Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1424294

J Med Palliat Care. 2024;5(1):48-56

Diagnostic performance of whole blood viscosity indices in predicting the presence and severity of coronary artery disease

Ahmet Kıvrak[1], Alp Yıldırım[2]

[1]Department of Cardiology, Ankara Etlik City Hospital, Ankara, Turkiye
[2]Department of Cardiology, Kırşehir Training and Research Hospital, Kırşehir, Turkiye

Cite this article as: Kıvrak A, Yıldırım A. Diagnostic performance of whole blood viscosity indices in predicting the presence and severity of coronary artery disease. *J Med Palliat Care*. 2024;5(1):48-56.

Received: 23.01.2024 ◆ **Accepted**: 17.02.2024 ◆ **Published**: 29.02.2024

ABSTRACT

Aims: Growing evidence suggests that blood viscosity plays a crucial role in both the development and acceleration of atherosclerosis. In this study, aimed to investigate the diagnostic performance of the mean platelet volume-age-total protein-hematocrit (MAPH) score, a new index for blood viscosity, in predicting the presence and severity of CAD in patients with suspected coronary artery disease (CAD).

Methods: We retrospectively evaluated 431 patients who underwent coronary angiography. SYNTAX score (SS) were divided into 3 groups; low group (<22), intermediate group (22-32) and, high group (≥32). Low (LSR) and and high (HSR) shear rates were derived using values of total protein and hematocrit. The MAPH score was calculated based on the threshold values of mean platelet volume, age, total protein, and hematocrit for predicting CAD.

Results: The median LSR (60.7 vs. 43.1, p<0.001), mean HSR (17.3±1.3 vs. 16.2±1.2, p<0.001), and mean MAPH score (2.7±0.8 vs. 1.6±0.5, p<0.001) were higher in the CAD group compared to the non-CAD group. These indices of blood viscosity were found to be higher in the intermediate-high SS group compared to the low SS group. The threshold value of MAPH score for predicting CAD was >2 (sensitivity=78.2%, specificity=70.0%). It also had a graduated threshold value (>3, sensitivity=71.1%, specificity=62.5%) in distinguishing intermediate-high SS than low SS groups. In predicting both the presence and severity of CAD, the MAPH score exhibited superior diagnostic performance relative to the levels of LSR and HSR.

Conclusion: In patients with suspected CAD, a gradual increase in the MAPH score demonstrated significant diagnostic performance in distinguishing both the presence and severity of CAD. In these patients, the MAPH score may serve as a potential screening tool and can be utilized for risk stratification.

Keywords: Blood viscosity, coronary artery disease, MAPH score, microcirculation, SYNTAX score

INTRODUCTION

Coronary artery disease (CAD) arises from intricate and prolonged atherosclerotic processes influenced by both environmental and genetic factors.[1] The onset and advancement of atherosclerosis are significantly influenced by traditional risk factors including hypertension, smoking, diabetes, obesity, inactive lifestyle, and age, as well as critical factors like lipid oxidation, leukocyte activation, platelet aggregation, and endothelial cell activation.[2,3] These risk factors involved in atherosclerosis can affect blood viscosity, which may lead to erythrocyte deformation.[4] Previous studies have demonstrated that any changes in hemorheological factors might have a pivotal role in the progression of atherosclerotic processes.[5,6]

Early atherosclerotic changes in coronary arteries are closely associated with variations in wall shear stress (WSS).[7] Plaque formation typically begins in areas of low WSS, and as the plaque develops, it changes the surrounding WSS landscape.[8] An experimental study on rabbits has demonstrated that arterial blockages lead to elevated levels of hematocrit (HCT) and total plasma protein (TP), which in turn influence the characteristics of blood flow and thereby impact WSS.[9] Blood viscosity, a determinant of shear stress, can be calculated using a validated equation based on HCT and TP levels for both low (LSR) and and high (HSR) shear rates.[6] On the other hand, advancing age and elevated mean platelet volume (MPV), crucial risk factors for atherosclerosis and CAD,[10,11] may influence both WSS and blood viscosity.[12,13] Therefore, a scoring system that incorporates these risk factors could exhibit superior diagnostic performance in predicting CAD.

Corresponding Author: Ahmet KIVRAK, a.kivrak89@gmail.com

It has been shown that the MAPH score, calculated using MPV, age, TP, and HCT, is a significant blood viscosity indicator in predicting the coronary slow-flow phenomenon (CSFP) and thrombus burden in patients undergoing coronary angiography (CAG).[14-16] However, we have not encountered any previous study that demonstrates its association with the presence and extent of CAD. We hypothesized that the MAPH score, which includes potential risk factors for CAD, could serve as a simple and readily accessible tool for predicting CAD before undergoing CAG. Hence, this study aimed to investigate the diagnostic performance of the MAPH score in predicting the presence and severity of CAD in patients undergoing CAG with a suspicion of CAD.

METHODS

Ethics

The study protocol received approval from the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.09.2022, Decision No: 146/03). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study was conducted on patients who underwent CAG between January 2018 and January 2022 in the Cardiology Department of Dışkapı Yıldırım Beyazıt Training and Research Hospital. Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Previous studies have reported a prevalence of CAD ranging from 30% to 52% in patients undergoing CAG due to suspected CAD.17,18 Accordingly, assuming a 45% prevalence of CAD in patients undergoing CAG, the necessary sample size was determined to be at least 281 patients with a 5% margin of error and 90% power.

Study Population

During the study period, 3456 patients over the age of 18 who underwent CAG following ischemia detected by myocardial perfusion scintigraphy were retrospectively evaluated. Exclusion criteria for patients included any autoimmune or systemic inflammatory diseases, peripheral artery disease, glucocorticoid therapy within the past 3 months, malignancies or hematological disease, thyroid disease, advanced/end-stage liver or renal failure, history of acute coronary syndrome or revascularization (such as prior percutaneous coronary intervention or coronary artery bypass grafting). After applying the exclusion criteria, 431 patients were included in the study.

Patient demographics and lab results were documented from their medical records. Traditional risk factors for CAD assessed included smoking, hypertension (identified by a systolic blood pressure ≥140 and/or diastolic blood pressure ≥90 mmHg and/or ongoing anti-hypertensive treatment), and diabetes mellitus (identified by fasting blood glucose ≥126 or glucose ≥200 mg/dl during a 2-hour oral glucose tolerance test or ongoing anti-diabetic treatment).

Laboratory Measurements

The complete blood count values of all of the patients were measured one day before the myocardial perfusion scintigraphy. A Beckman Coulter LH 780 device (Mervue, Galway, Ireland) and Hitachi Modular P800 autoanalyzer (Roche Diagnostics Corp., Indianapolis, IN, USA) were used to evaluate patients' venous blood samples. Levels of hemoglobin (photometrically), platelet count (impedance method), C-reactive protein (CRP) (immunoturbidimetric method), albumin (bromocresol green method), triglycerides and total cholesterol (enzymatic colorimetry), and high-density lipoprotein cholesterol (HDL-C) (homogeneous enzymatic colorimetry) were determined. The Friedewald formula was used to determine low-density lipoprotein cholesterol (LDL-C).[19]

The values for LSR and HSR were determined using hematocrit and total protein values, employing the method previously established and verified.[20] The threshold values for MPV, age, TP, and HCT in predicting CAD were determined by employing the Youden index in ROC Curve analysis. Levels above the threshold value for each parameter were assigned a score of 1 point, and the MAPH score was thus evaluated on a scale from 0 to 4.[15]

Coronary Angiography

CAG was carried out employing traditional Judkins methods. CAD was identified as coronary stenosis involving a narrowing of ≥50% in the lumen diameter, as determined by quantitative CAG. Individuals whose vessel diameter was under 1.5 mm and/or who exhibited less than 50% narrowing were categorized as part of the control group. The SYNTAX Score (SS) was computed for lesions with a stenosis of ≥50% diameter in vessels larger than 1.5 mm (www.syntaxscore.com).[21] SS values were categorized into three groups: <22 (low), 22-32 (intermediate), and ≥32 (high).[22]

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) and Medcalc 11.4.2 (MedCalc Software, Mariakerke, Belgium) software. Categorical data were represented in terms of frequency and percentage. Group-wise comparisons were made utilizing the Chi-square test (with post-hoc cell-wise analysis) and the Fisher's Exact test. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test. Data exhibiting a normal

distribution were presented as mean±standard deviation, and comparisons between groups were made using the Student's T-test or ANOVA test (post-hoc: Bonferroni test). Non-normally distributed data were displayed as median (interquartile range (IQR): 25-75 percentiles) and comparisons between groups were conducted using the Mann-Whitney U test or Kruskal-Wallis test (post-hoc: Dunn's test). Stepwise multivariable logistic regression analysis was used to evaluate independent predictors of the presence and severity of CAD. The evaluation of diagnostic performance was conducted through ROC analysis, and the cut-off values were determined using the Youden index method. Value of p <0.05 were considered statistically significant.

RESULTS

A total of 431 patients were analyzed in the study, including 239 males and 192 females with the mean age of 57.4±10.3 years. CAD was detected in 58.7% (n=253) of patients (median SS: 15, IQR=8-23), with 186 patients having low SS, 40 patients intermediate SS, and 27 patients high SS. The demographic and laboratory findings are shown in Table 1. The ratios of smoking and hypertension were higher in the CAD group compared to the non-CAD group, while the ratio of diabetes mellitus was comparable between the groups. The counts of neutrophil and monocyte, and the levels of MPV, HCT, LDL-C, CRP and total protein were higher in the CAD group compared to the non-CAD group, while the levels of HDL-C and albumin were lower. The median LSR (60.7 vs. 43.1, p<0.001) and mean HSR (17.3±1.3 vs. 16.2±1.2, p<0.001) were higher in the CAD group compared to the non-CAD group. Other laboratory parameters did not differ significantly in the CAD and non-CAD groups (Table 1).

Table 1. Demographic and laboratory findings associated with the presence of coronary artery disease

Variables	All population n=431	CAD		p
		No n=178	Yes n=253	
Age, years	57.4±10.3	55.2±10.7	58.9±9.6	<0.001*
Male gender, n (%)	239 (55.5)	94 (52.8)	145 (57.3)	0.377
BMI, kg/m²	27.9±6.0	27.6±5.8	28.1±6.2	0.398
Smoking, n (%)	214 (49.7)	70 (39.3)	144 (56.9)	<0.001*
Hypertension, n (%)	295 (68.4)	93 (52.2)	202 (79.8)	<0.001*
Diabetes mellitus, n (%)	158 (36.7)	58 (32.6)	100 (39.5)	0.141
Drugs, n (%)				
Beta-blockers	182 (42.2)	62 (34.8)	120 (47.4)	0.009*
ACE/ARB inhibitors	196 (45.5)	73 (41.0)	123 (48.6)	0.118
Calcium canal blockers	83 (19.3)	28 (15.7)	55 (21.7)	0.119
Diuretics	97 (22.5)	34 (19.1)	63 (24.9)	0.156
Antidiabetic agents	157 (36.4)	58 (32.6)	99 (39.1)	0.164
Multivessel disease, n (%)	113 (26.2)	0	113 (44.7)	-
SYTANX score	6 (0-17)	0	15 (8-23)	-
Laboratory findings				
Hemoglobin, g/dl	13.2±1.6	13.3±1.4	13.1±1.7	0.348
Neutrophil count, $\times10^9$/L	4.8±1.4	4.3±1.2	5.2±1.4	<0.001*
Lymphocyte count, $\times10^9$/L	2.2±0.7	2.2±0.6	2.1±0.7	0.177
Monocyte count, $\times10^9$/L	0.7±0.2	0.6±0.1	0.7±0.2	<0.001*
Platelet count, $\times10^9$/L	245.7±68.5	243.8±71	247.1±66.9	0.630
Mean platelet volume, fL	8.3±1.0	8.0±1.1	8.4±0.9	<0.001*
Hematocrit, %	41.1±5.1	39.0±5.4	42.5±4.4	<0.001*
HDL-C, mg/dl	45.2±11.1	47.9±11.2	43.4±10.6	<0.001*
LDL-C, mg/dl	123.7±35.3	118.5±32.4	135.4±37.5	<0.001*
Triglycerides, mg/dl	128 (94-195)	124 (91-185)	131 (96-203)	0.811
Creatinine, mg/dl	0.8 (0.7-1.0)	0.7 (0.6-0.9)	0.8 (0.6-1.1)	0.315
Albumin, g/dl	4.1±0.4	4.2±0.4	4.1±0.5	0.027*
CRP, mg/dl	0.5 (0.2-0.8)	0.4 (0.2-0.7)	0.6 (0.4-0.9)	0.035*
Total protein	72.3±6.9	70.0±5.7	73.9±7.2	<0.001*
WBV at LSR	52.6 (36.6-74.6)	43.1 (24.9-58.8)	60.7 (44.6-82.3)	<0.001*
WBV at HSR	16.9±1.4	16.2±1.2	17.3±1.3	<0.001*
MAPH score	2.3±0.7	1.6±0.5	2.7±0.8	<0.001*

Numerical variables were shown as mean±standard deviation or median (IQR). Categorical variables were shown as numbers (%). * P <0.05 shows statistical significance. Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; HSR, high shear rate; LSR, low shear rate; WBV, whole blood viscosity.

Table 2 displays the potential risk factors found to be associated with CAD. Among these potential risk factors, three different multivariable logistic regression models were created for independent predictors of CAD. In the Multivariable Model I and Model II regression analyses, HCT and total protein levels, which are components of LSR and HSR, were not included due to multicollinearity. Based on this, increased age, hypertension, smoking, higher monocyte levels, and elevated LDL-C levels were determined as shared independent predictors of CAD in both Model I and Model II. LSR in Model I (OR=1.03, p<0.001) and HSR in Model II (OR=1.92, p<0.001) were established as other independent predictors of CAD (Table 2).

For predicting CAD risk, the established optimal cutoff values are as follows: age over 47 years (AUC=0.588, sensitivity=91.3%, and specificity=25.8%), HCT above 42.2% (AUC=0.698, sensitivity=59.0%, and specificity=73.6%), MPV over 8.3 fL (AUC=0.622, sensitivity=58.1%, and specificity=65.2%), and TP above 72.2 g/L (AUC=0.669, sensitivity=60.5%, and specificity=68.5%). Based on the set threshold values, the MAPH score was computed and incorporated into Model III. However, its components (MPV, age, TP, HCT) were excluded from Model III due to the multicollinearity associated with the MAPH score. The Model III regression analysis indicated that hypertension, smoking, elevated monocyte and LDL-C levels, along with the MAPH score, are independent risk factors for CAD. Accordingly, it was determined that each one-unit increase in the MAPH score independently increased the likelihood of CAD by 2.83 folds (OR=2.83, p<0.001). The threshold value of the MAPH score for predicting CAD was determined to be >2 (AUC=0.792, sensitivity=78.2%, and specificity=70.0%). On the other hand, in predicting CAD, the MAPH score exhibited superior diagnostic performance relative to the levels of LSR and HSR (Figure 1A). Furthermore, Model III demonstrated greater variance explanation for CAD and a higher AUC value than both Model II and Model I (For Nagelkerke R2 → Model I: 0.45, Model II: 0.46, and Model III: 0.58 in Table 2; For AUC → Model I: 0.47, Model II: 0.48, and Model III: 0.58 in Figure 1B).

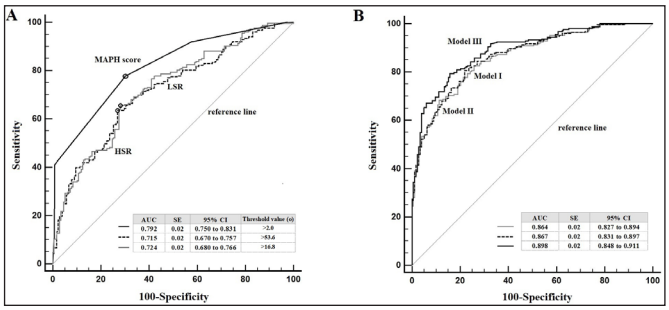

Figure 1. Diagnostic performance assessment of blood viscosity indices (A) and multivariable regression models (B) in predicting presence of CAD

Table 2. Multivariable regression models including whole blood viscosity indices to predict coronary artery disease

Variables	Univariable Regression			Multivariable Model I			Multivariable Model II			Multivariable Model III		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Age	1.04	1.02-1.06	<0.001*	1.03	1.01-1.07	0.003*	1.04	1.01-1.07	0.004*		not included	
Smoking	2.04	1.38-3.01	<0.001*	2.51	1.43-4.41	0.001*	1.81	1.11-2.98	0.018*	2.10	1.29-3.13	<0.001*
Hypertension	3.62	2.37-5.54	<0.001*	2.40	1.46-3.94	0.001*	2.95	1.80-4.82	<0.001*	3.45	2.10-5.68	<0.001*
Neutrophil count	1.28	1.05-1.56	<0.001*	-	-	-	-	-	-	-	-	-
Monocyte count	1.77	1.54-2.02	<0.001*	1.84	1.69-2.19	<0.001*	1.86	1.63-2.25	<0.001*	1.84	1.60-2.34	<0.001*
Hematocrit	1.16	1.11-1.21	<0.001*		not included			not included			not included	
Mean platelet volume	1.46	1.19-1.79	<0.001*	1.54	1.20-1.98	0.001*	1.57	1.22-2.01	<0.001*		not included	
HDL-C	0.96	0.95-0.98	<0.001*	-	-	-	-	-	-	-	-	-
LDL-C	1.02	1.01-1.03	<0.001*	1.03	1.01-1.05	<0.001*	1.92	1.55-2.38	<0.001*	1.03	1.01-1.05	<0.001*
Albumin	0.86	0.79-0.95	0.027*	-	-	-	-	-	-	-	-	-
CRP	1.07	1.01-1.12	0.035*	-	-	-	-	-	-	-	-	-
Total protein	1.10	1.06-1.13	<0.001*		not included			not included			not included	
WBV at LSR	1.03	1.02-1.04	<0.001*	1.03	1.02-1.04	<0.001*		not included			not included	
WBV at HSR	1.95	1.64-2.33	<0.001*		not included		1.92	1.55- 2.38	<0.001*		not included	
MAPH score	3.13	2.43-4.01	<0.001*		not included			not included		2.83	2.16-3.71	<0.001*
				Nagelkerke R^2=0.45			Nagelkerke R^2=0.46			Nagelkerke R^2=0.58		

In multivariable regression models, the effects of drugs were adjusted. * P <0.05 shows statistical significance.
Abbreviations: see Table 1, CI, confidence intervals; OR, odds ratio

The meaningful potential risk factors for CAD identified above also exhibited significant differences between the low SS group and the non-CAD group (Table 3). The ratio of multivessel disease, mean neutrophil level, mean MPV level, mean HCT, mean LDL-C level, and mean TP level were higher in mid-high SS groups compared to low SS group. In terms of blood viscosity indices, LSR, HSR, and the MAPH score were higher in the mid-high SS group compared to the low SS group (Table 3). Independently of other risk factors, it was determined that each one-unit increase in the MAPH score increased the likelihood of low SS by 2.98 folds compared to the non-CAD group, and the likelihood of mid-high SS by 1.78 folds compared to the low SS group (Table 4). The MAPH score exhibited superior diagnostic performance than LSR and HSR in predicting low SS (with the non-CAD group as reference) (Figure 2A) and mid-high SS (with the low SS group as reference) (Figure 2B).

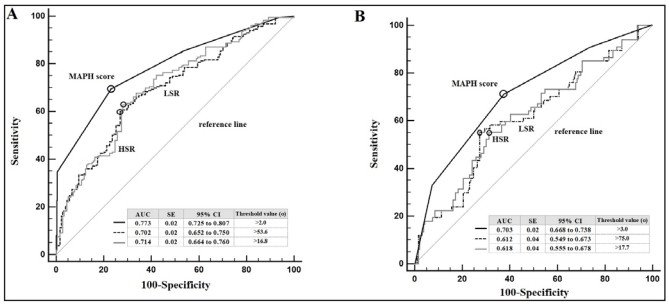

Figure 2. Diagnostic performance assessment of blood viscosity indices in predicting severity of CAD. A: Low SYNTAX score vs. non-CAD group. B: Intermediate -high SYNTAX score vs. low SYNTAX score

Table 3. Demographic and laboratory findings associated with the severity of coronary artery disease

Variables	CAD			p
	No n=178	Low SS n=186	Intermediate -High SS n=67	
Age, years	55.2±10.7[bc]	58.4±9.8[a]	60.2±9.3[a]	0.001*
Male gender, n (%)	94 (52.8)	100 (53.8)	45 (67.2)	0.108
BMI, kg/m²	27.6±5.8	28.2±6.0	28.5±6.5	0.459
Smoking, n (%)	70 (39.3)[bc]	107 (57.5)[a]	37 (55.2)[a]	0.002*
Hypertension, n (%)	93 (52.2)[bc]	149 (80.1)[a]	53 (79.1)[a]	<0.001*
Diabetes mellitus, n (%)	58 (32.6)	78 (41.9)	22 (32.8)	0.152
Drugs, n (%)				
Beta-blockers	62 (34.8)	85 (45.7)[a]	35 (52.2)[a]	0.007*
ACE/ARB inhibitors	73 (41.0)	92 (49.5)	31 (46.3)	0.264
Calcium canal blockers	28 (15.7)	40 (21.5)	15 (22.4)	0.293
Diuretics	34 (19.1)	46 (24.7)	17 (24.5)	0.370
Antidiabetic agents	58 (32.6)	77 (41.4)	22 (32.8)	0.188
Multivessel disease, n (%)	0	58 (31.2)[c]	55 (82.1)[b]	0.001*
SYTANX score	0	10.5 (7-16)[c]	29 (25-34)[b]	<0.001*
Laboratory findings				
Hemoglobin, g/dl	13.3±1.4	13.1±1.7	13±1.7	0.601
Neutrophil, $\times10^9$/L	4.3±1.2[bc]	4.9±1.5[ac]	5.4±1.4[ab]	<0.001*
Lymphocyte, $\times10^9$/L	2.2±0.6	2.1 (1.7-2.7)	2.0 (1.6-2.5)	0.252
Monocyte, $\times10^9$/L	0.6±0.1[bc]	0.7±0.2[a]	0.7±0.2[a]	<0.001*
Platelet count, $\times10^9$/L	243.8±71	247.6±66.6	245.6±68	0.873
Mean platelet volume, fL	8.0±1.1[bc]	8.3±0.9[ac]	8.6±0.8[ab]	<0.001*
Hematocrit, %	39.0±5.4[bc]	42.2±4.5[ac]	43.8±3.9[ab]	<0.001*
HDL-C, mg/dl	47.9±11.2[bc]	43.1±10[a]	43.8±12.2[a]	<0.001*
LDL-C, mg/dl	118.5±32.4[bc]	130.8±32.6[ac]	143.4±39.2[ab]	<0.001*
Triglycerides, mg/dl	124 (91-185)	132 (99-203)	115 (88-235)	0.939
Creatinine, mg/dl	0.7 (0.6-0.9)	0.8 (0.6-1.0)	0.8 (0.6-1.1)	0.548
Albumin, g/dl	4.2±0.4[bc]	4.1±0.5[a]	4.0±0.7[a]	0.034*
CRP, mg/dl	0.4 (0.2-0.7)[ab]	0.6 (0.2-0.9)[a]	0.7 (0.4-1.0)[a]	0.041*
Total protein	70.0±5.7[bc]	73.2±6.9[ac]	75.8±7.5[ab]	<0.001*
WBV at LSR	43.1 (24.9-58.8)[bc]	59.2 (42.5-79.6)[ac]	75.8 (50.5-88.9)[ab]	<0.001*
WBV at HSR	16.2±1.2[bc]	17.2±1.3[ac]	17.7±1.3[ab]	<0.001*
MAPH score	1.6±0.5[bc]	2.2±0.7[ac]	3.0±0.8[ab]	<0.001*

Numerical variables were shown as mean±standard deviation or median (IQR). Categorical variables were shown as numbers (%).
* P <0.05 shows statistical significance. Post-hoc analyzes were expressed as follows: a: P <0.05 vs. non-CAD group, b: P <0.05 vs. low SS group, c: P <0.05 vs. mid-hihg SS group.
Abbreviations: see Table 1

Table 4. Independent predictors of the presence and severity of CAD

Variables	Univariable Regression			Multivariable Regression		
	OR	95% CI	p	OR	95% CI	p
Low SS (ref: non-CAD)						
Smoking	2.10	1.38-3.18	0.001*			
Hypertension	3.68	2.31-5.86	<0.001*	2.08	1.16-3.71	0.014*
Neutrophil count	1.67	1.41-1.98	<0.001*	-	-	-
Monocyte count	1.81	1.65-2.10	<0.001*	1.78	1.62-2.04	<0.001*
HDL-C	0.96	0.94-0.98	<0.001*			
LDL-C	1.08	1.03-1.13	<0.001*	1.10	1.03-1.17	0.006*
Albumin	0.82	0.75-0.90	0.031*	-	-	-
CRP	1.05	1.01-1.10	0.045*	-	-	-
MAPH score	2.78	2.15-3.59	<0.001*	2.98	2.18-4.06	<0.001*
					Nagelkerke R2=0.50	
Mid-high SS (ref: low SS)						
Multivessel disease	10.12	5.04-20.31	<0.001*	11.78	5.68-24.40	<0.001*
Neutrophil count	1.13	1.04-1.24	0.023*	1.18	1.07-1.32	0.042*
LDL-C	1.08	1.02-1.15	0.015*	1.07	1.01-1.14	0.035*
MAPH score	1.59	1.16-2.17	0.004*	1.85	1.30-2.65	0.008*
					Nagelkerke R2=0.34	

In multivariable regression models, the effects of drugs were adjusted. * P <0.05 shows statistical significance.
Abbreviations: see Table 1, CI, confidence intervals; OR, odds ratio

DISCUSSION

To the best of our knowledge, this is the first study evaluating the MAPH score, a novel indicator of blood viscosity, for predicting CAD in patients with suspected CAD. The main findings of our study were as follows: 1) Higher MAPH scores were significantly associated with the presence and severity of CAD, 2) In predicting CAD, the MAPH score exhibited a superior diagnostic performance compared to LSR and HSR, 3) The gradual increase in MAPH scores demonstrated significant diagnostic performance in distinguishing the severity of CAD.

The SS is crucial for assessing the severity and extent of CAD, particularly for making revascularization decisions.[23] Despite this, it's noted that a considerable number of patients suspected of having CAD may exhibit normal coronary arteries when assessed via CAG, posing risks of unnecessary radiation exposure and financial burdens.[24,25] Therefore, there is an escalating interest in the use of cost-effective and easily accessible biomarkers for classifying patients with suspected CAD in clinical settings, aiming to streamline patient management and mitigate unwarranted diagnostic interventions.

The main cause of CAD, atherosclerosis, is known to have a prolonged incubation period, and its resultant diseases frequently manifest acutely, usually leading to a poor prognosis.[2] The pathophysiological mechanism of atherosclerosis is a multifaceted and complex process. It begins with the activation of the endothelium, which is then followed by a series of events including the accumulation of lipids, fibrous elements, and calcification, leading to vessel narrowing and the activation of inflammatory pathways.[26] Growing evidence suggests that blood viscosity is a critical factor in these processes. Blood viscosity, which represents the intrinsic resistance to blood flow within vessels, correlates directly with endothelial shear stress, influenced by the diameter of the vessel via the secretion of endothelial vasoactive factors.[27] Increased blood viscosity alters the WSS landscape, leading to a response in endothelial cells. Under normal physiological conditions, endothelial cells respond to normal shear stress by producing endothelial nitric oxide synthase (eNOS), encouraging the expression of genes that protect against atherosclerosis, and reducing endothelin-1 (ET-1) messenger ribonucleic acid (mRNA). However, in conditions of low shear stress, these cells increase the absorption of oxidized LDL-C and enhance the levels of several adhesion molecules such as ICAM-1, VCAM-1 and inflammatory cytokine such as tumor necrosis factor-alpha (TNF-α), while reducing the expression of eNOS and protein.[28,29] As a result, the rheological characteristics of blood alter, resulting in endothelial injury and inflammation, and this is accompanied by an increase in blood viscosity.[30]

Consistent with the aforementioned mechanisms, increased blood viscosity leads to a decrease in WSS, potentially exacerbating the severity of endothelial dysfunction.[31] This also suggests that blood viscosity might be a key player in the initiation of atherosclerotic plaque formation in areas with low WSS, in the acceleration of atherosclerosis, and in the increased probability of rupture.[32] In the current study, patients with CAD having higher levels of LSR and HSR is

consistent both with these mechanisms and with previous studies.[33-35] In a previous study, both LSR and HSR were found to be increased in patients with CAD compared to the control group. Also, it has been reported that LSR demonstrated a sensitivity of 82% and a specificity of 78% in predicting CAD, while HSR exhibited a sensitivity of 83% and a specificity of 77%.[33] In another study, it was found that both HSR and LSR were significantly higher in the group with severe coronary artery stenosis compared to the group with non-significant coronary artery stenosis. Furthermore, it has been reported that in predicting significant coronary artery stenosis, the LSR exhibited a sensitivity of 58.4% and a specificity of 62.1%, while the HSR showed a sensitivity of 61.5% and a specificity of 70.4%.[35] However, it is known that blood rheology is affected by coronary risk factors such as advanced age, hypertension, and smoking.[30] Additionally, increased MPV levels, which are associated with atherothrombotic disorders such as atherosclerosis,[36] may also have a potential impact on blood rheology.[37,38] On the other hand, it has been reported that antihypertensive drugs such as beta-blockers and angiotensin-converting enzyme inhibitors, or diabetic agents, can also affect blood viscosity.[39-41] Independent of these potential factors, both Model I and Model II regression analyses showed that LSR and HSR are independent predictors of CAD. Nonetheless, both LSR and HSR showed low sensitivity in forecasting the presence and severity of CAD. A previous study demonstrated that the sensitivities of LSR and HSR in distinguishing patients with significant coronary artery stenosis from those without were 58.4% and 61.5%, respectively.[35] Therefore, an improved blood viscosity index might exhibit better diagnostic performance in distinguishing both CAD and its severity.

Recently, the MAPH score, incorporating age and MPV parameters in addition to the components of LSR and HSR, has been introduced as a new index for blood viscosity.[15] It has been associated with a high thrombus burden in patients with both ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction.[14,15] In a study involving 260 patients who underwent primary percutaneous coronary intervention and had TIMI 0 flow, it was reported that the MAPH score predicted the presence of TIMI coronary flow after stent implantation with 78% specificity and 45% sensitivity.[42] In addition to these cohorts as a consequence of atherosclerosis, the predictive role of the MAPH score has also been investigated in patients with CSFP, which is a distinct angiographic clinical entity characterized by delayed coronary opacification in the absence of significant obstructive CAD. In the mentioned study, it was demonstrated that the MAPH score exhibited a sensitivity of 43% and a specificity of 86% in differentiating between CSFP and normal coronary flow.[16] Increasing evidence indicates that patients with CSFP are prone to atherosclerosis and obstructive CAD.[43,44] Consistent with these findings, the MAPH score was identified as a significant indicator in distinguishing both the presence and the severity of CAD, exhibiting better diagnostic performance than LSR and HSR. Moreover, the regression model incorporating the MAPH score explained a higher variance of CAD compared to the regression models that included the LSR and HSR indices. Furthermore, it also exhibited a graduated threshold value with a sensitivity of 71.1% and a specificity of 62.5% in differentiating patients with intermediate-high SS.

Limitations

Although this study is the first to evaluate the relationship between the MAPH score and CAD, it possesses certain limitations. Besides being single-centered and retrospective, the study evaluated the severity of luminal stenosis in coronary arteries solely through visual coronary angiograms. Additional information such as the luminal area, plaque burden, and characteristics related to the quantitative evaluation of atherosclerosis was not included in the study. Finaly, the MAPH score is a new biomarker, and each of its components requires cut-off points. Widespread adoption of the MAPH score necessitates multi-center, prospective studies involving a large number of participants.

CONCLUSION

In patients with suspected CAD, the MAPH score, a new indicator of blood viscosity, is associated with the presence and severity of CAD. A gradual increase in the MAPH score demonstrates significant diagnostic performance in distinguishing patients with high-risk CAD. In patients suspected of CAD, the MAPH score may serve as a potential screening tool and can be utilized for risk stratification.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 12.09.2022, Decision No: 146/03).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Turchetti G, Kroes MA, Lorenzoni V, et al. The cost-effectiveness of diagnostic cardiac imaging for stable coronary artery disease. *Expert Rev Pharmacoecon Outcomes Res.* 2015;15(4):625-633. doi: 10.1586/14737167.2015.1051037
2. Rafieian-Kopaei M, Setorki M, Doudi M, Baradaran A, Nasri H. Atherosclerosis: process, indicators, risk factors and new hopes. *Int J Prev Med.* 2014;5(8):927-946.
3. Wang L, Tang C. Targeting platelet in atherosclerosis plaque formation: current knowledge and future perspectives. *Int J Mol Sci.* 2020;21(24):9760. doi: 10.3390/ijms21249760
4. Soulis JV, Farmakis TM, Giannoglou GD, et al. Molecular viscosity in the normal left coronary arterial tree. Is it related to atherosclerosis? *Angiol.* 2006;57(1):33-40. doi: 10.1177/000331970605700105
5. Lowe GD, Lee AJ, Rumley A, Price JF, Fowkes FG. Blood viscosity and risk of cardiovascular events: the Edinburgh Artery Study. *Br J Haematol.* 1997;96(1):168-173. doi: 10.1046/j.1365-2141.1997.8532481.x
6. de Simone G, Devereux RB, Chien S, Alderman MH, Atlas SA, Laragh JH. Relation of blood viscosity to demographic and physiologic variables and to cardiovascular risk factors in apparently normal adults. *Circulation.* 1990;81(1):107-117. doi: 10.1161/01.cir.81.1.107
7. Mazzi V, De Nisco G, Hoogendoorn A, et al. Early atherosclerotic changes in coronary arteries are associated with endothelium shear stress contraction/expansion variability. *Ann Biomed Eng.* 2021;49(9):2606-2621. doi: 10.1007/s10439-021-02829-5
8. Arzani A. Coronary artery plaque growth: a two-way coupled shear stress-driven model. *Int J Numer Method Biomed Eng.* 2020;36(1):e3293. doi: 10.1002/cnm.3293
9. Higuchi Y. Influence of arterial occlusion on hematocrit and plasma protein concentration of femoral venous blood in rabbit. *Jpn J Physiol.* 1985;35(3):503-511. doi: 10.2170/jjphysiol.35.503
10. Khan HU, Khan MU, Noor MM, Hayat U, Alam MA. Coronary artery disease pattern: a comparision among different age groups. *J Ayub Med Coll Abbottabad.* 2014;26(4):466-469.
11. Pafili K, Penlioglou T, Mikhailidis DP, Papanas N. Mean platelet volume and coronary artery disease. *Curr Opin Cardiol.* 2019;34(4):390-398. doi: 10.1097/HCO.0000000000000624
12. Bapir M, Untracht GR, Hunt JEA, et al. Age-dependent decline in common femoral artery flow-mediated dilation and wall shear stress in healthy subjects. *Life.* 2022;12(12):2023. doi: 10.3390/life12122023
13. Kanda H, Yamakuchi M, Matsumoto K, et al. Dynamic changes in platelets caused by shear stress in aortic valve stenosis. *Clin Hemorheol Microcirc.* 2021;77(1):71-81. doi: 10.3233/CH-200928
14. Cakmak Karaaslan O, Coteli C, Ozilhan MO, et al. The predictive value of MAPH score for determining thrombus burden in patients with non-ST segment elevation myocardial infarction. *Egypt Heart J.* 2022;74(1):60. doi: 10.1186/s43044-022-00299-1
15. Abacioglu OO, Yildirim A, Karadeniz M, et al. A new score for determining thrombus burden in STEMI patients: the MAPH score. *Clin Appl Thromb Hemost.* 2022;28:10760296211073767. doi: 10.1177/10760296211073767
16. 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
17. Peerwani G, Aijaz S, Sheikh S, Virani SS, Pathan A. Predictors of non-obstructive coronary artery disease in patients undergoing elective coronary angiography. *Glob Heart.* 2023;18(1):26. doi: 10.5334/gh.1204
18. Ezhumalai B, Jayaraman B. Angiographic prevalence and pattern of coronary artery disease in women. *Indian Heart J.* 2014;66(4):422-426. doi: 10.1016/j.ihj.2014.05.009
19. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18(6):499-502.
20. de Simone G, Devereux RB, Chinali M, Best LG, Lee ET, Welty TK. Association of blood pressure with blood viscosity in American Indians: the Strong Heart Study. *Hypertension.* 2005;45(4):625-630. doi: 10.1161/01.HYP.0000157526.07977.ec
21. Serruys PW, Onuma Y, Garg S, et al. Assessment of the SYNTAX score in the Syntax study. *EuroIntervention.* 2009;5(1):50-56. doi: 10.4244/eijv5i1a9
22. He JQ, Gao YC, Yu XP, et al. Syntax score predicts clinical outcome in patients with three-vessel coronary artery disease undergoing percutaneous coronary intervention. *Chin Med J.* 2011;124(5):704-709.
23. Morice MC. Has the SYNTAX score become obsolete? *J Am Coll Cardiol.* 2018;72(12):1330-1331. doi: 10.1016/j.jacc.2018.07.023
24. Yokota S, Ottervanger JP, Mouden M, Timmer JR, Knollema S, Jager PL. Prevalence, location, and extent of significant coronary artery disease in patients with normal myocardial perfusion imaging. *J Nucl Cardiol.* 2014;21(2):284-290. doi: 10.1007/s12350 -013-9837-5
25. Ouellette ML, Loffler AI, Beller GA, Workman VK, Holland E, Bourque JM. Clinical characteristics, sex differences, and outcomes in patients with normal or near-normal coronary arteries, non-obstructive or obstructive coronary artery disease. *J Am Heart Assoc.* 2018;7(10):e007965. doi: 10.1161/JAHA. 117.007965
26. Jebari-Benslaiman S, Galicia-Garcia U, Larrea-Sebal A, et al. Pathophysiology of atherosclerosis. *Int J Mol Sci.* 2022;23(6):3346. doi: 10.3390/ijms23063346
27. Rodriguez I, Gonzalez M. Physiological mechanisms of vascular response induced by shear stress and effect of exercise in systemic and placental circulation. *Front Pharmacol.* 2014;5:209. doi: 10.3389/fphar.2014.00209
28. Ando J, Yamamoto K. Vascular mechanobiology: endothelial cell responses to fluid shear stress. *Circ J.* 2009;73(11):1983-1992. doi: 10.1253/circj.cj-09-0583
29. Ishibazawa A, Nagaoka T, Takahashi T, et al. Effects of shear stress on the gene expressions of endothelial nitric oxide synthase, endothelin-1, and thrombomodulin in human retinal microvascular endothelial cells. *Invest Ophthalmol Vis Sci.* 2011;52(11):8496-8504. doi: 10.1167/iovs.11-7686
30. Yagi H, Sumino H, Aoki T, et al. Impaired blood rheology is associated with endothelial dysfunction in patients with coronary risk factors. *Clin Hemorheol Microcirc.* 2016;62(2):139-150. doi: 10.3233/CH-151960
31. Kumar A, Hung OY, Piccinelli M, et al. Low coronary wall shear stress is associated with severe endothelial dysfunction in patients with nonobstructive coronary artery disease. *JACC Cardiovasc Interv.* 2018;11(20):2072-2080. doi: 10.1016/j.jcin.2018.07.004
32. Cowan AQ, Cho DJ, Rosenson RS. Importance of blood rheology in the pathophysiology of atherothrombosis. *Cardiovasc Drugs Ther.* 2012;26(4):339-348. doi: 10.1007/s10557-012-6402-4
33. Cekirdekci EI, Bugan B. Whole blood viscosity in microvascular angina and coronary artery disease: significance and utility. *Rev Port Cardiol (Engl Ed).* 2020;39(1):17-23. doi: 10.1016/j.repc.2019.04.008

34. Becker RC. The role of blood viscosity in the development and progression of coronary artery disease. *Cleve Clin J Med.* 1993;60(5):353-358. doi: 10.3949/ccjm.60.5.353

35. Ceyhun G, Birdal O. Relationship between whole blood viscosity and lesion severity in coronary artery disease. *Int J Angiol.* 2021;30(2):117-121. doi: 10.1055/s-0040-1720968

36. Karaman H, Karakukcu C, Kocer D. Can mean platelet volume serve as a marker for prostatitis? *Int J Med Sci.* 2013;10(10):1387-1391. doi: 10.7150/ijms.6126

37. Senen K, Topal E, Kilinc E, et al. Plasma viscosity and mean platelet volume in patients undergoing coronary angiography. *Clin Hemorheol Microcirc.* 2010;44(1):35-41. doi: 10.3233/CH-2010-1249

38. Nader E, Skinner S, Romana M, et al. Blood rheology: key parameters, impact on blood flow, role in sickle cell disease and effects of exercise. *Front Physiol.* 2019;10:1329. doi: 10.3389/fphys.2019.01329

39. Fornal M, Korbut RA, Lekka M, et al. Rheological properties of erythrocytes in patients with high risk of cardiovascular disease. *Clin Hemorheol Microcirc.* 2008;39(1-4):213-219.

40. Sumino H, Nara M, Seki K, et al. Effect of antihypertensive therapy on blood rheology in patients with essential hypertension. *J Int Med Res.* 2005;33(2):170-177. doi: 10.1177/147323000503300204

41. Irace C, Cutruzzola A, Parise M, et al. Effect of empagliflozin on brachial artery shear stress and endothelial function in subjects with type 2 diabetes: results from an exploratory study. *Diab Vasc Dis Res.* 2020;17(1):1479164119883540. doi: 10.1177/1479164119883540

42. Yurdam FS, Kis M. The relationship between TIMI flow and MAPH score in patients undergoing primary percutaneous coronary intervention for STEMI. *Int Heart J.* 2023;64(5):791-797. doi: 10.1536/ihj.23-024

43. Sadr-Ameli MA, Saedi S, Saedi T, Madani M, Esmaeili M, Ghardoost B. Coronary slow flow: benign or ominous? *Anatol J Cardiol.* 2015;15(7):531-535. doi: 10.5152/akd.2014.5578

44. Huang Q, Zhang F, Chen S, Dong Z, Liu W, Zhou X. Clinical characteristics in patients with coronary slow flow phenomenon: a retrospective study. *Medicine.* 2021;100(6):e24643. doi: 10.1097/MD.0000000000024643