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sSema4D levels are increased in coronary heart disease and associated with the extent of coronary artery stenosis

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ABSTRACT

Objective: The aim of this study was to evaluate the association between serum soluble semaphorin4D (sSema4D) and coronary heart disease (CHD) and the extent of coronary artery stenosis.
Methods: The study included 188 cases that underwent coronary angiography because of precordial pain. One hundred and twenty-eight cases were diagnosed with CHD; 60 cases with negative coronary angiography served as controls. Coronary stenosis was evaluated by the number of diseased coronary artery and Gensini scoring system. Serum sSema4D and C-reactive protein (CRP) levels were measured.
Results: Serum sSema4D levels in CHD patients were significantly higher than those of controls ($p < 0.001$) and the levels in those with acute coronary syndrome (ACS) were significantly higher than those with stable angina pectoris ($p < 0.05$) and controls ($p < 0.05$). Higher levels of serum sSema4D were observed in the group with high Gensini scores. Serum sSema4D concentration was positively correlated with the Gensini score ($r = 0.735$, $p < 0.001$) and was the only independent factor that significantly influenced the Gensini score ($p < 0.001$). Serum sSema4D levels were positively correlated with CRP levels in all subjects ($r = 0.182$, $p = 0.013$). Elevated sSema4D and CRP levels were independently associated with the presence of CHD.
Conclusion: Serum sSema4D levels were increased in CHD patients, especially in those with ACS. Serum sSema4D may be an independent risk factor for CHD and reflect the extent of coronary artery stenosis to some extent.

1. Introduction

Coronary heart disease (CHD) is a growing public health problem and a leading cause of morbidity and mortality in modern society [1]. The underlying mechanisms of CHD are complicated. Accumulating evidence indicates that inflammation, neovascularization in the atherosclerotic plaque, and activation of platelets are closely correlated with the occurrence and development of atherosclerosis and thrombus formation [2,3]. The semaphorins family is a class of conserved proteins with an extracellular amino-terminal “sema” domain that was originally identified in the nervous system and has a defined function as axon guidance molecules [4]. Semaphorin 4D (Sema4D), also known as CD100, is a 150-kDa type I integral membrane glycoprotein and a member of the family of class IV semaphorins. It is expressed by most hematopoietic cells, including B and T lymphocytes, neutrophils, platelets, monocytes, and endothelial cells. Among them, T cells exhibit the highest levels of Sema4D, followed by neutrophils, platelets, and monocytes. All of these cells participate in the pathogenesis of atherosclerosis. The expression of Sema4D is generally increased after cell activation [5–8]. Once Sema4D is activated in different cell types, a 120-kDa soluble exodomain fragment called soluble Sema4D (sSema4D) is generated from membrane CD100 by proteolytic cleavage [9]. sSema4D can remain in the circulation and is capable of binding to and activating its two major receptors Plexin-B1 and CD72 [10]. Sema4D has been reported to be involved in a wide range of diseases, including neurogenesis, angiogenesis, osteogenesis, chronic inflammatory diseases, tumor angiogenesis and progression, and atherosclerosis [11–16]. In atherosclerosis, Sema4D was shown to promote platelet-platelet interaction, the adhesion of platelet and monocyte to endothelial cells, which is the critical step in thrombus formation [7,17]. It has been demonstrated that aortic plaques of Sema4D$^{-/-}$ApoE$^{-/-}$ mice presented a significant decrease in lipid staining, macrophage infiltration, and intimal neovascularization [18]. Sema4D$^{-/-}$LDLR$^{-/-}$ mice showed reduced lipid deposition and accumulation of platelets, and they exhibited a sixfold decrease in the frequency of arterial occlusion postinjury in the aorta when compared

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with LDLR$^{-/-}$ mice after 6 months of a high-fat diet [17]. These findings suggest that Sema4D is involved in the progression of atherosclerosis, especially in dyslipidemic states; the loss of Sema4D expression confers an anti-atherogenic effect. However, current research is limited to cell and animal experiments; the role of serum sSema4D in CHD patients remains unknown and has not been investigated.

Inflammation in the propagation of atherosclerosis and susceptibility to cardiovascular events is well established [19]. C-reactive protein (CRP) is a well-known systemic and strong predictor of coronary events in patients with CHD [20,21]. The relationship between inflammation and sSema4D is unclear. However, one study illustrated that, under proinflammatory stimuli, in vitro–cultured monocytes, differentiated macrophages, and foam cells were shown to express Sema4D [22]. Therefore, the main objective of this study was to evaluate serum sSema4D levels in CHD patients to find the associations between serum sSema4D and the presence of CHD. Serum CRP levels were also measured to investigate the relationship between sSema4D and inflammation cytokines. The correlations of serum sSema4D with other traditional risk factors were also assessed in this study.

2. Materials and methods

2.1. Study subject

This study included 188 consecutive patients who underwent coronary angiography because of suspected CHD. Coronary angiograms were reported by two experienced technicians who were blinded to the patient's identity, clinical diagnosis, and the research. The diagnosis of CHD, acute coronary syndrome (ACS), and stable angina pectoris (SAP) were documented with clinical symptoms, electrocardiogram changes, coronary angiograms, and laboratory markers of myocardial troponin T and creatine kinase. Among the subjects, 128 were diagnosed with CHD (CHD group) and 60 with negative coronary angiography served as controls (control group). The CHD group included 82 with ACS and 46 with SAP. The number of diseased coronary artery and the Gensini scoring system were used to evaluate the severity of the coronary lesions. According to the number of the three major coronary arteries with stenosis > 50%, patients were divided into one-, two-, and three-disease groups; the left main lesion was attributed to the two-disease group, and lesions with more than three branches were attributed to the three-disease group. There were 38 subjects with one-vessel, 44 with two-vessel, and 46 with three-vessel disease in the CHD group. According to coronary stenosis scored by the Gensini scoring system [23], the CHD group included 34 patients with a low Gensini score (< 20), 26 with a middle score (20–40), and 68 with a high score (> 40). All participant data were recorded and systematically entered into a Microsoft Excel chart.

Patients were excluded if they suffered from severe valvular heart disease, severe hepatic or renal dysfunction, acute infection, cerebrovascular disease, autoimmune diseases, malignant tumor, pulmonary embolism, pulmonary heart disease, or mental illness.

All subjects were informed of the purpose, risks, and benefits of the study and signed the informed consent. This study was approved by the institutional ethics committee of the second Xiangya Hospital of Central South University.

2.2. Clinical characteristics

Clinical characteristics were obtained from all subjects on admission, including age, gender, history of smoking, medical history, and medication (i.e. anti-ischemic, lipid-lowering, anticoagulant, and antiplatelet aggregation medicines). All the subjects took at least 300 mg aspirin and 300 to 600 mg clopidogrel before coronary angiography and discontinued when the angiography is negative [24]. Electrocardiography, echocardiography, serum lipid levels, indexes of liver and kidney functions, and CRP levels were also recorded.

2.3. Blood assessment

Peripheral venous blood was drawn from all subjects in the early morning after hospitalization and stored in EDTA anticoagulation vacuum tubes. Plasma samples were immediately centrifuged at 3000*g* for 10 min, and serum samples were kept at −80 °C for measurement.

The serum sSema4D concentration was measured using an enzyme-linked immunosorbent assay kit (Catalog No. IC-SEMA4D-Hu, ImmunoClone) following the protocol. First, all kit components and samples were prepared at room temperature (18–25 °C) before use. The diluted standard and blank EP tubes were set up. The standard solution or serum samples were then added to the wells (100 μL/well) and incubated for 2 h at 37 °C. The liquid of each well was removed, and detection reagent A and B working solutions were added sequentially and incubated at room temperature for 1 h. After washing, 3,3′,5,5′-tetramethylbenzidine substrate was added to the wells and incubated for 30 min in the dark. Absorbance was finally measured at 450 nm by a plate reader (Rayto, RT-6500).

Serum triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), lipoprotein a [LP(a)], apolipoprotein B (APO-B), CRP, and indexes of liver and renal functions were measured at the central chemistry laboratory in our hospital using the automatic analyzer 7600 series from Hitachi Limited.

2.4. Statistical analysis

The data were analyzed using SPSS 22.0 medical statistician software. Quantitative data were expressed as the mean value ± standard deviation. Continuous variables with a non-normal distribution are presented as median value (interquartile interval), and qualitative variables are presented as frequencies. Normal distribution data were compared using Student's *t*-test between two groups, and one-way analysis of variance (ANOVA) was used to compare the difference among multiple groups. Spearman correlation analysis was performed to determine factors that correlated with Gensini score. To determine the independent parameters correlated with Gensini score, the parameters were tested using multiple backward stepwise regression analysis. Receiver-operating characteristic (ROC) curves were constructed, the area under the ROC curve (AUC) was calculated, and threshold values were estimated to detect sensitivity and specificity of sSema4D and CRP levels for the diagnosis of CHD. Stepwise multiple regression analysis was used to analyze the risk factors for CHD. A two-tailed p value < 0.05 was statistically significant.

3. Results

3.1. Basic characteristics

The clinical characteristics of the CHD and control group are shown in Table 1. Male gender, history of hypertension, and diabetes mellitus were higher in the CHD group than in the control group ($p < 0.05$). The TG blood levels were significantly higher and the HDL-C blood levels were significantly lower in the CHD group than in the control group ($p < 0.05$). There were no significant differences in age, TC, LDL-C, LP(a), APO-B, or indexes of liver and renal functions and other clinical characteristics between the two groups (Table 1).

3.2. Comparison of sSema4D and CRP levels in CHD and control group

Serum sSema4D levels in the CHD group and controls were 5.03 ± 2.15 ng/mL and 3.75 ± 1.85 ng/mL, and CRP levels in the CHD group and controls were 7.44 ± 15.15 mmol/L and 2.03 ± 5.22 mmol/L, respectively. The serum sSema4D and CRP levels in the CHD group were obviously significantly higher than in the control group (both $p < 0.05$, Table 1). Their levels were further

Table 1
Baseline characteristics and sSema4D levels in the CHD patients and controls

Variable	CHD (n = 128)	Control group (n = 60)	*p* value
Age (y)	61 ± 11	59 ± 11	0.205
Gender (male, %)	92 (71.8%)	29 (48.0%)	0.002
Hypertension, n (%)	86 (67.2%)	25 (41.7%)	0.001
Diabetes mellitus, n (%)	35 (27.3%)	8 (13.3%)	0.033
LVEDd (mm)	50.1 ± 7.6	49.4 ± 7.5	0.542
LAD (mm)	38.0 ± 6.1	37.5 ± 7.9	0.605
EF (%)	57.13 ± 6.01	58.43 ± 7.67	0.205
WBC ($\times 10^9$/L)	6.19 ± 2.91	5.47 ± 3.11	0.375
ALT (μ/L)	29.30 (14.4, 34.7)	24.47 (13.2, 31.6)	0.054
AST (μ/L)	26.14 (13.2, 31.4)	23.16 (12.5, 30.1)	0.467
Cr (μmol/L)	68.40 (58.7, 77.8)	65.30 (51.9, 72.2)	0.083
BUN (mmol/L)	5.52 ± 2.24	5.23 ± 2.13	0.591
UA (μmol/L)	304.23 ± 78.16	292.18 ± 85.14	0.253
TG (mmol/L)	1.95 ± 1.23	1.50 ± 0.82	0.004
TC (mmol/L)	3.98 ± 1.04	3.99 ± 0.88	0.944
HDL-C (mmol/L)	1.02 ± 0.28	1.18 ± 0.30	< 0.001
LDL-C (mmol/L)	2.44 ± 0.92	2.36 ± 0.75	0.524
LP(a) (mmol/L)	243.57 (64.3, 291.4)	218.42 (60.1, 229.2)	0.079
APO-B (mmol/L)	0.87 ± 0.25	0.79 ± 0.23	0.075
CRP (mmol/L)	7.44 ± 15.15	2.03 ± 5.22	< 0.001
sSema4D (ng/mL)	5.03 ± 2.15	3.75 ± 1.85	< 0.001

Data are expressed as means ± standard deviation for normally distributed data, median (interquartile range) for nonnormally distributed data, or number (%) for categorical variables.
WBC, white blood cell; LVEDd, left ventricular end diastolic dimension; LAD, left atrial diameter; EF, ejection fraction; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Cr, creatinine; BUN, blood urea nitrogen; UA, uric acid; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LP(a), lipoprotein a; APO-B, apolipoprotein B; CRP, C-reactive protein; sSema4D, soluble semaphorin4D.

compared among the control, SAP, and ACS groups. Levels of sSema4D in the ACS and SAP groups were 5.55 ± 2.21 ng/mL and 4.10 ± 1.70 ng/mL, and the CRP levels in these two subgroups were 9.72 ± 17.62 mmol/L and 3.37 ± 7.89 mmol/L. Serum sSema4D and CRP levels were highest in the ACS group. sSema4D in the ACS group were significantly higher than those in the SAP group ($p = 0.032$) and control group ($p = 0.015$); CRP in the ACS group were significantly higher than those in the SAP group ($p < 0.001$) and control group ($p < 0.001$). There were no significant differences in the levels of these two indexes between the SAP group and the control group. ANOVA test for trend analysis illustrated CRP increased with the severity of CHD, there is no significant trend with sSema4D (Table 2).

3.3. Relationship between levels of sSema4D, CRP, and the extent of coronary lesions in the CHD group

There were no significant differences in serum sSema4D among the one-, two-, and three-vessel disease groups. The levels of CRP were significantly higher in the three-vessel disease group when compared with the one- and two-vessel disease groups. ANOVA test for trend showed CRP increased with the number of diseased coronary artery (Table 2).

Levels of sSema4D in low, middle, and high Gensini score groups were 3.18 ± 1.05, 4.07 ± 1.08, and 6.30 ± 2.01 ng/mL; CRP levels in these three groups were 4.11 ± 10.35, 3.27 ± 4.07, and 10.28 ± 18.58 mmol/L, respectively. Levels of sSema4D and CRP were higher in the group with a high Gensini score than in those with a low and middle Gensini score and the controls ($p < 0.05$). The sSema4D levels in the group with a middle Gensini score were significantly higher when compared with the group with a low Gensini score and the controls ($p < 0.05$). On ANOVA test for trend, the expression of sSema4D elevated with the increase of Gensini score; sSema4D levels were positively correlated with the Gensini score ($r = 0.735$, $p < 0.001$, Fig. 1a) (Table 2).

The levels of CRP were slightly increased in the low- and middle-Gensini score groups when compared with the controls, but the difference was not significant (Table 2). There was no correlation between CRP levels and Gensini score by Spearman correlation analysis.

A multivariate stepwise regression analysis was further performed to evaluate the association between sSema4D and Gensini score in a model adjusted for the parameters including age, gender, hypertension, diabetes mellitus, TG, TC, LDL-C, HDL-C, Lp(a), APO-B, CRP and sSema4D; the result showed that serum sSema4D was the only independent factor that significantly influenced the Gensini score (standardized $\beta = 8.217$, 95% confidence interval [CI]: 6.884–9.550, $p < 0.001$).

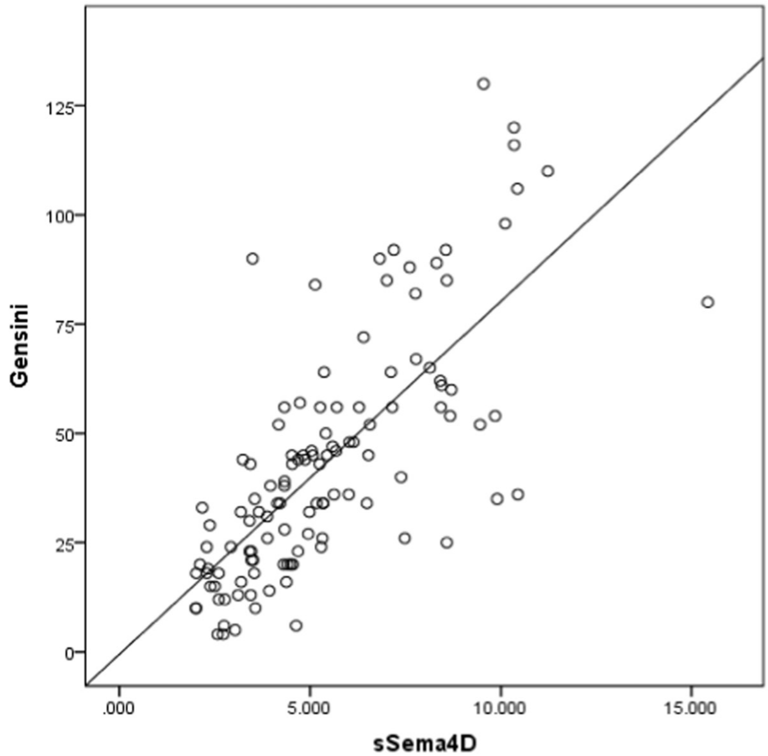
3.4. Relationship between sSema4D and other CHD risk factors

Spearman correlation analysis revealed that the sSema4D levels were positively correlated with age ($r = 0.323$, $p < 0.001$) and CRP ($r = 0.182$, $p = 0.013$) (Fig. 1b) but not with gender ($r = -0.105$, $p = 0.150$), TG ($r = -0.045$, $p = 0.536$), TC ($r = 0.058$, $p = 0.431$), HDL-C ($r = 0.015$, $p = 0.841$), LDL-C ($r = 0.040$, $p = 0.582$), and the presence of hypertension ($r = 0.010$, $p = 0.889$) and diabetes mellitus ($r = 0.081$, $p = 0.267$).

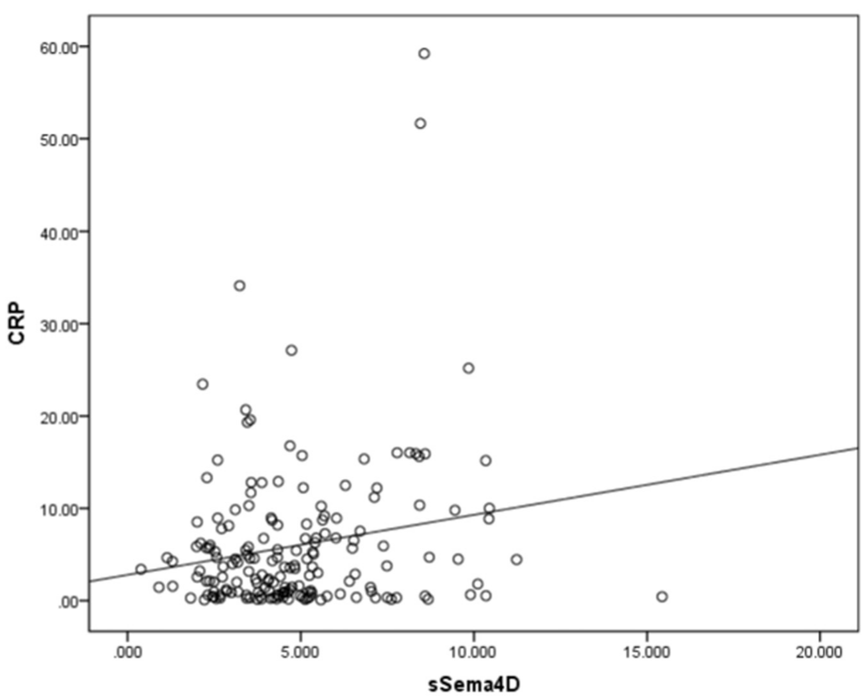
Table 2
Comparison of the levels of sSema4D and CRP in the CHD and control groups, different vessel disease and Gensini score groups.

Group	CRP (mmol/L)	ANOVA test for trend	sSema4D (ng/mL)	ANOVA test for trend
Control (n = 60)	2.03 ± 5.22	$F_1 = 18.13$	3.75 ± 1.85	$F_2 = 4.174$
SAP (n = 82)	3.37 ± 7.89	$P_1 < 0.001$	4.10 ± 1.70	$P_2 = 0.315$
ACS (n = 46)	9.72 ± 17.62***		5.55 ± 2.21*	
One-vessel (n = 38)	3.88 ± 7.39	$F_3 = 4.753$	5.03 ± 1.88	$F_4 = 0.763$
Two-vessel (n = 44)	4.58 ± 8.24	$P_3 = 0.01$	4.72 ± 2.23	$P_4 = 0.468$
Three-vessel (n = 46)	12.49 ± 21.86***		5.28 ± 2.28	
Low score (n = 34)	4.11 ± 10.35	$F_5 = 3.168$	3.18 ± 1.05	$F_6 = 46.522$
Middle score (n = 26)	3.27 ± 4.07	$P_5 = 0.405$	4.07 ± 1.08*	$P_6 < 0.001$
High score (n = 68)	10.28 ± 18.58***		6.30 ± 2.01**	

ANOVA test for trend: CRP increased with the severity of CHD ($F_1 = 18.13$, $P_1 < 0.001$); CRP increased with the number of diseased coronary artery ($F_3 = 4.753$, $P_3 = 0.01$); sSema4D elevated with the increase in Gensini scores ($F_6 = 46.522$, $P_6 < 0.001$).
SAP, stable angina pectoris; ACS, acute coronary syndrome.
Other abbreviations are as shown in Table 1.
* $p < 0.05$, compared to control, SAP or low score group.
** $p < 0.01$, compared to low- or middle-score group.
*** $p < 0.001$, compared to control, SAP, one-, two-vessel, low- or middle-score group.



(a)



(b)

Fig. 1. sSema4D levels were positively correlated with Gensini score ($r = 0.735$, $p < 0.001$) (a) and CRP ($r = 0.182$, $p = 0.013$) (b) in Spearman's correlation.

3.5. The ROC of sSema4D and CRP levels in predicting the presence of CHD

A cut-off sSema4D value of 5.24 ng/mL was determined to predict the presence of CHD with 44.4% sensitivity and 86% specificity (ROC AUC 0.686; 95% CI: 0.602–0.769; $p < 0.001$) (Fig. 2). A cut-off CRP of 3.61 mmol/L was found to predict CHD with 66.7% sensitivity and 84% specificity (ROC AUC 0.787; 95% CI: 0.714–0.859; $p < 0.001$) (Fig. 2). The combined detection of CRP and sSema4D predicts CHD with 77.8% sensitivity and 76% specificity (ROC AUC 0.818; 95% CI: 0.750–0.886; $p < 0.001$) (Fig. 2).

3.6. Analysis of the risk factors on the presence of CHD

A stepwise multiple regression was used to identify factors associated with the presence of CHD. The results showed that TG, HDL-C, CRP, and sSema4D were significantly associated with the presence of

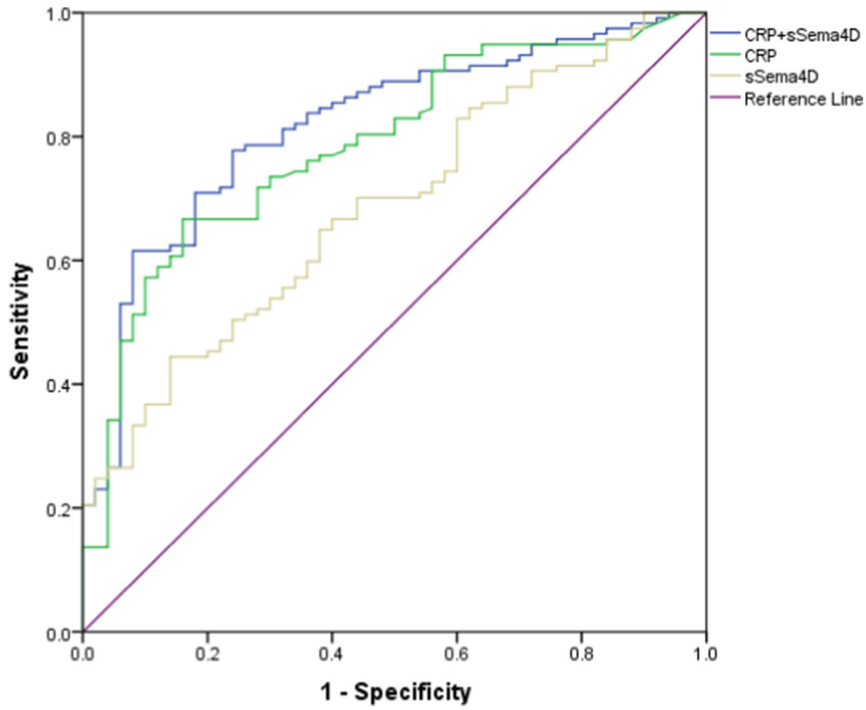


Fig. 2. Receiver-operating characteristic (ROC) curve analysis for predictive values of serum sSema4D and CRP concentrations in presence of CHD.

Table 3
Stepwise multiple regression analysis of the factors on the presence of CHD.

	B(95% CI)	Beta	*p*	Vif
TG	0.076(0.021, 0.130)	0.208	0.007	1.144
HDL-C	−0.310(−0.523, −0.097)	−0.217	0.005	1.140
CRP	0.010(0.002, 0.018)	0.004	0.011	1.223
sSema4D	0.040(0.013, 0.068)	0.224	0.004	1.176

CI, confidence interval.
Other abbreviations are as shown in Table 1.

CHD after adjusting for age, gender, hypertension, diabetes mellitus, TC, LDL-C, LP(a) and APO-B (Table 3).

4. Discussion

This is an exploratory study that aimed to evaluate serum sSema4D levels in CHD patients and controls without CHD. For the first time, we found that the serum levels of sSema4D were increased in CHD, especially in ACS patients, and positively correlated with the Gensini score of coronary artery lesion in the patients with CHD. Serum sSema4D was the only independent factor that significantly influenced the Gensini score. Elevated sSema4D and CRP levels were independently correlated with the presence of CHD.

Sema4D and its two major receptors, Plexin-B1 and CD72, were expressed on the surface of platelets, monocytes, macrophages, and T cells, which play pivotal roles in atherosclerosis [7]. Subsequent studies have shown a growing recognition of the role of Sema4D and its two receptors in platelet activation, atherosclerosis, and thrombotic diseases [7,17,18,25]. It has been demonstrated that Sema4D was expressed in human atheroma, more specifically in plaque macrophages and foam cells [20]; the degree of neovascularization and the infiltration of macrophages were decreased in the aorta plaque of $ApoE^{-/-}Sema4D^{-/-}$ mice when compared with that of the $ApoE^{-/-}$ mice after receiving a normal diet for 3 months [18]. The loss of the Sema4D gene conferred a protective function against atherosclerosis and significantly reduced thrombus formation and frequency of arterial occlusion in the mice model [17]. The potential mechanism by which sSema4D promotes atherosclerosis remains unknown, existing evidence points out its role in activating the platelet response, accelerating angiogenesis, and promoting cell-to-cell contact in monocyte-endothelial cell interaction [26–28]. Recently, elevated serum levels of sSema4D were reported in patients with atrial fibrillation and heart failure, but the specific mechanism remains unclear [29,30]. There are still no clinical data on sSema4D in CHD patients. Thus, we evaluated the levels of sSema4D in CHD patients and found that serum sSema4D levels were significantly higher in CHD patients than in those without CHD, and the levels were independently correlated with the presence and the extent of coronary artery stenosis.

The Thrombolysis in Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) scoring systems are the most popular and commonly used scoring tools in clinical practice for evaluating the risk of adverse outcomes in patients with ACS [31]. In the present study, both ACS and SAP patients were included; thus, the severity of coronary atherosclerosis was evaluated using the Gensini scoring system, by calculating a score based on the number of stenotic coronary artery segments, the degree of the lumen stenosis, and the localization of stenotic changes [23]. We found that elevated sSema4D is associated with an increased Gensini score in patients with CHD. Multivariate stepwise regression analysis demonstrated that sSema4D was the only factor that significantly influenced the Gensini score. However, we failed to find different sSema4D levels between the one-, two-, and three-vessel disease groups. This may be attributed to the fact that this convenient traditional classification may underestimate the degree of coronary artery disease [32]. Taken together, these findings provide a clue that sSema4D is associated with the presence and the severity of coronary atherosclerosis.

It has been demonstrated that T cells, monocytes, and platelets serve as a source of Sema4D in atheroma plaques [20]. Recently, studies have reported that Sema4D is correlated with the number of vulnerable atherosclerotic plaques, characterized by increased lipid deposition, frequency of arterial occlusion, and accumulation of macrophage and platelets [7,17,18]. Furthermore, Sema4D mediates neovascularization, and platelet activation occurs in the atherosclerotic plaque and accelerates plaque growth and instability [18,31]. Thus, it is reasonable to hypothesize that sSema4D is associated with the vulnerability of atherosclerotic plaque. Our study found that serum sSema4D levels were significantly higher in ACS patients than in SAP patients and controls, however, it didn't increase with the severity of CHD in ANOVA test for trend. This suggests that sSema4D levels may not accurately reflect the vulnerability of atheromatous plaque in the CHD.

Inflammation is a recognized pathogenic factor for atherosclerosis [33]. Chronic inflammation is linked with future cardiovascular disease events [34]. CRP is known as an unspecific marker for inflammation, associated with an acute-phase response [35]. In this study, the expression of CRP in ACS patients was significantly higher than in the control subjects, which is in accordance with previous studies [36,37]. Furthermore, we found the group with a high Gensini score had significantly higher CRP than the group with a low Gensini score and three-vessel disease had significantly higher CRP than one- or two-vessel disease. sSema4D was correlated with CRP, demonstrating that the role of sSema4D in CHD may be mediated by systemic inflammation. Whether sSema4D can be considered an inflammatory factor requires further investigation. We did not find a relationship between CRP and Gensini score, which is not consistent with previous findings. This discrepancy may explain by a relatively small-scale study and prevent the results from reaching the statistical significance.

The diagnostic value of sSema4D and CRP in CHD was analyzed in the current study. Single serum sSema4D and CRP had poor sensitivity (44.4% and 66.8%) but good specificity (86% and 84%) to diagnose CHD, and the AUC was no more than 0.80, whereas the combination detection of these two parameters had a 77.8% sensitivity and 76% specificity with AUC 0.818 using ROC analysis. It seems that sSema4D and CRP levels are equivocal in separating CHD patients from healthy controls by ROC curve analysis; a single test could not meet the requirements of clinical practice, although multivariate analysis demonstrated that their levels were independent markers for the presence of CHD. Combination detection appears to provide better sensitivity but less specificity. Larger-scale studies and basic research are needed to better define the predictive value and pathogenesis of sSema4D in CHD.

Atherosclerosis and related diseases remain the leading causes of death, despite advances in evidence-based therapy. Strategies direct at reducing the atherosclerosis burden and improving the stability of vulnerable plaques are urgently needed to decrease cardiovascular events. sSema4D is increased in CHD, especially in ACS patients, and positively correlated with the severity of the coronary artery lesion. It may be a new biomarker of atherosclerosis and CHD and a promising future approach for controlling cardiovascular events.

5. Conclusion

sSema4D levels were increased in CHD patients, especially in those with ACS. Serum sSema4D may be an independent risk factor for CHD and reflect the extent of coronary artery stenosis to some extent.

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Conflict of interest

The authors declare no conflict of interest.

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