Can changes in platelet count, mean platelet volume, and platelet distribution width be used to determine the severity of COVID-19?

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ABSTRACT

Objective: We aimed to investigate the relation of platelet count (PLT), mean platelet volume (MPV) and platelet distribution width (PDW) with other acute phase reactants in COVID-19 new corona virus.

Material and Methods: Thirty one patients with COVID-19 were included in to study. There were three groups as outpatient (Group 1, OP) (n=6), hospital (Group 2, H) (n=16) and intensive care unit (Group 3, IC) (n=9) in this analytic study.

Results: WBC (White Blood Cell), CRP (C-Reactive Protein) values were significantly different in all groups. PDW values were significantly lower in Group 3 than Group 1, 2. The result of ROC analysis was 10.9 as a cut-off value (Area under the curve, AUC)=0.407

Conclusions: This study indicates that lower PDW may frequently develop in COVID-19 cases and there is a relation between thrombocytosis and acute phase reactants, that is, the inflammatory response. So we can offer that PDW should be used as a marker of Covid-19 disease severity, but it needs more studies in the future.

Keywords: Mean platelet volume, Platelet count, Platelet distribution width, ARDS, COVID-19.

INTRODUCTION

The 2019 novel coronavirus (SARS-CoV-2), also known as COVID-19, is a crucial global public health problem in the world. On May 06, 2020, the total number of confirmed approximately cases had reached 3,747,356 globally, resulting in 258,970 deaths. Of the total confirmed COVID-19 cases, about 19.9% were severe, with a mortality rate of about 20% (1). Most of the cases often include comorbid diseases such as cardiovascular disease and diabetes, which can exacerbate the progression of the COVID-19 infection (2, 3). Furthermore, acute respiratory distress syndrome (ARDS) might lead to death in some severe COVID-19 cases, as this syndrome is often accompanied by multiple organ dysfunction syndromes (2, 4). Therefore, the early, simple, and effective diagnosis of severe COVID-19 pneumonia is of great significance in decreasing mortality and shortening the hospitalization period (5, 6).

The guidelines on the diagnosis and treatment of COVID-19 pneumonia have several criteria, including respiratory rate, haemoglobin oxygen saturation (SaO2), and oxygenation index (PaO2/FiO2) (4, 7). However, these criteria are susceptible to subjective and objective factors, which may lead to extended diagnosis time and the possibility of misdiagnosing severe COVID-19 cases (8). Therefore, it makes sense to determine a potential biomarker that could effectively diagnose severe COVID-19 (9). As a result, pneumonia has been studied most extensively in relation to COVID-19 (10-12). In addition, complications associated with COVID-19, including ARDS and cardiac injury, have been associated with increased mortality. For instance, one small-sample-sized study reported that the rate of thrombocytopenia was 12% (3), and another study (13) found that 36.2% of patients had a platelet count of less than 150 × 10⁹ /l (7).Platelets play a role in haemostasis during an inflammatory response. It has been demonstrated that changes in platelet count, especially during bacterial infections, might be associated with the severity and the mortality rate of the coronavirus disease.
Moreover, patients with thrombocytosis (among patients hospitalized due to community-acquired pneumonia) have been reported to carry a high risk of mortality (14).

The objective of our study was to investigate the relationship between the existence of thrombocytosis, platelets, and indexes with other acute phase reactants with the severity of COVID-19.

MATERIAL and METHODS

Our study is a retrospective case study that was performed according to the principles of the Declaration of Helsinki, approved by the ethics committee of Karatay University, Scientific Research Board (41901325-050.99), and registered on clinical trials.gov (NCT04378829). Thirty-one patients with a confirmed diagnosis of COVID-19 were evaluated in this study. These patients were selected to apply to Konya Training and Research Hospital between 21 March and 23 April 2020.

The patients were divided into three groups. The first group consisted of outpatients (OP); the second consisted of patients, who received standard treatment in the hospital (H); and the third group consisted of patients who had to be connected to a mechanical ventilator and intubated because of ARDS in the intensive care unit (IC). The inclusion criteria of the study were a diagnosis of COVID-19 confirmed using the polymerase chain reaction (PCR) method and a lung computed tomography (CT) scan with radiological findings. Patients were also included if the 14-day incubation period specified by the first studies (15) was observed; the haemogram and c-reactive protein (CRP) assays were regularly examined at least three times in 14 days; and the standard drug using the current treatment guidelines had been followed (16). The exclusion criteria included the presence of diseases, such as cardiovascular disease, thromboembolic disease, or sepsis disease, that required medication that would affect the bleeding clotting panel, and a lack of assays performed at the specified intervals. The following data were recorded from the patient by computer registration database: C-reactive protein (CRP), haemoglobin levels (Hb), white blood cell (WBC), platelet count, platelet distribution width (PDW), and mean platelet volume (MPV) for COVID-19 patients. When the COVID-19 diagnosis was made, it was scanned and recorded on the 7th and 14th days.

Statistical analysis

All statistical analyses were performed using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A “repeated measure analysis of variance (ANOVA)” test was used for inter-group comparisons, and Pearson and Spearman correlation tests were used to assess” the correlation between numerical and categorical parameters. A value of p <0.05 was considered statistically significant. The best cut-off values of platelet index in the differentiation of COVID-19 and ARDS were calculated with receiver operating characteristic (ROC) curve analysis.”

RESULTS

Demographic and clinical features

Thirty-one patients who tested positive for COVID-19 after a PCR test and a lung CT scan were included in the study. Of these patients, 17 were male and 14 were female. The average age of the patients was 63.25 ± 13.20. Six of the patients were outpatients (OP), 16 of the patients were in the normal clinic of the hospital, and 9 of the patients were intubated and had to use a mechanical ventilator while staying in the intensive care unit (IC). Among these patients, seven deaths occurred in the IC group, one death occurred in the H group and no deaths occurred in the OP group. One of the patients (6%) in the H group who received normal clinical treatment was transferred to the intensive care unit. Of the patients in Group 2, [n] (94%) were eventually discharged from the hospital While one (11.1%) of the patients in the IC group was discharged to the normal clinic in the hospital, one (11.1%) of the patients remained in the intensive care unit.

Haemoglobin and infection parameter findings

According to our analysis, there was no difference in Hb values (p=.05) between the groups. However, when the distribution of WBC and CRP recorded as an indication of infection for all patients was evaluated, there was a significant difference between the second and third measurements between the groups (p<.05, Table 1).

Platelet Index Findings

There was no difference between the groups in the platelet indexes except for the PDW values (p> 0.05). There was a significant difference in the first measurement of PDW values for group OP (p=.014, Figure 1). When the platelet indexes of the patients were evaluated, there was no significant difference for each measurement in all groups in terms of platelet count and MPV values (p> .05, Table 2). ROC analysis was also performed on the PDW values to evaluate the differential ability of disease severity. It was observed that the first PDW measurement was significantly above the diagonal curve compared to the second and third measurements (Figure 2). The cut-off value for the application of non-invasive ventilation or not was 10.9 % as the strongest value according to sensitivity and specificity (sensitivity=0.833/1-specificity=0.720; area under the curve (AUC) = 0.407).

Table 1. Distribution of hemoglobin and infection parameters by groups

|                     | Group OP (N=6) | Group H (N=16) | Group IC (N=9) | p     |
|---------------------|----------------|----------------|----------------|-------|
| Hb(g/dL) 1. measurement | 11.8±1.2      | 13.2±2.2       | 12.9±1.8       | 0.334 |
| Hb(g/dL) 2. measurement | 11.5±0.7      | 12.3±1.6       | 12.0±1.6       | 0.582 |
| Hb(g/dL) 3. measurement | 11.3±0.9      | 12.5±1.9       | 10.8±1.9       | 0.069 |
| WBC(10^3/mm) 1. measurement | 7.6±3.6      | 6.3±1.7        | 8.5±2.4        | 0.102 |
| WBC(10^3/mm) 2. measurement | 6.1±3.7      | 6.3±2.0        | 16.7±7.7       | 0.001*|
| WBC(10^3/mm) 3. measurement | 6.9±2.4      | 7.4±3.0        | 15.5±6.8       | 0.001*|
| CRP(mg/L) 1. measurement | 22.3±16.4    | 48.8±53.6      | 44.3±48.7      | 0.513 |
| CRP(mg/L) 2. measurement | 20.5±28.2    | 70.1±60.9      | 170.2±76.5     | 0.001*|
| CRP(mg/L) 3. measurement | 37.1±43.1    | 21.3±41.3      | 161.3±53.5     | 0.001*|

Hb: Hemoglobin value, WBC: White Blood cell, CRP: c-reactive protein. * p<0.05
The COVID-19 virus may cause damage to the alveolar and interlobular regions in the lungs and clinical deterioration due to hypoxemia in COVID-19 patients seems to be associated with the tendency for clotting, as well as many mechanisms that affect oxygenation (17, 18). The most effective factor in coagulation, thromboplastin counting, distribution, and width can also be caused by these effects, which led us to conduct this study. By determining the severity of the disease with a simple and inexpensive test based on a possible relationship of the mortality rate, we hope to find scientific and social benefits for future studies.

Table 2. Distribution of platelet indices by groups

|                  | Group OP (N=6) | Group H (N=16) | Group IC (N=9) | p   |
|------------------|----------------|----------------|----------------|-----|
| Plt(10^3/mm^3) 1. measurement | 206.5±49.8 | 215.2±6.3 | 198.1±31.3 | 0.748 |
| Plt(10^3/mm^3) 2. measurement | 207.6±69.7 | 267.8±111.3 | 247.1±94.1 | 0.462 |
| Plt(10^3/mm^3) 3. measurement | 231.8±50.0 | 315.5±134.0 | 244.5±108.5 | 0.203 |
| MPV(µm^3) 1. measurement | 10.3±0.8 | 10.1±0.9 | 11.1±1.1 | 0.076 |
| MPV(µm^3) 2. measurement | 10.3±0.7 | 10.0±0.7 | 10.4±0.7 | 0.510 |
| MPV(µm^3) 3. measurement | 10.3±0.3 | 9.7±1.1 | 10.7±0.6 | 0.051 |
| PDW(%) 1. measurement | 11.7±1.26 | 11.8±2.2 | 14.5±2.5 | 0.014* |
| PDW(%) 2. measurement | 12.0±1.6 | 11.7±2.14 | 12.3±1.54 | 0.757 |
| PDW(%) 3. measurement | 12.0±0.7 | 11.4±2.0 | 12.8±1.4 | 0.156 |

Plt: Platelet count, MPV: Mean platelet volume, PDW: Platelet Distribution Width. * p<0.05 Measurement times for 1, 2, 3 ?

Figure 1. The boxplot of mean PDW values for Group OP, Group H and Group IC for each measurement. PDW: Platelet distribution width.

Figure 2. The ROC analyze graphic of mean PDW values for Group OP, Group H and Group IC for each measurement. PDW: Platelet distribution width.

DISCUSSION

The COVID-19 virus may cause to damage the alveolar and interlobular regions in the lungs and clinical deterioration due to hypoxemia in COVID-19 patients seems to be associated with the tendency for clotting, as well as many mechanisms that affect oxygenation (17, 18). The most effective factor in coagulation, thromboplastin counting, distribution, and width can also be caused by these effects, which led us to conduct this study. By determining the severity of the disease with a simple and inexpensive test based on a possible relationship of the mortality rate, we hope to find scientific and social benefits for future studies.

In our study, the platelet indexes of COVID-19 patients were investigated in detail, and their relationship with the severity of the disease was determined.

As hospitals around the world continue to accept patients with COVID-19, the unknown pathogenesis behind the death rates witnessed is slowly occurring. In addition to established respiratory involvement, the coagulation system has recently been associated with controversial mechanisms (17). New data from cohort studies and autopsies predict that coagulopathy plays a potential role in COVID-19
pathogenesis. Although the exact mechanism remains controversial, more clinical implications are imperative to determine precise results (18).

In a retrospective multicenter cohort study from China, charts of 191 adult patients with laboratory-approved COVID-19 were analyzed. Unlike 32 (59%) of the 54 other survivors, only one of the 137 surviving patients reported cardiovascular problems. In addition to age and multi-organ failure evaluation scores, multivariate regression analysis showed increased in-hospital mortality rates associated with D-dimer levels > 1 μg/mL (p = .0033). Also, coagulopathy was common in 27 (50%) of 54 survivors and 10 (7%) of 137 survivors (p < .0001). It should be noted that sepsis is complicated by coagulopathy and is a potentially controversial mechanism behind the high mortality rates reported in COVID-19 patients. Also, 38 (70%) of surviving patients did not have sepsis (19).

Thrombus formation mechanisms are variable. Generally, evidence of viruses suggests that the inflammation of immune and non-immune cells can lead to an imbalance of procoagulant and anticoagulant conditions during infection. The risk of hematopathology is standard, as it plays an essential role in endothelial homeostasis regulation, and its structure is impaired in viral infections. In addition, the Von Willebrand factor, toll-like receptor activation, and tissue factor pathway activation caused by viral infection may play a role in the following clotting cascade leading to the formation of cross-linked fibrin clots (20). The breakdown of these clots according to the physiological response to the excessive activation of the clotting cascade is responsible for procoagulant D-dimer increases. With the antigen effect, platelets are activated, coordination WBC is ensured for pathogen clearance and clot formation occurs. Immune cells, platelets, and endothelial cells, therefore, all play a role in the clotting mechanism related to viral infections (21). In our study, the effects of the coagulation mechanism on platelet parameters in terms of platelet count, MPV, and PDW values were examined. Although there are numerical changes in all these parameters, a statistically significant difference was only found in relation to the PDW values (p = .014).

In the meta-analysis of Lippi et al. (17), nine studies with 1779 COVID-19 patients, in which 399 (22.4%) patients had a severe form of the disease, were discussed. The collected analysis revealed that the number of platelets was significantly lower in patients with more severe COVID-19. In a subgroup, analysis comparing the mortality and survival rates of patients, an even lower platelet count was observed in relation with mortality. In four studies, the low platelet count reporting data on the rate of thrombocytopenia was associated with an increased risk of severe COVID-19 more than five times as likely to be seen (odds ratio, 5.1; 95% confidence interval, 1.8-14.6). In our study, although the platelet values were low in the intensive care patients, there was no statistically significant difference found.

Regarding MPV and PDW values, no other study focused on COVID-19 and these values could be found in the literature. In this sense, our research has the feature of being the first to consider these parameters. In a study on MPV values (22), MPV was significantly lower in both ankylosing spondylitis patients and patients with active disease rheumatoid arthritis than in the control group.

After treatment, MPV values increased significantly. However, MPV values were slightly lower in rheumatoid arthritis patients compared to other patients. As a result, it is thought that MPV evaluation may provide additional information about inflammation. In our study, although MPV values decreased in the second measurement during the course of the disease, there was no expected change in intensive care patients.

In another study (22), the relationship between MPV, PLT, other acute phase reactants and radiological pulmonary tuberculosis was investigated. One hundred patients with pulmonary tuberculosis (Group 1), 50 patients with community-acquired pneumonia (Group 2), and 28 healthy control individuals (Group 3) were included in this analytical study. When the results were evaluated, WBC, erythrocyte sedimentation rate, CRP, PLT, and MPV values are both in Group 1 and Group 2 compared to Group 3, MPV values are in Group 1. This difference was found to be significantly higher than Group 3. Similarly, in our research, the most numerical changes in intensive care patients were seen in the first measurement of the PDW values. Moreover, meaningfulness was found with a repeated measure ANOVA test. In addition to a significant difference as indicated by ROC analysis. The ROC analysis was our purpose to evaluate as a diagnostic tool. Still, a considerable area could be determined on the diagonal curve for PDW values (AUC = 0.407), although the AUC value was relatively low.

Limitations: When the limitations related to our study were evaluated, we deduced that the number of patients included in the study could have been higher. The reason for the limited number of patients was the evaluation of one-month evaluation period, as well as the condition that the intensive care patients were diagnosed with definitive ARDS and required intubation in order to be connected to a diagnosis using the PCR method in addition to CT, as well as requiring the standard application of medication per the current treatment guidelines was another reason for the low number of patients included in our study.

CONCLUSION

Although all the platelet indexes did not have a sensitivity or specificity threshold value for early recognition of the severity of COVID-19, the PDW values did have a sensitivity or specificity threshold value. Also, PDW values significantly decreased, especially after the first values taken in relation to the severity of the disease. This study found that the PDW parameters can be used as a reference in future studies for the diagnosis of new coronaviruses and other respiratory pathogens.

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