Original Article

The value of serum Sema4D level in reflecting the inflammatory state of acute ST-segment elevation myocardial infarction

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Background: This study sought to investigate the expression of soluble semaphorin 4D (sSema4D) in acute ST-segment elevation myocardial infarction (STEMI) and to explore its value in evaluating the inflammatory status of acute myocardial infarction (AMI).

Methods: From October 2020 to June 2021, 100 patients with STEMI diagnosed at the Department of Cardiology of our hospital were selected as the STEMI group, 83 patients with unstable angina (UA) were selected as the UA group, and 78 patients with negative coronary angiography (CAG) were selected as the control group. The baseline data of the 3 groups of patients were recorded, the sSema4D levels were determined, the expression of sSema4D levels in AMI was analyzed, and the value of sSema4D levels in reflecting inflammatory state of AMI was explored.

Results: Compared with UA group and control group, the expression of sSema4D in peripheral blood of STEMI group was significantly increased (P<0.001), which could better reflect the inflammatory status of patients with STEMI than traditional inflammatory indicators [hypersensitive c-reactive protein (hs-CRP)] (P<0.05). The receiver operating characteristic (ROC) curve showed that sSema4D (AUC =0.780, cut-off =19.62, 95% CI: 0.629, 0.837, P<0.001) was more specific than hs-CRP (AUC =0.697, cut-off =3.39, 95% CI: 0.629, 0.765, P<0.001) in reflecting the inflammatory status of STEMI patients.

Conclusions: sSema4D levels have certain value in reflecting the inflammatory state of STEMI.

Keywords: Soluble semaphorin 4D (sSema4D); ST-segment elevation myocardial infarction (STEMI); hypersensitive c-reactive protein (hs-CRP); inflammatory response

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Introduction

Acute myocardial infarction (AMI) is a cardiovascular disease caused by myocardial ischemia necrosis, which is caused by the rupture or invasion of coronary atherosclerotic plaque and secondary occlusive thrombosis. It is characterized by an acute onset and high mortality. It is an acute and critical disease of the cardiovascular system.

Studies have proved that smoking, heavy drinking, hypertension, hyperlipidemia and diabetes are risk factors for coronary atherosclerotic heart disease (1-4). Atherosclerosis is not only the result of a large amount of lipid accumulation in the arterial wall, from the formation of lipid striae to the formation of complex atherosclerotic plaque and its complications, but also inflammatory reaction plays a vital role throughout each stage. Such as white blood cell infiltration and the changing expressions of endothelial inflammatory factors.

Semaphorin 4D (Sema4D), also known as CD100, is

a homodimer protein that belongs to the signal family of axon guidance proteins. The semaphorin family has become a popular area of research recently due to the multiple functions of these family members in the immune system, which plays an important role in T cell activation, antibody production, and intercellular adhesion (5). The expression of Sema4D usually increases after cell activation as well as under the stimulation of various inflammatory factors (6,7), Sema4D was activated to soluble Sema4D (sSema4D) on the cell surface. sSema4D was expressed by most hematopoietic cells including platelets, neutrophils, T and B lymphocytes, endothelial and monocytes cells. T cells express the highest level of sSema4D, followed by neutrophils, platelets, and monocytes. All these cells are involved in the pathogenesis of atherosclerosis (8,9). sSema4D has been proved to promote the interaction between platelets and platelets, as well as the adhesion of platelets to endothelial and monocytes cells, which is the key step in thrombosis (10).

More and more studies have shown that sSema4D is closely related to the occurrence and development of inflammation, while the study of sSema4D in STEMI is rare.

This study intends to explore the role and potential clinical significance of sSema4D in the occurrence and development of STEMI by detecting the expression of sSema4D in patients with STEMI; The difference of specificity and sensitivity between sSema4D and hs-CRP in reflecting the inflammatory status of patients with STEMI were also studied. We present the following article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-124/rc).

Highlight box

Key findings

- Our research results showed that changes in sSema4D levels had certain value in reflecting the inflammatory state of STEMI.

What is known and what is new?

- sSema4D promotes thrombosis and may accelerate plaque growth and instability. It is highly expressed in patients with heart failure and atrial fibrillation. CRP is a traditional inflammatory index, which can reflect the inflammatory state of acute myocardial infarction to some extent.
- No previous clinical researches have been conducted on sSema4D levels in patients with STEMI. Now, our study finds that sSema4D levels were not only highly expressed in STEMI group, but also more able to reflect the inflammatory state of STEMI group than CRP.

What is the implication, and what should change now?

- Serum Sema4D level can be used to reflect the inflammatory state of STEMI. The sSema4D levels may have auxiliary value in monitoring the condition of STEMI, which can be expected to become a new inflammatory index for the treatment of STEMI. We should pay more attention to the further study.

Methods

Subjects

From October 2020 to June 2021, 100 patients with STEMI (56 males and 44 females), 83 with unstable angina (UA) (47 males and 36 females), and 78 (47 males and 31 females) with negative coronary angiography (CAG) who had been admitted to the Department of Cardiology at our hospital were selected and included in this study. The study conforms to the provisions of the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of The Second Affiliated Hospital of Nantong University (No. 2019KN09), and all subjects signed the informed consent form.

Exclusion criteria and inclusion criteria

In order to be enrolled in this study, subjects must meet the following inclusion criteria: (I) be aged 18–75 years old; (II) meet the diagnostic criteria of the "Guidelines for Primary Diagnosis and Treatment of ST-segment Elevation Myocardial Infarction (2019)" (11); (III) have received a coronary intervention within 12 hours.

Subjects were excluded from the study if they met any of the following exclusion criteria: (I) had severe heart valve disease, severe congenital heart disease, pulmonary heart disease, or hypertrophic obstructive cardiomyopathy; (II) had liver dysfunction [which was defined as alanine transaminase (ALT) or total bilirubin >3 times the upper normal limit], or renal insufficiency (which was defined as serum creatinine >1.5 times the normal upper limit); (III) were at high risk of bleeding; (IV) had an active peptic ulcer or skin ulcer; (V) were allergic to antiplatelet drugs; (VI) had cardiogenic shock; (VII) had a malignant tumor; (VIII) had a left main lesion as shown by CAG.

Treatment methods

All patients were given aspirin (300 mg) and clopidogrel (300 mg) before surgery. After surgery, the patients were given nitrates, aspirin, clopidogrel, atorvastatin, beta blockers, and angiotensin converting enzyme inhibitors

according to the "Guidelines for Primary Diagnosis and Treatment of ST-segment Elevation Myocardial Infarction (2019)" (12) to exclude the influence of antiplatelet drugs on the experiment.

Research methods

General information about the patients was collected. Immediately after admission, 2 mL of cubital venous blood was drawn from each patient and placed in a dry lithium heparin blood collection tube and sent to the biochemical laboratory of our hospital for testing. Before surgery, 3 mL of blood was drawn from each patient and placed in dry lithium heparin blood collection tubes and centrifuged at 3,000 ×g for 15 min with a centrifuge. The supernatant was then carefully collected in EP tubes with a pipette. The EP tubes were numbered and grouped, and stored at –80 ℃ in a refrigerator awaiting testing.

All the routine laboratory tests were sent to the biochemical laboratory of our hospital (automatic blood analyzer source: Sysmex Model: XN-9100; automatic biochemical analysis source: Nanjing Sanhe Instrument Co., Ltd.; model: LAboSPECT008AS; Microplate Reader: Thermo Model: Multiskan FC).

Enzyme-linked immunosorbent assays

According to the protocol, the serum Sema4D concentration was measured with enzyme-linked immunosorbent assay kit. First, prepare all kit components and samples at room temperature (18–25 ℃) before use. Establish diluted standard EP tube and blank EP tube. Then add the standard solution or serum sample to the well (100 μL/well) and incubated at 37 ℃ for 2 hours. Remove the liquid from each well, add the working solution of test reagent A and B in turn, and incubate at room temperature for 1 hour. After washing, 3, 3', 5, 5' - tetramethylbenzidine substrate was added to the hole and incubated in the dark for 30 minutes. Finally, the absorbance is measured at 450 nm through a flat reader (Rayto, RT-6500).

Statistical analysis

The data were statistically analyzed using SPSS23.0 medical statistics software. The normally distributed quantitative variables are presented as the mean ± standard deviation. The non-normally distributed quantitative variables are represented by the interquartile P50 (P25, P75). The qualitative variables are represented as frequencies. The normally distributed measurement data were compared using the *t*-test, the categorical variables were compared using the chi-square test; differences among multiple groups were compared using a 1-way analysis of variance. The non-normally distributed data were tested using a non-parametric test. The receiver operating characteristic (ROC) and area under the curve (AUC) were used to compare the ability of CRP and sSema4D to reflect the inflammatory state of STEMI, and their sensitivity and specificity were calculated. Youden's index was used to determine the optimal cut-off value. A P value <0.05 was considered statistically significant.

Results

Basic features

There was no significant difference in the levels of clinical indicators, such as age, gender, smoking history, hypertension, diabetes, liver function (ALT), creatinine (Cr), total cholesterol (TC) and Low-Density Lipoprotein Cholesterol (LDL-C) among the groups. The levels of Inflammation index (hs-CRP) (P<0.05), and sSema4D (P<0.001) in STEMI group were higher than those in UA group and control group (*Table 1*). According to the results, sSema4D can better reflect the inflammatory reaction state than hs-CRP in STEMI group.

Levels of sSema4D in each group

Compared to the UA group and the control group, hs-CRP and sSema4D in the peripheral blood of the STEMI group were increased, and the differences were statistically significant (hs-CRP: P<0.05; sSema4D: P<0.001) (*Figures 1*,*2*). While the hs-CRP and sSema4D levels in UA group and the control group had no statistical significance (P>0.05).

Comparison of hs-CRP and sSema4D in reflecting the inflammatory state of STEMI

The ROC curve was drawn to evaluate the value of hs-CRP (AUC =0.697, cut-off =3.39, 95% CI: 0.629, 0.765, P<0.001) (*Figure 3*) and sSema4D (AUC =0.780, cut-off =19.62, 95% CI: 0.629, 0.837, P<0.001) (*Figure 4*) in reflecting the inflammatory state of STEMI. sSema4D is more effective than hs-CRP in reflecting the inflammatory state of STEMI [specificity (sSema4D *vs.* hs-CRP): 76.4% *vs.* 66.5%] (*Table 2*).

Table 1 Baseline characteristics and sSema4D expression in STEMI, UA, and control groups

Variable	STEMI group (n=100)	UA group (n=83)	Control group (n=78)	P value
Age (years)	65.0 (45.0, 72.0)	69.0 (56.0, 75.0)	63.0 (57.0, 70.0)	0.136
Gender (male), n (%)	56 (37.3)	47 (31.3)	47 (31.3)	0.835
Smoking, n (%)	53 (36.6)	48 (33.1)	44 (30.3)	0.794
Hypertension, n (%)	57 (35.6)	55 (34.4)	48 (30.0)	0.440
Diabetes, n (%)	29 (46.8)	19 (30.6)	14 (22.6)	0.223
ALT (U/L)	31.5 (19.0, 49.5)	28.0 (17.0, 40.0)	25.0 (19.0, 36.0)	0.172
Cr (μmol/L)	65.0 (52.3, 78.4)	68.2 (59.0, 83.0)	65.7 (56.4, 80.5)	0.118
TC (mmol/L)	4.43±1.34	4.18±1.07	4.20±1.01	0.206
LDL-C (mmol/L)	2.8 (2.2, 3.5)	2.7 (2.1, 3.4)	2.5 (1.9, 3.1)	0.064
NT-proBNP (pg/mL)	1,502.5 (698.5, 3,229.5)	570.0 (102.3, 1,312.0)	133.5 (57.1, 545.6)	<0.05
hs-CRP (mg/L)	10.3 (1.4, 35.2)	3.3 (0.9, 12.3)	0.5 (0.1, 2.4)	<0.05
sSema4D (ng/mL)	20.80 (18.52, 23.90)	17.71 (16.81, 19.76)	17.70 (16.49, 18.91)	<0.001

Data are represented as interquartile P50 (P25, P75) or n (%). sSema4D, soluble semaphorin 4D; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; ALT, alanine transaminase; Cr, creatinine; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; NT-proBNP, N-terminal precursor B-type brain natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein.

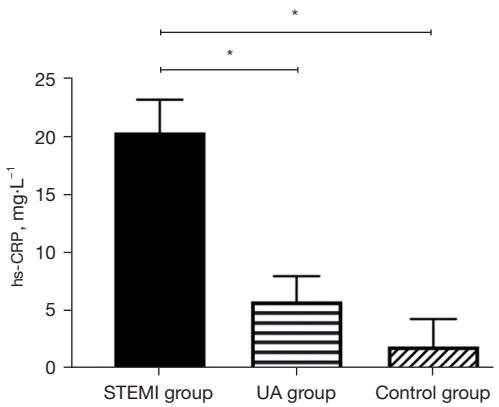

Figure 1 Comparison of hs-CRP levels in the STEMI group, UA group, and control group. *, P<0.05. hs-CRP, hypersensitive c-reactive protein; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

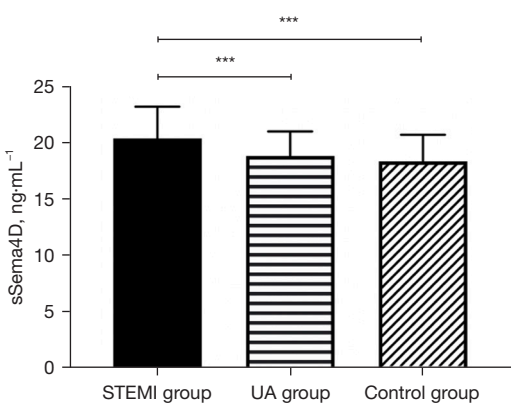

Figure 2 Comparison of serum sSema4D levels in the STEMI group, UA group, and control group. ***, P<0.001. sSema4D, soluble semaphorin 4D; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Discussion

At present, the diagnosis of STEMI mainly depends on troponin I, electrocardiogram, cardiac ultrasound (13), etc. At the same time, many studies have pointed out that STEMI is not only closely related to various acute and chronic inflammation in the process of occurrence and development, but also needed to solve the problem of restenosis caused by inflammatory reaction and neointimal hyperplasia after treatment (14). With the rapid development and popularization of percutaneous coronary intervention (PCI), the restenosis problem after PCI had attracted more and more attention. At present, it was generally recognized that the mechanism is hypoxia or hypoxia in the diseased vascular tissue, repeated balloon dilation and intravascular stent implantation, which cause

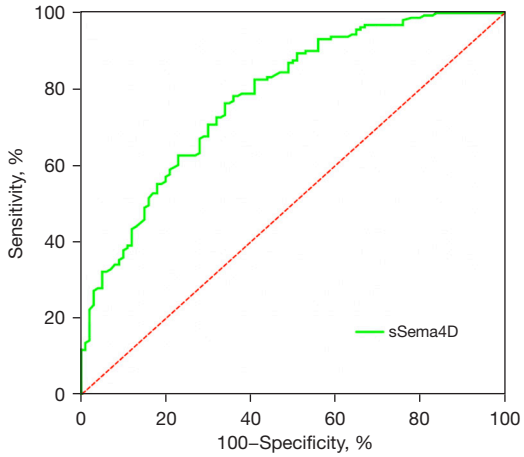

Figure 3 The ROC curve of sSema4D reflecting the inflammatory state of STEMI. sSema4D, soluble semaphorin 4D; ROC, receiver operating characteristic; STEMI, ST-segment elevation myocardial infarction.

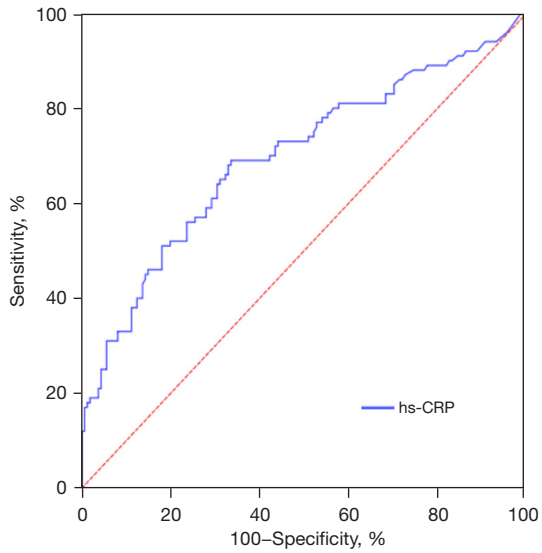

Figure 4 The ROC curve of hs-CRP reflecting the inflammatory state of STEMI. hs-CRP, high-sensitivity C-reactive protein; ROC, receiver operating characteristic; STEMI, ST-segment elevation myocardial infarction.

mechanical injury of vascular intima and local tissue necrosis. The potential inflammatory factors produced can cause acute and chronic inflammatory reaction of vascular wall. Therefore, it is important to find the switch of inflammatory reaction and monitor the occurrence of inflammatory reaction from the source (15).

sSema4D binds to a variety of receptors such as plexin B1/B2, CD72 and plexin C1, which mediate the effects of sSema4D on epithelial cells, immune cells, nerve cells, and endothelial cells, thereby playing a pleiotropic role in immune activation, angiogenesis, bone metabolism, and neurodevelopment (16-20). sSema4D has been confirmed to be expressed in foam cells and plaque macrophages (10). Mou (21) found a dual mechanism for the absence of Sema4D-mediated platelet activation and aggregation. As platelets express both Sema4D and plexinB1, Sema4D, which is initially attached to the surface of platelets, can act as a ligand for platelet-platelet interaction for initial coupling, and then induce platelet activation through the activation of the tyrosine kinase (Syk), thereby promoting thrombosis (22). A previous study has shown that Sema4D mediates the plexinB1 pathway to indirectly promote thrombosis (23). Thrombosis is an important pathological process of AMI.

The underlying mechanism by which sSema4D promotes atherosclerosis is unclear. Studies have shown that it plays a role in promoting cell-to-cell contact in monocyte-endothelial cell interactions, activating platelet responses accelerating angiogenesis and promoting cell-to-cell contact in monocyte-endothelial cell interactions (24-26). Other studies have reported that sSema4D is related to the number of vulnerable atherosclerotic plaques, characterized by increased lipid deposition, accumulation of macrophages and platelets, and increased frequency of arterial occlusion (22,23). Recently, studies have pointed out that the sSEMA4D level in patients with heart failure and atrial fibrillation is increased, but the exact mechanism is unclear (27,28). Can reported that sSema4D seems to be a novel biomarker of the recurrence after the catheter ablation

Table 2 Comparison of hs-CRP and sSema4D in reflecting the inflammatory state of STEMI

Factor	AUC	95% CI	P value	Cut-off	Sensitivity (%)	Specificity (%)
sSema4D	0.7800	0.629, 0.837	<0.001	19.62	66.0	76.4
hs-CRP	0.697	0.629, 0.765	<0.001	3.39	69.0	66.5

hs-CRP, high-sensitivity C-reactive protein; sSema4D, soluble semaphorin 4D; STEMI, ST-segment elevation myocardial infarction; AUC, area under the curve.

(CA) procedure in paroxysmal atrial fibrillation (PAF) (29). In addition, sSema4D activates platelets, mediates angiogenesis, and accelerates plaque growth and instability (30,31). A previous study showed that sSema4D down-regulated the expression of pro-inflammatory cytokines in macrophages because it weakened the NF of THP-1 macrophages stimulated by lipopolysaccharide-κ activation of B signal pathway (32).

Inflammation is known to be a causative factor in atherosclerosis (33). Chronic inflammation is associated with future cardiovascular events (34). Hs-CRP is a non-specific marker of inflammation and is associated with acute phase responses (35). This study found that sSema4D can reflect the inflammatory state of patients with STEMI, and after comparison, it was found that sSema4D has better specificity than hs-CRP. To sum up, sSema4D is significantly overexpressed in patients with AMI, reflecting the inflammatory status of patients with acute myocardial infarction. Compared with the current non-specific inflammatory indicators, sSema4D is more effective in reflecting the inflammatory status, and may have auxiliary value for monitoring the disease, and may become a new inflammatory indicator for preventing coronary atherosclerosis. More importantly, sSema4D is expected to be a therapeutic target for STEMI, which is worthy of further study.

Conclusions

In conclusion, our study shows that the change of sSema4D level has certain value in evaluating the inflammatory status of STEMI. Therefore, the sSema4D level may be an effective indicator to evaluate the inflammation of STEMI. We intend to expand the sample size and extend the follow-up time to further examine the correlation between the sSema4D level and the inflammatory status of STEMI.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-124/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-124/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-124/coif). KZ reports that this work was supported by the Jiangsu Provincial Health Commission Project (grant No. Z2021005), and Nantong Science and Technology Bureau Plan Project (grant No. MS12020016). The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committee of The Second Affiliated Hospital of Nantong University (No. 2019KN09), and all subjects signed the informed consent form.

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