ORIGINAL ARTICLE

# Effect of COVID-19 on platelet count and its indices

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## SUMMARY

BACKGROUND: *Easily accessible, inexpensive, and widely used laboratory tests that demonstrate the severity of COVID-19 are important. Therefore, in this study, we aimed to investigate the relationship between mortality in COVID-19 and platelet count, Mean Platelet Volume (MPV), and platelet distribution width.*

METHODS: *In total, 215 COVID-19 patients were included in this study. The patients were divided into two groups. Patients with room air oxygen saturation < 90% were considered as severe COVID-19, and patients with ≥90% were considered moderate COVID-19. Patient medical records and the electronic patient data monitoring system were examined retrospectively. Analyses were performed using the SPSS statistical software. A p-value <0.05 was considered significant.*

RESULTS: *The patients' mean age was 64,32 ± 16,07 years. According to oxygen saturation, 81 patients had moderate and 134 had severe COVID-19. Our findings revealed that oxygen saturation at admission and the MPV difference between the first and third days of hospitalization were significant parameters in COVID-19 patients for predicting mortality. While mortality was 8.4 times higher in patients who had oxygen saturation under 90 % at hospital admission, 1 unit increase in MPV increased mortality 1.76 times.*

CONCLUSION: *In addition to the lung capacity of patients, the mean platelet volume may be used as an auxiliary test in predicting the mortality in COVID-19 patients.*

KEYWORDS: *Coronavirus Infections. Blood Platelets. Mean platelet volume. Mortality.*

## INTRODUCTION

The World Health Organization (WHO)[1] declared a pandemic on March 11th, 2020, after the identification of > 118,000 novel 2019 coronavirus disease (COVID-19) cases in 114 countries. As of 7 May 2020, a total of 3,825,028 cases had been identified in 187 countries, and unfortunately, 267,996 patients had died[2].

The clinical spectrum of COVID-19 appears to be wide, encompassing asymptomatic infection, mild

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upper respiratory tract illness, severe viral pneumonia with respiratory failure, and even death. In particular, older age, d-dimer levels greater than 1 μg/mL, higher SOFA score on admission, and comorbidities such as cardiovascular disease, diabetes, chronic respiratory disease, and oncological diseases were associated with worse prognosis and in-hospital death[3,4]. Treatment strategies including drugs, vaccines, or targeted therapy approaches have been limited until now[5]. Easily accessible, inexpensive, and widely used laboratory tests that show the severity of COVID-19 are important. Mean platelet volume (MPV) and platelet distribution width (PDW) are widely and routinely used in clinical practice worldwide. Higher MPV and increased PDW have been found in sepsis, and PDW was found to be a poor prognostic factor in severe sepsis[6]. However, the role of these parameters in COVID-19 has not been investigated. In this study, we aimed to investigate the relationship between mortality in COVID-19 and platelet count, MPV, and PDW.

## METHODS

### Study setting

This is a retrospective cohort study that was conducted between April 01, 2020, and April 15, 2020, in a tertiary training and research hospital. The hospital where the study was conducted was designated as the coronavirus pandemic hospital in the province by the Ministry of Health. The hospital has a total of 400 patient beds, 85 of which are intensive-care beds. Patient medical records and the electronic patient data monitoring system were examined retrospectively. The study protocol was approved by the institutional review board of Sakarya University (IRB No:71522473/050.01.04/105).

### Study Group

Patients diagnosed with COVID-19 were included. Complete blood count, C-reactive protein (CRP), and biochemistry tests are routinely performed on patients who attend the emergency department with complaints compatible with COVID-19 such as cough, fever, and shortness of breath. Also, Lung Computed Tomography (CT) is performed on patients who have shortness of breath, after their examination by the responsible doctor. At the same time, oro-nasopharyngeal swab (ONS) samples are taken from the patients for molecular analysis to reach a definitive diagnosis. Patients with advanced bilateral pneumonia, and/or tachypnea (respiratory rate > 26/minute), and/or arterial oxygen saturation < 90% in room air are followed up in the intensive-care unit, while patients with moderate clinical symptoms are followed up in the hospital wards. A second swab sample was taken from hospitalized patients with a negative first sample. When one of the two samples taken was positive, the patient was diagnosed with COVID-19, and if both were negative, COVID-19 was excluded.

### Study design

The patients were divided into two groups according to the lowest oxygen saturation during their first two days after hospital admission. Patients with oxygen saturation < 90% in room air were considered severe COVID-19, and patients with ≥90% were considered moderate COVID-19. Complete blood count and CRP values were obtained from patients on the day of hospital admission and on the third day of hospital follow-up. Patients who were discharged within 28 days after diagnosis of COVID-19 and who continued to undergo follow-up in the hospital on the 28$^{th}$ day of patient monitoring were accepted as survivors. Patients who died within the 28 days of patient monitoring were recorded as non-survivors. Thrombocytopenia was defined as grade 1: absolute platelet count (APC) 150,000 – 100,000/mm$^3$; grade 2: 99,000 – 50,000/mm$^3$; grade 3: < 49,000/mm$^3$. Lymphopenia was defined as grade 1: absolute lymphocytes count (ALC) 1500- 1000/ul; grade 2: ALC 999–750/ul; grade 3: ALC < 750/ul.

### Statistical Analysis

Descriptive analyses were performed to provide information on the general characteristics of the study population. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of numerical variables was normal. Accordingly, two independent sample t-tests and one way ANOVA were used to compare the age between/among groups. The Mann Whitney U test and Kruskal Wallis H test were used to compare the non-normally distributed numeric variables between/among groups. The numeric variables were presented as the mean and standard deviations. Categorical variables were compared by the Chi-Square test. Categorical variables were presented as a count and percentage. A multiple logistic regression model was implemented to determine the risk factors independently associated with exit status and hospitalization time. A p-value < 0.05 was considered significant.

Analyses were performed using SPSS statistical software (IBM SPSS Statistics, Version 23.0. Armonk, NY: IBM Corp.)

## RESULTS

In total, 215 COVID-19 patients were included in this study. The study population consisted of 95 females and 120 males, and their mean age was 64,32 ± 16,07 years. According to oxygen saturation, 81 patients had moderate and 134 had severe COVID-19. Since nine of the patients were discharged ≤ 3 days, they did not have a third-day analysis. Thrombocytopenia was observed in 54 (25.1 %) patients on the hospital admission day and in 52 (24.1 %) patients on the third follow-up day. On admission day, 43 patients had grade 1, 9 patients had grade 2, and two patients had grade 3 APC. On the third follow-up day, 40 patients had grade 1, 8 patients had grade 2, and four patients had grade 3 APC. On admission day, severe COVID-19 patients had significantly higher white blood count (WBC), neutrophil, and CRP values than moderate COVID-19 patients ($p < 0.05$). On the third follow-up day, WBC, neutrophil, platelet, MPV, and CMV values were significantly higher in severe patients than moderate COVID-19 patients ($p < 0.05$). On admission day, 62 patients had grade 1, 34 patients had grade 2, and 44 patients had grade 3 ALC. On the third follow-up day, 52, 44, and 57 patients had grade 1, 2, and 3 ALC, respectively. The mean lymphocyte value was lower in severe COVID-19 cases compared to moderate COVID-19 cases both on the day of hospital admission and on the third follow-up day ($p < 0.05$). The difference among WBC, neutrophil, platelet, and CRP between two days in severe and moderate COVID-19 patients was significant ($p < 0.05$) (Table 1).

Among the 215 COVID-19 patients, 56 (26.04 %) of them died within the 28-day follow-up. The age of the deceased patients was greater that that of the survivors. Thrombocytopenia was observed in 22 (39.3 %) of the non-survivors and in 31 (19.5 %) of the survivors ($p=0.003$). WBC, neutrophil, CRP, and PDW in non-survivors were significantly higher than in survivors in both admission day and the third day of follow-up

**TABLE 1.** COMPARISON RESULTS OF THE HEMATOLOGICAL CHARACTERISTICS AND OTHER FEATURES BETWEEN SEVERE AND MODERATE COVID-19 PATIENTS.

| | Moderate COVID-19 ( ≥ 90 SaO2) | | Severe COVID-19 ( < 90 SaO2) | | p |
|---|---|---|---|---|---|
| | n | Mean±SD | n | Mean±SD | |
| Gender (Male) | 81 | 44 (54.3) | 134 | 76 (56.7) | 0.732 |
| Age (years) | 81 | 56.52 ± 15.95 | 134 | 69.04 ± 14.26 | < 0.001 |
| White blood count (K/uL) | 81 | 6485.11 ± 2016.83 | 134 | 8960.72 ± 5016.91 | < 0.001 |
| Neutrophil (K/uL) | 81 | 4283.67 ± 1846.83 | 130 | 7792.15 ± 7948.32 | < 0.001 |
| Lymphocyte (K/uL) | 81 | 1573.53 ± 523.33 | 134 | 1389.35 ± 1607.33 | < 0.001 |
| Platelet (K/uL) | 81 | 187.4 ± 59.82 | 134 | 208.63 ± 135.72 | 0.573 |
| Mean Platelet Volume (f/l) | 80 | 9.18 ± 1.24 | 132 | 9.61 ± 1.76 | 0.129 |
| Platelet Distribution Width (%) | 80 | 17.37 ± 2.32 | 132 | 17.72 ± 2.52 | 0.142 |
| C-reactive protein (mg/L) | 81 | 34.69 ± 43.05 | 133 | 107.53 ± 84.33 | < 0.001 |
| White Blood Count 2 (K/uL) | 70 | 5714.4 ± 2191.37 | 129 | 9855.51 ± 8228.18 | < 0.001 |
| Neutrophil 2 (K/uL) | 69 | 3795.51 ± 1959.37 | 127 | 8254.4 ± 7233.19 | < 0.001 |
| Lymphocyte 2 (K/uL) | 70 | 1501.57 ± 892.05 | 128 | 922.66 ± 486 | < 0.001 |
| Platelet 2 (K/uL) | 70 | 172.93 ± 67.58 | 128 | 217.82 ± 92.18 | < 0.001 |
| Mean Platelet Volume 2 (f/l) | 69 | 9.38 ± 1.42 | 123 | 9.85 ± 1.79 | 0.043 |
| Platelet Distribution Width 2 (%) | 70 | 17.96 ± 1.43 | 124 | 18.13 ± 1.66 | 0.144 |
| C-reactive protein 2 (mg/L) | 64 | 36.92 ± 41.73 | 124 | 119.57 ± 82.52 | < 0.001 |
| White Blood count difference (K/uL) | 70 | -757.19 ± 2359.37 | 129 | 1004.3 ± 8033.14 | 0.003 |
| Neutrophil difference (K/uL) | 69 | -511.11 ± 2048.64 | 123 | 585.45 ± 9756.85 | 0.006 |
| Lymphocyte difference (K/uL) | 70 | -29.19 ± 851.87 | 128 | -473.22 ± 1578.33 | 0.341 |
| Platelet difference (K/uL) | 70 | -10.57 ± 52.39 | 128 | 10.24 ± 126.49 | 0.001 |
| Mean Platelet Volume difference (f/l) | 68 | 0.08 ± 0.89 | 122 | 0.37 ± 1.59 | 0.301 |
| Platelet Distribution Width difference (%) | 69 | 0.61 ± 2.34 | 123 | 0.55 ± 2.45 | 0.913 |
| C-Reactive Protein difference (mg/L) | 64 | 0.85 ± 24.14 | 124 | 14.4 ± 94.77 | 0.040 |
| Hospitalization day | 81 | 6.01 ± 3.49 | 134 | 14.75 ± 8.6 | < 0.001 |

**TABLE 2.** DIFFERENCE IN AGE, GENDER AND HEMATOLOGICAL CHARACTERISTICS BETWEEN SURVIVORS AND NON-SURVIVORS OF PATIENTS WITH COVID-19

| | Survivors | | Non-survivors | | P |
|---|---|---|---|---|---|
| | n | Mean ± SD | n | Mean ± SD | |
| Gender (Male) | 159 | 87 (54.7) | 56 | 33 (58.9) | 0.697 |
| Age (years) | 159 | 61.15 ± 16 | 56 | 73.34 ± 12.58 | < 0.001 |
| White blood count (K/uL) | 159 | 7569.78 ± 3940.36 | 56 | 9329.21 ± 5046.97 | 0.011 |
| Neutrophil (K/uL) | 157 | 6037.69 ± 7077.53 | 54 | 7630.35 ± 4598.34 | < 0.001 |
| Lymphocyte (K/uL) | 159 | 1563.2 ± 1432.63 | 56 | 1162.14 ± 812.23 | 0.004 |
| Platelet (K/uL) | 159 | 207.69 ± 123.06 | 56 | 180.59 ± 78.14 | 0.094 |
| Mean Platelet Volume (f/l) | 158 | 9.34 ± 1.37 | 54 | 9.77 ± 2.11 | 0.189 |
| Platelet Distribution Width (%) | 158 | 17.44 ± 2.35 | 54 | 18.02 ± 2.69 | 0.040 |
| C-reactive protein (mg/L) | 159 | 67.87 ± 70.21 | 55 | 114.92 ± 94.73 | < 0.001 |
| White Blood Count 2 (K/uL) | 148 | 7499.39 ± 4804.14 | 51 | 11009.02 ± 10877.1 | 0.001 |
| Neutrophil 2 (K/uL) | 146 | 5777.12 ± 4695.94 | 50 | 9334.8 ± 9117.4 | < 0.001 |
| Lymphocyte 2 (K/uL) | 147 | 1259.44 ± 734.31 | 51 | 746.55 ± 477.17 | < 0.001 |
| Platelet 2 (K/uL) | 147 | 206.52 ± 84.72 | 51 | 188.78 ± 92.26 | 0.348 |
| Mean Platelet Volume 2 (f/l) | 146 | 9.45 ± 1.47 | 46 | 10.41 ± 2.07 | 0.005 |
| Platelet Distribution Width 2 (%) | 147 | 17.89 ± 1.55 | 47 | 18.63 ± 1.56 | 0.006 |
| C-reactive protein 2 (mg/L) | 137 | 78.3 ± 79.75 | 51 | 126.71 ± 75.31 | < 0.001 |
| White Blood count difference (K/uL) | 148 | -144.61 ± 3963.6 | 51 | 1920.67 ± 11237.2 | 0.182 |
| Neutrophil difference (K/uL) | 144 | -435.75 ± 7132.57 | 48 | 2072.73 ± 9731.54 | 0.175 |
| Lymphocyte difference (K/uL) | 147 | -285.1 ± 1545.15 | 51 | -406 ± 724.5 | 0.048 |
| Platelet difference (K/uL) | 147 | -0.05 ± 117.13 | 51 | 11.33 ± 68.25 | 0.561 |
| Mean Platelet Volume difference (f/l) | 145 | 0.05 ± 1.08 | 45 | 0.96 ± 1.94 | 0.005 |
| Platelet Distribution Width difference (%) | 146 | 0.46 ± 2.35 | 46 | 0.93 ± 2.57 | 0.389 |
| C-Reactive Protein difference (mg/L) | 137 | 8.15 ± 68.63 | 51 | 14.19 ± 100.72 | 0.091 |
| Hospitalization day | 159 | 11.92 ± 8.63 | 56 | 10.13 ± 7.08 | 0.456 |

*: Shown as count and percentage

(p=0.001). On the other hand, MPV in non-survivors was significantly lower than in survivors only in the third follow-up day (P < 0.005). The demographic and laboratory findings of survivors and non-survivors are seen in table 2.

According to the multiple logistic regression model for mortality, in case of an increase of 1 unit MPV difference (MPV differences between 1st and 3rd day), the probability of death increases 1.762 times. In addition, the probability of death of patients with oxygen saturation < 90 % is 8.405 times higher than that of patients with oxygen saturation ≥ 90 % (table 3).

**TABLE 3.** MULTIPLE LOGISTIC REGRESSION MODEL FOR MORTALITY.

| | β | SE of β | p | OR | 95% CI for OR |
|---|---|---|---|---|---|
| Age | -0.042 | 0.007 | < 0.001 | 0.959 | 0.945-0.973 |
| Oxygen saturation | 2.129 | 0.528 | < 0.001 | 8.405 | 2.987-23.646 |
| MPV diff | 0.566 | 0.166 | 0.001 | 1.762 | 1.272-2.440 |

β: regression coefficient, SE: standard error, OR: odds ratio, CI: confidence interval, MPV: Mean platelet volume

## DISCUSSION

Our findings revealed that oxygen saturation at admission and MPV difference between the first and third days of hospitalization were significant parameters in COVID-19 patients for predicting mortality. While, mortality was 8.4 times higher in patients who had oxygen saturation under 90 % at hospital admission, 1 unit increase in MPV between the first and third days of hospitalization increases mortality 1.76 times. In addition to the lung capacity of the patient, MPV may be used as an auxiliary test in predicting the mortality in COVID-19 patients.

Primary inflammation triggered by rapid viral replication and release of potent proinflammatory cytokines occurs in the early stages of COVID-19 infection[7]. In addition to pulmonary infiltrate and diffuse alveolar damage, widespread endothelial inflammation due to viral infection of the endothelial cell can strengthen the further secretion of various inflammatory cytokines[8]. Neutrophils and leukocytes might reinforce the cytokine storm other

than lymphocytes in COVID-19 because prominent lymphopenia has been developed in most COVID-19 patients, especially in severe ones[9]. In a meta-analysis, researchers found that severe illness was associated with lower lymphocyte and higher leukocyte counts[10]. In our study, while the leukocyte and neutrophil values of severe cases on the day of admission to hospital were higher than in mild cases, the lymphocyte values were low, too ($p < 0.05$). Moreover, on the third day of hospitalization, leukocyte and neutrophil levels were increased even more in severe cases and decreased in mild cases ($p < 0.05$). However, on the third day, although the lymphocyte values in severe cases decreased much more than in mild cases, the difference was not significant.

Zhao et al.[11] reported that a lymphocyte count of less than $1.5 \times 10^9$/L may be useful in predicting the severity of clinical outcomes. They found that there was a three-fold increased risk of severe COVID-19 with the presence of lymphopenia. Our study revealed that leukocyte and neutrophil values in non-surviving patients were higher than in survivors both on the day of admission and on the third day of the follow-up, but the difference in the increase between the first and third days was not significant. On the other hand, the decrease in lymphocyte values of the patients who died was significant. Therefore, the power of the decrease in lymphocyte value in showing mortality was higher than that of the elevation in leukocyte and neutrophils. So, clinicians should closely monitor patients with lymphopenia.

Some studies have found a relationship between thrombocytopenia and the severity of the COVID-19 and related mortality. It has been reported that mortality increases as platelet count decreases[12,13]. Interestingly in our study, although thrombocytopenia was more likely to occur in non-survivors than in survivors, we did not find any correlation between platelet level and disease severity or mortality.

**TABLE 4.** MULTIPLE LINEAR REGRESSION MODEL FOR HOSPITALIZATION DAY.

| | β | SE of β | p | 95% CI for β |
|---|---|---|---|---|
| Age | 0.053 | 0.035 | 0.130 | -0.016-0.121 |
| Oxygen saturation | 8.548 | 1.134 | < 0.001 | 6.310-10.786 |
| MPV difference | -0.905 | 0.382 | 0.019 | -1.658--0.152 |
| Constant | 3.508 | 2.173 | 0.108 | -0.780-7.796 |

β: regression coefficient, SE: standard error, CI: confidence interval, MPV: Mean platelet volume

Non-survivors had lower platelet counts than survivors on both admission day and third follow-up day, but this difference was not statistically significant. Similar to our study, other studies reported that platelet values were found to be normal in many patients at the time of hospital admission[14]. These differences between studies may be related to the time of the tests. Also, hydroxychloroquine, azithromycin, and enoxaparin treatment have been started in most countries when COVID-19 is suspected. These drugs can cause thrombocytopenia[15,16]. Another reason for the difference between studies may be that thrombocytopenia caused by drugs and thrombocytopenia caused by the disease present an intricate structure.

On the other hand, platelet indices, MPV, and PDW, were found to be higher in non-survivors on both admission day and third follow-up days. To our knowledge, this study is the first one specialized in the association between platelet indices and in-hospital mortality in patients with COVID-19. According to our results, every 1 unit increase in MPV increased mortality by 1.76 times. The mechanism of change in platelet indices in COVID-19 patients is probably multifactorial. Three hypotheses related to platelet count and structure are proposed in COVID-19. Firstly, as with other coronavıruses, thrombocytopenia is possibly due to infection of the bone marrow. Secondly, platelet destruction by the immune system. Thirdly, platelet consumption due to aggregation in the lungs[17]. Generally, platelet production increases as platelet count decreases. An increased number of young platelets is also functionally more active than older platelets. These changes may explain the increase in platelet indices, MPV, and PDW.

## LIMITATIONS

In this rapidly emerging new non-characteristic infection of the modern medical age, it is necessary to identify biomarkers that can predict the severity and prognosis of the disease. MPV and PDW can be a simple, economical, fast, and widely available laboratory parameter that can distinguish directly between COVID patients with and without a severe presentation of the disease. Moreover, MPV can also be used to predict the mortality in COVID-19. In order to show the strength of these parameters more clearly, studies with a large number of patients are needed.

## RESUMO

OBJETIVO: *Testes laboratoriais de fácil acesso, baixo custo e amplamente utilizados capazes de demonstrar a gravidade da COVID-19 são importantes. Portanto, neste estudo, o nosso objetivo foi investigar a relação entre a mortalidade na COVID-19 e a contagem de plaquetas, volume plaquetário médio (VMP) e largura de distribuição de plaquetas.*

MÉTODOS: *No total, 215 pacientes com COVID-19 foram incluídos no estudo. Os pacientes foram divididos em dois grupos. Pacientes com saturação de oxigênio < 90% em ar ambiente foram considerados casos graves de COVID-19 e pacientes com valores ≥90% foram considerados casos moderados. Os registros médicos dos pacientes e o sistema eletrônico de monitoramento de dados de pacientes foram analisados retrospectivamente. As análises foram realizadas utilizando o software estatístico SPSS. Um valor de p <0,05 foi considerado significativo.*

RESULTADOS: *A média de idade dos pacientes foi de 64,32 ± 16,07 anos. Com base na saturação de oxigênio, 81 pacientes eram casos moderados e 134 tinham COVID-19 grave. Nosso estudo revelou que a saturação de oxigênio no momento da internação e a diferença nos valores de VPM entre o primeiro e terceiro dia de internação foram parâmetros significativos para predizer mortalidade de pacientes com COVID-19. A mortalidade foi 8,4 vezes maior nos pacientes com saturação abaixo de 90% no momento da internação, mas um aumento de apenas 1 unidade no valor de VPM aumentou a mortalidade 1,76 vezes.*

CONCLUSÃO: *Além da capacidade pulmonar dos pacientes, o volume plaquetário médio pode ser utilizado como um teste auxiliar para prever a mortalidade de pacientes com COVID-19.*


PALAVRAS-CHAVE: *Infecções por Coronavirus. Plaquetas. Volume Plaquetário Médio. Mortalidade.*

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