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ORIGINAL ARTICLE

The Diagnostic and Predictive Roles of Neutrophil-Lymphocyte Ratio for Severity of Disease in COVID-19 Patients

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SUMMARY

Background: **Neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), and platelet-lymphocyte ratio (PLR) are inflammation markers in inflammatory, cardiovascular, and malignant diseases and are important to assess prognosis. The aim of the study is to show the correlation between the inflammation markers of NLR, LMR, and PLR identified in total blood count of patients with Coronavirus disease 2019 (COVID-19) with the disease severity.**

Methods: **A total of 409 patients attending hospital with clinical symptoms of COVID-19 and with positive quantitative reverse transcriptase-polymerase chain reaction (RT-PCR) test were divided into two groups as 61 severe patients and 348 non-severe patients. The levels of inflammation markers NLR, LMR, PLR, and c-reactive protein (CRP) were assessed.**

Results: **The mean age of 409 patients was 49.9 ± 18.3 years and 48.7% of all patients were female. In the severe patient group, NLR 8.94 ± 13.24, LMR 2.24 ± 1.46, and PLR 248 ± 254 were identified. NLR exhibited the largest area under the curve at 0.698, with the highest specificity (67%) and sensitivity (67.3%) among the other inflammation markers such as LMR and PLR. Consistent with the severity of disease in severe COVID-19 patients, NLR, PLR, CRP and other inflammation markers increase, while LMR is observed to reduce.**

Conclusions: **NLR and PLR, calculated with the simple, cheap, and easily accessible hemogram test requested for diagnosis and follow-up of COVID-19 disease, were correlated with the total score for radiological findings and duration of hospitalization, and we observed NLR and LMR may predict disease severity.**

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INTRODUCTION

Coronavirus disease (COVID-19) was first identified among pneumonia cases with unknown cause in Wuhan city in China in December 2019. The disease caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was accepted as a pandemic by the World Health Organization (WHO) in March [1]. Globally there have been nearly 81 million cases and more

than 2 million deaths; in Turkey there have been more than 2 million cases and more than 18,000 deaths [2]. COVID-19, without definite treatment can be rapidly spread by asymptomatic and mildly symptomatic patients, has a mortality rate varying from 2 - 5% for all ages [3]. Preventing spread of the disease with rapid diagnosis of disease, isolation of patients, and abiding by social distance rules is very important for public health [4].

Biomarkers showing inflammation and immune response are important for prognosis of COVID-19 [5]. C-reactive protein (CRP) is one of the main components of the inflammatory reaction and increases with inflammation, infection, and tissue injury [6]. It is an important marker of host resistance to pathogens and inflammation. Acute pulmonary injury developing in COVID-19 patients causes a clear increase in CRP levels [7]. Neutrophil-lymphocyte ratio (NLR) is an inflammation marker in inflammatory, cardiovascular, and malignant diseases [8]. NLR was found to be associated with mortality linked to all causes observed in COVID-19 [9]. Platelet-lymphocyte ratio (PLR) is associated with systemic inflammation created by the host immune response [10]. NLR and PLR values are clinically significant for prognosis of malignant diseases, cardiovascular diseases, systemic lupus erythematosus, inflammatory diseases like familial Mediterranean fever, and acute pancreatitis [11]. High NLR and PLR with low lymphocyte-monocyte ratio (LMR) is associated with poor prognosis in malignant diseases led by breast cancer [12]. Low lymphocytes are important for both diagnosis and prognosis of COVID-19. Especially at the time of first diagnosis, it was identified to be more sensitive to predict disease than other blood parameters [13]. NLR, PLR, and LMR levels are rapid measurement methods that can be obtained from a simple blood count and used for prediction of prognosis for the inflammatory process in active inflammatory diseases [14].

The aim of our study is to research the efficacy of NLR, PLR, LMR, and other inflammation markers to predict disease prognosis in COVID-19 patients and to direct early treatment planning with simple tests.

MATERIALS AND METHODS

The study protocol was permitted by Biruni University Faculty of Medicine Ethics Committee and the Ministry of Health. The study was completed according to the mandates of the Helsinki Declaration.

A total of 542 patients, aged over 18 years and not pregnant, attending Biruni University Hospital Internal Diseases, Infection and Chest Diseases clinics from 20 March - 10 September 2020 with suspicion of COVID-19 were retrospectively screened. The study included 409 patients with clinical findings consistent with COVID-19 (fever, cough, shortness of breath, shivering, muscle pain, throat pain, diarrhea, loss of taste and smell) and reverse transcription polymerase chain reaction (RT-PCR) nucleic acid test positive, while 133 patients were excluded from the study due to lack of adequate data. All patients had chest computed tomography (CT) taken to determine pulmonary involvement. The 409 patients (female: male 199: 210, mean age 49.9 ± 18.3 years) were divided into two groups as 61 severe and 348 non-severe patients. The patients who had one of the following three clinical manifestations were classified in the severe patient group: mean arterial oxygen saturation ≤ 93% in resting state; shortness of breath with respiratory rate (RR) > 30 times/min and/or partial pressure of arterial oxygen (PaO2)/oxygen concentration (FiO2) ≤ 300 mmHg (1 mmHg = 0.133 kPa).

All patients included in the study had oropharyngeal and nasal swab samples taken for COVID-19 RT-PCR nucleic acid test developed with the virus sequence stated in the Ministry of Health guidelines on admission, along with blood samples taken for laboratory tests (full blood count and CRP). NLR, LMR, and PLR were calculated according to blood count results. Patient age, gender, symptoms, and physical examination findings at the beginning of disease, treatment used, duration of hospitalization, intensive care requirements, and mortality status were recorded.

In our study, thoracic CT images taken with a Siemens Somatom Scope (Germany) 16-slice CT device, with section thickness 1.5 mm, obtaining images without gaps between slices (gapless) using low-dose radiation (mAs: 50, Kvp: 120), were assessed. CT positivity was defined by findings assessed as consistent with COVID-19 pneumonia (peripheral, bilateral ground glass appearance, multifocal rounded ground glass areas, reverse halo) and findings assessed as consistent with viral pneumonia including COVID-19 (peripheral and non-rounded multifocal, diffuse, perihilar or unilateral ground glass opacity, low numbers and very small peripheral and non-rounded ground glass areas). The severity of pulmonary involvement was obtained by dividing both lungs into three sections of upper, middle, and lower zones for a total of 6 regions. The volume involvement in each region was graded with 1 point for 0 - 25%, 2 points for 25 - 50%, 3 points for 50 - 75%, and 4 points for 75 - 100% [15].

Statistical analysis

Our study is a retrospective cross-sectional study. The fit to normal distribution of all data was analyzed with the Kolmogorov-Smirnov test. Categorical variables are given as percentage, while continuous variables are given as mean ± standard deviation. Categorical variables had the chi-squared test used, while continuous variables in two-way groups had the *t*-test applied. Pearson's correlation was used for numerical data. To evaluate the diagnostic accuracy, we carried out receiver operating characteristic (ROC) curve analysis. ROC curves were plotted to see the power of inflammation markers to differentiate the severity of disease. The area under the curve (AUC) was then estimated with 95% confidence interval. All data were tested using the SPSS

20.0 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY, USA) program and data with $p < 0.05$ were accepted as significant.

RESULTS

The demographic characteristics, comorbidities, and symptoms in the study groups are shown in Table 1. Gender distribution did not differ among the groups. In the severe patient group, the median age was 64.9 ± 14.1 years and in the non-severe patient group, the median age was 47.4 ± 17.6 years ($p < 0.001$). Comorbid diseases such as hypertension (47.5%, $p < 0.001$), type 2 diabetes mellitus (42.6%, $p < 0.001$), and coronary artery disease (26.2%, $p < 0.001$) were seen more commonly in the severe patient group compared to the non-severe patient group. The most common symptoms such as fever, cough, and malaise were similar in both groups, chest pain (49%, $p = 0.001$), dyspnea (62.3%, $p < 0.001$), and loss of smell and taste (19.7%, $p = 0.011$) were detected more in the severe patient group. In the severe patient group, chest CT positivity and total score for radiologic findings were higher than in the non-severe patient group ($p < 0.001$).

The laboratory findings for the study groups are shown in Table 2. The leukocyte and neutrophil levels were significantly higher in the severe patient group than the other group ($p < 0.001$). Lymphocyte and eosinophil counts were low in both groups and there was no significant difference between the groups according to lymphocyte and eosinophil counts ($p = 0.081$, $p = 0.086$, respectively). NLR value was detected 8.94 ± 13.24 in the severe patient group and 3.91 ± 4.11 in the non-severe patient group; there was significant difference between two groups ($p = 0.005$). LMR value was significantly lower and PLR value was significantly higher in the severe patient group compared to the non-severe patient group ($p = 0.038$; $p < 0.001$, respectively).

The duration of hospitalization, necessity for intensive care, and mortality rate were significantly higher in the severe patient group than the non-severe patient group ($p < 0.001$). This is shown in Table 3.

Comparison of ROC curves with sensitivity, specificity, AUC, cutoff, and asymptotic significance of NLR, PLR, LMR, and CRP in groups is shown in Table 4. AUC values for severity of disease with NLR, PLR, LMR, and CRP were detected as 0.698, 0.568, 0.589, and 0.792, respectively. All of them are above 0.5 and can be used as potential diagnostic markers.

The duration of hospitalization was significantly positively correlated with age ($r = 0.347$, $p < 0.001$), leukocyte ($r = 0,180$, $p < 0.001$), NLR ($r = 0.182$, $p = 0.001$), PLR ($r = 0.188$, $p = 0.001$), CRP ($r = 0.306$, $p \leq 0.001$), and respiratory rate ($r = 0.300$, $p < 0.001$) and significantly negatively correlated with arterial oxygen saturation ($r = -0.274$, $p < 0.001$). The total radiological score was significantly positively correlated with leukocyte ($r = 0.187$, $p = 0.003$), neutrophil ($r = 0.281$, $p < 0.001$), NLR ($r = 0.381$, $p < 0.001$), PLR ($r = 0.285$, $p < 0.001$), CRP ($r = 0.566$, $p < 0.001$), age ($r = 0.335$, $p < 0.001$), and respiratory rate ($r = 0.431$, $p < 0.001$) and significantly negatively correlated with arterial oxygen saturation ($r = -0.432$, $p < 0.001$), diastolic blood pressure ($r = -260$, $p = 0.001$), lymphocyte ($r = -0.234$, $p < 0.001$), and systolic blood pressure ($r = -0.152$, $p = 0.048$) (Table 5).

DISCUSSION

This study observed that many inflammation markers like NLR and PLR increased in COVID-19 patients, while LMR was reduced. As expected, hospitalization - duration, intensive care requirements, and mortality were higher in the severe patient group. NLR, LMR, and PLR were correlated with pulmonary involvement and hospitalization duration and were observed to predict the severity of disease in COVID-19 cases.

COVID-19 continues to be a serious problem with mean 3 - 5-day incubation duration, rapid transmission from person to person and high mortality worldwide. Though many biological medications such as antiviral agents like lopinavir/ritonavir, favipravir and remdesivir, anti-inflammatory drug such as colchicine, tocilizumab and anakinra, corticosteroids, antimalarial medications like hydroxychloroquine, continue to be used commonly for treatment, none have been proven to be a definite solution [16]. In order to end the pandemic around the world, broad-scale vaccine studies and rapid vaccination programs continue. The target of social immunization is to protect the physical and mental health of society and to reduce negative effects of the pandemic on the economies of countries.

COVID-19 progression may be observed from asymptomatic cases to severe clinical courses up to critical pneumonia, acute respiratory distress syndrome and death [17]. Just as with all infections, inflammation plays a basic role in the pathophysiology of disease. Identifying the inflammatory process and severe cases in the early period will ensure initiation of more aggressive treatments in the progression toward cytokine storm and lower mortality rates. China where the first COVID-19 case was observed identified that patients had normal or reduced leukocyte levels, reduced lymphocyte and eosinophil levels; while more serious cytopenia was identified in severe disease situations. A meta-analysis of 21 studies including 3,377 patients by Henry et al. observed more leukocytosis, neutrophilia, lymphopenia, and thrombocytopenia in severe patients [18]. There is a severe reduction in lymphocyte numbers linked to the cytokine storm when inflammatory mediators and cytokines come to the forefront at about 7 - 14 days into the disease [19]. While severe decreases in monocytes and eosinophils are observed in severe disease situations, eosinophils initially increase and then return to normal while regulation of the acquired immune cells of lymphocytes occurs later [20]. In our

Table 1. Demographic characteristics, comorbidities, and symptoms of the study population.

	Non-severe (n = 348)	Severe (n = 61)	p
Age (years)	47.4 ± 17.6	64.9 ± 14.1	p < 0.001
Gender (female)	168 (48.3)	31 (50.8)	0.714
Comorbidities			
Hypertension	53 (15.2)	29 (47.5)	p < 0.001
Diabetes mellitus	36 (10.3)	26 (42.6)	p < 0.001
COPD/Asthma	21 (6)	15 (24.6)	p < 0.001
Coronary artery disease	22 (6.3)	16 (26.2)	p < 0.001
Hyperlipidemia	20 (5.7)	13 (21.3)	p < 0.001
Atrial fibrillation	6 (1.7)	7 (11.5)	p < 0.001
Chronic renal failure	2 (6)	8 (13.1)	p < 0.001
Malignancy	6 (1.7)	6 (9.8)	0.004
Symptoms			
Fever	176 (50.6)	36 (59)	0.224
Cough	214 (61.5)	36 (59)	0.823
Fatigue	306 (87.9)	48 (77.7)	0.080
Dyspnea	58 (16.7)	38 (62.3)	p < 0.001
Taste/smell abnormalities	29 (8.3)	12 (19.7)	0.011
Diarrhea	22 (6.3)	4 (6.6)	0.562
Chest pain	95 (27.3)	30 (49.2)	0.001

Table 2. NLR, PLR, LMR, CRP, laboratory results, and clinical-radiological findings of the study population.

	Non-severe (n = 348)	Severe (n = 61)	p
Laboratory Results			
Leukocyte (10^3/mL)	6.99 ± 2.71	9.74 ± 5.36	p < 0.001
Neutrophil (10^3/mL)	4.60 ± 2.44	7.58 ± 5.05	p < 0.001
Lymphocyte (10^3/mL)	1.58 ± 0.75	1.38 ± 1.08	0.081
Monocyte (10^3/mL)	0.67 ± 0.28	0.72 ± 0.39	0.221
Eosinophil (10^3/mL)	1.14 ± 1.26	0.84 ± 0.94	0.086
Hemoglobin (g/dL)	13.40 ± 1.78	13.17 ± 2.21	0.201
Hematocrit	39.76 ± 4.62	38.34 ± 5.70	0.101
Platelet (10^3/mL)	227 ± 79	229 ± 16	0.914
NLR	3.91 ± 4.11	8.94 ± 13.24	0.005
LMR	2.68 ± 1.55	2.24 ± 1.46	0.038
PLR	172 ± 94	248 ± 254	p < 0.001
CRP (mg/L)	26.5 ± 42.5	86.6 ± 88.1	p < 0.001
Clinical and Radiological Findings			
Systolic blood pressure (mmHg)	119.7 ± 15.8	117.4 ± 22.3	0.475
Diastolic blood pressure (mmHg)	71.9 ± 7.4	68.8 ± 12.0	0.074
Heart beat (/minute)	83.9 ± 10.8	91.8 ± 14.1	p < 0.001
Oxygen saturation (%)	95.4 ± 3.4	91.4 ± 5.9	p < 0.001
Respiratory rate (/minute)	17.1 ± 2.8	20.7 ± 4.2	p < 0.001
Chest CT positivity	265 (76.1%)	61 (100%)	p < 0.001
Total score of radiological findings	3.5 ± 3.7	10.1 ± 6.2	p < 0.001

CRP - C-reactive protein, LMR - lymphocyte-to-monocyte ratio, NLR - neutrophil-to-lymphocyte ratio, PLR - platelet-to-lymphocyte ratio, CT - computerized tomography.

Table 3. Duration of hospitalization, necessity of intensive care unit, and mortality rate of the study population.

	Non-severe (n = 348)	Severe (n = 61)	p
Duration of hospitalization	2.6 ± 3.7	10.7 ± 5.9	p < 0.001
Necessity of intensive care unit	7 (2)	34 (55.7)	p < 0.001
Mortality	1 (0.3)	14 (22.9)	p < 0.001

Table 4. Sensitivity, specificity, AUC, cutoff, and asymptotic significance of parameters for severity of disease, necessity of intensive care unit, and mortality in studied groups.

	Sensitivity	Specificity	AUC	Cutoff	p
Severity of disease					
CRP	73.5%	71%	0.792	26.5	< 0.001
NLR	67.3%	67%	0.698	3.7	< 0.001
Neutrophil	65.3%	65.2%	0.675	4,675	< 0.001
Leukocyte	63.3%	60.1%	0.637	6,990	0.002
LMR	58%	57.1%	0.589	2.1	0.047
PLR	55.1%	58%	0.568	160.3	0.128
Necessity of intensive care unit					
CRP	73.2%	71.5%	0.838	28.5	< 0.001
NLR	73.2%	71.5%	0.785	3.9	< 0.001
Neutrophil	73.2%	72%	0.798	5,090	< 0.001
Leukocyte	73.2%	73.1%	0.773	7,975	< 0.001
LMR	61%	61.1%	0.667	2.1	< 0.001
PLR	63.4%	60.9%	0.647	166.3	0.002
Mortality					
CRP	80%	79.9%	0.884	51	< 0.001
NLR	73.3%	72.8%	0.713	4.3	0.005
Neutrophil	80%	74.6%	0.755	5,845	0.001
Leukocyte	73.3%	70.3%	0.764	7,990	0.001
LMR	66.7%	66.5%	0.647	1.9	0.053
PLR	53.3%	53.3%	0.476	155.9	0.749

CRP - C-reactive protein, LMR - lymphocyte-to-monocyte ratio, NLR - neutrophil-to-lymphocyte ratio, PLR - platelet-to-lymphocyte ratio.

study, leukocytosis and neutrophilia were observed in the severe patient group, with no significant decrease observed in lymphocyte and eosinophil counts. Similar to our study, a study including 140 patients by Zhang et al. did not identify a significant difference between severe patients and non-severe patients for eosinophil counts [21].

NLR, PLR, and LMR are inflammation markers in inflammatory, cardiovascular, and malignant diseases that may be rapidly obtained from simple blood counts [8]. These markers have significant clinical value for the prognosis of chronic disease [10,11]. A meta-analysis by Russel et al. found that NLR was associated with clinical prognosis of pneumonia, urinary tract infection and diabetic foot infection in critical patients with sepsis and low LMR was associated with the severity of symptoms in respiratory virus infections [22].

A study of 151 patients in Wuhan found higher NLR in patients with mortal outcome ($p < 0.001$) and it was demonstrated that NLR of 3.328 had a good predictive value for all-cause mortality in patients with COVID-19, with a sensitivity of 100.0% and a specificity of

Table 5. Relationship of total score of radiological findings and duration of hospitalization with other parameters.

	Total score of radiological findings		Duration of hospitalization	
	r	p	r	p
Age	0.335	p < 0.001	0.347	p < 0.001
Leukocyte	0.187	0.003	0.180	p < 0.001
Neutrophil	0.281	p < 0.001	0.229	p < 0.001
Lymphocyte	-0.234	p < 0.001	-0.130	0.021
Eosinophil	-0.133	0.033	-0.071	0.209
NLR	0.381	p < 0.001	0.182	0.001
LMR	-0.129	0.038	-0.158	0.005
PLR	0.285	p < 0.001	0.188	0.001
CRP	0.566	p < 0.001	0.306	p < 0.001
Systolic blood pressure	-0.152	0.048	0.022	0.747
Diastolic blood pressure	-0.260	0.001	-0.122	0.079
Heart beat	0.260	0.001	0.186	0.007
Oxygen saturation	-0.432	p < 0.001	-0.274	p < 0.001
Respiratory rate	0.431	p < 0.001	0.300	p < 0.001
Duration of hospitalization	0.440	p < 0.001		

CRP - C-reactive protein, LMR - lymphocyte-to-monocyte ratio, NLR - neutrophil-to-lymphocyte ratio, PLR - platelet-to-lymphocyte ratio.

84.0% [9]. Another study of severe cases by Yang et al. found that NLR and PLR increased in severe cases while LMR decreased, and NLR was associated with poor outcomes [5]. In our study, similar to these studies, NLR and PLR significantly increased, while LMR decreased, and NLR, PLR, and LMR were observed to be associated with hospitalization duration and pulmonary involvement, which is important for disease progression. A meta-analysis including 15 studies comparing severe and mild patients identified increased leukocytes, neutrophils, and NLR, reduced lymphocytes and platelets, and no difference in monocytes in the severe patient group [17].

Neutrophils have a major benefit by extracting the virus from the leukocyte population but this releases reactive oxygen species that can damage cell DNA in the cells. In addition, virus-related inflammatory factors (interleukin-6, interleukin-8, tumor necrosis factor-alpha, granulocyte colony stimulating factor, and interferon-gamma) released by lymphocytes and endothelial cells can activate neutrophils. Lymphocytes form the basis of the immune response triggered in viral infections. Systemic inflammation significantly reduces CD4+ T lymphocytes and suppresses CD8+ suppressant T lymphocytes increasing cellular immunity [5]. In lymphocytes, reduced lymphocyte apoptosis is connected to atrophy of lymphoid organs, and prevention of lymphocyte proliferation caused by lactic acidosis linked to disease [23, 24]. The inflammation triggered by this pathophysiological process increases NLR, and high NLR accelerates the progression of COVID-19. In clinics, symptoms become more severe, hospitalization duration lengthens, and ICU requirements and mortality increase.

The current study has some limitations. First, the results cannot be generalized to the whole population because the study was conducted in a single center and included only patients over 18 years of age. Second, the experimental data are limited. Finally, NLR, LMR, and PLR should be compared with other known inflammation markers in broader-scale studies.

CONCLUSION

COVID-19 has affected the whole world and continues to be a pandemic. Determining the severity of disease at the diagnostic stage for COVID-19 affects treatment decisions and disease monitoring processes. In this study, NLR, LMR, and PLR were correlated with pulmonary involvement and hospitalization duration, and we identified the predicted severe COVID-19 cases. We recommend assessment of NLR, PLR, and LMR with the simple, rapid, and practical full blood count for treatment choices to be made in the diagnosis and monitoring process for COVID-19.

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