Annals of Clinical and Analytical Medicine
Original Research

The effect of ABO blood types and mean platelet volume on mortality in COVID-19 patients in ICU

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Abstract

Aim: In COVID-19 infection, it is known that there are some risk factors such as age, gender, chronic disease and laboratory findings, and these factors increase morbidity and mortality. Within the scope of the study, it is aimed to evaluate the relationship between blood type and platelet indices and mortality in COVID-19 patients followed in the intensive care unit, since there are limited data on MPV levels of COVID-19 patients in the literature.

Material and Methods: After ethics committee approval, data on 322 COVID-19 patients who were followed up in the intensive care unit between March 1 and June 30, 2021 were retrospectively analyzed. Demographic data, comorbidities and mean platelet volume (MPV) measured in the complete blood count of the patients, mechanical ventilation status and type of intensive care discharge were recorded.

Results: When the patients were grouped as A Rh-positive (n=138) and non-A Rh-positive (n=183) patients according to their blood type, it was found that statistically higher mortality developed in A Rh-positive patients. MPV was found to be a good predictor of mortality. The threshold with the best sensitivity and specificity for MPV was calculated as 9.4 (sensitivity=77.0%, specificity=69.1%, negative predictive value (NPV)=44.8%, positive predictive value (PPV)=90.3%). According to the cut-off value, when patients with low MPV (MPV≤9.4, n=105) were compared with those with high MPV (MPV>9.4, n=216), statistically more deaths occurred in those with high MPV.

Discussion: In our study, it was concluded that COVID-19 disease is associated with ABO blood types and MPV. Blood type A and high MPV values were found to carry a higher risk for COVID-19 disease and severity and were associated with mortality.

Keywords

COVID-19, ABO Blood Types, Mean Platelet Volume, Mortality

DOI: 10.4328/ACAM.21339 Received: 2022-08-03 Accepted: 2022-11-09 Published Online: 2022-11-15
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Introduction

COVID-19 is a disease caused by the SARS-COV-2 virus that has led to a global pandemic situation [1,2]. In COVID-19 infection, it is known that there are some risk factors such as age, gender, chronic disease and laboratory findings, and these factors increase morbidity and mortality [3]. It has been proven that people with comorbidities such as cardiovascular disease, diabetes, and lung diseases are more vulnerable to COVID-19 disease than healthy individuals [4]. For this reason, in order to examine the morbidity and mortality situations associated with COVID-19, studies have been conducted to determine conditions that may make people who have had the disease more susceptible to infection, and also risk factors may be associated with the progression and severity of the disease [5,6]. Landsteiner's ABO blood types are carbohydrate epitopes found on the surface of human cells, and they are also genetically inherited. Previous studies have suggested a correlation between susceptibility to certain infections, including the SARS-COV-2 virus, as well as cardiovascular disease and cancers, and the ABO blood types [7,8]. Studies have shown that individuals with (O) blood type are less likely to be infected with the SARS coronavirus, while individuals with A blood type have a higher risk of mortality. In people who have severe COVID-19 disease, as a result of cytokine storm, lymphopenia, thrombocytopenia and leukopenia can be seen in the hemogram [9]. In addition to their functions in hemostasis, platelets play a critical role in the inflammatory response and their numbers may vary in line with the severity of the infection [10]. The number and size of platelets can change during infections. Mean platelet volume indicates the mean size of platelets and platelet activation. Mean platelet volume (MPV) is a parameter of the complete blood count (CBC) analysis. Changes in MPV levels have been used as a diagnostic and prognostic marker in diseases such as sepsis, infective endocarditis, pneumonia, brucellosis, cellulitis and acute pyelonephritis [11].

Within the scope of the study, it is aimed to evaluate the relationship between blood type and platelet indices and mortality in COVID-19 patients followed in the intensive care unit, since there are limited data on MPV levels of COVID-19 patients in the literature.

Material and Methods

After ethics committee approval, data on 322 COVID-19 patients who were followed up in the intensive care unit between March 1 and June 30, 2021 were retrospectively analyzed. Patients with positive oro-nasopharyngeal swab PCR test and blood type record and complete blood count results in their health records were included in the study. Demographic data, comorbidities and mean platelet volume (MPV) measured in the complete blood count of the patients, mechanical ventilation status and type of intensive care discharge were recorded. Individuals younger than 18 years of age and pregnant women were excluded from the study. All procedures followed were in accordance with the ethical standards of the committee responsible for human experiments (both institutional and national) and the 1975 Declaration of Helsinki as revised in 2008.

Statistical analysis

Data were entered into the Statistical Package for the Social Sciences (IBM® SPSS Statistics for Windows, Version 23.0, Armonk, NY, USA) software package. Descriptive statistics were used and quantitative variables werecharacterized using mean, maximum (max) and minimum (min) values. Percentages were used for qualitative variables. Whether the distributions were normal or not was determined using the Kolmogorov-Smirnov analysis. Normal distributions were reported as mean values and Student's t-test was used for intergroup comparisons. Pearson's chi-square test was used for the comparative analysis of qualitative variables, and Fisher's exact test was used if the sample size was ≤5. Non-parametric continuous variables were recorded as medians and they were compared using the Mann-Whitney U tests. The Inter Quartile Range (IQR) result was also given for the values recorded as median. Receiver operating characteristic (ROC) analysis was performed to determine the threshold value of factors that may affect mortality (MPV) and the ROC curve was drawn. The area under the ROC curve AUC (area under curve) was calculated. In addition, the value with the best sensitivity and specificity was accepted as the cut-off and patients were grouped as those with low MPV and high MPV values according to this threshold value. Multivariate analysis was performed using the variables found to have an effect on mortality in the univariate analysis, and the independent risk factors and odds ratio (OR) values that have an effect on mortality were found. A p-value <0.05 was considered statistically significant.

Results

Demographic data of the patients are shown in Table 1. The mean age was 61.6±0.7 years (median=61 years, min=29, max=92), with 190 males (59.2%) and 131 females (40.8%). 80.9% of the patients had comorbidities and 56.1% were smokers. The most common blood type was A (n=155, 48.3%), while Rh was the most common positive Rh (n=285, 88.8%). While the number of patients connected to mechanical ventilator (MV) was 261 and its rate was 81.3 %, the number of patients who were

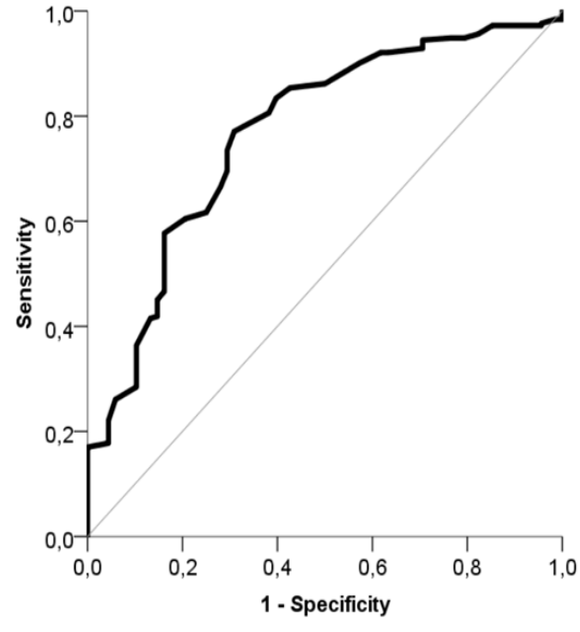

Figure 1. The ROC curve for MPV

applied noninvasive mechanical ventilator (NIMV) was 61 and its rate was 18.7%. In the follow-up patients, 78.8% (n=253) died. Both demographic and clinical comparisons of blood types are shown in Table 2. There was a difference between blood types only in terms of requiring MV (p=0.005). MV need was statistically less in patients in group O (p=0.04). Variables affecting mortality are shown in Table 3. In univariate analysis, factors affecting mortality were age (p=0.003), presence of comorbidity (p=0.001), number of comorbidities (p<0.001), blood type (p<0.001), MPV value (p<0.001) and requiring MV (p<0.001). According to multivariate analysis, increased number of comorbidities (OR=9.772, 95%CI=2.024-47.177, p=0.004), blood type A (OR=15.987, 95%CI=4.143-61.686, p<0.001), MPV (OR=2.102 for each unit increase, 95%CI=1.370-3.225, p<0.001) and MV administration (OR=159.576, 95%CI=40.828-623.694, p<0.001) were determined as independent risk factors for mortality. According to multivariate analysis, the effect of comorbidity on mortality was close to statistical significance (p=0.06). MPV was found to be a good predictor of mortality (AUC=0.768, 95%CI=0.718-0.813, p<0.001) (Figure 1). The threshold with the best sensitivity and specificity for MPV was calculated as 9.4 (sensitivity=77.0%, specificity=69.1%, negative predictive value (NPV)=44.8%, positive predictive value (PPV)=90.3%). According to the cut-off value, when patients with low MPV (MPV≤9.4, n=105) were compared with those with high MPV (MPV>9.4, n=216), statistically more deaths occurred in those with high MPV. (n=195, 90.3% and n=58, 55.2%, OR=7.525, 95%CI=4.162-13603, p<0.001, respectively). When the patients were grouped as A Rh-positive (n=138) and non-A Rh-positive (n=183) patients according to their blood type, it was found that statistically higher mortality developed in A Rh-positive patients (n=127, 92.0% and n=126, respectively, 68.9%, p<0.001, OR=5.223, 95%CI=2.617-10.423).

Table 1. Demographic data of the patients

Parameters	Data
Age, median (IQR)	61 (22)
Gender, n (%)	
Male	190 (59.2)
Female	131 (40.8)
Presence of comorbidity, n (%)	259 (80.7)
Number of comorbidities, n (%)	
0	62 (19.3)
1	108 (33.6)
2	77 (24.0)
3	43 (13.4)
4	31 (9.7)
Smoking status, n (%)	180 (56.1)
Blood type, n (%)	
O	74 (23.1)
A	155 (48.3)
B	48 (15.0)
AB	44 (13.7)
Rh, n (%)	
Negative	36 (11.2)
Positive	285 (88.8)
MPV (fl), median (IQR)	10.1 (2.1)
MV, n (%)	261 (81.3)
Mortality, n (%)	253 (78.8)

IQR; interquartile range, MPV; mean platelet volume, MV; mechanical ventilation

Table 2. Comparison in terms of blood types

Parameters	A (n=155)	B (n=48)	AB (n=44)	O (n=74)	P value
Age, mean±SD	60.9±14.6	61.4±13.8	63.2±14.8	61.2±11.7	0.260
Gender, n (%)					
Male	92 (59.4)	24 (50.0)	29 (65.9)	45 (60.8)	0.461*
Female	63 (40.6)	24 (50.0)	15 (34.1)	29 (39.2)	
Presence of comorbidity, n (%)	123 (79.4)	37 (77.1)	40 (90.9)	59 (79.7)	0.312
Smoking, n (%)	92 (59.4)	25 (52.1)	21 (47.7)	42 (56.8)	0.523
Rh, n (%)					
Negative	17 (11.0)	8 (16.7)	4 (9.1)	7 (9.5)	0.600
Positive	138 (89.0)	40 (83.3)	40 (90.9)	67 (90.5)	
MPV, mean±SD	10.1±1.3	10.1±1.4	10.5±1.5	10.2±1.2	0.280
MV , n (%)	135 (87.1)	42 (87.5)	32 (72.7)	52 (70.3)	0.005*

* Since there is more than one column in this comparison, unadjusted p-values were calculated by calculating the z-scores of each column to find out which column caused significance. According to this comparison, it was close to statistical significance (p=0.07) in group A and statistically significant (p=0.04) in group O. Bold p-values were statistically significant. SD; standard deviation, MV; mechanical ventilation, MPV; mean platelet volume

Discussion

In this study, it was observed that factors such as age, increased number of comorbidities, having A blood type, high MPV values and MV application affected mortality. It has been shown that having type A blood is associated with intensive care hospitalization and high mortality. In addition, the results of this study showed that MPV, which can be measured quickly and reliably, has an important predictive value for the diagnosis and treatment of COVID-19 disease. The relationship between ABO blood types and COVID-19 infection has been evaluated in previous studies and meta-analyses [12]. The relationship between ABO blood types and COVID-19 infection shows some differences according to studies. But generally, blood type A is associated with increased risk, while blood type O is associated with decreased risk. It has been determined that ABO blood types have predictive effects for the disease caused by the SARS-CoV-1 virus [13]. Studies show that blood type antigens can act as a receptor or trap for infectious organisms and affect susceptibility to disease in various ways as ABO antibodies [14]. In their study, Cheng et al. have found that the chance of being infected for SARS-CoV-1 infection is lower in O blood type hospital personnel compared to non-O blood type hospital personnel. Guillon et al. have found that anti-A antibodies specifically inhibited the adhesion of SARS-CoV-1 S protein-expressing cells to ACE-2-expressing cell lines [15]. Considering the nucleic acid sequence similarity and receptor angiotensin converting enzyme 2 (ACE2) binding similarity between SARS-CoV-1 and SARS-CoV-2, they suggested that lower O blood type and higher COVID-19 susceptibility of A blood type may be associated with the presence of natural anti-blood type antibodies, especially anti-A antibodies [16-18]. In vitro trials have shown that the interaction between the SARS-CoV-1 spike protein and the ACE-2 receptor can be attenuated through anti-A antibodies. Studies on animals also support that

Table 3. Examination of the variables affecting mortality

			Univariate		Multivariate	
Parameters	Discharged (n=68)	Ex (n=253)	p value	Odds ratio	95%CI	p value
Age, median (IQR)	57.5 (15.2)	62.0(22.0)	0.003	1.032	0.987-1.079	0.163
Gender, n (%)						
Male	35 (51.5)	155(61.3)	0.145			
Female	33 (48.5)	98 (38.7)				
Presence of comorbidity, n (%)	45 (66.2)	214 (84.6)	0.001	2.882	0.931-8.919	0.06
Number of comorbidties, n (%)			<0.001			
0	23 (33.8)	39 (15.4)	0.003	1 (ref)	--	--
1	28 (41.2)	80 (31.6)	0.324	1.316	0.377-4.585	0.662
2 and above	17 (25.0)	134 (53.0)	<0.001	9.772	2.024-47.177	0.004
Smoking, n (%)	35 (51.5)	145 (57.3)	0.389			
Blood type, n (%)			<0.001			
O	28 (41.2)	46 (18.2)	0.001	1 (ref)	--	--
A	16 (23.5)	139 (54.9)	<0.001	15.987	4.143-61.686	<0.001
B	9 (13.2)	39 (15.4)	0.983	2.076	0.492-8.761	0.320
AB	15 (22.1)	46 (18.2)	0.151	0.686	0.156-2.997	0.614
Rh, n (%)			0.304			
Negative	10 (14.7)	26 (10.3)				
Positive	58 (85.3)	227 (89.7)				
MPV, median (IQR)	9.0 (1.4)	10.4 (2.0)	<0.001	2.102	1.370-3.225	<0.001
MV , n (%)	16 (23.5)	245 (96.8)	<0.001	159.576	40.828-623.694	<0.001

Bold p-values were statistically significant. SD; standard deviation, MV; mechanical ventilation, CI; confidence interval, MPV; mean platelet volume.

it creates a protective mechanism by disrupting the interaction between these antibodies and the virus receptor [15]. In parallel with the studies, it is seen in this study that having blood type A may be associated with an increased risk of COVID-19, and it is thought that the same pathophysiological hypothesis may play a role in this effect. In a meta-analysis of 21 studies published by Franchini et al., low/very low evidence was found that O blood type is less susceptible to SARS-CoV-2 infection than non-O blood type [12]. In a study conducted with 265 COVID-19 patients, Li et al. reported that COVID-19 disease is more common in group A patients in the normal population and it is less common in patients with O blood type [19]. In a meta-analysis published by Pendu et al, a general consensus emerged in 34 recent studies that blood type O is associated with a lower risk of COVID-19, and other blood types are associated with higher risk [20].

In their study, Aktimur et al found that individuals with blood type A are associated with a higher risk for COVID-19 than individuals with other blood types. In the same study, it was also reported that patients with A blood type had a longer stay in the intensive care unit and may have a higher risk in terms of disease severity [21].

Parallel to the study given above, Ray et al. reported that blood type O is associated with less severe disease and lower risk of death in their study in which they included 225 COVID-19 patients [22].

In this study, MV application and mortality were statistically lower in patients in blood type O. In addition, a relationship was found between the severity of the disease, intensive care hospitalizations and blood type.

In a study conducted by Guillon et al. and included 265 COVID-19 patients, it was determined that the incidence of O blood type was lower and the incidence of A blood type was higher in patients with longer hospital stays [15].

Similarly, within the scope of this study, it was found that those with A blood type had more intensive care admissions and higher mortality compared to other blood types.

This was also supported by studies that Rh - blood type is protective against COVID-19 [23]. In our study, although there was no statistically significant difference between Rh types, it was found that patients with A Rh (+) blood type developed statistically higher mortality than patients with A Rh (-) blood type.

The lack of evidence of a COVID-19 association with negative blood types may be due to the smaller sample sizes, as Rh (-) blood types were less common in the data studied. More studies are needed to better understand the relationships between Rh-negative blood types and COVID-19.

MPV is a simple, inexpensive and readily available biomarker of platelet function and can be measured in almost any laboratory. MPV count is also used as a marker of inflammatory response. Platelet volume correlates with platelet function and activation [15]. In addition to primary hemostatic functions, platelets also play a role in the pathogenesis of infectious diseases [24].

Inflammatory cytokines have been shown to reflect both prothrombotic and proinflammatory states by regulating thrombopoiesis and MPV. Large and small circulating platelets are associated with the intensity of systemic inflammation. It has been shown that high MPV level is associated with vascular thromboembolic and ischemic diseases. Gumus et al. concluded that high MPV level may be a marker for the severity and prognosis of inflammation, and they found the MPV threshold value ≥8.74 fl in COVID-19 patients [25].

Similarly, in this study, MPV was found to be a good predictor

of mortality, and the threshold value with the best sensitivity and specificity for MPV was calculated as 9.4. According to the determined threshold value, statistically more deaths occurred in patients with high MPV than patients with low MPV. The limitations of the study were that it could not be evaluated statistically due to the small number of Rh (-) patients.

Conclusion

Within the scope of the study, it is concluded that COVID-19 disease is associated with ABO blood types. It has seen that A blood type carries a higher risk for COVID-19 disease and severity, and mortality was higher in A blood type. It is thought that having O blood type might protect against contracting COVID-19 and developing a severe infection. Further studies are needed to shed light on the relationship between blood types and COVID-19 infection.

MPV is a simple parameter measured in a complete blood count. The data obtained in the current study showed that MPV values were significantly higher in patients with mortal COVID-19 and MPV was a reliable marker in patients infected with COVID-19. However, studies with larger patient populations are needed to fully determine the role of MPV values in COVID-19 patients.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Kübra Taşkın, Cansu Akın, Dilek Erdoğan Arı, Hulya Yilmaz Ak, Tahsin Şimşek, Özlem Sezen, Kemal Saracoglu. *The effect of ABO blood types and mean platelet volume on mortality in COVID-19 patients in ICU. Ann Clin Anal Med 2022; DOI: 10.4328/ACAM.21339*