conflict of interest.

Ethics Committee Approval: The study was approved by The University of Health Sciences Fatih Sultan Mehmet Training and Research Hospital Clinical Research Ethics Committee (No: 11, Date: 11/06/2020).

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