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Relationship between mean platelet volume and intensive care unit requirement in COVID-19 patients

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ABSTRACT

Objective: Our primary aim in this study is to examine the relationship between the mean platelet volume (MPV) and the intensive care unit (ICU) requirement in patients with 2019 coronavirus disease (COVID-19). The secondary aim of the study is to investigate the relationship between age and the ICU requirement.

Material and Method: This retrospective observational study was conducted with patients who were diagnosed with COVID-19 in the emergency department of a tertiary hospital. The relationship between the ICU requirement and MPV was evaluated using the Mann-Whitney U test. ROC analysis was performed to determine the predictive accuracy of the 8.3 cut-off value of MPV in those younger than 58 years old patients. CHAID analysis was used as the decision tree method in analyzing the data. The relationship between ICU requirement and MPV were evaluated.

Results: There were 711 patients included in this study. The median age of the population was 64 (49-76). According to the CHAID analysis, the study population was divided into 2 classes as those who aged 58 years or younger (Younger Group) and those who older than 58 years (Older Group), and the relationship between the 8.3 threshold value of MPV and the ICU requirement was analyzed. For the Younger group, a significant difference was found in terms of ICU requirement based on the 8.3 threshold value of MPV.

Conclusion: Advanced age, high MPV and PLT values in COVID-19 patients, are associated with the ICU requirement. The 8.3 threshold value of MPV can be used as one of the parameters determining the ICU requirement in relatively young patients. In the geriatric age group, it is not beneficial to use MPV measurement to assign the ICU requirement. Multi-center studies with a large number of patients are needed to present the strength of the results of our study more clearly.

Keywords: COVID-19, mean platelet volume, intensive care unit, platelet count, CHAID

INTRODUCTION

In December 2019, a series of unknown cases of acute respiratory disease occurred in Wuhan, the capital of China's Hubei province. It has been shown that the disease is caused by "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). On February 11, 2020, the World Health Organization (WHO) has officially named the disease as 2019 coronavirus disease (COVID-19). The disease rapidly spread from Wuhan to other regions around the world (1-3).

Most patients show mild symptoms, but some patients (especially those who elderly and/or patients with comorbidities) experience severe symptoms. In these patients, following does occur rapidly: acute respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis and coagulation disorders. Patients with COVID-19 and severe pneumonia have a worse prognosis than patients with the milder type. Therefore, early recognition of risk factors is very important for the treatment and prognosis of patients (4-6).

Platelets play an important role in inflammation and coagulation procedure. Activated platelets secrete a large number of substances that belong to the main factors of inflammation. Mean platelet volume (MPV) has been recognized as a key marker of platelet activation. MPV is a useful prognostic indicator for critically ill patients (7,8).

Our primary aim in this study is to examine the relationship between MPV values and intensive care unit (ICU) requirement in COVID-19 patients. The secondary aim of the study is to investigate the relationship between age and the ICU requirement.

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MATERIAL AND METHOD

This retrospective observational study was carried out in the ED of a tertitary hospital between September 1, 2020 and November 1, 2020. The study was carried out with the permission of Research Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Date: 29.03.2021, Decision No: 2021/514/198/28). This study was carried out in accordance with the principles of the Declaration of Helsinki.

All COVID-19 patients over the age of 18 who were hospitalized between September 1, 2020 and December 1, 2020 were included in this study. The diagnosis of COVID-19 was determined based on the World Health Organization (WHO) guidelines. This study includes only patients who had positive results in the real-time Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) test of nasal and pharyngeal swab samples (9). The digital records of the Hospital Information Management System was used to collect data. For the patients who were included this study, their age; gender; vital signs; chronic diseases; and laboratory tests were recorded on a format the time of application to the emergency department.

Statistical Analysis

Statistical analyzes were performed with IBM SPSS Statistics 26 (SPSS) and MedCalc Version 19 software. Normality was tested to examine the relationship between variables and ICU groups. Age, PLT (platelet), MPV (mean platelet volume), PLT/MPV data could not meet the normality assumption.

Comparisons of groups, Mann-Whitney U test was used for quantitative data, reported as median and 25th-75th. Chi-square test was used for qualitative data and reported as frequency and percentage.

CHAID analysis, a decision tree method, was used to test the hypothesis that the MPV variable affects the requirement for ICU in relation to age. CHAID analysis has advantages such as modeling using continuous and/or categorical variables and describing the relationship network of variables. CHAID analysis can provide tree-shaped, easy-to-understand outputs by detailing the relationships between independent variables. Due to the advantages it provides, CHAID analysis is used for data analysis in many disciplines (10).

In order to investigate in detail the diagnostic accuracy of the MPV 8.3 value for the ICU requirement, a receiver operating characteristic (ROC) analysis was performed with using the DeLong method (11). The area under the curve (AUC), sensitivity, specificity, PPV, NPV, and Youden's J index (YJI) were calculated. YJI and AUC were calculated to evaluate predictive accuracy of MPV 8.3 cutoff in terms of ICU need.

Statistical significance was based on a value of $p < 0.05$.

RESULTS

The study was continued with the data of 711 patients after the exclusion criteria were applied. While 596 patients did not need ICU, 115 patients required ICU. The patients who needed ICU requirement were 62 males and 53 females. There was no significant difference between the genders in terms of ICU requirement (p=0.442).

The median age of the population included in the study was 64 (49-76). The median age of the group with ICU requirement was 75 (65-81), while that of the group that did not need ICU was 61 (47-74). When evaluated in terms of age, there was a significant difference between the groups determined according to ICU requirement (p<0.001) (**Table 1**).

Table 1. Demographic and comorbidity data of the study population

Variables	Category	IU		ICU		Total		Sig.
		n	%	n	%	n	%	p
Sex	Male	298	50.0%	62	53.9%	360	50.6	0.442
	Female	298	50.0%	53	46.1%	351	49.4	
COPD	No	566	95.0%	103	89.6%	669	94.1%	0.024
	Yes	30	5.0%	12	10.4%	42	5.9%	
DM	No	438	73.5%	81	70.4%	519	73.0%	0.499
	Yes	158	26.5%	34	29.6%	192	27.0%	
HT	No	394	66.1%	70	60.9%	464	65.3%	0.280
	Yes	202	33.9%	45	39.1%	247	34.7%	
CHF	No	570	95.6%	96	83.5%	666	93.7%	<0.001
	Yes	26	4.4%	19	16.5%	45	6.3%	
CAD	No	550	92.3%	92	80.0%	642	90.3%	<0.001
	Yes	46	7.7%	23	20.0%	69	9.7%	
AF	No	587	98.5%	109	94.8%	696	97.9%	0.011
	Yes	9	1.5%	6	5.2%	15	2.1%	
CRF	No	558	93.6%	103	89.6%	661	93.0%	0.119
	Yes	38	6.4%	12	10.4%	50	7.0%	
CND	No	560	94.0%	101	87.8%	661	93.0%	0.019
	Yes	36	6.0%	14	12.2%	50	7.0%	
Total		596	100	115	100	711	100.0	
		IU		ICU		Total		
		Median	IQR	Median	IQR	Median	IQR	
Age		61	47-74	75	65-81	64	49-76	<0.001

IU: Inpatient unit, ICU: Intensive care unit, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, HT: Hypertension, CHF: Congestive Heart Failure, CAD: Coronary Artery Disease, AF: Atrial Fibrillation, CRF: Chronic Renal Failure, CND: Chronic Neurological Disease Sig: Significance

When ICU groups were compared according to the measurements of PLT, MPV, MPV/PLT used in the study, there was a significant difference for PLT and MPV, but no significant difference for MPV/PLT (**Table 2**).

Table 2. Comparison of PLT, MPV, MPV / PLT values according to the intensive care needs of COVID-19 patients

Variables	ICU	N (711)	Mean Rank	Mann-Whitney U	25th	Median	75th	p
PLT (10^3/uL)	NO	596	349.01	30101.5	158000	202000	254000	0.039
	YES	115	392.25					
MPV (μm^3)	NO	596	348.78	29965	7.90	8.60	9.40	0.033
	YES	115	393.43					
MPV / PLT	NO	596	359.60	32122	32.90	42.39	58.39	0.287
	YES	115	337.32					

ICU: Intensive Care Unit, PLT: platelet, MPV: Mean Platelet Volume, p: Asymptotic Significance (2-tailed)

In the CHAID analysis made based on the hypothesis that MPV may affect the ICU requirement in relation to age, thresholds 58 and 73 for age are important threshold values determined by CHAID analysis. For patients aged 58 and younger, the cut-off value of MPV of 8.3 was also obtained as the output of the CHAID analysis. ICU requirement is calculated as 6% for those who aged 58 and younger, 14.8% for those who aged 58 to 73, and 30.6% for those who older than 73. For those who 58 years and younger, the ICU requirement was 0.8% for those whose MPV value was less than 8.3, while it was determined that for those over 8.3, it was 9.8% (**Figure 1**).

Chi-square and Fisher's Exact tests were performed in order to analyze the relationship of the threshold value of 8.3 for MPV with the ICU requirement after divided the study population into 2 classes (as Younger Group and Older Group). For the Younger group, based on the 8.3 threshold value of MPV, a significant difference was found in terms of ICU requirement (p=0.002), while no significant difference was found in the patients with Older group in terms of ICU requirement (p=0.558) (**Table 3**).

Table 3. The relationship of the threshold value of 8.3 MPV with the need for intensive care in COVID-19 patients according to the age limit of 58

		ICU		Total	Significance
		No	Yes	n	p
≤58	≤ 8.3	118 (99.2%)	1 (0.8%)	119	0.002*
	>8.3	148 (90.2%)	16 (9.8%)	164	
	n	266	17	283	
>58	≤ 8.3	133 (78.7%)	36 (21.3%)	169	0.558
	>8.3	197 (76.1%)	62 (23.9%)	259	
	n	330	98	428	

*Fisher's Exact Test (2-sided) ICU: Intensive Care Unit

ROC analysis was performed to describe the accuracy of 8.3 threshold value of MPV for predicting ICU requirement in patients aged 58 years and younger (Younger group). By ROC analysis, it was calculated that AUC 0.692 (0.591-0.794), sensitivity 94.1, specificity 44.4, positive predictive value 9.8%, negative predictive value 99.2% and YJI 0.39. The p value for the AUC value was calculated as 0.008 (**Table 4, Figure 2**).

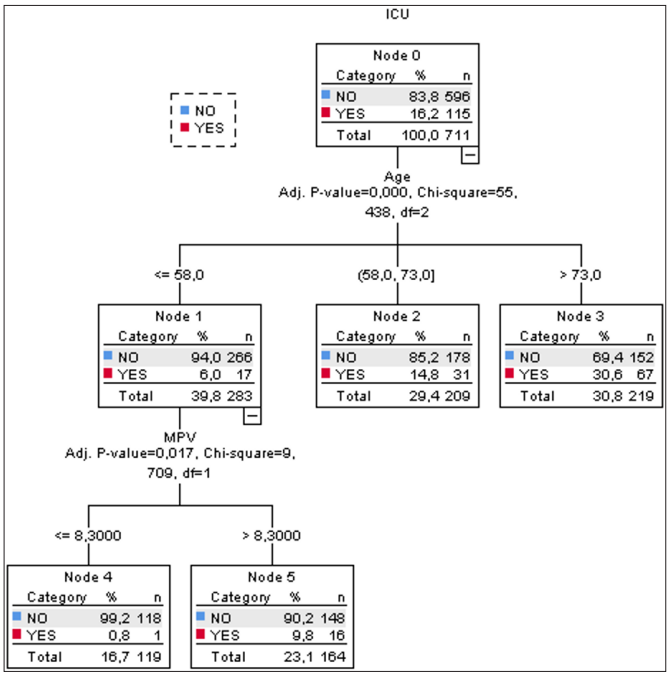

Figure 1. CHAID chart with MPV and age variables in terms of ICU requirement in COVID-19 patients

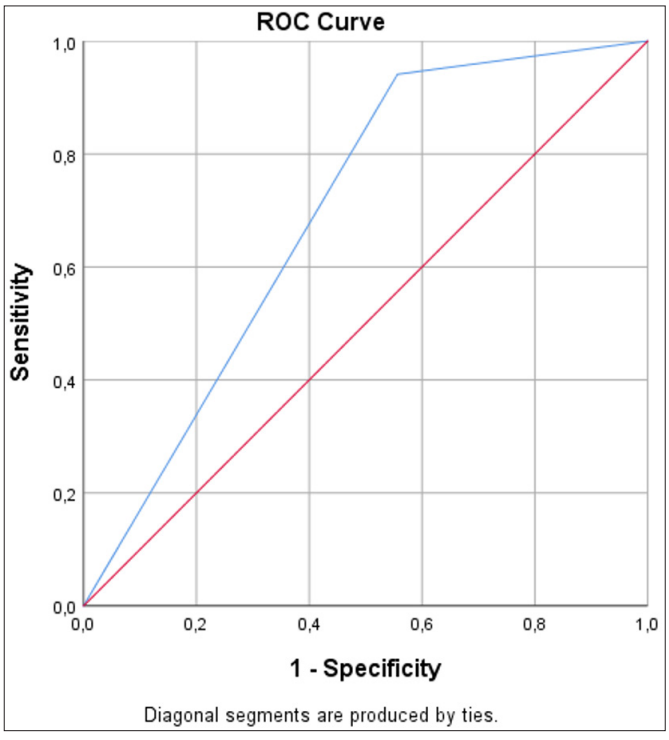

Figure 2. ROC graph for MPV threshold of 8.3 in terms of ICU requirement in COVID-19 patients under 58 years of age

Table 4. Predictive accuracy for MPV threshold of 8.3 in terms of ICU requirement in COVID-19 patients under 58 years of age

AUC	95% CI*	S. E.	p	Sensitivity	Spesifity	PPV	NPV	YJI
0.692	0.591 -0.794	0.052	0.008	94.1 %	44.4%	9.8%	99.2%	0.39

* Asymptotic 95% Confidence Interval, ICU: Intensive Care Unit, AUC: Area under the Curve, S.E.: Standart Error, p: Asymptotic Significance, PPV: Positive Predictive Value, NPV: Negative Predictive Value, YJI: Youden J Index

DISCUSSION

In our study, we concluded that advanced age, MPV and PLT values will have important predictive values in COVID-19 patients. In addition, CHAID analysis was applied and accordingly, it obtained the conclusion that 8.3 threshold value of MPV under 58 years old could predict the ICU requirement.

MPV is a simple, inexpensive and easily obtainable biomarker of platelet function and can be measured in almost all laboratories. It shows a correlation with platelet volume, platelet function and activation (12). Platelets, In addition, to primary hemostatic functions, it plays a role in the pathogenesis of infectious diseases (13). The some studies in the literature has been reported that megakaryocytes can be affected by cytokines such as IL-3 and IL-6 and this may lead to the production of more and more reactive platelets (14). In our study, we concluded that there is a positive correlation between high MPV and ICU requirement. The pathophysiological mechanism of MPV for predicting the prognosis of patients with COVID-19 is not clear, but there are opinions reported on this issue in the literature. For example, under the condition of inflammation, platelet production will increase due to the increased synthesis of thrombopoietin mediated by a wide variety of cytokines (15). MPV reflects the metabolism and proliferation of megakaryocytes and platelet production in the bone marrow. Initially, when infection occurs, the release of many inflammatory cytokines (such as interleukin-1 (IL-1), IL-3 and IL-6 and tumor necrosis factor-α (TNF-α)) increases and thrombopoietin increases and expression of young platelets in the bloodstream, It causes an increase of MPV (16). Additionally, after stress-induced platelet destruction, the decrease in platelet count further stimulates the megakaryocyte to produce a large number of platelets, resulting in an increase of MPV. Ultimately, it has been reported that, low prognosis in patients with decreased platelet count and high MPV may be associated with oxidative stress in activated platelets, increased risk of thrombosis and apoptosis (17).

In our study, it is seen that there is a positive correlation between advanced age and ICU requirement. As a matter of fact, many studies in the literature have reported that advanced age is associated with higher mortality and ICU admission in COVID-19 patients (18-20).

In a study recently reported from Turkey, a group of COVID-19 patients were compared with a healthy population in the pediatric age group. It has been emphasized that those with COVID-19 have higher MPV and lower lymphocyte values compared to the healthy group (21). In our study, MPV was found to be significant in predicting the ICU requirement. However, in the CHAID analysis, we concluded that this success is useful in patients aged 58 years and younger. This shows that MPV is not useful for determining the ICU requirement in the geriatric age group.

There are some limitations in our study. First, our study was conducted on a relatively small population from a single center and needs to be confirmed with a larger, multicenter cohort. In addition, due to the retrospective nature of our study, data was obtained from an electronic registration system, which might create limitations due to providing incomplete or outdated information.

CONCLUSION

Advanced age, high MPV and PLT values are associated with the ICU requirement in COVID-19 patients. The 8.3 threshold value of MPV can be used as one of the parameters determining the ICU requirement in relatively young patients. In the geriatric age group, it is not useful to use MPV to determine the ICU requirement. Multi-center studies with a large number of patients are needed to present the strength of the results of our study more clearly.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Research Ethics Committee of Kartal Dr. Lütfi Kırdar City Hospital (Date: 29.03.2021, Decision No: 2021/514/198/28).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and approved the final version.

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