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Correlation Between Hematological Parameters and Clinical Scoring Systems in Indicating the Severity of COVID-19 Disease

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ABSTRACT

Introductıon: In this study, it was aimed to determine the relation ship betwewn the blood parameters and scoring system which are used to determine the severity of COVID-19.

Methods: Patients, who were 18 years of age or older and were hospitalized due to COVID-19 were evaluated retrospectively. Inflammatory markers and scoring systems were used to determine the severity of the COVID-19 patients.

Results: In terms of the other hematolgical indices (NLR, PLR, MPV/LR, LMR, DFR, SII, and NLP), a significant difference was found between severe and-severe patient groups. All scoring systems were found to be significantly higher in the severe patient group. The SOFA showed the strongest correlation with the MPVPR. BCRSS showed the strongest correlation with the DFR.

Discussion and conclusion: It is suggested that applying a hematological parameter that predics the course of severe Covid-19 instead of scoring systems would be a rational, fast, and inexpensive approach.

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Introduction

Coronavirus disease 2019 (COVID-19), which first emerged as viral pneumonia cases of unknown etiology in Wuhan, China, at the end of 2019, has become a pandemic that has now affected the whole world.[1] In previous studies, the virus with 86.9% sequence similarity with the bat-derived SARS-like CoV (bat-SL-CoVZC45, MG772933.1) belonging to the Sarbecovirus subtype of the Betacoronavirus type was named 2019-nCoV.[2] Following the rapid spread of the epidemic, on January 30, 2020, the WHO declared the outbreak a public health emergency of international concern.[3] Symptoms of COVID-19 include fever, fatigue, and dry cough. In addition, sore throat and rarely diarrhea, nausea, or nasal discharge have been reported in patients.[4] COVID-19 is diagnosed by performing reverse transcription polymerase chain reaction (RT-PCR) of 2019-nCoV RNA in samples taken from the nasopharynx and oropharynx.[5] Although the majority of patients have mild disease, 14% need oxygen due to lung involvement and require hospitalization.[6] Early diagnosis is very important because the time between the development of acute respiratory distress syndrome (ARDS) in hospitalized patients is short and the mortality rate is high.[7]

Clinical assessment alone can underestimate or overestimate the severity of the pneumonia. It can also lead to inadequate decisions with regards to admitting a patient to an intensive care unit (ICU) or general medical treatment.[8] The change in hematological parameters provides data for clinicians about the clinic of COVID patients. High C-reactive protein (CRP), lactate dehydrogenase, complete blood count (CBC), and coagulation parameters have been found to be associated with ARDS, mortality, and complications.[9] Severity scores, on the other hand, have been defined as useful tools that help clinicians to predict the prognosis of the patient, and guide treatment-related decisions and make the diagnosis, treatment, and hospitalization decisions for the patient.[8]

Scoring COVID-19 patients is very difficult in emergency departments, as the patient burden is high. Although there are studies in the literature that have indicated that hematological parameters and scoring systems determine the severity of the disease, there are no studies that have determined the relationship between hematological parameters and scoring systems. In this study, it was aimed to determine the relationship between the blood parameters (neutrophil-lymphocyte ratio [NLR], platelet lymphocyte ratio [PLR], monocyte/lymphocyte ratio [MLR], mean platelet volume/lymphocyte ratio [MPVLR], MPV/platelet ratio [MPVPR], plateletcrit, D-dimer/fibrinogen ratio [DFR], neutrophil/lymphocyte-platelet scoring system [NLP] and immune-inflammation index [SII]) and scoring systems(the BRESCIA-COVID Respiratory Severity Scale [BCRSS], Sepsis-

Related Organ Failure Assessment [SOFA], quick SOFA [qSOFA], multi-lobular infiltration, hypo-lymphocytosis, bacterial coinfection, smoking history, hyper-tension, and age [MuLBSTA] score, and hemophagocytic syndrome [HScore]) which are used to determine the severity of the disease in patients admitted to the emergency service and pandemic outpatient clinics of Ankara City Hospital and hospitalized in the internal medicine ward.

Materials and Methods

In this study, 436 patients, who were 18 years of age or older, and were hospitalized in the internal diseases ward of Ankara City Hospital between 15 April 2020 and 01 January in 2021due to COVID-19 were evaluated retrospectively. Among the patients, those who did not want to participate in the study, those younger than 18 years of age, those with active malignancy and those who were pregnant were excluded from the study. Ethical approval for the study was granted by the Ethics Committee of Ankara City Hospital (Date: 24/02/ 2021, Number: E2-21-141).

Following the collection of throat and nasal swab samples in the emergency department and outpatient clinics, patients diagnosed with confirmed COVID-19 by reverse-transcriptase polymerase chain reaction (RT-PCR) were hospitalized. The age, gender, comorbidities, medications, fever, blood pressure, oxygen saturation, and respiratory rates of the patients in the study were recorded on the data collection forms. The hemogram, D-dimer, and fibrinogen tests of the patients were routinely studied. In addition, chest tomography was applied to the patients and the results were recorded. The patients were divided into two groups, as severe and non-severe, as recommended in the World Health Organization guidelines.[10] According to the stage of the disease, the first group comprised non-severe patients who had any of the following features: slight symptoms, fever, respiratory tract symptoms, or no radiological findings or pneumonia findings on radiological examination. The second group comprised severe patients who had any of the following features: tachypnea with a respiration rate >30 beats/min, resting oxygen saturation <92%, arterial partial oxygen pressure (PaO2)/fraction of inspired oxygen (FiO2) <301mmHg, radiological aggravation greater than 301% within 50 h, respiratory failure and mechanical ventilation, shock, or organ failure requiring admission to an ICU. Severe patients were also divided into two groups, as the survival group and death group, according to their prognosis.

Nine inflammatory markers were used to determine the severity of the COVID-19 patients, comprising the NLR, PLR, MLR, MPVLR, MPVPR, plateletcrit, DFR,

neutrophil/lymphocyte-platelet scoring system, and SII. The BCRSS, qSOFA, SOFA, MuLBSTA, and HScore were also applied to these patients.

Statistical analysis

The data were analyzed using SPSS for Windows 25.0 (IBM Corp., Armonk, NY, USA) and MedCalc 15.8 (Franz Faul, Universitat Kiel, Germany). While the frequency, percentage, mean, standard deviation, median, and IQR were used as descriptive statistical methods, the chi square ($\chi 2$) test was used to compare the qualitative data. The consistency of the data to normal distribution was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was used to compare the non-consistent data with normal distribution. While the receiver operating characteristic (ROC) curve was used to determine the discrimination of the variables, Binary logistic regression was used to determine the risk rates. Statistical significance was accepted as $\alpha=0.05$.

Results

Of the 436 patients included in our study, 251 (57.6%) were men, and the median (IQR) age of the patients was 47.00 (IQR 27.00) years. Of the patients included in our study, 50 (11.5%) were in the severe patient group, while 386 (88.5%) were in the non-severe patient category. No statistically significant difference was found between non-severe and severe patients in terms of MPRPV hematological index ($p = 0.104$). In terms of the other hematological indices (NLR, PLR, MPV/LR, LMR, DFR, SII, and NLP), a significant difference was found between severe and non-severe patient groups. In the severe patient group, the median NLR was 5.12 (5.56) vs. 2.41 (1.95) ($p> 0.0001$); the PLR was 232.10 (260.75) vs. 167.04 (113.75) ($p>0.0001$); the MPVLR was 9.16 (8.39) vs. 6.57 (3.94) ($p>0.0001$); the DFR was 0.22 (0.73) vs. 0.13 (0.12) ($p>0.0001$), the SII was 1.137.56 (1.828.17) vs. 487.02 (451.37) ($p>0.0001$), and the NLP (95% CI: 4–8 vs. 0–4) was significantly higher. The median LMR was found to be significantly higher in the non-severe patient group when compared to the severe patient group (2.39 (2.13) vs. 3.55 (2.50), $p> 0.0001$) (Table 1).

The SOFA, qSOFA, MuLBSTA, HSCORE and BCRSS scores were found to be significantly higher in the severe patient group when compared to the non-severe group. While the median (IQR) SOFA score was 3 (2) in the severe patient group, it was 0 (1) in the non-severe patient group ($p<0.0001$). While the median (IQR) qSOFA score was 2 (2) in the severe patient group, it was 0 (0) in the non-severe patient group ($p<0.0001$). While the median (IQR) MuLBSTA score was 11.5 (5.5) in the severe patient group, it was 5 (6) in the non-severe patient group ($p<0.0001$). The median (IQR) HScore was 75 (45.25) in the severe patient group, while it was 53 (51) in the non-severe patient group ($p<0.0001$). The median

(IQR) qSOFA score was 3 (4) in the severe patient group, while it was 0 (1) in the non-severe patient group (p<0.0001) (Table 1).

In the paired comparisons, a significant difference was found in terms of the hematological indices and scoring systems, and the risk that they caused in severe disease was evaluated using the backward stepwise multivariate logistic regression model, which was developed for severe disease. According to this model, male gender and increased PLR, SOFA, and BCRSS were found to be independent predictor factors for severe disease. In the multivariate logistic regression analyses, the BCRSS score in the highest tertile (HR: 8.835, 95% CI: 3.086–25.299, p <0.0001) was determined as an independent predictor of severe disease in COVID-19. In the multivariate analyses, male gender (HR: 3.254, 95% CI: 1.074 – 9.859, p =0.037), the PLR (HR: 1.005, 95% CI: 1.001–1.008, p =0.014), and SOFA (HR: 1.718, 95% CI: 1.097–2.689, p =0.018) were also found to be independent predictors of severe disease in COVID-19 (Table 2).

The values of the five scores in all of the patients with severe COVID-19 disease were calculated, and the predicted values of these scores were compared in the ROC analysis (Figure 1). Table 3 shows the areas under the curve (AUC) for the hematological indices (NLR:0.754, PLR:0.646, LMR:0.679, MPVLR:0.703, MPVPR:0.569, DFR: 0.698, SII: 0.712, and NLP:0.666) and scores (SOFA: 0.948, qSOFA: 0.943, MuLBSTA: 0.848, HScore: 0.665, and BCRSS: 0.967). All of the scores could be used as potential diagnostic biomarkers for subsequent analysis because their AUC was higher than 0.50. For severe disease risk, the SOFA optimal cut-off value was>1, while that of the qSOFA was >0, MuLBSTA was >5, HScore was >72, and BCRSS was >1.

In Table 4, the correlation between the scores and the hematological indices was evaluated. It was determined that the score that showed the strongest correlation with NLR was the MuLBSTA score (r=0.388, p<0.0001). It was determined that the score that showed the strongest correlation with PLR was the MuLBSTA score (r = 0.245, p<0.0001). It was determined that the score that showed the strongest correlation with LMR was MuLBSTA and the correlation was negative (r = –0.309, p<0.0001). It was found that the strongest correlation was for both the MPVLR and MuLBSTA was that with each other (r = 0.454, p<0.0001). The SOFA score that showed the strongest correlation with the MPVPR (r = 0.347, p<0.0001). The strongest correlation for both the DFR and BCRSS scores was that with each other (r = 0259, p<0.0001). It was determined that the score that showed the strongest correlation with the SII was the qSOFA (r = 0.295, p<0.0001). The strongest correlation for both the NLP and SOFA was that with each other (r = 0.419, p<0.0001). The score that showed the strongest correlation with the qSOFA was the NLR (r = 0.354,

p<0.0001). It was determined that the score that showed the strongest correlation with the HScore was the DFR (r = 0.221, p<0.0001).

Discussion

Although many studies have been conducted to predict the prognosis of COVID-19 patients, there are a limited number of studies that have shown the relationship between hematological indices and scoring systems. In this study, the correlation between the hematological indices and the scoring systems were evaluated at the first examination of the patients who applied to the emergency department or outpatient clinic.

In a study examining the clinical characteristics of COVID-19 patients, it was found that the majority of patients were men (58.1%) and the median age was 47 years.[11] In the current study, similar to the literature, the majority of the patients were men (57.6%) and the median (IQR) age was 47 years (IQR: 27.00).

In the hematological indices in this study (NLR, PLR, MPV/LR, LMR, DFR, SII, and NLP), a significant difference was found between the severe and non-severe patient groups. In this study, the PLR (HR: 1.005, 95% CI: 1.001–1.008, p= 0.014) was found to be an independent predictor factor for severe disease in the multivariate logistic regression developed for severe disease. In the ROC analysis, it was determined that the index that best predicted severe disease was the NLR (AUC: 0.754), followed by the MPVLR (AUC: 0.703), and DFR (AUC: 0.698). In a study by Yang et al., a significant difference was found between the severe COVID-19 patients and non-severe patients in terms of the NLR, PLR, and LMR.[12] In a study evaluating the relationship between the severity of COVID-19 patients and their hematological parameters, a significant difference was found between the severe and non- severe patients in terms of the MPV/LR, LMR, and DFR.[13] In a study by Mohammed et al., the SII was found to be an important marker in determining the intubation requirement and mortality in COVID-19 patients.[14] In a study by Núñez et al., the NLP was found to be significantly higher in cases that resulted in intensive care hospitalization and death.[15] The findings in the current study were consistent with the literature and it is suggested that the NLR, PLR, MPV/LR, LMR, DFR, SII, and NLP can be used to determine severe disease in COVID-19 patients.

According to a study evaluating the risk factors of COVID-19 patients, a high SOFA score was found to be associated with hospitalization and death.[16] In a study evaluating the qSOFA with regards to the prediction of prognosis in COVID-19 patients, it was found that the qSOFA was also high in patients with severe disease .[17] In a study by Iijima et al., it was found that a high MuLBSTA score can determine high-risk patients and life-threatening

situations.[18] In a study by Rodriguez-Nava et al., it was found that the BCRSS prediction rule performed well in predicting intensive care hospitalization in COVID-19 patients.[8] According to a study by Erden et al, when the use of Anakinra treatment was decided, the median BCRSS score was 3 and the rate of patients who had a BCRSS score of 3 or above was 88.2%.[19] In the current study, the SOFA, qSOFA, MuLBSTA, and BCRSS scores were found to be significantly different between the severe patients and non-severe patients in terms of admission to an ICU (<0.0001). In this study, with the multivariate logistic regression developed for severe disease, the BCRSS (HR: 8.835, 95% CI: 3.086–25.299, p <0.0001) and SOFA (HR: 1.718, 95% CI: 1.097–2.689, p =0.018) scores were found to be independent predictive factors for severe disease. The ROC analysis found that severe disease was best predicted by the BCRSS (AUC: 0.967) score, followed by the SOFA (AUC: 0.948) and qSOFA (AUC: 0.943) scores. Therefore, it is suggested that the SOFA, qSOFA, and MuLBSTA scores, and especially the BCRSS score, can be used to predict severe COVID-19 patients. There are no studies in the literature showing that the HScore has directly predicted severe disease in COVID-19 patients. In a study by Yang et al., the HScore was shown to detect patients with macrophage activation syndrome rather than detecting severe disease.[20] Although the HScore was significant in predicting severe disease in COVID-19 patients in the current study, it is suggested that further studies should be conducted to use the HScore to predict severe disease.

In this study, it was found that the BCRSS was more suitable for predicting severe patients and non-severe patients than the other scores. In the ROC analysis, the NLR (AUC: 0.754) was found to be the most successful hematological index in predicting severe disease. It was found that the hematological index most compatible with the BCRSS was the NLR (r = 0259, p<0.0001). Moreover, the NLR was found as the score that showed the strongest correlation with the qSOFA (r = 0.354, p<0.0001). Therefore, it is suggested that determining the NLR (cut off>3.35), which is easier to calculate than the BCRSS, will provide information about the prognosis of the patients in emergency departments with high patient burden. In the present study, while the NLP was the score that showed the strongest correlation with the SOFA (r = 0.419, p<0.000), the MPVLR was the score that showed the strongest correlation with the MuLBSTA (r = 0.454, p<0.0001). Since there are no other studies on this topic, it is suggested that conducting more studies will provide further insight into this topic.

The retrospective nature of this study, small sample size, and lack of randomization of the results meant that selection bias could not be ruled out.

Conclusion

Although the definitive diagnosis of COVID-19 is made via RT-PCR, this test cannot provide information on the prognosis of the patients. Moreover, it is very important to decide the course of the disease in the first examination of the patients who apply to the emergency service or outpatient clinics. Although scoring systems are suitable for determining the course of the disease, they require a lot of time to calculate in an emergency service or outpatient clinic environment that has intense patient burden. Therefore, it is suggested that applying a hematological parameter that predicts the course of severe Covid-19 instead of scoring systems would be a rational, fast, and inexpensive approach.

Declaration

The authors have no conflicts of interest to declare.

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