Original Article

The İmportance of Hematological Parameters in the Prognosis of Patients with Severe COVID-19, A Single-center Retrospective Study

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Abstract

Background: Inflammation biomarkers known as acute phase reactants (APRs) show significant variations in serum concentrations during inflammation brought on by both viral and noninfectious diseases. The erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP), the lactate dehydrogenase (LDH), the ferritin, the fibrinogen, the procalcitonin, the D-dimer, and the troponin I are all significant APRs. During inflammation, the serum levels of each of these positive APRs rise. The sensitivity and specificity of hematologic parameters and indices are as high as the inflammatory biomarkers mentioned above for monitoring disease severity and treatment response. **Aim:** We aimed to evaluate the differences in hematological parameters and indices, and to reveal their treatment and prognostic values, especially in deceased patients with COVID-19. **Materials and Methods:** The hemogram parameters of 169 critical patients with COVID-19 (125 males and 44 females) who received inpatient treatment at …. between 1 March 2020 and 31 December 2021 were analyzed retrospectively. The patients were divided into two groups—deceased (77) and surviving (92)—noting demographic data such as age and gender. All analyses were performed using SPSS 25.0. **Results:** Analyses of the hematological parameters used during the treatment processes revealed statistically significant differences between the two patient groups. White blood cell (WBC), neutrophil, and neutrophil-to-lymphocyte ratio (NLR) values were significantly higher (P = 0.019, P = 0.000 and P = 0.000, respectively) for deceased subjects, while lymphocyte, platelet and plateletcrit (PCT) values were significantly lower (for all values, P = 0.000). Platelet volume (MPV) and platelet distribution width (PDW), as well as MPV/PLT, PDW/PLT, MPV/PCT, and PDW/PCT, levels were significantly higher in deceased subjects (P = 0.000). Particularly in our deceased cases, receiver operating characteristic analyses were performed to reveal the importance of such analyses in prognostic status evaluation in COVID-19 since the hematological parameters are quite different. Cut-off values were determined for each parameter, and sensitivity and specificity ratios were calculated. While the sensitivities of MPV/PLT, PDW/PLT, MPV/PCT, and PDW/PCT indices are over 80%, neutrophil and white blood cell sensitivities were found to be lower (74%, 68.8%, respectively). **Conclusion:** In addition to

Introduction

The coronavirus disease (COVID-19), which emerged in December 2019 in Wuhan, China, is a serious global health problem.[1] Once the virus enters the body, it causes viremia, and the main clinical manifestations are fever, sore throat, fatigue, diarrhea, and other

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NLR, which is an important biomarker, the hematological indices MPV/PLT, PDW/PLT, MPV/PCT, and PDW/PCT can be used to determine the risk of death in patients with severe COVID-19.

Keywords: *COVID-19, hemogram, MPV/PCT, MPV/PLT, neutrophil-to-lymphocyte ratio*

non-specific symptoms. COVID-19 is caused by a new type of coronavirus—severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Acute respiratory distress syndrome (ARDS) can cause severe pneumonia, which can progress to multiple organ failure and death. Additionally, comorbidities such diabetes mellitus, HT, and cardiovascular disease increase illness severity and mortality.[3]

SARS-CoV-2 infection causes immunological dysregulation, as well as abnormalities in cytokine release and immune cell activation. Sepsis caused by SARS-CoV-2 has been found to correlate with patients' autoimmune profiles and characterize their clinical progression.[4]

During the incubation period and early stage of COVID-19, the lymphocyte count is normal or slightly decreased; however, 7 to 14 days after the onset of main symptoms, there is a general increase in inflammatory mediators (cytokine storm), resulting in marked lymphopenia and thrombocytopenia as a result of hyperactivation of platelets.[5] Patients with COVID-19 frequently experience lymphopenia, neutrophilia, and moderate thrombocytopenia in addition to other hematological abnormalities. Depending on the circumstances, the leukocyte count could be normal, low, or high. In some studies, lung imaging—the primary test for disease type classification—is supplemented with the lymphocyte count as a predictor of disease severity. Another predictor of the severity and prognosis of an illness is the platelet count.[6]

Inflammation biomarkers known as acute phase reactants (APRs) show significant variations in serum concentrations during inflammation brought on by both viral and non-infectious diseases. The erythrocyte sedimentation rate (ESR), the C-reactive protein (CRP), the lactate dehydrogenase (LDH), the ferritin, the fibrinogen, the procalcitonin, the D-dimer, and the troponin I are all significant APRs. During inflammation, the serum levels of each of these positive APRs rise.[7] Age, lymphopenia, leucocytosis, and elevated ALT, LDH, high-sensitivity cardiac troponin I, creatine kinase, d-dimer, serum ferritin, IL-6, prothrombin time, creatinine, and procalcitonin were also associated with death.[8]

The aim of this study is to examine the effectiveness of routine laboratory complete blood count parameters and rates as diagnostic and prognostic criteria for severe COVID-19.

Materials and Methods

In this retrospective single-center investigation, critical and/or intensive care patients followed up in our hospital with the diagnosis of severe acute respiratory syndrome-coronavirus 2 (SARS-Cov-2) infection between 01.03.2020 and 31.12.2021 were included. Reverse transcription polymerase chain reaction (RT-PCR) tests were performed on throat and nasopharyngeal swab samples from all patients screened upon admission to determine SARS-CoV-2 infection. The severity of the disease was determined according to the World Health Organization criteria; Patients with tachypnea (≥30/min), oxygen saturation in room air <90%, severe clinical condition with bilateral diffuse pulmonary infiltrate, and critical intensive care patients who developed ARDS were included. (Lively direction for COVID-19 clinical management. WHO REFERENCE NUMBER: WHO/2019-nCoV/clinical/2021.2 (https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2). The patients were examined in two groups as convalescent and deceased in the intensive care unit, and the hemogram parameters of both groups were compared retrospectively.

ROC analyzes (Receiver Operating Characteristics) were performed to reveal its importance in the evaluation of the prognostic status in COVID-19, especially in our deceased cases, since the hematological parameters are very different. Cut-off values were determined for each parameter, and sensitivity and specificity ratios were calculated. On the Sysmex XN-1000 hematological analyzer, a complete blood count was done.

Statistical analysis

SPSS 25.0 (Statistical Package for Social Sciences, Chicago, USA) was used for all analyses.

The Kolmogorov–Smirnov test was employed to define distribution. The median and interquartile range (IQR) were used to summarize the variables (Tukey's Hinges Percentile). Independent-Samples Mann–Whitney U Test was used to assess the variations in the patient group data. In addition, optimal cut-off values, sensitivity, and specificity values were determined by ROC analysis. The results were considered statistically significant when the *P* value was below 0.05 (two-tailed testing).

Inclusion and exclusion criteria

Inclusion criteria;

Table 1: Hematological parameters in COVID-19 groups

	Survivor *n*=92	Non-survivor *n*=77	*P*
Age (years)	57 (41-65)	68 (59-75)	0.000
Gender (M/F)	69/23	69/23	-
WBC (10^3/μL)	8.36 (6.85-11.51)	11.60 (8.26-16.68)	0.004
Neutrophil (N) (10^3/μL)	6.46 (4.68-9.31)	10.42 (7.30-15.62)	0.000
Lymphocyte (L) (10^3/μL)	0.850 (0.612-1.110)	0.430 (0.330-0.680)	0.000
N/L Ratio	7.75 (5.0212.83)	23.37 (14.46-35.63)	0.000
PLT (10^3/μL)	248 (199-315)	146 (110-225)	0.000
MPV (fL)	10.10 (9.50-10.60)	11.60 (10.85-12.35)	0.000
PDW (fL)	11.20 (10.10-12.27)	14.20 (12.20-16.20)	0.000
MPV/PLT	0.039 (0.030-0.052)	0.080 (0.048-0.116)	0.000
PDW/PLT	0.044 (0.033-0.044)	0.100 (0.062-0.160)	0.000
PCT (%)	0.25 (0.20-0.30)	0.18 (0.11-0.24)	0.000
MPV/PCT	40.24 (31.72-50.25)	68.49 (44.34-90.97)	0.000
PDW/PCT	44.13 (33.72-50.20)	85.24 (54.02-132.38)	0.000

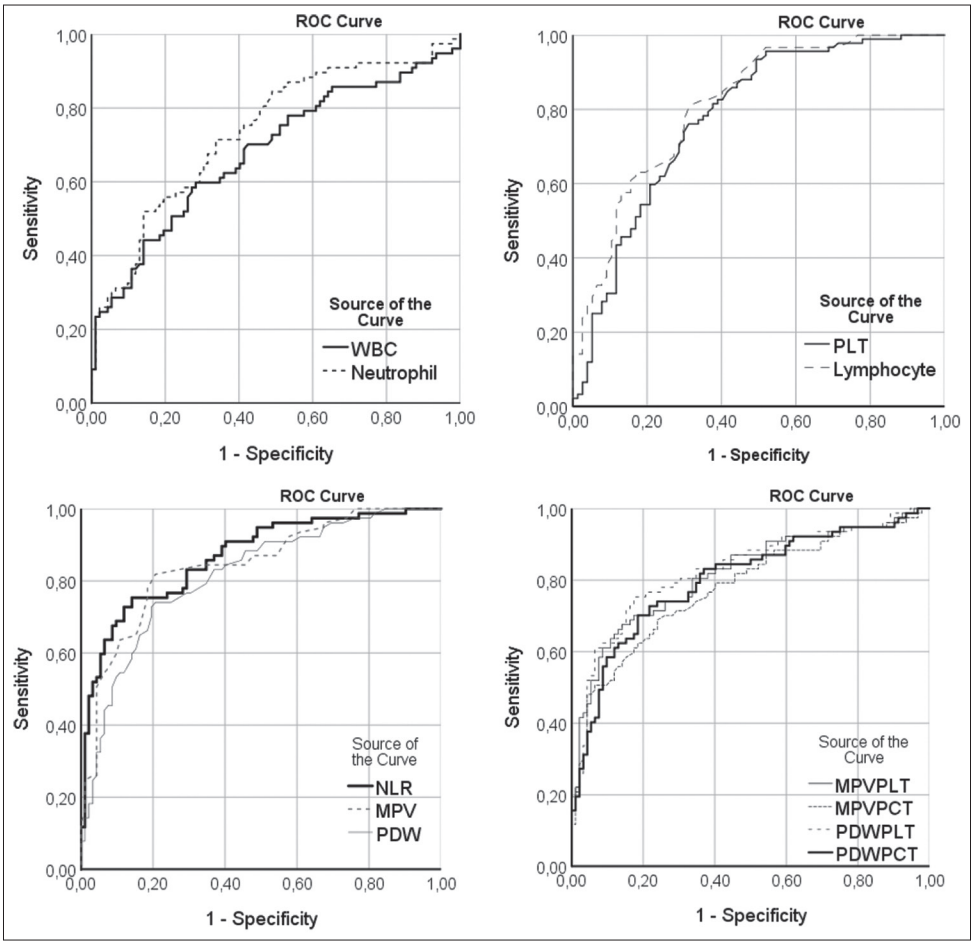

Figure 1: ROC analysis of WBC, Neutrophil, PLT, Lymphocyte, NLR, MPV, PDW, and hematologic indexes in SARS-CoV-2 patients

(1) Patients over the age of 18,
(2) Critical patients taken to intensive care,
(3) The length of stay in the ICU is more than 24 hours.

Exclusion criteria;
(1) Patients under 18 years of age,
(2) Patients with hematological malignancies,
(3) The length of stay in the ICU is less than 24 hours.

Results

The study had 169 patients in all, including 44 women and 125 males. 77 of our patients aged between 44 and 92 died, and 92 of them aged between 23 and 83

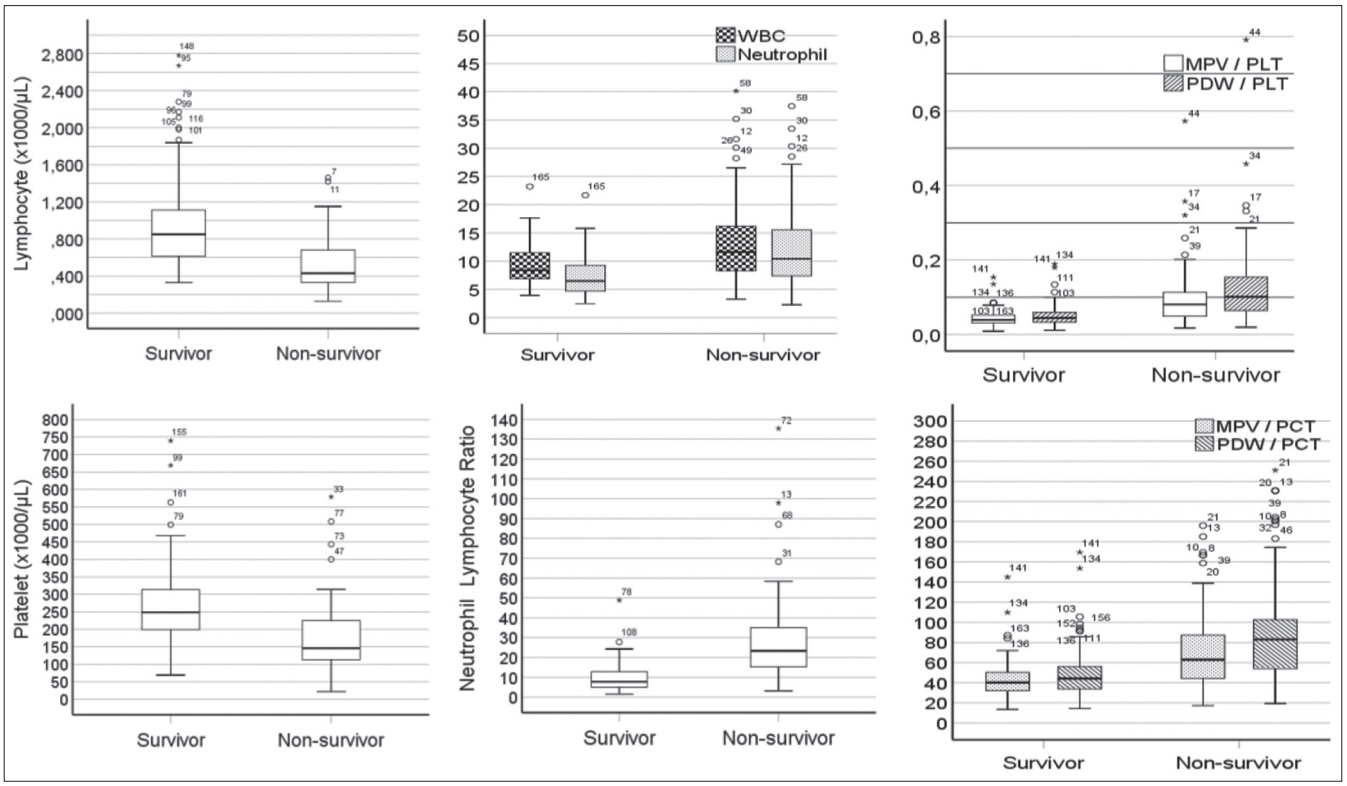

Figure 2: Box plots of Lymphocyte, Platelet, WBC, Neutrophil, Neutrophil Lymphocyte Ratio, and other hematologic indexes in SARS-CoV-2 patients

Table 2: ROC analyzes of parameters in COVID-19 survivor and non-survivor groups

	ROC Analysis					
	Sens. %	**Spec. %**	**Optimal Cut-off**	**AUC**	**ConfidenceInterval**	***P***
WBC	68.8	58.7	9.08	0.681	0.598	0.763	0.000
Neutrophil (N)	74.0	59.8	7.48	0.736	0.660	0.812	0.000
Lymphocyte (L)	81.5	67.5	0.575	0814	0.749	0.878	0.000
N/L Ratio	85.7	65.2	10.2	0.867	0.812	0.921	0.000
PLT	82.6	61.0	176.0	0.779	0.707	0.850	0.000
MPV	81.8	79.3	10.6	0.844	0.784	0.904	0.000
PDW	83.1	63.0	11.7	0.815	0.750	0.879	0.000
MPV/PLT	80.5	66.3	0.046	0.815	0.749	0.882	0.000
PDW/PLT	83.1	64.1	0.051	0.828	0.763	0.893	0.000
PCT (%)	84.8	51.9	0.182	0.724	0.646	0.802	0.000
MPV/PCT	81.8	54.7	41.8	0.779	0.707	0.850	0.000
PDW/PCT	83.1	66.3	49.5	0.801	0.732	0.869	0.000

Sens=Sensitivity, Spec=Specificity, ROC=Receiver Operating Characteristic, AUC=Area Under Curve

recovered and were discharged. Demographic structures and hematological parameters of both groups are given in Table 1. WBC, neutrophil, and NLR were significantly higher in the deceased (p: 0.000 for all), while lymphocyte and platelet and PCT values were significantly lower (p: 0.000 for all). MPV and PDW, as well as hematological index parameters MPV/PLT, PDW/PLT, MPV/PCT, and PDW/PCT were significantly higher in deceased patients (p: 0.000).

ROC analyzes were performed to reveal its importance in the evaluation of the prognostic status in COVID-19, especially in our deceased cases, since the hematological parameters are very different. Cut-off values were determined for each parameter, and sensitivity and specificity ratios were calculated. While the sensitivities of MPV/PLT, PDW/PLT, MPV/PCT, and PDW/PCT indices are over 80%, neutrophil and white blood cell sensitivities were found to be lower (74%, 68.8%, respectively) [Table 2, Figures 1 and 2].

Discussion

We found that WBC, neutrophil, and NLR values were

significantly higher, while lymphocyte, thrombocyte, and PCT values were significantly lower in deceased patients with COVID-19 compared to survivors. In addition, MPV, PDW, and other hematological index parameters (MPV/PLT, PDW/PLT, MPV/PCT, and PDW/PCT) were significantly higher in deceased patients with COVID-19.

Yardımcı *et al*.[9] reported that thrombocytopenia is one of the most common findings in patients with COVID-19 and that PCT, one of the platelet indices, has a predictive role in the correlation between platelet function and the clinical course of COVID-19 pneumonia. Seyit *et al*.[10] stated that the decrease in platelet count is higher than that of lymphocytes, which indicates that more importance should be given to thrombocythemia in the follow-up of patients with COVID-19.

In the current study, the lymphocyte count, which was already low in critical COVID-19 cases, was even lower in those who died. In addition, the significant decrease in platelet count according to prognostic weight in Seyit *et al*.'s[10] study supports our data. Likewise, Ahmadi *et al*.[6] noted that lymphocyte and platelet counts are the main indicators of disease severity and prognosis.

NLR increases with severe infection or systemic inflammation due to the severity of clinical status and outcome, as has been amply documented.[11] In the current study, increased neutrophil and decreased lymphocyte counts were used to define elevated NLR. The innate immune system's physiological reactions to systemic inflammation include lymphocyte death and neutrophil growth.[12] A growing body of research has shown that viral infection increases neutrophil levels and initiates neutrophil-mediated innate immune responses, even though it is widely known that neutrophil counts are enhanced during bacterial invasion.[13] According to Qin *et al*.,[14] severe COVID-19 cases tend to have greater NLRs, and NLR monitoring is effective in the early detection of critical illness. In Peng *et al*.'s[15] study, which compared patients with and without ARDS, the former group had elevated NLR levels but lower lymphocyte and platelet levels.

According to the ROC curve data, lymphocytes had a higher AUC value than other variables, at 0.836 (95% CI 0.776-0.886). The most accurate cut-off for lymphocytes was 0.87, which had a 70.97% sensitivity and an 88.05% specificity. There is rising interest in the connection between a reduced lymphocyte count in the peripheral blood and the development of ARDS brought on by SARS-CoV-2 since many COVID-19 patients with ARDS present with a dysregulated immunological state.[16]

In the ROC analysis of our AP and BPH case results, NLR was found to have a high AUC (0.867, 95% CI: 0.812-0.921) at the optimal cut-off value of NLR10.2 (sensitivity 85.7%, specificity 65.2%). In the critical-severe and non-survival groups, Çavuş Z *et al*. they stated that they found a high AUC (0.776, 95% CI: 0.741-0.803) when they used ROC with the NLR cut-off set to 3.1 (sensitivity 87%, specificity 54.1%). They reported that platelet-derived parameters, namely thrombocyte-derived parameters (PCT), mean platelet volume (MPV), and platelet distribution width (PDW) have prognostic value in COVID-19 pneumonia, according to their research results.[17]

The hematological analyzer during the hemogram test calculates MPV, a precise measurement of platelet size. The severity of the inflammatory process, the presence of the disease, the increased risk of disease development, the increased risk of thrombotic complications, the increased risk of death, and the patient's response to the recommended treatment must all be taken into account when establishing an MPV cut-off value, according to Korniluk *et al*.[18] In the ROC analysis of the current study, when 10.6 fL is taken as the optimal cut-off value, MPV with 81.8% sensitivity and 79.3% specificity may contribute to the treatment process and prognostic evaluation of critical COVID-19 cases. Zhao *et al*.[19] came to the conclusion that lower platelet crit and larger MPV and PDW are linked to a higher probability of poor prognosis in critically ill patients.

Platelet count and mean platelet volume are used to calculate PCT. In one study, Lippi *et al*.[20] explained that there is a relationship between prognosis and initial platelets in patients with COVID-19, and that PCT is found to be lower in patients with severe COVID-19 pneumonia, thus, a decrease in PCT is seen in patients who died in the intensive care unit due to sepsis.

In our study, the % PCT was significantly lower in the deceased than in the survivors (respectively, 0.18 and 0.25). We verified that it is simple PCT from routine complete blood counts can be simple and inexpensive a predictor of the clinical course of COVID-19 pneumonia.

Patients with elevated MPV and PDW or decreased PLT and PCT have a lower life time than patients with normal other PLT indicators, according to research by Zhang S *et al*.[21] Golwala *et al*.,[22] on the other hand, stated that they found MPV/PCT ratio to be a better predictor of mortality than platelet count or thrombocytocrit in their studies. In our study, patients with abnormally high MPV, PDW, and abnormally low PLT had a more severe prognosis. In addition, their indices were significantly higher in non-survivors. MPV/PLT, PDW/PLT, MPV/PCT,

and PDW/PCT indices with significantly higher values in non-survivors can be considered predictors of mortality.

Limitations

The limitations of our study include the low number of patients.

Retrospective and evaluation of the laboratory test data of the cases included in the study with Inclusion and exclusion criteria.

Some therapeutic drugs antibiotics and other basic parameters such as gender and age may have an effect on hematological indices. In addition, we could not compare it with other infective sepsis cases.

A larger prospective study should compare the effects of various therapeutics and pathogenic agents on disease severity.

Conclusion

This retrospective observational study demonstrated that in addition to the NLR, which is an important biomarker for the risk of death in severe COVID-19 cases, the hematological indices MPV/PLT, PDW/PLT, MPV/PCT, and PDW/PCT can be used. Low PCT levels and high MPV and PDW levels may be indicators of poor prognosis for patients with COVID-19. Low PCT, high MPV, PDW levels, and changes in other indices may be important factors in the early prognosis of pneumonia, but need to be supported by both prospective and larger sample studies.

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Conflicts of interest

There are no conflicts of interest.

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