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The Mean Platelet Volume in the Prognosis of Coronary Artery Disease Severity and Risk Stratification of Acute Coronary Syndromes

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ABSTRACT

Introduction: Platelets play a crucial role in thrombotic episodes. Mean Platelet Volume (MPV) is the primary indicator of platelet's activation; its measurement is easy and time-effective. **Aim:** We tested the hypothesis that MPV is correlated with SYNTAX score in patients that suffered from an Acute Coronary Syndrome (ACS). **Material and Methods:** One hundred and four (104) patients (79 male–25 female, mean age 64.2±11.1 years), who were hospitalized for an ACS and underwent coronary angiography, were included in the study. Syntax score, as an indicator of the severity of coronary artery disease (CAD), was calculated. We tried to investigate the correlation between the first measured MPV, CRP, Creatinine and high sensitivity Troponin with the Syntax score of the patient and the association of MPV and a possible Major Advanced Cardiac Event (MACE) during hospitalization. **Results:** The patients were divided into four groups according to the SYNTAX score: Group A (SYNTAX score: 0, n=12), group B: Mild CAD (SYNTAX score: 1–22, n=68), group C: Moderate CAD (SYNTAX score: 23–32, n=12), and group D: Severe CAD (SYNTAX score: ≥ 33, n=12). Four patients (3.8%) developed a MACE during their hospitalization. MPV was significantly correlated to Syntax score (r=0.658, p<0.001) and was found to be an independent predictor factor of MACE with HR=6.8 (95% Confidence Interval 1.46-33.36). The cut-off value of MPV was 7.5 with a sensitivity of 98% and a specificity of 30.8%. **Conclusion:** We determined a positive correlation between MPV and Syntax score, transforming this simple test in a possible factor of risk stratification in ACS.

Keywords: Mean platelet volume, Syntax score, acute coronary syndrome, prognosis.

1. INTRODUCTION

Acute Coronary Syndromes (ACS) is a highly prevalent group of emergency diseases, with a high risk of mortality (1). They include ST- elevation Myocardial Infarction (STEMI), non ST-Elevation Myocardial Infarction (NSTEMI) and Unstable Angina (UA) (2). Albeit the pathophysiological mechanism may differ, inflammation plays a vital role in the development of atherosclerotic plaques and the subsequent rupture and thrombosis (3).

Furthermore, platelets and their activation is the cornerstone of understanding the pathogenesis of ACS (4). Not only are platelets essential for the thrombotic vascular occlusion at the ruptured atherosclerotic plaque but also they contribute to the obstruction and impairment of coronary micro circulation (5). Platelet activation is a critical factor in the creation and evolution of atherothrombosis (6).

Risk stratification plays a crucial role in the management of patients with ACS (7). Patients estimated to be at higher risk may be managed with earlier and more aggressive treatment, whereas those with lower risk may be managed with less intensive treatment (8). Many biomarkers have been evaluated, and various scores have been created for risk stratification of ACS patients (9).

Mean Platelet Volume (MPV) is an easily marked biomarker of platelet activity (10). It is elevated in patients with ACS and its role, as a useful biomarker for risk stratification in ACS patients, has been studied with various results (11). MPV was found to be a strong, independent predictor of impaired reperfusion and 6-months mortality, not only in STEMI patients (12, 13), but also in NSTEMI patients (14, 15). Moreover, MPV

was correlated with reduced antiplatelet responsiveness (16) and seems to be an independent factor for slow coronary flow (17).

MPV relationship with the angiographic severity has been studied, and a positive correlation seems to be established (18, 19), although there are some concerns about several pitfalls in the methodology of using MPV as a reliable clinical marker (20).

We tested the hypothesis that MPV is correlated with the angiographic severity of ACS patients and the in-hospital mortality and the incidence of major cardiac adverse events (MACE) of these patients in our experience.

2. AIM

We tested the hypothesis that MPV is correlated with SYNTAX score in patients that suffered from an Acute Coronary Syndrome (ACS).

3. MATERIAL AND METHODS

One hundred four consecutive patients that suffered from an ACS were treated in the Coronary Unit of the Cardiology Department of General Hospital of Veroia and underwent coronary angiography were included in the study from November 2017 to September 2018. ACS was defined according to the Third Universal Definition of Myocardial Infarction as a combination of chest pain, electrocardiographic changes, and elevation of biomarkers (21). Exclusion criteria were: Cardiomyopathy, previous revascularization procedure, and any history of platelets disorder.

Selective coronary angiography was performed by the radial approach using the Judkins technique and Siemens angiographic system. Multiple views were obtained, with visualization of the left anterior descending (LAD) and left circumflex coronary artery in at least four projections, and the right coronary artery in at least two projections.

Data were analyzed offline, and the severity of Coronary Artery Disease was evaluated by calculating the SYNTAX score (22). This is derived from a computer algorithm consisting of 12 central questions. The total SYNTAX score is composed of the individual scores for each separate lesion with a diameter stenosis of ≥ 50% in a vessel of ≥ 1.5 mm in diameter by visual assessment (23). It has been used and validated in many populations, and its usefulness has been shown in many studies (24).

The patients were divided into four groups according to the SYNTAX score: Group A (SYNTAX score: 0, n=12), group B: Mild CAD (SYNTAX score: 1–22, n=68), group C: Moderate CAD (SYNTAX score: 23–32, n=12), and group D: Severe CAD (SYNTAX score: ≥ 33, n=12).

MPV, high sensitivity Troponin (hs-cTnT) and creatinine (25) were measured in blood samples obtained in the morning in all patients by admission.

Furthermore, a complete medical history was obtained from every patient.

Primary endpoints were MACE (Major Adverse Cardiac Events), defined as death, stent thrombosis, reinfarction, cardiogenic shock, sustained ventricular tachycardia, ventricular fibrillation, angina, symptoms of left ventricular dysfunction and stroke (26).

Statistical analysis

Initially, an estimation of the normality of the distribution of quantitative variables was made using the Shapiro Wilks test (data in each group < 50 patients). Continuous variables (quantitative) were recorded with the mean ± SD values and the categorical variables (qualitative) as a percentage (%). Comparison of the quantitative variables was performed using the non parametric test Kruskall Wallis. The exact significance level of each examination t was estimated by the Bonferroni method. Comparison of the qualitative variables was made using the χ^2 test of Pearson. In addition, the univariate association between MPV and Syntax score was examined using Pearson's coefficient. Then the univariate relationship of the variables with the combined endpoint (MACE–major complications as reinfarction, cardiogenic shock, sustained ventricular tachycardia, ventricular fibrillation, angina, symptoms of left ventricular dysfunction) was examined and variables showed a significant association were included in a multivariate model analysis (Binary logistic analysis model), where the prognostic value of MPV as an independent factor for adverse events was examined. It was expressed as Odds Ratio (OR) and 95% confidence interval (95% CI). Then, ROC (Receiver–Operations Characteristic) curves were created, in order to identify and graphically display the cutoff values, for the predictive role of MPV. The results were presented as Area Under the Curve (AUC) and the best cut off values assigned the points of higher sensitivity and specificity (Youden's index). Probability $p < 0.05$ was considered significant.

The study protocol was approved by the Scientific Committee of the Hospital (Number 65/2017) according

	Overall n=104	Group A n=12	Group B n=68	Group C n=12	Group D n=12	p
Syntax Score	14,6±13	0	1-22	23-32	≥33	
Age	64.2±11.1	63.16±12.4	63.29±11.	65±8.55	69.6±11.1	0.374
Gender (Male) n (%)	79 (76)	4 (33.3)	53 (77.9)	11 (91.7)	11 (91.7)	0.040
ACS						
STEMI n (%)	34 (32.7)	0	28 (41.1)	5 (41.7)	1 (8.3)	0.007
NSTEMI n (%)	31 (29.8)	2 (16.7)	16 (23.5)	4 (33.3)	9 (75)	0.160
UA n (%)	39 (37,5)	10 (83.3)	24 (35.3)	3 (25)	2 (16.7)	0.154
MPV	10.7±1.15	9.57±1.1	10.6±0.89	11.2±0.85	12.56±0.68	<0.001
hs-cTn	1.4±2.6	0.12±0.34	1.38±2.5	2.8±4.08	1.54±2.45	0.03
CRP	1.4±2.9	0.36±0.36	1.74±3.32	0.56±0.66	2.05±2.93	0.170
Creatinine	1.02±0.33	0.88±0.21	1±0.25	1.27±0.64	1.07±0.25	0.3
MACE	4 (3.8)	0	1 (1.5)	1 (8.3)	2 (16.7)	0.034

Table 1. Demographic Data of patients. p<0.001 is considered significant.

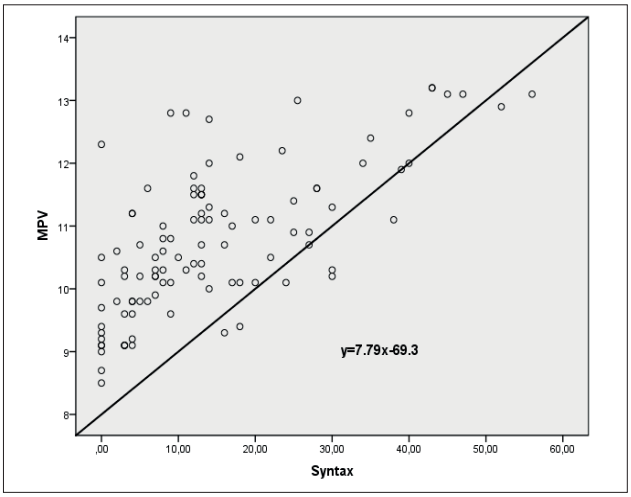

Figure 1. Correlation of Syntax score and MPV.

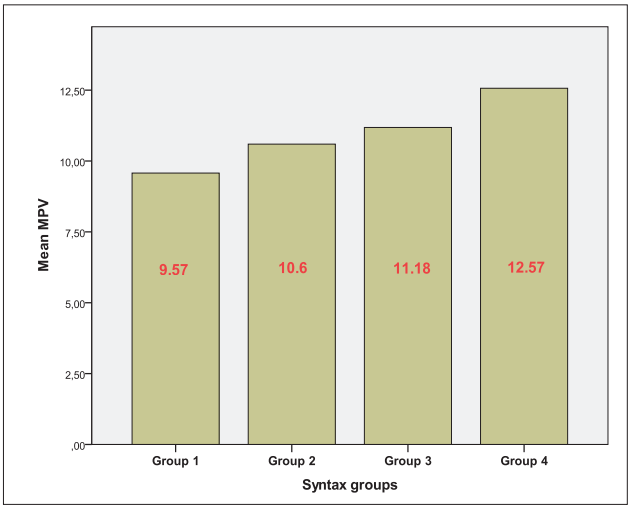

Figure 2. Mean MPV in relation with groups of patients sorted by SYNTAX score.

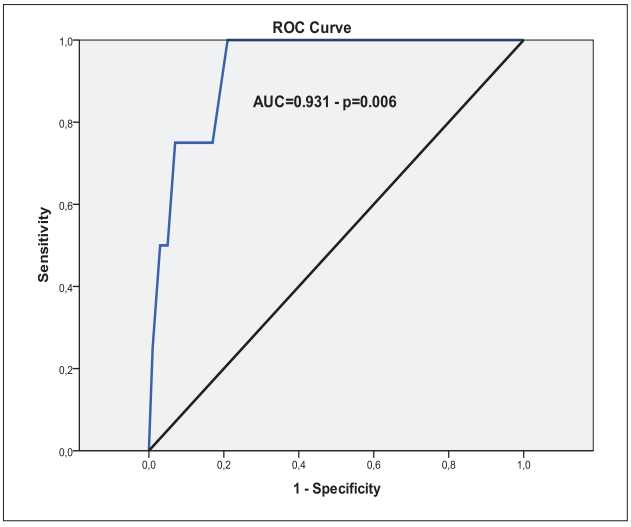

Figure 3. Characteristic ROC curves for MPV and adverse outcomes during hospitalization AUC: Area Under the Curve

to the Helsinki Declaration, and written consent was obtained from all patients. The statistical analysis was made using the SPSS.19 for Windows statistical package.

4. RESULTS

The baseline clinical and demographic data of all patients sorting by Syntax score groups are described in table 1. Patients with high Syntax score had higher MPV. This difference was sustained after the adjustment according to the Bonferroni test.

Syntax score and MPV were significantly correlated, ($r=0.658$, $p<0.001$) as is shown in Figure 1. Figure 2 illustrates the relation of Mean MPV with Syntax score groups as were defined above.

During the follow-up period, there were four events of MACE (3.8%), one event of cardiac mortality, two events of nonfatal reinfarction and one event of cardiac failure. Concerning MACE a binary logistic regression model was computed, and OR for MVP was 6.8 (95% Confidence Interval 1.46-33.36).

Figure 3 shows the ROC curve presenting the association between MPV and the occurrence of adverse events during hospitalization (AUC=0.931, p=0.004). Analyzed the ROC curves a cut-off point of 7.5 for MPV was selected, which resulted in 98% sensitivity (95% CI, 85-100%) and 30.8% specificity (95% CI, 26.7-62.6%) for the occurrence of adverse effects during the hospitalization period.

5. DISCUSSION

The main findings of the study were: a) There is a strong association between MPV and Syntax score, b) The MPV is an independent predictor of MACE and c) The cut-off value was 7.5 with a sensitivity of 98% and a specificity of 30.8%.

MPV is a highly sensitive marker of platelets activity, and it could link the pathophysiology of diseases related to thrombosis and inflammation (27). Typically, MPV is 7.2-11.7 fL in healthy subjects (28). When platelet production is decreased, young platelets become bigger and more active, and MPV levels increase. Increased MPV indicates increased platelet diameter, which can be used as a marker of production rate and platelet activation (2). Concerning platelet function, MPV seems to be an appropriate biomarker to link hematologic indices with CAD (10).

MPV has been related to Diabetes Mellitus (30), Atrial Fibrillation (31), Heart Failure (32), and Cancer (33) among others. About CAD, a meta-analysis showed that MPV is associated with CAD, and it might be helpful in risk stratification in these patients (34). Many studies suggested that MPV could be an independent predictor factor of long-term outcomes after PCI (35-39). MPV cut-off values for predicting poor clinical outcomes in patients with unselected coronary artery disease treated via PCI are 8.00 to 9.25 fL (40).

MPV and the severity of CAD have been positively correlated in some studies, either in an emergency setting, such as in patients undergoing primary PCI (41-43) or in patients suffering from stable CAD (41-46). In the majority of studies, the SYNTAX score was used as a measurement of the severity of CAD (22). Although the SYNTAX score has been validated in many populations, there is some controversy about its reproducibility,

which seems to be moderate (47). In our study, we used a team of experienced cardiologists to calculate the SYNTAX score, with low inter-observer variability.

While the use of MPV as a universal predictor of disease severity seems enticing, there is some methodological bias in its clinical use, and especially concerning MPV cut-off values (48). Although MPV is routinely reported and does not require professional interpretation, there is evidence that its accuracy and reliability reduces after 4 hours of blood storage (35). Moreover, there is a need for further research on whether increased platelet size is the cause or consequence of thrombosis (49).

As far as our study is concerned, the small population might be a severe drawback raising concerns about accurate results and bias. According to our findings, MPV was significantly correlated to Syntax score, and it might be an independent predictive factor of MACE during hospitalization.

Limitations: The study is retrospective and observational with a small sample. MPV was calculated via the methods of our hospital laboratory which is much different from the conditions of other centers or "real world." As a result, a new study should be performed to assure the results.

6. CONCLUSION

MPV seems to be a highly promising biomarker for risk stratification of ACS patients, even though more research on its exact pathophysiological meaning is needed. Finally, there is a need for more extensive studies so that MPV cut-off values could be assured.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution:** Ioannis Vogiatzis: led the writing of the protocol and the manuscript, carried out literature searches, conducted the analysis, paper preparation and paper editing. Antonios Samaras: provided all the interventional procedures, clinical experience, contributed to the paper preparation and editing and approved the final manuscript. Savvas Grigoriadis: provided clinical experience, carried out literature search, contributed to the paper preparation and editing. Evangelos Sdogkos: provided clinical experience and contributed to the paper preparation and editing. Kostantinos Koutsampasopoulos: provided clinical experience and contributed to the paper preparation and editing. Ioannis Bostanitis: provided interventional procedures, clinical experience, contributed to the paper preparation and editing and approved the final manuscript.
- **Conflicts of interest:** The authors report no relationships that could be construed as a conflict of interest.

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