DOI: 10.7860/JCDR/2022/52851.16215

Original Article

Internal Medicine Section

Prediction of Reperfusion Outcome using Platelet Indices in Primary Percutaneous Coronary Intervention- A Prospective Cohort Study

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ABSTRACT

Introduction: Platelets play a vital role in systemic inflammation and thrombus formation in ST Elevation Myocardial Infarction (STEMI). Understanding its role has diagnostic and prognostic implications in developing therapeutic strategies.

Aim: To estimate the prognostic accuracy of platelet indices-Mean Platelet Volume (MPV), Platelet Distribution Width (PDW) and MPV/Platelet Count (PC) ratio (MPV/PC ratio) on reperfusion outcome in STEMI patients.

Materials and Methods: This prospective cohort study enrolled 262 subjects, who presented with acute chest pain within a window period of 12 hours, and an Electrocardiogram (ECG) suggestive of STEMI. Blood samples collected on admission were measured for MPV and PDW. The major endpoints studied were angiographic thrombus burden and in-hospital Major Adverse Cardiovascular Events (MACE). Data was summarised by mean and Standard Deviation (SD) for continuous variables, frequency and percentage for categorical variables.

Results: This study demonstrated that Acute Coronary Syndrome-STEMI (ACS-STEMI) patients with larger PDW had Larger Thrombus Burden (LTB). PDW of more than 13 fL was the best cut-off for predicting LTB with a sensitivity of 67.01% and a specificity of 53.23%. There was no significant difference between the means of MPV in LTB and small thrombus burden. The total in-hospital MACE at the end of one week was 20.99% (n=55/262 patients). The maximum MACE was contributed by acute heart failure (12.6%), followed by cardiac death (6.1%) and stent thrombosis (1.5%). There was a significant association between increased PDW and in-hospital MACE, mortality and acute heart failure (p-value=0.024, p-value=0.03, p-value=0.02, respectively). The best cut-off PDW value for prediction of the composite MACE endpoint was 14.7 fL with sensitivity of 75.6% and specificity of 51.4% and the area under the Receiver Operating Characteristic (ROC) curve was 0.63 (95% CI, 0.57 to 0.69).

Conclusion: The study emphasised on the use of platelet indices, especially PDW, as a predictor of poorer reperfusion outcomes in primary Percutaneous Coronary Intervention (PCI) as evidenced by higher MACE rates in patients with higher PDW. Hence, PDW can help in predicting the thrombus burden even before doing the angiogram and such high-risk patients could benefit from early initiation of stronger antiplatelets, Glycoprotein (Gp) IIb/IIIa antagonist drugs and thrombus aspiration techniques.

Keywords: Acute coronary syndrome, Platelet activation, Thrombus burden

INTRODUCTION

Acute Coronary Syndrome (ACS), including unstable angina, Myocardial Infarction (MI), and sudden ischaemic death, are leading causes of morbidity and mortality. Despite immense advancements, prognosticating ACS remains a challenge, with little knowledge on mechanisms of ACS beyond the standard risk factors. Systemic inflammation is considered to be the hallmark of ACS and platelets are the primary source of inflammatory mediators [1].

Platelets play a crucial role at the site of plaque rupture by activating the thrombus formation which a major event in the development of ACS. It remains a significant challenge in the treatment of these patients. Novel antiplatelet strategies that prevent platelet endothelial cell interaction and activation may provide an efficacious intervention to improve the prognosis of patients with coronary atherosclerosis [2].

ACS itself is a proinflammatory state, with increased inflammatory markers like interleukin 3 (IL-3), IL-6, which stimulates megakaryocyte proliferation [3]. Larger platelets are released from the bone marrow due to the increase in serum thrombopoietin levels secondary to platelet consumption during acute MI [4]. Larger platelets are enzymatically and metabolically more active, and produce more thromboxane A2 [5]. The above facts suggest there should be a close association between platelets size, platelet reactivity and events secondary to their activity like ischaemic heart events. To show this association platelets volume indices could be used.

MPV, being a reliable index of the functional status of platelets, is an emerging as a risk marker for atherothrombosis. Elevated MPV may be suggestive of activated platelets, contributing to increased risk of ACS [6]. Moreover, evidence suggests that MPV may be a risk factor for recurrent MI independent of other risk factors as hypertension and dyslipidemia [7].

PDW is the relative distribution width of platelets in volume index. PDW is an indication of variation in platelet size, which can be a sign of active platelet release [8]. The PDW was found to independently predict long-term as well as in-hospital adverse outcomes in patients with ACS [9]. An increased PDW is associated with increased severity of Coronary Artery Disease (CAD) in patients with ACS [8]. PDW unlike MPV does not get elevated by platelet swelling which occurs during blood storage hence PDW is a more specific indicator of platelet activation [10].

Most studies have shown that platelet indices at the time of hospitalisation are a strong and independent predictor of impaired reperfusion and mortality in STEMI treated with primary PCI [11,12]. High PDW was found to be an independent predictor of adverse prognosis in patients with Heart Failure (HF) [13]. However, none of the studies has quantified the thrombus burden in the infarct- related artery or attempted to demonstrate a relationship between the thrombus burden and the platelet indices. Thus, understanding the role of platelets in ACS may lead to new concepts and development of therapeutic strategies [1]. In view of its diagnostic importance and

prognostic significance, our study in patient's diagnosed with ACS-STEMI aimed to emphasise the relationship between the platelet indices MPV, PDW and ACS. Hence, a prospective study was planned to evaluate the effectiveness of platelet indices which may determine the outcome of patients admitted with ACS-STEMI, and to estimate the diagnostic accuracy of platelet indices in determining the angiographic thrombus burden.

MATERIALS AND METHODS

A prospective cohort study was conducted at the university-level teaching hospital, in Government Medical College, Trivandrum, Kerala, India from April 2017 to May 2018, after obtaining ethical clearance from Institutional Review Board (IEC.No.05/15/2017/MCT). Written informed consent was taken from all the participants prior to the study.

The primary outcome was to determine the association between platelet indices, MACE and thrombus burden. The seven day in-hospital MACE included death, acute heart failure, reinfarction, stent thrombosis, or any repeat revascularisation. Thrombus burden in infarct related artery was graded according to Thrombolysis in Myocardial Infarction (TIMI) grading for thrombus burden [14]. The secondary outcome included estimation of the diagnostic accuracy of platelet indices in determining the angiographic thrombus burden.

Sample size calculation: Expecting an incidence of 28.75% of MACE in the study population, the study required a sample size of 240 subjects (p-value <0.05 and 80% power) [15].

Inclusion criteria: All patients above 18 years who were admitted with chest pain within the window period of 12 hours, with Killip class I-IV, an Electrocardiogram (ECG) diagnosis of STEMI according to the 2018 Fourth Universal Definition of MI and agreed to undergo primary PCI were invited to participate in the study [16].

Exclusion criteria: Pregnant women, subjects with history of previous cardiomyopathy, or previous MI or any revascularisation procedures Percutaneous Coronary Intervention (PCI), Coronary Artery Bypass Grafting (CABG), or congenital heart disease, history of intake of any drugs causing thrombocytopenia in the last six months were excluded from the study. Also patients with any platelet or bleeding disorders, or any recent blood transfusions, or any intercurrent fever with thrombocytopenia, Chronic Liver Disease (CLD), Chronic Kidney Disease (CKD) patients, any treatment with a fibrinolytic agent within the previous 24 hours were also excluded from this study.

Study Procedure

A structured questionnaire was used to record clinical and demographic profile of the patient. On admission 4 mL of blood was collected in prefilled Ethylenediaminetetraacetic Acid (EDTA) vials from each patient. Platelet indices were estimated within two hours of collection with automated Sysmex five part haematology analyser. All patients underwent PCI. The principal investigator who was blinded to the platelet indices analysed all the coronary angiograms.

The study population was divided into two groups comprising: 1) low thrombus burden (TIMI thrombus grade 1-3) and 2) high thrombus burden (TIMI thrombus grade 4-5) according to the bi-level thrombolysis in myocardial thrombus grading scale [17]. All were followed-up for a week to look for the primary and secondary outcomes.

STATISTICAL ANALYSIS

Data was summarised by Mean and SD for continuous variables and frequency and percentage for categorical variables. The Mann-Whitney U test and the Chi-square test was applied to determine the difference between groups. All tests were two-sided at α=0.05 level of significance. All analyses were done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

A total of 262 consecutive patients were included in the study. The mean age of the study population was 58.8±11.63 years. The baseline clinical and platelet characteristics of the study population is given in [Table/Fig-1,2]. There were 121 (46.2%) patients with STEMI Anterior Wall Myocardial Infarction (AWMI), 45 (17.2%) with Inferior Wall (IW) MI, 93 (35.5%) with IWMI+ Right Ventricular (RV) MI and 3 (1.1%) with Lateral Wall (LW) MI.

Variables	Frequency (n=262)	Percent (%)
Sex		
Male	192	73.6%
Female	70	26.7%
Co-morbidity		
Diabetes	121	46.2%
Hypertension	104	39.7%
Dyslipidemia	65	24.8%
Family h/o CAD	52	19.8%
Current or ex-smoker	154	58.8%

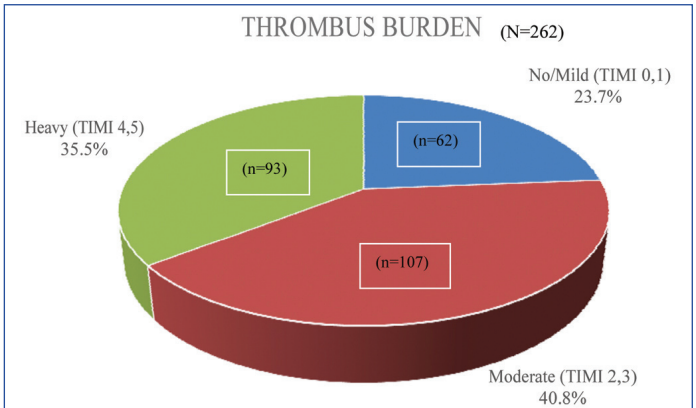
[Table/Fig-1]: Gender and baseline co-morbidity characteristics of the study population.

The total mean ischaemic period was 356.74±156.6 minutes. The mean ST resolution was 55.53±26.8% [Table/Fig-2]. The major risk factors for STEMI which were likely to affect the outcome were evenly matched and comparable in all the study groups.

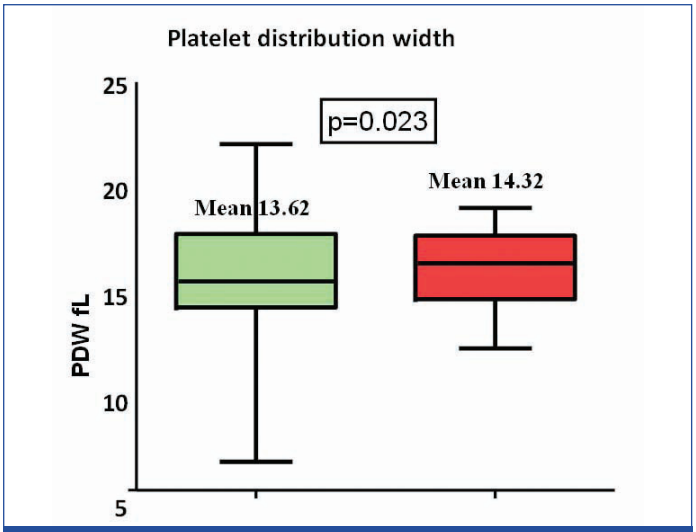
Parameter (n=262)	Mean±SD	Min	Max	Median
Age (years)	58.8±11.6	29	90	60
Mean Platelet Volume (MPV) (fL)	9.62±1.03	7.7	13.6	9.5
Platelet count (lacs/mm^3)	2.41±0.66	1.15	6.71	2.33
PDW* (fL)	13.87±2.44	1.75	21.2	15.3
MPV/PC ratio**	4.32±1.41	1.3	11.5	4.1
Total ischaemic period (minutes)	356.74±156.6	75	720	315
Door to balloon (minutes)	101.7±83.3	10	525	78
ST resolution (%)	55.5±26.8	0	100	60

[Table/Fig-2]: Baseline platelet and clinical characteristics of the study population.
*PDW: Platelet distribution width; **MPV/PC ratio is MPV/Platelet count ratio; SD: Standard deviation

The angiographic thrombus burden of the study population is given in [Table/Fig-3]. Among 262 study participants, 62 (23.7%) of them had only TIMI 0 or 1 thrombus grade, 107 (40.8%) of them had TIMI 2 or 3 thrombus grade and 93 (35.5%) of them had TIMI 4 or 5 thrombus grade. When the study population was divided into two groups comprising small thrombus burden and high thrombus burden according to the bi-level thrombolysis in myocardial thrombus grading scale, it was found that there was a significant difference between the means of PDW in either groups (p-value=0.023). The mean PDW in small thrombus burden was 13.62 fL which was significantly lower when compared to mean PDW of large thrombus burden (14.32 fL) [Table/Fig-4].

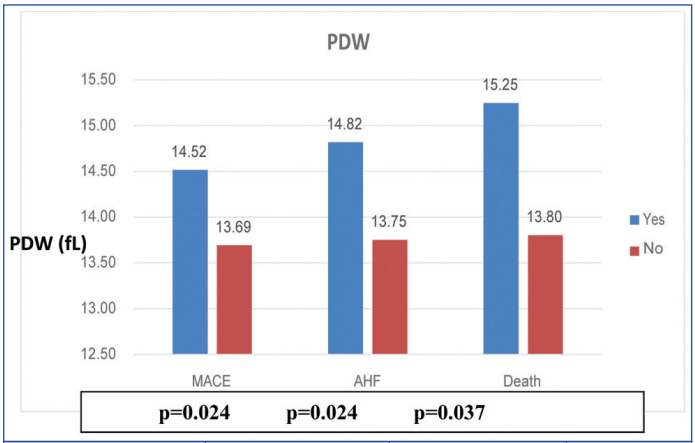


[Table/Fig-3]: Pie chart of the participants according to the angiographic thrombus burden.



[Table/Fig-4]: Boxplot of PDW and thrombus burden.
Higher PDW was associated with more thrombus burden; Green- Small thrombus burden; Red- Large thrombus burden

The total in-hospital MACE at the end of one week was 20.99% (55/262), out of which the maximum MACE was contributed by acute heart failure 12.6% (33/262 patients) [Table/Fig-5]. Other causes were cardiac death 6.1%, stent thrombosis (including probable) 1.5%, reinfarction 0.4%, and repeat revascularistion 0.4%.



Event		'n' out of 262 (%)	Mean PDW (fL)	p-value
MACE	Yes	55 (20.9%)	14.52	0.024
	No	207 (79.0%)	13.69	
AHF	Yes	33 (12.6%)	14.82	0.024
	No	229 (87.4%)	13.75	
Death	Yes	16 (6.1%)	15.25	0.037
	No	246 (93.9%)	13.80	

[Table/Fig-5]: Association of MACE, death and Acute Heart Failure (AHF) with PDW.
p-value <0.05 considered significant

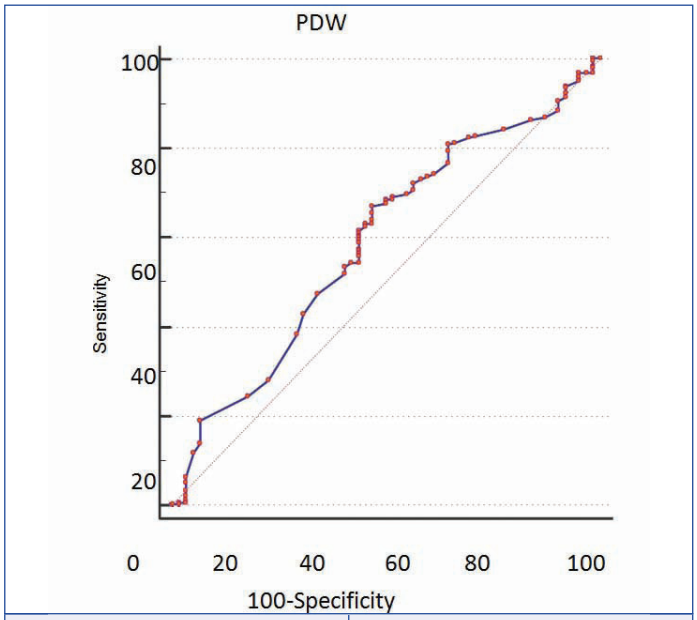
There was significant statistical difference between the patients with MACE and without MACE regarding mean PDW (p=0.024). The mean PDW of patients with AHF and mortality was also significantly higher to mean of PDW of patients without AHF or who survived [Table/Fig-5]. There was no significant difference in the mean MPV between the patients with MACE and without MACE.

On conducting logistic regression, it was seen that there was a significant positive relation for change in TIMI flow (after PCI) with MPV >9.1 (OR=2.658; 95% CI=1.293-5.467), presence of thrombus burden (OR=1.789; 95% CI=1.235-2.591) and diabetes (OR=2.090; 95% CI=1.039-4.204) [Table/Fig-6]. Change in TIMI flow ≥2 was found to have a statistically associated with lower total ischaemic period; with a protective OR=0.997 (95% CI=0.995-0.999). Association with Killip class, lower door to balloon time and ST resolution percentage were not statistically significant.

Parameter	B	S.E.	p-value	OR	95% CI for OR	
					Lower	Upper
Killip Class	0.431	0.409	0.292	0.650	0.291	1.449
MPV* >9.1	0.978	0.368	0.008	2.658	1.293	5.467
Some thrombus burden	0.582	0.189	0.002	1.789	1.235	2.591
Diabetes	0.737	0.357	0.039	2.090	1.039	4.204
Lower total ischaemic period (min)	0.003	0.001	0.001	0.997	0.995	0.999
Lower door to balloon time (min)	0.003	0.002	0.178	0.997	0.993	1.001
ST resolution > 70%	0.007	0.007	0.303	1.007	0.994	1.021
Constant	0.337	1.160	0.771	0.714		

[Table/Fig-6]: Logistic regression for change in TIMI flow ≥2; Adjusted association between selected risk factors and change in TIMI flow.
*MPV: Mean platelet volume; p-value <0.05 considered significant

The diagnostic accuracy of PDW to predict thrombus burden was determined using ROC curve analysis. The area under curve was 0.589 and the best cut-off point for PDW for identifying thrombus burden were found to be >13 fL with a sensitivity and specificity of 67.01% and 53.23%, respectively and Positive Predictive Value (PPV) of 82.5% and Negative Predictive Value (NPV) of 33.7% [Table/Fig-7]. The ROC was used to identify cut-off values for predicting the occurrence of MACE endpoints. The best cut-off PDW value for prediction of the composite MACE endpoint was 14.7 fL with sensitivity of 75.6% and specificity of 51.4%. The area under the PDW ROC curve was 0.63 (95% CI 0.57 to 0.69), with PPV as low as 22.6% but NPV of 91.8% [Table/Fig-8].



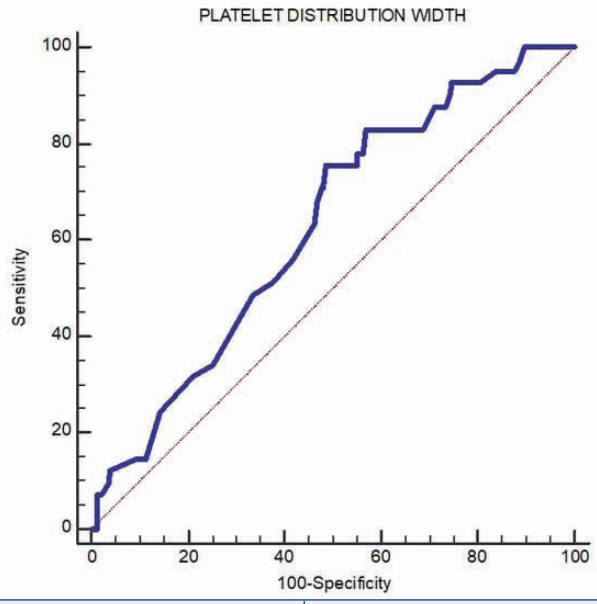
PDW	>13 fL
Sensitivity	67.01
Specificity	53.23
p-value	0.031
AUC (Area under the ROC curve)	0.589
Positive Predictive value (PPV)	82.5
Negative Predictive value (NPV)	33.7

[Table/Fig-7]: ROC curve of PDW to predict large thrombus burden.

DISCUSSION

The present study was designed to find a simple and cost-effective method to evaluate the association between platelets volume indices, and STEMI and to predict the occurrence of thrombus burden and clinical outcomes of STEMI patients undergoing primary PCI.

The mean MPV in this study was obtained as 9.62 fL with SD of 1.03 fL. These values were comparable to the recent Indian study, where the MPV ranged from 6.3 fL to 13.2 fL. (Median 9.1 fL; mean



PDW	>14.7 fL
Sensitivity	75.61
Specificity	51.38
p-value	0.0036
AUC (Area under the ROC curve)	0.629
Positive Predictive value (PPV)	22.6
Negative Predictive value (NPV)	91.8

[Table/Fig-8]: ROC curve of PDW to predict occurrence of Major Adverse Cardiac Events (MACE).

9.17 (SD 1.0 fL) [15]. In this study, the mean PDW was 13.87 fL with SD of 2.44 which was higher than what was observed in another Indian study where the mean PDW in was 10.84±2.2 fL [18].

Significance of PDW in ACS STEMI patients: MPV has been extensively evaluated but novel platelet indices such as PDW have been less well investigated as platelet activation markers. Various morphologic transformations occur during platelet activation such as spherical shape and pseudopodia formation. Thus, platelets with increased number and size of pseudopodia differ in size, which increases PDW. The PDW measures the variability in platelet size [19].

The highlight of this study is the association between PDW and the thrombus burden in the infarct related artery. The mean PDW in small thrombus burden was 13.62 fL which was significantly lower when compared to mean PDW of large thrombus burden. In a study among 13,701 healthy adults in United states, it was observed that PDW and not platelet count or MPV is an independent predictor of cardiovascular and all cause mortality [20].

PDW, being a very economical and automated machine given investigation, can be obtained immediately before the procedure. Hence, the cardiologist can identify those patients who are at high risk for thrombus, and initiate stronger antiplatelets and Gp IIb/IIIa antagonists quite early itself. A higher PDW value can also aid in deciding for thrombus aspiration techniques as well. Currently, thrombus aspiration usage does not have any objective criteria and depends solely on the visual estimation of thrombus by the interventionist. Thus, PDW have a role in the various treatment strategies of primary PCI, especially because it is a powerful predictor of thrombus burden and occurrence of MACE.

The findings of the present study, regarding PDW, are consistent with many other studies. Vagdatli E et al., showed that PDW is a more specific marker of platelet activation, since it does not increase like MPV during platelet swelling [10]. Bekler A et al., demonstrated increase in severity of coronary artery disease with increased PDW [8]. A retrospective study showed that PDW was significantly raised in patients with myocardial infarction and its estimation may help in early detection of myocardial infarction [21]. Bae MH et al., also concluded that PDW is a simple haematological marker that can be used as an aid for stratification of patients with MI [22].

Relation of platelet indices within-hospital mortality and MACE rates: There was no significant difference in the mean MPV between the patients with MACE or without MACE. One reason may be attributed to the change in the platelet volumes on adding varied amounts of EDTA reagent in the blood sample and prolonged time taken to process the blood sample.

However, the mean PDW of patients with MACE, acute heart failure and death were significantly higher to the mean of PDW of patients without MACE or acute heart failure or death [Table/Fig-5]. Moreover PDW >14.7fL correlated with higher MACE rates [Table/Fig-8]. These findings are in line with another similar study [12] which concluded that higher PDW values (≥ 16 fL) correlated with higher mortality rate as compared to PDW <16 fL (17.4% vs. 6.3%, p=0.0012). Interestingly, Celik T et al., demonstrated similar findings, an admission PDW level of 12.95 fL was associated with 60% sensitivity and 64% specificity in identifying in-hospital MACEs [19]. Thus, in accordance with the previous reports, the present study confirms that those having higher value of PDW have a poorer prognosis.

Diagnostic accuracy of platelet volume indices: An admission PDW of >13 fL was associated with 67.01% sensitivity and 53.23% specificity in its association with identifying thrombus burden. Thus, the study found that PDW can be used as a diagnostic aid for predicting the thrombus burden even before taking up the patient for Primary PCI. Numerous factors determine the magnitude of thrombus burden, of which platelets play a central role in the thrombotic occlusion of the Infarct-Related Artery (IRA) thus contributing to the pathophysiology of an acute MI [19]. Currently, there are no available studies which utilised PDW as a diagnostic parameter for identifying thrombus burden. Now, there is an objective way to predict thrombus burden prior to the primary PCI, which will be essential for deciding the treatment strategies.

Factors determining improvement in TIMI flow (postprocedure) on Logistic regression: This study revealed that the most important factors that influenced the prognosis of patients taken up for primary PCI were total ischaemic period, followed by door to balloon time, ST resolution, MPV, diabetes, and presence of thrombus burden. There was a significant positive correlation for improvement in TIMI flow with MPV >9.1, presence of thrombus burden and diabetes. Another study assessed "spontaneous" reperfusion of the IRA and short-term clinical outcome in 617 patients with STEMI. They demonstrated that an increased MPV is an independent correlate of both a patent IRA and a 30-day mortality among patients with STEMI [23]. Therefore, it is of clinical interest that MPV assessed at hospital admission is found to be a marker of IRA patency postprocedure.

Limitation(s)

This study did not measure other known inflammatory markers such as C-Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR). Also, platelet function tests such as thrombelastograph was not used. Dual antiplatelet therapy does not influence MPV in patients with CAD undergoing PCI. However, whether MPV/PC ratio is changeable by dual antiplatelet therapy is still unknown. Findings of the study necessitate further large-scale prospective studies to establish the relationship of platelet volume indices with thrombus burden and angiographic outcomes of primary PCI. Intravascular Ultrasound (IVUS) and Optical Coherence Tomography (OCT) may provide more accurate information on the amount of atherosclerotic plaque and severity of CAD, in the future, a new study should be performed to obtain the conclusion.

CONCLUSION(S)

The primary objective of this prospective study was to understand the relationship between platelet indices and the reperfusion

outcome (MACE) or thrombus burden. This study demonstrated that ACS-STEMI patients with larger PDW had larger thrombus burden and higher MACE rates. PDW is an inexpensive and easily available biomarker may help in risk stratification and management of STEMI patients. It can be used as a diagnostic aid for predicting the thrombus burden even before taking up the patient for primary PCI, and thereby identify high risk patients who could benefit from more potent antiplatelet or Gp IIb/IIIa antagonist drugs. Higher PDW is a predictor of poorer reperfusion outcomes as evidenced by the higher MACE rates and all-cause mortality. Further studies are needed to elucidate the diagnostic and prognostic value of platelet volume indices which might open up newer therapeutic options in the future.

Declaration: This study was presented at the Annual Conference of Cardiological Society of India, at Kolkata, in 2019.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 15, 2021
- Manual Googling: Dec 23, 2021
- iThenticate Software: Jan 08, 2022 (21%)

ETYMOLOGY: Author Origin

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 13, 2021**
Date of Peer Review: **Nov 20, 2021**
Date of Acceptance: **Jan 10, 2022**
Date of Publishing: **Apr 01, 2022**