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Original Scientific Paper

EVALUATION OF THE RELATIONSHIP OF MPV, RDW AND PVI PARAMETERS WITH DISEASE SEVERITY IN COVID-19 PATIENTS

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SUMMARY – Coronavirus was first detected in three severe pneumonia cases in Wuhan, China, in December 2019. Studies on red cell distribution width (RDW-CV) and mean platelet volume (MPV) laboratory parameters, which can be examined in complete blood count in COVID-19 patients, are still very limited. However, to the best of our knowledge, there are no studies examining the relationship between platelet volume index (PVI) and disease severity in COVID-19 patients, which was evaluated in this study. The aim of this study was to evaluate the relationship of disease severity in COVID-19 patients with their MPV, RDW, and PVI parameters. The study included 92 COVID-19 patients as a study group and 84 healthy individuals as control group. All laboratory data and radiological images were scanned retrospectively from patient files and hospital information system. Evaluation of the RDW-CV and MPV blood parameters, and PVI measured in COVID-19 patients yielded statistically significant differences according to the disease severity. We suggest that RDW-CV and PVI, evaluated within the scope of the study, may be the parameters that should be considered in the early diagnosis of the disease, from the initial stages of COVID-19. In addition, we think that the RDW-CV and MPV laboratory parameters, as well as PVI, which all are simple, inexpensive and widely used hematologic tests, can be used as important biomarkers in determining COVID-19 severity and mortality.

Key words: *COVID-19; Disease severity; Mean platelet volume; Red cell distribution width; Platelet volume index*

Introduction

Coronavirus was first detected in three severe pneumonia cases in Wuhan, China, in December 2019. Besides its flu-like symptoms, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes multiorgan failure and death with its rapid progression. This very contagious disease was accepted as a worldwide pandemic by the World Health Organization as of February 2020[1,2]. Coronavirus (COVID-19), which was first thought to be transmitted from bat, belongs to the betacoronavirus family, which is a subtype of the SARS group viruses. To exert its effect, coronavirus binds to the angiotensin-converting enzyme-2 receptor on the cell surface[3].

Pneumonia in COVID-19 patients is thought to be associated with neutrophil infiltration in the lungs and increased serum proinflammatory cytokines and chemokines, together with a high onset viral load[4]. Some studies have reported changes in hematologic parameters during acute infection caused by SARS-CoV-2[5-11].

Red cell distribution width (RDW), mean platelet volume (MPV), and platelets are some of the hematologic parameters. RDW is a routinely reported marker of complete blood count (CBC) and represents a mea-

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sure of red blood cell size heterogeneity[12]. The RDW laboratory parameter has been associated with many diseases such as social pneumonia, hypoxemia, and pulmonary embolism[13-15].

Platelets are one of the hematologic parameters as essential cells for host defense and repair, in addition to being known as the main effectors of hemostasis[16]. Platelets contribute to a variety of immune responses and a range of inflammatory disorders in the lungs and other organs[17,18]. Studies have reported that platelet count is a biomarker which is independently associated with disease severity and mortality risk in critically ill patients in intensive care unit (ICU)[19-21]. Recent studies have reported that platelet parameters may contribute to the diagnosis of diseases and have a prognostic value in some pathologies[22]. The MPV laboratory parameter is a promising marker that may indicate systemic inflammation[23,24]. The literature emphasizes that the MPV blood parameter can be useful in the diagnosis of inflammatory diseases such as pneumonia, as well as in the prognosis evaluation in chronic diseases such as tumors, diabetes, and coronary heart disease[25-27].

Since the COVID-19 pandemic is a recent situation, treatment and vaccination studies are still ongoing. Treatment methods are changing every day due to the development of new unknown symptoms and organ failure, and the literature is renewed in the light of new studies. Preventing progression of the disease with early diagnosis and effective treatment strategies of COVID-19, and reducing mortality is one of the main goals. Studies on RDW-CV and MPV laboratory parameters, which can be examined in CBC in COVID-19 patients, are still very limited. Platelet volume index (PVI; MPV/platelet ratio) can contribute to clarifying the activities of platelets that are involved in inflammation[28].

In some previous studies, it has been reported that PVI is one of the thromboembolism markers, and may be an important marker in evaluating the risk of cardiovascular disease in diabetes and hypertension[29,30]. However, to the best of our knowledge, there are no studies examining the relationship between PVI and disease severity in COVID-19 patients, and it was investigated in the present study.

In this study, we aimed to evaluate the relationship of disease severity in COVID-19 patients with their MPV, RDW and PVI parameters.

Subjects and Methods

Study participants

The study was conducted between March 15, 2020 and June 20, 2020 as a retrospective single-center study. The study included 92 COVID-19 patients as a patient group and 84 healthy individuals as control group. The study was approved by the Ethics Committee of the Yozgat Bozok University as of July 22, 2020, decision no. 2020-06-147. The study was carried out in accordance with the Helsinki Declaration. The patient group consisted of COVID-19 patients admitted to the Emergency Department with various symptoms and complaints, whose diagnosis was confirmed by real-time reverse transcription-polymerase chain reaction (rRT-PCR). The healthy control group consisted of people who presented to the hospital for general examination. COVID-19 patients were subdivided according to the diagnostic criteria of the COVID-19 (2019-nCoV Disease) Guide published by the Turkish Ministry of Health and updated with recent developments[31]. Accordingly, patient groups were defined as group 1 with mild severity, group 2 with medium severity, group 3 with high severity, and group 4 as critical cases. Group 1 patients had mild clinical symptoms and group 2 patients had fever, respiratory symptoms and radiological findings of pneumonia. Patients with any of the symptoms of shortness of breath, respiratory rate (RR) ≥30/min, oxygen saturation value ≤93% at rest, and (PaO2/FiO2) ≤300 mm Hg were included in group 3. Patients with respiratory failure requiring mechanical ventilation, clinical picture of shock or organ failure were included in group 4. In order to facilitate the clinicians' planning of COVID-19 patient follow up, in addition to the patient group diagnostic guide, it was also planned to evaluate COVID-19 patients in two groups where one group included patients with serious to critical severity and the other group included patients with mild to moderate severity.

Data collection

Patients included in the study were analyzed for age, gender, hospital admission symptoms, chronic disease history, clinical outcomes, survival, and CBC parameters determined on a Sysmex XN-1000 hematologic analyzer (Sysmex Co., Japan). Patient serum biochemistry was performed on a Roche Cobas C501

chemistry analyzer (Roche Diagnostics, Mannheim, Germany). All laboratory data and radiological images were scanned retrospectively from patient files and hospital information system. Data on patient clinical outcomes and survival were obtained from the hospital information system. PVI was calculated as PVI=MPV value (fl)/Plt *per* 1000 x100[32], and then recorded.

Statistical analysis

All data were statistically analyzed with the SPSS version 20.0 for Windows. Kolmogorov-Smirnov test and skewness-kurtosis method were used to evaluate normal distribution of all variables. Additionally, normal data distribution was evaluated by a histogram. The χ^2-test and Fisher exact test were used to compare proportions of categorical variables. Descriptive statistics was used to analyze patient demographic data. Numerical values were expressed as mean ± standard deviation and minimum-maximum values. Student's t-test was used for parametric variables within the scope of clinical research. Kruskal-Wallis H test and Mann-Whitney U test were used for statistical evaluation of non-parametric variables depending on their categorical (nominal or ordinal) and numerical independence status. Spearman rank correlation method was used for correlation of nonparametric data. According to clinical results of COVID-19 patients, RDW-CV, MPV and PVI values were evaluated with the receiver-operating characteristic curve (ROC). On ROC analysis, parameters with the area under the curve (AUC) value below 0.6 and without statistical significance ($p>0.05$) were excluded. The level of statistical significance was set at $p<0.05$.

Results

Between March 15, 2020 and June 20, 2020, 230 patients were admitted to the Emergency Department due to upper and lower respiratory tract infections. Of these, 92 patients had positive PCR test result, whereas 128 patients were diagnosed with other upper and lower respiratory tract infections and were excluded from the study. In our study, data on 92 patients admitted to the hospital with confirmed COVID-19 diagnosis were analyzed (Table 1). There was no significant difference in median age between 92 confirmed COVID-19 patients and 84 controls ($p>0.05$). In the patient group, there were 47 (51.1%) male and 45 (48.9%) female patients. In the control group, there were 43 male and 41 female subjects, yielding no significant between-group difference in gender composition ($p>0.05$).

Demographic and clinical characteristics of COVID-19 patients and healthy control group

Demographic characteristics and clinical findings of the 92 COVID-19 patients and 84 healthy control subjects are summarized in Table 1. Median age of COVID-19 patients and control subjects was 61.3 and 58.5 years, with no significant difference between the groups ($p<0.05$). Although median age of the COVID-19 patient groups was higher in critically ill patients, there was no statistically significant difference between the groups ($p>0.05$). Similarly, even though there was no statistically significant difference in gender distribution by clinical groups in the COVID-19 patient group, the proportion of male patients was higher than of female patients, especially in severe COVID-19 cases. Fever, dyspnea and cough were the most common clinical symptoms in study patients, as well as in COVID-19 patients with moderate disease severity. There was a statistically significant difference in the symptoms of dyspnea and joint pain ($p<0.05$) between the groups. Comorbidities were recorded in 54.9% (n=51) of COVID-19 patients. Table 1 shows comorbidity distribution in the patient and control groups. Accordingly, disease severity in patients with chronic obstructive pulmonary disease (COPD) and coronary artery disease comorbidities was higher in the severe and critical groups, and this difference was significantly higher as compared with other patient groups (mild and moderate) ($p<0.05$).

Laboratory characteristics of COVID-19 patients and healthy control group

Differences in laboratory findings between COVID-19 patients and control group are shown in Table 2. Patient group had higher leukocyte levels ($p<0.05$) and lower total protein levels ($p<0.05$) than control group. Besides, hypoalbuminemia (serum albumin ≤40 g/L) and lymphopenia (lymphocyte count ≤1.1x10^9/L) were observed in the COVID-19 patient

Table 1. Baseline clinical characteristics of COVID-19 patients and control subjects at admission

Characteristic	Control group, median	COVID-19 group, median	p value	Mild COVID-19 patients group median	Moderate COVID-19 patients group median	Severe COVID-19 patients group median	Critical COVID-19 patients group median	p value
Age (yrs) (min-max)	58.5 (22-82)	61.3 (23-94)	0.205	57 (28-73)	60.5 (41-82)	61 (23-94)	70.5 (35-81)	0.201
Gender			0.531					0.271
Male, n (%)	51 (55.4%)	44 (52.3%)		8 (47.1%)	24 (53.3%)	12 (75%)	5 (41.7%)	
Female, n (%)	41 (44.6%)	40 (47.6%)		9 (52.9%)	21 (46.7%)	4 (25%)	7 (58.3%)	
Comorbidity	41 (45.1%)	51 (54.3%)	0.264	10 (58.8%)	22 (48.9%)	7 (43.8%)	10 (83.3%)	0.141
Hypertension	25 (28.4%)	33 (36.7%)		6 (35.3%)	14 (31.1%)	7 (43.8%)	6 (50%)	0.598
Diabetes	18 (20.4%)	22 (24.4%)		4 (23.5%)	8(17.8%)	5 (31.3%)	5 (41.7%)	0.331
COPD	9 (10.2%)	12 (13.3%)		1 (5.9%)	2 (6.7%)	3 (12.5%)	6 (50%)	0.001*
CAD	9 (10.7%)	11 (12.2%)		0	4 (8.9%)	4 (25%)	3 (25%)	0.039*
Cerebrovascular disease	1 (1.1%)	1 (1.1%)		-	1 (2.2%)	0	0	0.780
Chronic kidney disease	5 (5.6%)	4 (4.4%)		1 (5.9%)	3 (6.7%)	0	0	0.592
Viral hepatitis	-	1 (1.1%)		0	0	0	1 (8.3%)	0.056
Asthma	6 (6.8%)	4 (4.4%)		0	2 (4.4%)	1 (6.3%)	1 (8.3%)	0.858
Symptom-sign								
Fever	-	47 (51.6%)		7 (14.9%)	24 (51.1%)	9 (19.1%)	7 (14.9%)	0.665
Dyspnea	-	46 (50.5%)		6 (13%)	20 (43.5%)	11 (23.9%)	9 (19.6%)	0.045*
Cough	-	42 (46.2%)		6 (14.3%)	23 (54. %8)	6 (14.3%)	7 (16.7%)	0.418
Weakness	-	27 (29.7%)		8 (29.6%)	14(51.9%)	2 (7.4%)	3(11.1%)	0.230
Sore throat	-	9 (9.9%)		4 (44.4%)	2 (22.2%)	2 (22.2%)	1 (11.1%)	0.226
Anosmia	-	5 (5.5%)		1 (20%)	2 (40%)	-	2 (40%)	0.271
Diarrhea	-	11 (12.1%)		2 (18.2%)	4 (36.4%)	2 (18.2%)	3 (27.3%)	0.506
Chest pain	-	5 (5.5%)			3 (60%)	1 (20%)	1 (20%)	0.372
Headache	-	4 (4.4%)		1 (25%)	1 (25%)	2 (50%)	-	0.306
Joint pain	-	17 (18.7%)		8 (47.1%)	7 (41.2%)	-	2 (11.8%)	0.008*

*p<0.05 was considered statistically significant; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease

group (p<0.05). L-lactate dehydrogenase (LDH) values were significantly higher than in healthy controls (p<0.05); however, RDW-CV levels and PVI were significantly higher in the COVID-19 patient group compared to healthy controls (p<0.05). Ferritin, C-reactive protein (CRP) and sedimentation acute phase reactants were significantly higher compared to the healthy control group (p<0.05). As shown in Table 2, difference in MPV values was not statistically significant (p=0.387).

Laboratory parameters according to disease severity in COVID-19 patients

Laboratory parameters of COVID-19 patients divided into 4 groups were compared to investigate the effect of disease severity on blood parameters. Differences in laboratory findings among groups are shown in Table 3. Analysis of the RDW-CV and MPV blood parameters, and PVI (in this study investigated in COVID-19 patients) yielded statistically significant difference according to disease severity (p<0.05). However, difference in the platelet laboratory param-

Table 2. Results of laboratory parameters in COVID-19 patients and control group

Laboratory parameter	Control group (mean ± SD)	COVID-19 patient group (mean ± SD)	p value
Red blood cell distribution width-CV (RDW-CV)(%)	12.8±0.7	13.6±1.3	0.000*
Mean platelet volume (MPV), fl	10.3±0.94	10.1±1.06	0.387
PVI (MPV/platelet ratio)	3.2±1.2	5.7±2.5	0.000*
Total protein (65-85 g/L)	73.2±4.5	69.8±7.8	0.048
Albumin (40-55 g/L)	46.13±2.5	39.8±4.8	0.000*
LDH, U/L	172.5±26	247.6±55.2	0.000*
Ferritin, mL/ng	364.5±54.4	58.4±49.9	0.003*
C-reactive protein (0-6 mg/L)	1.5±0.9	53.12±10.4	0.010*
Hemoglobin, g/L	14.2±1.2	13.8±1.8	0.276
Platelet x10^9/L	293±55.2	209.4±58.3	0.000*
WBC (4.0-10.0×10^9/L)	7.2±1.3	10.04±3.8	0.023*
Neutrophil (2.0-6.0×10^9/L)	4.1±1.23	5.7±3.5	0.013*
Lymphocyte (1.1-3.2×10^9/L)	2.3±0.7	1.6±0.9	0.000*

SD = standard deviation; PVI = platelet volume index; LDH = L-lactate dehydrogenase; WBC = white blood count; Mann-Whitney U test was used on statistical analysis; *p<0.05 was considered significant

Table 3. Laboratory parameters according to COVID-19 severity

Laboratory parameter	Mild COVID-19 group (mean±SD)	Moderate COVID-19 group (mean±SD)	Severe severity COVID-19 group (mean±SD)	Critical severity COVID-19 group (mean±SD)	p value
Red blood cell distribution width-CV (%)	13.2±1.9	13.5±0.8	13.6±1.19	14.4±1.16	0.000*
Mean platelet volume, fl	9.9±0.8	10.1±1.08	10.2±1.08	10.4±1.2	0.044*
PVI	5.01±1.8	5.4±2.04	5.8±2.02	7.8±4.4	0.000*
Total protein (65-85 g/L)	73±3.3	72.4±5.5	68.8±4.21	67.7±4.8	0.048*
Albumin (40-55 g/L)	40.8±3.3	40.2±4.2	40.1±4.1	36.2±3.8	0.000*
LDH, U/L	230.4±70	240.7±65	264.8±75	270.4±85	0.000*
C-reactive protein(0-6 mg/L)	26.8±4.2	43.7±7.2	57.7±6.8	102.5±20.7	0.010*
Platelet x10^9/L	219.7±104	203±52.6	201.6±80	200±68	0.704
WBC (4.0-10.0 × 10^9/L)	7.6±3.1	7.8±4	8±3.5	9.6±3.8	0.023*
Neutrophil (2.0-6.0×10^9/L)	4.1±1.23	5.7±3.5	6.1±3.3	6.8±3.9	0.013*
Lymphocyte (1.1-3.2×10^9/L)	1.9±0.8	1.6±0.9	1.5±0.6	1.19±0.8	0.000*

SD = standard deviation; LDH = L-lactate dehydrogenase; WBC = white blood count; PVI = platelet volume index; Kruskal-Wallis H test was used on statistical analysis; *p<0.05 was considered significant

eter among the disease severity groups was not statistically significant (p>0.05). Correlation between disease severity and laboratory parameters is shown in Table 4. Accordingly, RDW-CV, MPV and PVI values were found to have a moderately positive correlation with disease severity. Evaluation of the patient survival rate showed that 78% (n=71) of the patients survived and 22% (n=20) deceased. Analysis of lung images of COVID-19 patients showed involvement of the right upper lobe in 63.2% (n=53), right middle lobe in 65.5%

Table 4. Correlation between disease severity and laboratory parameters

Laboratory parameter	Correlation coefficient (r_s)	p value
RDW-CV	0.509	0.000*
MPV	0.383	0.028*
PVI	0.371	0.006*

Spearman rank correlation method was used on statistical analysis; *p<0.05 was considered significant; RDW-CV = red blood cell distribution width; MPV = mean platelet volume; PVI = platelet volume index

(n=57), right lower lobe in 77.9% (n=67), left upper lobe in 64% (n=54) and left lower lobe in 86% (n=74) of the patients.

ROC analysis for RDW-CV, MPV and MPV/Plt parameters

Laboratory parameters of the COVID-19 patients divided into mild-moderate and severe-critical severity groups according to their clinical findings are shown in Table 5. By dividing COVID-19 patients into two groups of mild-moderate and severe-critical severity, the AUC, cut-off, sensitivity, and specificity of RDW-CV and MPV laboratory parameters, and MPV/Plt ratio were analyzed with ROC curve to guide the clinician concerning diagnostic efficacy and follow-up of COVID-19 patients. However, mortality rates, cut-off points, sensitivity and specificity of these laboratory parameters were also analyzed with ROC curve in COVID-19 patients. The cut-off values, AUC, sensitivity and specificity of RDW-CV, MPV and MPV/Plt parameters, which were found to be statistically significant, were determined to be used in distinguishing the clinical pictures of COVID-19 cases and in their follow-up in critical care units. For the RDW-CV parameter, the AUC, cut-off, sensitivity and specificity were 0.734%, 13.65%, 95% and 66%, respectively. The AUC, cut-off, sensitivity, specificity of the MPV/Plt ratio were 0.745, 0.057, 80% and 65%, respectively. The AUC, cut-off, sensitivity and specificity of the MPV parameter were 0.714%, 11.05, 55% and 81%, respectively (Table 6, Fig. 1).

The AUC, cut-off, sensitivity and specificity for the RDW-CV parameter in predicting mortality were 0.800%, 13.75%, 89.3% and 71%, respectively. The AUC, cut-off, sensitivity and specificity of the MPV/Plt

Table 5. Laboratory parameters according to clinical groups of COVID-19 patients

Laboratory parameter	Mild-moderate COVID-19 group (mean ± SD)	Severe-critical COVID-19 group (mean ± SD)	p value
Red blood cell distribution width-CV (%)	13.2±1.9	13.6±1.19	0.000*
Mean platelet volume, fl	9.9±0.8	10.2±1.08	0.043*
PVI	5.3±1.9	6.7±2.3	0.000*
C-reactive protein (0-6 mg/L)	26.8±4.2	57.7±6.8	0.010*
Platelet x10^9/L	219.7±104	201.6±80	0.000*
WBC (4.0-10.0 × 10^9/L)	7.8±3.8	8.79±3.7	0.023*
Neutrophil (2.0-6.0×10^9/L)	5.5±3.4	6.4±3.6	0.013*
Lymphocyte (1.1-3.2×10^9/L)	1.6±0.7	1.5±0.7	0.000*

SD = standard deviation; WBC = white blood count; PVI = platelet volume index; Mann-Whitney U test was used on statistical analysis; *p<0.05 was considered significant

Table 6. ROC analysis of laboratory parameters for use in COVID-19 severity monitoring plan

Laboratory parameter	Cut-off value	AUC	p value	95% CI (lower bound- upper bound)	Sensitivity %	Specificity %
RDW-CV, %	13.65	0.734	0.001	0.634-0.834	95	66
MPV, fl	11.05	0.711	0.004	0.538-0.840	55	81
PVI	0.057	0.745	0.001	0.627-0.864	80	65

ROC = receiver operating characteristic curve; AUC = area under curve; 95% CI = 95% confidence interval; RDW = red cell distribution width; MPV = mean platelet volume; PVI = platelet volume index

ratio were 0.650, 0.057, 68% and 63%, respectively. Although it was found to be statistically significant in predicting mortality, as shown in Table 7, the specificity and sensitivity of the MPV parameter were found to be lower than RDW-CV and MPV/Plt ratio (Fig. 2).

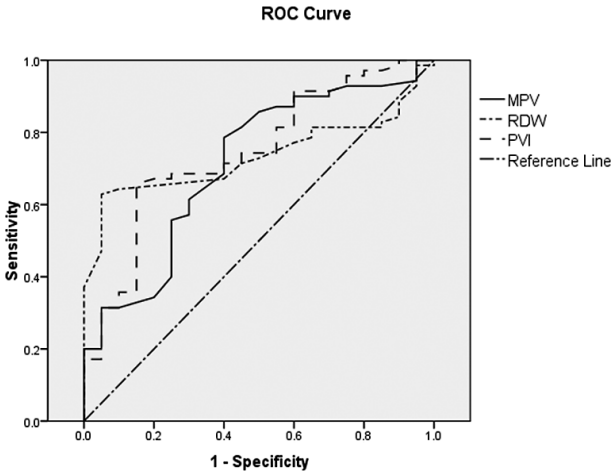

Fig. 1. ROC analysis of laboratory parameters according to clinical groups of COVID-19 patients.

MPV = mean platelet volume; RDW = red blood cell distribution width; PVI = platelet volume index

Discussion

COVID-19 is an acute infectious disease caused by a new coronavirus (SARS-CoV-2) and can progress from mild symptoms such as fever, dry cough, joint pain, and sore throat to a severe picture such as shortness of breath, respiratory failure and multiple organ dysfunction syndrome[33]. However, there also are asymptomatic patients presenting no symptoms. With increase in the number of asymptomatic COVID-19 patients, the potential risk of contagion increases[34]. Early diagnosis of the disease and active and effective treatment plans anticipating and containing exacerbation of the disease can reduce mortality. In the light of constantly updated information on COVID-19, easy-to-use, low-cost and widely used laboratory tests are important in determining the severity of the disease. Comparison of hematologic parameters in our study revealed that COVID-19 patient group had significantly higher white blood cell (WBC), neutrophil, LDH, ferritin and CRP values compared to the healthy control group ($p<0.05$). However, lymphocytes, platelets, total protein and albumin were significantly lower in COVID-19 patients ($p<0.05$). These data are consistent with those reported in the literature[35-38]. However, many studies report that lymphopenia is caused by depletion of lymphocytes by the immune system organs after lymphocyte invasion of SARS-CoV-2[35,36,39,40].

Evaluation of the RDW-CV laboratory parameter, which was investigated in this study, showed that this parameter was significantly higher in COVID-19 patients as compared with control group. It was also on rise in the critical patient group, and this difference

Table 7. ROC analysis of laboratory parameters to predict mortality

Laboratory parameter	Cut-off value	AUC	p value	95% CI (lower bound- upper bound)	Sensitivity %	Specificity %
RDW-CV %	13.75	0.800	0.000	0.634-0.834	89.3	71
MPV, fl	10.1	0.630	0.049	0.538-0.840	53	61
PVI	0.057	0.745	0.023	0.627-0.864	68	63

ROC = receiver operating characteristic curve; AUC = area under curve; 95% CI = 95% confidence interval; RDW = red cell distribution width; MPV = mean platelet volume; PVI = platelet volume index

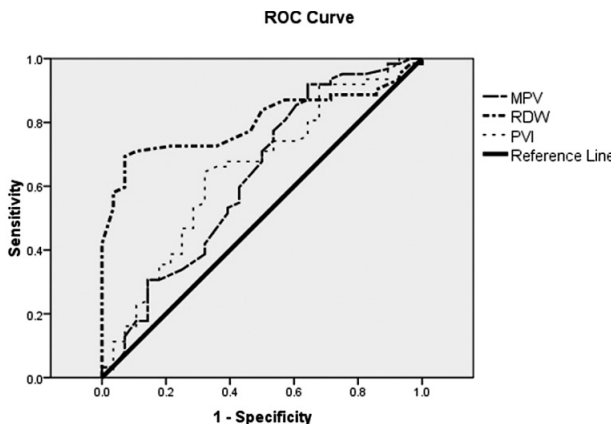

Fig. 2. Laboratory parameters for predicting mortality by ROC analysis.

MPV = mean platelet volume; RDW = red blood cell distribution width; PVI = platelet volume index

was significantly higher among patient groups. Furthermore, our study found that this parameter was significantly higher in COVID-19 patients in terms of predicting mortality. Regarding the RDW-CV parameter, when damage to the immune system and suppression of the bone marrow occurs in the human body, compensatory hyperplasia of the erythroid cell line is activated. However, a large number of immature red blood cells are released, which in turn increases the RDW. The RDW-CV laboratory parameter is increased in cases that develop multiorgan failure such as severe sepsis[41]. Similarly, in COVID-19, an increase in the RDW-CV laboratory parameter is common due to damage to the immune system. However, Kim *et al*. report that the RDW parameter was a predictor of mortality during multiorgan failures such as sepsis and septic shock[41]. Considering that COVID-19 may also progress to multiorgan failure, the RDW-CV results in our study support those literature reports. Accordingly, we suggest that the RDW-CV parameter may be a predictor of mortality in COVID-19 patients. In their study on COPD patients, Kalemci *et al*. found that the RDW laboratory parameter increased significantly with the disease severity and development of hypoxemia[42]. The fact that COVID-19 severely affects the lungs and causes hypoxemia in the advanced stages of the disease supports the RDW-CV results in our study.

Platelets are important immune cells that play a role in hemostasis and coagulation, as well as in the immune and inflammatory mechanisms[43]. Differences in platelet count and activity are associated with various diseases[44,45]; in acute respiratory failure, platelets tend to decrease as a result of damage to the lungs[46]. In a study conducted in atypical pneumonia patients, platelets were also decreased[47]. In our study, platelet levels were found to be significantly lower in COVID-19 patients compared to healthy controls. Considering that SARS-CoV-2 causes damage to the lungs, our findings are similar to the low platelet levels reported in the literature. However, another result of this study was that the platelet laboratory parameter did not help us evaluate the severity of the disease. Similarly, Wang *et al*. in their COVID-19 study report that platelet levels were not effective in evaluating the severity of the disease[48], which is similar to the findings in our study.

Evaluation of the MPV laboratory parameter, also investigated in this study, showed that there was no difference in MPV values between the healthy control group and COVID-19 patients. Korniluk *et al*. report that MPV acted as an acute phase reactant in different inflammatory conditions[49]. The increase in the MPV parameter during the inflammatory state is probably associated with increase in the percentage of large platelets due to the intracellular synthesis of pro-coagulatory and pro-inflammatory factors, and degranulation of granules[50]. It has been reported that a change in the MPV laboratory parameter is observed in sepsis and systemic inflammatory response syndrome compared to healthy population[51-53]. This difference between our study and previous studies has emerged because the selected patient population had a more severe clinical course in those studies. Moreover, in our study, difference was found between the groups on evaluating the severity of the MPV parameter, and there was an increasing trend towards the severe patient group. In our study, the fact that the MPV values in severe COVID-19 patients were significant compared to other COVID-19 groups can be useful in predicting disease severity. Two studies in the literature emphasize that the MPV parameter is a biomarker indicating poor prognosis[54,55]. In our study, the significance of the MPV laboratory parameter in the evaluation of mortality may be useful for clinicians in evaluating prognosis. In a study conducted in diabetic COVID-19 patients, it is reported that the MPV value was increased in these patients[23]. In our study, a significant increase was found in the MPV values of COVID-19 patients with comorbidities such as diabetes. If COVID-19 patients have comorbidities in their history, the MPV laboratory parameter may also be beneficial for clinicians in patient observation.

Since COVID-19 is a disease with multiple variables, many studies are still ongoing. In this study, the MPV/Plt ratio was found to be significantly higher in COVID-19 patients compared to healthy population. The importance of PVI in evaluating platelet activation and predicting mortality has been reported in previous studies[53,56]. Similar to our study, Ates *et al*. found that the MPV/Plt ratio was significantly higher in sepsis patients compared to control group[53]. Fei *et al*. state that PVI could be beneficial in the diagnosis and differential diagnosis of disease in their study of the influenza virus[57]. This study also found that PVI was

useful in evaluating disease severity and predicting mortality, as well as diagnosing COVID-19.

To facilitate the clinicians' planning follow up of COVID-19 patients, this study evaluated COVID-19 patients divided into two groups, i.e. a group of patients with serious to critical severity COVID-19 and group of patients with mild to moderate severity COVID-19. In addition to the patient group diagnostic guide, the RDW-CV, MPV and MPV/Plt ratio were found to be significantly higher in the serious-critical severity group as compared to the mild-moderate severity group; moreover, when the relationship between the groups was evaluated, moderate correlation was found with these laboratory parameter values. The high sensitivity of RDW-CV and PVI may help clinicians in the assessment of the patient clinical course from the first follow up.

This study had some limitations, including a relatively small sample size and single-center design.

Conclusion

In conclusion, we think that the RDW-CV laboratory parameter and PVI, which were evaluated within the scope of the study, may be the parameters that should be considered in the early diagnosis of the disease from the initial stages of COVID-19. In addition, we think that the RDW-CV and MPV laboratory parameters, and PVI, which are among the simple, inexpensive and widely used hematologic tests, can be used as important biomarkers in defining the disease severity and evaluating its mortality. We believe that these parameters will facilitate early clinical intervention in COVID-19, thereby contributing to the reduction of patient mortality.

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Sažetak

PROCJENA ODNOSA SREDNJEG VOLUMENA TROMBOCITA, ŠIRINE DISTRIBUCIJE ERITROCITA I INDEKSA VOLUMENA TROMBOCITA S TEŽINOM BOLESTI KOD BOLESNIKA S COVID-19

D. Atik i *H.B. Kaya*

Koronavirus je prvi put otkriven kod tri slučaja teške upale pluća u Wuhanu, Kina u prosincu 2019. godine. Istraživanja laboratorijskih parametara širine distribucije eritrocita (RDW-CV) i srednjeg volumena trombocita (MPV) koji se mogu testirati unutar kompletne krvne slike kod bolesnika s COVID-19 još uvijek su vrlo ograničena. Međutim, prema našim saznanjima, nema istraživanja koja bi se bavila odnosom indeksa volumena trombocita (PVI) i težine bolesti kod ovih bolesnika, a upravo to smo ispitivali u našem istraživanju. Cilj studije bio je procijeniti odnos težine bolesti u bolesnika s COVID-19 s parametrima MPV, RDW i PVI. Istraživanje je obuhvatilo 92 bolesnika s COVID-19 i 84 zdrave osobe kao kontrolna skupina. Svi laboratorijski podaci i radiološke snimke preslikane su retrospektivno iz bolesničkih kartona i bolničkog informacijskog sustava. Procjena krvnih parametara RDW-CV i MPV, kao i PVI izmjerenih u bolesnika s COVID-19 pokazala je statistički značajne razlike prema težini bolesti. Predlažemo da bi RDW-CV i PVI koji su istraživani u ovoj studiji mogli poslužiti kao parametri u ranoj dijagnostici bolesti već u početnom stadiju COVID-19. Uz to, smatramo da bi se laboratorijski parametri RDW-CV i MPV te PVI kao jednostavne, jeftine i široko primjenjivane hematološke pretrage mogli primijeniti kao važni biološki biljezi u utvrđivanju težine i smrtnosti COVID-19.

Ključne riječi: *COVID-19; Težina bolesti; Srednji volumen trombocita; Širina distribucije eritrocita; Indeks volumena trombocita*