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Prognostic Significance of Blood Parameters in COVID-19 Pneumonia

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ABSTRACT

Objective: We aimed to predict disease severity by studying the admission blood parameters of patients diagnosed with novel coronavirus disease 2019 (COVID-19).

Materials and Methods: We retrospectively reviewed the medical data of 217 patients diagnosed with COVID-19 infection and 86 sex-matched and age-matched healthy controls without this infection. The patient group was divided into the following two subgroups: the severe (n=93) group and the non-severe (n=124) group. We compared the demographic characteristics, admission complaints, and admission blood parameters of the patient group with those of the control group. We also compared the above-mentioned parameters of the two patient subgroups.

Results: The patient group had a significantly lower white blood cell count, lymphocyte count, monocyte count, and platelet count (p=0.002, p<0.001, p<0.001, and p<0.001, respectively) and a significantly higher C-reactive protein level (p<0.001) than the control group did. The leucocyte count, neutrophil count, neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and ferritin level were significantly higher in the severe disease subgroup than those in the non-severe subgroup (p<0.001). The lymphocyte count and lymphocyte to monocyte ratio (LMR) were significantly lower in the severe disease subgroup than those in the non-severe subgroup (p<0.001). We performed a logistic regression analysis and obtained the odds ratios (OR) of several factors. This analysis showed that NLR was positively correlated with the COVID-19 risk (adjusted OR 1.438, p=0.012). However, the association of PLR and LMR with COVID-19 risk remained unclear.

Conclusion: The ability to predict prognosis using blood parameters that are routinely assessed at admission can save considerable time and financial resources. We believe that we can predict the prognosis of COVID-19 patients using the admission NLR levels.

Keywords: COVID-19, neutrophil to lymphocyte ratio, blood parameters, prognosis

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INTRODUCTION

Initially known as 2019-nCoV, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) caused pneumonia in a large number of people in Wuhan, a city in China's Hubei province, in December 2019. Thereafter, the virus spread rapidly and caused a serious epidemic in China. In February 2020, the World Health Organization (WHO) termed the globally spread disease as coronavirus disease 2019 (COVID-19) and declared it a pandemic on March 11, 2020 (1). Thus far, about 73 million people have been infected with this virus, and the virus continues to spread at a consistent rate (2). This virus is mainly transmitted via droplets released from humans. It is believed that touching the eyes, nose, and mouth after contact with contaminated surfaces may cause this infection, although this is not the main route of transmission (3). The clinical spectrum of COVID-19 infection ranges from an asymptomatic infection to critical and fatal disease. Although the exact incidence of asymptomatic infections remains unknown, it is believed to be approximately 40% (4). Most patients with symptomatic infections develop mild disease (with mild or no pneumonia). About 15%–20% of the patients with symptomatic infections develop severe disease (e.g., that with dyspnea, hypoxia, or >50% lung involvement on imaging within 24–48 h). Severe disease may occur in healthy individuals of all ages; however, it predominantly involves adults of advanced age or those with certain comorbidities, such as hypertension, cancer, obesity, diabetes mellitus, chronic lung disease, and chronic kidney disease (5). Several studies have linked many clinical conditions, such as lymphopenia, thrombocytopenia, elevated levels of lactate dehydrogenase (LDH), elevated levels of liver enzymes, elevated levels of inflammatory markers [e.g., C-reactive protein (CRP) and ferritin] and inflammatory cytokines [i.e., interleukin 6 (IL-6) and tumor necrosis factor (TNF)-alpha], increased prothrombin time (PT), elevated levels of D-dimer (>1 µg/mL), elevated levels of creatine phosphokinase (CPK), and elevated levels of troponin, to poor prognosis and disease severity (6–9). Research is ongoing to enable early prediction of whether the disease would progress as mild disease or severe disease, based on the epidemiological, clinical, and laboratory data. Weak adaptive immune response is accompanied by severe inflammatory response that causes an imbalance in the immune response. Therefore, circulating biomarkers that can indicate inflammatory and immune status are important predictors for the prognosis of COVID-19 patients (10). Peripheral white blood cell count (WBC), neutrophil to lymphocyte

Table 1. Comparison of the demographic characteristics and blood parameters of the control group and patient group

	Control (n=86)	COVID-19 patients (n=217)	p
Age (Mean±SD)	59±11	62±14	0.547
Male sex, n (%)	47 (54)	116 (53)	0.352
CRP, g/L	0.002 (0.001–0.005)	0.1 (0.04–0.31)	<0.001
White blood cell count, $\times 10^9$/L	6.72 (5.95–9.64)	5.92 (5.1–8.75)	0.002
Neutrophil count, $\times 10^9$/L	4.32 (3.17–6.96)	4.37 (3.11–7.98)	0.586
Lymphocyte count,$\times 10^9$/L	2.78 (1.36–2.94)	1.48 (1.03–2.14)	<0.001
Monocytes, $\times 10^9$/L	0.52 (0.46–0.68)	0.44 (0.36–0.61)	<0.001
Platelet count $\times 10^9$/L	248.5 (198.75–303.5)	188.8 (139.2–236.8)	<0.001
NLR	2.49 (1.4–4.34)	2.57 (1.49–6.28)	0.367
PLR	119.73 (78.3–164.2)	121.3 (61.9–172.4)	0.253
LMR	3.42 (2.23–6.03)	3.69 (2.14–5.89)	0.129

SD: Standard deviation; CRP: C-reactive protein; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio

Table 2. Comparison of the demographic characteristics and blood parameters of the severe and non-severe COVID-19 subgroups

	Non-severe (n=124)	Severe (n=93)	p
Age (Mean±SD)	59±11	63±9	0.03
Male sex, n (%)	65±51	51±54	0.126
CRP, g/L	0.08 (0.05–0.22)	0.09 (0.04–0.28)	0.451
ESR, mm/h	11 (9-41)	52 (29–81)	<0.001
Ferritin, µg/L	67 (41–186)	231 (85–486)	<0.001
White blood cell count, $\times 10^9$/L	5.73 (5.41–7.65)	7.42 (5.81–9.87)	<0.001
Neutrophil count, $\times 10^9$/L	3.7 (2.95–4.56)	5.94 (4.12–8.74)	<0.001
Lymphocyte count, $\times 10^9$/L	2.03 (1.53–2.49)	0.96 (0.57–1.62)	<0.001
Monocytes, $\times 10^9$/L	0.56 (0.42–0.64)	0.51 (0.34–0.71)	0.358
Platelet count $\times 10^9$/L	202 (179–248)	185 (146–251)	0.512
NLR	1.95 (1.46–2.9)	4.93 (2.84–9.84)	<0.001
PLR	94.9 (72.5–159)	151 (107.6–249.7)	<0.001
LMR	4.9 (2.32–6.26)	2.21 (1.05–3.97)	<0.001

CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio

ratio (NLR), platelet to lymphocyte ratio (PLR), and lymphocyte to monocyte ratio (LMR) are the available predictors that act as markers of systematic inflammatory response in patients with viral pneumonia (11). We believe that being able to predict the prognosis of COVID-19 patients using blood parameters that can be measured at admission in a simple manner at a low cost would facilitate early decision making regarding treatment and hospitalization. Thus, we aimed to examine the demographic characteristics, mode of presentation, and admission blood parameters of patients who presented to our emergency department with a suspicion of COVID-19 infection and were later confirmed to have COVID-19.

MATERIALS and METHODS

This study retrospectively examined the medical records of patients aged >18 y who presented to the emergency department of Batman Regional State Hospital between July 1, 2020 and September 1, 2020 and were diagnosed with COVID-19 using reverse transcription-polymerase chain reaction (RT-PCR) test. The demographic characteristics, admission complaints, admission blood parameters, and outcomes (discharge, hospital admission, and 30-day mortality data) of the patients were recorded. We enrolled COVID-19 patients into the patient group and healthy controls who did not have COVID-19 into the control group; the patient group was further sub-divided into the severe and non-severe disease subgroups. The controls were selected from among healthy subjects who did not have any recorded comorbidity and tested negative on the RT-PCR test. The patients were categorized into the severe and non-severe COVID-19 subgroups as per the interim guidance issued by the World Health Organization (WHO) (12). Patients with an uncomplicated viral upper respiratory tract infection may complain of symptoms that are not specific to the

Table 3. Area under the curve

Test result variable(s)	Area	Std. error[a]	Asymptotic sig.[b]	Asymptotic 95% confidence interval	
				Lower bound	Upper bound
NLR	0.852	0.043	<0.001	0.676	0.938
PLR	0.789	0.034	<0.001	0.547	0.845
LMR	0.657	0.046	<0.001	0.492	0.748
Age	0.542	0.034	0.01	0.385	0.651

a: Under the nonparametric assumption; b: Null hypothesis: True area=0.5; NLR: Neutrophil to lymphocyte ratio; PLR: platelet to lymphocyte ratio; LMR: Lymphocyte to monocyte ratio

disease and include cough (with or without sputum expectoration), fever, fatigue, malaise, muscular pain, sore throat, nasal congestion, and headache. The non-severe disease subgroup also included patients with rare symptoms, such as nausea, diarrhea, and vomiting. Patients with severe disease were defined as those who had fever or any suspicion of respiratory infection accompanied by at least one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 ≤93% in room air (13–15). The two groups were compared with respect to blood parameters and demographic characteristics. Patients who had a negative RT-PCR test, those aged <18 y, and those whose medical records could not be accessed via the hospital automation system were excluded. This research was approved by the ethical committee of the Batman University (date: 10.11.2020, no: 2020/5-28).

Statistical Analysis

All the study data were analyzed using IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.) software package. The normality of the data was checked using the Kolmogorov-Smirnov test. Descriptive statistics included mean±standard deviation values for the normally distributed variables and median (minimum and maximum values) for the non-normally distributed variables. The Mann Whitney-U test was used to compare the non-normal quantitative variables, while independent samples t-test was used to compare the normal variables. The optimal cut-off values of the continuous age, NLR, PLR, and LMR were calculated using receiver operating curve (ROC) analysis. P value <0.05 was considered to indicate statistical significance for all comparisons.

RESULTS

Our study compared the demographic characteristics and blood parameters of 86 control subjects and 217 patients. There was no significant difference between the two groups in terms of sex distribution (p=0.352) or age (p=0.547).

The patient group had significantly lower WBC, lymphocyte, monocyte, and platelet counts (p=0.002, p<0.001, p<0.001, and p<0.001, respectively) and a significantly higher CRP level (p<0.001) than the control group did (Table 1). Two hundred and seventeen patients in the patient group were further divided into the following two subgroups: severe COVID-19 subgroup (n=93) and non-severe COVID-19 subgroup (n=124). The mean

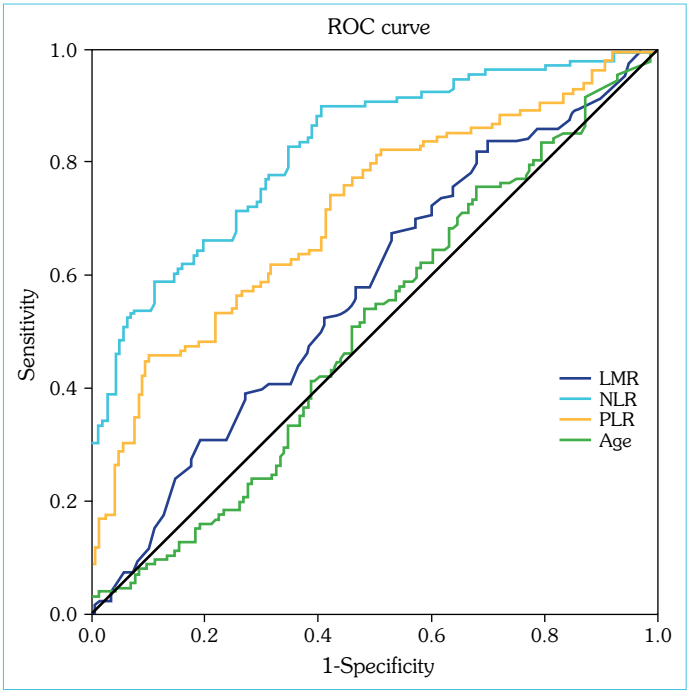

Figure 1. ROC analysis of the blood parameters

ROC: Receiver operating characteristics; LMR: Lymphocyte to monocyte ratio; NLR: Neutrophil to lymphocyte ratio; PLR: Platelet to lymphocyte ratio

age of the patients in the severe disease subgroup was significantly higher than that of those in the non-severe disease subgroup (p=0.03). The sex distribution in the two subgroups was comparable (p=0.126). The most common complaint was dyspnea (28.5%) in the severe disease subgroup and fever (26%) and cough (21%) in the non-severe disease subgroup. In the severe disease subgroup, the leucocyte count, neutrophil count, NLR, PLR, and ferritin level were significantly higher than those in the non-severe disease subgroup were (p<0.001). The lymphocyte count and LMR were significantly lower in the severe disease subgroup than those in the non-severe disease subgroup (p<0.001). The platelet count, monocyte count, and CRP level of both the subgroups were comparable (p=0.512, p=0.358, and p=0.451, respectively) (Table 2). An ROC analysis was performed for both the groups; the sensitivity, specificity, and area under the curve values for the NLR, PLR, LMR, and AGE levels are shown in Figure 1. NLR, PLR, and LMR values were important for discriminating severe

Table 4. The odds ratio and adjusted odds ratio in the neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, and lymphocyte to monocyte ratio

Indicators	Crude odds ratio (OR)	p	Adjusted odds ratio (ORa)*	p
NLR	1.294 (1.132–1.854)	0.034	1.438 (1.184–1.748)	0.012
PLR	0.982 (0.781–1.152)	0.754	1.102 (1.007–1.126)	0.628
LMR	0.825 (0.792–0.984)	0.156	0.786 (0.679–1.006)	0.235

*: Adjustment for age and sex

COVID from non-severe COVID. When we plotted the ROC curve, the area under the curve was 0.852 (95% CI 0.676–0.938; p<0.001), 0.789 (95% CI 0.547–0.845; p<0.001), and 0.657 (95% CI 0.385–0.651; p<0.001) for NLR, PLR, and LMR values, respectively (Table 3). Moreover, we performed logistic regression analysis and calculated the odds ratios (ORs) of factors that could influence COVID-19 progression. Age and sex are known to affect the blood test results; therefore, we excluded the effects of these confounders by adjusting the results for age and sex to obtain the adjusted OR. The analysis revealed that the risk of COVID-19 was significantly correlated to the NLR level in the positive direction (adjusted OR 1.438, p=0.012). However, the association of PLR and LMR with COVID-19 risk remained unclear (Table 4).

DISCUSSION

The clinical spectrum of symptomatic COVID-19 cases ranges from mild to critical disease. Previous studies have reported a rate of 81% for mild disease, 14% for severe disease, and 5% for critical disease (16). Severe disease can appear in healthy individuals of any age; however, the prognosis remains poor, predominantly in the elderly and adults with certain underlying medical comorbidities. Previous studies have attempted to associate specific demographic characteristics and laboratory abnormalities with the disease severity in COVID-19 patients (6, 7).

We found that an increased NLR level was correlated to disease severity and worse prognosis in patients infected with COVID-19. NLR is calculated by the ratio of neutrophil count to lymphocyte count, and it has been proposed as a biomarker for systemic inflammation. A high NLR results from an increased neutrophil count and a reduced lymphocyte count. A disordered immune response may culminate into excess inflammation and even death. The change in the leucocyte count is one of the most important factors associated with the severity of the Middle East Respiratory Syndrome Coronavirus (MERS-CoV) disease (17, 18). Studies on patients infected with MERS-CoV have shown that leucocytosis with neutrophil and monocyte predominance develops in these patients; further, all patients who died rapidly had developed lymphopenia (19). Similarly, most recent studies have shown that the cytokine storm that occurs in infected patients is associated with disease severity; moreover, these patients had higher levels of inflammatory cytokines and chemokines as well as an elevated NLR (20). These findings are in agreement with our results. We believe that the increase in the CRP level and the neutrophil count that we detected in our patients may be attributable to the increased possibility of exposure to bacterial infections because of a failure in the immune system of COVID-19 patients.

CONCLUSION

Based on our findings, we believe that the prognosis of COVID-19 patients can be predicted using the NLR value that can be measured from the blood samples collected from the emergency department at the time of admission.

Ethics Committee Approval: The Batman University Clinical Research Ethics Committee granted approval for this study (date: 10.11.2020, number: 2020/5-28).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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Author Contributions: Concept – NGK; Design – NGK; Supervision – NGK; Resource – NGK; Materials – NGK; Data Collection and/or Processing – NGK, CG; Analysis and/or Interpretation – NGK; Literature Search – NGK, CG; Writing – NGK; Critical Reviews – NGK.

Conflict of Interest: The authors have no conflict of interest to declare.

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