Original Article

Diagnostic value and method of soluble transferrin receptor for suspected coronary artery disease: a case-control study

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Background: Many studies have pointed out that iron overload in the body is a risk factor for coronary atherosclerosis (AS), while there are also studies that show that iron deficiency is associated with coronary AS. There is still no consensus on how iron metabolism affects coronary artery disease (CAD). This study aimed to analyze the relationship between iron metabolism indexes and CAD, investigate the diagnostic value of soluble transferrin receptor (sTfR) in suspected CAD, and establish a diagnostic model.

Methods: This was a retrospective study. A total of 268 people with CAD-like symptoms who underwent coronary angiography in the Department of Cardiovascular Medicine, The Second Affiliated Hospital of Anhui Medical University from September 2022 to May 2023 without other chronic diseases or related medication history were included in the study and formed a continuous series including 188 CAD patients and 80 control subjects. Each iron metabolism index was divided into a grade variable according to tertile. The comparison of CAD morbidity between the tertiles and nonlinear correlation test was conducted to investigate the relationship between iron metabolism indexes and CAD risk. We used restricted cubic spline (RCS) to plot the relationship curve between sTfR and CAD risk and to determine the sTfR value corresponding to the minimal odds, according to which we divided the total sample into the "sTfR low level" subgroup and the "sTfR high level" subgroup. Logistic regression analyses were used to establish diagnostic models in both subgroups. The diagnostic efficiency of the indexes and models was compared by receiver operating characteristic (ROC) analysis.

Results: There is a "J" shape correlation between sTfR and CAD risk. Age/sTfR ratio [area under the curve (AUC) =0.690, 95% confidence interval (CI): 0.598–0.782, specificity 0.488 and sensitivity 0.842] has the best diagnostic efficiency in the "sTfR low level" subgroup. The diagnostic efficiency of sTfR (AUC =0.701, 95% CI: 0.598–0.803, specificity 0.541 and sensitivity 0.797) in the "sTfR high level" subgroup was higher than that of cardiac troponin I (cTnI) (AUC =0.674, 95% CI: 0.564–0.784, specificity 0.719 and sensitivity 0.653). The specific diagnostic methods were as follows: (I) When sTfR ≤1.087 mg/L, calculate the age/sTfR ratio, which indicates the diagnosis of CAD when the result is >58.595; (II) We can directly make a preliminary clinical diagnosis of CAD when sTfR >1.205 mg/L. Except for the above 2 cases, we can initially rule out a diagnosis of CAD.

Conclusions: The iron metabolism index sTfR correlates with CAD morbidity in a "J" shape. With superior diagnostic efficacy than cTnI, sTfR can assist in diagnosing CAD in patients with CAD-like symptoms. In addition, sTfR can provide guidance for the management of body iron levels in CAD patients.

Keywords: Soluble transferrin receptor (sTfR); iron metabolism; atherosclerosis (AS); coronary artery disease (CAD)

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Introduction

Background

Iron plays an irreplaceable role in the human body (1). In addition to participating in the synthesis of heme to transport oxygen, iron participates in various physiological processes, such as energy production and cell respiration (2). At present, iron metabolism indexes, such as soluble transferrin receptor (sTfR) and ferritin, are often used clinically to evaluate pathological states, such as anemia and infection (3,4). However, with continuous deepening of research, increasing evidence shows that iron metabolism also plays an important role in the process of atherosclerosis (AS) (5). Current mainstream views are as follows. The red blood cells in blood vessels can infiltrate atherosclerotic plaques via neovasculates and are subsequently cleaved by oxidized lipids in the plaques to release hemoglobin (Hb), which is oxidized to produce various iron-containing groups or directly to release free iron. These iron-containing products either participate directly as oxidants or as catalysts to promote the oxidation of lipids or proteins, which leads to plaque progression and vascular remodeling. In addition, non-transferrin-binding iron in serum can directly participate in lipid oxidation in plaques through the Fenton reaction, generating reactive oxygen species (ROS) and thus promoting plaque progression (6). Current clinical guidelines clearly indicate that iron supplementation can effectively reduce the risk of future cardiovascular events in patients with heart failure and myocardial infarction (7), which also demonstrates the nonnegligible role of iron metabolism in cardiovascular diseases.

Many scholars have sought to establish a relationship between changes in the iron metabolism index and progression of coronary artery disease (CAD) but have failed to obtain a unified and convincing conclusion, with some conclusions even contradicting each other (8). In addition to sampling error, the difference between ethnicities and the unreasonable adjustment of confounding factors (9), the main reason is that the physiological mechanism underlying these indexes has not been fully explored. However, a 2019 study by Grammer *et al.* may explain these paradoxes. Previous studies have been based on the understanding that the progression and prognosis of CAD correlate positively or negatively with iron content in the human body, but Grammer first pointed out that serum iron, transferrin saturation (TSAT), sTfR and STFR-F index (sTfR/log ferritin) are associated with the mortality of CAD patients in a "J" shape; that is, the iron metabolism index needs to be controlled within a narrow range, and both lower and higher values of these indexes indicate an increase in mortality (10). Nevertheless, the study did not deeply explore the reasons why sTfR and other iron metabolism indexes are associated with CAD progression and prognosis in a "J" shape and the mechanism of abnormal iron content affecting coronary AS.

Rationale and knowledge gap

Clinically, for patients with symptoms such as chest pain and/or chest tightness, clinicians need to prioritize the investigation of CAD, and before invasive coronary artery examination, a non-invasive, convenient, rapid and accurate early diagnosis method is needed. At present, troponin I (cTnI)/hypersensitive cTnI is commonly used as the first choice for the early diagnosis of CAD, but it has some limitations. Due to the time-varying characteristics, cTnI

Highlight box

Key findings
- Soluble transferrin receptor (sTfR) correlates with coronary artery disease (CAD) morbidity in a "J" shape and can assist in diagnosing CAD while other iron metabolism indexes are not associated with CAD in any shape.

What is known and what is new?
- Iron metabolism is involved in the progress of atherosclerosis and sTfR has been considered as a potential index in the diagnosis and evaluation of CAD.
- We found a "J-shape" correlation between sTfR and CAD morbidity, explored the underlying mechanism, established a diagnostic model and confirmed a superior diagnostic value of sTfR for CAD compared to cardiac troponin I (cTnI).

What is the implication, and what should change now?
- sTfR can help us diagnose CAD more accurately before invasive testing, especially in suspected CAD patients without myocardial injury.

should be monitored continuously for 6 h in patients with suspected myocardial infarction patient at an early stage, and the lower limit range of cTn concentration could not be detected, resulting in low diagnostic accuracy (11). cTnI released from cardiomyocytes into the blood may contact with the body's immune system and produce antibodies, and the latter's negative interference may also affect the accuracy of cTnI (12). In addition, for CAD without myocardial injury, the diagnostic value of cTnI is greatly reduced. Although hypersensitive cTnI has a high sensitivity, its inherent low specificity leads to a high false positive rate, and the diagnostic threshold is greatly affected by gender, age and other factors (13). Therefore, the academic community has not stopped exploring better early diagnosis indexes of CAD. Due to the important role of iron metabolism in coronary AS, iron metabolism indexes may replace cTnI or serve as supplementary and provide more information for the early diagnosis of CAD. In addition, these indexes can help clinicians better manage the iron content of patients, which may become a new target in CAD treatment.

Objective

This study attempted to analyze the relationship between iron metabolism indexes and CAD, investigate the diagnostic value of these indexes on suspected CAD, explore the underlying mechanism and establish a diagnostic model. We present this article in accordance with the STARD reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-450/rc).

Methods

Participants

This was a retrospective study. Before starting the study, we first estimate the sample size through the package "pwr" of R. In the Student's *t*-test, we determined the significance to be 0.05, the efficacy to be 90%, and the effect value to be 0.80 according to the Cohen effect value benchmark (14). It was calculated that the sample size of each group should be at least 34 people. In the Chi-squared test, we determined the significance to be 0.05, the efficacy to be 90%, and the effect value to be 0.50, and the sample size was calculated to be at least 43 people. Therefore, we need to ensure that the sample size of the total sample or subgroup in the later analysis would meet the above requirements.

Inclusion criteria: patients with CAD-like symptoms (including chest pain, chest distress, dyspnea on exertion and decreased exercise capacity) who underwent coronary angiography in the Department of Cardiovascular Medicine, The Second Affiliated Hospital of Anhui Medical University from September 2022 to May 2023. Exclusion criteria were as follows:

(I) Patients diagnosed with acute myocardial infarction at the time of admission.
(II) Patients with previous coronary stent implantation.
(III) Patients with cardiovascular diseases other than CAD.
(IV) Patients with chronic diseases of other systems, infections or malignancies.
(V) Patients with a history of surgery, trauma, blood transfusion or blood donation within 1 month before admission.
(VI) Patients who used iron or anticoagulant drugs within 1 month before admission.

Potentially eligible participants were identified in the ward when they completed coronary angiography. Finally, 268 subjects were included and formed a continuous series including 188 CAD patients and 80 control subjects. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Second Affiliated Hospital of Anhui Medical University (No. YX2022-110). Informed written consent was obtained from all participants.

Clinical index

Sex, age, height, weight, body mass index (BMI), smoking history, hypertension history, and diabetes history of the study population were collected through medical record. The first serological test results from venous blood samples collected in the fasting state after admission and before coronary operation were collected, including total bilirubin (TBil), direct bilirubin (DBil), indirect bilirubin (IBil), glucose (Glu), triglycerides (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), serum creatinine (Scr), C-reactive protein (CRP), neutrophil count (NEU), Hb, N-terminal pro-B-type-natriuretic peptide (NT-proBNP), cTnI, and fibrinogen (Fib). The coronary angiography records of the sample population were reviewed by two interventional clinicians with more than 10 years of operating experience to determine the presence of a subepicardial coronary artery with >50% stenosis

in diameter which is currently recognized as the gold standard for diagnosing CAD (15). If present, the patient was included in the case group; otherwise, the patient was included in the control group. If the two clinicians disagree, the third clinician with more than 15 years of operating experience interprets it again and the three discuss it to reach the final conclusion. The interval between the first venous blood sample collected after admission and coronary angiography was less than 48 hours and during which we did not give patients any treatment other than antiplatelet drugs, statins, and β-blockers which would not affect the degree of coronary stenosis in the short term. Serum samples taken from the sample population before surgery were sent to Shanghai Hengyuan Biotechnology Co., Ltd. Serum iron levels (Iron) were determined by atomic absorption spectrometry using an iCE 3400 AAS atomic absorption spectrometer. Serum ferritin (Ferritin) and human sTfR levels were determined by ELISA (the ELISA plates were supplied by Shanghai Hengyuan Biotechnology Co., LTD and their catalog numbers were HB586-Hu and HB1092-Hu, respectively); total iron binding capacity (TIBC) was determined by ferrozine colorimetry using Labsystems Multiskan MS 352 ELISA (the ELISA plate was supplied by Shanghai Hengyuan Biotechnology Co., LTD and the catalog number was P-856-SH). TSAT was calculated by the formula (serum Iron/TIBC) ×100%. STfR/Ferritin was also calculated as a joint index of iron metabolism. The clinical information and reference standard results were not available to the performers/readers of the index test; the clinical information and index test results were not available to the assessors of the reference standard.

Statistical analysis

RStudio 2023.03.0 (16) was used for data analysis and processing. In addition to "base" (17), the R packages used include "nortest" (18), "psych" (19), "stats" (17), "pROC" (20), "ggplot2" (21), "smoothHR" (22), "survival" (23), "rms" (24), and "Hmisc" (25). The P value tests were two-sided. First, the Kolmogorov–Smirnov test was used to detect the normality of the data. Continuous variables with a normal distribution are expressed as the mean (standard deviation, SD); continuous variables with a nonnormal distribution are expressed as the median (25% quartile, 75% quartile); and categorical variables are expressed as the percentage of the number of cases in the total sample. Independent sample Student's *t*-test was used for intergroup comparison for continuous variables with a normal distribution. The rank sum test was used for intergroup comparison for continuous variables with a nonnormal distribution. The Chi-squared test was used for categorical variables. Restricted cubic spline (RCS) was used to test nonlinear correlation, plot the sTfR-CAD relation curve and determine the corresponding sTfR value to the lowest odds according to which we divided the total samples into the "sTfR low level" subgroup and the "sTfR high level" subgroup. Univariate and multivariable logistic regression was used to screen risk factors, correct confounders and establish diagnostic models in the two subgroups. We used stepwise regression to select variables and establish the optimal diagnostic model. Receiver operating characteristic (ROC) curves were employed to analyze and compare the diagnostic efficiency of the indexes and models and get cut-off value. For a more accurate comparison, all statistical results in this study were set to three decimal places. In all of the above statistical processes, we ignore the missing values. The significance of all the above test results was divided into two levels: "significant" ($P<0.05$, marked with "*" in charts) and "extremely significant" ($P<0.01$, marked with "**" in charts).

Results

Preliminary comparison between the case and control groups

In our study, 367 people were initially included, and after excluding 99 people, 268 people were finally included as the cohort, including an average age of 61 years old, 156 males, 112 females, 74 smokers, 62 patients with diabetes and 172 patients with hypertension. Average sTfR was 1.082 mg/L; average blood glucose was 5.736 mmol/L; average CRP was 7.394 mg/L; and average Fib was 3.070 g/L. There were 212 patients with NT-proBNP <900 pg/mL and 79 patients with cTnI =0 μg/L. The flow of participants is shown in *Figure 1*.

First, we used the total sample population as the object and tested the normality of all continuous variables. It was concluded that only "TIBC" and "HDL-C" were normally distributed in both the CAD patient and control groups; the others were not. Independent sample Student's *t*-test was used for TIBC and HDL-C, the rank sum test was used for the remaining continuous variables, and the Chi-squared test was used for categorical variables. The results showed that age ($P=0.005$), cTnI ($P<0.001$) and Fib ($P=0.001$) were

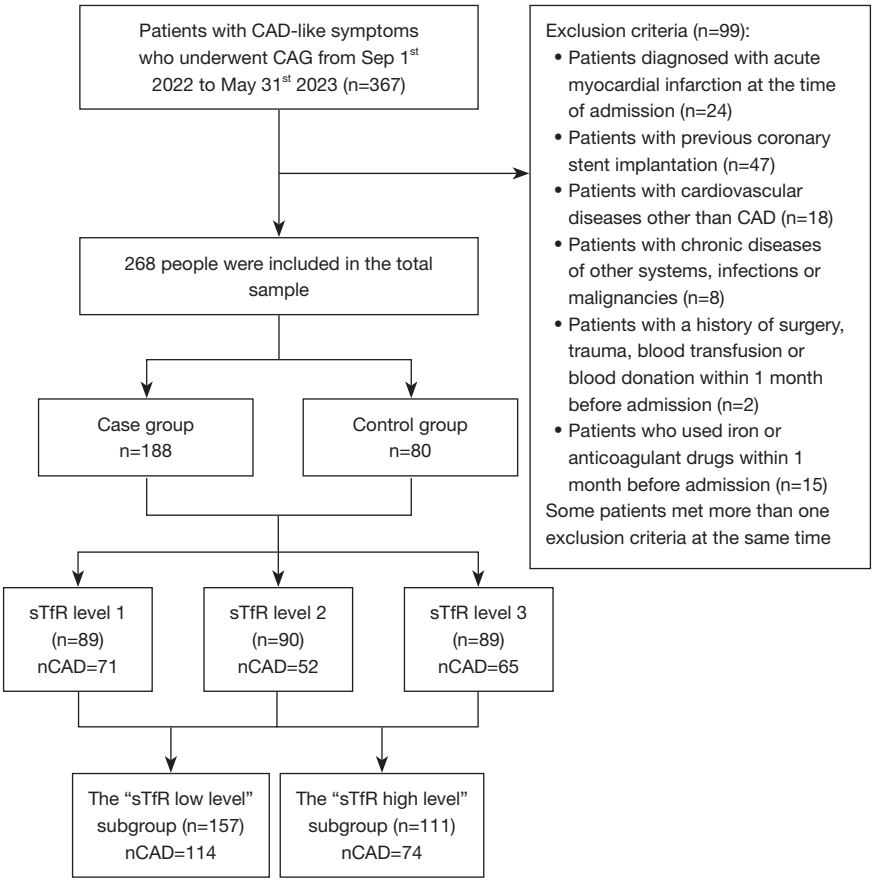

Figure 1 Flow of participants. CAD-like symptoms include chest pain, chest distress, dyspnea on exertion and decreased exercise capacity. Different "sTfR level" was divided according to tertile of sTfR; the "sTfR low level" subgroup and the "sTfR high level" subgroup were divided according to sTfR with 1.087 mg/L as a cutoff. CAD, coronary artery disease; CAG, coronary angiography; sTfR, soluble transferrin receptor; nCAD, number of CAD patients.

extremely significantly different between the case group and the control group. Smoking history (P=0.023) and NT-proBNP (P=0.016) were significantly different. Notably, the remaining variables, including the iron metabolism indexes we focused on, did not differ significantly between the case and control groups. Detailed results are provided in *Table 1* (the first row of each variable in *Table 1* is the result of the comparison of differences between the case group and control group from the total sample population).

Identification of the relationship between iron metabolism indexes and CAD morbidity

Each numerical variable of the iron metabolism index was divided into a grade variable according to tertile, namely, "Level 1" (89 people, iron from 3 to 11 μmol/L, ferritin from 11 to 149 μg/L, sTfR from 0.57 to 0.93 mg/L, TSAT from 5.4% to 21.9%, TIBC from 29 to 49 μmol/L, sTfR/Ferritin from 0.61 to 3.08 mg/μg), "Level 2" (90 people, iron from 11 to 17 μmol/L, ferritin from 149 to 312 μg/L, sTfR from 0.93 to 1.16 mg/L, TSAT from 21.9% to 32.4%, TIBC from 49 to 59 μmol/L, sTfR/Ferritin from 3.08 to 7.25 mg/μg), and "Level 3" (89 people, iron from 17 to 30 μmol/L, ferritin from 312 to 1,120 μg/L, sTfR from 1.16 to 4.36 mg/L, TSAT from 32.4% to 88.5%, TIBC from 59 to 84 μmol/L, sTfR/Ferritin from 7.25 to 400.00 mg/μg). A 2×2 contingency table was established, and a Chi-squared test was carried out on the population in Level 1 and Level 2 with "whether CAD is present" and level as categorical variables. Similarly, a 2×2 contingency table was established, and a Chi-squared test was carried out on the population in Level 2 and Level 3 with "whether CAD

Table 1 Difference between the case group and control group in the total sample and subgroups

Variable	Sample	Cases	Controls	P (cases *vs.* controls)
Male (n)	Total	114/188 (60.638%)	42/80 (52.500%)	0.27
	The "sTfR low level" subgroup	69/114 (60.526%)	22/43 (51.163%)	0.38
	The "sTfR high level" subgroup	45/74 (60.810%)	20/37 (54.054%)	0.63
Age (years)	Total	62.500 (55.750, 71.000)	58.080 (12.205)	0.005**
	The "sTfR low level" subgroup	62.500 (56.000, 70.000)	56.260 (13.326)	0.003**
	The "sTfR high level" subgroup	63.000 (54.000, 71.000)	60.190 (10.543)	0.29
Height (cm)	Total	165.000 (158.000, 170.000)	165.000 (159.800, 170.000)	0.49
	The "sTfR low level" subgroup	165.000 (158.000, 170.000)	165.000 (158.000, 170.000)	0.62
	The "sTfR high level" subgroup	161.500 (158.000, 170.000)	165.800 (162.000, 170.000)	0.07
Weight (kg)	Total	68.000 (59.380, 75.000)	69.470 (11.308)	0.19
	The "sTfR low level" subgroup	67.500 (60.000, 75.000)	70.160 (10.800)	0.21
	The "sTfR high level" subgroup	67.700 (13.002)	68.680 (11.970)	0.69
BMI (kg/m^2)	Total	24.920 (23.180, 27.590)	25.540 (3.443)	0.28
	The "sTfR low level" subgroup	24.890 (23.030, 27.740)	26.110 (3.312)	0.07
	The "sTfR high level" subgroup	24.950 (23.320, 27.320)	24.880 (3.518)	0.70
Smoking (n)	Total	60/188 (31.915%)	14/80 (17.500%)	0.02*
	The "sTfR low level" subgroup	41/114 (35.965%)	8/43 (18.605%)	0.06
	The "sTfR high level" subgroup	19/74 (25.676%)	6/37 (16.216%)	0.38
Diabetes (n)	Total	48/188 (25.532%)	14/80 (17.500%)	0.21
	The "sTfR low level" subgroup	27/114 (23.684%)	7/43 (16.279%)	0.43
	The "sTfR high level" subgroup	21/74 (28.378%)	7/37 (18.919%)	0.40
Hypertension (n)	Total	128/188 (68.085%)	44/80 (55.000%)	0.06
	The "sTfR low level" subgroup	79/114 (69.298%)	25/43 (58.140%)	0.26
	The "sTfR high level" subgroup	49/74 (66.216%)	19/37 (51.351%)	0.19
Iron (μmol/L)	Total	15.000 (11.000, 19.000)	15.209 (6.605)	0.72
	The "sTfR low level" subgroup	15.228 (6.408)	15.539 (6.484)	0.79
	The "sTfR high level" subgroup	14.401 (6.898)	14.825 (6.811)	0.76
Ferritin (μg/L)	Total	209.500 (115.500, 426.000)	193.280 (129.000, 452.100)	0.80
	The "sTfR low level" subgroup	218.000 (120.400, 389.300)	176.530 (107.500, 450.500)	0.51
	The "sTfR high level" subgroup	206.700 (105.000, 457.500)	214.000 (162.000, 451.300)	0.34
sTfR (mg/L)	Total	1.025 (0.838, 1.253)	1.070 (0.197)	0.35
	The "sTfR low level" subgroup	0.865 (0.773, 0.980)	0.960 (0.805, 1.035)	0.02*
	The "sTfR high level" subgroup	1.295 (1.222, 1.423)	1.234 (0.133)	<0.001**
TSAT (%)	Total	27.900 (19.354, 36.633)	27.302 (19.839, 36.434)	0.88
	The "sTfR low level" subgroup	28.376 (14.204)	30.325 (14.471)	0.80
	The "sTfR high level" subgroup	27.398 (15.299)	26.830 (18.270, 32.200)	0.70

Table 1 *(continued)*

Table 1 *(continued)*

Variable	Sample	Cases	Controls	P (cases *vs.* controls)
TIBC (μmol/L)	Total	54.030 (11.886)	54.080 (12.257)	0.98
	The "sTfR low level" subgroup	53.630 (11.561)	54.030 (11.254)	0.84
	The "sTfR high level" subgroup	54.650 (12.426)	54.140 (13.489)	0.88
sTfR/ferritin (mg/μg)	Total	4.618 (2.550, 9.269)	5.324 (2.540, 8.452)	0.97
	The "sTfR low level" subgroup	3.871 (2.323, 7.248)	5.284 (2.249, 8.976)	0.32
	The "sTfR high level" subgroup	6.506 (2.878, 12.393)	6.111 (2.605, 8.006)	0.15
TBil (μmol/L)	Total	12.500 (9.400, 16.750)	12.900 (10.200, 15.800)	0.56
	The "sTfR low level" subgroup	13.200 (10.180, 16.700)	13.190 (4.725)	0.52
	The "sTfR high level" subgroup	11.500 (8.900, 17.450)	13.600 (10.800, 16.900)	0.14
DBil (μmol/L)	Total	2.200 (1.700, 2.900)	2.400 (1.700, 3.000)	0.69
	The "sTfR low level" subgroup	2.400 (1.775, 2.900)	2.395 (0.931)	0.66
	The "sTfR high level" subgroup	2.100 (1.500, 2.900)	2.400 (1.600, 3.100)	0.32
IBil (μmol/L)	Total	10.600 (7.650, 13.550)	10.800 (8.350, 13.250)	0.58
	The "sTfR low level" subgroup	10.900 (8.200, 13.720)	10.800 (3.904)	0.53
	The "sTfR high level" subgroup	9.500 (7.500, 13.100)	12.200 (4.988)	0.15
Glu (mmol/L)	Total	5.450 (4.920, 6.425)	5.260 (4.670, 6.000)	0.07
	The "sTfR low level" subgroup	5.555 (4.965, 6.655)	5.170 (4.670, 5.765)	0.02*
	The "sTfR high level" subgroup	5.380 (4.850, 6.080)	5.525 (1.039)	0.95
TC (mmol/L)	Total	4.105 (3.507, 4.850)	4.108 (0.778)	0.45
	The "sTfR low level" subgroup	4.035 (3.465, 4.782)	3.996 (0.735)	0.56
	The "sTfR high level" subgroup	4.195 (3.972, 4.942)	4.241 (0.818)	0.58
TG (mmol/L)	Total	1.295 (0.990, 1.998)	1.340 (0.910, 1.820)	0.87
	The "sTfR low level" subgroup	1.290 (0.950, 1.860)	1.380 (0.860, 1.792)	0.75
	The "sTfR high level" subgroup	1.300 (1.070, 2.170)	1.340 (1.110, 1.985)	>0.99
HDL-C (mmol/L)	Total	1.113 (0.274)	1.149 (0.241)	0.30
	The "sTfR low level" subgroup	1.090 (0.923, 1.330)	1.192 (0.238)	0.16
	The "sTfR high level" subgroup	1.094 (0.263)	1.099 (0.238)	0.92
LDL-C (mmol/L)	Total	2.450 (2.058, 3.007)	2.520 (0.661)	0.63
	The "sTfR low level" subgroup	2.455 (2.010, 2.990)	2.405 (0.548)	0.40
	The "sTfR high level" subgroup	2.450 (2.150, 3.200)	2.654 (0.758)	>0.99
Scr (μmol/L)	Total	70.000 (58.000, 84.750)	68.690 (21.018)	0.13
	The "sTfR low level" subgroup	69.500 (60.000, 80.000)	67.280 (15.878)	0.22
	The "sTfR high level" subgroup	75.000 (57.000, 91.250)	68.000 (59.000, 81.000)	0.37
Neu ($\times 10^9$/L)	Total	4.040 (3.005, 5.195)	3.840 (2.990, 4.570)	0.27
	The "sTfR low level" subgroup	3.960 (3.007, 4.825)	4.040 (0.985)	0.90
	The "sTfR high level" subgroup	4.180 (2.970, 5.485)	3.380 (2.820, 4.290)	0.13

Table 1 *(continued)*

Table 1 *(continued)*

Variable	Sample	Cases	Controls	P (cases *vs.* controls)
Hb (g/L)	Total	133.000 (123.000, 143.000)	137.000 (126.000, 145.500)	0.13
	The "sTfR low level" subgroup	133.000 (123.800, 140.000)	137.100 (15.070)	0.11
	The "sTfR high level" subgroup	134.000 (120.000, 145.000)	136.000 (123.000, 145.000)	0.63
CRP (mg/L)	Total	0.990 (0.200, 5.940)	0.470 (0.080, 2.425)	0.056
	The "sTfR low level" subgroup	0.685 (0.150, 4.250)	0.360 (0.030, 1.900)	0.048*
	The "sTfR high level" subgroup	1.400 (0.410, 8.105)	0.950 (0.115, 8.050)	0.43
cTnI (μg/L)	Total	3.750 (0.000, 8.325)	0.010 (0.000, 2.800)	<0.001**
	The "sTfR low level" subgroup	3.350 (0.002, 7.175)	0.010 (0.000, 2.500)	0.001**
	The "sTfR high level" subgroup	4.000 (0.000, 10.100)	0.000 (0.000, 4.600)	0.004**
NT-proBNP (pg/mL)	Total	81.000 (27.000, 295.000)	50.000 (12.000, 104.500)	0.02*
	The "sTfR low level" subgroup	95.000 (42.000, 259.000)	45.000 (10.000, 100.000)	0.002**
	The "sTfR high level" subgroup	70.500 (16.750, 349.750)	63.000 (15.000, 443.000)	0.87
Fib (g/L)	Total	3.010 (2.610, 3.530)	2.650 (2.370, 2.980)	0.001**
	The "sTfR low level" subgroup	2.990 (2.550, 3.440)	2.530 (2.295, 2.945)	0.01*
	The "sTfR high level" subgroup	3.205 (0.883)	2.655 (2.490, 3.022)	0.03*

Data are presented as n (%), median (25% quartile, 75% quartile), or mean (standard deviation). The "sTfR low level" subgroup and the "sTfR high level" subgroup were divided according to sTfR with 1.087 mg/L as a cutoff. *, P<0.05; **, P<0.01. sTfR, soluble transferrin receptor; BMI, body mass index; TSAT, transferrin saturation; TIBC, total iron binding capacity; TBil, total bilirubin; DBil, direct bilirubin; IBil, indirect bilirubin; Glu, glucose; TC, total cholesterol; TG triglycerides; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; Scr, serum creatinine; Neu, neutrophil count; Hb, hemoglobin; CRP, C-reactive protein; cTnI, troponin I; NT-proBNP, N-terminal pro-B-type-natriuretic peptide; Fib, fibrinogen.

is present" and level as categorical variables. The five iron metabolism indexes and the joint index sTfR/ferritin were analyzed according to the above statistical methods. The results showed significant differences in CAD morbidity between Levels 1 and 2 and between Levels 2 and 3, which were divided according to sTfR at the same time. CAD morbidity in sTfR Level 2 was 57.778%, which was significantly lower than that in Level 1 (79.775%) and Level 3 (73.034%). However, there was no significant difference in CAD morbidity among the three levels divided according to the other four iron metabolism indexes and the joint index sTfR/ferritin. The morbidity in different levels and the results of Chi-squared test are shown in *Table 2*.

To further explore the relationship between iron metabolism indexes and the odds of CAD, we applied the nonlinear correlation test between these indexes and the odds by RCS, suggesting a nonlinear correlation with the latter only for sTfR (P for nonlinear =0.003); other indexes were not related to CAD in any shape (P for overall is >0.05) as shown in *Table 3*. When we used the joint index sTfR/Ferritin in the nonlinear correlation test, R hinted at a singular information matrix and was not able to fit the variable. Therefore, we did not incorporate sTfR/ferritin into the ensuing analysis. We plotted the RCS curve between sTfR and odds ratio (OR) with the median sTfR in the total sample as the preliminary reference value and specified that the value of sTfR corresponding to the lowest odds was 1.087 mg/L. Next, we plotted the RCS curve with 1.087 as the reference value (shown in *Figure 2*), from which we can clarify that the relationship between sTfR and the OR showed a "J-shaped correlation" rather than a simple positive or negative correlation. For further analysis, we divided the total samples into the "sTfR low level" subgroup and the "sTfR high level" subgroup according to sTfR with 1.087 mg/L as a cutoff.

Exploration of the mechanism underlying sTfR and CAD and establish diagnostic models

As mentioned above, comparing differences between the

Table 2 Chi-square test for CAD morbidity in different level of iron metabolism indexes

Index	CAD in level 1 (n=89)	CAD in level 2 (n=90)	CAD in level 3 (n=89)	χ^2 (level 1 *vs.* 2)	P (level 1 *vs.* 2)	χ^2 (level 2 *vs.* 3)	P (level 2 *vs.* 3)
Iron	61 (68.539%)	68 (75.556%)	59 (66.292%)	0.774	0.38	1.441	0.23
Ferritin	63 (70.787%)	64 (71.111%)	61 (68.539%)	<0.001	>0.99	0.045	0.83
sTfR	71 (79.775%)	52 (57.778%)	65 (73.034%)	9.075	0.003**	3.951	0.047*
TSAT	61 (68.539%)	62 (68.889%)	65 (73.034%)	<0.001	>0.99	0.199	0.66
TBIC	64 (71.910%)	63 (70.000%)	61 (68.539%)	0.014	0.91	0.002	0.96
sTfR/ferritin	63 (70.787%)	62 (68.889%)	63 (70.787%)	0.013	0.91	0.013	0.91

*, P<0.05; **, P<0.01. CAD, coronary artery disease; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; TIBC, total iron binding capacity.

Table 3 Nonlinear relationship test between iron metabolism indexes and OR of CAD

Index	P for overall	P for nonlinear
Iron	0.91	0.83
Ferritin	0.24	0.14
sTfR	0.006**	0.003**
TSAT	0.90	0.79
TBIC	0.40	0.25
sTfR/ferritin	–	–

"P for overall" refers to the significance of all forms of correlation and "P for nonliner" refers to the significance of nonliner correlation. *, P<0.05; **, P<0.01. OR, odds ratio; CAD, coronary artery disease; sTfR, soluble transferrin receptor; TSAT, transferrin saturation; TIBC, total iron binding capacity.

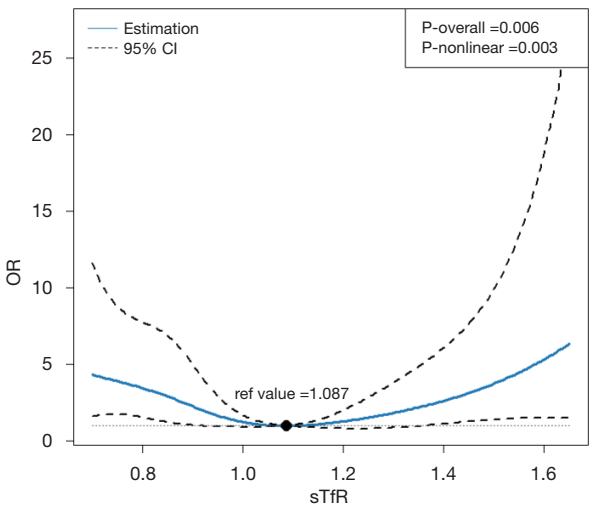

Figure 2 Restricted cubic spline curve of sTfR to OR of CAD. There is a nonlinear (J-shaped) correlation between sTfR and odds of CAD (P for nonlinear =0.003) and the sTfR value corresponding to the lowest odds was 1.087 mg/L. sTfR, soluble transferrin receptor; OR, odds ratio; CI, confidence interval; CAD, coronary artery disease.

CAD case group and the control group in the total sample suggested extremely significant or significant differences in age, cTnI, NT-proBNP, Fib and smoking history. Taking all the samples as objects, whether CAD was present was a bivariate result, and the above variables were included in the univariate logistic regression model one by one as independent variables to obtain univariate models 1–5 (shown in *Table 4*). The results suggested that age and Fib had extremely significant predictive value for CAD; cTnI and smoking history had significant predictive value, whereas NT-proBNP had no significant value in CAD prediction.

In the "sTfR low level" subgroup, we first compared differences between the CAD patients and the control group. The results indicated extremely significant differences in age (P=0.003), cTnI (P=0.001) and NT-proBNP (P=0.002) and significant differences in sTfR (P=0.02), Glu (P=0.02), CRP (P=0.048) and Fib (P=0.01). The second row of each variable in *Table 1* shows the results of the comparison of differences between the case and control groups in the low sTfR subgroup. We used sTfR, age, Glu, cTnI, NT-proBNP, Fib and CRP as independent variables and included CAD as a result in univariate logistic regression models to obtain the univariate models 6–12 in *Table 4*. The findings suggest that indexes other than Glu and CRP can predict the morbidity of CAD. Age, cTnI, NT-proBNP and Fib were incorporated

Table 4 The prediction models established by logistic regression in the total sample and subgroups

Model	Variable	Coefficients	Std.Error	*Z*	P
Univariate model 1	Age	0.037	0.012	2.963	0.003**
Univariate model 2	cTnI	0.042	0.021	1.964	0.049*
Univariate model 3	NT-proBNP	<0.001	<0.001	1.037	0.30
Univariate model 4	Fib	0.484	0.181	2.672	0.008**
Univariate model 5	Smoke	0.793	0.333	2.379	0.02*
Univariate model 6	sTfR	–3.528	1.485	–2.376	0.02*
Univariate model 7	Age	0.058	0.018	3.133	0.002**
Univariate model 8	Glu	0.310	0.169	1.833	0.07
Univariate model 9	cTnI	0.197	0.079	2.501	0.01*
Univariate model 10	NT-proBNP	0.003	0.001	1.989	0.047*
Univariate model 11	Fib	0.545	0.254	2.150	0.03*
Univariate model 12	CRP	0.033	0.032	1.032	0.30
Univariate model 13	Age/sTfR	0.053	0.014	3.818	<0.001**
Univariate model 14	sTfR	4.458	1.609	2.771	0.006**
Univariate model 15	cTnI	0.024	0.017	1.370	0.17
Univariate model 16	Fib	0.432	0.264	1.638	0.10
Multivariable model 1	sTfR	–3.694	1.510	–2.446	0.01*
	Age	0.060	0.019	3.176	0.002**
Multivariable model 2	sTfR	–3.106	1.720	–1.806	0.07
	cTnI	0.184	0.079	2.323	0.02*
Multivariable model 3	sTfR	–2.955	1.638	–1.804	0.07
	NT-proBNP	0.003	0.001	2.015	0.04*
Multivariable model 4	sTfR	–3.231	1.519	–2.127	0.03*
	Fib	0.530	0.263	2.014	0.04*
Multivariable model 5	sTfR	–3.313	1.540	–2.151	0.03*
	Age	0.051	0.019	2.618	0.009**
	Fib	0.360	0.256	1.408	0.16
Multivariable model 6	sTfR	3.480	1.629	2.136	0.03*
	cTnI	0.015	0.016	0.922	0.36
Multivariable model 7	sTfR	4.157	1.585	2.624	0.009**
	Fib	0.393	0.268	1.464	0.14

Univariate models 1–5 were established in the total sample; univariate models 6–13 and multivariate models 1–5 were established in the "sTfR low level" subgroup; univariate models 14–16 and multivariate models 6–7 were established in the "sTfR high level" subgroup. The "sTfR low level" subgroup and the "sTfR high level" subgroup were divided according to sTfR with 1.087 mg/L as a cutoff. *, P<0.05; **, P<0.01. cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type-natriuretic peptide; Fib, fibrinogen; sTfR, soluble transferrin receptor; Glu, glucose; CRP, C-reactive protein.

Table 5 ROC analysis in the total sample and subgroups

Sample	Index	AUC (95% CI)	Cut-off value	Specificity	Sensitivity
Total sample	cTnI	0.681 (0.611–0.751)	0.035	0.638	0.695
STfR low level subgroup	sTfR	0.618 (0.520–0.716)	0.920	0.605	0.623
	cTnI	0.688 (0.599–0.777)	0.035	0.649	0.696
	NT-proBNP	0.678 (0.579–0.777)	105.000	0.861	0.436
	Age/sTfR	0.690 (0.598–0.782)	58.595	0.488	0.842
	MM1	0.684 (0.590–0.777)	1.503	0.465	0.868
STfR high level subgroup	sTfR	0.701 (0.598–0.803)	1.205	0.541	0.797
	cTnI	0.674 (0.564–0.784)	0.505	0.719	0.653

The "sTfR low level" subgroup and the "sTfR high level" subgroup were divided according to sTfR with 1.087 mg/L as a cutoff. ROC, receiver operating characteristic; AUC, area under the curve; 95% CI, 95% confidence interval; cTnI, troponin I; sTfR, soluble transferrin receptor; NT-proBNP, N-terminal pro-B-type-natriuretic peptide; MM1, the multivariable model 1, expressed as ln[p/(1−p)] = 0.060 × age − 3.694 × sTfR.

into binary logistic regression as covariables combined with sTfR, and multivariate models 1–4, as shown in *Table 4*, were obtained. The results indicate that age and Fib can be used as covariables to copredict the morbidity of CAD with sTfR. When cTnI and NT-proBNP were incorporated into the model as covariables with sTfR, sTfR lost significant predictive value. When age and Fib were incorporated into multivariable logistic regression with sTfR at the same time, we obtained multivariate model 5 (hereinafter referred to as MM5), and Fib lost significance in predicting CAD while age and sTfR maintained significance. After removing some variables through multiple hypothesis tests for regression coefficients and refitting, we obtained the multivariable model 1 (hereinafter referred to as MM1), which only included age and sTfR. We demonstrated that there was no significant difference in fitting accuracy between MM1 and MM5 by analysis of variance (P=0.134) so we think MM1 is the optimal diagnostic model. According to the regression coefficient, age in MM1 correlated positively with CAD morbidity, whereas sTfR correlated negatively with the latter. Hence, we calculated the age/sTfR ratio as a new index. When the age/sTfR ratio was incorporated into univariate logistic regression, we obtained univariate model 13 in *Table 4*, which showed an extreme significance of the age/sTfR ratio (P<0.001) as an independent risk factor for CAD.

The "sTfR high level" subgroup was less complex. There were extremely significant differences in sTfR (P<0.001) and cTnI (P=0.004) and significant differences in Fib (P=0.028) between the CAD patients and control groups as shown in *Table 1*. After incorporating the above three indicators into univariate logistic regression models, the univariate models 14–16 in *Table 4* were obtained. Only sTfR was an independent risk factor for CAD (P=0.006). After cTnI and Fib were incorporated into binary logistic regression as covariables, the multivariate models 6–7 in *Table 4* were obtained, suggesting that cTnI affects the significance of sTfR to some extent in predicting CAD but that Fib has a minimal effect on it.

Comparison of the efficacy of different indexes and models in diagnosis of CAD

For the whole cohort, only cTnI was selected for ROC analysis, of which the area under the curve (AUC) was 0.681 and the best cutoff value was 0.035. The specificity and sensitivity of the best cutoff values are shown in *Table 5*. Since cTnI was not compared with other indicators in the total sample, the ROC curve is not shown here.

For the "sTfR low level" subgroup, we selected cTnI, NT-proBNP, sTfR, age/sTfR ratio, and the score of MM1 [calculated by exp (0.060 × age − 3.694 × sTfR) according to the regression coefficient] and plotted the ROC curve (*Figure 3*). The results suggest that the AUC is ordered as age/sTfR > cTnI > MM1 > NT-proBNP > sTfR. The AUC values, the optimal cutoff values, and the corresponding specificity and sensitivity are provided in *Table 5*.

For the "sTfR high level" subgroup, since only sTfR could be used as an independent risk factor for CAD, we selected sTfR and cTnI to plot the ROC curve. As expected, the AUC of sTfR was significantly larger than that of cTnI.

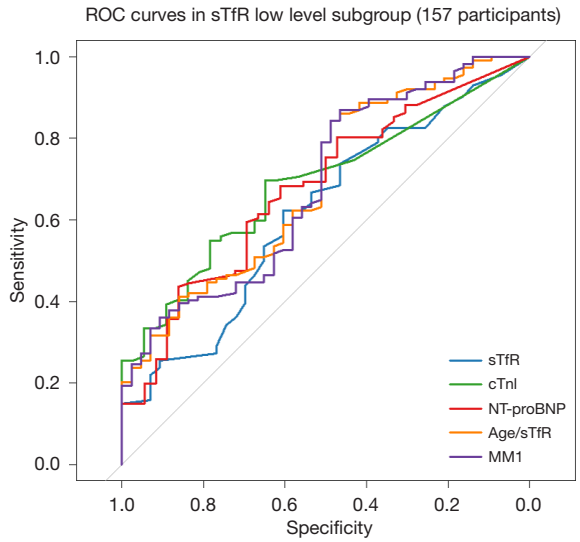

Figure 3 Multiple ROC curves in the "sTfR low level" subgroup. MM1 expressed as ln[p/(1–p)] = 0.060 × age – 3.694 × sTfR. The AUC is ordered as age/sTfR (0.690) > cTnI (0.688) > MM1 (0.684) > NT (0.678) > sTfR (0.618). The optimal cutoff value of age/sTfR is 58.595 with specificity 48.80% and sensitivity 84.20%. ROC, receiver operating characteristic; AUC, area under the ROC curve; sTfR, soluble transferrin receptor; cTnI, cardiac troponin I; NT-proBNP, N-terminal pro-B-type-natriuretic peptide; MM1, the multivariable model 1.

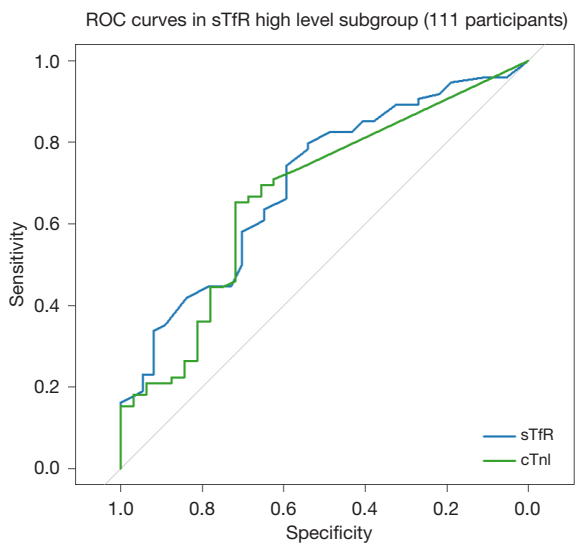

Figure 4 Multiple ROC curves in the "sTfR high level" subgroup. The AUC is ordered as sTfR (0.701) > cTnI (0.674). The optimal cutoff values of sTfR is 1.205 mg/L with specificity 54.10% and sensitivity 79.70%. ROC, receiver operating characteristic; AUC, area under the ROC curve; sTfR, soluble transferrin receptor; cTnI, cardiac troponin I.

Table 6 The cross tabulation of the sTfR-related diagnostic model by the results of CAG

Category	CAG (+)	CAG (–)	Total
sTfR-related diagnostic model (+)	155	39	194
sTfR-related diagnostic model (–)	33	41	74
Total	188	80	268

"sTfR-related diagnostic model (+)" means sTfR ≤1.087 mg/L and the age/sTfR ratio >58.595 at the same time or sTfR >1.205 mg/L and "sTfR-related diagnostic model (+)" means any case other than the above. CAG, coronary angiography; sTfR, soluble transferrin receptor.

The ROC curve and detailed analysis results are shown in *Figure 4* and *Table 5*.

Through the above analysis, therefore, we can make a preliminary clinical diagnosis of CAD when sTfR ≤1.087 mg/L and the age/sTfR ratio >58.595 at the same time or sTfR >1.205 mg/L [this part of the sample contains 194 people, number of CAD patients (nCAD) =155]. Except for the above case, we can initially rule out a diagnosis of CAD (this part of the sample contains 74 people, nCAD =33). The cross tabulation of the sTfR-related diagnostic model by the results of coronary angiography is shown in *Table 6*. Reviewing the above analysis, we found that the sample size of the subjects in each step of the analysis was larger than previously estimated. Since no additional interventions were performed on the subjects during our study, there were no adverse events.

Discussion

Key findings

sTfR correlates CAD morbidity in a "J" shape and can assist in diagnosing CAD while other iron metabolism indexes are not associated with CAD in any shape. The sTfR level corresponding to the lowest CAD odds was 1.087 mg/L on different sides of which the effect of sTfR on CAD was opposite. In the "sTfR low level" subgroup with sTfR ≤1.087 mg/L, elevated sTfR is a protective factor. The age/sTfR ratio is the best diagnostic index for CAD with a higher diagnostic value than cTnI, especially for patients without myocardial injury and it indicates the presence of CAD when the age/sTfR ratio >58.595. On the contrary, elevated sTfR is a risk factor in the "sTfR high level" subgroup with sTfR >1.087 mg/L. sTfR is a superior index than cTnI or even the only index for the diagnosis

of CAD and it indicates the presence of CAD when sTfR >1.205 mg/L in this subgroup.

Strengths and limitations

In general, the innovation of our research is with regard to the sTfR value corresponding to the lowest CAD odds by RCS and in establishing a diagnostic model of sTfR to CAD. Of course, there are many limitations to our study. Our study population was entirely composed of hospitalized patients with suspected CAD, not including healthy people with no related symptoms, which inevitably led to a certain degree of bias in the results. In addition, our study sample was not large enough, and more clinical data are needed to verify our conclusion.

Comparison with similar research and explanations of findings

Since 1981, when Sullivan proposed that iron is a risk factor for cardiovascular diseases (26), the academic community has continuously conducted related studies on iron metabolism and CAD. However, due to the complexity of the AS mechanism and the diversity of human physiological processes related to iron metabolism (27), the full picture of the mechanism between the two has remained elusive (5). Regarding how iron metabolism in the human body affects the development of CAD, different studies have been unable to reach a consistent conclusion due to various factors, such as the study population, observation indicators, and covariate adjustment (8,9). As indicated in our preliminary analysis, there was no difference in iron metabolism indexes and their combination between the case and control groups in the entire sample. Nonetheless, we showed by logistic regression that age, cTnI, Fib, and smoking history were independent predictors of CAD in the total sample. For comparison with the subsequent statistical results, we found that the AUC of cTnI was 0.681. Since the total sample was not the focus of this study, we did not carry out further statistical analysis or discussion on this part.

When we divided the total sample into three levels according to the tertile of each index, the CAD morbidity in "Level 2" according to sTfR was significantly lower than that in "Level 1" and "Level 3". The nonlinear correlation test and RCS curve verified the "J-shaped" correlation between sTfR and CAD, which was consistent with the results of Grammer's study (10). However, our data could not prove any form of correlation between CAD and other indexes, including serum iron, ferritin, TIBC and TSAT, by either the Chi-squared test between tertiles or the nonlinear correlation test. This is consistent with Thomas G DeLoughery's view: the iron components in the human body that affect the process of AS are mainly iron in the active state in cells, and sTfR, which reflects the demand for iron in the cell, has a higher fitting degree (28). However, ferritin, which only reflects intracellular stored iron, is regulated by multiple factors, such as inflammation, and its level may not have a causal relationship with the progression of AS (29). In addition, many previous studies have suggested that the joint index sTfR/ferritin weakens the effect of the acute phase on ferritin, which may be the best indicator to evaluate iron metabolism (30-32), though our study did not find a correlation with CAD pathogenesis. In summary, we believe that sTfR is the best indicator to evaluate the effect of iron metabolism on CAD, and we focused on sTfR in analyses.

After confirming the "J-shaped correlation" between sTfR and CAD, we determined through the coordinates of the RCS curve that the sTfR level corresponding to the lowest CAD odds was 1.087 mg/L on different sides, of which the effect of sTfR on CAD was opposite.

Below, we discuss our findings in the "low sTfR subgroup" with sTfR ≤1.087 mg/L. The myocardial injury reflected by cTnI and the cardiac function impairment reflected by NT-proBNP are the results mediated by AS rather than induction factors of AS (33,34), and it can be seen from multivariate models 2–3 that sTfR could not predict CAD under the influence of either. Therefore, we discuss cTnI and NT-proBNP separately from other indexes. Consistent with previous studies, we concluded that age is a risk factor for CAD (35), and when it was included in multivariable logistic regression as a covariate with sTfR, the regression coefficients and significance of either age or sTfR did not decrease compared with the results when they were used as single variables to predict CAD. Therefore, we believe that advanced age does not promote CAD by altering iron metabolism. This study demonstrates that Fib can serve as an independent predictor of CAD regardless of confounding factors, which is consistent with previous studies showing that Fib is highly associated with cardiovascular risk (36) and plays a role as a core molecule in the coagulation system, the inflammatory response and the renin-angiotensin system (RAS). The RAS promotes inflammation by increasing IL-6, which upregulates Fib levels. Fib can promote the development of AS by promoting coagulation, inhibiting

fibrinolysis and inducing platelet aggregation. It can also promote the development of AS by accumulating in the artery wall and inducing LDL-C aggregation. In addition, Fib can promote inflammation by inducing exposure of proinflammatory cytokines on monocytes and chemokines on endothelial cells and fibroblasts (37). Interestingly, when both Fib and sTfR were included in logistic regression, the regression coefficient of sTfR decreased in absolute value and became less significant, reflecting a certain collinearity in the influence of Fib and iron metabolism on CAD. We hypothesize that Fib, which is an effector and stimulator of the inflammatory response, is involved in the process by which free radicals produced by intracellular iron through the Fenton reaction promote the inflammatory response and thus promote progression of AS. When age and Fib were included in the multivariable logistic regression as covariables together with sTfR, Fib lost its significance as a predictor of CAD, suggesting a high degree of collinearity between Fib and age; that is, serum Fib correlated positively with age. This is also consistent with a previous report (38). From this, we conclude that the best diagnostic model for CAD related to sTfR in the "low sTfR subgroup" is MM1, expressed as $\ln[p/(1-p)] = 0.060 \times \text{age} - 3.694 \times \text{sTfR}$. Based on the regression coefficient, advanced age is a risk factor and elevated sTfR is a protective factor in this subgroup. Therefore, we used the age/sTfR ratio as a new index that was shown to be an independent risk factor for CAD by univariate logistic regression. We included sTfR, cTnI, NT-proBNP, age/sTfR ratio and MM1 scores in ROC analysis. It is beyond our expectation that the diagnostic efficacy of age/sTfR was stronger than that of other indexes; cTnI was slightly inferior, and MM1 was the third most useful. Overall, the efficacy of the heart failure index NT-proBNP in diagnosing CAD was inferior to the first three, and the efficacy of sTfR alone in diagnosing CAD was lowest. In addition, we found that compared with cTnI, the specificity of MM1 and the age/sTfR ratio were lower, but the sensitivity was better because myocardial injury reflected by cTnI is the downstream effect of CAD; conversely, age and iron metabolism are upstream induction factors, as mentioned above. It is conceivable that the age/sTfR ratio has a higher diagnostic value for suspected CAD than cTnI, especially for patients without myocardial injury.

In the "high sTfR subgroup" with sTfR >1.087 mg/L, only sTfR can diagnose CAD; other indexes, including cTnI, have no diagnostic value. Interestingly, our results show that Hb was not able to predict CAD in the whole sample or in any subgroup, denying the previous view that Hb is an independent risk factor for CAD (39) and demonstrating that the predictive effect of elevated sTfR on CAD is not based on the effect of anemia, as previously assumed (40). By ROC analysis, the diagnostic efficiency of sTfR was higher than that of cTnI, and the optimal cutoff value of sTfR was 1.205 mg/L. Notably, elevated sTfR had an irreplaceable role in diagnosing CAD and weakened the diagnostic value of other indexes, including cTnI, in this subgroup. Therefore, it is reasonable to speculate that the elevation of sTfR in this subgroup may be a downstream effect of coronary AS, rather than a serologic manifestation of intracellular iron deficiency, which promotes CAD pathogenesis by influencing intracellular energy metabolism, as previously assumed. We hypothesize that the mechanism of elevated sTfR caused by coronary AS is as follows: chronic coronary stenosis causes a decrease in the partial pressure of oxygen in myocardial tissue and chronic ischemia of cardiomyocytes, which promotes expression of myoglobin in cardiomyocytes to correct the hypoxic state by negative feedback (41). The molecular structure of myoglobin contains a porphyrin ring, which is a complex of iron ions (42). Therefore, upregulation of expression of myoglobin will inevitably lead to increased demand for iron ions in cardiomyocytes and then upregulate expression of TfR, resulting in an increase in sTfR. Of course, this mechanism needs to be verified in animal models. In addition, we found that the optimal cutoff value of cTnI in the high sTfR subgroup was much higher than that in the low sTfR subgroup because we hypothesized that the number of non-CAD patients in the high sTfR subgroup was too small (37 objects), such that the extreme level of cTnI in this population had a greater impact on the statistical results.

Implications and actions needed

Our model only includes sTfR and age. At present, sTfR has been widely used in clinical diagnosis and evaluation of anemia with its convenience and economy. The results can be obtained quickly by ELISA after obtaining patients' venous blood. Age is the basic information of patients. Therefore, it is not difficult to translate our model into CAD diagnosis. Our study has shown that our model can make the initial diagnosis of CAD more accurately and quickly than cTnI, especially in patients without myocardial injury, and buy more time for patient treatment in the ward or emergency. Secondly, the sensitivity of our model is significantly higher than that of cTnI, and it has a better

exclusion effect for non-CAD patients with CAD-like symptoms such as cardiac neurosis (43) and intercostal neuralgia (44). In addition, studies have shown that iron content management may lead to better outcomes in CAD patients (45), while sTfR as well as our model may provide guidance for this work.

Conclusions

The iron metabolism index sTfR correlates with CAD morbidity in a "J" shape and can assist in diagnosing CAD in patients with CAD-like symptoms. With superior diagnostic efficacy, sTfR may be an alternative to, at least a supplement to cTnI in the diagnosis of CAD. In addition, sTfR can provide guidance for the management of body iron levels in CAD patients, which has been shown to be a potential new target for the treatment of cardiovascular disease.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-23-450/rc

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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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of The Second Affiliated Hospital of Anhui Medical University (No. YX2022-110). Informed written consent was obtained from all participants.

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