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Original Article

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Platelet indices in acute coronary syndrome patients

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Abstract

***Background & Aims*:** platelets play crucial role in acute coronary syndromes (ACS). The importance of platelets in the development and spread of acute coronary syndromes (ACS) is well known. Most studies tried to find an association between platelet indices and cardiovascular diseases (CVD) risk factors; however, the results contradict, and despite the relative ease of obtaining the platelet indices, their use in clinical practice is still limited. This study aimed to investigate the relationship between platelet indices and other influencing factors including age, gender, underlying diseases, and fat profile in determining the risk of ACS.

***Materials & Methods*:** From September 2019 to March 2020, a consecutive of 101 patients (76 men and 25 women) admitted to the CCU in firoozabadi hospital, Tehran, Iran, were enrolled in this cross-sectional study. Patients who had a history of platelet disorders, myeloproliferative disorders, thyroid dysfunctions, receiving blood products, cancers and chemotherapy, and patients who had missing Mean platelet volume (MPV) in current or prior admissions were excluded from the study. Patients were divided into the MI and the UA (Unstable Angina) groups. Data were presented as means ± SD and qualitative variables as frequency (percentage) were considered. Statistical analyzes were performed with SPSS software version 20.

***Results*:** The mean age of patients was 62.5 ± 13.16 years. Age, gender, underlying disease, troponin, ejection fraction, HDL, LDL, cholesterol, and triglyceride were assessed in the patients. The mean fasting blood sugar and LDL were significantly different between the two groups of MI and Unstable Angina (UA), in which P-values were 0.001 and 0.02, respectively. Comparing platelet indices, including platelet count, PDW, and MPV in the two groups, indicated a difference in the PDW variable (P-value 0.008).

***Conclusion*:** Platelet count did not show any significant changes or relation with MI and UA patients. MPV was not significantly higher in the MI group than the UA group, but higher MPV values were related to a higher mortality rate. Elevated PDW was significantly correlated with both MI groups and mortality, thus can be used as a prognostic factor.

***Keywords*:** Coronary Artery Disease, Acute Coronary Syndrome, Myocardial Infarction, Platelet

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Introduction

Acute coronary syndromes (ACS) ranging from unstable angina (UA) to myocardial infarction (MI) are common causes of mortality in developing countries (1,2). In 2010, heart disease caused 16 million deaths and 293 million disabilities Disability-adjusted life years (DALYs). Cardiovascular diseases cause 30% of deaths and 11% of reported disabilities (3). According to the Iranian Ministry of Health, cardiovascular disease and stroke cause 50% of the country's deaths. Most heart attacks in Iran occur between the ages of 40 and 60. Early treatment of heart attacks in golden time can significantly reduce complications (4). Following an acute myocardial infarction and the onset of a complication, the person is deprived of normal life. It makes tremendous psychological and social burden for the patient, as well as long life medications, considerable cost on the patient and the health care system. These complications can be reduced or even prevented by further studies on ACS patients and collecting variables that contribute to cardiovascular events.

Risk factors such as smoking, high cholesterol, obesity, diabetes and hypertension are known in MI (5). Clinical manifestations include persistent angina, ACS, heart failure, and sudden death. The term ACS consists of myocardial infarction with elevated ST-segment (STEMI) and acute coronary syndrome without ST-segment elevation (NSTE-ACS), which itself includes myocardial infarction without ST-segment elevation (NSTEMI) and unstable angina (UA). Approximately two-thirds of ACS patients are NSTE-ACS, and the rest are STE (6,7).

In the protocol of acute myocardial infarction management services in Iran, the main measures to detect cardiac events are ECG, measuring cardiac enzymes, echocardiography, and angiography (8,9). Although the Troponin test, as one of the enzymatic studies in stroke management, has sensitivity and specificity for heart damage but reaches its peak after 12 hours, which lasts up to 10 days. The CK-MB isoform of creatine kinase in the heart muscle peaks 10-24 hours after MI and usually returns to normal within 2-3 days; Therefore, it is not a suitable factor for diagnosing acute MI. However, if the level of this enzyme rises again, it can be used to indicate the progression of a heart attack. Lactate dehydrogenase (LDH) is also released 42 hours after injury and peaks after 12 hours, which lasts up to 7 days (10-12). Thus the downside to cardiac enzymes is their delayed increase relative to the heart attack event.

The importance of platelets in the development and spread of atherosclerosis and thrombosis is well known (13). Platelet volume index (PVI) can directly estimate platelet function and can be easily calculated through most new automated blood analyzers (14). Larger platelets are more metabolically and enzymatically active than smaller ones, and they produce more thromboxane A2 due to containing more alpha granules, thus having a high expression of adhesive glycoproteins (15).

Therefore, most studies have aimed to find an association between PVIs and CVD risk factors, such as obesity, diabetes, and hypertension, to better understand platelet proliferation mechanisms (16,17). However, the obtained results contradict, and despite the relative ease of obtaining these indicators, their use in clinical practice is still limited due to the lack of standardization of measurement methods and interpretation of results. Therefore, this study aimed to investigate the relationship between platelet indices and other influencing variables such as age, sex, underlying diseases, and fat profile in determining the risk of myocardial infarction, considering the role of platelets in the formation of atherosclerotic plaques.

Materials & Methods

Population and study design:

In this cross-sectional study, we evaluated patients admitted to the CCU of Firoozabadi Hospital, Tehran, Iran, from September 2019 to March 2020. Patients with a history of thrombocytopenia and platelet disorders, thalassemia and myeloproliferative disorders, thyroid dysfunctions, history of receiving platelets or other blood products, previous history of cancers and chemotherapy, and patients who had missing Mean platelet volume (MPV) in current or prior admissions

were excluded from the study. In total, 101 patients presenting with chest pain and diagnosed with Acute Coronary Syndrome were included in the study.

Definitions and groups:

According to ECG findings and cardiac biomarkers, patients were divided into Group A, MI (Myocardial Infarction) group, Positive troponin with or without elevated ST-segment, STEMI (ST-Elevation Myocardial Infarction), and NSTEMI (Non-ST Elevation Myocardial Infarction); and Group B, UA (Unstable Angina), Negative troponin in the absence of ST-segment changes but diagnosed as ACS.

Laboratory values such as platelet count, Mean Platelet Volume (MPV), and Platelet distribution width (PDW) were obtained from hospital records and compared between two groups.

Statistical analysis:

Data were analyzed using the SPSS version 20 package. Continuous variables were reported by "Mean ± SD," and Median and Quartiles were used when not normally distributed. Definite values and percentages were used to describe categorical variables. We performed a T-test or ANOVA to compare continuous variables, and Mann-Whitney U and Kruskal-Wallis tests were applied to assess values which were not normally distributed. Chi-squared test and Fisher's exact were performed to compare a variable between categories.

Results

In total, 101 patients were included in the study, of which 76 were men and 25 were women, indicating the significantly higher population of men in CCU admitted patients. The mean age of patients was 62.5 ± 13.16 years. In terms of the patients being divided into two groups, 84 patients were in the AMI group, 59 of whom suffered from STEMI, while the other 15 experienced NSTEMI, and the remaining 27 patients were in the UA group. The majority of patients (93 participants) were discharged from the hospital, while eight patients passed away. Table 1. shows the basic information studied, including age, gender, study group, and outcome.

Table 1. demographics and clinical characteristics of the participants

Characteristic	
Sex, male, n (%)	76 (75.2)
Age (years), year, mean ± SD	62.5 ± 13.6
Male	60.33 ± 12.66
Female	68.08 ± 14.96
Diagnosis, n (%)	46.13±5.83
Myocardial infarction	74 (73.3)
NSTEMI*	15 (14.9)
STEMI*	59 (58.4)
Unstable angina	27 (26.7)
Comorbidities, n (%)	
HTN*	21 (20.7)
DM* type II	38 (37.6)
Dyslipidemia	19 (18.8)
Previous ischemic heart disease	23 (22.7)
No prior medical history	37 (36.6)
Outcome, n (%)	
Death	8 (7.92)
Discharge	93 (92.08)

*NSTEMI: Non ST-Elevation Myocardial Infarction, STEMI: ST-Elevation Myiocardial Infarction, HTN: Hypertension, DM: Diabetes Mellitus.

Age, Fasting Blood Sugar, triglyceride, cholesterol, HDL, LDL, Ejection Fraction, Troponin, and Hospitalization Days are compared between the two groups, and the results are demonstrated in Table 2. The mean fasting blood sugar and LDL are significantly different between the two groups AMI and UA, in which P-values were 0.001 and 0.02, respectively.

Table 2. comparison of clinical and laboratory variables between ACS groups

	MI* group	**UA* group**	**P value**
Age (years), mean ± SD	62.69 ± 13.57	61.04 ± 13.91	0.57
Platelet indices, mean ± SD			
Absolute count (10^3/µL)	227.03 ± 75.18	234.74 ± 79.85	0.6
MPV* (fl)	13.02 ± 2.51	10.62 ± 2.63	0.008
PDW* (fl)	10.31 ± 2.11	10.23 ± 1.22	0.8
Laboratory data, mean ± SD			
Fasting blood sugar (mg/dL)	175.81 ± 17.67	112.75 ± 28.85	0.001
Triglyceride (mg/dL)	156.62 ± 74.36	161.39 ± 64.55	0.83
Cholesterol (mg/dL)	179.08 ± 44.81	197.94 ± 42.12	0.12
HDL* (mg/dL)	46.54 ± 42.83	38.35± 9.70	0.41
LDL*(mg/dL)	135.60 ± 44.81	113.00 ± 48.02	0.02
Troponin (ng/mL)	13658.63 ± 1718.82	82.27 ± 286.3	0.001
EF* (%), mean ± SD	44.05 ± 9.21	55.43 ± 8.71	0.001
Hospitalization days, mean ± SD	3.85 ± 0.17	3.50 ± 0.75	0.49

*MI: Myocardial Infarction, UA: Unstable Angina, MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, EF: Ejection Fraction.

The comparison of platelet indices (PLT, PDW, MPV) in the two groups is shown in Table 3, indicating the PDW being significantly higher in the AMI group.

Table 3 shows a comparison of hospitalization days, age, creatinine, troponin, ejection fraction, LDH, HDL, LDL, cholesterol, triglyceride, and FBS based on the outcome, indicating that having higher EF, or lower Cr or FBS results in significantly better outcomes.

Platelet indices PDW and MPV were significantly lower in discharged patients comparing to deceased patients, as shown in Table 3.

Table 3. clinical and laboratory differences of the patients based on outcome

	Outcome		**P value**
	Discharge	**death**	
Age, mean ± SD	61.99 ± 13.95	65.25 ± 8.92	0.36
Platelet indices, mean ± SD			
Absolute count (10^3/µL)	228.78 ± 76.16	233.12± 81.18	0.88
MPV* (fl)	10.12 ± 1.94	11.70 ± 0.45	0.04
PDW* (fl)	12.02 ± 2.66	14.96 ± 2.07	0.02
Laboratory data, mean ± SD			
Creatinine (mg/dL)	1.14 ± 0.71	1.82 ± 0.61	0.02

Fasting blood sugar (mg/dL)	152.42 ± 91.84	274.40 ± 122.80	0.01
Triglyceride (mg/dL)	156.79 ± 97.58	175.25 ± 66.68	0.65
Cholesterol (mg/dL)	183.06 ± 82.26	197.25 ± 83.98	0.76
HDL* (mg/dL)	45.02 ± 38.68	37.60 ± 13.44	0.34
LDL*(mg/dL)	125.53 ± 42.80	183.00 ± 91.92	0.045
Troponin (ng/mL)	10133.20 ± 16030.24	8818.74 ± 14862.76	0.80
LDH* (U/L)	697.55 ± 653.10	1272.75 ± 648.28	0.70
EF* (%), mean ± SD	52.82 ± 9.08	35.00 ± 7.07	0.001
Hospitalization days, mean ± SD	3.58 ± 2.31	3.75 ± 1.48	0.77

*MPV: Mean Platelet Volume, PDW: Platelet Distribution Width, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, LDH: Lactate Dehydrogenase, EF: Ejection Fraction.

Discussion

Platelets and their function play a key role in cardiovascular events. Coronary artery stenosis is a major cause of myocardial infarction, which consequently may lead individuals to death. Since vascular occlusion is most of the time directly caused by platelet aggregation thus, evaluating parameters related to platelet is crucial for preventing new episodes of cardiovascular attacks .

The first important index is the absolute platelet count. Some believe that platelet count and size are contrary to each other. It is assumed that the larger platelets will have a lower absolute count in order to maintain the total effectiveness of platelet mass (18). We investigated the relationship between platelet count and adverse outcomes of coronary accidents. Our findings showed no significant correlation between presentation of ACS (227.03 ± 75.18 10^3/μL in MI group vs. 234.74 ± 79.85 10^3/μL in UA group; P: 0.60) nor outcome and absolute platelet count (228.78 ± 76.16 10^3/μL in the discharged group vs. 233.12 ± 81.18 10^3/μL in death group; P: 0.88).

Hendra et al. by comparing platelet indices between the infarct group and non-infarct patients, reported that platelet count did not differ significantly between the two groups (19).

In another study, Boos et al. evaluated time-dependent changes of platelet indices in ACS patients and found no significant changes in platelet count over time (20).

Khandekar et al. evaluated platelet profile in ischemic spectrum among 210 Indian populations and found no significant differences in platelet count between different groups of ischemic patients (21).

MPV (Mean Platelet Volume):

Mean platelet volume indirectly implies that platelet destruction and reproduction are relatively high. This can cause more activity than smaller-sized platelets. Recent studies demonstrated that larger platelets induce more platelet aggregation even with antiplatelet therapy (22,23). Therefore, patients with higher MPV are at higher risk of vascular occlusion. Our findings support the hypothesis that people diagnosed with acute MI have more MPV than patients who did not show ECG changes or positive cardiac biomarkers (ACS, Unstable angina patients). However, this difference was not statistically significant (10.315 ± 2.11 vs. 10.231 ± 1.22; P: 0.080). Cameron et al. demonstrated that not only mean platelet volume correlates with more ischemic events, but MPV also remained specifically high for several weeks after the infarction (24). Some may believe that MPV is increased due to severe illness, such as every other critical situation. In contrast, Martin et al. compared platelet volume and distribution in 15 cases with myocardial infarction and 22 healthy people. Based on this survey, MPV was increased by a mean of 0.98 fl in the study group compared with the control group in the first 12 hours of MI (P< 0.001). Mean platelet volume was found to be higher in the MI group even after six weeks after the infarction (by a mean of 1.24 fl; P< 0.001). The authors suggested that since the mean

age of platelets is eight days and there was an increase right in the first 12 hours of infarction, there was a strong probability that the process of platelet volume increase has been started days before the event. In addition to that, whereas platelet volume remained bigger even weeks after the ischemia has gone, it is highly probable that MPV is chronically high in these people (25). In evaluating the role of MPV in ACS outcome, Małyszczak et al. reported that both low and high MPV are significantly related to a higher 5-year mortality rate than normal MPV cases (34.7% vs. 24.7%), Which is along with of our study (26). According to our results, MPV was measured significantly higher in patients who died because of MI (11.70 ± 0.45 vs. 10.12 ± 1.94; P: 0.04).

PDW (Platelet Distribution Width):

Platelet distribution width (PDW) reflects whether platelets are equal or different in size and shape. As previously mentioned, platelets start to get larger when they are activated. The two most commonly used markers to indirectly describe platelet activation by their size are MPV and PDW. PDW is less investigated compared with MPV, and recent studies even indicate that novel PDW evaluation is more prognostic than prior marker (MPV) in cardiovascular events (27). The result of this study suggest that PDW significantly increases in the acute MI group (13.024 ± 2.5121 vs. 10.623 ± 2.6351; P: 0.008). Our findings are in agreement with the study of Abdullah S. Assiri et al. who examined 212 patients in a case-control study and found that PDW was significantly higher in MI cases than in control groups (15.88 ± 1.5 fl vs. 11.96 ± 1.8 fl, respectively, P <0.001), and PDW was higher even in UA patients than MI groups (18.1 ± 1.8 fl vs. 11.96 ± 1.8 fl, respectively, P < 0.019) (28).

Rechciński et al reported that PDW ≥ 16 fL significantly increased the mortality rate in comparison with PDW < 16 fL (17.4% vs. 6.3%, P: 0.0012), suggesting PDW as an independent prognostic factor for ACS mortality (29).

In favor of this conclusion, we observed that in patients who ended up with death, PDW was higher when compared with the discharged group and this difference was statistically significant (14.96 ± 2.07 vs. 12.02 ± 2.66; P: 0.02). Furthermore, not even higher PDW is related to higher occlusive events. Michał Kowara et al. demonstrated that high PDW in ACS patients correlates with higher mortality even after treating with PCI. They found that higher values of PDW are significantly related to LV dysfunction in long-term follow-up (30).

Cardiac parameters:

Troponin is generally known as a cardiac biomarker that is elevated when ischemia happens. It is routinly measured when ST segment changes are likely to seen. Theoretically two types of troponin, I and T is specific and sensitive for myocardial damage. Cardiac troponin level, start to elevate about two or three hours after the myocardial injury. We measured troponin concentration and as expected, mean troponin level was significantly higher in MI groups than unstable angina patients (13658.63 ± 1718.82 *vs.* 82.27 ± 286.30 ng/ml; P: 0.001).

Ejection Fraction (EF), has been remarkabkly reduced in patients with acut myocardial infarction. EF, is an indicator of left ventricle function and is measured by echocardiography. Our data showed that patients with ST segment changes, had lower EF when compared with other ACS patients (44.05 ± 9.215 *vs.* 55.43 ± 8.710 %; P: 0.001). Ohlow et al. demonstrated that left ventricular ejection fraction had been significantly decreased in ST segment elevation/depression patients (58.7 ± 12.6 *vs.* 48.1 ± 12.4 %; P< 0.01) (31).

Laboratory findings:

Several factors including sex, smoking, age, uncontrolled blood pressure and diabetes play a major role in developing cardiovascular events. Dyslipidemia is an important but preventable risk factor for plaque rupture and myiocardial infarction (32). We measured lipid profile in our study and found that only elevated Low-Density Lipoprotein is highly related to myocardial infarction. Mean LDL level in MI group was 135.60 ± 44.819 mg/dL that was significantly higher than unstable angina patients (113.09 ± 48.026 mg/dL; P: 0.02). the rest of the lipid profile did not show any significant differences between groups (Table 1). In a

recent study, Kaneko et al. evaluated lipid profile and its effect on cardiovascular disease. They found that LDL more than 140 mg/dL is remarkably correlated with more vascular and ischemic events. However alongside elevated LDL (≥ 140 mg/dL), low HDL (<40 mg/dL) and elevated triglycerides (≥150 mg/dL) were also found to be a meaningful relation with vascular accidents (33). Kurihara et al. conducted a study to examine the correlation between LDL and plaque rupture. They reported atherosclerotic plaques are more likely to be ruptured in elevated LDL cases (P: 0.007). Furthermore, they found that higher baseline LDL levels tend to cause more vascular events than normal baseline LDL levels; even with statin therapy (34).

Limitations and Strengths:

To mention our study's strength, we can outline that this is a cohort study which allows us to examine and follow changes and determine how these changes influence the outcome. We also extracted various information like cardiac parameters, hematologic indices, and metabolic profiles. We examined how these variables are related to the clinical diagnosis and outcome.

Our study faces limitations which are worth mentioning. First, our study population was relatively small. Although we enrolled 101 patients, for a more resolute conclusion, a bigger sample size is recommended. The second limitation was missing data which restricted us from studying more holistically. Third problem that we are aware of was the fact that we did not include the type of treatments and did not determine the relationship between different types of treatments and platelet indices.

Taken together, for more comprehensive conclusions, we suggest a prospective cohort study with long-term follow ups and a bigger study population which examines a complete profile of cardiac, hematologic, and metabolic parameters and considers different types of treatments among ACS patients.

Conclusion

In general, we outlined the changes and possible effects of platelet indices among ACS patients' outcomes. Platelet count did not show any significant changes or relation with MI groups and UA patients. A similar result was analyzed with the final outcome. MPV was not significantly higher in the MI group compared with the UA group, but higher values of MPV related to higher mortality rate. Elevated PDW was significantly correlated with both MI groups and mortality, thus can be used as a prognostic factor.

Acknowledgments

No Declared

Conflict of interest

The authors have no conflict of interest in this study.

Ethical statement:

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Firoozabadi Hospital, Tehran, Iran. All patients provided written informed consent before participating in the study.

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