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High Mean Platelet Volume and Mean Platelet Volume/Platelet Ratio Predict Mortality for COVID-19 Patients in Intensive Care Unit

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Abstract: Mean platelet volume to platelet count ratio can be a new marker of mortality in critical COVID-19 cases in intensive care unit to retrospectively examine the factors predicting death rate in COVID-19 cases. 106 patients infected with COVID-19 in intensive care units were enrolled in this research. The patients' hospital records and the patient management tools were thoroughly examined. The Interleukin-6, C-reactive protein, procalcitonin, leukocyte count, neutrophil count, neutrophil %, neutrophil/lymphocyte ratio, and neutrophil/albumin ratio were significantly higher among nonsurvivors (p=0.0001, p=0.004, p=0.003, p=0.049, p=0.007, p=0.009, p=0.007, and p=0.0001, respectively). While the survivors had lower widths of platelet distribution and red blood cell distribution, as well as lower mean platelet volume and mean platelet volume to platelet count ratio (p=0.016, p=0.03, p=0.005, and p=0.049, respectively), they had higher hemoglobin, platelet, mean corpuscular hemoglobin concentration, lymphocyte % and monocyte % (p=0.022, p=0.033, p=0.042, p=0.008, and p=0.04, respectively). In the logistic regression, five features -including high levels of C-reactive protein, procalcitonin, pro-brain natriuretic peptide, mean platelet volume to platelet count ratio, and low level of platelet- were found to be mortality predictors for COVID-19 patients in intensive care unit (p=0.045, p=0.025, p=0.017, p=0.027, and p=0.041, respectively). Mean platelet volume to platelet count ratio, neutrophil count to lymphocyte count, and neutrophil count to albumin ratio predict mortality in critical cases of COVID-19 which will contribute to the early detection of the disease and to the effective treatment of the patients.

Keywords: COVID-19; Mortality; Mean Platelet Volume.

1. Introduction

The coronavirus family affects camels, cows, and bats causing outbreaks every decade in the last 30 years. A new strain of the family was defined in the early days of 2020 in Wuhan, China (1). World Health

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Organization (WHO) named this new strain SARS-CoV-2 on February 11, 2020 (severe acute respiratory syndrome coronavirus 2) (World Committee on Virus Classification) (2-4). Globally, as of April 3, 2022, just over 489 million COVID-19 patients with over 6 million registered deaths (5).

There is still no consensus on the modes of transmission, the treatment methods, and the follow-up protocols for COVID-19 infection which has become a burden for global public health. Severe pneumonia, acute cardiac injury, acute respiratory distress syndrome (ARDS), and septic shock are among the probable complications that may increase the mortality rates. Clinical findings and bilateral, multiple, and atypic ground glass appearance on thorax tomographic examination increase the probability of COVID-19 infection which can be confirmed by PCR-based tests. Poor prognostic factors are multilobular infiltration, lymphopenia, co-infection, smoking, hypertension, and advanced age (> 60 years).

Cases of COVID-19 fall into four different groups: mild, moderate, severe, or critical (6). Currently, COVID-19 researches have mainly concentrated on the risk factors and the prediction of mortality for the mild and moderate (81 %) COVID-19 cases, consisting of the vast percentage of the total cases (7-11). The average mortality rate of severe (14 %) and critical (20 %) cases is 50 % (1, 12, 13). Almost none of the researchers has announced risk factor prediction and mortality analysis for severe and critical cases. Therefore, identifying the risk factors related to the prognosis and severity of the infection might prove useful to determine the high-risk patients at the initial evaluation phase (14). Several predictive markers have been introduced to academic literature such as identifying high-risk groups in the general population (15), diagnosing COVID-19 (16), and predicting mortality and serious disease progression.

Mean platelet volume (MPV) to platelet count (MPV/Plt) ratio (MPR) was proposed as a prognostic marker in SARS-CoV-2. Thrombocyte count enhances inflammatory states due to cytokine-mediated rise of thromboepoietin levels. On the other hand, MPV reflects the increased production of megakaryocytes in the bone marrow and the expression of young thrombocytes in the circulation. Decreased thrombocyte count enforces megakaryocytes to augment more thrombocytes through immune system stimulation resulting in higher MPV. Negative consequences of activated thrombocytes tend to increase oxidative stress, thrombosis, and apoptosis (17, 18).

Understanding pathophysiologic mechanisms of progressive disease contributes to more aggressively approaching patients that are at risk of developing a critical infection. Our aim is to investigate the correlation between the hematologic and inflammatory parameters and the mortality rates of critical COVID-19 patients in the ICU.

2. Material and Methods

2.1. Study Design and Participants

106 COVID-19 patients in the ICU were included in the study. The patients' hospital records and the patient management tools were thoroughly examined.

Any verified case was assumed as a positive result on the reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasopharyngeal swab specimens. Those with COVID-19 evidence in thorax CT such as ground-glass opacities -either alone or in combination with pulmonary consolidations- were included.

Demographic features of the non-pregnant patients aged between 25 and 96 years old were recorded, and they were divided into 2 subgroups according to the mortality status of survivors and non-survivors. Written informed consent papers were received from all patients. The study was approved by the Ethics Committee of the Bagcilar Training and Research Hospital (Date: May 29, 2020; IRB Number: 2020.05.2.05.061) and was performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki.

Data was gathered through the patient management system and the COVID-19 records of the health care institutions. We compiled 59 specifications -containing the demographic data and the laboratory test results as well. The patients were mainly either discharged or deceased. Mortality count throughout the hospitalization period was acquired from the discharge registers.

2.2. Definitions

All covariates were obtained from the electronic records: gender, age, and laboratory results including all hemogram parameters (leukocyte/white blood cell-WBC-, hemoglobin (Hgb), hematocrit (Hct), red blood cell (RBC), Platelet (Plt), plateletcrit (PCT), red blood cell distribution width (RDW), platelet distribution width (PDW), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), basophil count and %, eosinophil count and %, lymphocyte count and %, monocyte count and %, MPV, neutrophil count, neutrophil %, interleukin-6 (IL-6), C-reactive protein (CRP), procalcitonin, d-dimer, fibrinogen (FBG), ferritin, glucose, lactate dehydrogenase (LDH), creatinine, urea, uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkalen phosphatase (ALP), gama glutamil transpherase (GGT), total bilirubin, direct bilirubin, total protein, albumin, anti-HBs, Anti-HCV, Anti-HIV, HBsAg, sodium (Na), Calcium (Ca), Clor (Cl), Potassium (K), pro-BNP, prothrombin time % (PT), INR, activated partial thromboplastin time (APTT), thyroid

stimulating hormone (TSH), 25-OH vitamin D, free T4, and free T3).

2.3. Statistical Analysis

The Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) was used to analyze the data. All data were expressed as the mean ± SD. The Student's t-test was used to analyze the difference between the groups. The Chi-square test was used to analyze the quantitative data. For the evaluation of the correlation of variables, Pearson correlation and Spearman's rho correlation analysis were administered. The variables that proved to be significant in univariate analysis were also included in multivariate logistic regression. $p<0.05$ was accepted as significant.

3. Results

3.1. Demographic and Clinical Specifications

Of the 106 verified COVID-19 patients -including those in the ICU-, the prevalences of female and male patients were 37.7 % and 62.2 %, respectively. The demographics and laboratory findings were shown in Tables 1 and 2.

3.2. The Comparison of Survivors and Non-Survivors

Compared with survivors (median age=62.7), non-survivors (median age=69.6) were older (p=0.016), whereas the gender distribution of both groups was similar (p=0.122).

In the non-survivor group, while the mean IL-6, CRP, Procalcitonin, WBC, PDW, RDW, MPV, neutrophil count, neutrophil %, neutrophil count/lymphocyte count ratio (NLR), MPV/Plt ratio (MPR), neutrophil count/albumin ratio (NAR), urea, direct bilirubin, Pro-BNP levels were significantly higher compared to survivors (p=0.0001, p=0.004, p=0.003, p=0.049, p=0.016, p=0.03, p=0.005, p=0.007, p=0.009, p=0.007, p=0.049, p=0.0001, p=0.001, p=0.016, p=0.002) (table 1-2), they had lower hemoglobin, platelet, MCHC, lymphocyte %, monocyte %, albumin and calcium levels (p=0.022, p=0.033, p=0.042, p=0.008, p=0.04, p=0.0001, p=0.008) (Table 1-2).

Logistic regression analysis showed that CRP (p=0.045), Procalcitonin (p=0.025), MPR (p=0.027), Pro-BNP (p=0.017) and thrombocytopenia (p=0.041) are associated with higher mortality rates (Table 3).

Table 1: Age, Gender and Hemogram Characteristics of Critical Patients with COVID-19.

		Survivor (n:39)		Non-Survivors (n:67)		p
Age (Year)		62.79±14.67		69.67±13.53		**0.016***
Gender	Male	28	71.79 %	38	56.72 %	0.122+
	Female	11	28.21 %	29	43.28 %	
Total leukocyte Count ($\times10^3$/L)		10.42±6.27		13.01±6.57		**0.049***
Hemoglobin (g/dL)		11.3±2.52		10.19±2.26		**0.022***
Hematocrit (%)		35.29±7.87		32.99±6.53		0.109*
Platelet Count ($\times10^3$/L)		316.51±167.47		258.69±108.75		**0.033***
Red blood Cell Count ($\times10^{12}$/L)		4.09±1.00		3.8±0.81		0.100*
Plateletcrit (%)		0.33±0.17		0.28±0.11		0.100*
Platelet Distribution Width (%)		11.86±2.11		13.09±2.63		**0.016***
Red Cell Distribution Width (%)		14.59±2.04		15.72±2.78		**0.03***
Mean Corpuscular Hemoglobin (pg)		27.82±1.96		27.35±2.71		0.343*
Mean Corpuscular Hemoglobin Concentration (MCHC)		32.04±1.67		31.26±2.00		**0.042***
Mean Corpuscular Volume (fL)		86.83±4.83		87.41±7.06		0.651*
Basophil Count ($\times10^3$/L)		0.03±0.02		0.04±0.04		0.468‡
Basophil (%)		0.28±0.20		0.28±0.24		0.602‡
Eosinophil Count ($\times10^3$/L)		0.09±0.12		0.07±0.12		0.423‡
Eosinophil (%)		1.02±1.5		0.56±0.92		0.243‡
Lymphocyte Count ($\times10^3$/L)		0.98±0.49		0.93±0.75		0.145‡
Lymphocyte (%)		11.7±8.28		8.36±5.91		**0.008‡**
Monocyte Count ($\times10^3$/L)		0.6±0.39		0.64±0.47		0.801‡
Monocyte (%)		5.88±2.36		4.99±2.15		**0.04‡**
Mean platelet Volume (fL)		10.3±0.89		10.92±1.12		**0.005***
Neutrophil Count ($\times10^3$/L)		8.73±5.95		11.32±5.99		**0.007‡**
Neutrophil (%)		81.25±10.49		85.81±7.04		**0009***

*Independent t test ‡Mann Whitney U test +chi-square test.

Table 2: Biochemistry Characteristics of Critical Patients with COVID-19.

	Survivor (n:39)	**Non-Survivors (n:67)**	**p**
Interleukin -6 (pg/mL)	132.95±303.9	588.81±1106.12	**0.0001‡**
C-reactive Protein (mg/L)	104.98±85.3	162.56±105.84	**0.004‡**
Ferritin (ml/ng)	599.16±684.37	598.78±457.23	0.337‡
Fibrinogen (mg/dL)	502.27±168.09	491.09±154.3	0.792*
D-dimer (ng/mL)	3.1±7.63	2.64±2.35	0.063‡
Procalcitonin (ng/mL)	1.52±4.67	5.89±19.92	**0.003‡**
Neutrophil/Lymphocyte Ratio (NLR)	11.29±9.6	17.79±16.33	**0.007‡**
Mean Platelet Volume/Platelet Count Ratio (MPV/Plt)	0.04±0.02	0.05±0.03	**0.049***
Fibrinogen / Platelet Count Ratio	1.86±1.32	2.22±1.13	0.102‡
Neutrophil Count/Albumin Ratio (NAR)	28.63±6.85	33.91±6.52	**0.0001***
Serum Urea (mg/dL)	50.88±34.72	86.13±57	**0.001***
Serum Creatinine (mg/dL)	1.02±0.81	1.57±1.73	0.053‡
Serum Uric Acid (mg/dL)	4.76±2.85	5.44±3.18	0.306‡
Direct Bilirubin (mg/dL)	0.17±0.11	0.45±1.51	**0.016‡**
Total Bilirubin (mg/dL)	0.58±0.28	0.94±2.59	0.902‡
Serum Total Protein (g/dL)	5.99±0.75	5.78±0.73	0.160*
Serum Albumin (g/dL)	2.94±0.51	2.6±0.39	**0.0001***
Serum Sodium (Na) (mEq/L)	139.59±6.51	139.69±8.06	0.949*
Serum Calcium (Ca) (mg/dL)	8.24±0.62	7.93±0.55	**0.008***
Serum Chlor (Cl) (mmol/L)	102.54±6.5	102.01±7.17	0.708*
Serum Potassium (K) (mEq/L)	43±0.81	4.29±0.7	0.960*
Serum LDH (U/L)	500.79±328.18	595.07±509.97	0.177‡
Serum Pro-BNP (pg/ml)	6405.72±11473.39	11397.89±12469.74	**0.002‡**

*Independent t test ‡Mann Whitney U test.

4. Discussion

While the death rates caused by the Coronavirus strains were respectively 10% [19] in Severe Acute Respiratory Syndrome (SARS) and 34 % (20) in Middle East Respiratory Syndrome (MERS), the initially reported death rate for COVID-19 was around 2 %. Studies conducted over time have shown that the mortality of COVID-19 was to be ranging from 4 % to 28 % (21-23). In their study with hospitalized patients, Mikami et al. found the mortality rate among COVID-19 patients to be 25.9 % (24). In a meta-analysis by Jia et al., patients with more severe illnesses were found to yield a much higher mortality rate than those with mild or moderate illnesses (25). Thus, it proves favorable to concentrate on those who are more probable to develop serious diseases at the time of diagnosis so as to reduce mortality. It is possible to obtain an early prognosis with fewer resources during the early stages, as well as to effectively manage the treatment with various hemogram and inflammatory parameters to prevent complications, and thus, reduce the mortality rate in the recurring waves of the COVID-19 pandemic.

Many studies showed that the age (24, 26) and the levels of CRP were taken as high-sensitivity predictors for COVID-19 mortality (27) that might prove useful in identifying the major COVID-19 cases (28, 29).

Gemin's study showed that CRP levels were related to severe COVID-19 pneumonia and mortality (30). Initial laboratory findings of non-survivors exhibited higher levels of CRP along with Procalcitonin in Mikami's study (24). Consistent with the literature, our study also shows that mortality increases with aging and increased CRP-Procalcitonin levels.

Leukocytosis, neutrophil count, and neutrophil ratio % (24) were all related to severe COVID-19 pneumonia and mortality in Gemin's study (30). Some of the studies showed that neutrophils count and NLR were significant predictors of critical illnesses (31, 32). In a multivariate logistic regression analysis by Yan et al., high levels of NLR were found to be associated with death being an independent risk factor to predict in-hospital mortality among COVID-19 cases (33). This study, instead of including a specific group of patients, includes all groups either with patients who died, patients with ongoing treatments, or patients discharged. The study was conducted with patients in the ICU, a more specific group found to be associated with NLR mortality. In Varim et al.'s study conducted, on 144 patients, results suggest that COVID-19 patients with high NAR values be closely followed and be treated in ICU due to the close relation with early mortality (34).

Table 3: Mortality associated risk factors for critical patients with COVID-19.

	B	S.E.	p	OR	95 % OR Lower limit	Upper limit
Age (Year)	0.02	0.03	0.593	1.02	0.96	1.08
Interleukin-6 (pg/mL)	0.01	0.01	0.07	1.01	1.00	1.02
C-reactive Protein (mg/L)	0.01	0.01	**0.045**	1.01	1.00	1.02
Procalcitonin (ng/mL)	0.29	0.13	**0.025**	0.75	0.58	0.96
Total Leukocyte Count ($\times 10^3$/L)	-0.23	0.22	0.285	0.79	0.52	1.21
Hemoglobin (g/dL)	0.03	0.24	0.901	1.03	0.64	1.66
Platelet Count ($\times 10^3$/L)	-0.02	0.01	**0.041**	0.98	0.96	1.00
Platelet Distribution Width (%)	0.21	0.25	0.397	1.23	0.76	2.00
Red Cell Distribution Width (%)	-0.42	0.30	0.163	0.66	0.36	1.19
Mean Corpuscular Hemoglobin Concentration (MCHC)	-0.64	0.38	0.097	0.53	0.25	1.12
Neutrophil / Lymphocyte Ratio (NLR)	0.08	0.05	0.147	1.08	0.97	1.19
Mean platelet volume/Platelet Count Ratio (MPV/Plt)	-1.78	1.44	**0.027**	0.00	0.00	0.00
Monocyte (%)	2.10	2.76	0.446	8.18	0.04	1.99
Serum Urea (mg/dL)	0.02	0.02	0.125	1.02	0.99	1.05
Direct Bilirubin (mg/dL)	0.74	0.47	0.385	1.14	0.00	2.20
Serum Albumin (g/dL)	-1.02	2.40	0.670	0.36	0.00	3.54
Serum Pro-BNP (pg/ml)	0.00	0.00	**0.017**	1.00	1.00	1.00
Neutrophil Count/Albumin Ratio (NAR)	0.03	0.20	0.874	0.97	0.65	1.44

In our study, a significant correlation was found between increased leukocytosis, which was consistent with other studies (24), neutrophil count, neutrophil ratio (%), NLR and NAR, and decreased lymphocyte count and mortality.

Wenhua et al.'s study showed that direct bilirubin and LDH were significant predictors of critical illnesses in COVID-19 patients (31). In our study, a significant relationship was found between mortality and high levels of direct bilirubin, but no significant relationship could be found with LDH. Earlier research also suggested the relation between the increasing LDH levels and the high mortality risk of COVID-19 (31). According to the observation of Ji et al., COVID-19 patients with serum levels of LDH higher than 500 U/L exhibited a dramatic disease advance in a multivariate Cox analysis, in comparison to the group with LDH levels < 250 U/L ([35). Even though no significant relationship was spotted between the LDH levels and the mortality rates in our study, the median LDH values of our living and deceased patients were found to be 500 and 595, respectively. Because both survivors and non-survivors were in the ICU having serious respiratory failure, they had hypoxia in tissue level, leading to increased LDH.

Mikami et al's study showed that preliminary findings of non-survivors show higher IL-6 levels and increased IL-6 levels as an independent prognostic risk factor, adding to even higher levels among survivors. (24). Liang et al.'s study showed that serum IL-6 and IL-10 levels in COVID-19 cases proved to be significantly higher in the critical group in proportion to the moderate and severe disease groups. Accordingly, this showed that cytokine storms in higher amounts are related to the development of a more serious disease, and thus can be used as a predictor for swift diagnosis for patients. Given the high cytokine levels caused by SARS-CoV-2, it may be critical in the early treatment stage to reduce cytokine-related lung damage in the group with high levels of IL-6 (36). A statistically significant relationship was found between IL-6 levels and mortality rate among our patients in the critical group.

In Sundas et al.'s study, they concluded that RDW is an important parameter that can greatly assist clinicians in different stages of COVID-19 patient evaluation, such as identifying PCR false negatives at initial triage, at the referral centers, and in the community, as well as predicting complications, and monitoring progression (37). According to the findings of Gong et al., RDW- long with other parameters- was associated with severe COVID-19 patients (38). Likewise, Wang et al., in another research, also suggested that NLR and RDW, when combined together, accurately diagnose with an accuracy ratio of 85.7 % and can be useful to predict patients' staging, thus enabling to administer the necessary treatment promptly on time (39). In our study, a significant relationship was also found between the increased RDW values and mortality rates in accordance with the literature.

High levels of Platelet Distribution Width (PDW) indicate the destruction of the newly produced immature platelets and parallel size variations (40). In COVID-19, PDW is expected to be found high as a result of increasing cytokine release and platelet production, and the destruction mechanism affected by inflammation (41). In a study by Ozcelik et al., COVID-19 groups were compared to influenza

pneumonia groups, and PDW proved to be significantly higher among COVID-19 cases compared to influenza cases (42). In accordance with the literature, increased PDW was found to be associated with mortality in our study. Although high rates of venous thromboembolism and the evidence of endothelial dysfunction caused by COVID-19 have been reported, the precise etiology of the increased thrombotic risk associated with COVID-19 infection is not fully elucidated. Thrombocytosis was related to disease activity in SARS and was considered to be secondary to the direct effect of the virus or the inflammatory cytokines (43). A previous study with primates revealed that IL-6 induced thrombocytosis in a dose-dependent response (46). The incoherence between high IL-6 levels and deficiency of thrombocytosis in the deceased could be related to the harm of endothelium and latter platelet expenditure by viral infection, reduced platelet release from megakaryocytes in the lung, or direct damage of hematopoiesis (45) which might indicate that the lack of reactive thrombocytosis might mark a weak reaction to COVID-19 (24).

An increase in MPV values is a sensitive and prognostic marker for platelet activity and thromboinflammation (46), and also is associated with some specific viral infections (47). Therefore, in Comer et al.'s research, in which they evaluated clinical platelet parameters and circulating platelet activity in severe (intensive care) and non-severe (non-intensive care) COVID-19 patients, it was shown that the increased MPV among patients with severe and mild COVID-19 disease is associated with the disease severity in COVID-19 (48). MPV and MPR proved to be significantly lower in the COVID-19 group than in the influenza group, in a study by Özçelik et al. (42). In Zhong et al.'s research with 85 cases, high MPR levels were spotted to be an independent risk factor for severe pneumonia in COVID-19 cases (18). Guclu et al. found that the decreased MPV values were associated with mortality in the follow-up of the COVID-19 cases (49), in contrast to the other studies supporting a significant relationship between high MPV and mortality in patients hospitalized in the ICU (50). In a mortality study with 100 patients, it was found that MPR is not significantly associated with mortality (29). Survivors had a more significant decrease in hemoglobin levels and platelet counts. (24). In our study with the critically conditioned COVID-19 patients hospitalized in the ICU, it has been found that there is a significant relationship between increased MPV and MPR and decreased hemoglobin and platelet and mortality.

The major drawbacks of the present study are its retrospective design and low sample size limiting the researchers to reach a more precise conclusion. Additionally, the patient group was selected from patients at the first 6 months of the epidemic when the variant of SARS-CoV-2 was yet to be identified.

5. Conclusion

MPV, MPR, and NLR are easily available hematologic parameters that can be used to evaluate the risk of the disease progression. Even in limited laboratical environments, these parameters can help physicians to classify and identify COVID-19 patients with a higher risk of a severe inflammatory state.

Limitations of the Study

Low number of patients included in the study.

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Conflict of Interests

The authors declared no conflict of interest.

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This study received no financial support.

Author Contributions

ES, AEA, SK designed the research. Collected the data ES, CY, CCB. Analysis and interpretation of data SOS, AEA. Wrote the manuscript read and approved final script ES, SOS.

Ethical Approval

The study was approved by the Ethics Committee of the Bagcilar Training and Research Hospital (Date: May 29, 2020; IRB Number: 2020.05.2.05.061)

Data sharing statement

All data relevant to the study are included in the article.

Informed Consent

Informed consent was obtained from all participants included in the study.

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