RESEARCH ARTICLE / ARAŞTIRMA MAKALESI

Relationship Of Platelet Subgroups With Prognosis And Mortality İn Patients With Mild, Severe And Critical COVID-19

Hafif, Şiddetli Ve Kritik COVID-19 Hastalarında Trombosit Alt Gruplarının Prognoz Ve Mortalite İle İlişkisi

Zeynep ERGENÇ[1], Gülsüm KAYA[2], Özlem Karaca OCAK[3], Özgür İNCE[4]
Serkan GÜNAY[5], Hasan ERGENÇ[1]

[1] *Yalova State Hospital, Department of Internal Medicine, Yalova, TÜRKİYE*
[2] *Yalova State Hospital, Department of Support and Quality Directorate, Yalova, TÜRKİYE*
[3] *Medicana İnternational Hospital, Department of General Surgeon, Samsun, TÜRKİYE*
[4] *Medicana İnternational Hospital, Department of Pulmonology, Samsun, TÜRKİYE*
[5] *Hitit University Erol Olcok Training and Research Hospital, Department of Emergency, Çorum, TÜRKİYE*

Yazışma Adresi / Correspondence:
Hasan ERGENÇ
MD, Yalova State Hospital, Department of Internal Medicine, Yalova, TÜRKİYE

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Zeynep ERGENÇ http://orcid.org/0000-0001-7598-4508 drzeyneperturk@gmail.com
Gülsüm KAYA http://orcid.org/0000-0003-2517-5512 gulsumkaya78@gmail.com
Özlem Karaca OCAK http://orcid.org/0000-0003-3637-4074 karacaocakozlem@gmail.com
Özgür İNCE http://orcid.org/0000-0002-1783-0292 dr.ozgurince@hotmail.com
Serkan GÜNAY http://orcid.org/0000-0002-8343-0916 drsrkngny@gmail.com
Hasan ERGENÇ http://orcid.org/0000-0003-0519-0264 hasanergenc.dr@gmail.com

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Abstract

Aims This study investigates whether platelet-related indicators including platelet count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), Plateletcrit (PCT), and platelet large cell ratio (P-LCR) could be effective biomarkers in the prognostic of 2019-novel coronavirus disease (COVID-19) fatality.

Materials and Methods Out of 380 patients diagnosed with COVID-19, 98 patients were randomly and retrospectively were included in our study. Detection of COVID-19 was performed according to the World Health Organization (WHO) guidelines and using quantitative polymer chain reaction (qPCR). Clinical and laboratory data and medical records for all study participants were collected from a digital version of their health history at Ayancik State Hospital and Diyarbakır Gazi Yaşargil Training and Research Hospital. All patients were followed up daily until discharge or death and were eventually classified into three categories: Mild, severe, and critical patients. Data analysis was performed using SPSS-26 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z), and a 95% confidence level was selected. $P < 0.5$ was considered statistically significant.

Results Of participants, 64.3% of the patients are 65 years and older, 54.1% are male, 60.2% survived, 39.8 % died and 35.7% are in critical condition. The mortality rate is higher in males and 65 years and older. While PLT (190,24) and PCT (0,21) measurements were higher in surviving patients, MPV (10,67), PDW (16,15) and P-LCR (30,82) measurements were higher in deceased patients. PDW and PCT measurements are more effective in predicting mortality state according to Roc analysis. The measurement that best predicts the deceased status of patients who are positive according to the cut-off value determined is PDW (0.621), and the measurement that best estimates the surviving patients is PLT (0.925).

Conclusion In our study, it was concluded that high MPV, PDW and P-LCR and low platelet values are associated with poor prognosis of COVID-19 disease, and PDW and PCT measurements are more effective in predicting mortality in patients with COVID-19 infection. Laboratory parameters such as MPV, PDW, P-LCR, PDW, and PCT can provide clinicians with predictions of prognosis and mortality from COVID-19 disease.

Keywords COVID-19; Platelets count; Platelet indices; Prognosis; Disease severity; Mortality

Özet

Amaçlar Bu çalışmada amaç, trombosit sayısı (PLT), ortalama trombosit hacmi (MPV), trombosit dağılım genişliği (PDW), Plateletkrit (PCT) ve trombosit büyük hücre oranı (P-LCR) dahil olmak üzere trombositle ilgili göstergelerin yeni koronavirüs hastalığı 2019 (COVID-19)'da mortalite üzerine etkili biyobelirteçler olup olamayacağını araştırmaktadır.

Gereç ve Yöntemler Çalışmaya, COVID-19 tanılı 380 hastadan rastgele ve retrospektif olarak 98 hasta çalışmamıza dahil edildi. COVID-19 tanısı, Dünya Sağlık Örgütü (DSÖ) yönergelerine göre ve kantitatif polimer zincir reaksiyonu (qPCR) kullanılarak yapıldı. Ayancık Devlet Hastanesi ve Diyarbakır Gazi Yaşargil Eğitim ve Araştırma Hastanesi'ndeki çalışmaya alınan hastaların özgeçmişine ait bilgiler ile klinik ve laboratuvar verileri hastane bilgi sisteminden alındı. Tüm hastalar günlük olarak takip edildi ve hafif, şiddetli ve kritik hastalar olmak üzere üç kategoriye ayrıldı. Veri analizi SPSS-26 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z) kullanılarak yapıldı ve %95 güven düzeyi seçildi. $P < 0.5$ istatistiksel olarak anlamlı kabul edildi.

Bulgular Katılımcıların %64,3'ü 65 yaş ve üzerinde, %54,1'i erkek, %60,2'si taburcu oldu, %39,8'i exitus (ex) oldu ve %35,7'sinin durumu kritikti. Ölüm oranı erkeklerde ve 65 yaş ve üzerinde daha yüksekti. Taburcu olan hastalarda PLT (190,24) ve PCT (0,21) ölçümleri daha yüksek bulunurken, ex hastalarda MPV (10,67), PDW (16,15) ve P-LCR (30,82) ölçümleri daha yüksekti. Belirlenen cut-off değerine göre pozitif olan hastaların ölüm durumunu en iyi tahmin eden ölçüm PDW (0,621), yaşayan hastaları en iyi tahmin eden ölçüm ise PLT (0,925) idi.

Sonuç Çalışmamızda yüksek MPV, PDW ve P-LCR ile düşük trombosit değerlerinin COVID-19 hastalığının kötü prognozu ile ilişkili olduğu ve PDW ve PCT ölçümlerinin COVID-19 hastalarında mortaliteyi öngörmede daha etkili olduğu sonucuna varıldı. MPV, PDW, P-LCR, PDW ve PCT gibi laboratuvar parametreleri, klinisyenlere COVID-19 hastalığından prognoz ve mortalite tahminleri sağlayabilir.

Anahtar Kelimeler COVID-19; trombosit sayısı; Trombosit indeksleri; prognoz; Hastalık şiddeti; Ölüm oranı

INTRODUCTION

A pneumonia outbreak occurred in December 2019 in Wuhan, China. This epidemic could not be brought under control and soon spread to all provinces of China. Then it spread all over the world, especially in Europe. It was named Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) by the WHO. The disease caused by this virus was named COVID-19 (1). SARS-CoV-2 first appeared in Turkey on March 11, 2020, and spread throughout the country in a short time.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus belonging to the beta-coronavirus family. This virus is highly contagious and spreads by droplet or direct contact[1]. The course of the post-infectious disease differs in people. Lung involvement has a very broad clinical spectrum, from mild to critical (2).

Early detection of severe cases and early initiation of treatment significantly reduce mortality and hospital stay (3). Therefore, there is a need for biomarkers that will provide quick, simple, and easy results regarding the clinical course of the disease in the early period.

COVID-19 causes a tendency to thrombosis in both the venous and arterial systems with the activation of the coagulation system by several risk factors such as increased inflammation, platelet activation, endothelial dysfunction, and stasis in the blood flow due to immobilization (4). It has been revealed that there are dynamic changes in the early period of hemogram parameters such as white blood cell (WBC) count, neutrophil count, lymphocyte count, and neutrophil/lymphocyte ratio (NLR) in the course of COVID-19 (5). However, no comprehensive research was found in the literature on dynamic changes in platelets and their subgroups at the time of admission in COVID-19 cases. Platelets are blood cells that are effective not only in hemostasis but also in inflammation and immune response. Studies are showing that thrombocytopenia develops especially in COVID-19 cases with lung involvement (6).

In this study, we aimed to demonstrate that the parameters of platelet counts, plateletcrit (PCT, %), mean platelet volume (MPV, %), platelet distribution width (PDW, %), and platelet larger cell ratio (P-LCR, %) can be used as predictors of mortality in the early period.

MATERIAL and METHODS

A total of 98 patients with COVID-19 infection admitted to Ayancik State Hospital and Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital between April 4, 2020, and August 28, 2020, were retrospectively analyzed in this multicenter study.

Written informed consent was obtained from all study participants and was previously approved by the Ethics Committee of Medicana International Samsun Hospital (decision no 7156, 09.12.2021). All study procedures were by the principles of the 1964 Helsinki Declaration and subsequent 2013 amendment.

Clinical and laboratory data and medical records of all study participants were digitally recorded at Ayancik State Hospital and Health Sciences University Diyarbakır Gazi Yaşargil Training and Research Hospital. All patients were followed up daily until discharge or death and finally classified into two categories: Mortality and Disease Severity.

Statistical Analysis

Statistics for categorical (qualitative) variables were presented as frequency and (n (%)), and for numerical (quantitative) variables as mean, standard deviation (mean ± sd), minimum, maximum, and median (Max-Min (M) values were used for numerical (quantitative) variables.

In the study, the relationship between right/exitus (EX) status, disease severity, and group variables was analyzed using the chi-square test, the differences in measurements by survivin/ex status, disease severity, demographic characteristics (gender, age) independent groups t, one-way ANOVA tests.

In addition, Tukey (variances homogeneous), Tamhane (variances nonhomogeneous) multiple comparison tests (post hoc) were used for disease severity. ROC analysis was used for cut-off values/ EX status, prediction levels, and probabilities of disease severity of the identified measurements.

Sensitivity (detection rate of EX status, disease severity), specificity (survival, rate of detection of mild survivorship), positive predictive (EX status of the positive value of the measurement, the rate of being critical), negative predictive (survival of the negative value of the measurement, light circumvention) probabilities were calculated. The chi-square test; is a testing technique used to determine the relationship between two categorical variables.

Independent groups t-test; is a test technique used to compare two independent groups in terms of quantitative variables. One-way ANOVA test; Independent k (k> 2) is the test technique used to compare the group in terms of quantitative variable ROC analysis; These are the test techniques in which the relevant disease variable is predicted according to the cut-off values of the measurements in the diagnostic tests.

Data analysis was performed using SPSS-26 for Windows (Statistical Package for Social Science, SPSS Inc. Chicago IL, USA®Z), and a 95% confidence level was selected. P < 0.5 was considered statistically significant.

RESULTS

The comparison of laboratory parameters according to the death and survival status of the patients included in the study is shown in Table 1. It was observed that there was a significant difference between the laboratory parameters of PLT, MPV, PCT, PDW and P-LCR of the patients who died and those who survived (p= 0.001, p=0.023, p=0.000, p=0.000 and p=0.003, respectively). When the laboratory distribution of the patients was evaluated according to age, surviving and EX, there was no significant difference between PLT, MPV, PCT, PDW and P-LCR (**Table 1).**

Table 1: Comparison of Measurements According to Mortality Status and Age

	Outcome	**Alive**	**EX**	**t**	**p**
laboratory parameters	PLT	190,24±56,67	157,49±38,33	3,412	**0,001***
	MPV	10,28±0,87	10,67±0,78	-2,303	**0,023***
	PCT	0,21±0,06	0,16±0,04	4,766	**0,000***
	PDW	13,94±2,59	16,15±1,57	-5,238	**0,000***
	P-LCR	26,65±7,05	30,82±6,22	-2,995	**0,003***
	Age	**65<**	**65≥**	**t**	**p**
Alive patients **laboratory parameters**	PLT	201,11±47,64	181,06±62,58	1,364	**0,178**
	MPV	10,27±0,79	10,28±0,95	-0,018	**0,986**
	PCT	0,22±0,05	0,2±0,06	1,564	**0,123**
	PDW	14,17±1,97	13,75±3,04	0,607	**0,546**
	P-LCR	27,63±5,83	25,83±7,93	0,972	**0,335**
EX patients **laboratory parameters**	PLT	162,13±20,17	156,29±41,94	0,562	**0,579**
	MPV	10,45±0,51	10,73±0,83	-0,911	**0,368**
	PCT	0,17±0,02	0,16±0,04	0,109	**0,914**
	PDW	16,5±0,37	16,06±1,75	0,704	**0,486**
	P-LCR	29,7±3,04	31,1±6,81	-0,861	**0,397**

* **p <0.05** significant difference, **p> 0.05** no significant difference; t test

ROC Analysis of Measures Determined for Mortality Status is shown in **Table 2**. Laboratory parameters such as PLT, MPV, PCT, PDW, P-LCR have been shown to make a statistically significant difference in estimating the mortality status of patients (p<0.05). In addition, PDW and PCT measurements were found to be more effective in predicting mortality **(Figure 1).**

Table-2 ROC Analysis of Measurements Determined for Mortality Status

Variable	Domain	p	95% CI	
			Lower	Top
MPV	0,623	**0,040***	0,512	0,734
PDW	0,760	**0,000***	0,664	0,856
P-LCR	0,680	**0,003***	0,575	0,785
PLT	0,674	**0,004***	0,569	0,780
PCT	0,741	**0,000***	0,644	0,839

** **p <0.05** significant area, p> 0.05 not significant; ROC*

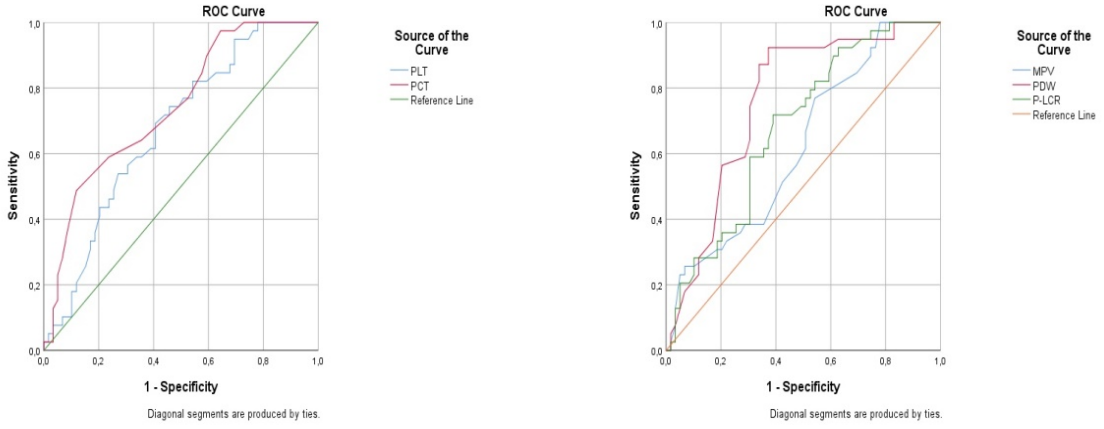

Figure 1: ROC curves for MPV, PDW, P-LCR and PLT, PCT rates of Mortality cases

DISCUSSION

There were many hematological parameters used in the early period of prognosis in COVID-19 infection. Especially, neutrophil-lymphocyte ratio, lymphopenia, C-reactive protein, D-dimer, LDH, ferritin, and high levels of interleukin-6 (IL-6) are among the laboratory parameters used as predictors of mortality in the early period (7). Studies are showing that platelet count and its subgroups can be used in the early prognosis of many diseases with acute and chronic inflammation (6,8). It is said that dynamic changes in platelets and subgroups, especially in the early period of the course of COVID-19 infection, may be associated with mortality in the early period (9,10). This study reveals that thrombocytes and their subgroups can be used as biomarkers to predict disease severity and mortality in the early period.

In the literature, the number of studies revealing the relationship between platelet subgroups and COVID-19 infection in a multifaceted manner and by evaluating all subgroups one by one is very insufficient. The results of our study revealed that Platelet count, MPV, PCT, PDW, and P-LCR values can be used in the early period in determining

disease severity and mortality. In particular, the fact that Plt and PCT values are high at the time of application in COVID-19 infection reveals that the clinical course will be mild in the early period. As in our study, studies are showing that the development of thrombocytopenia, especially in the early period, can be used as a poor prognostic marker in COVID-19 infection (6,11-13).

In a study conducted with 73 critically ill patients diagnosed with COVID-19, the relationship between PLT, MPV, PDW, and PCT values at the time of admission with mortality and prognosis was examined. It was determined that the patients who recovered had high platelet counts at the time of admission. In the same study, it was observed that critically ill patients with high MPV, PDW, and P-LCR values at the time of admission had more severe disease and died (10). In our study, our patients with ex were found to have high MPV, PDW, and P-LCR values at the time of admission, which is consistent with the literature.

In a study by Çelik et al., it was revealed that P-LCR values are high at the time of admission in people with coronary artery disease, and this elevation may be associated with thrombus formation and mortality in the coronary arteries (14). In a study conducted by DerisBesada et al (2020), it was revealed that vascular complications and diabetic nephropathy development were higher in patients with high P-LCR values (15).

Limitations

One of the limitations of this study was its small sample size, and it is suggested that these studies be performed on larger sample sizes to confirm the findings of this study and obtain more accurate results. The results of this study can be used as a baseline for more detailed future studies of the role of platelet count and platelet indices in diagnosing disease severity and mortality in COVID-19 patients.

CONCLUSİON

This study reveals that Platelet count and its subgroups can be predictive of the clinical course and prognosis in COVID-19 patients. It was determined that the prognosis was good especially for the patients whose Platelet and PCT values were high at the time of admission. It was determined that patients with high MPV, PDW, and P-LCR values at the time of admission were critically ill patients who needed mechanical ventilators, and most of these patients were ex. PDW was found to be the best predictor of clinical course and mortality, especially in the early period. Further studies are needed to confirm our results so that the Platelets and platelets change can be used as a marker to predict disease severity and mortality in COVID-19.

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Ethıcal Declerations

Ethics committee approval of this study was obtained from Medicana International Samsun Hospital with the date of 09 December 2021 and number 7156.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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Author Contributions:

Z.E. and H.E.: Concept, design, literature search, data analysis, manuscript preparation; G.K., ÖKO, ÖI: Concept, Design, Data acquisition, manuscript review, literature search.

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