Research Article,

An Easy Parameter That Can Predict Intensive Care Unit Admission in Patients with COVID-19 in the Early Stage: Neutrophil to Lymphocyte Ratio

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Abstract:

Background: The coronoavirus disease (COVID-19) pandemic has caused more than 60 million confirmed cases and approximately 1.5 million deaths all over the world as of December 1st, 2020. So it's important to predict the clinical course of infected patients and to prevent the disease course from worsening with early intervention.

Aim: This study aimed to evaluate the new generation inflammation markers such as neutrophil to lymphocyte ratio (NLR), mean platelet volume (MPV) and red blood cell distribution width (RDW) in predicting the need for intensive care of COVID-19 patients.

Methods: The retrospective cross-sectional study included 112 patients whose hemogram parameters were checked simultaneously with the diagnosis of COVID-19, hospitalized in public hospitals in Antalya province between March 16th and June 15th, 2020. Patients treated in the intensive care unit (ICU) and treated only in the ward were compared according to laboratory data, and the predictive effect of study parameters on the need for intensive care was investigated.

Results: Of the patients 43.8% were female and 56.3% were male. The average age was 49.48 ± 17.12 years. The percentage of patients admitted to the ICU was 19.6% and, died was 5.4%. While MPV was found to be statistically significantly lower in COVID-19 patients who need intensive care, NLR and RDW were found to be statistically significantly higher. Decreased MPV and increased NLR were determined as independent risk factors for ICU admission. In addition, the optimal cut-off value was calculated as ≤ 10.4 for MPV (with 77.27% sensitivity and 66.67% specificity) and > 5.3 for NLR (with 72.73% sensitivity and 91.11% specificity) in predicting ICU admission.

Conclusion: NLR, which is checked at the first admission in patients with suspected COVID-19, is an easy, fast, cheap and very valuable test in determining the severity of SARS-cov2 infection and predicting the need for intensive care.

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Introduction:

The coronavirus disease (COVID-19) pandemic that started in Wuhan, China in December 2019 and spread rapidly all over the world has caused more than 60 million confirmed cases and approximately 1.5 million deaths all over the world as of December 1st, 2020.[1]

The disease has a wide range from asymptomatic cases to severe pneumonia accompanied by respiratory failure, death due to severe respiratory failure and / or multiorgan involvement.[2-4] As with many infectious or systemic diseases, early diagnosis and treatment of particularly risky groups is important in COVID-19 disease. At this point, some laboratory parameters are important in the detection of risky patients, like age and accompanying comorbidities.[5,6]

Red blood cell distribution width (RDW), mean platelet volume (MPV), neutrophil and lymphocyte are cheap tests routinely used by physicians in

clinical practice as part of complete blood count and RDW, MPV and neutrophil to lymphocyte ratio (NLR) are the next generation inflammatory markers associated with many diseases, indicative of systemic inflammation.[7-10]

There are studies in which the severity of some infectious diseases is associated with these tests in the literature. For example; Kaya et al. found that NLR and RDW levels were significantly higher in community-acquired pneumonia cases treated in the intensive care unit (ICU) compared to inpatients in the clinic, and also showed that increased NLR was associated with mortality.[11] Farghly et al. found that increased MPV and RDW levels at the time of first hospitalization were associated with mortality in community-acquired pneumonia cases, and they suggested that RDW and MPV could increase the performance of existing prognostic scales in these patients.[12] Similarly, Ekin et al. argued that NLR is an independent parameter predicting the severity of the disease in cases of acute pancreatitis.[13] Wang et al. reported that RDW can be a predictor of COVID-19 prognosis,[14] while Liu et al. reported that NLR is the most useful prognostic factor in determining the prognosis of patients with COVID-19 pneumonia.[2]

In this study, it was aimed to evaluate new generation inflammation markers such as RDW, MPV and NLR in predicting the need for intensive care of COVID-19 patients.

Materials and Methods:

This retrospective cross-sectional study included 112 patients hospitalized with the diagnosis of COVID-19 in Antalya province, Turkey between March 16th and June 15th, 2020. Inclusion criteria of the patients are as follows:

Study group:

1. Having been diagnosed with COVID-19 by using SARS-cov-2 reverstranscriptase polymerase chain reaction (SARS-cov-2 RT-PCR) method from nasopharyngeal swab samples,
2. Being over the age of 18,
3. Being treated in public hospitals,
4. Patients whose research laboratory parameters (RDW, MPV, NLR, sedimentation and CRP) have been checked simultaneously with the diagnosis of COVID-19.

Patients treated in the ICU and treated only in the ward were compared according to these laboratory data, and the predictive effect of research parameters on admission to the ICU was investigated.

Data collection:

The demographic characteristics, symptoms, underlying comorbidities and chest computed tomography (CT) scans of the patients were obtained from electronic medical records, and patient files prepared by the contact tracing teams of Health Directorate, Antalya province.

Statistical Analysis:

Statistical analysis was made using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY). Descriptive analyses were presented using mean±SD (range), median (range) or n (%), where appropriate. Categorical data were analyzed by Pearson chi-square and Fisher's exact test. Normality assumption was checked by Shapiro Wilks test. Mann–whitney U test and Student's t test were used for analysis of non-normally and normally distributed numerical data, respectively. ROC (Receiver Operating Characteristic) analysis was performed to distinguish patients according to NLR and MPV values and determine the cut-off point in predicting ICU admission, and the results were presented with the Area Under the Curve (AUC), cut-off points, sensitivity and selectivity values. Spearman correlation test was used to analyze the relationship between hospital stay and other variables. Multivariate logistic regression analysis was performed to determine the risk factors affecting ICU admission in patients and the results were presented with Odds Ratio (OR) and 95% confidence intervals. A p-value of less than 0.05 was considered statistically significant.

Ethics Statement:

Prior to the study, approval was obtained from the Ministry of Health COVID-19 Scientific Research Platform and from the Clinical Research Ethics Committee of the University of Health Sciences, Antalya Training and Research Hospital. The study was conducted in accordance with the Helsinki Declaration.

Results:

The average age of the patients in our study group was calculated as 49.48 ± 17.12 (18-92). Of the patients 49 were female (43.8%) and 63 (56.3%) were male. The percentage of patients admitted to the ICU was 19.6% and, died was 5.4%. The

average age and length of hospital stay increased significantly in patients hospitalized in the ICU compared to the patients who were treated only in the service. In addition, malignancy, dyspnea, positive chest CT findings, and mortality were significantly more common in patients admitted to the ICU. While MPV and lymphocyte were found to be statistically significantly lower among laboratory parameters in patients treated in the ICU; RDW, neutrophils, NLR, sedimentation and CRP were significantly higher. Detailed demographic, clinical and laboratory features comparing patients hospitalized only in the ward and those treated in the ICU are presented in Table 1.

Table 1. Comparison of patients treated in only ward and pateints treated in ICU±ward

Variables	Patients treated in only ward (n=90)	Patients treated in ICU±ward (n=22)	p
Age (years)	46.12±16.44(34-58)	63.23±12.55(53-77)	**<0.001[1]**
Female	45.18±16.06(33-52)	64.6±14.91(55-78)	**0.001[1]**
Male	46.84±16.85(34-60)	62.08±10.77(52.5-69)	**0.004[1]**
Gender			
Female	39(43.3%)	10(45.5%)	0.857[2]
Male	51(56.7%)	12(54.5%)	
Underlying comorbidities			
HT	22(24.4%)	6(27.3%)	0.784[2]
DM	13(14.4%)	3(13.6%)	0.999[3]
Chronic pulmanary diseases	8(8.9%)	5(22.7%)	0.128[3]
Cardiovascular disease	5(5.6%)	1(4.5%)	0.999[3]
Chronic renal failure	1(1.1%)	1(4.5%)	0.356[3]
Malignant diseases	1(1.1%)	5(22.7%)	**0.001[3]**
Symptoms			
Fever	36(40%)	9(40.9%)	0.938[2]
Cough	39(43.3%)	12(54.5%)	0.344[2]
Dyspnea	12(13.3%)	15(68.2%)	**<0.001[2]**
Fatigue	37(41.1%)	6(27.3%)	0.232[2]
Diarrhea	7(7.8%)	2(9.1%)	0.999[2]
Anosmia	1(1.1%)	1(4.5%)	0.356[3]
Ageusia	4(4.4%)	1(4.5%)	0.999[3]
Pozitive chest CT findings			
No	51(56.7%)	5(22.7%)	**0.004[2]**
Yes	39(43.3%)	17(77.3%)	
Length of hospital stay (days)			
Ward only	5(4-9)	8(5-11)	**0.042[4]**
ICU only	-	10(8-17)	-
ICU±ward	5(4-9)	20(12-23)	**<0.001[4]**
Mortality			
No	90(100%)	16(72,7%)	**<0.001[3]**
Yes	0(0%)	6(27,3%)	
Laboratory measurements			
WBC (10³/mm³)	5.9(4.6-7.5)	7.15(6.1-9.2)	**0.024[4]**
HGB (g/dL)	13.56±1.62(12.3-14.6)	12.12±2.25(10.5-14)	**0.009[1]**
RDW (%)	12.9(12.5-13.6)	13.7(12.8-15)	**0.004[4]**
MPV (μm³)	10.93±0.97(10.2-11.6)	10.18±0.81(9.6-10.4)	**0.001[1]**
Neutrophil (10³/mm³)	3.5(2.8-5)	5.9(5-6.9)	**<0.001[4]**

Lymphocyte (10^3/mm³)	1.5(1-1,9)	0.6(0,5-0,9)	**<0.001[4]**
NLR	2.48(1.71-3.71)	9.17(3.45-12.4)	**<0.001[4]**
Sedimentation	15.5(9-25)	27.5(20-42)	**<0.001[4]**
CRP (mg/L)	10.3(4.4-34)	94.15(40.8-158.4)	**<0.001[4]**

Data are presented as n (%), mean ± SD (min-max) or median (min-max) values. [1]Student's t test, [2]Pearson chi-square test, [3]Fisher's exact test, [4]Mann-Whitney U test.
ICU=Intensive care unit, HT=Hypertension, DM=Diabetes mellitus, CT=Computerized tomography, WBC=White blood cell, HGB=Hemoglobin, RDW=Red cell distribution width, MPV=Mean platelet volume, NLR=Neutrophil to lymphocyte ratio, CRP=C reactive protein

In all COVID-19 patients, there was a statistically significant positive moderate correlation between the length of hospital stay and age (r = 0.528; p <0.001), sedimentation (r = 0.487; p <0.001) and CRP (r = 0.566; p <0.001); a weak positive correlation with neutrophil (r = 0.218; p = 0.021) and NLR (r = 0.376; p <0.001) and a weak negative correlation with lymphocytes (r = -0.364; p <0.001). In COVID-19 patients treated in the ICU, a moderate positive correlation was found between the length of hospital stay and sedimentation (r = 0.449; p = 0.036) (Table 2).

Table 2. Correlation of study parameters with length of hospital stay

Variables	COVID + patients		Patients treated in only ward		Patients treated in ICU±ward	
	r	p	r	p	r	p
Age (years)	0.528	**<0.001**	0.434	**<0.001**	0.015	0.946
WBC (10^3/mm³)	0.076	0.429	-0.068	0.524	-0.05	0.825
HGB (g/dL)	-0.133	0.161	-0.028	0.791	0.403	0.063
RDW (%)	0.145	0.128	0.005	0.964	-0.396	0.068
MPV (μm³)	-0.077	0.421	0.148	0.164	0.003	0.989
Neutrophil (10^3/mm³)	0.218	**0.021**	0.016	0.878	-0.148	0.510
Lymphocyte (10^3/mm³)	-0.364	**<0.001**	-0.210	**0.047**	0.326	0.139
NLR	0.376	**<0.001**	0.145	0.172	-0.393	0.070
Sedimentation	0.487	**<0.001**	0.383	**<0.001**	0.449	**0.036**
CRP (mg/L)	0.566	**<0.001**	0.439	**<0.001**	0.152	0.500

Spearman correlation test.
ICU=Intensive care unit, WBC=White blood cell, HGB=Hemoglobin, RDW=Red cell distribution width, MPV=Mean platelet volume, NLR=Neutrophil to lymphocyte ratio, CRP=C reactive protein

The multivariate logistic regression analysis was performed to determine the risk factors that independently affect admission to ICU. While age, HGB, RDW and CRP were not determined as risk factors for ICU admission; presence of dyspnea (OR: 7.276; 95% CI: 1.149-46.069; p = 0.035), decreased MPV (OR: 0.099; 95% CI: 0.022-0.448; p = 0.003) and increased NLR (OR: 1.467; 95% CI: 1.053-2.043; p = 0.023) were determined as independent risk factors for ICU admission (Table 3).

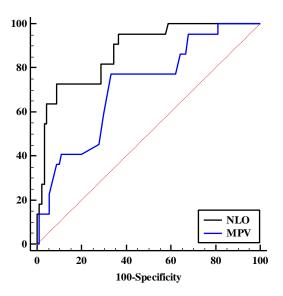**Table 3. Logistic regression of ICU admission predictors**

Variables	OR (%95CI)	p
Age	1.04(0.981-1.102)	0.191
Dyspnea	7.276(1.149-46.069)	0.035

HGB (g/dL)	1.404(0.741-2.659)	0.298
RDW (%)	1.354(0.623-2.945)	0.444
MPV (µm³)	0.099(0.022-0.448)	**0.003**
NLR	1.467(1.053-2.043)	**0.023**
CRP (mg/L)	1.004(0.986-1.023)	0.641

ICU=Intensive care unit, WBC=White blood cell, HGB=Hemoglobin, RDW=Red cell distribution width, MPV=Mean platelet volume, NLR=Neutrophil to lymphocyte ratio, CRP=C reactive protein

As a result of the ROC analysis, the optimal cut-off values determined by Youden index for NLR and MPV in predicting admission to ICU are given in Figure 1. Optimal cut-off values for NLR was >5.3 [(AUC = 0.876 (95% CI: 0.800-0.930; p <0.001); sensitivity = 72.73%; specificity = 91.11%)] and for MPV was ≤10.4 [(AUC = 0.715 (95% CI: 0.622-0.797; p = 0.001); sensitivity = 77.27%; specificity = 66.67%)] for predicting ICU admission. According to the ROC analysis findings, it was determined that the AUC value of NLR was higher than MPV (p = 0.049) (Figure 1).

	AUC	Cut-off value	Sensitivity (%)	Spesificity (%)	p value (NLR and MPV)
NLR	0.876(95% CI: 0.800-0.930; p<0.001)	>5,3	72.73 (95%CI: 49.8-89.3)	91.11 (95%CI: 83.2-96.1)	**0.049**
MPV	0.715(95% CI: 0.622-0.797;	≤10,4	77.27 (95%CI: 54.6-92.2)	66.67 (95%CI: 55.9-76.3)	

p=0.001)				

ICU=Intensive care unit, MPV=Mean platelet volume, NLR=Neutrophil to lymphocyte ratio

Discussion:

This study revealed that NLR and RDW are statistically significantly higher and MPV is significantly lower in COVID-19 patients treated in ICU than patients treated in only ward. Decreased MPV and increased NLR were identified as independent risk factors for ICU admission. While the optimal cut-off value for NLR was calculated as > 5.3 with 72.73% sensitivity and 91.11% specificity; for MPV was calculated as ≤10.4 with 77.27% sensitivity and 66.67% specificity in predicting ICU admission.

It is obvious that in the management of the COVID-19 pandemic, which continues to strain the capacity of health systems, making the prediction of the clinical course of infected patients with objective parameters is important in preventing the density in health institutions. Occurrence of health conditions that require ICU hospitalization in patients strains the capacity of the second and third level health services. Laboratory parameters are effective in predicting the clinical course to help clinicians in patient management. There are many studies that have been and are being conducted in order to predict the clinical course of infected patients and to prevent the disease course from worsening with early intervention. Although there are various studies[15-17] evaluating the changes in hematological parameters in COVID-19 disease in the literature, the number of studies investigating the laboratory parameters that can predict the severity of the disease at the first application and / or diagnosis is more limited. Many studies agree that WBC, neutrophil increase and HGB decrease in patients infected with SARS-cov2, especially high CRP and low lymphocyte can be prognostic markers.[18] The results of our study also support these studies.

We found it appropriate to focus on these two hematological parameters in this part of the study, since increasing NLR and decreasing MPV were identified as independent risk factors for ICU admission in our study. In one of the studies evaluating NLR, thought to have prognostic significance, Liu et al. Studied 115 COVID-19 patients and found the risk of developing severe disease as 50% in those with age ≥ 50 and NLR ≥

3,13 at the time of first admission.[2] In their study with 161 COVID-19 patients, Wang et al. Found that NLR was statistically significantly higher in those who had severe infection than those who had more moderate infection.[19] Lagadinou et al. Stated in their study with 64 adult patients in Greece that NLR, LDH, d-dimer, CRP, fibrinogen and ferritin could predict the severity of SARS-cov2 infection.[20] In our study, the presence of dyspnea, decreased MPV and increased NLR were determined as independent risk factors for ICU admission, and NLR > 5.3 and MPV ≤ 10.4 were found as optimal cut-off values for predicting admission to ICU. One of the parameters that can give an idea to examine the course of COVID-19 patients is the mean platelet volume expressed as MPV. In a study by Mermutluoğlu et al. Compared with hospitalized COVID-19 patients and healthy individuals, MPV levels at presentation were found to be significantly higher in the patient group compared to the control group. It was stated that the MPV level was lower on the 5th day of the follow-up compared to the time of first presentation in the patient group, and it was stated that the high MPV level in the early stage of the disease and the low course in the follow-up may be related to the prognosis and therefore MPV level can be used as a good prognostic factor in the follow-up of COVID-19 infection. [21] In his study with diabetic patients, Özder evaluated the patients before, during and after SARS-cov-2 infection and showed that MPV value increased significantly during COVID-19 infection, and fell back to its original level after laboratory-approved recovery. In addition, he divided the patients into three groups as asymptomatic COVID-19, symptomatic COVID-19 and severe COVID-19 and although not statistically significant, MPV level was found to be the highest in severe COVID-19 patients.[22] Aktaş et al. Conducted a study with the laboratory results (at their first admission to the emergency department) of COVID-19 patients who were hospitalized in the service and intensive care unit, and they found that MPV levels above 65 years of age were high, but this elevation level was not statistically significant. When they compared the patients hospitalized in the service and ICU, they stated that the MPV level was higher in the patients hospitalized in the service than the patients in the intensive care unit, but this difference was not statistically significant too.[23] Contrary to Özder's study, MPV level was found to be

statistically significantly lower in those who had severe COVID-19 infection in our study, while Aktaş's research results and our results support each other.

The fact that our study was retrospective, that the MPV value was interpreted according to a single laboratory result due to its cross-sectional nature, and that laboratory parameters were not compared with repetitive tests during the clinical course of the patients can be shown as the limitations of our study. However, the fact that we found a high specificity and sensitivity and a cut-off value in the ROC curve, especially for NLR, makes our study strong.

Conclusion:

NLR, which is checked at the first admission in patients with suspected COVID-19, is an easy, fast, cheap and very valuable test in determining the severity of SARS-cov2 infection and predicting the need for intensive care. Due to the difference in data on MPV in the literature, this parameter needs to be repeatedly evaluated and examined in a wider patient group and in various stages of the disease.

Conflict of interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References:

[1] WHO. Available online: https://www.who.int/emergencies/diseases/novel-coronavirus-2019 (accessed on 01 December 2020).

[2] Liu J, Liu Y, Xiang P, et al. Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage. J Transl Med 2020;18:206.

[3] CDC. Available online: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html?CDC_AA_refval=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019ncov%2Fabout%2Fsymptoms.html (accessed on 01 December 2020).

[4] Lowenstein CJ, Solomon SD. Severe COVID-19 Is a Microvascular Disease. Circulation 2020;142(17):1609-11.

[5] Posso M, Comas M, Roman M, et al. Comorbidities and Mortality in Patients

With COVID-19 Aged 60 Years and Older in a University Hospital in Spain. Archivos de Bronconeomologia 2020;56(11):756-8.

[6] Harrison SL, Fzio-Eynullayeva, Lane DA, Underhill P, Lip GYH. Comorbidities associated with mortality in 31,461 adults with COVID-19 in the United States: A federated electronic medical record analysis. Plos Med 2020;17(9):e1003321.

[7] Kılınçalp S, Çoban Ş, Akıncı H, Hamamcı M, Karaahmet F, Coşkun Y. Neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, and mean platelet volume as potential biomarkers for early detection and monitoring of colorectal adenocarcinoma. Eur J Cancer Prev 2015;24(4):328-33.

[8] Lee YH, Song GG. Neutrophil-to-lymphocyte ratio, mean platelet volume and platelet-to-lymphocyte ratio in Behçet's disease and their correlation with disease activity: A meta-analysis. Int J Rheum Dis 2018;21(12):2180-7.

[9] Amir T, Toujani S, Khaled SB, et al. The Neutrophil-lymphocyte ratio in patients with community-acquired pneumonia. European Respiratory Journal 2018;52(62):PA2620.

[10] Ghosh P, Gerhardson I, Dahlen B, Bossios A. Neutrophil-to-lymphocyte ratio in patients with bronchiectasis and its correlation with low-grade inflammation; preliminary results from a single tertiary center. European Respiratory Journal 2020;56(64):2049.

[11] Kaya Y, Taş N, Çanakçı E, et al. Relationship of neutrophil-to-lymphocyte ratio with presence and severity of pneumonia. J Clin Anal Med 2018;9(5):452-7.

[12] Farghly S, Abd-Elkader R, El Zohne RA, Abd El-Kareem DM. Mean platelet volume change (MPV) and red blood cell distribution width (RDW) as promising markers of community-acquired pneumonia (CAP) outcome. The Egyptian Journal of Bronchology 2020; 14:23.

[13] Ekin N, Araç E, Araç S. Can Hematological Parameters Predict the Severity of Acute Pancreatitis? Duzce Med J 2020;22(2):79-83.

[14] Wang C, Zhang H, Cao X, et al. Red cell distribution width (RDW): a prognostic indicator of severe COVID-19. Ann Transl Med 2020;8(19):1230.

[15] Usul E, Şan İ, Bekgöz B, Şahin A. Role of hematological parameters in COVID-19 patients in the emergency room. Biomark Med 2020; 14(13):1207-15.

[16] Fan BE, Chong VCL, Chan SSW, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol 2020; 95:E131-53.

[17] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clin Chem Lab Med 2020;58(7):1131-4.

[18] Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clin Chem Lab Med 2020;58(7):1021-8.

[19] Wang C, Deng R, Gou L, et al. Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. Ann Transl Med 2020;8(9):593.

[20] Lagadinou M, Salomou EE, Zareifopoulos N, marangosm, Gogos C, Velissaris D. Prognosis of COVID-19: Changes in laboratory parameters. Infez Med 2020;28(1):89-95.

[21] Mermutluoğlu Ç, Dursun R, Aktar F, et al. Evaluation of Inflammatory and Hematological Parameters in Patients Diagnosed with COVID-19. Authorea 2020.

[22] Özder A. A novel indicator predicts 2019 novel coronavirus infection in subjects with diabetes. Diabetes Res Clin Pract 2020; 166:108294.

[23] Aktaş A, Sener K, Yılmaz N, Tunç M, Yolcu S. Is Mean Platelet Volume Useful for Predicting the Prognosis of COVID-19 Diagnosed Patients? IJRSMHS 2020;5(7):8-11.