International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Impact of Mean Platelet Volume on Outcomes among Patients under 45 Years Presenting with First Episode of Acute Coronary Syndrome

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Abstract: ***Introduction: There is an increased tendency for acute coronary syndrome (ACS) among young population in the recent years. Arterial thrombosis is the key process in the development of ACS, in which platelets play a pivotal role. Mean platelet volume which has direct correlation with platelet activity can be a useful prognostic marker for patients with ACS. Detecting the risk factors associated with worse outcome will be useful to prevent major adverse cardiac and cerebrovascular events in young patients with ACS. Objectives: To study the impact of mean platelet volume (MPV) at the time of admission on six - month major adverse cardiac events (MACE) among patients less than 45years presenting with first episode of Acute Coronary syndrome. Methods: It is a prospective observational study conducted in the department of cardiology, Government medical college Kozhikode from October 2021 to September 2022. A total of 160 patients were included in the study. Results: The study population was classified into tertiles based on their MPV range (Group 1= <9.6fl, Group 2= 9.7 to 11.5 fl and Group 3 = >11.5 fl) and the number of patients in each group were: first tertile (N=66) second tertile (N=84) and third tertile (N=10), with a mean age of 37.94 ± 4.09, 37.44 ± 4.3, 35.4 ± 3.69 respectively. Majority of the patients were in the age group of 35 - 40 years in all the three tertile. Gender distribution showed a majority of male participants. Comorbidities like diabetes, hypertension and dyslipidemia were commonly seen. Smoking and alcoholism were the common addictions seen in the study participants, but there was no significant difference between the tertiles. NSTEMI was the most common type of MI in patients of first tertilewhile STEMI was the most common MI in the other 2 groups. There was a statistically significant difference in the type of MI between the 3 groups (P value=0.007). Ejection fraction was >50 for majority of the patients of 1st & 2nd tertiles whereas higher number of participants in the 3rd tertile had ejection fraction between 40 - 50 (P value=0.004). Majority of the study participants belonged to Killip & TIMI class I in Group 1 & 2. patients in 3rd tertile had more participants in Killip & TIMI class II. The MPV at baseline and follow up was compared and the values were comparable in group 1 but there was a statistically significant decrease in MPV in group 2 & 3 (P value <0.05). Single vessel disease (SVD) was the most common angiogram finding across the 3 groups with a significantly higher proportion amongst the third tertile (P value =0.01). Multivariate regression showed model, baseline MPV, Killip & TIMI class were significant predictors of follow up MPV values. Conclusion: Patients with higher MPV values had severe disease at presentation and developed adverse cardiovascular events on follow up. MPV is a simple and inexpensive laboratory test that could be used in concert with other standard biochemical cardiac markers to help predict the risk of significant cardiovascular events in young population***

Keywords: Mean platelet volume (MPV), Acute Coronary Syndrome (ACS), NSTEMI, STEMI, biochemical cardiac markers

1. Introduction

Acute coronary syndrome (ACS) is becoming the leading cause of morbidity and mortality in developing countries like India. The spectrum of presentation is wide from unstable angina to acute myocardial infarction[1]. Platelets play a crucial role in the pathogenesis of atherosclerosis and thrombus formation after coronary plaque rupture. Platelet activation leads to the formation of free arachidonic acid, which can be transformed into prostaglandins, such as thromboxane A2, one of the most potent vasoconstricting and platelet - aggregating substances, or into leukotrienes, which can amplify the acute inflammatory response. Consequently, larger and hyperactive platelets play a pivotal role in accelerating the formation and propagation of intracoronary thrombus, leading to the occurrence of acute thrombotic events[2].

These observations have led to the hypothesis that increased mean platelet volume (MPV) may be a potentially useful predictor in cardiovascular risk stratification[3] Previous studies have shown that the Mean platelet volume which has direct correlation with platelet activity and can be a useful prognostic marker for patients with ACS. Majority of studies published in this regard and systematic reviews have established the value of MPV as a good prognostic marker in ACS, stable Ischemic heart disease (IHD) and even in patients without established IHD but with predisposing conditions. But several questions still remain unanswered, the mechanism for association between platelet volume and prognosis being one amongst them.

An increase in MPV in patients with cardiovascular risk factors like hypertension, Diabetes mellitus and chronic kidney disease has been reported in various studies[4 - 6] The association between elevated MPV and poor clinical outcome in patients (without age restriction) with ACS is well documented, but less is known about MPV as a potential predictor of outcomes after MI in young patients. To analyze these aspects, we need studies to find out the MPV during the acute event and also the changes in MPV on follow up and correlate these changes to the prognosis.

2. Objective

a) To study the predictive value of mean platelet volume (MPV) at the time of admission on six - month major adverse cardiac events (MACE) among patients less than 45years presenting with first episode of Acute Coronary syndrome.
b) To study the change in MPV in the post ACS period among these patients and correlate it to the outcomes at six months.

Relevance of the Study
Mean Platelet Volume (MPV), a measure of platelet size is an inexpensive and simple biological marker of platelet function. The association between elevated MPV and poor clinical outcome in patients (without age restriction) with ACS is well documented, but less is known about MPV as a potential predictor of outcomes after MI in young patients. Young patients who are likely to have a lower incidence of conventional risk factors for CAD (which may have an independent confounding effect on platelet volume) may be more suited to demonstrate the prognostic impact of platelet volume than a heterogeneous population. Detecting the risk factors associated with worse outcome will be useful to prevent major adverse cardiac and cerebrovascular events in young patients with ACS. The current risk scores fail to identify the young individuals at risk for their first MI. Therefore, these patients rarely receive preventive medication and counseling for lifestyle modification, that could reduce the incidence of heart disease.

3. Materials and Methods

Prospective Cohort study conducted at a tertiary care centre in north kerala after obtaining clearance from institutional ethical committe

Inclusion criteria:
Patients above 18 years admitted with a diagnosis of unstable angina, non ST elevation myocardial infarction or ST elevation myocardial infarction.

Exclusion Criteria:
1) Patients above 45years
2) Patients with a definite past history of ACS or SIHD
3) Patients on Antiplatelet therapy for any disease
4) Patients who die before the sample for analysis could be taken
5) Patients with severe comorbid illness limiting life expectancy to less than one year
6) Patients not willing to give consent

Method of collection data
A Total of 160 patients were enrolled in the study

Data was collected regarding demographic features, Killip class presentation, TIMI risk score, ECG findings, and comorbidities.

Complete blood count was analyzed (Using Automated hematology analyser Sysmax make XP 100 model, 3part WBC differential). Blood needed is 50 microliter for one test. Whole blood K3EDTA was added. Random blood sugar (RBS), Renal function test, Troponin I or CKMB values in hospital, major change in lab values were noted From pre discharge echo - left ventricular ejection fraction, mitral regurgitation, pulmonary arterial hypertension if any and RV function was noted. In patients who underwent coronary angiogram while in hospital, data was collected regarding the details of coronary artery involvement as well as details of revascularization performed if any. Patients were followed up for 6months and MPV at 6 months was noted. In patients undergoing Coronary angiogram during the follow up period, details of the coronary anatomy and revascularization was noted Data was collected during follow up regarding antiplatelet medications and compliance Mean platelet volume was repeated at follow up visit. During follow up, all cases was divided into three groups according to MPV data. Low MPV group was defined as patients with lowest 25% of data, High MPV group defined as patients with highest 25% of data and Medium MPV group will include other patients.

Outcome Measures

Primary outcome:
A composite of all - cause mortality, non - fatal acute coronary syndrome (STEMI, NSTEMI or Unstable Angina) or nonfatal stroke. Each event will be counted only once.

Secondary outcome:
1) Hospitalization with non - fatal ACS (each event will be counted separately)
2) Hospitalization with non - fatal Stroke (each event will be counted separately)
3) Cardiovascular mortality

Data management and stastical analysis:
Data was analyzed using Statistical Package for Social Services (SPSS) software (SPSS 20 for windows, SPSSInc, IL, USA). Categorical variables were presented as frequencies and percentage. Quantitative variables were presented as measures of central tendency and dispersion. Chisquare test was used as a test of significance for categorical variables. A p value of less than 0.05 was considered as statistically significant

4. Results

The present study was carried out in the Department of Cardiology at a tertiary care hospital. A total of 160 patients who fulfilled the inclusion criteria were enrolled in the study.

The demographic characteristics & mean MPV of the entire population is showed in Table 1. The mean age of the study population was 37.52 ± 4.2 years. The mean baseline MPV was 9.6 fL which reduced to 9.47 fL at follow up.

Sex distribution in study population

Out of 160 patients enrolled in the study 73.75 % were males

Table 1: Age and MPV of the study population

Parameter	Mean ± SD	Minimum	Maximum
Age (years)	37.52 ± 4.2	28	44
Baseline MPV (fL)	9.6 ± 1.16	7.5	13.4
Follow up MPV (fL)	9.47 ± 1.12	7.6	13.2

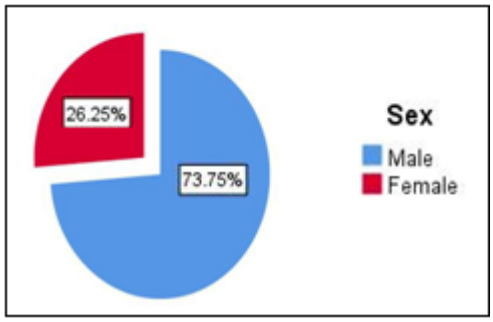

Figure 1: Sex distribution of the study population

The study population was classified into tertiles based on their MPV range

There were 66 participants in Group 1, 84 in Group 2 & 10 participants in Group 3.

The various measured parameters were compared between these 3 groups.

1) Demographic characteristics of the groups

Table 2 & Figures 2&3 below shows the comparison of age, sex and age group distribution between the 3 groups. All the 3 groups were comparable based on the various demographic parameters.

Table 2: Demographic characteristics of the Three groups

Parameter	1st Tertile (n = 66)	2nd Tertile (n = 84)	3rd Tertile (n = 10)	P value
Age	37.94+ 4.09	37.44 + 4.3	35.4 + 3.69	1.99[at]
Age Group				
Less than 35 years	14 (21.2%)	17 (20.2%)	2 (20%)	0.479#
35 - 40 years	31 (47%)	48 (57.1%)	7 (70%)	
Greater than 40 years	14 (31.8%)	19 (22.6%)	1 (10%)	
Addiction history	52: 14	60: 24	6: 4	0.354
Sex (M: F)				

[at]Using One wayAnova #Using Fisher exact test

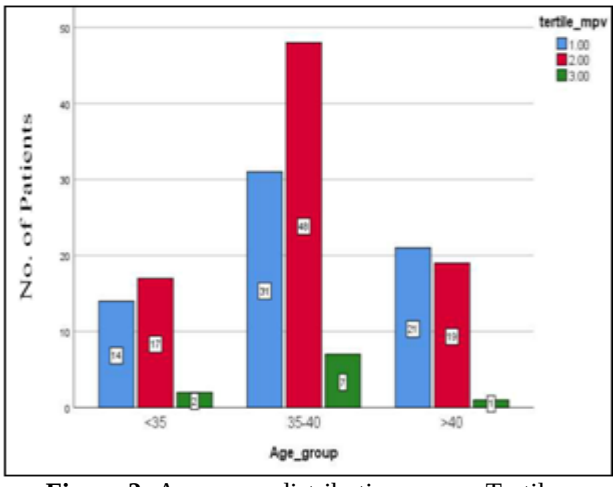

Figure 2: Age group distribution among Tertiles

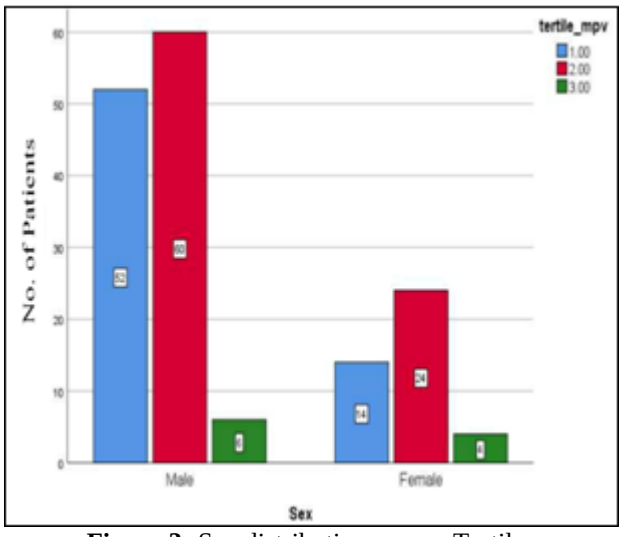

Figure 3: Sex distribution among Tertiles

2) Comorbidities & addiction history

Table 3 below shows the comparison of various comorbidities & addiction history between the 3 groups. There was no statistically significant difference between the 3 groups for these parameters.

Table 3: Comparison of comorbidities & addiction history between the three groups

Parameter	1st Tertile (n = 66)	2nd Tertile (n = 84)	3rd Tertile (n = 10)	P value
Comorbidities				
Diabetes mellitus	8 (12.1%)	16 (19%)	1 (10%)	0.287#*
Hypertension	5 (7.6%)	10 (11.9%)	2 (20%)	
Dyslipidemia	12 (18.2%)	8 (9.5%)	0 (0%)	
Diabetes mellitus+ hypertension	3 (4.5%)	6 (7.1%)	2 (20%)	
Addiction history				
Smoking	13 (19.7%)	15 (17.9%)	1 (10%)	0.221#*
Alcohol	9 (13.6%)	12 (14.3%)	1 (10%)	
Smoking + Alcohol	1 (1.5%)	10 (11.9%)	0 (0%)	

#Using Fisher exact test

3) Type of MI

The distribution of the type of MI (STEMI, NSTEMI or UA) between the 3 groups is shown in Table 4 below. NSTEMI was the most common type of MI in patients of 1st tertile. On the other hand, STEMI was the most common MI in the other 2 groups. There was a statistically significant difference in the type of MI between the 3 groups.

Table 4: Distribution of type of MI between the threee groups

Type of MI	1st Tertile (n = 66)	2nd Tertile (n = 84)	3rd Tertile (n = 10)	P value
STEMI	26 (39.4%)	55 (65.5%)	6 (60%)	0.007#*
NSTEMI	28 (42.4%)	25 (29.8%)	4 (40%)	
UA	12 (18.2%)	4 (4.8%)	0 (0%)	

#Using Fisher exact test *P value < 0.05

4) Ejection fraction, Killip & TIMI class

Table 5 & Figures 4 - 6 below shows the distribution of the 3 groups based on ejection fraction, TIMI &Kilipp classification. Ejection fraction was >50 % for majority of the patients of 1st& 2ndterrtiles whereas higher number of participants in the 3rdtertile had ejection fraction between 40

- 50 %. The difference in distributioon was statistically significant between the 3 groups. Majority of the study participants belonged to Kilip & TIMI class I in Group 1 & 2. On the other hand, patients in 3rd tertile had more participants in Kilip& TIMI class II. The difference was statisticallly significant.

Table 5: Comparisonn of ejection fraction, Kilip& TIMI class between the three groups

Parameter	1st Tertile (n = 66)	2nd Tertile (n = 84)	3rd Tertile (n = 10)	P value
Ejection fraction (%)				
≥ 50	58 (87.9%)	57 (67.90%)	4 (40%)	0.004#*
40 - 50	7 (10.60%)	20 (23.80%)	6 (60%)	
30 - 40	1 (1.50%)	6 (7.1%)	0 (0%)	
< 30	0 (0%)	1 (1.2%)	0 (0%)	
Kilip class				
Class I	60 (90.9%)	56 (66.70%)	3 (30%)	<0.001#*
Class II	6 (9.10%)	28 (33.30%)	7 (70%)	
TIMI class				
Class I	60 (90.9%)	58 (69%)	3 (30%)	<0.001#*
Class II	6 (9.10%)	26 (31%)	7 (70%)	

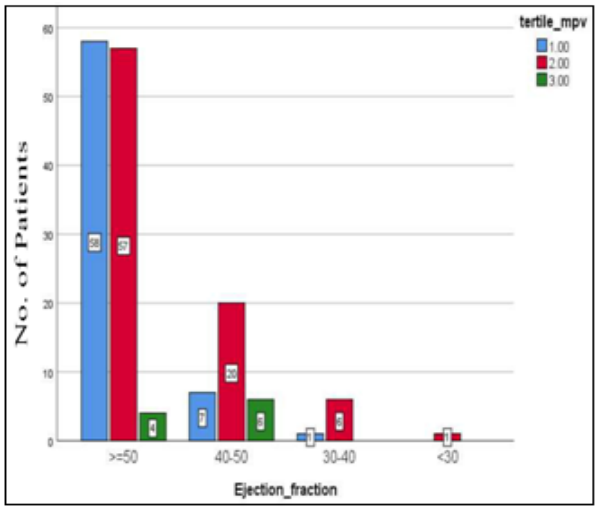

Figure 4: Ejection fraction among the study tertiles

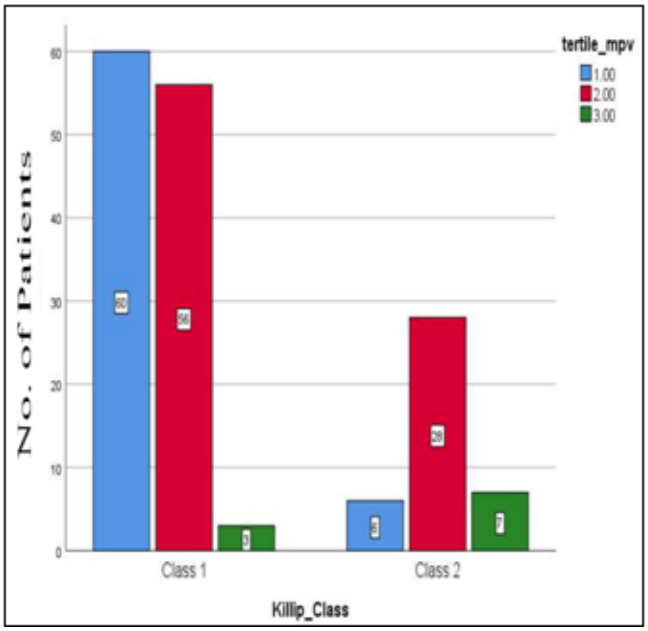

Figure 5: Kilip class among study tertiles

5) Mean platelet volume

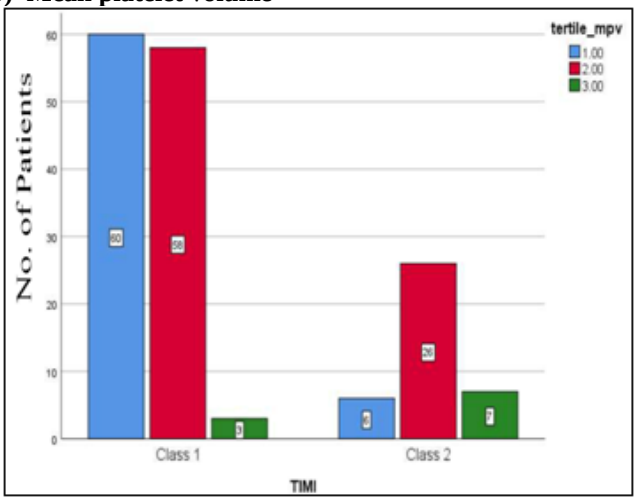

Figure 6: TIMI score among the tertiles

The MPV at baseline and follow up was compared in the 3 groups as shown in Table 6 & Figure 7 below. The values were comparable in group 1 with no statistically significant difference. However, there was a statistically significant decrease in MPV in group 2 & 3.

Table 6: Comparison of pre & post treatment MPV values in the three groups

CAG Finding	Baseline Value (fL)	Follow up Value (fL)	p value $
1st Tertile	8.55± 0.54	8.59± 0.64	0.477
2nd Tertile	10.08 ± 0.45	9.86 ± 0.66	<0.001*
3rd Tertile	12.47 ± 0.64	12.02 ± 0.99	0.021*

$Using paired T test *P value <0.05

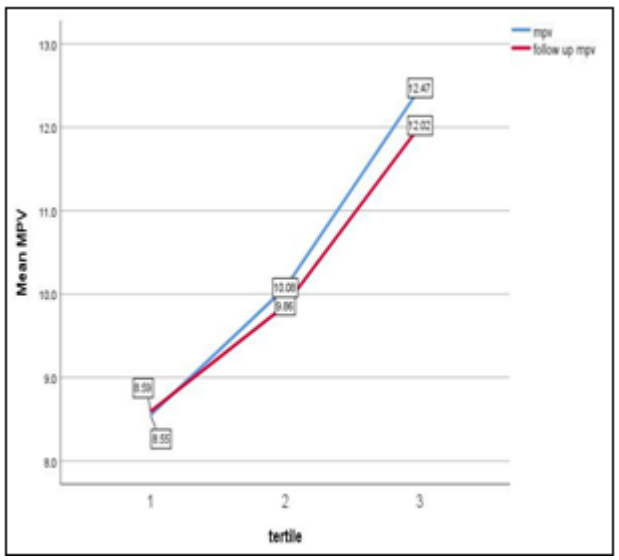

Figure 9: Comparison of mean MPV values

6) CAG procedure

Table 7 below shows the angiogram findings in the 3 study groups. Single vessel disease was the most common finding in all the 3 groups. The difference was statistically significant between the 3 groups.

Table 7: Coronary angiogram findings in the three groups

CAG Finding	1st Tertile (n= 66)	2nd Tertile (n= 84)	3rd Tertile (n= 10)	p value
Single vessel disease (SVD)	13 (19.7%)	25 (29.8%)	4 (40%)	0.01#*
Double vessel disease (DVD)	6 (9.1%)	19 (22.66%)	1 (10%)	
Triple vessel disease (SVD)	0 (0%)	1 (1.2%)	0 (0%)	
Normal	8 (12.1%)	0 (0%)	0 (0%)	

#Using Fisher exact test *P value < 0.05

7) Cardiovascular events

There was 2 nonfatal ACS reported in group 3. None of the other study participants reported any cardiovascular events.

8) Predictors of MPV

A multivariate linear regression was run to find the predictors for follow up MPV values (Table 8). The model along with the variables explained 81.8% of the variation in follow up MPV values for the entire study population (R^2 value for the model was 0.818). Among the independent variables that were tested in the model, baseline MPV, Kilip& TIMI class were significant predictors of follow up MPV values in the study population.

Table 8: Multivariate linear regression model for follow up MPV values

Independent variable	Beta value	P value	Lower bound for 95% CI	Upper bound for 95% CI
Baseline MPV	.865	<0.001*	.787	.943
Ejection fraction	.029	.728	- .136	.194
Kilip class	- .300	.034*	- .577	- .023
TIMI class	.358	.010*	.087	.629
Type of MI	.039	.529	- .083	.161
*P value <0.05				

5. Discussion

The present study was carried out in a tertiary care hospital to study the impact of mean platelet volume (MPV) among patients under 45 years who presented with first episode of acute coronary syndrome. Study subjects who fulfilled the inclusion criteria were enrolled in the study. A total of 160 study participants were recruited. The whole cohort was then divided into three groups based on tertiles of the reported MPV. The three tertiles were comparable to each other in age, sex distribution, comorbidities and addiction history. STEMI was the most common type of MI in the 2nd& 3rdtertiles whereas NSTEMI was the most common MI in the 1sttertile. There was a statistically significant difference in ejection fraction, Killip & TIMI class between the three tertiles. The MPV values were similar at baseline & follow up in the 1sttertile. On the other hand, there was a statistically significant decrease in MPV at follow up for the 2nd& 3rdtertiles. Single vessel disease was the most common angiogram finding across all the three tertiles. Non - fatal ACS was reported in two patients of the 3rdtertile whereas there were no other reported cardiovascular events in the other tertiles. A multivariate linear regression model was run to study the predictors of follow up MPV in the study population. Baseline MPV, Kilip& TIMI class were the significant predictors for follow up MPV values.

Larger platelets with greater MPV were associated with higher platelet reactivity, which is a major risk factor for atherothrombosis[7]. Several studies have found that elevated MPV levels are linked to higher vascular mortality and other cardiovascular events, such as MI[8 - 10]. As a result, MPV has been proposed as a simple metric of platelet functional state and may be a risk factor for vascular adverse events. In the present study, cardiovascular events in the form of non fatal ACS were observed in 2 patients in the 3rdtertile, therefore indicating an association of cardiovascular events with elevated MPV.

The mechanisms underlying increased platelet volume remain unknown. Several explanations exist to explain the increase in MPV in acute coronary syndrome. (ACS). One possible cause is platelet consumption and the release of larger and more immature platelets from bone marrow into the circulation[11, 12]. Another theory is that platelets in some people are bigger and more metabolically active, predisposing them to ACS. However, if the increase in platelet volume is a temporary phenomenon that occurs after ACS, it must normalize within a few months of the occurrence. The results in the present study were in concordance with this hypothesis as the MPV in the 2nd& 3rd tertiles reduced significantly at follow up.

Muscari et al.[13] discovered a direct link between an MPV of 8.4 fl (the highest tertile of its distribution) and ischaemic ECG changes, whereas Pizzulli et al.1[4] discovered higher MPV values in patients with documented coronary artery disease than in controls, and in unstable angina more than instable angina. Furthermore, among patients with unstable angina, MPV was larger in those who required rapid revascularisation. Finally, MPV has been linked to coronary syndrome X[15]

All the participants were on antiplatelet therapy in the present study. The effect of antiplatelet drugs like aspirin, clopidogrel on MPV have been studied previously. In a study by Luca et al.[16] there was a significant paradoxical increase in MPV, with a reduction in platelet count. in patients of ACS. In another study by Higaki et al.[17] there was no significant effect on MPV at follow up in patients of stable CAD undergoing coronary intervention. The results of the present study were in contrast with the results of Luca et al. &Higaki et al. as there was a significant reduction in MPV in patients of the 2nd& 3rdtertiles from baseline to follow up. Several variables could explain the lack of functional significance of big platelet size. The rise in MPV could be caused by an increase in the synthesis of bigger circulating reticulated platelets produced from bone marrow in the bloodstream[18]. Indeed, both megakaryocyte ploidy and the fraction of circulating reticulated platelets have been demonstrated to correlate with the MPV[19.] The results of the present study were in contrast with the results of Luca et al. &Higaki et al. as there was a significant reduction in MPV in patients of the 2nd& 3rdtertiles from baseline to follow up. Several variables could explain the lack of functional significance of big platelet size. The rise in MPV could be caused by an increase in the synthesis of bigger circulating reticulated platelets produced from bone marrow in the bloodstream.

6. Conclusions

Patients with higher MPV values had severe disease at presentation and developed adverse cardiovascular events on follow up. MPV is a simple and inexpensive laboratory test that could be used in concert with other standard biochemical cardiac markers to help predict the risk of significant cardiovascular events in young patients

7. Limitations

Firstly, the follow up period for the study participants was not long due to time constraints and thus long - term association between MPV and cardiovascular events could not be studied.

Secondly, most of the patients who presented with STEMI had undergone emergency revascularization and hence might have affected the outcome

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