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ORIGINAL ARTICLE

Evaluation of the Relationship Between Semaphorin 4D Levels and the Coronary Slow Flow Phenomenon

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ABSTRACT

Background: Coronary slow flow (CSF) is a frequently observed angiographic and clinical condition linked to various complications, including stable and unstableangina pectoris, acute coronary syndromes, hypertension, and potentially fatal arrhythmias. Semaphorin 4D (Sema4D), a recently identified type 1 transmembrane glycoprotein, has been implicated in processes such as inflammation, oxidative stress, atherosclerosis, and angiogenesis. Elevated Sema4D levels have been documented in individuals with atrial fibrillation, acute coronary syndrome, and heart failure.

Aim: This study aimed to assess the association between Sema4D levels and both the presence and severity of CSF.

Study Design: Cross-sectional observational study.

Methods: The study comprised 79 patients diagnosed with CSF and 81 healthy control subjects. Serum levels of Sema4D were measured, and coronary flow was assessed using the thrombolysis in myocardial infarction frame count (TFC) method.

Results: Sema4D concentrations were significantly higher in the CSF group compared to the control group ($p<0.001$). Notably, Serum4D levels showed a positive correlation with high-sensitivity C-reactive protein ($r=073$, $p<0.001$), mean TFC ($r=088$, $p<0.001$), and the neutrophil-to-lymphocyte ratio ($r=0.37$, $p<0.001$).

Conclusion: Sema4D may serve as a biomarker associated with CSF and could aid in identifying patients with CSF-related unstable angina.

Keywords: Semaphorin 4D, coronary slow flow, inflammation, biomarker, TIMI frame count

INTRODUCTION

Coronary slow flow (CSF), a commonly observed angiographic and clinical finding, is characterized by delayed forward movement of contrast medium to the distal segments of a specific coronary artery during coronary angiography, in the absence of obstructive coronary artery disease, coronary vasospasm, acute myocardial infarction, coronary ectasia, connective tissue disorders, coronary embolism, heart failure, or myocardial and valvular disease.[1] The incidence of CSF varies widely, ranging from 1% to 7% of all coronary angiographic procedures.[1] CSF can present with a variety of clinically significant manifestations and complications, including acute coronary syndromes, stable and unstable angina pectoris, hypertension, and potentially fatal arrhythmias, such as sudden cardiac death.[1-4] Although the primary risk factors and underlying pathophysiological mechanisms of CSF remain unclear, several contributing processes have been proposed, including small-vessel disease, endothelial dysfunction, marked inflammation, subclinical atherosclerosis, and abnormal flow patterns in the epicardial coronary arteries.[5-9]

Semaphorin 4D (Sema4D), also known as CD100, belongs to the class 4 semaphorin family. It is a type 1 transmembrane glycoprotein with a molecular weight of 150 kDa. Sema4D is broadly expressed by various cell types, including endothelial cells, platelets, B and T lymphocytes, monocytes, and neutrophils. Its primary receptors are Plexin-B1 and CD72.[10,11] Sema4D has been identified as a key pathophysiological factor involved in numerous biological processes such as chronic inflammation, immune system development and maturation, atherosclerosis, angiogenesis, osteogenesis, neurogenesis, and tumor formation and progression.[12-16] Elevated Sema4D levels have been observed in patients with heart failure and chronic atrial fibrillation (AF) when compared with healthy individuals. These findings suggest that Sema4D may play a significant role in the onset and progression of these conditions.[14] Moreover, a study by Xiang et al.[17] demonstrated a significant and independent positive association between Sema4D levels and left atrial diameter in chronic AF. Additionally, Can et al.[18] reported that Sema4D may serve as a potential marker for predicting recurrence in patients with paroxysmal AF (PAF) who have undergone catheter ablation.

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As there are no existing studies in the literature examining the association between Sema4D and CSF, this study was undertaken to address that gap. It also represents the first attempt to clarify the role of Sema4D in the pathogenesis of CSF. Furthermore, the study aimed to explore the relationship between Sema4D and established inflammatory markers in the context of stable angina pectoris.

METHODS

Study Population

This study was designed as a cross-sectional observational investigation. A total of 1,762 consecutive patients who underwent coronary angiography between November 2019 and May 2021 at a high-volume training and research hospital were considered for inclusion. These procedures were performed due to symptoms, clinical and physical examination findings, or evidence of myocardial ischemia identified through exercise stress testing or noninvasive imaging modalities such as myocardial perfusion scintigraphy or stress echocardiography. Based on coronary angiography findings, the study population was divided into two groups. The patient group included 79 consecutive individuals with angiographically confirmed normal coronary artery anatomy who exhibited slow coronary flow in the absence of atherosclerotic coronary artery disease. The control group consisted of 81 randomly selected subjects who had undergone coronary angiography and were found to have both anatomically normal coronary arteries and normal coronary flow, including appropriate myocardial blush and clearance. The control group selection was performed independently by three experienced invasive cardiologists who were blinded to the purpose of the study.

Patients in both study groups presented with typical chest pain or angina-equivalent symptoms and had positive findings on either an exercise stress test or noninvasive imaging modalities, including myocardial perfusion imaging, stress echocardiography, or coronary computed tomographic angiography. Demographic, clinical, and laboratory data for all participants were documented by cardiologists at the time of cardiac catheterization. Moreover, all subjects underwent 12-lead surface electrocardiography and two-dimensional (2D) transthoracic echocardiography prior to the coronary angiography procedure. Echocardiographic assessments were conducted using a Vivid S5 system (GE Healthcare, WI, USA) equipped with a 1.7/3.4-MHz phased-array transducer, with patients positioned in the left lateral decubitus posture. These evaluations were performed to assess left ventricular structure and function, including ejection fraction, and were independently carried out by two non-invasive cardiologists who were blinded to the study outcomes. Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane method of disks based on 2D images obtained from the apical four- and two-chamber views.

Smoking was defined as regular cigarette use, either in the past or concurrently, prior to or during the study period. Diagnoses of hypertension, hyperlipidemia, and diabetes mellitus were made in accordance with current relevant clinical guidelines.[19-21] A documented history of these conditions and/or the sue of antihypertensive, lipid-lowering, or antidiabetic medications, including insulin, was considered indicative of the corresponding disease in this study. Renal function was assessed by calculating the glomerular filtration rate using both plasma creatinine levels and the Cockcroft-Gault formula.[19] Furthermore, height and weight were measured for all participants, and body mass index was calculated by dividing body weight in kilograms by the square of height in meters (kg/m^2).

In this study, CSF was defined angiographically by the following criteria: (a) absence of obstructive epicardial coronary artery disease, (b) delayed antegrade passage of contrast medium resulting in distal vessel opacification consistent with either thrombolysis in myocardial infarction (TIMI)-2 flow or a corrected TIMI frame count >27 frames, and (c) delayed distal vessel opacification in at least one epicardial coronary artery. Participants who were using vasoactive medications before or during the study underwent a 3-day "washout" period prior to coronary angiography to minimize potential interference with study outcomes.

The main exclusion criteria for this study included moderate to severe valvular heart disease, a history of chronic ischemic heart disease or previous percutaneous coronary intervention or coronary artery bypass grafting, acute coronary syndromes, heart failure with reduced or mid-range ejection fraction, cardiomyopathies, congenital structural heart disease, moderate to left ventricular hypertrophy, peripheral vascular disease, stroke, myopericarditis, active infections, chronic obstructive pulmonary disease, pulmonary hypertension, recent trauma or major surgery within the past 3 months, cardiac syndrome X, acute or chronic renal or hepatic dysfunction, pheochromocytoma, hematologic disorders, thyroid dysfunction, acute or chronic inflammatory diseases, malignancy, autoimmune diseases, and the use of specific medications that may influence blood viscosity or platelet structure and function, such as antiplatelet or anticoagulant agents, corticosteroids, immunosuppressive drugs, and statins.

Participants were eligible for inclusion if they were between 18 and 80 years of age and capable of providing written informed consent, which was a mandatory requirement for enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Haliç University Ethics Committee (approval no: 64, date: 30.03.2022).

Coronary Angiography Procedure

Coronary angiography was carried out by two experienced interventional cardiologists who were blinded to the study results. The procedure was performed via either the femoral or radial artery using the standard Judkins technique and a monoplane cine angiography system. Coronary images were captured at a frame rate of 30 frames per second in both right and left oblique views, utilizing cranial and caudal angulations. All participants received the nonionic contrast agent iopromide (Ultravist 370, Schering AG, Berlin, Germany) during the procedure. Coronary blood flow was quantitatively assessed using the TIMI frame count (TFC) method by three experienced interventional cardiologists who were blinded to the study data. The intra- and interobserver coefficients of variation (CV) were 3.6% and 6.4%, respectively.

In this method, the number of cine frames required for the contrast agent to reach predefined distal coronary landmarks in the left anterior descending (LAD) artery, left circumflex (LCX) artery, and right coronary

artery (RCA) was measured and recorded. The initial frame was defined as the frame in which the concentrated contrast dye completely filled the width of the proximal coronary artery lumen, touching both edges and advancing distally beyond that point. The final frame was identified as the frame when the leading edge of the contrast first reached the distal landmark. The TFC for each artery was calculated by subtracting the initial frame from the final frame. The predefined distal landmarks were the distal bifurcation of the LAD, commonly referred to as the "moustache," for the LCX, and the first branch of the posterolateral artery for the RCA. Since the LAD is longer than the LCX and RCA, its TFC is naturally higher; therefore, the corrected TIMI frame count (cTFC) for the LAD was obtained by dividing its TFC by 1.7. The mean TFC for each participant was calculated by adding the TFC values for the LAD, LCX, and RCA and dividing the sum by three. According to a previous study,[22] the standard corrected mean values for normal coronary artery visualization were 36.2±2.6 frames for the LAD, 22.2±4.1 for the LCX, and 20.4±3 frames for the RCA. Moreover, the corrected mean TFC (cTFC) for the LAD was reported as 21.1±1.5 frames.[22] In the present study, participants with a TFC exceeding the previously reported normal range by more than two standard deviations (SD) in any of the LAD or LCX arteries or RCA were classified as having CSF.

Experimental Method

Blood samples were collected from the antecubital veins of all participants by venipuncture early in the morning after 12 h of fasting and prior to the coronary angiography procedure. Samples were collected into vacuum tubes containing ethylenediaminetetraacetic acid as an anticoagulant. Serum was immediately separated by centrifugation at 3,000 g for 15 min and stored at -80 °C until analysis. Routine hematological, coagulation, and biochemical tests were performed on the same day as blood collection. Hematological parameters were measured using a Coulter LH 780 Hematology Analyzer (Beckman Coulter Ireland, Inc., Mervue, Galway, Ireland). Serum high-sensitivity C-reactive protein (hs-CRP) was measured at admission by enzyme-linked immunosorbent assay (ELISA) using commercial kits (Hitachi 917 analyzer, Boehringer Mannheim, Germany). Biochemical parameters, including fasting blood glucose and lipid profiles, were analyzed using an Abbott Diagnostics C8000i autoanalyzer (Abbott, Germany) with commercial reagents. Low-density lipoprotein (LDL) cholesterol was calculated using Friedewald's formula for samples with triglyceride levels ≤400 mg/dL. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) were determined by dividing the absolute counts of neutrophils, platelets, and monocytes by the absolute lymphocyte count, respectively.

Serum Sema4D levels were measured using a commercial ELISA kit according to the manufacturer's instructions (intra-assay CV <8%; inter-assay CV <10%; Nepenthe Research Technology Laboratory, Cat. No: NE010156601, Gebze-Kocaeli, Türkiye). The assay's sensitivity range for Sema4D concentrations was 0.31-20 ng/mL. All samples were analyzed in duplicate, and the mean values were used for subsequent analyses.

Statistical Analysis

The Kolmogorov-Smirnov test was applied to assess whether the study variables followed a normal distribution. Continuous variables with normal distribution were expressed as mean±SD, while non-normally distributed continuous variables were presented as medians. Categorical variables were reported as frequencies and/or percentages (%). Differences between the two groups were analyzed using Student's t-test for normally distributed continuous variables and the Mann-Whitney U test for non-normally distributed continuous variables. Chi-squared or Fisher's exact tests were used for categorical variables. Correlation analyses between variables employed either Spearman or Pearson correlation tests, depending on the distribution of the data. Receiver operating characteristic (ROC) curve analysis was conducted to assess the diagnostic value of Sema4D, hs-CRP, NLR, PLR, and MLR in distinguishing patients with CSF in any of the three coronary arteries from those with normal coronary blood flow. Moreover, multiple linear regression analysis was used to identify significant independent predictors of Sema4D levels. A two-sided p value <0.05 was considered statistically significant, with a type 1 error rate of 5%. Standardized β coefficients and 95% confidence intervals (CI) were reported. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics for Windows, version 21.0 (Armonk, NY, USA).

RESULTS

A total of 160 participants were included in this study, with 79 patients in the CSF group (53.1% male) and 81 subjects in the coronary normal blood flow (CNF) group (40.7% male). The baseline demographic and clinical characteristics of both groups are summarized in Table 1. No significant differences were found between the groups except for systolic blood pressure, hypertension, smoking history, hyperlipidemia, family history, and antiplatelet drug use, all of which were higher in the CSF group compared to the control group (p<0.001). LVEF was similar between the groups (p=0.948). Serum Sema4D levels were significantly elevated in the CSF group compared to the CNF group (7.78±0.87 vs. 4.23±0.88; p<0.001) (Figure 1).

Baseline laboratory parameters for the groups are presented in Table 2. Levels of hs-CRP, LDL, total cholesterol, and the NLR were significantly higher in the CSF group than in controls (p<0.001). In contrast, lymphocyte counts were significantly lower in the CSF group (p=0.03). Other laboratory values showed no significant differences between the two groups (all p values >0.05).

As expected, patients with CSF showed significantly higher cTFC values compared to those in the CNF group (Table 3). Among the CSF patients, 56 (71.0%) exhibited slow flow in all 3 coronary vessels, 12 patients (15.1%) had slow flow in 2 vessels, and 11 patients (13.9%) had slow flow in 1 vessel. When analyzing CSF distribution by affected coronary artery, the RCA was the most frequently involved vessel, affecting 48 patients (60.7%). The TFC values for the LAD, LCX, and RCA, as well as the mean TFC, were all significantly higher in the CSF group compared to the CNF group (all p values <0.001).

Correlation analysis was conducted to assess the relationship between Sema4D and established inflammatory markers in patients with CSF. Sema4D showed a significant positive correlation with the NLR (r=0.37, p<0.001), hs-CRP (r=0.73, p<0.001), and mean TFC (r=0.88, p<0.001) (Figure 2). Moreover, strong correlations were found between Sema4D and the TFC for the Cx (r=0.80, p<0.001), LAD (r=0.84, p<0.001), and RCA (r=0.88, p<0.001).

Table 1. Baseline demographic, clinical, and laboratory features of the CSF and control groups

	CSF (n=79)	CNF (n=81)	p value
Age, y	58.30±11.21	60.11±9.82	0.27
Gender (F/M), n	37/42	48/33	0.11
DM, n (%)	19 (24%)	14 (17%)	0.29
HT, n (%)	61 (77%)	17 (21%)	**<0.001**
Hyperlipidemia, n (%)	41 (51%)	13 (16%)	**<0.001**
Smoking, n (%)	58 (73%)	14 (17%)	**<0.001**
Family history, n (%)	35 (44%)	15 (18%)	**<0.001**
Antiplatelet, n (%)	44 (55%)	13 (16%)	**<0.001**
Beta-blocker, n (%)	46 (58%)	54 (66%)	0.27
Calcium channel blocker, n (%)	8 (10%)	3 (3%)	0.10
ACE inhibitors/ARB, n (%)	19 (24%)	9 (11%)	0.05
SBP, mmHg	142.09±24.6	124.38±14.01	**<0.001**
DBP, mmHg	88±15.04	70.37±10.04	**<0.001**
LVEF, %	59.68±4.19	59.20±4.16	0.948
GFR, (mL/min/1.73 m^2)	128.45±5.80	130.25±6.30	0.455
Hemoglobin, g/dL	13.91±1.69	13.91±1.69	0.13
Neutrophil, x10^3	4,414±1,297	4,468±1,415	0.80
Lymphocyte, x10^3	2,395±696	2,170±665	**0.03**
Neutrophil/lymphocyte, ratio	2.66±0.90	1.99±0.66	**<0.001**
Total cholesterol, mg/dL	168.58±32.72	143.74±26.51	**<0.001**
LDL, mg/dL	133.56±43.68	114.44±33.77	**0.002**
HDL, mg/dL	44.82±8.06	45.69±10.81	0.56
TG, mg/dL	138.42±7.15	134±5.88	0.31
hs-CRP, mg/dL	2.62±0.36	1.60±0.32	<0.001
Semaphorin 4D, ng/mL	7.78±0.87	4.23±0.88	<0.001

Values are expressed as means±standard deviation or number (%), as appropriate; statistically significant values are highlighted in bold.
F/M: Female/male, ACE: Angiotensin-converting enzyme, ARB: Angiotensin receptor blocker, CNF: Coronary normal flow, CSF: Coronary slow flow, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HT: Hypertension, HDL: High-density lipoprotein, hs-CRP: High-sensitivity C-reactive protein, LDL: Low-density lipoprotein, LVEF: Left ventricular ejection fraction, TC: Total cholesterol, TG: Triglyceride, SBP: Systolic blood pressure, GFR: Glomerular filtration rate

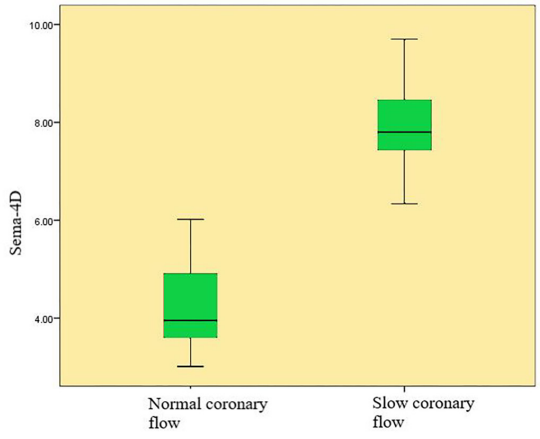

Figure 1. Sema4D levels in patients with the CSF and CNF
Sema4D: Semaphorin 4D, CSF: Coronary slow flow, CNF: Coronary normal flow

Multiple linear regression analysis revealed that NLR and the TFC for Cx and RCA were significant predictors of Sema4D levels in patients with CSF ($p<0.002$, $p<0.027$, and $p<0.001$, respectively; model $R^2=0.81$, $p<0.001$) (Table 4).

A ROC analysis was conducted to examine the potential of Sema4D in predicting CSF. The areas under the curve (AUCs) were utilized to assess the diagnostic accuracy of serum Sema4D in distinguishing patients with CSF in at least one coronary artery from those with normal CNF (Figure 3). The discrimination ability was very high (AUC=0.990, 95% CI: 0.98-1.00; $p<0.001$). Using a cut-off value of 5.79 ng/mL for Sema4D, CSF presence could be predicted with 97.1% sensitivity and 95.4% specificity. The negative predictive value was 95.0%, and the positive predictive value was 97.3%.

DISCUSSION

This study showed a strong link between elevated Sema4D levels and the presence and severity of CSF in patients undergoing coronary

Table 2. Comparison of angiographic features between the CSF and CNF groups

	CSF (n=79)	CNF (n=81)	p value
TFC, LCX	18.17±1.99	31.78±3.99	**<0.001**
TFC, RCA	17.49±1.93	33.83±4.08	**<0.001**
TFC, LAD (corrected)	17.81±1.81	33.32±3.92	**<0.001**
TFC, mean	17.82±1.15	32.98±2.64	**<0.001**

Values are expressed as means±standard deviation or number (%), as appropriate; statistically significant values are highlighted in bold.
CNF: Coronary normal flow, CSF: Coronary slow flow, LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery, TFC: Thrombolysis in myocardial infarction frame count

Table 3. Correlation analysis of Sema4D levels with inflammatory and neurohormonal markers in patients with CSF

	r	p
Lymphocyte count	0.16	**0.03***
NLR	0.27	**<0.001***
TC (mg/dL)	0.28	**<0.001***
LDL (mg/dL)	0.13	0.09
TG (mg/dL)	0.194	**0.014****
hs-CRP	0.73	**<0.001***
TFC, LCX	0.80	**<0.001***
TFC, RCA	0.88	**<0.001***
TFC, LAD	0.84	**<0.001***
TFC, mean	0.88	**<0.001***
SBP, mmHg	0.72	**0.032**
DBP, mmHg	0.68	**0.045**
Family history	0.20	**0.011****
Smoking	0.43	**<0.001****
Hypertension	0.48	**<0.001****
Hyperlipidemia	0.23	**0.002****
Antiplatelet drug	0.33	**<0.001****

*Pearson correlation coefficient, **Spearman correlation coefficient.
Correlation coefficient (r); CSF: Coronary slow flow, DBP: Diastolic blood pressure, hs-CRP: High-sensitivity C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio; LDL: Low-density lipoprotein, TC: Total cholesterol, TFC: Thrombolysis in myocardial infarction frame count, TG: Triglyceride, SBP: Systolic blood pressure, Sema4D: Semaphorin 4D

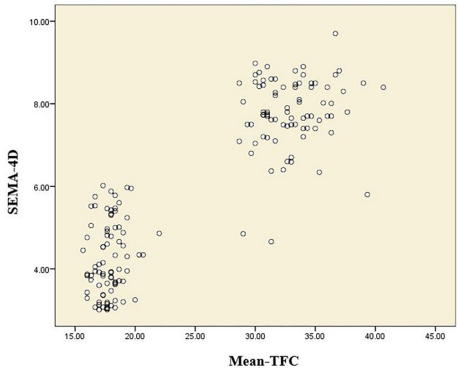

Figure 2. Correlation between serum Sema4D levels and mean TFC
Sema4D: Semaphorin 4D, TFC: Thrombolysis in myocardial infarction frame count

angiography for stable angina pectoris. Sema4D levels were also significantly correlated with inflammatory and oxidative stress markers, including hs-CRP and NLR. The degree of CSF, as measured by the mean TFC, was significantly associated with Sema4D levels. Additionally, Sema4D emerged as a novel and valuable biomarker in clinical settings for patients with stable angina pectoris, demonstrating strong diagnostic performance with high sensitivity and specificity in distinguishing patients with CSF in at least one coronary artery from healthy individuals.

Previous studies have identified smoking, hypertension, hyperlipidemia, male gender, obesity, and metabolic syndrome as major risk factors.[1] However, the precise underlying pathophysiological mechanisms and causes of CSF remain unclear. In line with prior research, our study found higher rates of hypertension, hyperlipidemia, and smoking in the CSF group compared to those with normal coronary flow.

The CSF phenomenon shares risk factors similar to those of atherosclerosis. Possible pathophysiological mechanisms involved in the development of CSF include endothelial dysfunction, chronic severe inflammation, oxidative stress, widespread atherosclerosis, vasomotor dysfunction in the microvasculature, small-vessel disease, and increased platelet count and/or activity.[1-4] Intravascular ultrasound studies have previously demonstrated the important roles of both epicardial coronary artery disease and microvascular dysfunction in the onset and progression of CSF.[23] De Bruyne et al.[24] highlighted the strong connection between abnormal slow flow in coronary arteries and atherosclerotic heart disease, which results from chronic severe inflammation, oxidative stress, free radical damage, and endothelial dysfunction, even without angiographically visible lesions.

Endothelial injury and dysfunction caused by inflammation, oxidative stress, and free radical damage may contribute to CSF development.[1-4] Various inflammatory markers, including paraoxonase, malondialdehyde, erythrocyte superoxide dismutase, visfatin, hs-CRP, NLR, and PLR, have been reported to be significantly associated with the presence of CSF in previous studies.[25-27] Consistent with these findings, our study found elevated levels of hs-CRP, interleukin-6,[28] and NLR in the CSF group compared to the CNF group. Moreover, Sema4D, identified as a novel inflammatory marker, was also shown to be increased in patients with CSF. A significant positive correlation was detected between Sema4D, hs-CRP, and NLR in patients with CSF.

CSF can be a significant cause of transient myocardial hypoperfusion, abnormal results on exercise stress tests, and impaired ventricular wall motion and function in patients with CNF who have stable

Table 4. Multiple linear regression analysis identifying independent predictors of Sema4D levels in patients with CSF

	Univariate		Multivariate	
	OR (CI 95%)	**p value**	**OR (CI 95%)**	**p value**
NLR	0.642 (0.292-0.992)	<0.001	-0.330 (-0.536-0.123)	0.002
TFC, RCA	0.200 (0.183-0.216)	<0.001	0.134 (0.089-0.179)	<0.001
TFC, LCX	0.211 (0.187-0.236)	<0.001	0.047 (0.005-0.089)	0.027
Lymphocyte count	0.000 (0.000-0.001)	0.034		
TC	0.018 (0.008-0.027)	<0.001		
TG	0.010 (0.002-0.018)	0.011		
hs-CRP	2.354 (2.011-2.698)	<0.001		
Family history	1.007 (0.354-1.661)	0.003		
Smoking	1.857 (1.300-2.413)	<0.001		
Hypertension	2.060 (1.526-2.594)	<0.001		
Hyperlipidemia	1.189 (0.550-1.827)	<0.001		
Antiplatelet drug	1.478 (0.870-2.086)	<0.001		
TFC, mean	0.222 (0.203-0.241)	<0.001		
TFC, LAD	0.200 (0.180-0.220)	<0.001		

Statistically significant values are highlighted in bold. Adjusted R^2, 0.81; p value <0.001.
CSF: Coronary slow flow, hs-CRP: High-sensitivity C-reactive protein, NLR: Neutrophil-to-lymphocyte ratio, LDL: Low-density lipoprotein, TC: Total cholesterol, TFC: Thrombolysis in myocardial infarction frame count, TG: Triglyceride, SBP: Systolic blood pressure, CI: Confidence interval, OR: Odds ratio

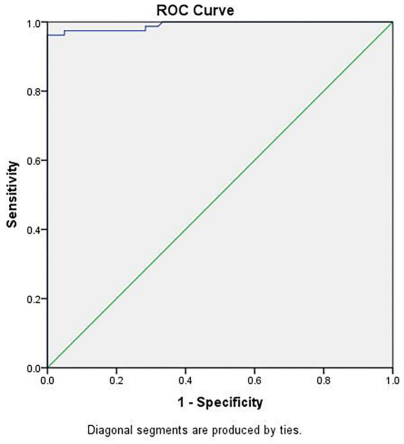

Figure 3. Receiver operating characteristic curve analysis to distinguish patients with CSF from those with CNF
CSF: Coronary slow flow, CNF: Coronary normal flow, ROC: Receiver operating characteristic

angina pectoris that is resistant to optimal medical treatment.[1,2] It may also contribute to various major adverse cardiovascular events (MACE), including stable angina pectoris, acute coronary syndromes, life-threatening arrhythmias, and sudden cardiac death.[1-4] Although the prognostic importance of CSF has been examined in multiple studies, the findings have been inconsistent. While some observational studies suggested a benign prognosis, others identified an association between CSF and MACE.[29,30] Nonetheless, the precise pathophysiological mechanisms linking CSF to MACE remain unclear.

Sema4D plays a role in inflammation, oxidative stress, atherosclerosis, and angiogenesis, potentially contributing to disease development and progression. Previous studies have reported associations between Sema4D and AF, heart failure, and coronary artery disease.[17,30,31] Willner et al.[32] found that Sema4D levels were elevated and correlated with N-terminal pro-brain natriuretic peptide in cases of acute heart failure. Lu et al.[30] also observed similar findings in heart failure patients, with the highest levels seen in those with diabetes. Moreover, Gong et al.[31] reported a link between Sema4D and coronary artery disease, noting increased levels particularly in patients with acute myocardial infarction. In this study, Sema4D was identified as an independent risk factor for developing coronary artery disease.[31] Furthermore, Xiang et al.[17] demonstrated a connection between elevated serum Sema4D levels and the presence of AF, especially in the non-paroxysmal group, highlighting Sema4D as a key independent risk factor for atrial remodeling. Consistent with Xiang et al.,[17] Can et al.[18] reported increased Sema4D levels in patients with PAF. They also investigated the relationship between Sema4D levels and AF recurrence following catheter ablation, finding significantly higher Sema4D levels in the non-ablation PAF group compared to patients who underwent ablation.[18] Moreover, Sema4D level showed a significant positive correlation with both hs-CRP and the NLR in PAF.[18]

Since no previous studies have shown a connection between Sema4D and CSF, we explored and identified this significant relationship in the present study. Furthermore, for the first time, we demonstrated an association between Sema4D and well-known inflammatory and oxidative markers such as hs-CRP and NLR in patients with CSF, highlighting an important role of Sema4D in the pathophysiology of CSF. These results indicate that elevated Sema4D levels may contribute to the presence and progression of inflammation, oxidative stress, and

endothelial and vasomotor dysfunction-key mechanisms involved in the development of CSF. Moreover, significant positive correlations were observed between Sema4D levels and the mean TFC, as well as the TFC values of all three coronary arteries, suggesting a potential role of Sema4D in the progression and severity of atherosclerosis leading to CSF. Our study also demonstrated, via ROC analysis, that Sema4D serves as a significant independent predictor for the presence of CSF. Sema4D appears to promote the secretion and activation of various pro-inflammatory cells, oxidative markers, and cytokines, triggering vascular inflammation, remodeling, and vasomotor dysfunction-particularly in endothelial and smooth muscle cells-which may accelerate the onset and progression of CSF. Overall, the main findings of this study support the idea that Sema4D may be involved in various coronary pathologies and that its levels can be detected through blood tests in clinical practice. This increase in Sema4D may be associated with chronic endothelial inflammation and oxidative stress in CSF.

Study Limitations

The present study has several limitations. First, it was conducted at a single center and was non-randomized, which may introduce selection bias. Second, the sample size was relatively small. Nevertheless, we were able to show a strong association between Sema4D level and both the presence and extent of CSF. Third, the potential coexistence of non-obstructive coronary artery disease and CSF could not be assessed due to the absence of data on atherosclerotic characteristics and coronary plaque burden, which could be assessed by intravascular ultrasonography-a technique not routinely used in clinical practice. Finally, the study's cross-sectional design meant there were no short- or medium-term follow-up data on MACEs.

CONCLUSION

This study demonstrated a statistically significant correlation between elevated serum Sema4D levels and the presence and extent of CSF in patients with stable angina pectoris who underwent coronary angiography. Furthermore, Sema4D was found to be associated with well-known inflammatory markers such as hs-CRP and NLR in this condition. Sema4D may have a critical role in the development and progression of coronary atherosclerosis, which can manifest as isolated CSF. To clarify this relationship, further large-scale, multicenter clinical studies are needed. Sema4D shows promise as a biomarker for identifying the presence and extent of CSF in patients with stable angina.

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Informed Consent: Consent form was filled out by all participants.

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