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RESEARCH ARTICLE

The value of the platelet count and platelet indices in differentiation of COVID-19 and influenza pneumonia

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Abstract

It is difficult to distinguish coronavirus disease-2019 (COVID-19) from other viral respiratory tract infections owing to the similarities in clinical and radiological findings. This study aims to determine the clinical importance of platelet count and platelet indices in the differentiation of COVID-19 from influenza and the value of these parameters in the differential diagnosis of COVID-19. The medical records of the patients and the electronic patient monitoring system were retrospectively analyzed. Demographic characteristics, admission symptoms, laboratory findings, radiological involvement, comorbidities, and mortality of the patients were recorded. Forty-three patients diagnosed with influenza and 54 diagnosed with COVID-19 were included in the study. The average age of the COVID-19 patients was lower than that of the influenza patients (influenza: 60.5 years, COVID-19: 52.4 years; pp = 0.024),.024), and the male gender was predominant in the COVID-19 group (influenza: 42%, COVID-19: 56%). According to laboratory findings, the mean platelet volume (MPV) and MPV/platelet ratio were statistically significantly lower, whereas the eosinophil count and platelet distribution width levels were significantly higher ($p < 0.05$) in the COVID-19 group. It was found that the most common symptom in both groups was dyspnea and that the symptom was more prevalent among influenza patients. In the diagnosis of COVID-19, the platelet count and platelet indices are easily accessible, inexpensive, and important parameters in terms of differential diagnosis and can help in the differentiation of COVID-19 from influenza during seasonal outbreaks of the latter.

KEYWORDS
disease control, immune responses, immunopathology, influenza virus, SARS coronavirus

1 | INTRODUCTION

Coronavirus disease-2019 (COVID-19), caused by the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has affected over 30 million people worldwide and has resulted in the death of approximately 1 million people since December 2019. It is a highly contagious disease that spreads via contact and aerosol transmission.[1] Similar viral epidemics have occurred in the past. One such epidemic, influenza, happened in 1918, and from that year onwards, it has been resulting in

the outbreak of a highly contagious viral respiratory tract disease, which is common in the period ranging from October to the end of March or early April.[2] The radiological and laboratory findings of these two diseases, which are similar in terms of symptoms and clinical pictures, share several commonalities. They both present with the classic symptoms of fever, cough, shortness of breath, and fatigue.[3] Therefore, it is often necessary to differentiate between these two illnesses. The common laboratory findings of viral infections are lymphopenia, leukopenia, and thrombocytopenia.[4,5] In particular, COVID-19 has been shown to exert

significant effects on the hematopoietic system and hemostasis.[6] Studies have emphasized that patients diagnosed with COVID-19 are susceptible to hypercoagulation and thrombotic events.[7] Microvascular thrombosis has been observed in autopsies performed on patients.[7] Abnormal coagulation parameters, such as elevated D-dimer level and prolonged prothrombin time, have been detected in COVID-19 patients.[8] Mean platelet volume (MPV) describes the average size of the circulating platelets and is a possible indicator of platelet function and activation.[9] Inflammatory cytokines are known to induce the release of large platelets from the bone marrow by stimulating thrombopoiesis.[10] It has been established that MPV is a key factor associated with mortality in many diseases.[11,12] However, the prevalence of thrombocytopenia has been emphasized in many studies.[13] Research has revealed the need for a more detailed probe on the effects of platelet count and platelet indices on the physiopathology and prognosis of the disease.

We aimed to determine the clinical significance of platelet distribution width (PDW), MPV, and MPV/platelet ratio and ascertain the value of these parameters in the differential diagnosis of COVID-19 using peripheral blood samples obtained from patients at the time of hospital admission.

2 | MATERIALS AND METHODS

Our study was designed retrospectively. The data of influenza patients who were followed up and treated in the pulmonary and intensive care units during the previous influenza season were obtained from the hospital records. Besides this, the data of COVID-19 patients who were followed up and treated in the pulmonary and intensive care unit in April and May 2020 were recorded. All patients were selected based on the testing of their nasopharyngeal swab samples by real-time reverse-transcription polymerase chain reaction (RT-PCR) and disease confirmation.

Demographic characteristics, admission symptoms, laboratory findings, radiological involvement, comorbidities, and mortality of the patients were recorded. The two patient groups were compared by examining the hemogram parameters (platelet, PDW, MPV, hemoglobin, white blood cell, and eosinophil) obtained at the time of hospital admission.

Radiological involvement assessed each of the five lobes of both lungs for the presence of abnormalities including the presence of ground-glass opacities, mixed ground-glass opacities, or consolidation, as Li et al.[14] described their study in "European Radiology" in March 2020.

2.1 | Inclusion and exclusion criteria

Influenza and COVID-19 patients whose diagnoses were confirmed with RT-PCR were included in the study. Patients with hematological diseases, those diagnosed with cancer, those using drugs that may affect platelet functions, pregnant women, and those <18 years of age were excluded from the study.

2.2 | Statistical analysis

Statistical evaluations were performed using the "Statistical Package for Social Sciences Program" (SPSS version 16; SPSS Inc.). Continuous variables were expressed as mean $\pm SD$ and categorical variables as percentages. A χ^2-test was used to compare the proportions. Student's t-test was employed for parametric variables, and Mann–Whitney U-test was used for non-parametric variables to compare the means. $p < .05$ was considered statistically significant.

2.3 | Ethics committee approval

After obtaining scientific research approval for the study from the Ministry of Health General Directorate of Health Services, the ethics committee approval was obtained from Recep Tayyip Erdoğan University Clinical Research Ethics Committee (Ethics Committee Approval No: 2020-160).

3 | RESULTS

Ninety-seven patients, 43 of whom were diagnosed with influenza and 54 of whom were diagnosed with COVID-19, were included in the study. The mean age was 52.4 ± 17.2 in the COVID-19 group and 60.5 ± 17.3 in the influenza group. The mean age was significantly higher in the influenza group than in the COVID-19 group ($p = .024$). Although the gender distribution in the COVID-19 group was 44% (24) women and 56% (30) men, it was 58% (25) women and 42% (18) men in the influenza group.

In the patient groups included in the study, the most common comorbidity was hypertension, with 49% in the influenza group and 31% in the COVID-19 group exhibiting the condition. The distribution of other comorbidities is shown in Table 1.

When the symptoms were examined in both groups, it was found that dyspnea was most common in both influenza (93%) and COVID-19 (80%), and it was statistically significantly higher in the influenza group. Although the second most common symptom was cough in the influenza group, it was fever in the COVID-19 group. The distribution of symptoms is represented in Table 1.

With regard to the distribution of radiological results, no statistical difference was found between the two groups in the evaluation of terms of five lung lobes scores ($p > .05$).

The mean hospital stay was 6.2 ± 3.3 days in the influenza group and 9.5 ± 6.4 days in the COVID-19 group, which was statistically significant ($p = .002$). Among the patients included in the study, mortality occurred in two patients in the influenza group and four in the COVID-19 group. These figures were not statistically significant ($p = .586$).

When the laboratory findings of the two groups were compared, MPV and MPV/platelet ratio were lower in the COVID-19 group ($p = .027$ and .034, respectively). The PDW level was found to be significantly higher in the COVID-19 group than in the influenza group ($p < .001$) (Figures 1 and 2). Absolute eosinophil count and percentage were also significantly higher in the COVID-19 group than in the

TABLE 1 Demographic characteristics of the COVID-19 and influenza patients

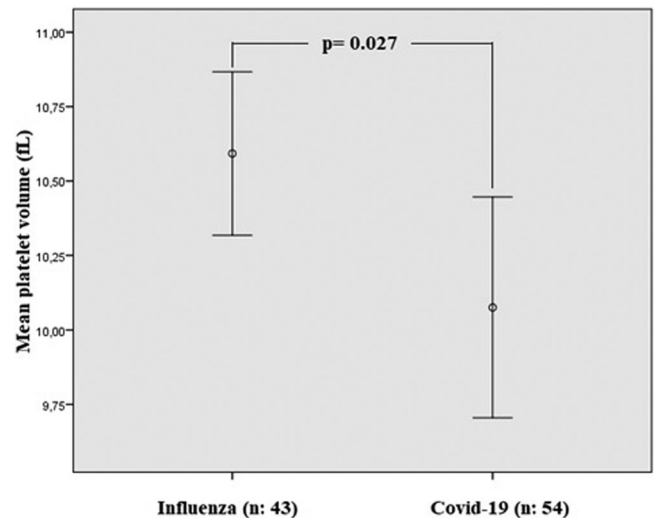|	COVID-19 (n = 54)	Influenza (n = 43)	p value
Age, year	52.4 ± 17.2	60.5 ± 17.3	.024
Gender, n (%)			.180
Female	24 (44)	25 (58)	
Male	30 (56)	18 (42)	
Comorbidity, n (%)			
HT	17 (31)	21 (49)	.082
DM	4 (7)	8 (19)	.096
CHF	13 (24)	4 (9)	.057
ASHD	3 (5)	5 (11)	.280
CRF	12)	4(9)	.099
Malignancy	2 (5)	2 (5)	.816
Asthma	2 (4)	2 (5)	.816
COPD	5 (9)	6 (14)	.469
Symptoms, n (%)			
Fever	36 (67)	11 (26)	<.001
Cough	17 (31)	29 (67)	<.001
Dyspnea	43 (80)	40 (93)	<.001
Sputum	12 (22)	3 (7)	.001
Myalgia	16 (30)	4 (9)	<.001
Vomiting/diarrhea	7 (13)	2 (5)	.014
Hospitalization period, days	9,5 ± 6,4	6,2 ± 3,3	.002
Being in intensive care, n (%)			.803
Yes	9 (17)	8 (18)	
No	45 (83)	35 (82)	
Intubation status, n (%)			.086
Yes	6 (11)	2 (5)	
No	48 (89)	41 (95)	
Mortality status, n (%)			.586
Yes	4 (7)	2 (5)	
No	50 (93)	41 (95)	

Data are shown as mean ± SD and n (%).
Abbreviations: ASHD, atherosclerotic heart disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CRF, chronic renal failure; DM, diabetes mellitus; HT, hypertension.
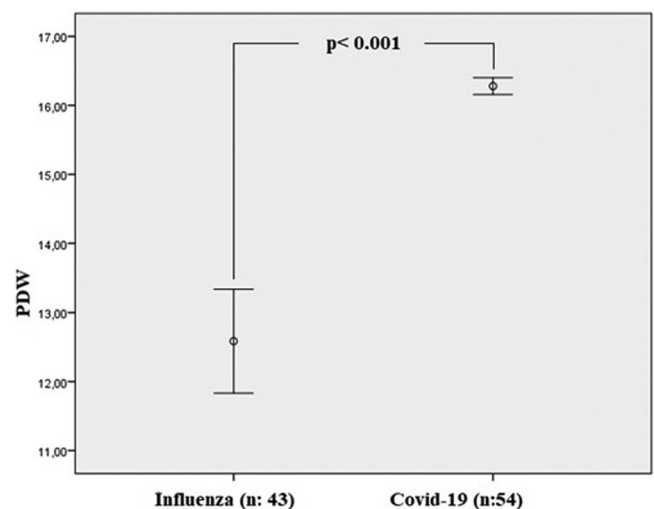

FIGURE 1 Peripheral blood mean platelet volume levels (fL) of the influenza and COVID-19 patients

the literature findings, it was observed that the proportion of male patients was higher. When the laboratory parameters were evaluated, it was noted that the MPV and MPV/platelet ratio were significantly lower and absolute eosinophil count and PDW level were significantly higher in the COVID-19 patients than in the influenza patients. In addition, it was inferred that the hospitalization period of the COVID-19 patients was longer than that of the influenza patients. We can explain the longer hospital stay of COVID-19 patients, the fact that it is a multi-systemic disease, it has more extra-pulmonary complications, and it can turn into macrophage activation syndrome by the increased immune response.[15] It has been reported in the literature that fever and shortness of breath are the most common symptoms observed in influenza patients. In our study too,

influenza group (p = .013 and .035, respectively) (Figure 3). There was no significant difference in terms of other laboratory parameters between the two groups (Table 2).

4 | DISCUSSION

This was a descriptive, cross-sectional study comparing the clinical features and hemogram parameters of COVID-19 and influenza patients. In our research, the average age of the COVID-19 patients was found to be lower than that of the influenza patients. Similar to

FIGURE 2 Peripheral blood platelet distribution width (fL) levels of the influenza and COVID-19 patients
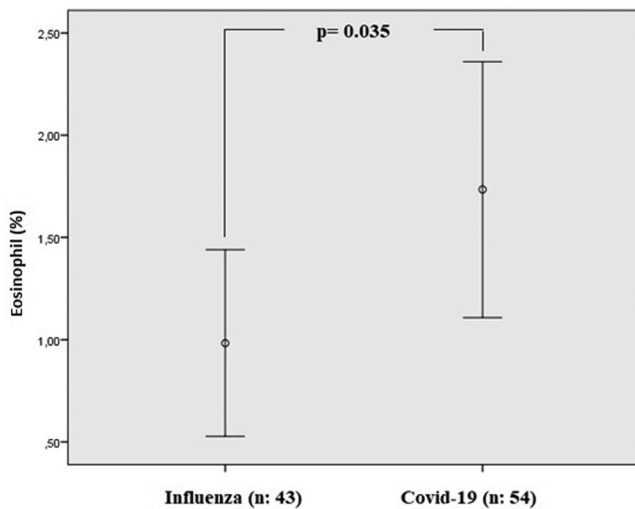
FIGURE 3 Percentage of peripheral blood eosinophils in the influenza and COVID-19 patients

the most common symptom in both groups was dyspnea, which was statistically significantly higher in the influenza patients. Although fever was the second most common symptom in COVID-19 patients, cough took that position in influenza.[16]

Just like lymphopenia, thrombocytopenia in COVID-19 pneumonia is also a significant diagnostic finding.[17] The most challenging disease group for the clinician to make a differential diagnosis with COVID-19 is other viral pneumonias. A co-infection risk exists especially in the case of pneumonias that occur in the influenza season, which is between December and March. Therefore, the differential diagnosis of COVID-19 pneumonia with other viral pneumonias, such as influenza, becomes important. Although the tests that are based on RT-PCR and those that detect specific immunoglobulins are presently the most commonly used ones, additional diagnostic methods are required as the sensitivities and specificities of the currently-available procedures are low.[18–20] In our study, it was found that influenza pneumonia and COVID-19 were similar in many aspects and that there is no statistically significant difference between these two diseases in many of the parameters, both radiologically and symptomatically.

In our study, we found that similar to COVID-19, which presents with thrombocytopenia, lymphopenia, and coagulopathy, the platelet and lymphocyte counts in influenza cases are also significantly lower than the reference values. This finding agrees with the literature reports.[21] Differences in these laboratory parameters, which are lowered in both viral diseases, may provide guidance for diagnosis. In the study by Tang et al., which compared 73 patients with COVID-19 and 75 patients with H1N1 pneumonia, the mean platelet counts of the COVID-19 and influenza patients were 166.5×10^3 and 123×10^3, respectively. In our study too, the platelet count was found to be 208×10^3 in the COVID-19 group and 195×10^3 in the influenza group. When these two levels are compared, it is evident that the mean platelet levels of the influenza patients are lower than those of the COVID-19 patients.[21]

Studies in the literature have highlighted the relationship between thrombocytopenia and clinical severity of COVID-19 and mortality.[22–24] Although the changes in platelet count and

TABLE 2 Laboratory findings of the COVID-19 and influenza patients

Parameters	COVID-19 (n = 54)	Influenza (n = 43)	p value
Age	52,4 ± 17.2	60.5 ± 17.3	.024
CRP (mg/dl)	6,5 (1.8–17.9)	6.6 (2.0–13.9)	.574
Leukocyte count (/ml)	5530 (4207–7275)	5060 (3760–9930)	.808
Neutrophil count (/ml) (absolute)	4087 ± 2600	4780 ± 2909	.314
Neutrophil percentage (%)	65 ± 13	65 ± 17	.929
Lymphocyte count (/ml) (absolute)	1372 ± 780	1311 ± 698	.708
Lymphocyte percentage (%)	25 ± 12	25 ± 15	.990
Eosinophil count (/ml) (absolute)	60 (10–145)	10 (0.0–85)	.013
Eosinophil percentage (%)	0.9 (0.3–2.3)	0.3 (0.0–1.4)	.035
Hemoglobin (gr/dl)	13.0 ± 1.7	12.5 ± 2.2	.221
Hematocrit (%)	39 ± 5	40 ± 7	.342
Platelet count (×10³/ml)	208 ± 74	195 ± 79	.395
PDW	16.2 (15.9–16.6)	12.2 (10.6–14.2)	<.001
RDW	40.3 (38.1–43.6)	41.3 (40.0–43.1)	.318
MPV	10.07 ± 1.36	10.59 ± 0.89	.027
MPV/platelet ratio	0.047 (0.034–0.063)	0.059 (0.045–0.082)	.034

Note: Data are shown as mean ± SD and median (IQR).
Abbreviations: CRP, C reactive protein; MPV, mean platelet volume; PDW, platelet distribution width, RDW, red cell distribution width.

function during the course of the disease are thought to be multifactorial, three main hypotheses have been put forth. The first is the bone marrow suppression caused by the infection and the decrease in the production of the platelets, the second is the destruction of the platelets as a result of the increased immune response, and the third is the consumption of the platelets by the formation of the microthrombi in the lungs and other organs.[13,23]

MPV defines the size of the platelets and is also a marker of inflammation.[25] In the literature, while MPV levels are found to be elevated in many diseases, it has been observed that they are lowered in viral diseases.[25–27] In the case of active inflammation, it has been reported that the platelet count increases because of the increased inflammatory cytokine activity and that the breakdown of these larger, young platelets at the inflammation site lowers the MPV.[28] In our study, it was found that MPV levels were low in both viral diseases and were statistically significantly lower in COVID-19 than in influenza ($p = .027$). In a study by Güçlü et al.,[23] the decrease in MPV in the follow-up of COVID-19 patients was found to be associated with mortality. As the number of people who succumbed to the disease was low in our study, such a comparison could not be made.

PDW, another platelet index, shows the platelet size distribution range. A high PDW level refers to the destruction and, in parallel, the size variations in the newly produced immature platelets.[29] In COVID-19, it is expected that the PDW value will be higher as a result of platelet production and destruction mechanisms influenced by the increased cytokine release and inflammation. Similar to the literature, the PDW level was found to be statistically significantly higher in COVID-19 patients than in the influenza patients in our study.[13,23]

Eosinophils play a prominent role in cell growth, adhesion, chemotaxis, degranulation, cell-to-cell interactions, and complement activation. In addition, eosinophils synthesize, store, and secrete cytokines, chemokines, and growth factors. Besides this, they function as antigen-presenting cells and regulate the processes associated with both T1 and T2 immunity. Although they have long been known to play a role in defense against helminths, their interactions with other pathogens continue to be investigated, and eosinopenia is known to occur especially in viral infections.[30] Recently, eosinophils have been shown to exhibit a variety of other functions, including immunoregulation and antiviral activity.[31] In a study by Yun et al. that compared 32 COVID-19 patients and 57 Influenza A and 84 Influenza B patients, the number of platelets in COVID-19 patients; It has been reported that the percentage and absolute number of eosinophils are decreased ($p < .05$).[17] In a study conducted by Chen et al.,[32] eosinopenia was found more often in patients with severe COVID-19 when compared with the influenza patients. In our study, similar to the data in the literature, when the influenza and COVID-19 groups were compared, it was found that both the absolute eosinophil count and the percentage were statistically significantly lower in influenza than in COVID-19.

5 | CONCLUSION

Sufficient data are not available in the literature about thrombocytopenia and the mechanisms of change in platelet indices that develop during the course of COVID-19. Further studies are needed to demonstrate the effects of these parameters on the early diagnosis of the disease, its differentiation from other viral pneumonias, prognosis, and mortality.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Neslihan Özçelik, Songül Özyurt, and Bilge Y. Kara: Purpose and design of the study, data collection, analysis and interpretation of data, drafting of manuscript, reviewing the paper, advice, and final approval. Neslihan Özçelik, Songül Özyurt, and Bilge Y. Kara: Interpretation of data, reviewing the paper, advices, and final approval. Aziz Gümüş: Design of the study, analysis and statistical interpretation of data. Ünal Şahin: Purpose and design of the study, acquisition of data, final approval.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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