

Original Article

High Sensitive CRP and Platelet Volume Indices in Acute Coronary Syndrome and their Impact in Prognostication

Anindya Sundar Trivedi¹, Debaprasad Chakrabarti², Sutanuka Khasnabish³,
Amrit Kumar Bhattacharyya⁴

Background : Elevated levels of serum highly sensitive C-Reactive Protein (hs-CRP) serve as a strong independent predictor of risk for Myocardial Infarction (MI), stroke, peripheral arterial disease and overall cardiovascular mortality. Studies have demonstrated that hs-CRP, measured at either presentation or discharge, may have prognostic value in patients with acute coronary syndromes. Platelets and their activity have an important role in initiation of atherosclerotic lesions and coronary thrombus formation.

Aims and Objective : The primary objective was to estimate the average of hs CRP among patients with Acute Coronary Syndrome (ACS) and the correlation of hs-CRP and platelet volume indices with conventional risk factors. The secondary objective was to assess its role as a prognostic marker in patients with ACS.

Materials and Methods : Hundred subjects admitted with ACS and equal number of age and sex matched healthy control were studied. Diagnosis of ACS was made based on the American College of Cardiology and European Society of Cardiology guidelines for acute MI. The baseline clinical characteristics were analysed. Blood samples were collected for estimation of hs-CRP, platelet volume indices and other routine parameters. Patients were followed up for a period of 1 month for adverse cardiac events. A probability value of <0.05 at 95% Confidence Interval (CI) was considered significant.

Observation : Mean hs-CRP level in the cohort of ACS patients (7.053±4.833) was higher than the control group (1.942±1.099). Additionally hs-CRP was found to be a significant prognostic marker for predicting the adverse events in patients of ACS (p<0.01). It was also observed that ACS patients had higher Mean Platelet Volume (MPV) (10.97) compared with control groups (9.21)(p<0.001). Further, on logistic regression analysis significant positive correlation existed between Mean Platelet Volume (MPV) (14.942±2.842) and adverse outcomes (p<0.01), whereas platelet count, Platelet to Large Cell Ratio (PLCR), Platelet Distribution Width (PDW) and Plateletcrit were not.

Conclusion : hs-CRP level and MPV are simple, yet reliable indicators for adverse cardiac outcomes and can be used in risk stratification of ACS patients.

[J Indian Med Assoc 2024; 122(4): 38-42]

Key words : ACS, Platelet Volume Indices, hs-CRP.

Cardiovascular Disease (CVD) is major global health problem and reaching epidemic proportions in the Indian subcontinent and low and middle income countries, accounting for majority of all deaths. Elevated levels of serum C-Reactive Protein (CRP) serve as a strong independent predictor of risk of MI, stroke, peripheral arterial disease and cardiovascular mortality. The risk factors for cardiovascular disease such as age, obesity, smoking and diet are all factors that would increase CRP levels in the body. An association between minor CRP elevation and future

Editor's Comment :

- Markers like hs-CRP and MPV are simple, yet reliable indicators for predicting adverse cardiac events.
- Elevated levels of these markers may play a significant role for risk stratification in patients with acute coronary syndrome.

cardiovascular events has been recognised, leading to a recent recommendation to measure CRP in patients at risk for heart disease¹. A high sensitivity-CRP (hs-CRP) measures low levels of CRP with a sensitivity as low as 0.04 mg/dl. Several studies have demonstrated that hs-CRP measured at either presentation or discharge, may have prognostic value in patients with Acute Coronary Syndromes².

Platelets activation is a hallmark of ACS. Platelets and their activity have an important role in initiation of atherosclerotic lesions and coronary thrombus formation. Platelet size when measured as Mean Platelet Volume (MPV), is a marker of platelet function and is positively associated with indicators of platelet

Department of Medicine, Tripura Medical College and Dr BRAM Teaching Hospital, Hapania, Agartala 799014

¹MBBS, MD (Med), Ex Postgraduate Trainee

²MBBS, MD (Medicine), Professor and Corresponding Author

³MBBS, MD (Pathology), Assistant Professor, Department of Pathology

⁴MBBS, MD (Med), Postgraduate Trainee (Hematology), Cambridge (UK), Ex Professor and Head

Received on : 13/04/2023

Accepted on : 06/12/2023

activity. An increased MPV, an indicator of larger and more reactive platelets has been associated with myocardial damage in ACS and has been found to be predictive of an unfavourable outcome among survivors of AMI³.

Another platelet volume index, Platelet Distribution Width (PDW) reflects the variance in platelet size due to active platelet release. The PDW increases when there are increased number of larger platelets as well as smaller platelets in circulation. It indicates heterogeneity of platelet sizes by providing the relative width of distribution of platelets by volume. It could be used as a marker platelet reactivity as well as index of short term mortality⁴.

AIMS AND OBJECTIVE

The primary objective was to estimate the average of hs-CRP among patients with acute coronary syndrome and the correlation of hs-CRP and platelet volume indices with conventional risk factors. The secondary objective was to assess its role as a prognostic marker in patients with acute coronary syndrome.

MATERIAL AND METHODS

This study was conducted at Tripura Medical College and Dr BRAM Teaching Hospital as a prospective hospital based case control study. The ethical approval for the study was obtained from Ethical Review Committee of our institute.

A total of hundred subjects admitted with ACS in our hospital and equal number of age and gender matched controls were studied after obtaining informed consent. Sample size was calculated by using statistical formula :

$$\begin{aligned} \text{Sample size (n)} &= \{Z_{(1-\alpha/2)}\}^2 \times SD^2 / d^2 \\ &= 1.96^2 \times 5.01^2 / 1^2 \\ &= 96 \text{ (Rounded off to 100)} \end{aligned}$$

Where, $Z_{(1-\alpha/2)} = 1.96$ SD (Sample Standard Deviation) = 5.01⁵ $d = 1$ mg/l on either side specified precision

Sampling method : Convenience non random sampling technique was used to achieve the sample size. Diagnosis of acute coronary syndrome was made based on the American College of Cardiology and European Society of Cardiology guidelines for acute MI⁶.

Inclusion Criteria :

- (1) Patients above 18 years of age.
- (2) Having ACS including unstable angina, STEMI, NSTEMI enrolled as per ESC, ACCF, AHA, third universal definition of MI, 2012.

Exclusion Criteria :

- (1) Diagnosis of ACS not confirmed.

- (2) Subjects not willing to give consent.

- (3) Primary platelet disorder, bleeding and clotting disorder.

- (4) Patients suffering from CKD, cancer.

- (5) Patients discharged before completion of the treatment or lost in follow-up.

At the time of admission, a detailed clinical history, including presenting complaints, risk factors, family history and clinical examination with special reference to cardiovascular system was conducted. Various anthropometric measurements including waist to hip ratio was calculated. The normal WHR for males was taken at <0.9 and for females <0.85⁷. Blood samples were collected on admission for hs-CRP, platelet volume indices and other routine parameters. Fully automated five part analyzer was used for Complete Blood Count including platelet indices. Normal reference range of platelet count was taken at 150-450x10⁹/L, for MPV : 6.1-12fl, for PDW :9-17fl, for Plateletcrit : 0.19-0.39% and for PLCR 19.7-42.4%.

All patients were followed up for a period of 1 month for any adverse cardiac outcome (Pump failure, requirement of rescue interventional procedures and mortality from cardiovascular cause).

Statistical Analysis :

Statistical analysis was performed using the software microsoft excel office 2016 and IBM SPSS software for windows version 22. The categorical variables were compared by chi square test. Continuous variables were presented as mean (\pm SD) and were compared by unpaired t test. Multiple logistic regression analysis was used to analyze the association between parameters.

A probability value of <0.05 at 95% Confidence Interval (CI) was considered significant.

OBSERVATION

Out of hundred patients, majority of cases were above 60 years of age. As per AHA ACS criteria, 33% had NSTEMI, 57% had STEMI and 10% had unstable angina.

With regard to distribution of risk factors significant difference were observed in the prevalence amongst Cases Versus Controls (Table 1). Amongst adverse events, pump failure was seen in 15%, failed thrombolysis in 11%, requirement of rescue interventional procedures in 1% and mortality due to cardiovascular cause were 3% in our study.

It was observed that hs-CRP level was significantly elevated among ACS cases than controls (Table 2). Further, doing multiple logistic regression analysis it was observed that probability of adverse cardiac outcome increases with increase in hs-CRP level (Fig 1).

Table 1 — The risk factors exposures of the Case and Control subjects are enumerated

| Variables | Total (n) n=200 | Case N=100 | Control N=100 | P value |
|-------------------|---------------------|---------------------|---------------------|----------|
| Mean age | 54.31± 15.22(SD) | 63.12± 14.10(SD) | 59.97± 10.89(SD) | (0.08)NS |
| Age group : | | | | |
| <40 years | 39 | 6 | 9 | NS |
| 41-60 | 97 | 37 | 44 | NS |
| >60 | 64 | 57 | 47 | NS |
| Smoking history | 75 | 50 | 25 | <0.01 |
| Alcoholism | 28 | 26 | 2 | <0.01 |
| Hypertension | 54 | 53 | 1 | <0.01 |
| Diabetes Mellitus | 25 | 24 | 1 | <0.01 |
| Dyslipidaemia | 82 | 69 | 13 | <0.01 |
| CAD | 4 | 4 | 0 | - |
| Obesity | 57 | 43 | 14 | <0.01 |

Significance at p<0.05 at 95% CI

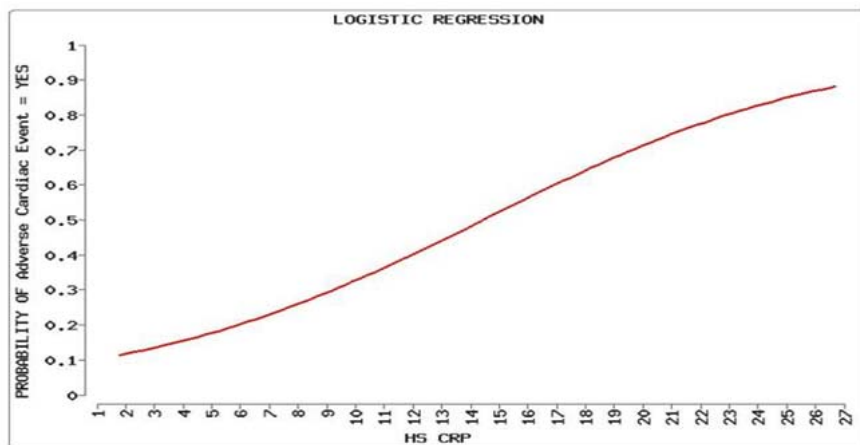
Table 2 — Comparison of hs-CRP and platelet indices among Case and Control

| Variables | Controls Mean±SD | Case Mean±SD | P value |
|----------------|---------------------|------------------|---------|
| hs-CRP | 1.942±1.099 | 7.053±4.833 | <0.01 |
| Platelet count | 213980±60439.298 | 230580±67599.591 | 0.06 |
| MPV | 11.041±2.135 | 14.942±2.842 | <0.001 |
| PLCR | 13.423±2.593 | 18.276±2.662 | <0.001 |
| Plateletcrit | 34.29±8.331 | 38.691±9.184 | <0.001 |
| PDW | 10.284±0.081 | 12.266±0.047 | <0.01 |

After analysing the data on platelet, we found that platelet count was not significantly different between groups, although it was numerically higher in subjects with ACS than control subjects. Platelet indices like MPV, PDW, PLCR and plateletcrit were significantly elevated in cases compared to control subjects (Table 2).

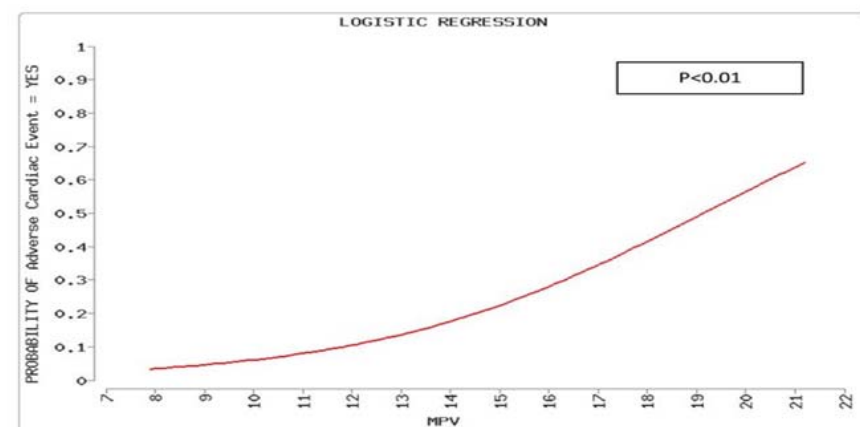
With regard to post-discharge cardiac events it was observed that platelet volume indices were higher in patients with adverse cardiac events compared to those without. However, out of all the indices which were numerically higher, only mean platelet volume level was found to be statistically significant (Table 3).

Further, applying multiple logistic regression analysis to determine the correlations between platelet indices and cardiac events it was observed that Mean Platelet Volume (MPV) remained statistically significant predictor of adverse outcomes in ACS cases (p<0.01) whereas platelet count, PLCR, PDW and plateletcrit were not (Figs 2 & 3).



Statistical significance at p<0.05 at 95% CI

Fig 1 — Multiple logistic regression analysis showing increasing probability of adverse cardiac outcome with increase in hs-CRP



Statistical significance at p<0.05 at 95% CI

Fig 2 — Multiple logistic regression analysis shows that probability of adverse cardiac outcome increases with increase in MPV level

DISCUSSION

With the present epidemiological transition from infectious diseases to non-communicable diseases, cardiovascular diseases remains a major cause of morbidity and mortality, accounting for 53% of all deaths in India⁸.

Our study shows that increase in hs-CRP is significantly elevated in ACS patients and it significantly increases the risk of developing ACS events (P<0.01). Further it was found that hs-CRP level was

| Table 3 — Comparison of Platelet volume indices amongst cases with or without adverse outcome | | | |
|---|------------------------|--------------------------------|---------|
| | Adverse outcome (mean) | Without Adverse outcome (mean) | P value |
| Platelet count | 230980 | 210560 | 0.18 |
| MPV | 15.014 | 10.009 | <0.01 |
| PLCR | 20.27 | 15.37 | 0.16 |
| Plateletcrit | 0.226 | 0.284 | 0.26 |
| PDW | 13.08 | 12.9 | 0.17 |

a significant prognostic indicator for predicting the adverse outcome of ACS events (p<0.01) which was in concurrence with studies by Raju H Badiger, *et al*⁹.

Frits Haverkate, *et al*¹⁰ similarly in their study showed that raised circulating concentrations of hs-CRP are predictors of coronary events in patients with both stable or unstable angina. However, in contrary Daniel Rios Pinto Ribeiro, *et al*¹¹ showed that although the hs-CRP level was not a good marker in predicting combined major cardiovascular events within 30 days after ST elevation Myocardial Infarction but it was an independent predictor of 30 day mortality.

In our study, platelet count was no different between cases and controls. In contrast, several previous trials depicted significant difference in platelet count in patients of Myocardial Infarction compared to controls¹².

Our data showed that the platelet count was not significant as a prognostic indicator of combined ACS events. However, Q Ly Hung, *et al*⁹ showed that only in STEMI, a higher platelet count on presentation was independently associated with adverse clinical outcomes.

Platelet volume indices shows that the mean MPV, PLCR and plateletcrit were significantly higher in ACS patients than in control subjects whereas differences in platelet count were not. Several previous studies have also supported the notion that MPV is significantly high in patients of STEMI compared to matched controls^{13,14}. In contrary in the work done by Akula, *et al*¹⁵ could not find similar difference. Strong positive correlations between MPV and PDW in patients of Acute Coronary Syndrome indicate that these parameters directly reflect platelet characteristics. While highly prothrombotic larger platelets increase the MPV, simultaneously the PDW is increased because of heterogeneity in platelet size.

Logistic regression analysis showed that only MPV has significant positive predictive correlation with adverse outcomes in ACS, whereas the correlation with other indices is insignificant. Our results are similar with the findings of Tomasz Rechcinski, *et al*¹⁶. Platelet volume indices particularly MPV are indicators of the

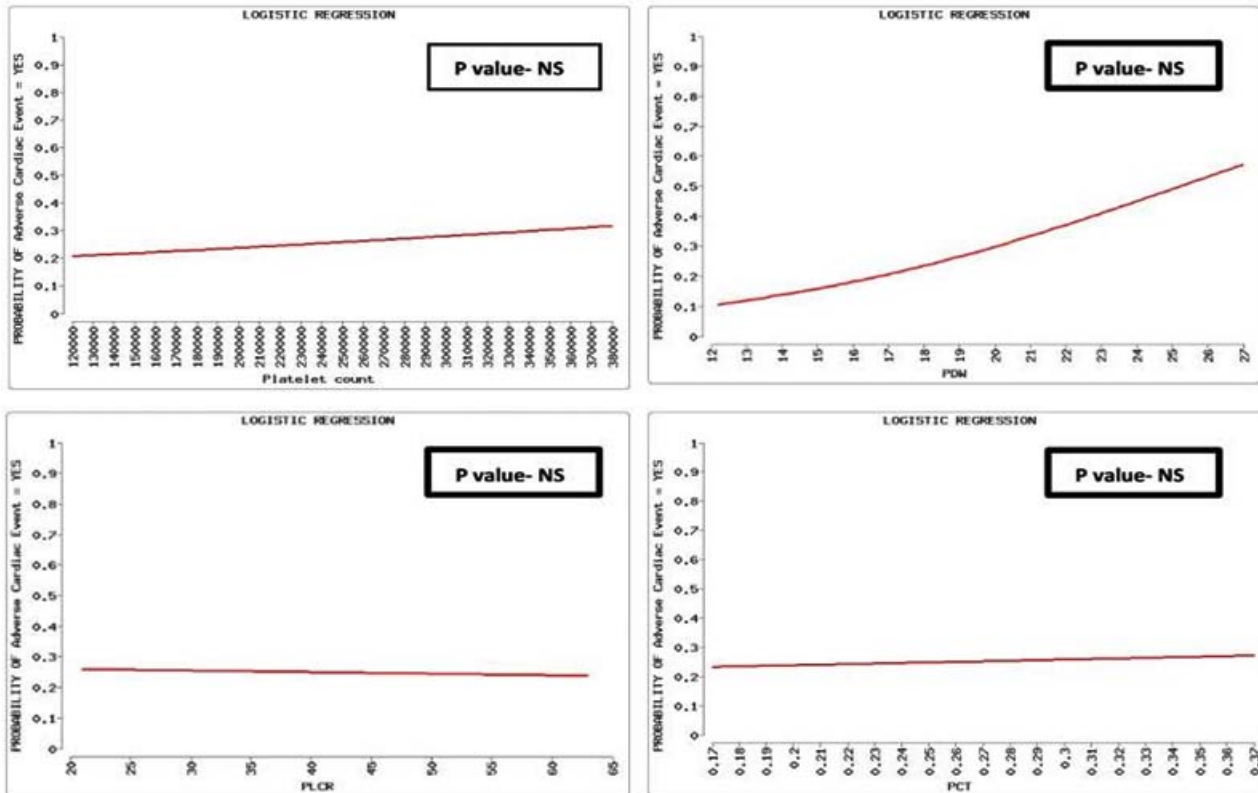


Fig 3 — Multiple logistic regression analysis showing insignificant correlation between probability of adverse cardiac events & platelet count, PDW, PLCR, PCT

degree of damage already done and that these markers maintain their strength and predictive value for a long time. Large platelets are metabolically and enzymatically more active than small platelets and produce more thromboxane A₂ which could also explain the significant correlation between mean platelet volumes and adverse cardiac outcomes among the ACS patients.

The measured indices in our study is in tune with previous studies, with has shown that MPV can be used in diagnostic workup because of their prognostic value^{17,18}.

LIMITATION

Our study has several limitations. Firstly, our sample size was small, hence, it is not empowered to draw a definite conclusion. Second, as it was observational study, strength of our conclusions can be challenged. Finally, as we did not follow up our patients with coronary angiogram, the atherosclerotic burden and the culprit lesion could not be ascertained.

CONCLUSION

This study depicts that hs-CRP level and MPV are simple, yet reliable indicators for adverse cardiac outcomes in ACS patients. Inflammatory markers like hs-CRP, an easily available test has shown robust correlation with clinical events in such patients. Likewise Mean Platelet Volume (MPV) is useful marker to predict the adverse clinical events in the entire spectrum of ACS patients. Similar studies done on larger group of patients, followed up for a longer duration can offer better understanding on the relationship of platelet volume indices and hs-CRP in acute coronary patients and their impact on outcome.

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