Diagnostic Accuracy of Mean Platelet Volume in the Diagnosis of Acute Coronary Syndromes among Patients with Acute Chest Pain at the Emergency Room of Philippine Heart Center

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ABSTRACT

Introduction. Mean platelet volume (MPV), an index for platelet size, is believed to be associated with acute coronary syndromes (ACS). This study aims to establish the association of MPV and ACS in the local setting and to further evaluate the diagnostic accuracy of MPV in the detection of ACS.

Methodology. Adult patients presenting with chest pain seen at the ER were submitted for complete blood count (CBC). Specimens were processed for MPV and platelet count using Beckman-Coulter ACT 5Diff hematology auto-analyzer. Patients were grouped into ACS and non-ACS. Independent t-test was used for analysis. Diagnostic cut-off point was determined using Receiver Operating Characteristic (ROC) Curve.

Results. A total of 150 adult patients was examined for MPV and platelet counts. There was a significant difference of MPV between the two groups (p value <0.0001). The MPV of patients with ACS was increased at 8.3 fL compared to 7.3 fL in patients not diagnosed with ACS. At cut-off point of 8.4 fL, the positive predictive value and specificity for ACS were 100%, sensitivity of 43.6 and a negative predictive value of 46.2. The number of platelets was increased in non-ACS group.

Conclusion. The MPV of acute chest patients diagnosed with ACS was significantly higher compared to patients not diagnosed with ACS. Increased MPV at 8.4 fL was highly specific and predictive of ACS. However, the sensitivity and negative predictive value were low. The platelet count of non-ACS group was increased.

Key words : Mean platelet volume, MPV, Acute coronary syndromes, ACS

INTRODUCTION

The clinical use of mean platelet volume (**MPV**) is unknown.[1] Although it is routinely measured in hematological auto-analyzers for more than a decade, many laboratories do not usually include this in the final report of complete blood count. The primary reason is the lack of standardization of this value.[1,2] Another reason is the limited evidence that this measurement adds any valuable information in the clinical situation.[1]

However, there are increasing data attributing MPV with acute coronary syndromes. Mean platelet volume, as an index of platelet size and function, have been found to be increased in patients having disease conditions under the spectrum of acute coronary artery syndromes (**ACS**).[2-7] The major reason for this is that increased platelet activity plays a crucial role in the development of acute myocardial infarction.[2] Though there are well-established risk factors identified in the formation of atherosclerosis that bring about ACS, myocardial infarction (**MI**) could only and likely to happen if there are large and hyperactive platelets in the circulation.[2,3]

The effective screening of patients at the emergency room for acute coronary syndrome remains a challenge. Currently, cardiac coronary related diseases continue to be the leading cause of morbidity in most of the countries and the number one cause of deaths since the beginning of twentieth century.[3] The association of increased MPV with a critical disease like ACS may possibly emerge this measurement as a simple and accessible test to estimate platelet

activity. This will further help to stratify cardiovascular risk among patients with acute coronary syndromes.[4]

The main objective of this study is to determine whether there is an association between mean platelet volume and the diagnosis of acute coronary syndromes in a local setting. We further aim to estimate the diagnostic accuracy of MPV in the detection of acute coronary syndromes in patients with acute chest pain.

METHODOLOGY

This is a diagnostic accuracy study approved by the Philippine Heart Center- Institutional Ethics Review Board conducted at the emergency room (ER) and ER Point-of-care testing (POCT) satellite laboratory of the Philippine Heart Center with data gathered from May 12, 2012 to July 22, 2012 and from June 1, 2013 to August 31, 2013. Included in the study were consecutive adult (≥21 years old) patients with chest pain and informed consent was obtained. Excluded were chest pain patients having serious concurrent illnesses where increase platelet count and mean platelet volume were expected as a result of reactive process from a known injury such as trauma, gastrointestinal bleeding, hyperthyroidism, hematopoietic malignancy, (platelet count >1,000 x 109/L)[8] and sepsis. Patients whose specimens for CBC are not processed within 15 minutes from blood extraction are likewise not included in the study.

The sample size computed is n= 150 at 95% confidence level with a relative error of 15% and assumed ACS rate among patients presenting with chest pain at the emergency room of 34.3% based on the previous study done by Lamorena et al. on ER patients presenting with symptoms suggestive of ACS in the Philippine Heart Center.[9] The variables of the study included mean platelet volume and platelet count as measured by Beckmann Coulter ACT 5 Diff *(Beckmann-Coulter, Inc, Fullerton California)* and the diagnoses of these patients.[10]

In the emergency room, the charts of all adult patients who came in due to acute chest pain were reviewed every 8-hour shift for chief complaint and laboratory tests ordered. Informed consent was performed on all eligible patients and was submitted for complete blood count. At least 4 ml of blood was extracted through venipuncture and was collected using a lavender-top (ethelynediaminetriacetic acid/EDTA) vacutainer *(BD, Franklin Lakes, NJ USA)*. The collected specimen in the lavender-top was fed through the manual-loading probe of Beckman Coulter ACT 5Diff hematology auto-analyzer. The result generated by the machine for platelet count and mean platelet volume were recorded. The reference standard followed for all the parameters of complete blood count was based on the Standard Operating Procedure Manual of the Department of Laboratory Medicine (DLM) of Philippine Heart Center. Smears of each of the specimen were performed and stained with Wright's stain to verify and confirm the results generated by the automated analyzer. CBC tests of all qualified patients were performed by licensed medical technologists and trained staff of the Point-of-Care-Testing Section of DLM. Out of 172 patient charts reviewed, 150 patients were included in the study. Informed consent was unable to be performed in twelve (12) patients and ten patients could not be submitted for CBC because they were discharged immediately. The clinical diagnosis of the patients as written by the cardiology fellow trainee on duty at the emergency room was recorded. Admitted patients were followed-up for the final diagnosis upon discharge and were the recorded diagnosis for such patients. Diagnoses of patients at the emergency room were based on their medical chart as written by the cardiology fellow trainee who examined them. The basis for the diagnosis of ACS and non-ACS was based solely on what is written by the cardiology fellow trainee at the emergency room. All of the hospital staff involved in the study, including the cardiology fellow trainees and the medical technologists, was blinded during the entire study.

Data was described as mean ±SD or frequency and percent distribution comparing the ACS and non-ACS patients. To determine if there is a statistically significant difference of the mean platelet volume and platelet count of these two groups, Independent t-test was used. Cut-off points of MPV were computed with their respective scores of diagnostic accuracy parameters (sensitivity, specificity, positive and negative predictive values), as determined by the area under the curve of Receiver Operating Characteristic (ROC) curve.

RESULTS

A total of 150 adult patients with chest pain were included in the study and 101 of these patients are diagnosed with acute coronary syndrome. The rest of the chest pain patients in the non-ACS category had heterogeneous diagnoses. These wide variety of diagnoses range from pulmonary problems such as chronic obstructive pulmonary disease, pleural effusion, pneumonia, and pulmonary tuberculosis to other cardiac causes like congestive heart failure, valvular heart diseases and pericardial effusion, and even non-cardiac etiology particularly costochondritis.

Table 1 shows the baseline characteristics of the patients included in the study. Patients with ACS tend to be older. The mean age under ACS category was 62 years old compared to 56 years old in non-ACS group. Majority of the population in both groups were males. Hypertension was the most common risk factors seen in 58 patients and significantly associated with the diagnosis of ACS. There were 14 patients who had previous myocardial infarction or stroke and showed a notable relationship with ACS. Aspirin was by far the most common anti-platelet medication used by patients in the study.

The mean platelet volume of patients diagnosed with ACS was remarkably higher than patients who were not diagnosed with acute coronary syndrome at p value <0.0001 (Table 2). The ACS patients had an average MPV of 8.3 compared to only 7.3 mean MPV among non-ACS patients. On the other hand, the platelet number of patients not diagnosed with ACS was increased than patients who had a diagnosis of ACS (Table 3). Patients who were not diagnosed with acute coronary syndrome had an average platelet number of 269, 000 in contrast to 235,000 in ACS patients.

The computed cut-off points of mean platelet volume predictive in the diagnosis of acute coronary syndrome are shown in Table 3. The overall diagnostic accuracy of MPV, calculated as the area under the curve by the ROC curve revealed a significant test with a value under the curve of 0. 868 and p value less than 0.0001. At 8.4 fL cut-off result, positive predictive value is 100% and a 46.2% negative predictive value. A lower value of 7.3 fL MPV shows a higher negative predictive value of 75% and 78% positive predictive value. The cut-off points of MPV between 7.6 fL and 7.8 fL showed fairly acceptable parameters of diagnostic accuracy in detecting acute coronary syndromes. A cut-off value of 7.8 fL satisfactorily predict the diagnosis of ACS having the sensitivity of 80.2%, specificity of 75.5%, positive predictive value of 87.1% and negative predictive value of 64.9 %. Alternatively, a value of 7.7 fL showed relatively similar values of diagnostic accuracy.

Table 1. Baseline characteristics of patients in the study according to diagnosis of chest pain (PHC, 2013)

Characteristics	ACS (n=101)		Non ACS (n=49)		Total		p
	N	%	N	%	N	%	
Age							
Mean + std. dev		62.63 ¬+ 12.446		56.63 + 18.289		60.67 + 14.822	**0.04***
Sex							
Male	73	72.3	38	77.6	111	74.0	0.49**
Female	28	27.7	11	22.4	39	26.0	
Risk factors							
Hypertension	58	57.4	10	20.4	68	45.3	**<0.00**
Smoking	41	40.6	20	40.8	61	40.7	1.00**
Diabetes mellitus	27	26.7	8	16.3	35	23.3	0.22**
Dyslipidemia	7	6.9	2	4.1	9	6.0	0.71***
Previous MI / Stroke	14	13.9	0	-	14	9.3	**0.00***
Medication							
Aspirin	24	23.8	7	14.3	31	20.7	0.26**
Clopidogrel	6	5.9	3	6.1	9	6.0	1.00***
Warfarin	0	-	1	0.2	1	0.7	0.33***
Fondaparinux	1	1.0	0	-	1	0.7	1.00***

*Independent t-test (significant p value<0.05)   **Chi Square test (significant p value <0.05)   ***Fisher's Exact Test (significant p value <0.05)

Table 2. Mean platelet volume and platelet count according to diagnosis of chest pain (PHC, 2013)

Characteristics	ACS (n=101)		Non ACS (n=49)		Total		p
	N	%	N	%	N	%	
MPV (fL)							
Mean + std. dev		8.279 + 0.7356		7.276 + 0.5356		7.951 + 0.8238	**<0.00***
Platelet Count							
Mean + std. dev		235.75 + 74.651		269.53 + 98.156		246.79 + 84.241	**0.02***

*Independent t-test (significant p value <0.05)

Table 3. Cut-off points of mean platelet volume predictive of ACS diagnosis

Platelet Volume (fL)	ACS	Non-ACS	Sn* %	Sp* %	PPV* %	NPV* %	Kappa Test
>8.4	44	0	43.6	100.0	100.0	46.2	0.335 +
<8.4	57	49					0.052
Total	101	49					**<0.0001**
>7.8	81	12	80.2	75.5	87.1	64.9	0.535 +
<7.8	20	37					0.072
Total	101	49					**<0.0001**
>7.7	83	14	82.2	71.4	85.6	66.0	0.525 +
<7.7	18	35					0.073
Total	101	49					**<0.0001**
>7.6	85	18	84.2	63.3	82.5	66.0	0.479 +
<7.6	16	31					0.077
Total	101	49					**<0.0001**
>7.3	93	25	92.1	49.0	78.8	75.0	0.451 +
<7.3	8	24					0.078
Total	101	49					**<0.0001**

*Sn=Sensitivity, Sp=Specificity, PPV=Positive Predictive Value, NPV=Negative Predictive Value
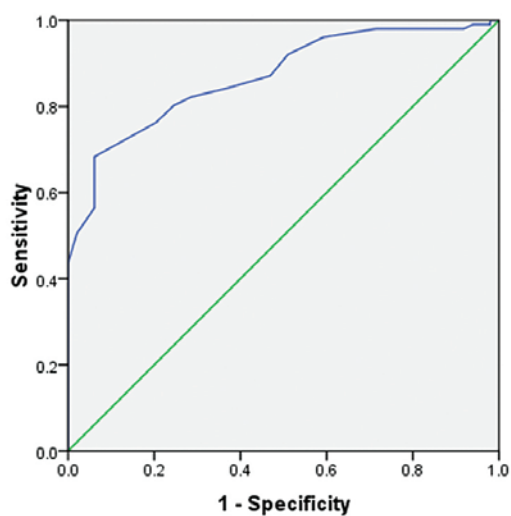
Diagonal segments are produced by ties.

Figure 1. The ROC curve of MPV values in association with the diagnosis of ACS (AUC=0.868, Cut-off values 8.4, 7.8, 7.7, 7.6, 7.3).

Figure 1 is the ROC curve showing a significant association between mean platelet volume and the diagnosis of acute coronary syndrome at p value <0.0001. The value under the area is 0.868.

DISCUSSION

This study showed that there was an association between MPV and the diagnosis of ACS in patients having chest pain at the ER. The MPV of patients who were diagnosed with acute coronary syndrome was significantly higher compared to patients not diagnosed with ACS. The computed average MPV of patients under ACS group was 8.3 fL while non-ACS patients had 7.3 fL. Cut-off points predictive of ACS are calculated based on the area under the curve of the ROC curve revealed a significant test. An MPV of 8.4 fL was highly specific for the diagnosis of ACS.. While the MPV of ACS patients are increased, the number of platelets was significantly decreased compared to non-ACS group. ACS patients are older and composed mostly of males. Hypertension and patients who had previous MI or stroke were also significantly associated with the diagnosis of acute coronary syndromes.

The size and density of the platelets are markedly heterogeneous in the human circulation. The functional activity of platelets is correlated with their sizes.[1, 3, 7] Larger platelets are more likely to be reactive because it contained more granules or active substances that may have important role in coagulation and eventually in thrombus formation and even atherosclerotic plaques.[2] It is in this proposition that the critical role of the platelets in the pathogenesis of acute coronary syndromes sets in.[3] This assumption has even made more substantial by the fact that various drugs used in the management of acute coronary syndromes have anti-platelet activities.[3]

With the observation that the activity of the platelets depends on its size and MPV is reliable index of platelet size, many recent studies have hypothesized that there is an increased MPV in patients with acute coronary syndromes.[4] Though there were several data have already supported this claim, the reason for the increased in the platelet size is not fully understood.[2] Previous studies have provided several possible explanations. Some authors believed that physiological changes of body metabolism and secretion of biologically active substances as a result of aging or complications of diabetes mellitus and obesity might play a role.[2] Others are convinced that toxins derived from tobacco smoking and the actual processes during the development of acute coronary events may possibly contribute to the stimulation of bone marrow to produced more larger platelets.[2] More recent study had shown that platelet size and activity potentially in some ways is genetically determined.[2] This genomic-wide association study had identified three specific genetic features strongly associated with increased mean platelet volume.[2] Notice that most of these explanations are all attributed to the known risk factors of acute coronary syndromes such as aging, obesity, diabetes mellitus and cigarette smoking. Consequently, most the available studies had shown positive correlation between increased MPV and these risk factors.[2,3,7]

However, in a large-scale study made by the group of Klovaite, increased MPV is associated with myocardial infarction independent of other known risk factors after an extensive multifactorial adjusted analysis.[2] This finding is also supported by the study made by Lippi et al. where they concluded that MPV is a useful marker for the risk stratification of ACS patients admitted at the emergency room.[4]

The value of MPV predictive of acute coronary syndromes varies from one study to the other. In this study, the cut off points between 7.6 fL to 7.8 fL had shown satisfactory results of all parameters in diagnostic accuracy of MPV predictive of acute coronary syndromes. This finding is relatively similar to the 7.8 fL cut-off point established by Klovaite et al. with the highest risk of developing myocardial infarction. Higher values are noted in the other studies ranging from 8.0 fL to 10.3 fL.[3-7] The group of Khandekar have recorded an average MPV of 10.3 fL among MI patients, Lippi and his group showed 8.0 fL cut-off in their result and Mercan et al. have documented values ranging from 8.9 fL to 10.1 fL dependent upon the severity of ischemic conditions in the spectrum of ACS.[3,4,7] It is also noted that these values are fairly within the range of recommended normal range of MPV in textbooks of laboratory medicine.[8] Meaning, the increased MPV observed in this study and other previous studies are still within the range of normal platelet-size and not an abnormally large-sized and non-functional platelets usually found in patients with hematolymphoid lesions.[8]

An additional finding in this study is the increased number of platelets of the non-ACS group compared to that of ACS patients.

Theoretically, this result may be explained by consumption of the platelets during the development of acute coronary event.[2] Thereby, decreasing the actual number of free platelets in the circulation.[2] In the study made by Klovaite et al., platelet count is not associated with increased risk of myocardial infarction. Either the platelet count is decreased or increased in ACS patients; the number of platelets is not significantly associated with ACS based on previous studies.[2] The limited number of patients under the non-ACS group may have contributed to this finding. This insufficient number of otherwise control or normal group might be one of the limitations of this study.

Another potential limitation of this study is the sample size. Sample collection was limited by procedures such as CBC not routinely done for chest pain patients at the emergency room and patients complaining of chest pain without significant electrocardiographic findings were quickly discharged. Hence, there were patients who failed to be included in the study. Some of the patients had vague diagnosis because of limited diagnostic work-up brought about by financial constraint. Other probable clinical factor that may affect MPV like the onset of chest pain is not recorded in many of the medical charts of patients included in the study.

Even with a limited population size, the association of increased MPV and diagnosis of acute coronary syndromes is clearly established. From this initial finding, many questions are expected to come out and the existing data presented in this study need to be validated in a larger population. Further investigation in the sizes of the platelets corresponding to the severity of ischemia under the spectrum of disease conditions in ACS would also be beneficial. To explore the correlation of MPV with other known risk factors of ACS such as hypertension, cigarette smoking, diabetes mellitus and others is likewise valuable in the effective risk assessment of chest pain patients at the emergency room. Since platelet activity depends on platelet size as measured through MPV, increased MPV among ACS patients also mean that this test might possibly be an acceptable screening tool in identifying patients who are good candidate for a more expensive platelet function tests like Anti-Xa, P2Y12 and aspirin assays, which are all available in this institution.

CONCLUSION

The MPV of chest patients diagnosed with acute coronary syndromes was significantly higher compared to patients not diagnosed with ACS. In contrast, the number of platelets in non-ACS group was elevated than ACS patients. The calculated average MPV of patients with ACS was 8.3 fL while non-ACS patients had 7.3 fL. Cut-off points predictive of ACS were computed based on the area under the curve of the ROC revealed a significant test (AOC is equal to 0.868 95% CI (0.812-0.924) p = <0.0001). At cut-off point of 8.4 fL, the positive predictive value was highly specific at 100% and a low negative predictive value at 46%.

AUTHOR DISCLOSURE

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APPENDIX

Definition of Terms

Acute coronary syndrome (ACS) – a spectrum of clinical conditions ranging from ST-elevation myocardial infarction (MI) to non-ST segment elevation and unstable angina. (Taken from the ACC/AHA 2002 Guideline Update for the Management of Patients with UA and NSTEMI: A report of the ACC/AHA Task force on Practice Guidelines).[11]

   a. ST- elevation MI – presence of a clinical syndrome of acute ischemia with either chest pain or a crescendo pattern of ischemic pain on minimal exertion, plus electrocardiographic ST-segment elevation and/or biomarker evidence of acute ischemic injury (elevated troponin or CK-MB);

   b. Non-ST-elevation MI – presence of a clinical syndrome of acute ischemia with either chest rest pain or a crescendo pattern of ischemic pain on minimal exertion, plus electrocardiographic changes and/or biomarker evidence of acute ischemic injury (elevated troponin or CK-MB);

   c. Unstable angina – at least one of the following features: (1) angina pectoris occurring at rest (or with min exertion) and usually lasting more than 20 min (if not interrupted by nitroglycerin), (2) being severe and described as frank pain and of new onset (within 1 month), and (3) occurring with a crescendo pattern (more severe, prolonged, or frequent than previously)

1. Non-Acute Coronary Syndrome (Non-ACS) – refers to clinical conditions of patients having chest pain at the ER other than what are included in the definition of acute coronary syndrome.

2. Mean platelet volume (MPV) – is the arithmetic mean of the extrapolated histogram of the platelets.[10]

3. Platelet count – is the actual count of platelets that are determined using a 64 channel pulse-height analyzer.[10]