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Comparison of neutrophil lymphocyte ratio, platelet lymphocyte ratio, and mean platelet volume and PCR test in COVID-19 patients

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SUMMARY

OBJECTIVE: The polymerase chain reaction test, used in the diagnosis of COVID-19, can be positive with delay, and thorax tomography is used for the diagnosis of the disease. We aimed to compare the relation between thorax tomography findings, PCR test results, and neutrophil lymphocyte ratio; platelet lymphocyte ratio and mean platelet volume neutrophil lymphocyte ratio; platelet lymphocyte ratio and mean platelet volume in COVID-19 patients.

METHODS: COVID-19 patients were divided into three groups, according to baseline laboratory and thorax tomography findings: Group A: thorax tomography finding positive – polymerase chain reaction test positive; Group B: thorax tomography finding negative – polymerase chain reaction test positive; and Group C: thorax tomography finding positive – polymerase chain reaction test negative. Neutrophil lymphocyte ratio, platelet lymphocyte ratio, and mean platelet volume values were compared between these three groups.

RESULTS: Group C neutrophil lymphocyte ratio level and polymerase chain reaction level were statistically higher than that of group B ($p<0.001$ in both). Mean platelet volume was not statistically significant between groups ($p>0.005$ for all). A positive correlation was detected between neutrophil lymphocyte ratio and C-reactive protein ($r=0.421$, $p<0.001$). Similarly, positive correlation was found with polymerase chain reaction and C-reactive protein ($r=0.243$, $p=0.001$).

CONCLUSION: The thorax tomography finding can be detected earlier in the disease before the polymerase chain reaction test. The sensitivity of the polymerase chain reaction test varies according to the tester, the way of performing it, and the quality of the test. Therefore, especially in patients with polymerase chain reaction negative and thorax tomography findings, neutrophil lymphocyte ratio and platelet lymphocyte ratio levels should be evaluated, and patients should be followed up upon suspicion of COVID-19 diagnosis.

KEYWORDS: Neutrophils. Lymphocytes. Blood platelets. Mean platelet volume. Polymerase chain reaction. Coronavirus infections.

INTRODUCTION

Coronavirus-19 Disease (COVID-19) first appeared in Wuhan, China. The disease spread rapidly from Wuhan to other regions. The World Health Organization (WHO) declared COVID-19 disease as a pandemic on March 11, 2020. COVID-19 cases were also reported in Turkey on the same dates. Typical symptoms of COVID-19 are fever, sore throat, fatigue, cough, and shortness of breath. The incubation period of the virus was from five to 19 days. Based on this, the isolation period was determined as 14 days[1].

Rapid and accurate detection of COVID-19 is essential to control outbreaks in the community and hospitals. Each country has developed unique algorithms for the diagnosis of this epidemic. Based on current diagnostic criteria, laboratory

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examinations, including nasopharyngeal and oropharyngeal swab tests, have become a standard assessment in the diagnosis of COVID-19 infection. Among the current diagnostic tests for coronavirus, reverse transcription polymerase chain reaction (RT-PCR) is performed. In a series of 51 patients with confirmed COVID-19 infection, RT-PCR positivity was demonstrated in the first test of 71% throat swabs or sputum samples[2]. RT-PCR results usually become positive after a few days (2–8 days)[3]. In patients with contact history and fever, sore throat, fatigue, cough, or shortness of breath, COVID-19 infection is diagnosed with typical thorax computed tomography (CT) features despite negative RT-PCR results[4].

OBJECTIVE

Due to inflammation, number of lymphocytes decrease and the number of neutrophils increase in patients with COVID-19. Studies have reported that NLR is a predictive factor for disease progression, poor prognosis, and severe cases of COVID-19[5-8]. Depending on the severity of inflammation, lymphocyte, neutrophil, and platelet counts, besides mean platelet volume (MPV) is varied. Studies have suggested that neutrophil lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) reflect inflammation more effectively and strongly than the number of lymphocytes, platelets, and neutrophils separately in inflammatory disease[9,10]. Similarly, MPV has been used as an indicator of inflammation in inflammatory diseases[11,12]. Based on this hypothesis, we aimed to compare the relation between CT findings, PCR test results and NLR, PLR, and MPV in COVID-19 patients.

METHODS

The study was performed retrospectively using data from the Public Health Management System, which is the pandemic registration system of the Provincial Health Directorate, Bolu, Turkey. AbantIzzetBaysal University Faculty of Medicine Ethics Committee approval was obtained (Ethics approval number: 2020/140). Patients diagnosed with COVID-19 older than 18 were included in the study. Patients' symptoms, CT findings, PCR test, and white blood cell count (WBC), lymphocyte (LYM), neutrophil (NEU), platelet, MPV, albumin, AST, ALT, ALP, GGT, and urea levels were recorded from the pandemic recording system at the time of diagnosis of COVID-19. NLR was obtained by dividing the neutrophil count by the lymphocyte count. PLR was obtained by dividing platelet count by lymphocyte count. COVID-19 patients were divided into three groups according to baseline laboratory and CT findings: Group A: CT finding positive – PCR test positive; group B: CT finding negative – PCR test positive and group C: CT finding positive – PCR test negative. NLR, PLR, and MPV values were compared between these three groups.

Statistical analysis

IBM Statistics15.0 (SPSS) statistical software was used to evaluate the data. Descriptive statistics are presented as Mean ± SD and Median (min–max). The consistency of continuous variables to normal distribution was examined with Kolmogorov-Smirnov tests. The data were evaluated statistically with one-way ANOVA. *Post hoc* analyzes were evaluated using TUKEY HSD and Tamhane tests. Categorical variables were evaluated with χ^2 analysis. Receiver-operating characteristic (ROC) curve analyzes were performed to determine the cut-off values of NLR, PLR, and MPV (CRP for comparison), area under the curve (AUC), sensitivity and specificity to predict COVID-19 disease. Pearson's correlation test was used for the relation between the continuous variable. Statistical significance value accepted was $p < 0.05$.

RESULTS

A total of 153 patients with COVID-19 were included in the study. There were 38 patients (19%) in group A, 85 patients (41%) in group B, and 80 patients (40%) in group C. The median age of group A was 55.4±15, of group B was 53.1±16.6, and of group C was 54.8±16.6 (p=0.7). WBC levels are as follows: group A., 5.05 (2.5–10.6) uL; group B, 6.3 (2.1–19.8) uL; group C, 7.5 (2.6–28) uL (p<0.001) (Figure 1). In subgroup analysis, WBC level of Group C was statistically higher than that of groups A and B (p<0.001 and p=0.001, respectively). The NEU level was similarly significant among groups, and the NEU level of group C was statistically higher than in groups A and B (p=0.001 and p<0.001, respectively, Table 1). Among hemogram parameters, MPV, lymphocyte, and RDW levels were not statistically significant (p>0.05 for all). CRP level was 21 (0.1–135) mg/L in group A, 4.45 (0.1–292) mg/L in group B, and 43.4 (0.1–450) mg/L in group C (p<0.001, Figure 1). In subgroup analysis, the CRP level of group C was significantly higher than in both groups A and group B (p=0.003 and p<0.001, respectively). AST levels were 28 (11–90) U/L in group A, 29 (14–90) U/L in group B, and 26 (9–130) U/L in group C (p=0.02). When subgroups were compared, the AST level of group B was statistically significantly higher than group C (p=0.02). There was no difference between ALT, GGT, ALP, and total bilirubin levels (p>0.05 for all) (Table 1).

The NLR value was 2.1 (0.45–60) in group A, 1.92 (0.51–17.4) in group B, and 3.5 (0.63–44.8) in group C (p=0.004)

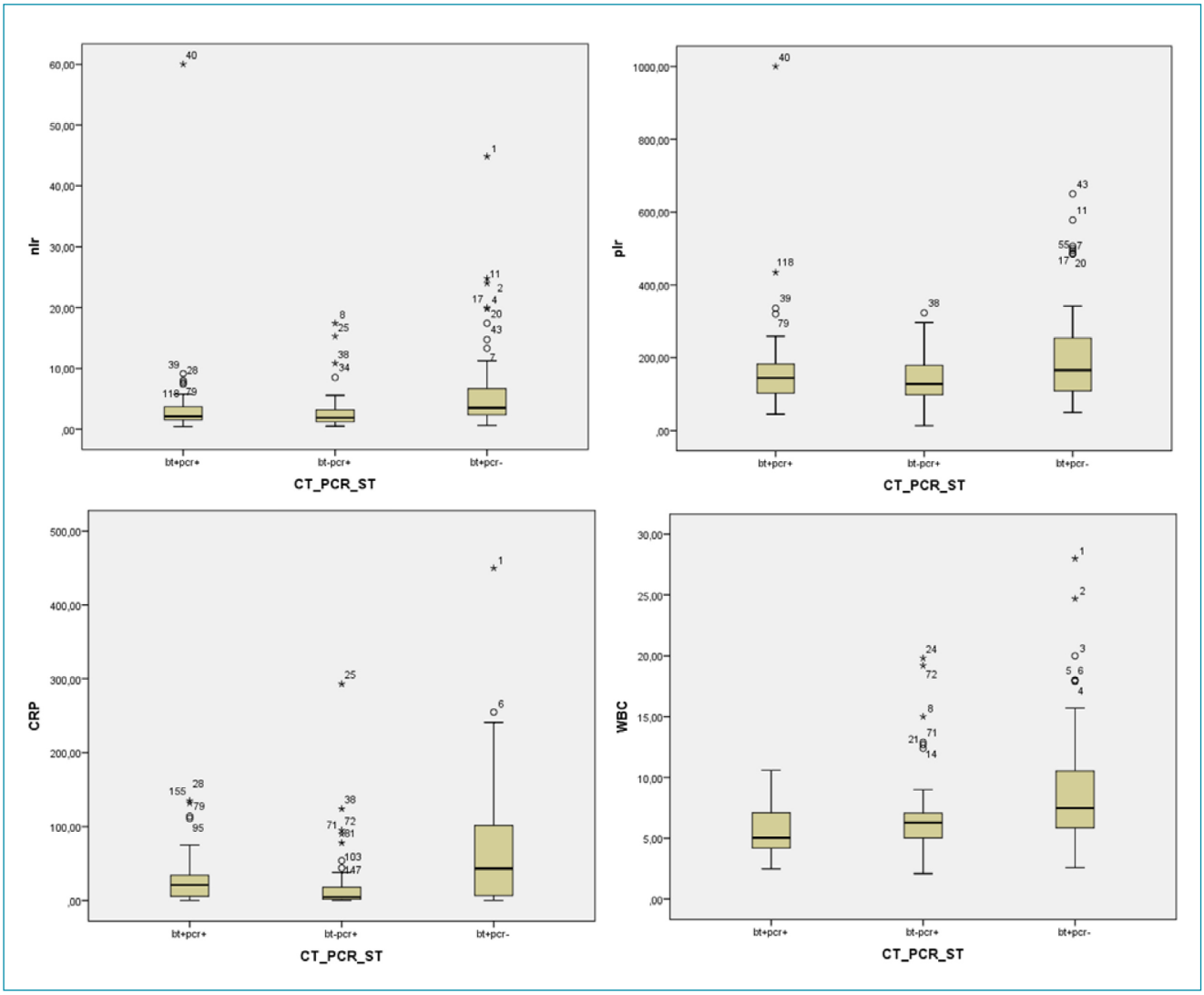

Figure 1. Neutrophil lymphocyte ratio (NLR); Platelet lymphocyte ratio (PLR); C reactive protein (CRP) and white blood cell (WBC) levels in group A (CT +, PCR +), group B (CT-, PCR +), and group C (CT +, PCR-).

(Figure 1). Group C NLR level was statistically higher than that of group B (p<0.001). The PLR level was similarly statistically significant between the groups (p=0.009), and the PLR level of group C was significantly higher than that of group B (p<0.001). In subgroup analysis, NLR and PLR levels were not statistically significantly in Group C than in Group A (p>0.05) (Table 1). Correlation analysis was performed between WBC, NLR, PLR, MPV, AST, and CRP. A positive correlation was detected between NLR and CRP (r=0.421, p<0.001). Similarly, positive correlation was found for PLR and CRP (r=0.243, p=0.001).

A ROC analyze performed to determine sensitivity and specifity of hemogram parameters (WBC, NEU, NLR, PLR) and CRP in detecting early COVİD-19 patients (Figure 2). The best cut-off values in predicting group C were WBC >6.4uL (68% sensitivity, 60% specificity, AUC=0.699, p<0.001), NEU >3.77 (72% sensitivity, 60% specificity, AUC=0.695, p<0.001), NLR >2.33 (75% sensitivity, 60% specificity, AUC=0.723, p=0.037), PLR >140 (60% sensitivity, 55% specificity, AUC=0.599, p<0.017), and CRP >11.8 mg/L (68% sensitivity, 60% specificity, AUC=0.708, p<0.001). With ROC analysis, NLR revealed a more sensitive diagnostic value than CRP, WBC, NEU, and PLR in predicting Group C patients with 75% sensitivity and 60% specificity (Figure 2).

DISCUSSION

In our study, NLR and PLR were significantly higher in the patient's group with CT (+) – PCR (-) (group C) than

Table 1. Laboratory data and demographic characteristics of group A (CT +, PCR +), group B (CT -, PCR +), and group C (CT +, PCR -).

	Group A	Group B	Group C	p
Mean±SD				
Age (years old)	55.4±15	53.1±16.6	54.8±16.6	0.07
Urea (mg/dL)	33.9±1.1	32.2±1.4	44±2.2	<0.001
ALT (U/L)	37.1±3.7	23.8±1.5	38.8±3.7	0.1
GGT (U/L)	42.2±5.6	50±3.2	45±7.3	0.9
Total bilirubin (mg/dL)	0.91±0.25	0.90±0.33	0.97±0.34	0.4
Median (min–max)				
NLR	2.1 (0.45–60)	1.92 (0.51–17.4)	3.5 (0.633–44.8)	0.004
PLR	144 (44–1000)	128 (12.8–323)	165 (49–650)	0.009
WBC (uL)	5.05 (2.5–10.6)	6.3 (2.1–19.8)	7.5 (2.6–28)	<0.001
NEU (uL)	3.25 (1.2–7.6)	3.3 (1.2–8.3)	4.6 (1.1–15.3)	<0.001
Lymp (uL)	1.4 (0.1–4.7)	1.7 (0.5–16)	1.35 (0.4–4.4)	0.06
MPV (fL)	8 (6.7–10)	8.32 (5.4–11)	8.05 (5.9–10)	0.89
RDW (%)	15.3 (12.5–27)	15.05 (11.9–24.5)	15.02 (12–20.1)	0.76
AST (U/L)	28 (11–90)	29 (14–90)	26 (9–130)	0.02
ALP (U/L)	86 (50–140)	76 (23–181)	77 (39–137)	0.76
CRP (mg/L)	21 (0.1–135)	4.45 (0.1–292)	43.4 (0.1–450)	0.001

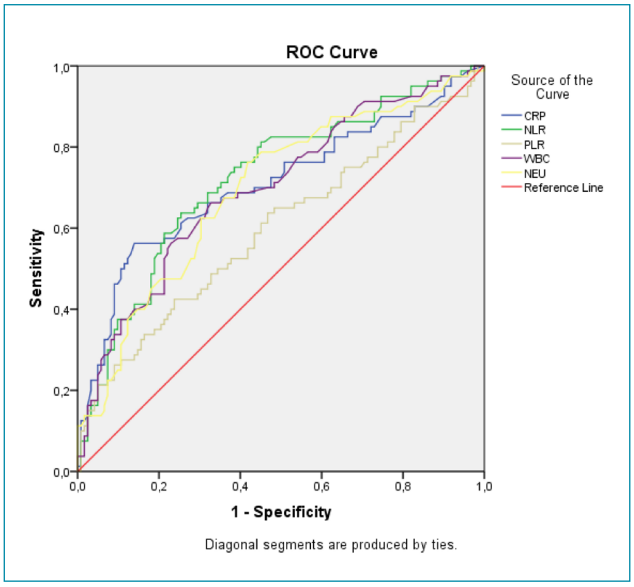

Figure 2. Roc curve of Neutrophil lymphocyte ratio (NLR), Platelet lymphocyte ratio (PLR), C reactive protein (CRP), neutrophil (NEU), and white blood cell (WBC) count for the detection of early COVID-19 patients.

those with CT (+) – PCR (+) (group A) and CT (-) – PCR (+) (group B) at the time of initial diagnosis. Significant positive correlation was found with the CRP used as an inflammatory marker and NLR-PLR. Similarly, WBC and NEU were significantly higher in group C. With these results, patients in group C were considered those with the highest inflammation in the early period, thus confirming the hypothesis that inflammation parameters, NLR, and PLR may be high in these patients. It has been reported that the PCR test may take 19 days to become positive[13]. Before PCR became positive, we showed that CT finding and hemogram parameters (WBC, NEU, NLR, PLR, CRP) can be used in the diagnosis of COVID-19. The most important of these parameters was NLR (75% specificity).

Although the COVID-19 median incubation time has been reported as three days[14]. Coronavirus (SARS-CoV-2) is transmitted from person to person with a relatively low mortality rate, causing a rapid epidemic[14]. Fever, cough, and shortness of breath are the dominant symptoms; and gastrointestinal symptoms have been reported to be rare[14-16]. In the first admission, fever developed only in 43.8% of patients, and in 83.4% after

hospitalization[17]. COVID-19 cases can be missed due to the absence of fever. In our study, fever was observed in 88 out of 203 patients (43%), cough in 62 (30%), dyspnea in 34 (17%), and non-respiratory symptoms in 41 patients (20%). Other symptoms in our study were joint pain (1%), sore throat (1%), headache (1%), anosmia (2%), diarrhea (1%), and weakness (4%). Studies have found that lymphopenia is common and severe[15,18]. NLR has been shown to be an independent prognostic biomarker in progressing to pneumonia in COVID-19 patients[19]. NEU releases a large amount of reactive oxygen species that can induce cell DNA damage and expose the virus from the cells. Thus, antibody-induced cell-mediated cytotoxicity (ADCC) can directly kill the virus, expose the virus antigen, and stimulate cell-specific and humoral immunity[20]. In addition, NEU can be triggered by virus-related inflammatory factors[21]. On the other hand, systemic inflammation caused by viral infection significantly reduces the number of lymphocytes[22]. Thus, virus-induced inflammation has been reported to increase NLR. In many studies, it has been found that NLR[9,10] and PLR[23] can show more systemic inflammation than NEU and LYM alone. In our study, NLR and PLR were found high in patients with CT (+) – PCR (-). In patients with CT (+) – PCR (-), high NLR and PLR was considered as the period with the highest inflammation.

There were some limitations in this study. First, the data were obtained from a single clinical research center, not from multiple clinical research centers. Second, the data are limited. In addition, the results of this study may differ from those of other academics and need further improvement in clinical cases.

CONCLUSION

COVID-19 is a rapidly spreading disease. The clinical manifestations of this disease can vary even in patients with the same viral infection; the severity of the condition may be related to the number of immune system cells. The CT finding can be detected earlier in the disease before the PCR test. The sensitivity of the PCR test varies according to the tester, the way of performing it, and the quality of the test. Therefore, especially in patients with PCR negative and CT findings, NLR and PLR levels should be evaluated, and patients should be followed up by suspecting the diagnosis of COVID-19.

AUTHORS' CONTRIBUTION

SO: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft. **EO:** Data Curation, Formal Analysis, Writing – Original Draft. **MED:** Conceptualization.

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