



Original Article

Could Mean Platelet Volume Differentiate Acute Coronary Syndrome (ACS) Types?

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ABSTRACT

Introduction: Evaluation of platelet volume indices is proposed by literature in predicting and differentiating coronary diseases. Therefore, this study aimed to compare the mean number and volume of platelets in patients with unstable angina (UA), STEMI, and NSTEMI.

Material and Methods: In this cross-sectional study, ACS patients were compared for mean platelet volume (MPV) and mean platelet count (MPC), stratified by type of the ACS (unstable angina, STEMI, and NSTEMI). Demographics, pre-existing medical diseases, and medication history were also compared for justification.

Results: A total of 75 patients were studied in 3 age and sex match groups UA (n=25), STEMI(n=25), and NSTEMI (n=25). The MPV in UA patients was significantly higher than in the group of patients with STEMI (P = 0.031). Moreover, the MPC in patients with UA was significantly lower than in the group of patients with STEMI (P = 0.02). The results showed no statistically significant difference between patients with unstable angina and NSTEMI and no significant difference between patients with STEMI and NSTEMI.

Conclusion: In all three groups of ACS patients, the MPV and MPC were in the normal range. So, considering these factors alone may not help to differentiate between these three groups of patients.

GRAPHICAL ABSTRACT

MYOCARDIAL INFARCTION



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Introduction

ST-segment elevation myocardial infarction (STEMI), and Non-ST-segment elevation myocardial infarction (UA/NSTEMI) are all variants of acute coronary syndromes (ACS) [1]. Unstable angina is characterized by at least one of the following: It has developed in the last two months and has at least a class 2 severity in the Canadian Cardiovascular Society classification, or has occurred at rest and has lasted more than twenty minutes, or the severity, duration or frequency of previous angina has increased to class 2 severity [2]. In the case of myocardial infarction, an increase in cardiac enzymes with ischemic symptoms, and new electrocardiographic or echocardiographic changes are considered diagnostic [3,4].

Impaired blood homeostasis, excessive accumulation, and lack of platelet function are associated with the development of cardiovascular disease. Platelets also play a central role in blood homeostasis in healthy and sick individuals. Platelets and coagulation are also known to have potential roles in the formation of atherosclerotic plaques through thrombosis [5].

The platelet release reaction at the atherosclerotic plaque gets immoderate by consequent platelet release from the bone marrow. The persistence of platelet enlargement after discharge also supports their chronic enlargement in patients with myocardial infarction [6]. In atherosclerosis, platelets are activated by binding to the structure below the endothelium, leading to the release of granules containing thromboxane A₂ (TXA₂, serotonin, and platelet-growing factor and other vasoconstrictors). On the other hand, the appearance of IIb/IIIa receptors occurs on the platelet surface [7]. Platelet adhesion was found to be higher in patients with MI than in healthy people in one study. Among ischemic heart patients, those with higher platelet counts and higher platelet aggregation rate are more likely to die compared with adenosine diphosphate. Therefore, increased platelet activity is associated

with increased severity of ischemic heart disease [8]. Enlarged platelets have a stronger potential for thrombosis than smaller platelets. Therefore, there must be a relationship between platelet size and events caused by increasing their activity, including ischemic heart disease. Platelet volume indices have been used to show this relationship [9]. According to the findings of the American Heart Association, Platelet indices, including platelet distribution width, can be effective in predicting heart disease mortality, recommending measuring platelet counts in all patients with ACS [10]. Therefore, this study compared MPC and MPV in unstable angina and MI patients with and without ST-segment elevation.

Materials and Methods

This cross-sectional analytical study was performed on patients who were admitted to the cardiac ward of Imam Reza Hospital in Mashhad, Iran with symptoms of the acute coronary syndrome from January to December 2019.

Inclusion criteria were adult patients (over 18 years), having symptoms of ACS, having a complete medical record, and having informed consent. Patients with a history of chronic liver and kidney disease, history of major surgery, and significant trauma in the past two weeks, and patients with incomplete medical records were not included. Patients who were not satisfied to continue the study or cases deceased during the study were excluded from the final analysis.

Sample size

Based on the Mathur *et al.*'s [11] study using the test formula of two means related to a quantitative trait in two communities, 23 patients were obtained. By considering 20% of the sample loss, 25 patients were determined for each group, as shown in equation 1.

where μ is mean of each group and σ is the variance. $Z_{1-\alpha/2}$ represents the statistical significance level and Z_{1-B} shows the power.

Equation 1: Sample size determination formula

$\alpha=$	0/05	$Z_{1-\alpha/2}=$	1.961150826
$\beta=$	0/2	$Z_{1-\beta}=$	0.841623031
$\mu_1=$	261		
$\mu_2=$	251		
$SD_1=$	11		
$SD_2=$	13	$n=$	23

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

Procedure

A diagnosis was made of patients referring to the Emergency Department, based on clinical manifestation, ECG findings, examination of cardiac enzymes, and exclusion of unqualified individuals. Sampling of this study followed the simple available method and based on the diagnosis, 25 patients were recruited for each group of STEMI, NSTEMI, and unstable angina. Routine tests were performed during the first six hours of referral in patients suspected of ACS along with recording demographic data. 5 cc of venous blood was taken from the brachial vein in tubes containing ethylenediaminetetraacetic acid (EDTA) and a complete blood cell count was performed. Then, small platelet index values including mean platelet volume and platelet count were recorded in the checklist, followed by comparing the mean platelet volume and platelet count between the three groups.

Data analysis

Nominal data were compared with each other by the Chi-square test. The Kolmogorov-Smirnov test was used to determine the normality of the data distribution. To assess the association between quantitative variables, T-test was run. For non-parametric data, the Mann-Whitney-U statistical test was used. Analysis of Variance (ANOVA) with Tukey's Test for Post-Hoc was used to explain the comparison of the mean in more than two groups. For erratically distributed data, the Kruskal-Wallis test was also utilized. The correlation between the variables was evaluated using the Pearson test for normally distributed data, while Spearman's correlation was applied if data were abnormally

distributed. The data obtained were entered into SPSS software version 22 after the initial review. P values lower than 0.05 were considered statistically significant.

Ethical considerations

We provided a written letter of introduction to officials from the institution and chose research centers. The aim of the study was described for all research units, and formal consent was acquired. The project manager maintained all of the patients' information confidential. All ethics declarations of Helsinki and the research ethics council of the University of Medical Sciences were considered at all phases of the study. Mashhad Medical University's Research Council authorized the proposal, and it was given the code of ethics (IR.MUMS.Medical.REC.1398.217) and a letter of introduction.

Results

A total of 75 patients were included in the study, which was divided into three groups of 25 patients. Based on clinical conditions, these individuals were in the groups of unstable angina (14 men and 11 women: mean age: 56.36 years), STEMI (14 men and 11 women; (mean age: 57.04 years), and NSTEMI (12 males and 13 females; mean age: 56.2 years). Table 1 shows the demographic and primary results in three groups. As can be observed, there was no statistically significant difference in mean age or sex between the three groups. The background characteristics and underlying diseases of the subjects in the three groups at the beginning of the study are summarized in Table 1, where the history of hypertension, hyperlipidemia, diabetes, chronic

obstructive pulmonary disease, stroke, ischemic heart disease, history of smoking, use of beta-blockers, angiotensin-converting enzyme inhibitors, aspirin, angiotensin receptor blockers, statins, and history of heparin or warfarin use in patients were evaluated as underlying factors. In

terms of the aforementioned criteria, no significant differences were detected between the tested groups. It should be noted that none of the patients had a recent history of heparin and warfarin and a history of stroke.

Table 1: Demographic and initial findings (baseline) in three groups of patients

Variable			<i>N (%) or Mean±SD group NSTEMI</i>	<i>N (%) or Mean±SD Unstable angina group</i>	P-value
Sex	Male	14(56)	12(48)	14(56)	0.807*
	Female	11(44)	13(52)	11(44)	
Age	Year	57.04±5.42	56.20±6.47	56.36±6.44	0.876**
Platelet count	×10 ³ /μL	327±60	306±38	289±44	0.027**
MPV	FL	10.4±0.6	10.5±0.6	10.9±0.8	0.073***
History of high blood pressure	Positive	10(40)	11(44)	11(44)	0.947*
History of hyperlipidemia	Positive	12(48)	11(44)	11(44)	0.948*
History of diabetes	Positive	7(28)	8(32)	9(36)	0.832*
History of chronic obstructive pulmonary disease	Positive	3(12)	4(16)	2(8)	0.685*
History of taking statins	Positive	12(48)	11(44)	11(44)	0.948*
History of ischemic heart disease	Positive	4(16)	5(20)	5(20)	0.916*
History of smoking	Positive	7(28)	7(28)	7(28)	1*
History of using beta-blockers	Positive	4(16)	4(16)	5(20)	0.911*
ACEIs history	Positive	6(24)	5(20)	6(24)	0.927*
History of aspirin use	Positive	10(40)	11(44)	11(44)	0.947*
History of using ARBs	Positive	5(20)	6(24)	4(16)	0.779*

* Chi-square test, ** ANOVA test *** Kruskal-Wallis

Figure 1 and Table 2 show the platelet count in the three groups. The mean platelet count in patients with unstable angina ($289\pm44\times10^3/\mu\text{L}$) was significantly lower than in the group of patients with STEM ($327\pm60\times10^3/\mu\text{L}$), ($P = 0.02$; Tukey's Test for Post-Hoc). However, there was no statistically significant difference between

patients with unstable angina ($289\pm44\times10^3/\mu\text{L}$) and NSTEMI ($306\pm38\times10^3/\mu\text{L}$), ($P = 0.425$; Tukey's Test for Post-Hoc). There was also no difference in myocardial infarction between patients with myocardial infarction with STEMI ($327\pm60\times10^3/\mu\text{L}$) and NSTEMI ($306\pm38\times10^3/\mu\text{L}$), ($P = 0.299$).

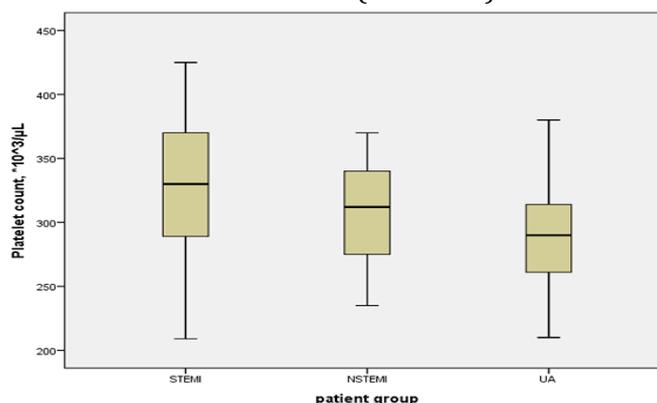


Figure 1: MPC in different groups of study

MPV was evaluated in three groups (Figure 2 and Table 3). As can be seen, the MPV in patients with unstable angina ($10.9 \pm 0.8\text{fl}$) was more than that of STEMI subjects ($10.4 \pm 0.6\text{fl}$), ($P = 0.031$), but no statistically significant difference was found

between patients with unstable angina ($10.9 \pm 0.8\text{fl}$) and STEMI ($10.5 \pm 0.6\text{fl}$), ($P=0.093$). There was no significant difference between patients with STEMI ($10.4 \pm 0.6\text{fl}$) and STEMI ($10.5 \pm 0.6\text{fl}$), ($P = 0.889$).

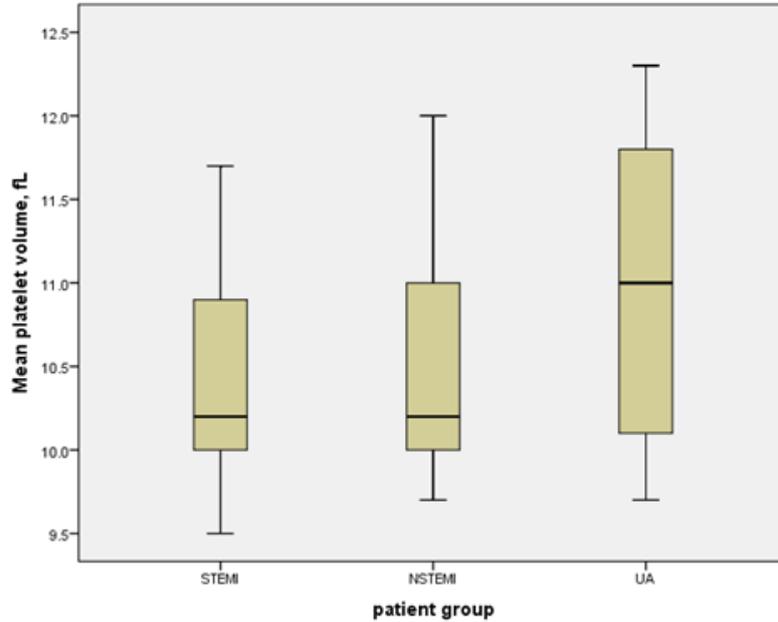


Figure 2: MPV in different groups of study

Figures 3, 4, 5 and 6 show the correlation between MPV and platelet count in three groups including unstable angina, STEM, and STEMI, as well as all patients. As observed, a significant negative (inverse) Spearman correlation was observed

between MPV and platelet count in patients with unstable angina ($P < 0.05$), ($r = -0.841$), STEM ($P < 0.05$), ($R = -0.801$), STEMI ($P < 0.05$), ($r = -0.857$) and all patients studied ($P < 0.05$), ($r = -0.817$).

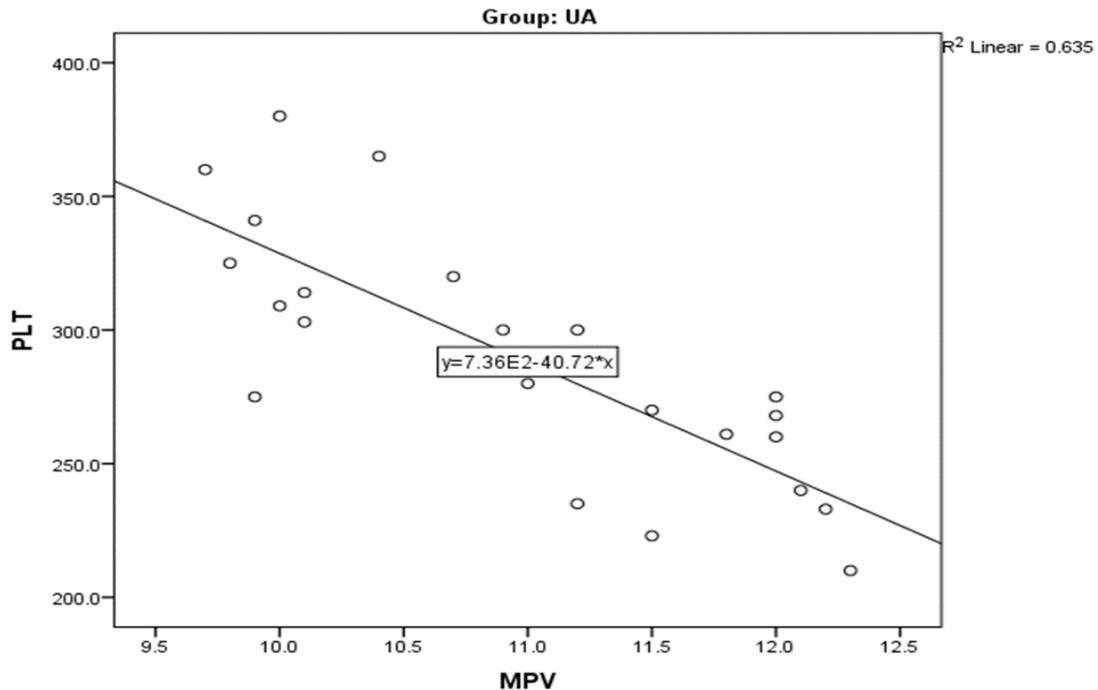


Figure 3: Inverse correlation between MPV and MPC in patients with unstable angina

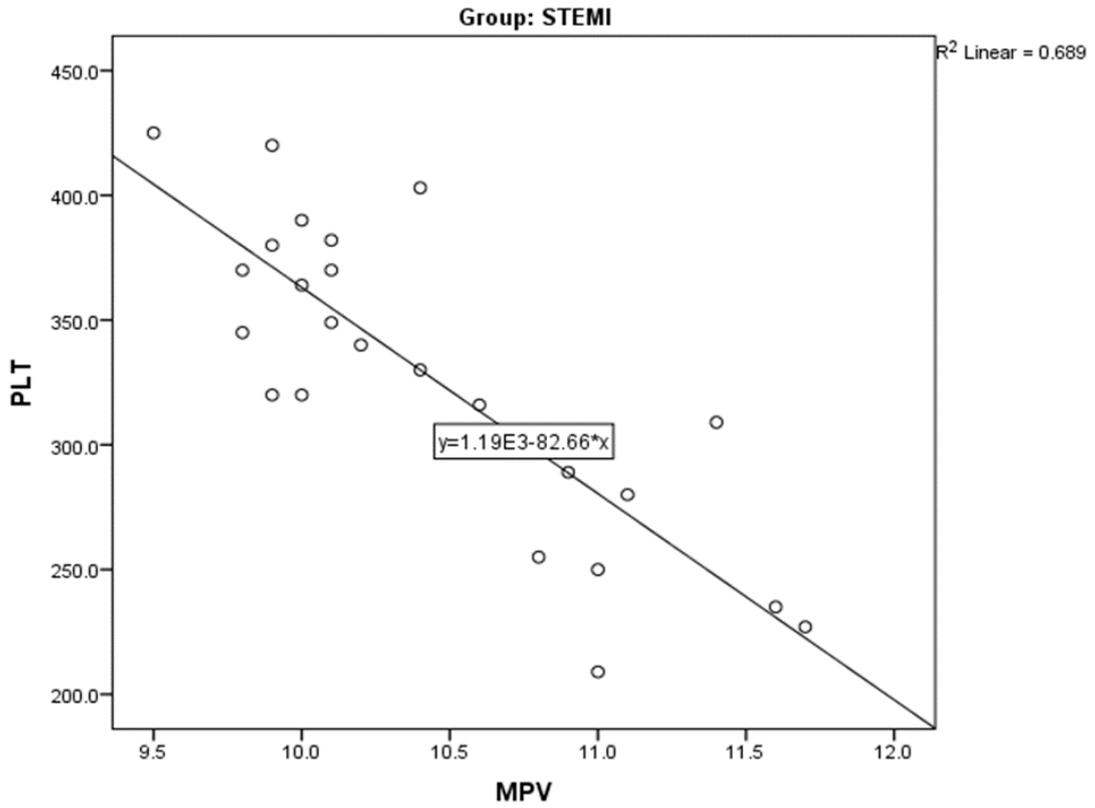


Figure 4: Inverse correlation between MPV and MPC in patients with STEMI

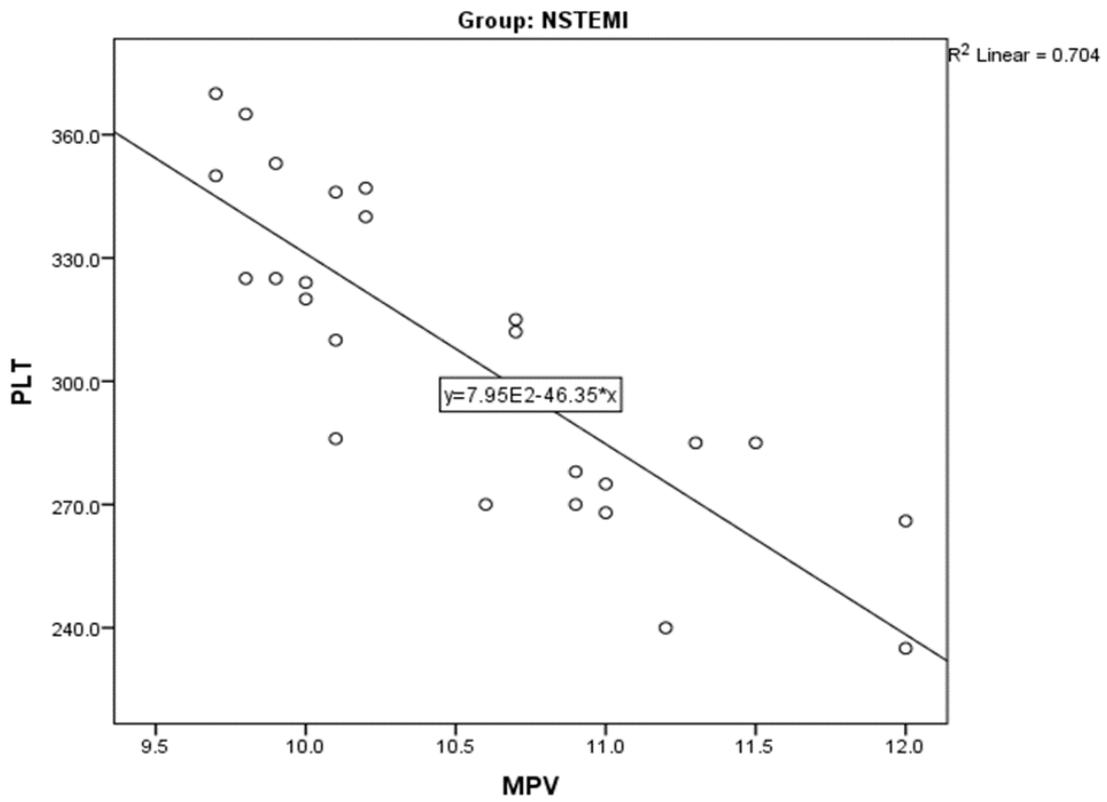


Figure 5: Inverse correlation between MPV and MPC in patients with STEMI

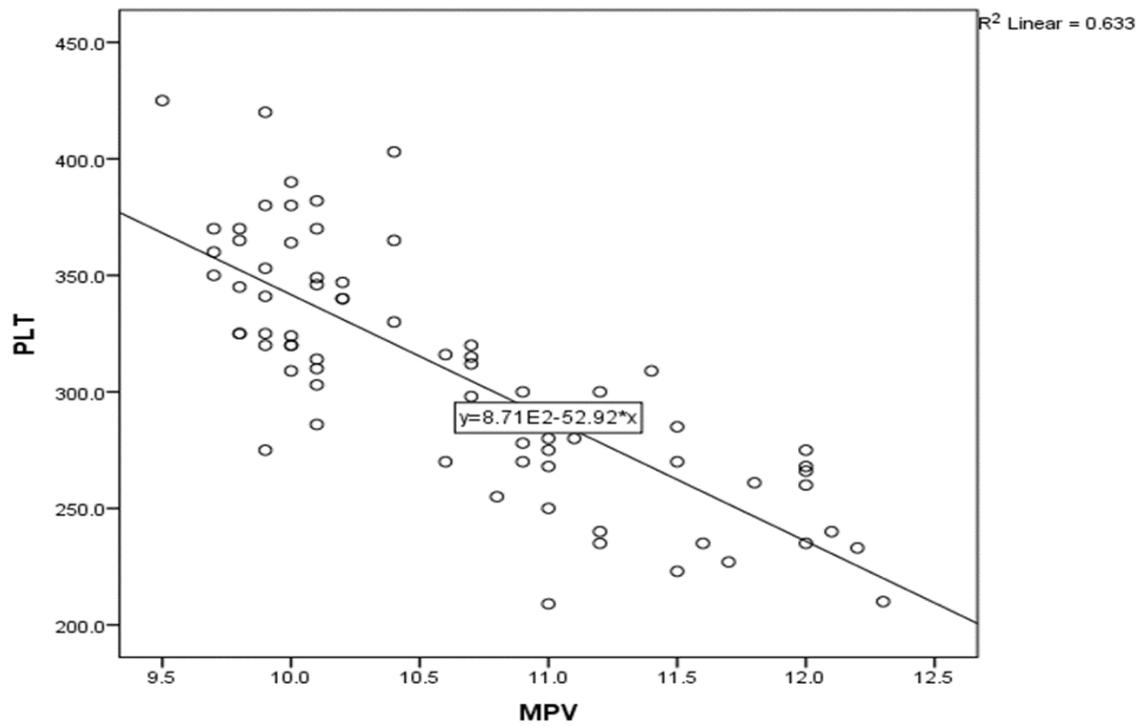


Figure 6: Inverse correlation between MPV and MPC in all patients studied

A comparison between MPV and MPC in patients with and without underlying diseases is shown in Tables 2 and 3. Except for aspirin use, no significant relationship was found in mean platelet volume and platelet count between patients with underlying factors and patients without underlying factors ($P > 0.05$). Platelet count was found to be significantly higher in patients taking aspirin ($329 \pm 52 \times 10^3 / \mu\text{L}$) than in patients without aspirin use ($291 \pm 43 \times 10^3 / \mu\text{L}$) ($P = 0.001$), exclusive of the study groups. While considering the grouping, there was a significantly higher rate of platelet count in aspirin consumers than that of

non-consumers in STEMI and NSTEMI ($P = 0.036$ and 0.004 , respectively); the UA group did not show such a difference ($P = 0.107$). Mean platelet volume was significantly lower in patients with aspirin use ($10.3 \pm 0.6\text{fl}$) that of patients without aspirin use ($10.8 \pm 0.7\text{fl}$) ($P = 0.003$), exclusive of the study groups. While considering the grouping, there was a significantly higher platelet volume in aspirin consumers than that of non-consumers in STEMI and NSTEMI ($P = 0.014$ and 0.021 , respectively); the UA group did not show such a difference ($P = 0.267$).

Table 2: Comparison of Mean MPV in patients with underlying factors and patients without underlying factors

Properties	patients with underlying disease	patients without underlying disease	P-value
Gender (male)	306±54	308±46	0.845*
History of high blood pressure	308±57	306±45	0.877*
History of hyperlipidemia	306±56	308±45	0.866*
History of diabetes	300±54	310±49	0.393*
History of chronic obstructive pulmonary disease	311±58	307±49	0.827*
History of statin use	306±56	308±45	0.866*
History of ischemic heart disease	303±62	308±47	0.763*
History of smoking	307±55	307±49	0.989*
History of using beta-blockers	311±66	306±47	0.777*
ACEIs history	317±64	304±46	0.340*
History of aspirin use	329±52	291±43	0.001*
History of ARBs	304±45	308±52	0.797*

*Independent samples T-test

Table 3: Comparison of Mean MPC in patients with underlying factors and patients without underlying factors

Properties	patients with underlying disease	patients without underlying disease	P-value
Gender (male)	10.7±0.7	10.5±0.7	0.282*
History of high blood pressure	10.6±0.8	10.6±0.7	0.822*
History of hyperlipidemia	10.7±0.8	10.5±0.6	0.478*
History of diabetes	10.7±0.8	10.6±0.7	0.896*
History of chronic obstructive pulmonary disease	10.5±0.7	10.6±0.7	0.800*
History of statin use	10.7±0.8	10.5±0.6	0.478*
History of ischemic heart disease	10.8±0.9	10.5±0.7	0.491*
History of smoking	10.6±0.8	10.6±0.7	0.869*
History of using beta-blockers	10.5±0.9	10.6±0.7	0.457*
ACEIs history	10.5±0.8	10.6±0.7	0.365*
History of aspirin use	10.3±0.6	10.8±0.7	0.003
History of ARBs	10.7±0.7	10.6±0.7	0.511*

*Mann-Whitney test was used for comparison

Discussion

Atherosclerosis is known as the main cause of ACS. Platelets play a key role in the onset of atherosclerosis and the formation of coronary clots. Large platelets have been shown to be more homeostatically active. Evaluation of platelet volume indices can be important in predicting and differentiating coronary facts [12]. Therefore, the aim of this study was to compare the mean number and volume of platelets in patients with unstable angina, STEM, and STEMI.

Our study subjects that were stratified based on the ACS type were head-to-head age and sex-matched. MPV was highest in unstable angina patients, while they were holding the lowest MPC values in comparisons. The highest MPC was in patients with STEMI. In all study groups, MPV and MCV were inversely correlated. In the case of past medical and medication history, aspirin users were having higher MPV than non-users ($P = 0.001$), while the MPC was lower in aspirin users than non-users ($P = 0.003$). Finally, these differences were not helpful in differentiation of ACS types as the changes were happening in the normal clinical values.

The average platelet volume rises in individuals with chronic stable angina, unstable angina, and myocardial infarction, according to several studies [13, 14]. In addition, some studies have linked a large mean platelet volume to a poor outcome in hospitalized ischemia patients [15].

In this study, the mean platelet volume in patients with unstable angina was higher than that of patients with STEMI. This finding is in agreement with the results of previous studies on increasing mean platelet volume in acute coronary syndrome [16]. In some of these studies, the mean platelet volume in patients with unstable angina has been reported to be higher than that of those who suffered from myocardial infarction [17]. This shows that, contrary to unstable angina, platelet depletion is not a long-term underlying condition before myocardial infarction.

An increase in MPV occurs following platelet degradation, and following a decrease in the number of secondary platelets by their destruction, the body synthesizes larger platelets to maintain normal homeostasis and increase platelet mass to gradually replace the lost platelet count [18]. The MPC in individuals with unstable angina, on the other hand, was lower than in those with STEMI, according to the findings of this study. Some investigations, however, found no significant difference in platelet count between individuals with unstable angina and those who had a myocardial infarction [17].

Taking all of these observations into consideration, platelet behavior in unstable angina differs from that of myocardial infarction and ST-segment elevation. ST-segment elevation myocardial infarction is produced by an immediate underlying process of general platelet activation that is unrelated to platelet volume

alterations. Instead, unstable angina is a condition produced by a persistent loss of platelets, which causes an increase in platelet size as a protective strategy against a steady loss of platelets. This mechanism in unstable angina might imply long-term abnormalities in platelet production, which could be produced by an atherosclerotic process in blood vessel walls, predisposing the person to acute vascular events. As a result, a thorough understanding of the mechanisms that control platelet production will aid in the treatment of individuals with unstable angina in the future [19]. The rise in mean platelet volume in unstable angina was attributed to an increase in the number of big platelets released from the spleen following catecholamine stimulation, similar to what happens in heart failure [20]. Few studies have indicated no change in mean platelet volume in unstable angina and acute coronary syndrome, contrary to the findings of the current study and previous studies cited [21].

Another finding of our study was the lack of difference in mean platelet volume and platelet count by age and sex in the subjects, which was consistent with previous studies [20]. Furthermore, a decrease in mean platelet volume was found in patients with a history of aspirin use compared with acute coronary syndrome patients without a history of aspirin use. This can be explained by the effect of aspirin in reducing platelet aggregation and adhesion.

In sum, our study shows that MPC and MPV, which are sometimes hardly evaluated due to complex laboratory procedures, other biomarkers like brain natriuretic peptide (BNP) and cardiac troponin I (cTnI) with levels of C-reactive protein (CRP) shown to be related to cardiovascular events, should be investigated for differentiation of ACS types along with the clinical findings [22-25].

Conclusion

There was a significant difference only in terms of platelet count and mean platelet volume between the two groups of unstable angina and STEM. In all three groups of patients with coronary syndrome, the MPC and MPV were in the normal range, so considering the platelet count and mean platelet

volume alone may not be so helpful to differentiate these three groups of patients.

As for limitations, although the small number of samples makes this finding a little questionable, other studies with more samples can be helpful in this regard. Based on the findings of this study and considering previous studies, platelet indices and especially mean platelet volume might not help diagnosis and differentiation of ischemic heart disease with confidence. Also, there are problems and limitations in sampling, calculating and comparing the values of these indexes by different devices and different laboratories that have not made their clinical use possible so far and studies in this field are still ongoing.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study.

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