Effect of combining sST2/HDL-C ratio with risk factors of coronary heart disease on the detection of angina pectoris in Chinese: a retrospective observational study

Yifan Zhang, Lili Zhang, Zhong Chen^

Department of Cardiology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China
Contributions: (I) Conception and design: Y Zhang, Z Chen; (II) Administrative support: Z Chen; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: L Zhang; (V) Data analysis and interpretation: Y Zhang, Z Chen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.
Correspondence to: Dr. Zhong Chen. Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, No. 600, Yishan Road, Shanghai 200233, China. Email: zhongchen7498@hotmail.com.

Background: Soluble suppression of tumorigenicity 2 (sST2), a member of the interleukin-1 receptor family, binds IL-33, preventing its interaction with membrane-bound form ST2 (ST2L), thereby blocking its protection against atherosclerosis. High-density lipoprotein cholesterol (HDL-C), a variety of lipoproteins with mean size of 8–10 nm and density of 1.063–1.21 g/mL, not only acts as lipid transporters that transport cholesterol reversely, but also carries a variety of proteins and microRNAs endowing it with the ability to prevent cardiovascular disease. Most studies on the relationship between sST2 and coronary heart disease (CHD) are limited to acute myocardial infarction (AMI). The present study set out to investigate the association between the sST2/HDL-C ratio and angina pectoris.

Methods: A retrospective single-center cohort study was conducted and a total of 250 patients with chest pain that formed a convenience series, hospitalized between January 2018 and August 2020, were enrolled. Patients with AMI, acute and chronic heart failure, structural heart disease, renal insufficiency [estimate glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2], rheumatic immune diseases, malignant tumors and severe infections were excluded. Patients with missing data were also excluded. Two hundred and nine patients were finally enrolled. Levels of sST2, HDL-C and sST2/HDL-C ratio were measured and calculated after admission. The angina pectoris was diagnosed by combining clinical features, coronary angiography results and cardiac troponin I levels. The diagnosis value of sST2/HDL-C on angina pectoris was analyzed by binary logistic analysis and the receiver operating characteristic (ROC) curve and area under the ROC curve (AUC) assesses.

Results: Patients with stable angina pectoris (SAP) or unstable angina pectoris (UAP) accounted for a larger proportion (28.8% *vs.* 42.9%, P=0.035) in patients with the higher sST2/HDL-C ratio. Binary logistics regression showed that for every unit of sST2/HDL-C increase, the risk of angina pectoris increased by 38.8% (OR =1.388, P=0.018). By subgroup analysis, a stronger association was found in non-diabetic patients (OR =1.551, P=0.006), non-hypertension patients (OR =1.700, P=0.025), non-smokers (OR =1.527, P=0.049) and patients aged <65 y (OR =1.693, P=0.019). ROC curve showed that AUC was higher [0.643 (0.566, 0.719) *vs.* 0.618 (0.540, 0.696)] and the sensitivity of diagnosis increased significantly (84.0% *vs.* 49.3%) by combining sST2/HDL-C with risk factors of CHD.

Conclusions: A higher ratio of sST2/HDL-C was associated with an increased risk of angina pectoris. sST2/HDL-C combined with CHD risk factors showed increased diagnostic value in identifying angina pectoris.

Trial Registration: Clinical trial: ChiCTR-DDD-17013908.

^ ORCID: 0000-0002-3618-5073.

Introduction

Background

With the increasing prevalence of coronary heart disease (CHD), CHD became an important contributor to death in China, being the cause of 40% of deaths in the Chinese population (1). At present, the gold standard for the diagnosis of CHD mainly relies on cardiovascular imaging which is invasive and radioactive (2). Meanwhile, increased myocardial enzymes are limited to the diagnosis of acute myocardial infarction (AMI) (3). Hence, there has been growing interest in finding other biomarkers to improve the accuracy of diagnosis of angina pectoris and among these emerging biomarkers (4-9), soluble suppression of tumorigenicity 2 (sST2) is a promising biomarker.

Rationale and knowledge gap

There are two forms of ST2 in the body. One is membrane-
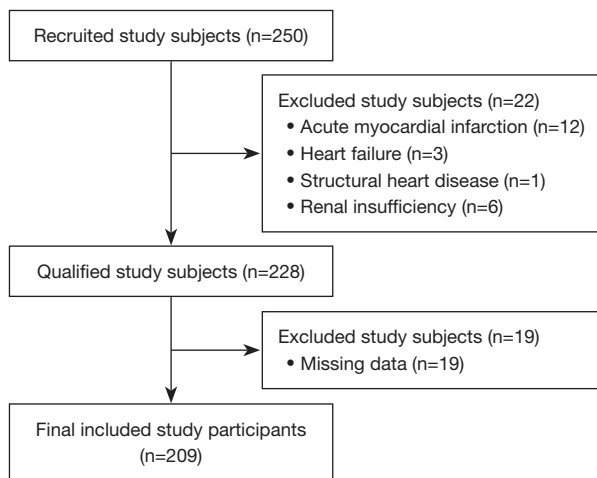

Highlight box

Key findings

• The sST2/HDL-C ratio was positively associated with the risk of angina pectoris, with a stronger association among people with low-risk of cardiovascular disease. Combining sST2/HDL-C with traditional CHD risk factors could improve the diagnostic specificity of angina pectoris.

What is known and what is new?

• sST2 is associated with the development of cardiovascular disease. Many studies are focused on changes in sST2 levels in acute myocardial infarction, while several studies have shown no significant increase in sST2 in patients with angina pectoris.

• We found that sST2/HDL-C can help identify angina pectoris more accurately, especially in population with low-risk of cardiovascular disease.

What is the implication, and what should change now?

• This study implied that sST2/HDL-C is appropriate to be used as a screening indicator. Further studies targeting people at low cardiovascular risk are needed to verify whether the specificity of this new model could be further confirmed.

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bound form ST2 (ST2L), which can bind to IL-33, playing a role in preventing hypertrophy and fibrosis and modulation of Th1/Th2; while the other is sST2, which acts as a decoy receptor, binding to free IL-33 and blocking ST2/IL-33 signaling (10,11). Many studies have shown that soluble ST2 is associated with the development of cardiovascular disease (CVD) such as aortic dissection, heart failure, acute coronary syndrome and atrial fibrillation (12-15). The presence of inflammatory cells in coronary plaques from patients with UAP provides the basis for the atherosclerotic inflammatory hypothesis that was supported by plenty of evidence (16,17). It was demonstrated that Th cells play an important role in the inflammation of plaque formation. It was suggested that most Th2-associated cytokines, such as IL-5 and IL-13, could induce M2 macrophage, which resolves inflammation and regresses atherosclerosis (15,18,19). The binding of IL-33 and ST2L on the T cells can mediate the TH2 immune response by facilitating the differentiation of naïve T cells into Th2 cells and activating resting Th2 cells (20,21). sST2, a decoy receptor produced by the identical mRNA of ST2L, also binds to IL-33, thus blocking the effects on Th2 cells by preventing IL-33 from interact with ST2L (22).

Besides the cholesterol intimal infiltration, atherosclerotic coronary artery disease has a more complex pathogenesis which involves chronic inflammation of the coronary artery wall driven by activation of immune systems, eventually leading to the rupture or erosion of the plaque which leads to myocardial infarction (23). From a molecular mechanism perspective, it was reported that sST2 blocked the effects of IL-33 on Th2 cells, aggravating the inflammation and the burden of plaque. Such mechanism confers the potential of IL-33 and sST2 as indicators of the plaque burden and predictors of coronary events which is a noninvasive and nonradioactive index, compared with cardiovascular imaging of coronary angiography, the gold standard for the diagnosis of CHD. However, most of the current studies on the relationship between sST2 and CHD are limited to changes in sST2 levels in AMI, and several studies have shown no significant increase in sST2

Figure 1 The flowchart of participants.

in patients with unstable angina and chronic coronary syndrome (14,24,25).

High-density lipoprotein cholesterol (HDL-C), a variety of lipoproteins with mean size of 8–10 nm and density of 1.063–1.21 g/mL, not only acts as lipid transporters that transport cholesterol reversely, but also carries a variety of proteins and microRNAs. Such features endow it with the ability to prevent CVD (26).

Objective

We speculated that in the development of coronary atherosclerosis, the promoting effects of sST2 are antagonized by the protective effects of HDL-C. This study set out to validate the hypothesis that the ratio of sST2/HDL-C, a new parameter for balance between atherosclerosis promoting and protective factors can help identify angina pectoris more accurately. We present the following article in accordance with the STARD reporting checklist (available at https://cdt. amegroups.com/article/view/10.21037/cdt-22-520/rc).

Methods

Study population

We conducted a retrospective study at the Department of Cardiology, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China, from January 2018 to August 2020. The exclusion criteria were AMI, acute and chronic heart failure, structural heart disease, renal insufficiency [estimate

glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2], rheumatic immune diseases, malignant tumors and severe infections. The sample size was calculated using PASS15 and 228 subjects were planned to be included (an estimated sample size of 190 patients, including 20% missing data to be excluded). Missing or indeterminate data on the index test and reference standard were excluded. 209 subjects with chest pain that formed a convenience series were finally included in the study (*Figure 1*). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital East Campus. A waiver of consent was obtained due to the retrospective nature of the study (decision date: 2016-6-12; decision number: 2016-006).

Collection of clinical and biochemical variables

Information including age, medical conditions and medication history are collected after enrollment. Fasting venous blood is collected to test hemoglobin, leukocytes, albumin, uric acid, creatinine, D-dimer, fasting blood glucose (FBG), NT-proBNP, cardiac troponin I (cTnI), creatine kinase myocardial band (CK-MB), myoglobin, cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C and triglycerides. The tester was not aware of the study subject's diagnosis.

Diagnosis of angina pectoris

The diagnosis of angina pectoris including stable and unstable angina pectoris (SAP and UAP) was made by reviewing all patients' clinical features, coronary angiography images, CK-MB and cTnI levels. There were no adverse events happened. Patients with chest pain who have at least one coronary stenosis ≥50% and no elevation of CK-MB and cTnI are diagnosed as angina pectoris. Patients with one or more of the following three main ischemic symptoms: (I) rest angina pectoris (lasting >20 minutes); (II) new-onset of severe angina pectoris within 2 months; (III) increasing pattern of angina pectoris (frequency, intensity, duration) (27) without elevations in CK-MB and cTnI are defined as UAP. The others are defined as SAP. The assessors were not aware of the subject's index test results.

Quantitative detection of sST2

Venous blood was drawn 10 minutes before the

coronary angiography and there were no adverse events happened. The ethylenediaminetetraacetic acid (EDTA) anticoagulation sample was immediately centrifuged at 2,000 g for 10 min, and the plasma was placed in –80 ℃ refrigeration for unified testing. sST2 concentration was detected using the enzyme-linked immunosorbent assay (ELISA) method, with the kits purchased from Shanghai Jinkang Biotechnology Co., Ltd. (China). The tester was not aware of the subject's diagnosis.

Statistical methods

Continuous variables which conform to the normal distribution are presented as means ± SD. The other continuous variables are presented as median and quartile. Categorical variables are presented as percentages. The study subjects were divided into Q1 group (sST2/HDL-C ≤488 pg/mL) and Q2 group (sST2/HDL-C >488 pg/mL). The χ^2-test (for categorical variables), independent sample t-test or Kruskal–Wallis H test (for continuous variables) were used to assess the differences among patients with different sST2/HDL-C ratios. The effect of sST2/HDL-C on angina pectoris risk and subgroup analyses was analyzed by binary logistic analysis. The AUC [area under the receiver operating characteristic (ROC) curve] was used to assess the ability of different models to identify angina pectoris. The statistical PASS 15, software packages R and SPSS 25.0 were used to analyze data. All statistical tests were two-sided, and a P value less than 0.05 was considered statistically significant.

Results

Baseline characteristics and outcomes of subjects

Two hundred and nine patients were enrolled and divided into 2 groups according to the median of the sST2/HDL-C ratio. The baseline data were shown in *Table 1*. In the higher sST2/HDL-C ratio group (Q2), patients have lower cholesterol levels and patients with SAP or UAP accounted for a larger proportion (28.8% *vs.* 42.9%, P=0.035).

Relationship between the sST2/HDL-C ratio, CHD risk factors and angina pectoris

Smoking and sST2/HDL-C have a significant predictive impact on the risk of angina pectoris. Smokers had a 110.6% increased risk of angina pectoris compared with non-smokers (OR =2.106, P=0.015). For every unit of sST2/HDL-C increase, the risk of angina pectoris increased by 38.8% (OR =1.388, P=0.018; *Figure 2*).

Results of subgroup analyses

It was shown in subgroup analyses that there was a stronger association between sST2/HDL-C and angina pectoris in non-diabetic patients (OR =1.551, P=0.006), non-hypertension patients (OR =1.700, P=0.025), non-smokers (OR =1.527, P=0.049) and patients aged <65 years (OR =1.693, P=0.019; *Table 2*).

Identification of angina pectoris with various multivariable logistic regression models

As shown in *Table 3* and *Table 4*, the model including traditional CHD risk factors (age, diabetes, hypertension, smoking) had an AUC of 0.618 (0.540, 0.696) in identifying angina pectoris with 72.4% specificity and 49.3% sensitivity (*Figure 3*, *Table 5*). After combining traditional CHD risk factors with sST2/HDL-C, the AUC was 0.643 (0.566, 0.719) with 37.3% specificity and 84.0% sensitivity (*Figure 4*, *Table 5*).

Discussion

Key findings

The present study demonstrated that the sST2/HDL-C ratio was positively associated with the risk of angina pectoris, and there exists a stronger association between sST2/HDL-C and angina pectoris among non-smokers, patients without diabetes mellitus, hypertension, or aged <65 years old. Furthermore, combining sST2/HDL-C with traditional CHD risk factors could improve the diagnostic sensitivity of angina pectoris.
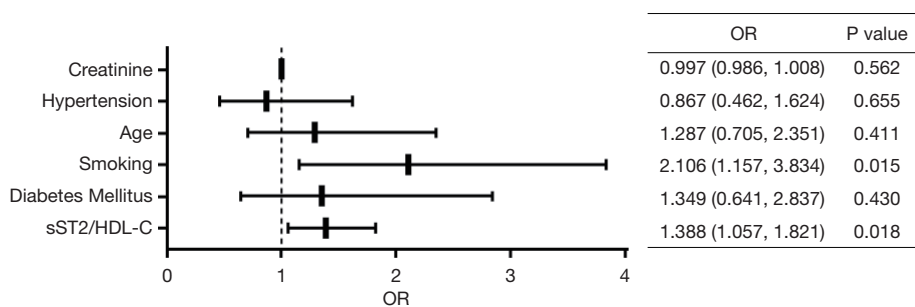
Strengths and limitations

Our findings suggest that sST2/HDL-C is effective in distinguishing angina patients in population with low-risk of CVD. At the same time, both indicators are relatively easy to obtain. However, several limitations of this study should be mentioned. First, our study only involved Chinese patients, thus our conclusions could not be applied to other populations universally. Secondly, the findings came from single-center and relatively small sample study. Thirdly,

Table 1 Baseline characteristics of the study subjects

Characteristics	sST2/HDL-C (n=209)		P value
	Q1 (≤488 pg/mL) (N=104)	Q2 (>488 pg/mL) (N=105)	
Age (years)	65.12±13.69	64.25±12.84	0.637
Male	89 (85.6)	93 (88.6)	0.519
Laboratory indexes			
Hemoglobin (g/L)	139 [126, 150]	140 [130, 150]	0.511
WBC (×10^9/L)	5.9 [5.1, 7.8]	6.5 [5.1, 7.3]	0.300
Albumin (g/L)	40 [37, 44]	40 [37, 43]	0.357
Uric acid (μmol/L)	371 [311, 430]	371 [294, 444]	0.778
Creatinine (μmol/L)	73 [60, 84]	74 [62, 90]	0.370
D-dimmer (μg/L)	0.24 [0.16, 0.47]	0.28 [0.16, 0.54]	0.634
FBG (mmol/L)	5.30 [4.92, 6.17]	5.40 [5.05, 6.15]	0.639
Serum biomarkers of myocardial fibrosis and damage			
NT-proBNP (ng/mL)	89 [31, 374]	108 [33, 749]	0.745
cTnI (μg/L)	0.01 [0.00, 0.02]	0.01 [0.01, 0.04]	0.073
CK-MB (μg/L)	1.50 [1.00, 2.20]	1.50 [1.02, 2.28]	0.767
Myoglobin (μg/L)	27.55 [20.95, 39.45]	29.30 [22.18, 42.15]	0.234
sST2 (pg/mL)	391.29 [257.47, 477.37]	672.15 [562.38, 798.46]	<0.001
Lipid parameters			
LDL-C (mmol/L)	2.81±0.84	2.63±0.77	0.101
HDL-C (mmol/L)	1.15 [0.87, 1.40]	0.99 [0.88, 1.10]	<0.001
Triglyceride (mmol/L)	1.18 [0.87, 2.07]	1.29 [0.97, 1.81]	0.717
Cholesterol (mmol/L)	4.33±1.14	3.97±0.99	0.017
Cardiovascular disease and risk factors			
Hypertension	67 (64.4)	68 (64.8)	0.959
Diabetes mellitus	20 (19.2)	21 (20.0)	0.889
Smoking	53 (51.0)	51 (48.6)	0.730
UAP + SAP	30 (28.8)	45 (42.9)	0.035
UAP	15 (16.9)	20 (25.0)	0.192
SAP	15 (16.9)	25 (29.4)	0.049
Medical history, n (%)			
ACEI/ARB	48 (46.2)	55 (52.4)	0.368
Anticoagulant drugs	69 (66.3)	71 (67.6)	0.845
B-receptor blockers	48 (46.2)	43 (41.0)	0.448
Lipid-lowering drugs	64 (61.5)	61 (58.1)	0.612
CCB	33 (31.7)	41 (39.0)	0.269

Data are expressed as mean ± SD, number of patients (percentage) or median [IQR]. WBC, white blood cells; FBG, fasting blood glucose; NT-proBNP, N-terminal pro-B-type natriuretic peptide; cTnI, cardiac troponin I; CK-MB, creatine kinase myocardial band; sST2, soluble suppression of tumorigenicity 2; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; UAP, unstable angina pectoris; SAP, stable angina pectoris; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

	OR	P value
Creatinine	0.997 (0.986, 1.008)	0.562
Hypertension	0.867 (0.462, 1.624)	0.655
Age	1.287 (0.705, 2.351)	0.411
Smoking	2.106 (1.157, 3.834)	0.015
Diabetes Mellitus	1.349 (0.641, 2.837)	0.430
sST2/HDL-C	1.388 (1.057, 1.821)	0.018

Figure 2 Binary logistic regression analysis of sST2/HDL-C and CHD risk factors for prediction of angina pectoris. sST2, soluble suppression of tumorigenicity 2; HDL-C, high density lipoprotein cholesterol; CHD, coronary heart disease; OR, odd ratio.

Table 2 Effect of sST2/HDL-C on angina risk in subgroup analysis

	Number of participants	OR (95% CI)	P value
Diabetes mellitus			
Yes	41	1.023 (0.499, 2.100)	0.950
No	168	1.551 (1.135, 2.121)	0.006
Smoking			
Yes	104	1.389 (0.950, 2.033)	0.090
No	105	1.527 (1.002, 2.326)	0.049
Hypertension			
Yes	135	1.228 (0.870, 1.733)	0.242
No	74	1.700 (1.068, 2.704)	0.025
Age			
≥65 years	105	1.297 (0.888, 1.895)	0.178
<65 years	104	1.693 (1.089, 2.632)	0.019

sST2, soluble suppression of tumorigenicity 2; HDL-C, high density lipoprotein cholesterol; OR, odd ratio.

to ensure data integrity, we have removed all missing and indeterminate values. This may result in selection bias. So further sample expansion or refinement of missing or indeterminate values is needed to reduce such bias.

Comparison with similar researches

An association between sST2 and AMI has been found, but multiple studies have failed to find an association between sST2 and SAP or UAP (14,24). Even so, there was a study demonstrating higher serum concentrations of sST2 in patients with microvascular angina (28). Such a paradox illustrates whether sST2 is a marker for angina pectoris remains controversial. We hypothesized that the effect of elevated sST2, aggravating the plaque burden is antagonized

by the protective effects of HDL-C. Such a hypothesis is tested in patients with angina pectoris by a novel parameter, the sST2/HDL-C ratio, which eliminates the balance of the effect of circulating sST2 that increases the plaque burden and the atheroprotective effect of HDL-C.

Explanations of findings

After adjusting for the atheroprotective factors, a positive association was found between circulating sST2 and the risk of angina pectoris. Subgroup analysis showed that the effect size of this relationship was more significant in patients without hypertension, non-diabetes mellitus, non-smokers, or younger patients, demonstrating the stronger association between sST2/HDL-C and the risk of angina pectoris in

Table 3 Identification of angina pectoris with various multivariable logistic regression models

Factors	B value	Standard error	Wald value	OR (95% CI)	P value
Include traditional CHD risk factors					
Hypertension	−0.140	0.314	0.197	0.870 (0.470, 1.611)	0.657
Diabetes	0.296	0.372	0.633	1.344 (0.648, 2.788)	0.426
Smoking	0.712	0.300	5.653	2.039 (1.133, 3.667)	0.017
Age	0.006	0.012	0.316	1.007 (0.984, 1.030)	0.574
Include traditional CHD risk factors and sST2/HDL-C					
Hypertension	−0.155	0.318	0.238	0.856 (0.459, 1.597)	0.625
Diabetes	0.291	0.380	0.588	1.338 (0.636, 2.817)	0.443
Smoking	0.729	0.304	5.740	2.074 (1.142, 3.767)	0.017
Age	0.007	0.012	0.404	1.008 (0.985, 1.031)	0.525
sST2/HDL-C	0.313	0.137	5.212	1.367 (1.045, 1.788)	0.022

OR, odds ratio; CHD, coronary heart disease; sST2, soluble suppression of tumorigenicity 2; HDL-C, high density lipoprotein cholesterol.

Table 4 Identification of angina pectoris with old and new models

Old model	New model	AUC (95% CI)	P value
Traditional CHD risk factors	–	0.618 (0.540, 0.696)	0.005
Traditional CHD risk factors	+ sST2/HDL-C	0.643 (0.566, 0.719)	<0.001

AUC, area under curve; CHD, coronary heart disease.
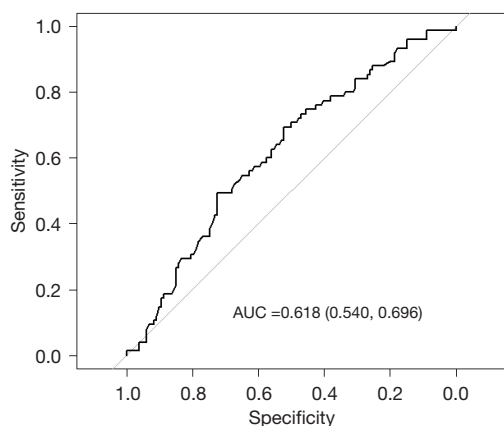
Figure 3 ROC curve of using traditional CHD risk factors to identify angina pectoris. The specificity of using traditional CHD risk factors in identifying angina pectoris was 72.4%, and the sensitivity was 49.3%. ROC, receiver operating characteristic curve; AUC, area under ROC curve; CHD, coronary heart disease.

Table 5 The cross-tab of the risk of angina assessed by the old and new model and the results of the reference standard

Reference standard	Risk (old model)		Risk (new model)	
	≤41.9%	>41.9%	≤29.4%	>29.4%
No	97	37	50	84
Yes	38	37	12	63

relatively healthier people. There are pieces of evidence suggesting that HDL-C correlates with cardiovascular risk only in healthy individuals and plasma HDL-C levels are inversely associated with the risk of CVD, which can explain the reason why the sST2/HDL-C ratio is more strongly associated with the risk of angina pectoris in patients without hypertension or diabetes mellitus (29,30).

A novel finding in this study is the magnification of the

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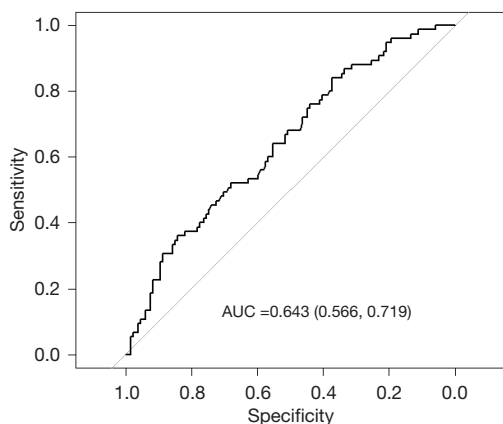
Figure 4 ROC curve of combining traditional CHD risk factors with sST2/HDL-C to identify angina pectoris. The specificity of combining sST2/HDL-C with traditional CHD risk factors in identifying angina was 37.3%, and the sensitivity was 84.0%. ROC, receiver operating characteristic curve; AUC, area under ROC curve; CHD, coronary heart disease.

relationship between the sST2/HDL-C ratio and the risk of angina pectoris in non-smokers. A variety of studies have proved that impaired serum lipid profile and vascular inflammation induced by cigarette smoking result in adverse effects on the cardiovascular system (31-33). Our findings suggested that the sST2 mediated plaque burden may be stronger in non-smokers. However, the P value for non-smokers in the subgroup study was borderline (P=0.049), hinting that such association may not be reliable. Meanwhile, we found that among the younger patients, the relationship between sST2/HDL-C and angina pectoris was stronger. Numeric studies suggested that aging might contribute to the susceptibility to atherosclerosis (34,35). This finding indicates that sST2 plays a secondary role in plaque formation in a high-risk group of CHD, and plays a major role in healthier people, which facilitates risk assessment of CVD earlier in healthier people. Hence, it is implied that sST2/HDL-C is appropriate to be used as a screening indicator in population with low-risk of CVD. Furthermore, we found that combining sST2/HDL-C with traditional CHD risk factors can improve the sensitivity of the diagnosis of angina. The specificity of the new model is only 37.3%. Many studies suggested that sST2 was related to the occurrence and development of various diseases. This may result in a lower specificity of the model. Since subgroup analysis suggested that sST2/HDL-C was more significant in the diagnosis of angina in

younger and healthier people, sensitivity should play a more important role in screening people at low risk for possible angina pectoris. Furthermore, sST2/HDL-C should be more effective in identifying angina pectoris patients in the population at lower cardiovascular risk referring to the result of the subgroup analysis, so that the specificity of the new model should be higher in such population.

Implications and actions needed

sST2/HDL-C combined with CHD risk factors showed increased diagnostic value in identifying angina pectoris, especially for younger and healthier people. This suggests that sST2/HDL-C is more appropriate in screening CHD in the population. Further studies targeting people at low cardiovascular risk are needed to verify whether the specificity of this new model could be confirmed. Meanwhile, multicenter, prospective and large-sample studies are needed to further clarify the role of sST2/HDL-C in the diagnosis of angina pectoris.

Conclusions

In summary, a higher level of sST2/HDL-C ratio was an independent predictor of angina pectoris. The predictive value of this relationship was stronger in patients without hypertension, non-diabetes mellitus, non-smokers and younger patients.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-22-520/rc

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