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Neutrophil to lymphocyte ratio, lymphocyte to monocyte ratio and platelet to lymphocyte ratio to predict the severity of COVID- 19

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ABSTRACT

Introduction: In this study, we aimed to investigate and compare the prognostic impacts of C-reactive protein (CRP), white blood cell (WBC) count, neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), platelet-to-lymphocyte ratio (PLR), Red Cell Distribution Width (RDW) biomarkers in laboratory-confirmed COVID-19 cases as well as to explore the most useful diagnostic biomarkers and optimal cutoff values in COVID-19 patients.
Methods: A total of 233 patients were admitted to Emergency Department (ED) of Pamukkale University Hospital during two months (March–April 2020) and underwent Sars CoV-2 PCR (Polymerase Chain Reaction), complete blood count (CBC), and CRP tests in sequence due to complaints of COVID-19. The laboratory results and demographic findings were collected from the public health management system retrospectively. The patients with positive Sars CoV-2 PCR test along with hospitalization data were also recorded.
Results: The CRP ($p = 0.0001$), lactate dehydrogenase (LDH) ($p = 0.038$), PLR ($p = 0.0001$) and NLR ($p = 0.001$) remained significantly higher in the patients with positive Sars CoV-2 PCR test result. By contrast, eosinophil ($p = 0.0001$), lymphocyte ($p = 0.0001$), platelet levels ($p = 0.0001$) were calculated as significantly higher in negative Sars CoV-2 patients.
Conclusion: In the light of the obtained results, the CRP, LDH, PLR and NLR levels remained significantly higher in COVID-19 positive patients, while eosinophil, lymphocyte, and platelet levels were significantly elevated in COVID-19 negative patients.

1. Introduction

Towards the end of 2019, several cases of unexplained viral pneumonia were reported in Wuhan, Hubei Province, China. The Chinese Centre for Disease Control and Prevention (CCDC) identified and sequenced a novel coronavirus by means of throat swab samples in January [1]. Named after "Corona Virus Disease" in 2019 by the World Health Organization (WHO), COVID-19 pandemic rapidly spread from China to other countries, developing into a major public health issue [2,3]. As of July 7, 2020, COVID-19 has been confirmed in 11,468,979 cases and has resulted in 251,446 deaths worldwide in 216 countries (https://covid19.who.int/). Human-to-human transmission of COVID-19 occurs among close contacts, mostly between family members and friends, either via direct contact or through droplets. The common clinical manifestations of the disease can be listed as fever, dry cough, fatigue, sputum production, dyspnea, sore throat, and headache [4,5].

Those, most notably with advanced age and underlying disorders, including cardiovascular diseases, hypertension, diabetes, cancer, and chronic obstructive pulmonary disease, have been categorized as risk groups [5,6]. The primary method of diagnosing COVID-19 is nucleic acid detection by real-time Polymerase Chain Reaction (PCR). Radiologic assessments with chest computerized tomography (CT) showed peripheral, multilobar areas of ground-glass opacity, and laboratory examinations supported the clinical diagnosis [7].

Rapid clinical diagnosis is key to symptomatic treatment, urgent access to the intensive care unit, and patient isolation in an attempt to prevent the transmission of the disease. Despite some widely-recognized challenges, such as long turnaround time for results and presence of the hospitals without PCR infrastructure, PCR is still the gold standard of COVID-19 diagnosis [8]. Widely-used techniques, such as serum biochemical and hemogram analysis, might be faster, easy-to-measure, routine, and low-cost techniques facilitating the diagnosis and prognosis of this disease [5]. However, these widely-used techniques fail to establish the diagnosis of COVID-19 accurately, while only making physicians suspect the presence of this disease.

Biomarkers of inflammation derived from the peripheral blood, such as white blood cell (WBC) count, neutrophil (NEU)-to-lymphocyte (LYM) ratio (NLR), platelet-to-lymphocyte ratio (PLR), and serum C-reactive protein (CRP) levels have been investigated as independent predictors for prognosis of systematic inflammatory diseases [9,10].

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CRP is an acute inflammatory protein that increases up to 1000-fold at sites of infection or inflammation. Recent studies have suggested that elevated NLR and LDH can be considered independent biomarkers for indicating poor clinical outcomes, while elevated LDH values were associated with the severity of COVID-19 disease [7,11].

In this study, we aimed to investigate and compare the prognostic impacts of CRP, WBC count, NLR, PLR, Red Cell Distribution Width (RDW) biomarkers in laboratory-confirmed COVID-19 cases as well as to explore the most useful diagnostic biomarkers and optimal cutoff values in COVID-19 patients.

2. Methods

The present study was approved by the Ethics Committee of the Pamukkale University Training and Research Hospital, Denizli, Turkey. A total of 233 patients were admitted to Emergency Department (ED) of University Hospital during two months (March–April 2020) and underwent Sars CoV-2 PCR, CBC, and CRP tests in sequence due to complaints of COVID-19. Laboratory results and demographic findings were collected from the public health management system retrospectively. The patients with positive Sars CoV-2 PCR test along with hospitalization data were also recorded. The data on demographic characteristics and results of the laboratory tests of the enrolled patients were collected from an electronic medical records network used by our institutional system. The charts were reviewed and analyzed by three biochemistry physicians and four emergency medicine clinicians. An extensive study plan was devised prior to the study.

The patients with complaints, such as difficulty in breathing or shortness of breath, fever, cough, sore throat, diarrhea, olfactory and gustatory dysfunction, were exposed to PCR amplification in case of possible infection. The enrolled patients were examined by ED clinicians, and their PCR samples were collected. Those with dyspnea, respiratory rate > 28 / min, $SaO_2 < 93\%$ at room air, $PaO_2/FiO_2 < 300$ and/or > 50% increase in lung infiltration within 24 to 48 h were hospitalized in the departments of Chest Diseases and Infectious Diseases, both of which are sub-disciplines under Internal Medicine. On the other hand, the patients were hospitalized to the intensive care unit in the case of severe pneumonia, acute respiratory distress syndrome (ARDS), sepsis, septic shock, arrhythmia, cardiogenic shock, acute renal failure or multiorgan failure.

The combined naso-oropharyngeal swabs were collected from the patients and analyzed with reverse-transcription polymerase chain reaction (RT-PCR) in Central Laboratory of our hospital. The complete blood count analysis was carried out on Mindray BC-6800 system through the electrical impedance method, while CRP levels were analyzed with electrochemilumisence method on Cobas 702 AutoAnalyzer (Roche Diagnostics GmbH, Mannheim, Germany). Neutrophil/lymphocyte as well as platelet/lymphocyte ratios were calculated in accordance with the CBC results. Eosinophil and RDW-SD results were also analyzed. In CBC, involving neutrophil, lymphocyte and platelet counts, we analyzed 22 parameters, which we used for calculating the ratios, in our hematology laboratory.

2.1. Statistical analysis

All the statistical analyses were carried out using SPSS 25.0 software. A Kolmogorov-Smirnov test was performed for the normality of the sample data, and the continuous variables were defined by the mean ± standard deviation, median (interquartile range %25–%75), while the categorical variables were expressed as frequency and percent. In order to compare the independent groups, an Independent Samples *t*-test was used for the parametric test assumptions, and a Mann-Whitney *U* test for non-parametric assumptions. The Logistic Regression models were performed to identify the factors affecting Sars CoV-2 positivity. First, we made use of univariate Logistic Regression models for LDH, eosinophil, NLR, CRP and PLR, and then conducted two different models with the significant variables. The Roc analysis was performed for optimal cut-off values to predict Sars CoV-2 positivity. We exploited Youden Index values to identify the optimal cut-off values. In addition, p value less than 0.05 was set as the statistical significance level.

3. Results

The mean age turned out to be 37.99 ± 14.73 years ($n = 123$) in the negative Sars CoV-2 group, while 44.16 ± 18.56 years in the positive group ($n = 110$) ($p = 0.022$). The demographic and clinical data of all the patients included are demonstrated in Table 1.

The CRP, LDH, PLR and NLR levels remained significantly higher in the patients with positive Sars CoV-2 PCR test result (respectively: $p < 0.0001$; $p = 0.038$; $p < 0.0001$; $p = 0.001$). By contrast, eosinophil, lymphocyte, platelet levels were calculated as significantly higher in negative Sars CoV-2 patients (respectively: $p < 0.0001$; $p < 0.0001$; $p < 0.0001$). Age and laboratory results are presented in Table 2.

Of 110 Sars CoV-2 positive patients, 75 were hospitalized in different clinics, whereas 35 were monitored with self-isolation in their home.

We analyzed the optimal cut-off values calculated by the ROC analysis, and the ROC curves are presented in Fig. 1. The areas under the curve (AUC) of CRP, LDH, NLR, PLR, Eosinophil and RDW-SD were found as 0.691 ($p < 0.0001$), 0.589 ($p = 0.038$), 0.615 ($p = 0.007$), 0.669 ($p < 0.0001$), 0.696 ($p < 0.0001$), and 0.562 ($p = 0.151$), respectively.

The optimal cut-off values for all the parameters are provided in Table 3. Among these parameters, eosinophil occupied the maximum area with 0.696 (0.619–0.774) ($p < 0.0001$), while the smallest area with $p = 0.151$ belonged to RDW-SD (AUC area 0.562 with 0.428–0.645, 95% confidence interval).

CRP, Eosinophil, NLR, and PLR correlated significantly with Sars CoV-2 PCR positivity, based on the logistic regression analysis of laboratory parameters associated with Sars CoV-2 PCR positivity. However, multivariate analysis showed that odds ratio of PLR and CRP correlated with Sars CoV-2 positivity (respectively; $p = 0.05$; $p = 0.006$) (Table 4).

4. Discussion

The present study consisting of patients admitted only to ED with flu-like symptoms and fever reveals that CRP, LDH, NLR, PLR and Eosinophil might be considered as effective diagnostic tools. C-reactive protein (CRP) is an acute-phase protein synthesized by hepatocytes that generate one of the major novel inflammatory markers. In our study, CRP levels were observed to increase in COVID-19 patients in response to proinflammatory cytokines, which had also been reported to increase in a large body of previous research [12,13].

In recent years, researchers have drawn on some ratios in the diagnosis and prognosis of many inflammatory conditions, some of which can be cited as neutrophil/lymphocyte, platelet/lymphocyte, and monocyte/lymphocyte ratio. This study suggests that these aforementioned ratios might serve as useful predictors in diagnosing Sars CoV-2 positive patients.

Based on the retrospective analysis of clinical data from 443 COVID-19 patients, Shang et al. argued that NLR, CRP and platelets could help to identify the severity of the disease, and that all these parameters should

Table 1
The demographic and clinical data of all the patients.

Characteristics	Positive SARS CoV-2	Negative SARS CoV-2
Number of subjects	110	123
Median age (years)	42 (18–86)	34 (18–85)
Mean ages (years)	44.16 ± 18.56	37.99 ± 14.73
Number of females	48 (%43.6)	52 (%42.3)
Number of males	62 (%56.4)	71 (%57.7)

Table 2
Age and laboratory results.

	Sars CoV-2 negative		Sars CoV-2 positive		p
	mean ± s.d.	med (iqr 25%–75%)	mean ± s.d.	med (iqr 25%–75%)	
Age (years)	37.99 ± 14.73	34 (27–45)	44.16 ± 18.56	42 (27.75–58)	0.022* (z = −2.294)
CRP mg/dl	7.09 ± 19.38	1.17 (0.57–3.73)	33 ± 56.02	5.39 (0.85–45.99)	0.0001* (z = −4.439)
LDH IU/ml	201.65 ± 80.96	182 (157–213)	227.21 ± 91.81	201 (164–255)	0.038* (z = −2.073)
Hemoglobin (g/dl)	15.2 ± 12.85	13.9 (12.8–15.7)	13.96 ± 1.87	14.1 (13–15.23)	0.805 (z = −0.246)
Hematocrite (%)	41.77 ± 4.72	41.6 (38.8–45.8)	41.24 ± 5.29	41.8 (38.85–44.7)	0.704 (z = −0.38)
Eosinophil	0.19 ± 0.16	0.14 (0.08–0.25)	0.12 ± 0.14	0.07 (0.02–0.17)	0.0001* (z = −4.891)
Neutrophil	5.48 ± 2.3	5.12 (3.86–6.89)	6.1 ± 7.43	4.26 (3.44–6.76)	0.084 (z = −1.728)
Lymphocyte	2.68 ± 0.84	2.58 (2.1–3.21)	1.9 ± 0.97	1.85 (1.15–2.4)	0.0001* (t = 6.605)
Platelet	269.88 ± 66.55	267 (226–315)	233.72 ± 70.13	235.5 (186.75–282.5)	0.0001* (t = 4.037)
RDW-SD	40.27 ± 3.32	40.2 (38.1–41.9)	40.71 ± 4.39	40 (38.48–42.63)	0.588 (z = −0.541)
MPV	9.63 ± 1.11	9.6 (8.9–10.3)	9.54 ± 1.04	9.45 (8.8–10.3)	0.529 (t = 0.630)
Platelet/Lymphocyte	109.14 ± 38.6	100 (81.82–131.05)	156.47 ± 112.51	125.67 (96.74–175.44)	0.0001* (z = −4.241)
Neutrophil/Lymphocyte	2.28 ± 1.45	1.87 (1.5–2.57)	4.74 ± 7.93	2.42 (1.6–4.05)	0.001* (z = −3.35)

s.d: Standard deviation; med: median; iqr: interquartile range; z: Mann Whitney U test; t: Independent samples t-test iqr: interquartile range; CRP: C-reactive protein; LDH: Lactate dehydrogenase; RDW-SD: Red Cell Distribution Width; MPV: Mean platelet volume.
* $p < 0.05$ statistically significant.

be taken into consideration in the clinic, though NLR was the best determinant of all [14]. When it comes to our study, the number of eosinophils in particular remained low, whereas the PLR rate proved more appropriate for clinical use.

In a retrospective study on 72 COVID-19 in-patients, Ding et al. tried to establish the correlation between the time of hospitalization and hematological blood parameter follow-ups [15]. Of 72 patients, lymphopenia and leukopenia developed in 39 (54.2%) and 20 (27.8%) patients, respectively, while 15 (20.8%) patients were identified as severe cases and 57 (79.2%) as non-severe cases. The leukocyte and neutrophil count as well as neutrophil-lymphocyte ratio (NLR) were significantly higher in non-severe patients, whereas the lymphocyte count always tended to decrease in severe patients. The researchers observed an increasing tendency in the number of platelets in non-severe patients during the follow-up period. They also reported a positive correlation between NLR and length of hospitalization, starting from Day 5 after hospitalization, suggesting that NLR was somewhat related to the days of hospitalization and involved in predicting the prognosis for COVID-19 patients. In our study, NLR and PLR ratios were significantly higher in the infected patients than their non-infected counterparts, with no difference between neutrophil counts. The decrease in PLR ratio indicates that the decrease in the number of platelets was greater

Table 3
ROC analysis for Sars CoV-2 positive patients.

	AUC (95% CI)	Cut-off	Sensitivity %	Specificity %	p
CRP	0.691 (0.613–0.770)	1.9	66	67	0.000*
LDH	0.589 (0.505–0.673)	190	60	62	0.038*
NLR	0.615 (0.532–0.699)	1.81	70	46	0.007*
PLR	0.669 (0.590-0.747)	102.8	70	52	0.000*
Eosinophil	0.696 (0.619-0.774)	0.10	62	69	0.000*
RDW-SD	0.562 (0.428–0.645)	39.35	60	39	0.151

AUC: Area under ROC Curve; CRP: C-reactive protein; LDH: Lactate dehydrogenase; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; RDW: Red Cell Distribution Width;
* $p < 0.05$ statistically significant.

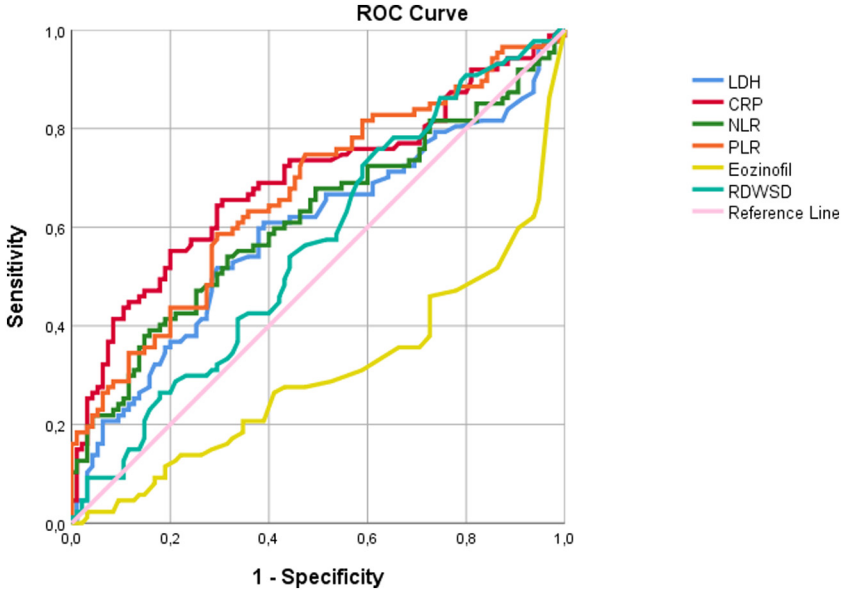

Fig. 1. The ROC curve of lactate dehydrogenase (LDH), C reactive protein (CRP), neutrophil-lymphocyte ratio (NLR) platelet-lymphocyte ratio (PLR), eosinophil and red cell distribution width standard deviation (RDW-SD) for discriminating between Sars CoV-2 positive and negative groups.

Table 4
Laboratory parameters to predict COVID-19 disease.

	Univariate analysis		Multivariate analysis model 1		Multivariate analysis model 2	
	O.R. (%95C.I.)	*p*	O.R. (%95C.I.)	*p*	O.R. (%95C.I.)	*p*
LDH	1.004 (1.000–1.007)	0.056	–		–	
Eosinophil	0.028 (0.004–0.217)	0.001*	0.254 (0.032–2.002)	0.194	–	
NLR	1.274 (1.099–1.476)	0.001*	1.020 (0.924–1.126)	0.691	–	
CRP	1.025 (1.012–1.038)	0.000*	1.016 (1.002–1.030)	0.022*	1.019 (1.006–1.033)	0.05*
PLR	1.012 (1.006–1.018)	0.000*	1.007 (1.001–1.014)	0.031*	1.009 (1.002-1.0.015)	0.006*

Odds ratios were given with 95% CI and *p* values; LDH: Lactate dehydrogenase; NLR: Neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; PLR: Platelet-to-lymphocyte ratio;
* $p < 0.05$ statistically significant.

than that of lymphocytes, which implies that thrombocytopenia needs to be attached more importance in the follow-up of COVID-19 patients. In addition, we hold that PLR rate may be instrumental in the follow-up and diagnosis along with the NLR rate recommended by Ding et al. [15].

In their study on 69 non-severe and 24 severe cases diagnosed with COVID-19, Yang et al. reported that age, WBC count, NLR, LMR (lymphocyte-to-monocyte ratio), PLR, CRP, and d-NLR (derived NLR ratio) rates were significantly higher in severe patients than the other patients, while the lymphocyte count was significantly lower [8]. In addition, when they compared the crude odds ratio with the adjusted odds ratio after logistic regression analysis by excluding possible effects of age and gender in order to identify the factors that could affect the progression of the disease, the researchers concluded that NLR positively correlated with the risk of COVID-19. Therefore, NLR can be recommended in clinical practice to assess the prognosis and severity of clinical symptoms in COVID-19 patients.

Qu et al. suggested that elevated PLR level in the blood parameters of 30 patients with COVID-19 diagnosis extended the length of hospital stay and was associated with the prognosis of the disease [16]. They found that, although the PLR ratio indicated no significant difference in severe and non-severe patients during hospitalization, this ratio turned out to be significantly different once the peak platelet count was reached. They concluded that when the PLR value reaches the peak platelet count in the course of treatment, it might act as an independent influencing factor, notably for critical cases. In our study, infected and non-infected patients were compared rather than a comparison based on disease severity, and the PLR cut-off ratio was specified as 102.8, sensitivity as 70%, and specificity as 52%.

Interestingly, LDH levels identified in Sars CoV-2 patients increased. Lactate dehydrogenase (LDH) catalyzes the reversible conversion of pyruvate to lactate, the last stage of aerobic glycolysis [17]. Brandon et al. investigated LDH levels of 1532 patients either at admission or at earliest time during hospitalization in 9 eligible studies out of 289 studies reviewed, eventually identifying LDH elevation in 600 (49.8%) of 1206 patients [17]. Severe disease symptoms developed in 188 (15.6%) patients, 159 (84.6%) of whom had high LDH, in contrast to 441 (43.3%) non-severe patients who also manifested high LDH. Though the LDH cutoff values were reported to range between 240 and 253.2 U/L in these reviewed studies, the one in our study turned out to be 190. We thus suggest that our cutoff value for LDH, with 60% sensitivity and 62% specificity, might function better in distinguishing between infected and non-infected patients rather than identifying the severity of the disease.

5. Limitations

The findings presented in the study were obtained only from a limited number of patients presenting to our ED. We are of the opinion that the conduct of these tests with simpler devices and in a larger number of hospitals might facilitate the diagnosis of the disease. In the study, a detailed examination was not performed for PCR negative patients with lung involvement on tomography. However, their clinical symptoms, the treatment they received, the clinical course of the service and intensive care unit, and the admittance parameters were included in the study. Due to moderate sensitivity of the PCR tests, the patients with false negative results were assessed in accordance with the available results.

6. Conclusion

We hold that it would be appropriate to evaluate the disease according to these clinical and biochemical parameters in addition to the exploitation of real time PCR. In the light of the obtained results, the CRP, LDH, PLR and NLR levels remained significantly higher in COVID-19 positive patients, while eosinophil, lymphocyte, and platelet levels were significantly elevated in COVID-19 negative patients. Furthermore, since our study is retrospective and requires further data, future studies are needed to evaluate these biomarkers and optimal cutoffs.

Compliance with ethical standards

Pamukkale University Faculty of Medicine Ethics Committee was approved the study.

Author contribution statement

1-Conceptualization: M.S. and E.A. 2- Data curation: M.S., E.A., R.N., A.Y, and M.O. 3-Formal analysis: H.S., H.A. and A.O. 4-Writing - original draft: M.S. and E.A. 5-Writing - review & editing: M.S. and E.A. 6-Validation: H.S. and H.A. 7-Project administration: M.S., E.A., and A.Y. 8-Supervision: M.S.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

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