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Diagnostic importance of admission platelet volume indices in patients with acute chest pain suggesting acute coronary syndrome

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ABSTRACT

Objective: Acute coronary syndrome (ACS) is a challenging issue in cardiovascular medicine. Given platelet role in atherothrombosis, we sought to determine whether platelet indices can be used as diagnostic tests for patients who suffered from an acute chest discomfort.

Methods: We prospectively enrolled 862 patients with an acute chest pain and 184 healthy matched controls. They were divided into four groups: 184 controls, 249 of non-ACS, 421 of unstable angina (UA), and 192 of myocardial infarction (MI) cases. Blood samples were collected at admission to the emergency department for routine hematologic tests.

Results: The mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (P-LCR) were significantly greater in patients with MI compared with those of non-ACS or control subjects. Negative and significant correlations existed between MPV, PDW, and P-LCR values and platelet count ($P < 0.001$). Receiver operating characteristic (ROC) curves showed that the MPV, PDW, and P-LCR with cut-off values of 9.15 fL, 11.35 fL, and 20.25% and with area under the curves of 0.563, 0.557, and 0.560, respectively, detected MI patients among those who had chest discomfort. The sensitivities and specificities were found to be 72% and 40%, 73% and 37%, and 68% and 44% for MPV, PDW, and P-LCR, respectively.

Conclusion: An elevated admission MPV, PDW, and P-LCR may be of benefit to detect chest pain resulting in MI from that of non-cardiac one, and also for risk stratification of patients who suffered from an acute chest discomfort.

1. Introduction

Acute coronary syndrome (ACS) includes the full spectrum of clinical manifestations from unstable angina (UA) to non-ST elevation myocardial infarction (MI) and ST-segment elevation MI.[1] Despite advances in the ACS diagnosing and implementing therapies, identifying myocardial ischemia has been remained as a challenge for physicians, and they hospitalize

the more number of low-risk patients with suspected myocardial ischemia.[2] Troponin and the MB isoenzyme of creatine kinase (CK-MB) are the routine biochemical markers, which are used to detect ACS. Troponin, as the most sensitive and tissue-specific cardiac marker, is now considered as the gold-standard biochemical tool for ACS risk stratification; however, it is undetectable in about 40–60% of patients suffering from an ACS.[3] Therefore, using a multimarker approach may be of benefit to diagnose the spectrum of clinical manifestation, like ACS.

It has been previously demonstrated that the atherosclerosis is a chronic inflammatory disease. Atherosclerotic lesions in large and medium-sized arteries can contribute to the ischemia of the heart, brain or extremities leading to infarction.[4] Plaque rupture and thrombosis are the important complications of the atherosclerotic lesions resulting in ischemia. Some factors have been investigated regarding this issue, and one of the main suspected factors is platelet circulating in our blood flow. Platelets are a source of inflammatory mediators, and they are being influenced in contact with artery surface. The activated platelets release the mediators, and then, platelet adhesion and its atherothrombotic potential can lead to the release of mediators, the progression of inflammatory process, and the propagation of intracoronary thrombus predisposing to thrombotic events.[4,5]

Mean platelet volume (MPV), as a component of complete blood count, is the most common and reliable index to identifying the platelet size and its activation status.[6] An increased MPV is associated with known cardiovascular risk factors, including diabetes mellitus, hypertension, hypercholesterolemia, and obesity.[6–8] Some investigations have demonstrated the correlation between elevated MPV and ACS,[9,10] and also the association between increased one and percutaneous coronary intervention outcomes, including mortality and stent restenosis.[11–14] However, some studies have also shown that MPV cannot be considered as either a marker of platelet activation or a cardiovascular risk factor.[6,15] In addition, other platelet indices including platelet distribution width (PDW) and platelet large cell ratio (P-LCR) have also been shown to be correlated with ACS.[9]

Hereby, in the present study, our aim was to determine any correlations between the platelet indices, including platelet count, MPV, PDW, and P-LCR and the spectrum of ACS among patients who suffered from an acute new-onset chest discomfort admitted to our emergency department.

2. Materials and methods

2.1. Study patients

We prospectively enrolled 862 patients with a chief complaint of acute chest discomfort suggestive of ACS who were admitted to the emergency department of Seyyed-al-Shohada Heart Center, Urmia, West-Azerbaijan province, Iran, from August 2012 through April 2013. All patients whose chest pain had been begun more than 30 min before arriving to the hospital were excluded. This study was approved by our local ethics committee in the Urmia University of Medical Sciences, and all patients were provided written informed consent.

The patients were hospitalized based on their evaluation at admission, including taking history, physical examinations, ischemic changes in a standard 12-lead electrocardiogram (ECG), and/or increased cardiac biomarkers. The diagnosis of MI was based on either patients who suffered from a chest pain lasting more than 20 min with or without ST-segment elevation in ≥ 2 contiguous leads and/or the elevation of cardiac biomarkers (troponin or CK-MB) more than two-fold of the upper limit of normal value or those who suffered from a chest pain without ST-segment elevation associated with the elevation of cardiac biomarkers. The UA was considered as patients with typical chest pain and/or ischemic changes in the 12-lead ECG without significant alteration in the cardiac biomarkers similar to the MI cases. Non-ACS patients served as patients whose chest pain was atypical and cardiac biomarkers were not significant and/or no ischemic changes were observed in the ECG. All admitted patients were given 300 mg of chewable aspirin before blood sample to be collected. In addition, 184 healthy matched controls were also enrolled to compare its measured laboratories with those of patients who had acute chest pain. The control participants had normal ECG without any history of chest pain or ischemic heart diseases.

2.2. Biochemical evaluation

All patients underwent taking history and full physical examination associated with paraclinic evaluations, including hematologic tests and a standard 12-lead ECG at admission. Blood samples were collected using venipuncture for routine hematologic assessments into tubes containing ethylenediamine tetra-acetic acid (EDTA). The platelet indices were analyzed within 30 min after sampling by an automated cell counter (Sysmex KX21-N, Kobe, Japan). The troponin samples showing positive qualitative test along with the ischemic changes in ECG were reanalyzed to titrate.

2.3. Statistical analysis

The patients were categorized into four groups, including control, non-ACS, UA, and MI. Continuous variables were reported as mean ± standard deviation, and analyzed using t-test, one-way ANOVA, and Tukey's post hoc test. Categorical variables were also analyzed using Chi-square test. In addition, the Pearson correlation coefficient was used for identifying association between two continues variables. Receiver operating characteristic (ROC) curve was also constructed to detect the accuracy of platelet volume indices for diagnosing ACS.

All analyses were performed using SPSS, version 16.0 (SPSS, Chicago, Illinois, USA). The p value of <0.05 was considered statistically significant.

3. Results

The study participants comprised of 1046 ones were divided into four groups: (1) 184 controls; (2) 249 with non-ACS; (3) 421 with UA; and (4) 192 MI cases. The baseline clinical characteristics and biochemical measurements were depicted in Tables 1 and 2. The mean age of patients was significantly

Table 1 — Baseline characteristics of the patients with ACS and control subjects.

	Control ($n = 184$)	Non-ACS ($n = 249$)	UA ($n = 421$)	MI ($n = 192$)	p-value[*]
Age (years)	52.8 ± 14.3	49.9 ± 15.1	60.5 ± 12.7	59.6 ± 12.6	<0.001
Tukey test[**]	a	a	b	b	
Gender					<0.001
Male	73 (39.7%)	152 (61%)	237 (56.3%)	139 (72.4%)	
Female	111 (60.3%)	97 (39%)	184 (43.7%)	53 (27.6%)	
BMI (kg/m^2)	27.6 ± 4.7	28.1 ± 4.6	28.1 ± 4.8	27.3 ± 4.6	0.204
Tukey test[**]	a	a	a	a	
Hypertension	1 (0.5%)	44 (17.7%)	251 (59.6%)	79 (41.1%)	<0.001
Diabetes mellitus	0 (0%)	18 (7.2%)	122 (29%)	60 (31.2%)	<0.001
Dyslipidemia	2 (1.1%)	15 (6%)	79 (18.8%)	28 (14.6%)	<0.001
Smoking, current	30 (16.3%)	31 (12.4%)	107 (25.4%)	80 (41.7%)	<0.001
Family history of CAD	32 (17.4%)	30 (12%)	130 (30.9%)	51 (26.6%)	<0.001
Prior MI	0 (0%)	7 (2.8)	113 (26.8)	22 (11.5%)	<0.001
Prior PCI	0 (0%)	7 (2.8%)	77 (18.3%)	4 (2.1%)	<0.001
Drug history					
β-blocker	3 (1.6%)	32 (12.9%)	211 (50.1%)	46 (24%)	<0.001
Statins	0 (0%)	15 (6%)	195 (46.3%)	36 (18.8%)	<0.001
Nitrates	0 (0%)	18 (7.2%)	173 (41.1%)	26 (13.5%)	<0.001
Aspirin	0 (0%)	25 (10%)	252 (59.9%)	42 (21.9%)	<0.001
Dual anti-platelet	0 (0%)	8 (3.2%)	105 (24.9%)	13 (6.8%)	<0.001

ACS: acute coronary syndrome, BMI: body mass index, CAD: coronary artery disease, MI: myocardial infarction, PCI: percutaneous coronary intervention, UA: unstable angina.
Values are presented as mean ± SD or number (%).
[*]$p < 0.05$ was considered statistically significant.
[**]Having the same letter indicates non-significant difference between two groups based on Tukey post hoc test.

higher in the UA and MI groups compared with controls ($p < 0.001$), and also it was statistically greater in both groups compared with that of non-ACS participants with similar significances, $p < 0.001$ (Table 1). Most of the patients were male in all groups except control subjects, and their differences were significant ($p < 0.001$). All cardiovascular risk factors and drug histories were also statistically significant among groups (Table 1).

Platelet count was not significantly different among groups ($p = 0.160$), although its value was slightly higher in MI than in UA or non-ACS cases (2.8% increase and 0.8% increase, respectively). MPV level was significantly higher in MI patients than that of non-ACS or control subjects (3.1% increase, $p = 0.003$, and 4.1% increase, $p = 0.019$, respectively). PDW level was also significantly higher in MI group compared with non-

ACS or control groups (7.6% increase, $p = 0.033$, and 9.8% increase, $p = 0.005$, respectively). The mean of P-LCR has only been found to be significantly higher in MI and UA groups compared with control group (11.25% increase, $p = 0.001$, and 7.8% increase, $p = 0.018$, respectively) (Table 2). Because the females were more than males in control groups, we compared the platelet indices in groups divided by gender. Accordingly, there was no significant differences in terms of platelet indices between both sexes, except platelet count that was higher in female than male, $p < 0.001$ (Table 3).

When comparing the differences of platelet volume indices, including MPV, PDW, and P-LCR between subgroups by known cardiovascular risk factors among all patients irrespective being control or having chest pain, MPV was found to be significantly higher in patients who had a history of

Table 2 — Biochemical measured values in the patients with ACS and control subjects.

	Control ($n = 184$)	Non-ACS ($n = 249$)	UA ($n = 421$)	MI ($n = 192$)	p-value[*]
Platelet count ($\times 10^9$/L)	234.7 ± 64.1	226.8 ± 62.7	222.2 ± 64.9	228.7 ± 62.6	0.160
Tukey test[**]	a	a	a	a	
MPV (fL)	9.3 ± 0.9	9.4 ± 1	9.5 ± 1	9.7 ± 1	0.002
Tukey test[**]	a	a	a, b	b	
PDW (fL)	11.9 ± 1.8	12.2 ± 1.9	12.5 ± 2.1	13.2 ± 7.9	0.006
Tukey test[**]	a	a	a, b	b	
P-LCR (%)	21.3 ± 6.5	22.2 ± 7.5	23.1 ± 7.2	24 ± 7.5	0.001
Tukey test[**]	a	a, b, c	b, c	c	

ACS: acute coronary syndrome, fL: femtoliter, MI: myocardial infarction, MPV: mean platelet volume, PDW: platelet distribution width, P-LCR: platelet large cell ratio, UA: unstable angina.
Values are presented as mean ± SD.
[*]$p < 0.05$ was considered statistically significant.
[**]Having the same letter indicates non-significant difference between two groups based on Tukey post hoc test.

Table 3 – Platelet indices of the patients with acute coronary syndrome (ACS) and control subjects based on sex difference.

	Total ($n = 1046$)	Control ($n = 184$)	Non-ACS ($n = 249$)	UA ($n = 421$)	MI ($n = 192$)
Platelet count ($\times 10^9$/L)					
Male	213.7 ± 57.2	220.36 ± 63.4	213.9 ± 57.6	210.1 ± 56	215.9 ± 55.6
Female	244.2 ± 68.2	244.2 ± 63	246.8 ± 65.5	237.8 ± 72	262.1 ± 68
p-value*	<0.001	0.013	<0.001	<0.001	<0.001
MPV (fL)					
Male	9.5 ± 1	9.4 ± 0.8	9.4 ± 1	9.5 ± 0.9	9.7 ± 1
Female	9.6 ± 1	9.3 ± 0.9	9.5 ± 1	9.7 ± 1.1	9.9 ± 1
p-value*	0.148	0.696	0.458	0.064	0.105
PDW (fL)					
Male	12.4 ± 4.8	11.9 ± 1.7	12.1 ± 1.8	12.3 ± 2	13.2 ± 9.2
Female	12.4 ± 2.1	11.9 ± 1.8	12.3 ± 2	12.6 ± 2.2	13.1 ± 2.2
p-value*	0.978	0.969	0.493	0.122	0.933
P-LCR (%)					
Male	22.5 ± 7.1	21.4 ± 6.1	21.9 ± 7.3	22.2 ± 6.9	23.4 ± 7.3
Female	23.1 ± 7.5	21.1 ± 6.7	22.6 ± 7.6	23.8 ± 7.6	25.6 ± 7.9
p-value*	0.148	0.754	0.479	0.100	0.071

ACS: acute coronary syndrome, fL: femtoliter, MI: myocardial infarction, MPV: mean platelet volume, PDW: platelet distribution width, P-LCR: platelet large cell ratio, UA: unstable angina.
Values are presented as mean ± SD or number (%).
*$p < 0.05$ was considered statistically significant.

hypertension and ACS diagnosis compared with those did not (9.6 ± 1 vs. 9.4 ± 1 fL, $p = 0.005$; 9.6 ± 1 vs. 9.4 ± 1 fL, $p = 0.023$; respectively). The participants with a history of hypertension and ACS diagnosis had the higher P-LCR value compared with them without both of those (23.7 ± 7.3 vs. $22.2 \pm 7.2\%$, $p = 0.002$; 23.4 ± 7.3 vs. $22.2 \pm 7.4\%$, $p = 0.032$; respectively). In addition, PDW was only significantly higher in cases with MI history compared with those without it (13.3 ± 9.2 vs. 12.3 ± 2 fL, $p = 0.006$) (Fig. 1).

Pearson correlation analysis was used to determine the correlations between platelet count and platelet volume indices among all patients. Accordingly, There were strong and negative correlations between platelet count and MPV ($r = -0.390$, $p < 0.001$), PDW ($r = -0.221$, $p < 0.001$), and P-LCR ($r = -0.398$, $p < 0.001$). When comparing these correlations in each group separately, all correlations were significant except platelet count and PDW in MI cases, $p = 0.069$ (Table 4).

Furthermore, ROC curve analysis demonstrated that the admission values of MPV, PDW, and P-LCR were useful diagnostic tools to detect MI cases among patients suffering from an acute chest discomfort (area under the curve [AUC] = 0.563, 95% confidence interval [CI] 0.519–0.607, $p = 0.006$; AUC = 0.557, 95% CI 0.513–0.601, $p = 0.013$; and AUC = 0.560, 95% CI 0.515–0.604, $p = 0.010$; respectively). The best cut-off points, sensitivities, and specificities for identifying MI were 9.15 fL, 72%, and 40%; 11.35 fL, 73%, and 37%; and 20.25%, 68%, and 44% for MPV, PDW, and P-LCR, respectively (Fig. 2).

4. Discussion

We found that the platelet volume indices, including MPV, PDW, and P-LCR increased in patients diagnosed with MI compared with those with non-ACS or controls. These parameters were also found to be accurate diagnostic tests for the detection of MI. These findings are in agreement with those of previous studies showed that the elevated platelet volume indices in patients with ACS can be used as prognostic or diagnostic tests.[2,9,10,16,17]

Platelets are potential blood cells in terms of cardiovascular disease mechanism. As the platelets increase in activity in the setting of atherothrombotic events such as ACS, their size also enhances accordingly. The larger one is being more reactive and produces more proinflammatory and prothrombotic mediators leading to coronary related clinical events. MPV is a routine measurement of complete blood count showing the mean of circulating platelet size, and its predictive value concerning clinical assessments in the cardiovascular medicine has been previously reported.[6] In addition, it has been demonstrated that the platelet count is inversely associated with MPV,[18] suggesting that platelet consumption during acute coronary events can lead to production of bigger one by megakaryocyte activity and consequent elevated MPV value.[19,20] Martin and coworkers[21] demonstrated that MPV increased during 2 years follow up in the patients diagnosed with MI, and elevated ones correlated with recurrent MI and death. It was considered as an independent predictor of recurrent MI; however, there was not any correlation in terms of platelet counts between study groups. They also showed no correlation between increased MPV and known ischemic heart disease risk factors, including hypertension, dyslipidemia, fibrinogen, white blood cell count, and plasma viscosity. Other studies[9,10] found that MPV values in patients with MI increased compared with those of stable coronary artery disease (CAD) or controls. None of the mentioned investigations could show difference between MI and UA patients. We also could not show any differences between MI and UA patients in terms of platelet indices values.

In addition, Khandekarand et al[9] have evaluated the platelet volume indices in the patients with MI and UA compared with those with stable CAD and controls, and they demonstrated that the elevated PDW and P-LCR were associated with developing ACS the same as MPV. By contrast, Khode and coworkers[17] have shown that there was no significant differences in terms of PDW and P-LCR values
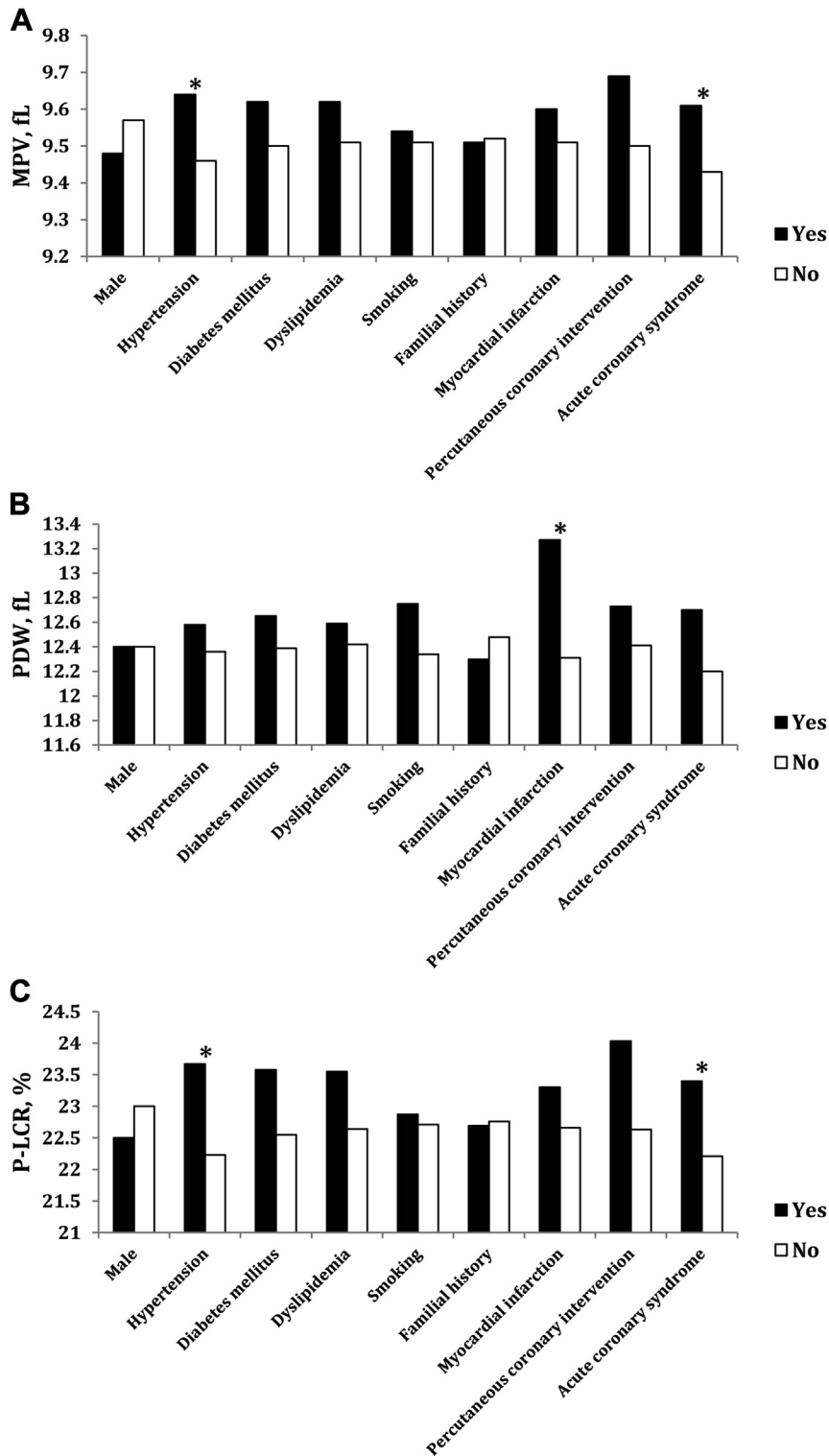
Fig. 1 – Platelet volume indices' difference among subgroups, each subgroup was categorized as either with a feature and a prior history or without them: labeled yes or no. fL: femtoliter, MPV: mean platelet volume, PDW: platelet distribution width, P-LCR: platelet large cell ratio.

between MI and stable CAD or control cases; however, elevated MPV was associated with MI. We demonstrated that elevated admission PDW and P-LCR were associated with MI similar to MPV. Hereby, we believe that the diagnostic and

prognostic values of platelet volume indices may be similar to each other, but we need further prospective studies to evaluate the correlation between CAD and both the PDW and P-LCR values to conclude more definitely.

Table 4 – Correlations between platelet count and platelet volume indices among all patients.

	Total	Control	Non-ACS	UA	MI
MPV					
r	−0.390	−0.475	−0.370	−0.405	−0.317
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001
PDW					
r	−0.221	−0.476	−0.358	−0.407	−0.132
p-value*	<0.001	<0.001	<0.001	<0.001	0.069
P-LCR					
r	−0.398	−0.483	−0.360	−0.429	−0.306
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001

ACS: acute coronary syndrome, MI: myocardial infarction, MPV: mean platelet volume, PDW: platelet distribution width, P-LCR: platelet large cell ratio, UA: unstable angina.
*Pearson correlation was used.

Recently published study by Lippi and et al[2] showed the diagnostic accuracy of MPV for ACS among patients with chest pain compared with non-cardiac chest pain. They concluded that MPV measurement might be considered as the risk stratification of patients with chest pain suggestive of ACS in the emergency departments. Furthermore, a new meat-analysis by Chu and colleagues[6] stated that the increased MPV was associated with recurrent MI and death during follow up in the patients with MI, and coronary restenosis following stenting. Based on these findings, it has been remained unknown that whether MPV value will change practice guidelines in cardiovascular medicine.
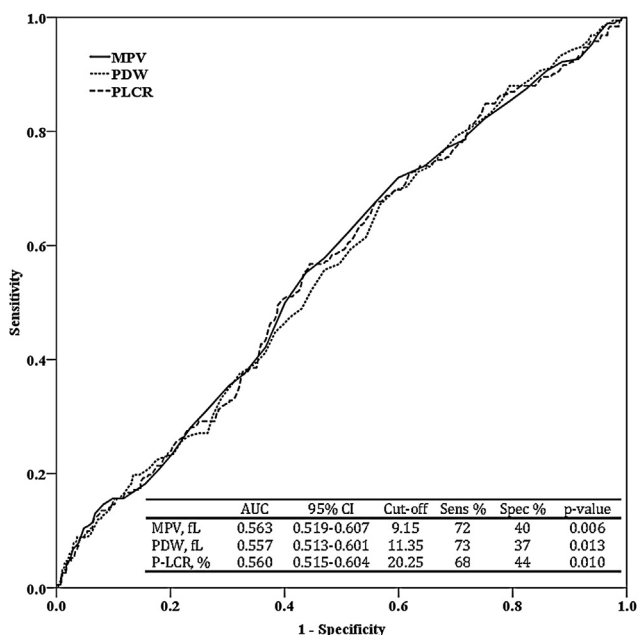
Fig. 2 – Diagnostic accuracy of platelet volume indices. Receiver operating characteristic (ROC) curves were constructed to detect acute myocardial infarction (MI) among healthy controls and patients suffering from an acute chest pain. AUC: area under the curve, CI: confidence interval, MPV: mean platelet volume, PDW: platelet distribution width, P-LCR: platelet large cell ratio; Sens, sensitivity, Spec: specificity.

The other important study by Martin and colleagues[20] concerning the role of platelets in coronary obstruction during ACS concluded that the circulating larger and more active platelets in ACS can influence therapeutic options in the future; however, in a large scale study on 2009, De Luca and colleagues[15] found that there were not any correlations between MPV and platelet activity and the extension of CAD according to coronary angiography and carotid intima media thickness. They indicated that MPV cannot be considered either as platelet activity marker or CAD risk factor.

None of the above mentioned investigations demonstrated the difference of MPV between UA and MI. Notably, Mathur and colleagues[22] conducted a study in terms of the differentiation between UA and MI by platelet activation indices, and revealed that the MPV was lower in MI than that of UA. This finding is contradictory to those of present and other studies showing no difference, and supports this issue that we need further investigations to elucidate the correlation between platelet indices and patients with acute chest pain.

The limited numbers of literature have confirmed the diagnostic accuracy of MPV in the setting of ACS. As they have reported MPV values as a diagnostic test for distinguishing the development of ACS, including AUC = 0.661 reported by Lippi[2] and AUC = 0.800 reported by Chu,[16] and also AUC = 0.620 to predict the occurrence of MI.[17] Surprisingly, no study has demonstrated neither diagnostic nor prognostic values of PDW or P-LCR in the patients with ACS so far, and the present study is the first one showing those practical values. It is worth noting to mention that, all AUC values for platelet volume indices were about 0.560; therefore it may be normal to have cut-off values close to the mean of control participants, and relatively low sensitivities and specificities for our markers may be attributable to either this point or the small sample size of our cohort. Further large scale sized studies are needed to examine this hypothesis again.

Platelet volume indices can be influenced by some factors such as gender and taking anti-platelet agents. Accordingly, we showed that there were no significant differences regarding the platelet volume indices between both sexes in all patients together and each gender separately. Furthermore, in the present study, all patients with acute chest pain compatible with ACS were given aspirin following admission and before blood sampling. Besides, the previous use of aspirin or dual anti-platelet was also significantly higher in the UA and MI groups compared with non-ACS or control groups, and those uses were also higher in the UA than MI group. However, there were no significant differences with respect to the platelet volume indices between UA and MI groups. Concerning this issue, Shah and et al[23] have demonstrated that MPV was a reproducible marker of platelet activation and did not influence by administering 81 mg of aspirin. There was no study showing the impact of aspirin on PDW and P-LCR, we believe that these markers may be the same as MPV, but further studies considering the effects of aspirin or other anti-platelet drugs on platelets are needed to clarify this notion.

We found that the admission MPV, PDW, and P-LCR values were higher in the patients with MI compared with those of non-ACS or controls. In addition, our results did not show any differences in terms of cardiac risk factors among groups,

except MPV and P-LCR, which were found to be higher in participants who had hypertension or ACS as compared to those did not, and PDW was only higher in patients with a previous history of MI than those without it. Also of importance was that the platelet volume indices, including MPV, PDW, and P-LCR were found to be diagnostic tools to detect MI among patients suffering from chest discomfort.

4.1. Study limitations

The main limitation of present study which I would note is that we did not measure quantitatively troponin level and platelet aggregability in all patients; hence comparing between these parameters and platelet volume indices have not been evaluated. Comparing conventional cardiac markers with platelet indices, in this setting, may be more useful than those alone, as we did.

5. Conclusion

This study showed that the elevated admission MPV, PDW, and P-LCR may be of benefit for detecting patients with MI and for risk stratification of patients suffering from an acute chest pain. Further large-scale and prospective studies are required to elucidate the diagnostic and prognostic value of these parameters and those potential roles in defining new treatment options for ACS.

Conflicts of interest

All authors have none to declare.

Acknowledgment

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