The relationship between triglyceride/high-density lipoprotein cholesterol ratio and coronary microvascular disease

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Research Article

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Abstract

Background: Triglyceride/high-density lipoprotein (TG/HDL-C) is a novel marker of insulin resistance. Recently, it has been documented that this index is related to the occurrence of coronary artery diseases. However, no research has reported whether TG/HDL-C is associated with the occurrence of coronary microvascular disease (CMVD).

Aim: This study set out to investigate the association betweentriglyceride/high-density lipoprotein cholesterol ratio(TG/HDL-C) and occurrence of coronary microvascular disease(CMVD).

Methods: 175 patients with CMVD diagnosed in the department of cardiology in our hospital from October 2017 to October 2021 were selected as the study group and 175 patients without chest pain and history of cardiovascular disease who underwent physical examination in the medical examination center of our hospital were selected as the

non-CMVD group. The clinical data were compared between the two groups. The risk factors of CMVD were analyzed using logistic regression, and the efficacy of independent risk factors in predicting CMVD was analyzed by a receiver operating characteristic (ROC) curve.

Results: Compared with healthy group, the proportion of female, hypertension, type 2 diabetes, platelet count, total cholesterol, C-reactive protein and triglyceride/high-density lipoprotein ratio were increased in CMVD group ($P < 0.05$), but albumin level and high-density lipoprotein cholesterol were decreased ($P < 0.05$). Logistic regression analysis suggested that C-reactive protein, female, albumin and triglyceride/high-density lipoprotein were independent risk factors for CMVD, with the area under the curve of 0.754, 0.651, 0.722 and 0.789 the 95% confidence interval of (0.681-0.827), (0.571-0.730), (0.649-0.794) and (0.718-0.859) ($P< 0.001$), respectively.

Conclusion: Triglyceride/high-density lipoprotein(TG/HDL-C) is an independent risk factor for occurrence of CMVD.

Introduction

Coronary microvascular disease (CMVD) prevalently occurs in the population with cardiovascular risk factors. It has been reported that over 35% of patients with stable angina pectoris and approximately 10%-15% of patients with acute coronary syndrome do not suffer from obstructive coronary artery disease following coronary angiography[1], who are eventually regarded as CMVD. Moreover, the incidence of major adverse cardiovascular events is higher in CMVD patients than in Non-CMVD, which seriously afflicts the prognosis of patients[2]. Since CMVD is mainly manifested by angina pectoris, it is difficult to be distinguished from angina pectoris caused by obstructive coronary artery disease due to its non-specific clinical manifestations. Currently, exercise stress test is the traditional method for the diagnosis of CMVD[3]. However, the study of Mygind *et al.* has shown that exercise stress test has low sensitivity and specificity for the diagnosis of CMVD[4]. Although cardiac magnetic resonance, positron

emission tomography, transthoracic doppler echocardiography, and dynamic myocardial perfusion computed tomography have been proved to be able to evaluate coronary vascular function. Regrettably, the aforementioned medical examination methods have not been widely utilized in clinical practice because of their high cost, complex operation, and high radiation dose. Therefore, it is of enormous significance for clinicians to find a simple indicator that can predict the occurrence of CMVD in patients with angina pectoris and high-risk factors of coronary artery disease.

TG/HDL-C has been verified as a simple indicator of insulin resistance[5], which has been implicated in the development of diabetes[6]and metabolic syndrome[7].Also, patients with high TG/HDL-C have an increased risk of cardiovascular disease[8]. On the other hand, TG/HDL-C has been manifested as a predictor for cardiogenic death and vascular reconstruction in unstable angina pectoris[9]. At present, there has hitherto been no research about the association between TG/HDL-C and CMVD. In this study, we designed to delve into the association between TG/HDL-C and CMVD, thus providing novel ideas for the early diagnosis of CMVD in angina pectoris patients, expecting to improve the prognosis of CMVD patients.

Methods

The research subjects: from October 2019 to October 2021, 705 patients with suspected stable angina pectoris underwent coronary angiography in our hospital.

Exclusion criteria were as follows: patients with previous percutaneous coronary intervention surgery, coronary artery bypass transplantation, new myocardial infarction within 3 months, valvular heart disease (mitral stenosis, mitral regurgitation, aortic stenosis, aortic incompetence); cardiomyopathy (dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, myocarditis), pulmonary thromboembolism, anemia, active bleeding or bleeding tendency, patients with severe hepatic and renal insufficiency: alanine aminotransferase or aspartate aminotransferase $\geq$ 3 times the upper limit of normal and glomerular filtration rate < 60 $ml \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$ patients with severe heart failure (left ventricular ejection fraction$\leq$35%) left ventricular hypertrophy (defined by echocardiography as 12mm left ventricular wall thickness), patients with blood system diseases, malignant tumors, severe infections, trauma, and autoimmune diseases.

All patients stopped taking vasoactive drugs (calcium antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and nitrates) at least 5 days before entering the study. The patients who had physical examination in the medical examination center of our hospital in 2021 and had no history of chest pain and cardiovascular disease were selected as the healthy subjects (n =388).Control subjects were adjusted according to age and gender by propensity score matching method and 175 subjects were selected as the final control group.

All procedures will be carried out in accordance with the Helsinki declaration. The research protocol has been approved by the human ethics committee of each institution. All participants enrolled in the study

signed their consent after being fully informed of the purpose of the research. All of them were agreed to use their medical information for research purpose.

Definition of CMVD

CMVD was defined as the absence of coronary artery stenosis and epicardial spasm, and the inversion of lactate levels in the coronary artery and between the coronary sinuses or the coronary flow reserve ratio induced by adenosine triphosphate was less than 2.5 in the acetylcholine challenge test. The diagnosis process was described in Figure 1.

Angiographical identification of epicardial spasm

There are angina pectoris symptoms and ischemic ECG changes. In ACh experiment, coronary angiography indicates that the coronary artery is temporarily, completely or sub completely occluded (≥90% stenosis).Those who meet the above two requirements are considered to be positive finding for angiographical identification of epicardial spasm.

Lactate measurement in ACh-provocation test

Myocardial ischemia was assessed on the basis of detecting the increase of lactate production in coronary artery circulation. Paired blood samples were collected from aortic root (LAR) and coronary sinus (LCS) simultaneously at three time points using coronary sinus catheter: at baseline, 1 minute after 100g acetylcholine was administered through left coronary artery, and intracoro- nary isosorbide mononitrate (ISDN) after administration.The formula for calculating lactic acid yield is: (LCS-LAR) /LAR×100 (%). Under normal circumstances, the ratio is negative. If it is positive, it clearly indicates the occurrence of myocardial ischemia.

Intracoronary ACh-provocation test

Incremental doses (20g, 50g, and 100g) were administered by injection of acetylcholine chloride into the left coronary artery over a period of 30 seconds, with coronary angiography (CAG) administered 1 minute after the onset of each stimulation.Acetylcholine was administered every five minutes. Subsequently, 50g of acetylcholine was injected into the right coronary artery without the FloWire, followed by CAG. After the administration of intracoro- nary isosorbide mononitrate (ISDN) and CAG at an interval of 10 min, adenosine triphosphate (ATP;150g·kg^{-1}·min^{-1}) was ad-ministered via the central vein until maximal hyperemia was achieved for the calculation of ATP-CFR. ATP-CFR was calculated by the formula: hyperemia average peak velocity (APV)/Post-ISDN APV.

Data collection

General clinical data were obtained from the electronic medical record system of patients after admission. Elbow venous blood (4 ml) was harvested from each enrolled patient on an empty stomach the day after admission, followed by testing of their blood routine and biochemical indexes in the anticoagulant tube. The diagnostic standard of hypertension is based on the standard definition of the

2020 international society of Hypertension Global Hypertension Practice Guide[10]. The diagnostic criteria for type 2 diabetes are based on the recommendations of the American Diabetes Association[11].

Statistical analysis

SPSS 26.0 data software was utilized for statistical analysis. All measurement data were first tested for normal distribution and the data conforming to normal distribution was expressed as (x ± s). *T*-test was applied for inter-group comparison between the two groups. Data with skewed distribution was summarized as M (P25, P75). A non-parametric test was adopted for the comparison between the two groups. Count data were displayed as example (%). Rank sum test was employed for the comparison between the two groups. The risk factors of CMVD in enrolled patients were analyzed by multivariate logistic regression. A receiver operating characteristic (ROC) curve was used to evaluate the diagnostic efficiency of TG/HDL-C for CMVD. All tests were the two-sided test, and the test level was set as $P < 0.05$.

Results

Comparison of clinical data between two groups

There was no significant difference regarding age, body mass index, heart rate at admission and proportion of smoke and drinking between CMVD and Non-CMVD group. Patients in CMVD group had a higher proportion of female, hypertension and type 2 diabetes ($P < 0.05$,Table 1).

Table 1 Comparison of general clinical data between CMVD group and non-CMVD group

Variable	CMVD group n=175	Non-CMVD group n=175	P value
Age,years	57.83±10.94	57.68±11.73	0.846
Female	110(62.86	80(45.71)	0.029
Body Mass Index(kg/m^2)	24.46±12.76	24.11±13.08	0.733
Heart rate at admission(bpm)	72.26±11.28	71.65±12.52	0.423
Hypertension	76(43.43)	39(22.28)	0.021
Type 2 Diabetes	95(54.29	30(17.14)	0.017
Smoke	80(45.71)	60(34.29	0.379
Drinking	36(20.57)	26(14.86)	0.768

Comparison of laboratory data between two groups

Compared with Non-CMVD group, platelet count, C-reactive protein(Crp), Triglyceride(TG), and TG/HDL-C were increased in patients of CMVD group, accompanied by decreased albumin and high-density

lipoprotein cholesterol(HDL-C) ($P < 0.05$,Table 2).

Table 2 Comparison of laboratory data between the CMVD group and the Non-CMVD group

Variable	CMVD group n=175	Non-CMVD group n=175	P value
White blood cells(10 /L	5.96±1.55	5.75±1.62	0.249
Red blood cell(10 /L	4.42±0.43	4.35±0.49	0.097
Hemoglobin(g/L)	134.86±12.82	132.54±13.77	0.133
Platelet count(10 /L	201.33±57.08	121.96±57.78	0.043
Neutrophil(10 /L	3.38±1.46	3.25±1.10	0.334
Creatinine(umol/l)	66.78±14.62	64.24±14.51	0.164
Crp(mg/L)	3.62±6.58	2.10±4.77	0.022
Albumin(g/L)	39.07±3.17	43.15±4.1	0.039
ALT(U/L)	18.64±8.77	20.75±8.09	0.085
AST(U/L)	23.07±10.41	22.12±11.93	0.194
HDL-C(mmol/l)	0.91±0.22	1.28±0.57	0.013
LDL-C(mmol/l)	2.39±0.77	2.35±0.79	0.563
TC(mmol/l)	4.43±1.02	4.12±0.97	0.144
TG[M(P_{25},P_{75}),umol/L)]	2.37(1.81,3.29)	1.04(0.82,1.38)	0.006
FBG(mmol/l)	5.06±1.81	4.77±1.16	0.327
TG/HDL-C[M(P_{25},P_{75}),umol/L)]	2.48(1.76,3.66)	0.92(0.61,1.24)	0.001

ALT:Alanine aminotransferas AST:Aspartate aminotransferase;Crp:C-reactive protein; FBG Fasting blood glucose HDL-C:High-density lipoprotein cholesterol LDL-C Low density lipoprotein cholesterol TC:total cholesterol TG triglyceride

Multivariate Logistic regression analysis

Clinical indicators with statistically significant differences were included in the logistic regression analysis, the results showed that Crp, Albumin, TG/HDL-C and Female were independent risk factors for CMVD ($P < 0.05$,Table 3).

Table 3 Binary Logistic regression analysis of risk factors for CMVD

Variable	B	SE	Wald	OR Value	95%Cl	P value
Hypertension	0.140	0.084	0.540	1.158	0.677-1.854	0.360
Diabetes	0.890	0.202	2.836	0.873	0.464-1.083	0.093
Blood platelet	0.428	0.251	1.294	1.273	0.925-1.861	0.255
Crp	1.014	0.277	3.792	1.683	1.140-3.456	0.011
Albumin	0.722	0.330	4.824	2.052	1.080-3.905	0.028
TG/HDL-C	0.549	0.108	5.523	1.826	1.320-2.973	0.005
Female	0.434	0.220	3.844	1.545	1.001-2.382	0.049

Crp:C-reactive protein HDL-C:High-density lipoprotein cholesterol TG triglyceride

The results of the ROC curve

The area under ROC curve of TG/HDL-C was 0.789,95Cl(0.718-0.859),P 0.001 higher than female 0.651,95Cl(0.571-0.730),P 0.001,albumin 0.722,95Cl(0.649-0.794),P 0.001 and Crp 0.754,95Cl(0.681-0.827),P 0.001. The results illustrated that TG/HDL-C had superior test efficiency. (Figure 2)

Discussion

When the anterior coronary arterioles and arterioles have structural abnormalities and or dysfunction under the action of various risk factors, resulting in exertional angina pectoris or there is objective evidence of myocardial ischemia, we call it coronary microvascular disease(CMVD)[12].The abnormal structure and dysfunction of coronary microcirculation can affect the metabolic process of the cardiovascular, which have a great impact on the occurrence, development, evolution and prognosis of cardiovascular diseases. It has also been reported that cardiovascular disease can also induce and aggravate the structural abnormalities and dysfunction of coronary microcirculation[13]. At present, coronary intervention and coronary artery bypass grafting are commonly used in clinical myocardial reperfusion treatment, which can open the narrow epicardial coronary artery in time, but can not solve the problem of abnormal myocardial blood perfusion caused by coronary microcirculation. Therefore, if we can find a simple index to identify coronary microcirculation disease, it has important clinical significance to improve the prognosis of patients with coronary microvascular disease.

Clinical studies on risk factors related to coronary microvascular disease are still few. The research team of Li et al.[14] found that C-reactive protein in the coronary microvascular disease group was significantly higher than that in the non coronary microvascular disease group, suggesting that inflammatory response may be involved in the pathogenesis of coronary microvascular disease; Gokce et al.[15] found that the platelet aggregation rate in the coronary microvascular disease group was significantly higher than that in the non coronary microvascular disease group, suggesting that the dysfunction of platelets

may play a role in the process of coronary microvascular disease; The research report of Yildiz et al.[16] suggested that the increase of blood uric acid in patients with coronary microvascular diseas as one of the risk factors of cardiovascular disease. Some researches suggested that coronary microvascular disease may be related to obesity[17], smoking[18], hyperlipidemia, hypoalbuminemia, insulin resistance[19]. However, there is no final conclusion about the indicators for identifying coronary microvascular disease.

In our study, we found that compared with Non-CMVD group, patients in CMVD group had a higher proportion of female, high blood pressure and type 2 diabetes, it is consistent with the previous research results of Bairey[20]et al. In the comparison of the two groups of laboratory indicators, we found that platelet count, C-reactive protein, TG concentration were increased in patients of CMVD group, accompanied by decreased albumin levels and high-density lipoprotein cholesterol. Previous studies by Goel PK[21] have shown that the increase of platelet aggregation rate will lead to high shear stress and slow blood flow, accelerate endothelial cell damage, and easily lead to microvascular dysfunction.

The increased expression of inflammatory factors such as C-reactive protein will lead to the aggravation of vascular endothelial oxidative stress, the decline of endothelial mediated vascular motor function, and the decline of the fibrinolytic capacity of the body. These factors are important pathophysiological mechanisms of coronary microvascular lesions[22].

High triglyceride and low high density lipoprotein will accelerate the speed of lipid peroxidation and the degree of endothelial cell damage, resulting in microcirculation disturbance[23].Previous studies have shown that low albumin levels can lead to systemic inflammatory response and excessive oxidative stress, easy to lead to microvascular diseases[24].

Studies have confirmed that TG and HDL-C are the main index reflecting the body's blood lipid, which are related to the occurrence of atherosclerosis[25]. TG/HDL-C is a new composite index, it is not only can reflect the disorder of blood lipid metabolism, but also is related to insulin resistance[26]. Previous studies on lipid parameters and coronary flow reserve fraction in patients with inflammatory bowel disease found that compared with the healthy control group with CFR $\geq$ 2, the patients with CFR < 2 had higher TG concentration and lower HDL-C concentration. It suggests that TG and HDL-C may be related to coronary microvascular disease[27].

In our study, we found that TG/HDL-C in CMVD group was higher than that in Non-CMVD group, multivariate logistic regression analysis indicated that Crp, female, albumin and TG/HDL-C were independent risk factors for CMVD. Compared with Crp, female and albumin, the area under TG/HDL-C curve was the largest, indicating that TG/HDL-C is more efficient in identifying coronary microvascular diseases.

The mechanism by TG/HDL-C is associated with coronary microvascular disease is unclear and it may be related to insulin resistance. Insulin resistance can directly exacerbate vascular endothelial cell injury,

activate the damage repair mechanism of the body, and accelerate the aggregation of platelets, white blood cells, and other inflammatory factors[28]. Meanwhile, when insulin resistance, the compensatory increase in the number of vascular smooth muscle cells and the decrease in the content of the body's own vasodilator factors lead to the imbalance of vascular contraction and expansion, vascular endothelial damage and cause microvascular endothelial dysfunction[29]. In addition, when insulin resistance occurs, the expression of serum adiponectin and adhesion molecules in vivo also increases, which in turn affects the body's own vascular regulation and accelerates vascular endothelial injury and myocardial ischemia[30].

Limitations

There are still some limitations in this study. Firstly, our research is a single-center study with small sample size, so selection bias cannot be ruled out. Secondly, the specific mechanism of TG/HDL-C on coronary microcirculation disease is still unknown. Further experimental verification is needed to obtain more supporting evidence and clarify the mechanism. Thirdly, the follow-up of the study case is still in progress, so there is no further analysis on the prognosis. In the future, more samples are needed to conduct a prospective multi-center study to further validate our conclusions.

Conclusion

In conclusion, TG/HDL-C could be utilized as an independent risk factor for the occurrence of CMVD, thereby providing some clinical reference data for the examination of coronary microcirculation function in patients with non-large vascular obstructive angina pectoris.

Abbreviations

ATP
adenosine triphosphate
CAG
coronary angiography
CMVD
coronary microvascular disease
LCS
coronary sinus
LAR
aortic root
ISDN
intracoro- nary isosorbide mononitrate
ROC
receiver operating characteristic

Declarations

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Authors' contributions

LP contributed to the conception and design of the study. LP and YY contributed to data acquisition, analysis, and interpretation. LP drafted the manuscript. LP and WL critically revised the manuscript. All authors gave their approval and are responsible for all aspects of this manuscript, in terms of its integrity and accuracy.

Data Availability

The datasets used during the present study are available from the corresponding author upon reasonable request.

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of Jiading branch of shanghai general hospital and conducted in accordance with the standards of the National Research Council. Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

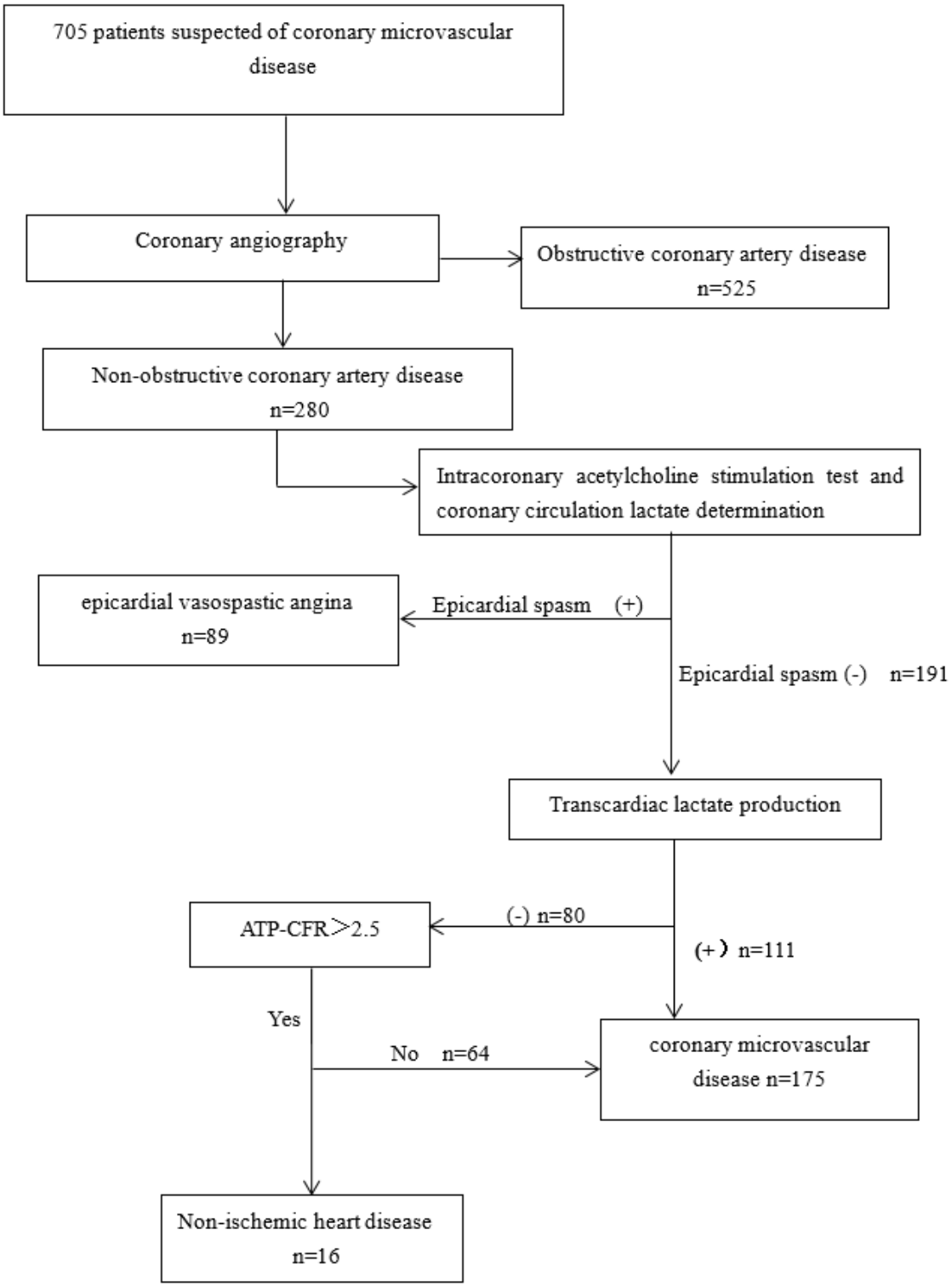

Figure 1

The diagnosis process of coronary microvascular disease

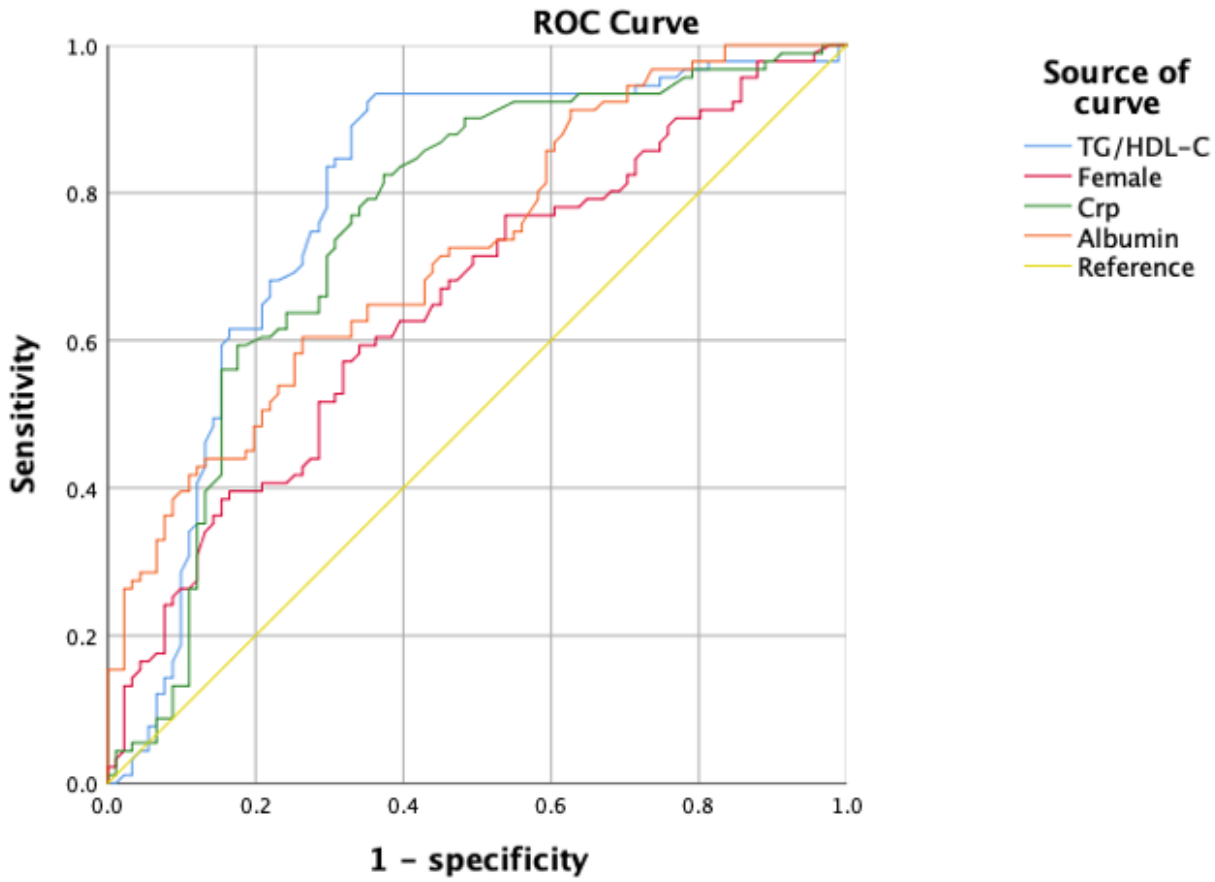

Figure 2

ROC Curve Analysis of HG/HDL-C,Female,Crp and Albumin.