Research Article

E Journal of Cardiovascular Medicine

EJCM 2023;11(2):70-77

DOI: 10.32596/ejcm.galenos.2023.2023-01-05

A Novel "Mean Platelet Volume-Age-Total Protein-Hematocrit (MAPH)" Score for Blood Viscosity: Predictive Capabilities for Coronary Slow-Flow Phenomenon

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Abstract

Objectives: The coronary slow-flow (CSF) phenomenon is a unique clinical angiographic entity defined as delayed coronary opacification without significant occlusive coronary artery disease. Although the etiology has not been clearly revealed, multifactorial causes that affect blood viscosity and thrombus formation are considered in the pathogenesis. We aim to investigate the usability of the novel Mean Platelet Volume-Age-Total Protein-Hematocrit (MAPH) score in predicting the CSF phenomenon.

Materials and Methods: A total of 266 patients, 98 diagnosed with CSF and 168 with normal flow, were included in this retrospective cohort study. Coronary angiography images of these patients and blood samples during their hospitalization were retrospectively evaluated by two experienced cardiologists. CSF diagnosis was made according to TIMI-flow and TIMI frame-rate criteria.

Results: In the analysis of the study, there were significant differences regarding age, smoking, hematocrit percentage, mean platelet volume, total protein, and MAPH score parameters (all p-values <0.01). In addition, multivariate analysis revealed that smoking, hematocrit percentage, total protein, and MAPH score parameters were independent predictors of the CSF

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Received: 07.01.2023 **Accepted:** 02.05.2023

Cite this article as: Akhan O, Kış M. A Novel "Mean Platelet Volume-Age-Total Protein-Hematocrit (MAPH)" Score for Blood Viscosity: Predictive Capabilities for Coronary Slow-Flow Phenomenon. EJCM 2023;11(2):70-77.

DOI: 10.32596/ejcm.galenos.2023.2023-01-05

phenomenon (all p-values <0.05). After the receiver operating characteristic curve analysis to show the discrimination of the MAPH score in the formation of CSF, the area under the curve was found to be 0.719 (95% confidence interval 0.656-0.781, p<0.001). With a cut-off 2.5, the MAPH score sensitivity is 43%, and the specificity is 86% for predicting CSF.

Conclusion: According to the findings of our study, we believe that the novel MAPH score can be used to predict blood viscosity in CSF. There is also a need for multicenter studies involving more patients on the subject. In the current situation, our study will contribute to the literature and can guide future studies.

Keywords: Coronary angiography, coronary slow flow, MAPH score, blood viscosity, microcirculation

Introduction

The coronary slow-flow (CSF) phenomenon was first described as a unique clinical condition in 1972. It was defined as delayed distal opacification of the coronary artery in the absence of significant coronary artery disease (CAD)[1]. Syndrome Y and primary or idiopathic CSF are also used for the nomenclature of this phenomenon[2,3]. CSF phenomenon should be differentiated from slow flow associated with coronary intervention, occlusive CAD, coronary ectasia, and coronary embolism. It is observed in approximately 1-7% of all angiographies[4-6]. Multifactorial causes such as microvascular abnormalities, endothelial dysfunction, increased markers of inflammation, and anatomical factors related to epicardial arteries are suspected for the pathogenesis[4,5,7]. CSF diagnosis can be based on TIMI flow classification and TIMI frame rate criteria[8]. The most common criteria are TIMI-2 current rating (for example, three or more pulses required to opacify the vessel) or a corrected frame count of more than 27[9]. Patients with CSF frequently present with chest pain; some may have acute coronary syndrome features such as ECG changes and troponin increases[5,7,10]. Studies show that CSF is also related to ventricular arrhythmias and ECG changes. It has also been reported that affected patients usually young males[11,12]. Patients with CSF diagnosis presenting with anginal complaints were not classified as having any chronic coronary syndrome in the 2019 ESC guideline, and there is no clear consensus report on prognosis and treatment in CSF[4,5,13].

Increased blood viscosity may be associated with acute coronary syndromes because it can cause thrombus formation[14-16]. It has been shown in studies that many parameters can accompany the increase in blood viscosity, and various scorings have been planned over these parameters to reveal this situation. As an example, the shear rate [includes total protein and hematocrit (Htc)], systemic immune-inflammation index (multiplying the value of platelet and neutrophil/lymphocyte ratio), and PALSE score (includes total protein levels, age, left atrium diameter, systolic pulmonary artery pressure, and left ventricular ejection fraction) can be listed[17-21]. Furthermore, in a recent study in the literature, it was stated that the Mean Platelet Volume-Age-Total Protein-Hematocrit (MAPH) score [includes age and blood viscosity biomarkers such as mean platelet volume (MPV), total protein, and Htc] could be used as a new score to reveal the thrombus burden in patients with ST-elevated myocardial infarction[22].

Based on the results of this study, this score could be used as an indicator of blood viscosity. Furthermore, the CSF phenomenon may also be associated with blood viscosity regarding literature and definition. Considering this information, we planned to investigate the usability of the novel MAPH score in predicting CSF.

Materials and Methods

Our study is a retrospective cohort study that included 98 patients who underwent coronary angiography in 2022 and were diagnosed with CSF. Coronary angiography images of these patients and blood samples taken routinely

at the time of the first admission to the hospital were retrospectively evaluated. In addition, hemogram-related parameters (Htc, MPV etc.), total protein, albumin, lipid parameters, and renal function tests were evaluated from blood samples. In addition, age, gender, body mass index, diabetes, hypertension, smoking history, medications used, heart rate and blood pressure values during hospitalization, and left ventricular ejection fraction values were also evaluated from the hospital files of the patients.

In the study, hypertension was defined as a systolic blood pressure of 140 mmHg and diastolic blood pressure of over 90 mmHg (with a mean of repeated measurements), the use of antihypertensive drugs, and diabetes mellitus as a fasting blood glucose of 126 and above, and the use of blood sugar-lowering medication. In addition, smoking was defined as patients who quit or continued to smoke and were included in the study.

Left ventricular ejection fraction values evaluated using Simpson's method were obtained from the hospital information system[23].

Angiography evaluations were performed by two experienced cardiologists based on cineangiography recordings. Absence of occlusive epicardial CAD (no stenosis of 40% or more), delayed distal vessel contrast opacification (TIMI-2 flow or greater than 27 corrected TIMI frame count), and these criteria are valid for at least one coronary vessel were used as the definition of CSF[8].

In addition, 168 control patients without CSF were included in the study as the control group. Exclusion criteria of the study patients who were admitted with acute coronary syndrome, hematologic, oncologic, or inflammatory diseases, cardiac surgery history, moderately advanced valve disease, cardiomyopathies, heart failure, renal failure, liver and thyroid dysfunction, connective tissue diseases, obstructive CAD, coronary angioplasty history, presence of coronary angiography images that are not suitable for evaluation, with insufficient image quality, no-reflow phenomenon, coronary embolism, coronary ectasia, and use of exogenous vasoconstrictor agents.

Receiver operating characteristic (ROC) curve analysis by the Youden index was used for each parameter of the MAPH score to determine a cut-off value. Values at and above the cut-off were scored as 1, values below the cut-off were scored as 0, and the total score was obtained by summing the scores for each parameter. The study was conducted with the approval of the Bilecik Şeyh Edebali University Non-Invasive Clinical Research Ethics Committee (approval no: E-10333602-050.01.04-034066, date: 09.11.2022).

Statistical Analysis

Statistical analysis was performed using SPSS Windows version 24.0. First, the normality of the distribution of continuous variables was checked using the Kolmogorov-Smirnov test. Then, mean ± standard deviation was presented for continuous variables and number and frequency for categorical variables. Student's t-test was used to compare continuous variables. Next, a comparative analysis of categorical variables was performed using Pearson’s chi-square and Fisher’s exact test. In line with the results of the ROC curve analysis, logistic regression analysis was performed to evaluate whether the MAPH score was an independent predictor of slow flow in stable CAD patients. Finally, ROC curve analysis was performed again for sensitivity and specificity and the statistics were completed. P-value <0.05 was considered significant.

Results

A total of 266 patients, 98 diagnosed with CSF, were included in the study. The clinical characteristics, demographic data, and medications used by the patients of the study population are shown in Table 1. The mean age and smoking percentages were higher in the CSF group than in the normal flow group (58.28±6.21 vs. 54.87±11.46, p=0.007; 26% vs. 11%, p=0.001, respectively). There was no significant difference between other clinical features, demographic data, and treatments used.

Considering the clinical laboratory characteristics of the study, Htc, MPV, and total protein values were significantly higher in the slow-flow group compared to the normal-flow group (p<0.001, p=0.005, and p<0.001,

Table 1. Baseline clinical features, demographic data, and medication

Variables	Coronary slow-flow (n=98)	Normal-flow (n=168)	Total (n=266)	p-value
Age (mean±SD)	58.28±6.21	54.87±11.46	56.12±9.98	0.007
Male gender, n (%)	55 (56)	77 (45)	132 (49)	0.105
BMI, kg/m^2 (mean±SD)	28.02±5.13	27.57±5.1	27.73±5.11	0.485
Heart rate, /min (mean±SD)	71.67±8.83	73.89±9.27	73.08±9.16	0.057
Blood pressure, mmHg (mean±SD)				
Systolic	130.24±18.28	127.90±13.97	128.76±15.70	0.241
Diastolic	72.17±11.17	73.23±9.78	72.84±10.31	0.420
Hypertension, n (%)	40 (40)	65 (38)	105 (39)	0.732
Diabetes mellitus, n (%)	10 (10)	22 (13)	32 (12)	0.484
Smoking, n (%)	26 (26)	19 (11)	**45 (16)**	**0.001**
Medication, n (%)				
Beta-blocker	24 (24)	42 (25)	66 (24)	0.926
ACE inhibitor	43 (43)	59 (35)	102 (38)	0.156
ARB	16 (16)	19 (11)	35 (13)	0.243
The Dhp CCB	15 (15)	28 (16)	43 (16)	0.771
Oral nitrate	6 (6)	12 (7)	18 (6)	0.749
Statin	22 (22)	42 (25)	64 (24)	0.639
Acetylsalicylic acid	23 (23)	43 (25)	66 (24)	0.699
Clopidogrel	3 (3)	12 (7)	15 (5)	0.164
Warfarin	13 (13)	16 (9)	29 (10)	0.345
NOAC	6 (6)	8 (4)	14 (5)	0.632

SD: Standard deviation, n: Number of patients, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, Dhp CCB: Dihydropyridine calcium channel blocker, NOAC: Novel oral anticoagulant, Group 1: Slow flow, Group 2: Normal flow

respectively), and no significant difference was observed in the findings other than the MAPH score and linked parameters (Htc, MPV and total protein) in univariate logistic regression (Table 2). Multivariate logistic regression analysis also showed that the MAPH score was an independent predictor of CSF [odds ratio: 0.615, 95% confidence interval (CI): 0.381-0.993, p=0.047]. Table 3 summarizes univariate and multivariate logistic regression analyses in predicting CSF.

After the ROC curve analysis to show the discrimination of the MAPH score in the formation of CSF, the area under the curve was found to be 0.719 (95% CI 0.656-0.781, p<0.001) (Figure 1). With a cut-off level of 2.5, the MAPH score sensitivity is 43%, and the specificity is 86% for the prediction of CSF (Table 4).

Discussion

Our study found statistical differences between the slow-flow and normal-flow groups in the univariate analysis regarding age, smoking, Htc percentage, MPV, total protein, and MAPH score parameters. In addition, multivariate analysis revealed that smoking, Htc percentage, total protein, and MAPH score parameters were independent predictors of the CSF phenomenon. Considering these findings, we can state that the MAPH score can be used to predict CSF, following the purpose of our study.

The CSF phenomenon is a clinical condition with specific angiographic diagnostic criteria, and many studies show that this situation is primarily seen in young smoking male patients[8,9-12]. In our study, similar to the

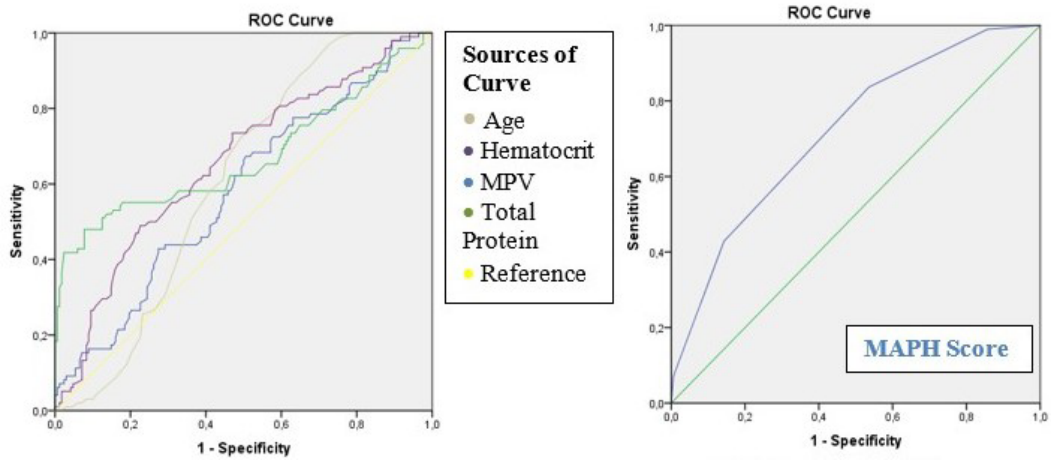

Figure 1. ROC curve analysis to show the discrimination of the MAPH score in the formation of CSF

ROC: Receiver operating characteristic, MAPH: Mean Platelet Volume-Age-Total Protein-Hematocrit, CSF: Coronary slow-flow, MPV: Mean platelet volume

Table 2. Clinical laboratory and left ventricular ejection fraction findings

Laboratory parameters	Coronary slow-flow (n=98)	Normal-flow (n=168)	Total (n=266)	p-value
WBC, x10³/L	9.07±3.54	8.48±2.33	8.70±2.84	0.104
Neutrophil, x10³/L	5.85±3.23	5.25±1.93	5.47±2.50	0.060
Lymphocyte, x10³/L	2.42±0.81	2.55±1.21	2.50±1.08	0.354
Hemoglobin, gr/dL	14.68±1.53	14.32±1.40	14.45±1.45	0.058
Hematocrit, %	44.80±4.15	42.40±4.53	43.29±4.54	<0.001
Platelet, x10³/L	284.91±42.96	279.05±72.41	281.21±63.15	0.467
MPV, fL	9.10±1.23	8.72±0.95	8.86±1.07	0.005
Glucose, mg/dL	105.33±22.34	111.78±32.43	109.40±29.24	0.083
Urea, mg/dL	31.38±9.33	33.26±10.94	32.57±10.40	0.157
Creatinine, mg/dL	0.82±0.16	0.85±0.19	0.84±0.18	0.151
Total protein, mg/dL	7.14±1.03	6.65±0.89	6.83±0.97	<0.001
Albumin, mg/dL	3.30±1.18	3.49±0.91	3.42±1.02	0.160
Total kolesterol, mg/dL	181.23±37.21	187.94±39.54	185.46±38.76	0.174
Triglyceride, mg/dL	178.90±84.72	167.16±90.48	171.46±88.42	0.297
HDL, mg/dL	39.98±8.84	49.56±48.14	46.03±38.87	0.052
LDL, mg/dL	107.06±30.88	110.91±32.87	109.5±32.15	0.347
MAPH score	2.33±0.85	1.54±0.92	1.83±0.97	<0.001
LVEF, % (mean±SD)	59.54±2.59	58.83±5.33	59.09±4.52	0.224

n: Number of patients, WBC: White blood cell, Htc: Hematocrit, MPV: Mean platelet volume, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, MAPH: Mean Platelet Volume-Age-Total Protein-Hematocrit, LVEF: Left ventricular ejection fraction, Group 1: Slow flow, Group 2: Normal flow

literature, the CSF phenomenon was detected primarily in young men and smokers.

Although the etiology has not been established, microvascular abnormalities, endothelial dysfunction, increased inflammatory markers, and anatomical factors may cause thrombus formation and increased blood viscosity, leading to the CSF phenomenon[4,5,7]. In a study conducted by Akpinar et al.[17] in 2014 investigating the relationship between complete blood count and CSF, it was shown that this might be a subclinical inflammation condition due to the increase in white blood cells and neutrophils. In this study, increases in red cell distribution

Table 3. Uni- and multivariate logistic regression analysis to predict coronary slow-flow

	Univariate logistic regression			Multivariate logistic regression		
Variables	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	0.965	0.940-0.991	0.008	0.987	0.955-1.020	0.432
Hematocrit	0.882	0.829-0.937	<0.001	0.913	0.847-0.985	0.018
MPV	0.715	0.560-0.913	0.007	0.810	0.596-1.102	0.179
Total protein	0.552	0.406-0.750	<0.001	0.665	0.450-0.984	0.041
MAPH score	0.377	0.272-0.521	<0.001	0.615	0.381-0.993	0.047
Smoking	0.353	0.183-0.680	0.002	0.433	0.209-0.899	0.025

MPV: Mean platelet volume, MAPH: Mean Platelet Volume-Age-Total Protein-Hematocrit, CI: Confidence interval, OR: Odds ratio

Table 4. Curve analysis to detect best cut-off values for the MAPH parameters and the MAPH score for differentiating normal and coronary slow-flow

Variable(s)	AUC	95% CI	Std. Error	Cut-off	Sens.	Spec.	Sign.
Age	0.608	0.542-0.675	0.034	57.5	58%	59%	0.003
Hematocrit	0.656	0.588-0.724	0.035	43.65	61%	62%	<0.001
MPV	0.580	0.510-0.651	0.036	8.72	55%	56%	0.029
Total protein	0.671	0.596-0.745	0.038	7.13	58%	57%	<0.001
MAPH Score	0.719	0.656-0.781	0.032	2.5	43%	86%	<0.001

AUC: Area under the curve, CI: Confidence interval, Std: Standart, MAPH: Mean Platelet Volume-Age-Total Protein-Hematocrit, Sens.: Sensitivity, Spec.: Specificity, Sign.: Significance

width and platelet cell distribution width were also shown in CSF, and it was shown that this could lead to an increase in cell deformability and microvascular blood flow resistance (p<0.001 and p=0.028, respectively). In this study, the MPV value was also significantly higher in the CSF group compared to the control group (MPV: 8.63±1.10, 8.22±0.83; respectively, p<0.001). However, no significant difference was found between Htc values (p=0.671)[13-17]. Similarly, our study's MPV values were significantly higher.

Cetin et al.[18], investigating the relationship between blood viscosity and CSF, concluded that blood viscosity calculated using total protein and Htc data is an independent predictor of CSF[19-23]. In our study, Htc and total protein values were significantly higher in the CSF group, similar to the previous study.

Senen et al.[24] showed a correlation between MPV (that is a platelet function marker) values and blood viscosity in CAD. In addition, another study also showed that an MPV value greater than 8 fL may be related to the increased incidence of CAD and stroke[25]. In our study, MPV values were significantly higher in the CSF group, and the laboratory values detected were 8 fL and above.

As mentioned above, blood viscosity may be related to age, Htc percentage, MPV, and total protein parameters. Furthermore, recent studies have stated that the MAPH score created using these parameters can reveal the thrombus burden in myocardial infarction with and without ST elevation[22,26].

We believe that the MAPH score, which is a new score and an indicator of blood viscosity, can be used as a predictor for CSF based on the literature and the results of our study. We can state that future multicenter studies that investigate the possible relationship between the MAPH score and CSF involving more patients and with subgroup analyses of smokers and nonsmokers with CSF to reveal the potential effects of smoking on the study results can be guided by our research.

Study Limitations

The limitations of our study can be listed as the retrospective nature of our research and the possible effects of interobserver variability, although standard diagnostic methods have been used. CSF is more common in smokers, but since smoking in this group is significantly different from the control group, it may affect the parameters in the MAPH score. The low sensitivity of the MAPH score predicting CSF can also be considered among the limitations of our study.

Conclusion

According to the findings of our study, we believe that the novel MAPH score can be used to predict blood viscosity in CSF. There is also a need for multicenter studies involving more patients on the subject.

Ethics

Ethics Committee Approval: The Bilecik Şeyh Edebali University Non-Invasive Clinical Research Ethics Committee approved this study (approval no: E-10333602-050.01.04-034066, date: 09.11.2022).

Informed Consent: Retrospective cohort study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Akhan O, Kış M, Design: Akhan O, Kış M, Data Collection and/or Processing: Akhan O, Kış M, Analysis and/or Interpretation: Akhan O, Kış M, Literature Search: Akhan O, Kış M, Writing: Akhan O.

Conflict of Interest: All authors declare that there is no conflict of interest.

Financial Disclosure: This research received no specific grants from any funding agency in the commercial or not-for-profit sectors.

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