



# A New Score for Determining Thrombus Burden in STEMI Patients: The MAPH Score

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## Abstract

**Aim:** to investigate whether the MAPH score, which is a new score that combines blood viscosity biomarkers such as mean platelet volume (MPV), total protein and hematocrit, can be used to predict thrombus burden in ST-segment elevation myocardial infarction (STEMI) patients.

**Methods:** A total of 473 consecutive patients with STEMI were included in the study. Intracoronary tirofiban/abciximab infusion was applied to patients with thrombus load  $\geq 3$  and these patients ( $n = 71$ ) were defined as the patient group with high thrombus load. MPV, age, hematocrit and total protein values of the patients were recorded. High shear rate (HSR) and low shear rate (LSR) were calculated from total protein and hematocrit values. Cut-off values were determined for high thrombus load by using Youden index, and score was determined as 0 or 1 according to cut-offs. The sum of the scores was calculated as the MAPH score.

**Results:** The mean age of the patients included in the study was  $59.6 \pm 12.6$  ( $n = 354$  male, 74.8%). There was no difference between the groups in terms of gender, HT and DM ( $P = .127$ ,  $P = .402$  and  $P = .576$ , respectively). In the group with high thrombus load; total protein, MPV and hematocrit values were higher ( $P < .001$ ,  $P = .001$  and  $P = .03$ , respectively). Comparison of receiver operating characteristic (ROC) curve analysis revealed that the MAPH score had better performance in predicting higher thrombus load than both other self-containing parameters and HSR and LSR.

**Conclusion:** The MAPH score may be a new score that can be used to determine thrombus burden in STEMI patients.

## Keywords

ST-segment elevation myocardial infarction, MAPH score, thrombus burden

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## Introduction

Acute coronary syndrome is a condition that requires immediate intervention as a result of partial or total occlusion of the coronary arteries.<sup>1</sup> In ST-segment elevation myocardial infarction (STEMI), there is complete obstruction due to intracoronary thrombosis.<sup>2</sup> The increase in blood viscosity, which is one of the mechanisms responsible for the etiopathogenesis of thrombus formation, has been discussed in many studies and it has been shown that many parameters are associated with the increase in viscosity.<sup>3-7</sup> High shear rate (HSR) and low shear

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rate (LSR) are the most studied biomarkers calculated using total protein and hematocrit values.<sup>8,9</sup> It has been stated in recent studies that mean platelet volume (MPV) elevation is directly proportional to the tendency to thrombosis.<sup>10–13</sup> In the study conducted by Cetin et al. in which a new score they named PALSE was revealed, it is emphasized that parameters such as age and total protein are important in demonstrating thromboembolism in patients with atrial fibrillation ablation plan.<sup>14</sup>

The aim of this study is to investigate the usability of the MAPH score, which we developed as a new score, in determining the thrombus burden in STEMI patients and the patients who may need additional treatment such as tirofiban/abciximab.

## Material and Methods

### Study Population, Collection of Blood Samples and Laboratory Measurement

Four hundred seventy three patients with ST-elevation myocardial infarction that had been treated with primary percutaneous coronary intervention in our hospital between January 2021 and July 2021 were included in this retrospective cohort study. The patients who had thrombophilia, COVID-19 infection or vaccination history in the last 2 months or missing laboratory results were excluded from the study. The demographic and medical characteristics of the patients were obtained from their files and routine laboratory parameters were examined. Considering that intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are not available in our clinic and their use is not common in routine or emergency cases, thrombus grade was performed using angiographic images of the patients. The images were evaluated by two different cardiologists working in the same center where the patients were processed and who were blinded to the patient information. Thrombus grade was taken as the average of the ratings made by two cardiologists. Intra and interobserver variability was calculated using Cohen's kappa value. Patients with a thrombus grade <3 were included in the low thrombus grade group and those with ≥3 thrombus grade were included in the high thrombus grade group. Thrombus load were determined according to thrombolysis in myocardial infarction thrombus scale.<sup>15</sup>

The patients in both groups have taken acetylsalicylic acid, P2Y12 inhibitors loading and maintenance, and UFH treatment according to weight. During the CCU follow-ups, beta blocker, ACEI/ARB and diuretic (furosemide or spironolactone) if necessary were administered to all patients who did not have any contraindications. In addition to this standard treatment, in the group with high thrombus load, a 24-h infusion of GP2b3a receptor antagonist was given as a push-up dose after imaging in the angiography laboratory.

Hypertension (HT) was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or current use of antihypertensive medication. DM was defined as fasting serum glucose ≥126 mg/dL, hemoglobin A1c ≥6.5%, or the use of blood glucose lowering agents.

Blood samples were collected, and the laboratory measurements of serum values of hemotocrit, total protein, MPV, CRP and albumin, lipid parameters, liver and kidney function tests were performed and analyzed with appropriate kits and HSR and LSR were calculated using serum total protein and hemotocrit levels for all patients. The predictive cut-off values of MPV, total protein, age and hemotocrit for high thrombus grade were determined using the Youden index. The values higher from the cut-off were considered as a score of 1 and MAPH score was calculated as the sum score of 0 or 1 by the cut-off in each ratio.

The study was approved by the local Clinical Research Ethics Committee of our hospital (no:1590, date: 14.10.2021). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

### Statistical Analysis

Kolmogorov-Smirnov test was used to determine whether variables were homogeneously distributed. Continuous variables were expressed as mean ± standard deviation or lower and upper bound and compared using Student's t-test and Kruskal-Wallis test for variables without normal distribution. Categorical variables were presented as total number and percentages and compared using the chi-square test and correlations between variables with Spearman's correlation. Receiver operating characteristic (ROC) curve analysis and Youden index were performed to demonstrate the sensitivity and specificity of MPV, age, total protein and hematocrit. levels. Pairwise comparison of ROC curve analysis was used to compare the discriminative power of variables for high thrombus grade. Intra and interobserver variability was calculated using Cohen's kappa value. A two-tailed *P*-value of <.05 was considered as statistically significant and 95% confidence interval (95% CI) was presented for all OR. All statistical analyses were performed using SPSS (Inc. Released 2007, SPSS for Windows, Ver 16.0, Chicago, SPSS Inc.) and MedCalc v19.6.1.

## Results

The mean age of the patients was 59.6 ± 12.6 years and 354 (74.8%) of them were male. The group which the patients had high thrombus grade consisted of 71 patients (mean age 63.1 ± 12.0 years, n = 48 [67.6%] male) and the control group consisted of 402 patients (mean age 59.2 ± 12.5 years, n = 306 [76.1%] male). The baseline characteristics and laboratory results of the groups are summarized in Table 1. The patients in both groups were similar in terms of gender and the frequency of HT and DM (*P* = .127, *P* = .402 and *P* = .576, respectively) and the patients with higher thrombus grade were older (*P* = .015). When the groups were compared in terms of laboratory results; total protein, MPV, hematocrit levels of high thrombus grade group were higher and the difference was statistically significant between groups (*P* < .001, *P* = .001 and *P* = .03,

**Table 1.** The baseline characteristics and laboratory results of the groups.

Variables	High thrombus grade group (n = 71)	Low thrombus grade group (n = 402)	P
Age, years	63.1 ± 12.0	59.2 ± 12.5	.0015*
Gender, male (%)	48(67.6)	306(76.1)	.0127
HT, n (%)	48(67.6)	241(59.9)	.402
DM, n (%)	45(63.3)	220(54.7)	.576
Chronic kidney disease, n (%)	2(2.8)	18(4.4)	.665
COPD, n (%)	8(11.2)	50(12.4)	.782
Smoking, n (%)	42(59.1)	243(60.4)	.837
Malignancy, n (%)	1(1.4)	4(0.9)	.634
Glucose, mg/dL	159.1 ± 90.3	150.6 ± 64.4	.858
Urea, mg/dL	35.2 ± 14.7	36.2 ± 19.4	.665
Creatinine, mg/dL	0.6 ± 0.2	0.7 ± 0.1	.166
LDL, mg/dL	128.5 ± 35.0	135.1 ± 39.1	.207
HDL, mg/dL	43.1 ± 9.8	42.5 ± 12.0	.705
Total cholesterol, mg/dL	194.3 ± 42.6	203.7 ± 50.8	.180
Triglyceride, mg/dL	163.8 ± 108.0	170.2 ± 114.7	.687
HGB, gr/dL	12.6 ± 1.9	12.9 ± 1.6	.307
WBC, 10 <sup>3</sup> /mL	12.7 ± 3.8	12.0 ± 3.2	.158
Platelets, 10 <sup>3</sup> /mL	247.7 ± 82.0	240.8 ± 65.4	.432
Hematocrit, %	45.5 ± 4.7	43.2 ± 4.6	.030*
MPV, fL	8.9 ± 1.0	8.5 ± 0.9	.001*
Total protein, g/L	70.6 ± 5.2	63.7 ± 5.6	.000*
Albumin, g/L	37.7 ± 4.7	37.9 ± 3.7	.859
Troponin, ng/L	8396.2 ± 870.3	6104.5 ± 847.7	.097
CK-MB, µg/L	30.2 ± 12.7	27.9 ± 13.6	.284
MAPH score	2.6 ± 0.9	1.3 ± 0.8	.000*
HSR	1.4 ± 1.3	1.3 ± 1.1	.002*
LSR	25.1 ± 2.8	23.6 ± 2.8	.004*
CAD severity only IRA, n (%)	30 (42)	144 (35)	.753
IRA + noncritical lesion in other coronary artery, n (%)	22 (32)	165 (41)	
IRA + critical lesion in other coronary artery, n (%)	19 (26)	93 (24)	
Door to balloon time, min	34.3 ± 7.3	33.3 ± 8.7	.498

HT: hypertension; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; LDL: low density lipoprotein cholesterol; HDL: high density lipoprotein cholesterol; HGB: hemoglobin; WBC: white blood cell count; MPV: mean platelet volume; CK-MB: creatine kinase-MB; MAPH: MPV + age + total protein + hematocrit; HSR: high shear rate; LSR: low shear rate.

respectively). HSR, LSR and MAPH scores were significantly higher in the high thrombus grade group than in the control group.

When the angiographic images were evaluated, the intraobserver variabilities for thrombus grade were 0.940 (0.905-0.975) and 0.893 (0.846-0.940), respectively and the intraobserver variability was 0.846 (0.792-0.900). It was observed that 4.2% of the patients included in the study were thrombus grade 5, 5.2% grade 4, 16.9% grade 3, 21.6% grade 2, and 23.5% grade 1 thrombus. The mean thrombus grade value in the high thrombus grade group was 3.3 ± 0.8, while

**Table 2.** Correlation analysis of variables with thrombus grade.

Variables	Rho, P value
Thrombus grade-total protein	0.496, .000
Thrombus grade-hematocrit	0.087, .204
Thrombus grade-MPV	0.103, .133
Thrombus grade-MAPH score	0.710 to 0.000
Thrombus grade-age	0.124, .071
Thrombus grade-HSR	0.270, .007
Thrombus grade-LSR	0.269, .007

MPV: mean platelet volume; MAPH: MPV + age + total protein + hematocrit; HSR: high shear rate; LSR: low shear rate

the mean value in the control group was 0.8 ± 0.1 ( $P < .001$ ). The correlation analysis showed that the most significant correlation with thrombus burden was with the MAPH score (Table 2).

MPV, total protein, hematocrit and age cut-off values that predict high thrombus load were calculated according to ROC analysis and Youden index; for age >51 years AUC:0.574, sensitivity:91%, specificity:28.9%; for hematocrit >45.9% AUC:0.564, sensitivity 53.2%, specificity 61.6%; for MPV >9.2 fL AUC:0.621, sensitivity 40.8%, specificity 78.5%; for total protein >67 g/L AUC:0.774, sensitivity 61.9%, specificity 85.1%, and for MAPH score >2 AUC:0.837, sensitivity 56.3%, specificity 92.2% were determined as cut-off values. (Figure 1). Pairwise comparison of ROC curve analysis concluded that the MAPH score had better performance to both other self-containing parameters as well as HSR and LSR values for predicting high thrombus load (Table 3- Figure 2).

## Discussion

In the present study, the high thrombus grade in patients with STEMI was associated with older age, higher hematocrit, total protein and MPV levels. The MAPH score consisting of these all four parameters was also higher in these patients and the best correlation was found between higher thrombus grade and MAPH score. Furthermore, MAPH score's performance to predict thrombus load was better than the others alone.

Blood viscosity has a significant effect on the formation of intravascular clots and is affected by a number of factors in the blood as hematocrit, erythrocyte and platelet aggregation, the amount of protein and erythrocyte deformability.<sup>16,17</sup> Coronary thrombus load is an important factor affecting the success of percutaneous coronary procedure (PCI). It also has a serious importance on the prognosis after MI (in-hospital death, Q-wave myocardial infarction, urgent or emergent coronary artery bypass surgery and stroke).<sup>18-20</sup> MPV elevation, which is a marker of platelet function, is associated with an increased risk of cardiovascular diseases such as myocardial infarction, stroke and transient ischemic attack. In their study, Han et al. showed that the incidence of stroke and coronary artery disease was higher in the group with MPV >8 fL.<sup>21</sup> Vizioli et al. predicted that the MPV value should not be

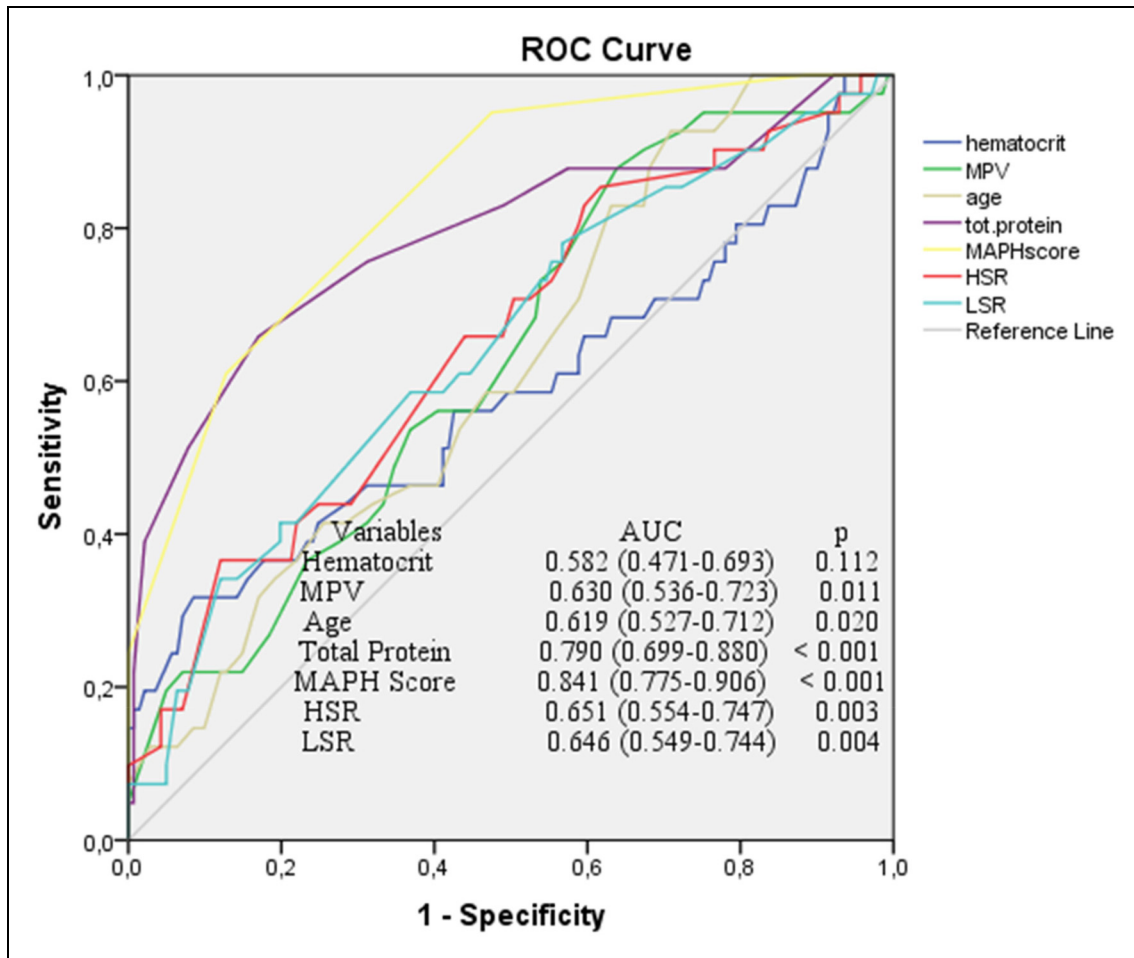


Figure 1. ROC curve analysis of variables.

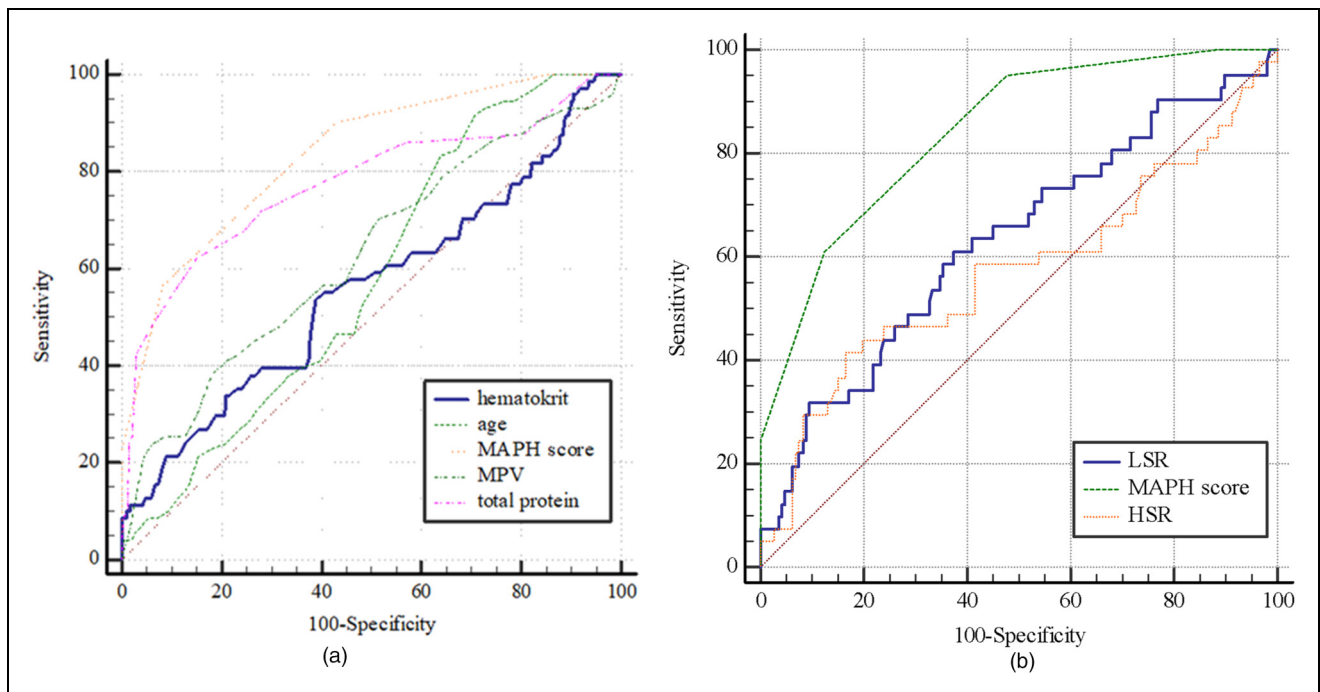
Table 3. Pairwise comparison of ROC curve analysis.

	Difference between AUC	CI 95%	Z statistics-p value
<b>Model I</b>			
Age-hematocrit	0.0217	-0.0760 to 0.119	0.435-.663
Age-MPV	0.0456	-0.0515 to 0.143	0.921-.357
Age-total protein	0.194	0.0960 to 0.292	3.882-.0001
Age-MAPH score	0.255	0.180 to 0.331	6.621-<.0001
Hematocrit-MPV	0.0673	-0.0423 to 0.177	1.204-.228
Hematocrit-total protein	0.216	0.123 to 0.308	4.565-<.0001
Hematocrit-MAPH score	0.277	0.205 to 0.349	7.518-<.0001
MPV-MAPH score	0.210	0.130 to 0.290	5.151-<.0001
MPV-total protein	0.148	0.0454 to 0.251	2.825-.0047
MAPH score-total protein	0.061	0.00424 to 0.119	2.105-.0353
<b>Model II</b>			
HSR-LSR	0.0603	-0.0524 to 0.173	1.048-.294
HSR-MAPH score	0.272	0.171 to 0.373	5.293-<.0001
LSR-MAPH score	0.212	0.108 to 0.316	3.986-.0001

ROC: receiver operating characteristic; MPV: mean platelet volume; MAPH: MPV + age + total protein + hematocrit; HSR: high shear rate; LSR: low shear rate

considered insignificant as it affects prognosis in MI and stroke.<sup>22</sup> In our study, in parallel with these data, we determined that the MPV cut-off value of 9.2 fL may be an indicator of increased thrombus burden in STEMI patients.

Advanced age, where the age of 65 is often considered the limit, has an increased risk for all thromboembolic events.<sup>23,24</sup> In this study, it was determined that the thrombus load was higher in people over 51 years of age. Such a result



**Figure 2.** Pairwise comparison of variables for high thrombus grade A: comparison of MAPH score, age, hematocrit and total protein; B: comparison of MAPH score, HSR and LSR.

can be explained by the fact that the mean age of the patients included in the study was around 60 and the older population often presents with non-STEMI. In the study conducted with a new scoring system called the PALSE score, which was recently published, it was shown that the cut-off value of 60 years is distinctive in predicting thromboembolic conditions such as spontaneous echo contrast or the presence of left atrial thrombus in patients with paroxysmal atrial fibrillation who are scheduled for cardioversion or catheter ablation.<sup>14</sup> These data give rise to the idea that the age limit can be lowered, as in our study.

The amount of total protein consisting of albumin, fibrinogen and globulins are the most important serum elements that regulate the plasma viscosity.<sup>25–28</sup> In the study of Briley et al. it was found that non-albumin serum proteins were higher in cases with the higher grade of SEC in patients with acute stroke.<sup>29</sup> Globulins, which consist of structures such as carrier protein and antibodies together with fibrinogen, constitute 40% of blood plasma proteins. While fibrinogen is involved in blood coagulation, proteins in the globulin structure carry lipids, elements such as iron and copper. In the study published by Zhang et al. in 2019, beta 2 microglobulin levels were shown to be correlated with the Gensini score in patients with acute coronary syndrome.<sup>30</sup> In another study we conducted, beta 2 microglobulin levels were positively correlated with Timi frame count in patients with slow coronary flow.<sup>31</sup> In our current study, we concluded that the total protein level is closely related to the classification of thrombus burden.

There are studies showing an increase in the risk of both venous and arterial thrombosis with higher hematocrit levels.<sup>32–35</sup> While

this increased risk is directly related in men, the same result is observed in both very low and very high hematocrit values in women. In the study of Sorlie et al. in the 1980s, it was shown that the increase in the hematocrit level was an independent risk factor for coronary artery disease and mortality.<sup>36</sup> Similarly, in another study conducted on this subject, high hematocrit values were found to be more effective in cardiovascular mortality in women under 65 years of age.<sup>37</sup>

HSR and LSR are parameters that are classically formulated from total protein and hematocrit values, which are indicators of serum viscosity and are used in many thrombogenic conditions, including no-reflow.<sup>38–40</sup> The MAPH score, which we created by adding age in addition to these parameters that have an effect on viscosity, showed a better performance in showing increased thrombus load in STEMI patients according to both self-forming hematocrit, age, total protein and MPV values, and compared to known biomarkers such as HSR and LSR.

## Conclusion

MAPH score is a new score that can determine the higher thrombus grade patients in STEMI and it can be used to select the ones who will be candidates for further therapies like glycoprotein 2b/3a antagonists.

## Limitations

The most important limitations of this study are it is retrospective and single center. Thrombus grade was calculated by evaluating only angiographic images. IVUS or OCT could not be used. Furthermore, MAPH score is a new biomarker and

needs cut-off points for each ratios. For the MAPH score to become widespread, multi-center, prospective studies with a large number of participants are needed. Finally, since patients STEMI were included in the study, the results should not be generated to all patients with atherosclerosis or non-STEMI.

### Author's Contribution

Conceptualization: OOA, M.Karadeniz, AY, Data curation: OOA, NYK, AY, Formal analysis: OAA, SA, AY, M.Karadeniz, Investigation: OOA, NYK, MD, FD, Methodology: OOA, NYK, SA, AY, Software: OOA, AY, MD, FD, Supervision: OOA, MD, M.Kaplangiray, Validation: OOA, MD, AY, Visualization: FD, M.Kaplangiray, SA, Writing-original draft: OOA, AY, M.Karadeniz, Writing-review-editing: OOA, MD, SA

### Declaration of Conflicting Interests

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### Ethical Approval


All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed consent

Informed consent was obtained from all individual participants included in the study.

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