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Clinical Significance of Platelet Indices (Mean Platelet Volume and Mean Platelet Volume-to-Lymphocyte Ratio) in Acute Coronary Syndrome: A Hospital-based Observational Study

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Abstract: ***Background**: The role of platelet indices, such as mean platelet volume (MPV) and MPV-tolymphocyte ratio (MPVLR), in diagnosing, and predicting the severity, and fatality in acute coronary syndrome (ACS) has not been extensively studied, particularly in Indian patients. Therefore, the study aimed to investigate the clinical significance of MPV and MPVLR in ACS. **Materials and methods**: This hospital-based observational study was conducted in tertiary care hospital in India. It included 110 ACS cases and an equal number of age- and sex-matched controls with chest pain of noncardiac origin. The primary objective was to compare MPV and MPVLR in ACS patients and controls. Secondary objectives included examining the associations between MPV, MPVLR, and different ACS types, as well as their correlation with the global registry of acute coronary events (GRACE) risk score and inhospital major adverse cardiovascular events (MACE). **Results**: Higher MPV and MPVLR were observed in ACS cases compared to controls [(11.1 ± 1.1 fL; 10.6 ± 1.3 fL, p < 0.01), (7.63 ± 4.9 fL/mm3; 4.74 ± 1.6 fL/mm3, p < 0.01) respectively]. Significant associations were found between platelet indices (MPV, MPVLR) and various ACS types (p < 0.01). Both indices positively correlated with the severity of heart failure, GRACE score, and inhospital MACE (p < 0.01). MPVLR showed a positive correlation with the duration of hospital stay [(r: 0.21; p = 0.03), but MPV did not (r: 0.13; p = 0.17)]. The GRACE score demonstrated the highest discriminating capacity in predicting inhospital mortality compared to platelet indices. Additionally, MPV serves as a more effective prognostic marker than MPVLR in predicting inhospital mortality. **Conclusion**: Both MPV and MPVLR are higher in ACS than in healthy individuals. Therefore, both may be used as discriminating markers for differentiating cardiac and noncardiac chest pain when cardiac biomarkers are not available. Additionally, both have good sensitivity for predicting the severity of the disease, inhospital mortality, and MACE in ACS.*

Keywords: MPV, MPVLR, ACS

1. Introduction

Acute coronary syndrome (ACS) constitutes a significant noncommunicable disease attributed to the formation of platelet-rich coronary thrombus and plaque rupture, resulting in myocardial ischemia and infarction. The associated mortality burden is estimated to be 5–8% within 6 months of diagnosis.[1] The ACS spectrum encompasses ST-elevation ACS (STE-ACS) and non-ST- elevation ACS (NSTE-ACS). NSTE-ACS further classifies into non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) based on evidence of cardiac muscle enzymes.[2]

Mean platelet volume (MPV), a parameter indicating platelet size, is positively correlated with platelet activity. Increased MPV, indicative of more reactive platelets, has been associated with atheroembolism and myocardial damage in ACS.[1,3] Larger platelets exhibit greater metabolic and enzymatic activity compared to smaller ones. They secrete and express higher levels of mediators, such as adhesion proteins (fibrinogen, thrombospondin, and fibronectin), growth factors (platelet-derived growth factor, transforming growth factor, and basic fibroblast growth factor), and chemotactic and mitogenic factors [platelet factor, coagulation factors (factor V and factor XI), and interleukin-1 and cluster of differentiation 40 (CD40) ligand].[4,5]

Simple and routine tests like MPV have the potential to aid in the early prediction of the risk of ACS in acute care medical facilities.[6,7] MPV has emerged as a robust and independent predictor of impaired reperfusion and 6-month mortality, not only in ST-elevation myocardial infarction (STEMI) patients but also in those NSTEMI.[6–9]

The MPV-to-lymphocyte ratio (MPVLR) represents another novel marker implicated in the diagnosis and prognosis of ACS. There are very few studies investigating its association with ACS patients. These simple, readily available, and cost-effective parameters (MPV and MPVLR) could serve as markers for ACS, especially in resource-poor countries where expensive markers like troponin may not be easily accessible or affordable. These observations prompt the hypothesis that increased MPV and MPVLR may serve as potential predictors in ACS diagnosis, risk stratification, and prognostic markers.

2. Materials and Methods

This hospital-based observational study was conducted at our tertiary healthcare facility in India.. It was a case–control study, including a total of 110 patients as cases and an equivalent number of controls. All consecutive ACS patients aged >18 years were recruited as cases. Age- and sex-matched controls with noncardiac chest pain and a normal electrocardiogram (ECG) were included as controls.

Objective

The primary objective was to compare the MPV and MPVLR in patients with ACS to controls. The secondary objectives were—(1) to determine the association between MPV, MPVLR, and different types of ACS; (2) To determine the association between MPV, MPVLR, and the global registry of acute coronary events (GRACE) risk score, inhospital major adverse cardiovascular events (MACE).

Inclusion and Exclusion Criteria

All patients aged 18 years with a diagnosis of ACS[10] were included as cases. Patients meeting any of the following criteria were excluded from the study—renal failure, hepatic failure, myeloproliferative disorder, malignancy, platelet disorders, coagulation abnormalities, on antiplatelet therapy or any drug affecting platelet function (e.g., hydroxyurea or antineoplastic agents), anemia (hemoglobin levels <12 gm/dL in men and <10 gm/dL in women), previous myocardial infarction within the last 6 months, atherosclerotic cardiovascular diseases (ASCVD) including stroke or peripheral artery disease (PAD), history of preeclampsia, sepsis, recent blood transfusion, major operation, trauma, or connective tissue disorders.

Methodology

All patients admitted to the emergency ward, general medicine, or cardiology department were recruited after fulfilling the eligibility criteria of this study. Written informed consent was obtained from all participants. Diagnostic tools included a 12-lead ECG and troponin (Tn T or I) for ACS diagnosis. Detailed history, general, and systemic examinations were conducted. Venous samples were collected for complete hemogram testing in vacutainers containing K2 ethylenediaminetetraacetic acid 5.4 mg. MPV was measured within 1–2 hours of collection using the SYSMEX XN-1000B3 analyzer with an impedance flow cytometry technique. MPV in femtoliters (fL) was recorded. Absolute lymphocyte count values (in 1000/mm³) for calculating MPVLR were obtained from routine hemograms. MPVLR (fL/mm³) is the ratio of MPV to absolute lymphocyte count. The GRACE risk score was calculated upon admission for mortality prediction. Participants were observed throughout their hospital stay and monitored for any MACE. MPV and MPVLR values from non-ACS chest pain patients were also collected. Patients were managed according to accepted guidelines during the study period. Data were recorded in Excel and analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 24, employing appropriate statistical tests.

Statistical Analysis

Categorical variables were presented as frequencies and percentages. The data were compared using the Chi-squared test if the data were normally distributed or Fisher's exact test, as deemed appropriate. Quantitative data were expressed as mean ± standard deviation (SD) and compared using an independent sample *t*-test or Mann–Whitney *U* test, as appropriate. When comparing more than two means, either one-way analysis of variance (ANOVA) or the Kruskal–Wallis test was employed, depending on the data distribution. The association of MPV or MPVLR with severity and other parameters was tested using the Pearson correlation test. Receiver operating characteristic (ROC) curve analysis was conducted to assess the discrimination capacity of the GRACE score, MPV, and MPVLR in predicting early in hospital mortality. The Youden index was used to determine the optimum cutoff point for establishing sensitivity and specificity. A significance level of $p \leq 0.05$ was considered statistically significant.

3. Results

The study comprised 110 ACS cases and 110 controls. In both ACS and control groups, the majority of patients were males (70.9 and 64.5%, respectively). The mean age was 56.7 ± 11.3 years for cases and 56.1 ± 10.9 years for controls. The majority of ACS cases were in the elderly category, with 32.7% aged 50–59 years and 30.9% aged 60–69 years. Among the ACS cases, 72.8% had STEMI, while 14.5 and 12.7% had NSTEMI and UA, respectively. Table 1 provides detailed baseline characteristics for cases and controls. The study observed a higher prevalence of diabetes in cases compared to controls (46.4 vs 24.5%). Among the cases, only 24.5% (n = 27) had dyslipidemia. Total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were higher in controls than in cases (Table 1).

Mean MPV was higher in cases than in controls (11.1 ± 1.1; 10.6 ± 1.3 fL, $p < 0.01$).

Similarly, the mean MPVLR was higher in cases than controls (7.63 ± 4.9; 4.74 ± 1.6 fL/mm^3, $p < 0.01$). Significant associations were observed between MPV (p-value < 0.01) and MPVLR ($p < 0.01$) with various types of

Table 1: Baseline characteristics of participants

Parameters	*Case (n = 110) (mean ± SD or percentage)*	*Control (n = 110) (mean ± SD or percentage)*	*p-value*
Age (in years)	56.7 ± 11.3	56.1 ± 10.9	0.11
Male:female	70.9 ± 29.1%	64.5 ± 35.5%	0.31
Diabetes	46.4%	24.5%	<0.01
Hypertension	52.7%	45.5%	0.280
Dyslipidemia	24.5%	23.6%	>0.05
Obesity	31.8%	13.6%	<0.01
Hypothyroidism	6.3%	6.3%	>0.05
Tobacco user	59.1%	29.1%	<0.01
Alcoholic	24.5%	16.4%	0.13
Total cholesterol (mg/dL)	162.6 ± 54.96	169.2 ± 50.63	0.21
Triglyceride (mg/dL)	137.3 ± 63.75	145.5 ± 88.43	0.64
LDL (mg/dL)	105.1 ± 41.5	107.54 ± .35.05	0.31
HDL (mg/dL)	37.48 ± 10.5	40.43 ± 10.5	0.02
VLDL (mg/dL)	28.04 ± 13.4	27.7 ± 11.6	0.85
Hemoglobin (gm/dL)	13.1 ± 1.7	13.2 ± 1.5	0.656
TLC (10^3 cells/mm^3)	11.42 ± 4.93	8.01 ± 2.13	<0.01
Platelet count (lakhs/mm^3)	2.7 ± 0.8	2.6 ± 0.7	0.343
MPV (fL)	11.1 ± 1.1	10.6 ± 1.3	<0.01
MPVLR (fL/mm^3)	7.63 ± 4.9	4.74 ± 1.6	<0.01

$p < 0.05$ is considered significant; HDL, high-density lipoprotein; LDL, low-density lipoprotein; MPV, mean platelet volume; MPVLR, mean platelet volume-to- lymphocyte ratio; SD, standard deviation; TLC, total leukocyte count; VLDL, very low-density lipoprotein

ACS (Table 2). The mean GRACE scores were 123.60 ± 31.84, 106.63 ± 18.66, and 68.57 ± 22.82 for patients with STEMI, NSTEMI, and UA, respectively. A significant positive correlation was found between MPV and GRACE score (*r*: 0.41; $p < 0.01$),and similarly, MPVLR showed a significant positive correlation with GRACE score (*r*: 0.31; $p < 0.01$)

The mean hospital stay was 5. 57 ± 2.62, 6.81 ± 2.95, and 7.25 ± 4.34 days for UA, NSTEMI, and STEMI, respectively. No significant correlation was observed between MPV and duration of hospital stay (*r*: 0.13; $p = 0.17$). However, a significant positive correlation was observed between MPVLR and duration of hospital stay (*r*: 0.21; $p = 0.03$). Congestive heart failure (CHF), stroke, cardiovascular (CV) death, reinfarction, shock, and arrhythmia occurresd ($n = 31$), 0.9% ($n = 01$), 11.8% ($n = 13$), 0.9% ($n = 01$), 16.4% ($n = 18$), and 8.2% ($n = 09$) of cases, respectively. MACE was reported in 6.3% of NSTEMI cases, while STEMI cases exhibited MACE in 31.1% of instances. MACE was not observed in any cases of UA.

Mean MPVLR was significantly higher among those with MACE (8.78 ± 4.51 fL/mm^3) compared to those without MACE [(6.99 ± 4.97 fL/mm^3) ($p < 0.01$)]. Similarly, mean MPV was significantly higher among those with MACE (11.67 ±1.02 fL) compared to those without MACE [(10.74 ± 0.96 fL) ($p < 0.01$)].

MPV and MPVLR correlated significantly with the severity of heart failure (Table 3). Mean MPV ($p < 0.01$) and MPVLR ($p < 0.01$)

were significantly higher among patients with CHF compared to those without CHF. Both mean MPV ($p < 0.01$) and MPVLR ($p = 0.03$) were significantly higher among patients with shock compared to those without shock. Additionally, both mean MPV ($p < 0.01$) and MPVLR ($p < 0.01$) were significantly higher among patients with arrhythmia compared to those without an arrhythmia (Table 4). Inhospital fatality occurred in 16.2% of cases, while the rest were discharged. Mean MPV was significantly higher among those who died (11.91 ± 1.05 fL) compared to those who were discharged [(10.96 ± 1.03 fL) ($p < 0.01$)]. Similarly, mean MPVLR was significantly higher among those who died (8 .97 ± 3.94 f L/mm^3) compared to those who were discharged [(7.45 ± 4.97 fL/mm^3) ($p = 0.04$)].

According to ROC curve analysis, the optimal cutoff values for GRACE score, MPV, and MPVLR to determine positivity for inhospital mortality were GRACE score >153.0 (AUC: 0.923, $p < 0.001$) sensitivity 92.3% and specificity 93.8%; MPV >11.25 fL (AUC: 0.753, $p = 0.003$) with sensitivity 76.9% and specificity 66.0% and MPVLR >6.68 fL/mm^3 (AUC: 0.675, $p = 0.041$) with sensitivity of 76.9% and specificity of 63.9%.

In addition, a subgroup analysis examined the distribution of MPV and MPVLR in different subgroups. MPV was higher in diabetic participants than in nondiabetic participants in the ACS category ($p = 0.04$ and $p = 0.04$, respectively). However, no

Table 2: Comparison of MPV and MPVLR in different subtypes of ACS

Platelet indices	*UA*	*NSTEMI*	*STEMI*	*p-value*
MPV (fL) (mean ± SD)	10.2 ± 0.6	10.9 ± 0.68	11.2 ± 1.1	<0.01
MPVLR (fL/mm^3) (mean ± SD)	4. ± 0.9	6.04 ± 1.9	8.5 ± 5.3	<0.01

$p < 0.05$ is considered significant; ACS, acute coronary syndrome; MPV, mean platelet volume; MPVLR, mean platelet volume-to-lymphocyte ratio; NSTEMI, non-ST segment elevation myocardial infarction; SD; standard deviation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina

Table 3: Mean platelet volume, MPVLR in different ACS categories and its correlation with Killip class

Killip class	Unstable angina (%)	NSTEMI (%)	STEMI (%)	MPV (fL) (mean ± SD)	MPVLR (fL/mm3) (mean ± SD)
Killip I	100	87.5	53.7	10.68 ± 0.97	7.00 ± 4.83
Killip II	–	12.5	25.9	11.73 ± 0.87	8.22 ± 3.89
Killip III	–	–	9.8	11.58 ± 0.58	7.18 ± 4.22
Killip IV	–	–	11.0	11.96 ± 1.23	11.35 ± 6.69
p-value				<0.01	<0.01

p < 0.05 is considered significant; ACS, acute coronary syndrome; MPV, mean platelet volume; MPVLR, mean platelet volume-to-lymphocyte ratio; NSTEMI, Non-ST segment elevation myocardial infarction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction

Table 4: Mean platelet volume and MPVLR across various MACE components among cases (n = 110)

MACE components		*MPV (fL) (mean ± SD)*	*MPVLR (fL/mm^3) (mean ± SD)*
Shock	Yes	11.86 ± 0.98	9.38 ± 5.42
	No	10.92 ± 1.03	7.28 ± 4.71
	p-value	<0.01	0.03
Arrhythmia	Yes	10.79 ± 0.94	7.59 ± 2.54
	No	11.10 ± 1.09	7.63 ± 5.03
	p-value	0.51	0.32
Heart failure	Yes	11.82 ± 0.91	8.72 ± 3.80
	No	10.78 ± 0.99	7.20 ± 5.19
	p-value	<0.01	<0.01

p < 0.05 is considered significant; MACE, major adverse cardiac event; MPV, mean platelet volume; MPV- LR, mean platelet volume-to-lymphocyte ratio; SD, standard deviation statistically significant difference in mean MPVLR was observed between diabetic and nondiabetic groups within the ACS category. Hypertension and obesity did not influence MPV and MPVLR in ACS cases.

4. Discussion

Acute coronary syndrome is emerging as the predominant cause of morbidity and mortality globally, including in India. Prominent cardiological societies recommend measuring cardiac troponin I and cardiac troponin T as the preferred biochemical cardiac biomarkers for diagnosing ACS. However, the diagnostic efficiency of cardiac troponins within 2–4 hours of symptom onset is limited, necessitating the exploration of other laboratory biochemical tests to discriminate the chest pain as cardiac or noncardiac in origin. The pivotal role of platelets in the initiation and progression of ACS has been well-known. Platelet activation results in the formation of larger and hyperactive platelets, leading to the synthesis of various vasoconstricting prostaglandins (e.g., thromboxane A 2) and platelet- aggregating substances. Consequently, larger and hyperactive platelets play a crucial role in accelerating the formation and propagation of intracoronary thrombus, contributing to acute thrombotic events. Platelet indices, such as MPV and MPVLR, correlate with platelet activation. Hence, these platelet indices can serve as surrogate diagnostic markers for ACS diagnosis and prognosis. Additionally, increased MPV may be a potentially valuable predictor in cardiovascular risk stratification.

In our study, the majority of cases were STEMI (72.8%). Our study exhibited a higher frequency of STEMI, attributed to our center being a percutaneous coronary intervention (PCI)-capable tertiary-level referral hospital in central India. Notably, only one-fourth of the cases in our study had dyslipidemia. Although the mean levels of cholesterol (LDL, HDL, and TG) were higher in controls than in cases, the difference was statistically insignificant. It is recognized that high TC is typically associated with high ASCVD risk, a relationship not supported by our study. This discrepancy may be explained by the fact that lipid levels can undergo changes during ACS as part of the acute phase response. The first observation of a decrease in serum cholesterol levels during AMI was reported by Biorck et al. in 1957. Several early studies have also noted reductions in TC, LDL, and HDL levels by 47, 39, and 11%, respectively, with a simultaneous 50% increase in TG levels during ACS.

Correlation of MPV and MPVLR with ACS

Various studies have explored the role of platelets in AMI as both a diagnostic and prognostic parameter. Several studies support the use of MPV in ACS as a surrogate diagnostic parameter, while others present contrasting views. However, limited research has been conducted to understand the significance of MPVLR. The identification of larger platelets during routine hematological analysis may serve as an early diagnostic method for detecting reactive platelets and subsequent thrombosis, especially in scenarios where troponin is negative or testing is not readily available. Additionally, MPV and MPVLR may function as prognostic markers for early mortality. In our study, we observed that both MPV and MPVLR were higher in cases than in controls (p = 0.002 and p = 0.0001, respectively).

In a study by Yilmaz et al., statistically significant differences in MPV were noted among the NSTEMI, UA, and stable coronary heart disease (CHD) groups (10.4 ± 0.6, 10 ± 0.7, 8.9 ± 0.7 fL, respectively). The study suggested that higher MPV correlates with an increased risk of STEMI but ischemic complications. Another study by Pal et al. found that MPV was higher in ACS patients than in non-ACS cases (11.44 ± 1.23 vs 9.91 ± 1.27 fL, *p*-value < 0.001). The negative predictive value of MPV for ACS diagnosis within 6 hours of presentation was reported as 82.53%. Slavka et al. investigated the association of MPV with the risk of ischemic heart disease and vascular disease among 206,554 subjects from 1996 to 2003. They found that the highest MPV category (≥11.01 fL) had a higher risk of ischemic heart disease compared to the lower category (8.71–9.60 fL category) (HR = 1.8 vs 1.2, respectively).

To our knowledge, limited studies have explored the role of MPVLR in ACS. In 2016, Hudzik et al. investigated the

prognostic significance of MPVLR in diabetic patients with STEMI undergoing PCI. They found that elevated MPVLR was associated with worse angiographic features, indicating a greater thrombus burden. Elevated MPVLR emerged as an independent risk factor for both early and late mortality following STEMI.[18] Chen et al. in 2020 suggested a positive correlation between the GRACE score and MPVLR. Their study indicated that the combination of GRACE score and MPVLR accurately predicted the occurrence of short-term MACE in patients with STEMI after PCI.[27] In our study, we observed that MPVLR was higher in cases than in controls and exhibited a positive correlation with the severity of the disease.

Correlation with Disease Severity, Duration of Hospitalization, Mortality, and MACE

In our study, we observed a consistent pattern wherein the duration of hospitalization correlated with the severity of the disease. The mean hospital stay ranged from lower to higher durations in the order of UA, NSTEMI, and STEMI groups. Although MPV did not exhibit a correlation with the duration of hospitalization, MPVLR, on the other hand, demonstrated a significant correlation. Additionally, both MPV and MPVLR were higher in cases with severe heart failure compared to milder forms. Significant correlations were found between both MPV and MPVLR with the GRACE score, CHF, cardiogenic shock, and MACE.

Furthermore, our study revealed MPV and MPVLR elevation in patients with cardiogenic shock compared to those with ACS without shock. Contrarily, a study by Supel et al. focused on the prognostic role of MPV in ACS with (n = 53) vs without shock (n = 53). They found no significant difference in MPV between the two groups on day 01 (8.91 ± 1.11 fL vs 8.57 ± 0.74 fL). Additionally, MPV didn't differ between fatal and nonfatal cardiogenic shock (8.90 ± 1.18 vs 8.93 ± 1.05 fL).[28] The significance of MPV as a predictor of poor inhospital outcomes in ACS with cardiogenic shock is currently under scrutiny.

Elevated MPV has recently been discussed as a predictor of death in patients with ACS. Our study revealed that the mean MPV and MPVLR among those who died were significantly higher than in survivors. Moreover, MPV and MPVLR positively correlated with MACE.

In our findings, it was observed that MPV possesses a greater discriminative capability for in hospital mortality compared to MPVLR. Nonetheless, it's noteworthy that GRACE exhibits the highest predictive power for mortality.

5. Conclusion

We observed high MPV and MPVLR in cases compared to the control group. Both parameters demonstrate potential for risk stratification in ACS. MPV and MPVLR exhibited positive correlations with the severity of heart failure. However, only MPV did not show a significant correlation with the duration of hospital stay. Furthermore, they proved to be valuable predictors of in hospital mortality during hospitalization.

In resource-limited settings where cardiac biomarkers are either unavailable or unaffordable, MPV and MPVLR could serve as discriminatory factors for chest pain, distinguishing between cardiac and noncardiac origins. Additionally, these parameters demonstrate promise in predicting early mortality and major adverse events.

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