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## The Predictive Value of Different Combinations of Biological Indices for Coronary Atherosclerotic Heart Disease

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### Abstract:

**Objective:** To investigate the association between the novel biological indices and coronary artery disease (CAD).

**Methods:** A total of 819 patients with CAD and 783 patients without CAD were selected from the First Affiliated Hospital of Xinjiang Medical University. The ratio of biological indicators between the two groups was compared, and the relationship between the ratio and the severity of CHD was analyzed.

**Results:** The levels of FPG/HDL-C, TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, MHR, and AST/ALT in the CAD group were significantly higher than those in the control group ( $P < 0.01$ ). Logistic regression results showed that TC/HDL-C, MHR, FPG/HDL-C, and AST/ALT were independent risk factors of CAD (OR= 1.328~2.960), TG/HDL-C was an independent protective factor (OR=0.820),  $P < 0.01$ . ROC curve analysis results showed that TC/HDL-C, MHR, FPG/HDL-C, AST/ALT, and TG/HDL-C had a predictive value for diagnosis of CAD (AUC=0.560~0.775;  $P < 0.001$ ). Spearman correlation analysis showed that FPG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and AST/ALT ( $r_s = 0.138\sim0.229$ ) were positively correlated with the severity of coronary artery stenosis ( $P < 0.001$ ).

**Conclusion:** TC/HDL-C, MHR, FPG/HDL-C, AST/ALT are risk factors of CAD. FPG/HDL-C has the highest predictive value for CAD. The ratios of FPG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and AST/ALT are positively correlated with the severity of coronary artery stenosis. The combined detection of these biological combinations has predictive value for early CAD diagnosis and the evaluation of coronary artery disease severity.

**Keywords:** Coronary artery disease; Biological indices; Coronary artery severity; Predictive value

## Introduction

Coronary artery disease (CAD) is considered one of the most serious burden health issues worldwide and has become the leading cause of mortality and disability [1]. CAD has complex pathophysiological features and is considered to be a complex disease involving multiple factors. With further understanding of CAD, some new risk factors have been found besides hypertension, diabetes mellitus, dyslipidemia, and smoking. It has been reported that 15% to 20% of CAD patients lack established traditional risk factors [2,3]. Therefore, finding new risk factors and biomarkers is very helpful for the early detection and prevention of CAD in clinical practice. Monocyte to high density lipoprotein ratio (MHR), Triglyceride / high density lipoprotein ratio (TG / HDL-C), and triglyceride uveal index (TyG) [4-6]. These indices can be used to evaluate the prognosis of coronary heart disease. In a retrospective study by wang J et al, the fibrinogen/albumin ratio (FAR) is valuable for diagnosing CAD and evaluating the severity of coronary artery disease [7]. These biomarkers are more accessible, convenient, and economical, and can complement traditional prognostic indicators, providing new information for clinical evaluation and treatment. Therefore, identifying more sensitive and specific biological indicators from traditional and non-traditional risk factors for CAD is critical for predicting adverse cardiovascular events and improving treatment outcomes [8].

In this study, 2000 cases of coronary heart disease from the First Affiliated Hospital, Xinjiang Medical University, and normal controls were retrospectively analyzed. To find new biomarkers related to coronary heart disease (CHD) and analyze their relationship with CAD and the severity of coronary artery disease.

## Materials and Methods

All subjects in this study were selected from patients hospitalized in the cardiology department of the First Affiliated Hospital of Xinjiang Medical University between January 2019 and December 2021, as well as individuals who underwent physical examinations during that period. Based on the inclusion and exclusion criteria, a total of 1,602 individuals were ultimately selected. The participants were divided into two groups based on their history of CAD and a control group: CAD group, consisting of 819 individuals, including 565 males and 254 females, with an average age of  $(56.13 \pm 10.13)$  years. Control group, composed of 783 individuals, including 511 males and 272 females, with an average age of  $55.43 \pm 9.11$  years. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University.

**Inclusion criteria****CAD group:**

1. Coronary angiography (CAG) guidelines of the American College of Cardiology (ACC) / American Heart Association (AHA) were used as the diagnostic criteria for CHD. After CAG, the diagnosis was made when the diameter of the left main coronary artery (LMCA), left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA) was 50% or more.
2. The patient has complete medical records and participates voluntarily.

**Exclusion criteria:**

1. Patients with abnormal liver and kidney function;
2. Patients with malignant tumors or hematological diseases;
3. Patients with neurological dysfunction;
4. Patients with congenital heart disease;
5. Patients with congenital and autoimmune diseases;
6. Hypothyroidism or hyperthyroidism of the thyroid gland;
7. Patients with incomplete case data and poor compatibility.

All study subjects were unrelated individuals with long-term residence in Xinjiang and signed informed consent forms before being included in the study.

**Control group:**

Gender- and age-matched with the CAD group; subjects with normal coronary arteries and no prior CAD were included in the control group.

Assessment of coronary artery disease severity: The severity of coronary artery disease in CHD was measured using the Gensini score. Gensini scoring system: LMCA, LAD, LCX, and RCA were observed. The scores of 1, 2, 4, 8, and 16 for any coronary artery stenosis  $\leq$  25%, 26% -50%, 51% -75%, 76% -90%, and 91% -99%, respectively, and 32 for total occlusion of the coronary artery. The integral calculation of coronary artery for a single lesion needs to be multiplied by the corresponding coefficient according to the location of coronary stenosis: LMCA lesion  $\times$  5, LAD proximal lesion  $\times$  2.5, LAD mesothelial lesion  $\times$  1.5, LCX opening lesion  $\times$  3.5, LCX proximal lesions  $\times$  2.5, LCX anterior lesion, LCX posterior lesion, RCA (proximal, mesothelial, distant) lesion  $\times$  1. The total score for each coronary artery lesion was the sum of the Gensini scores for each CHD patient [9]. Coronary stenosis was classified as mild (1-7 points), moderate (8-14 points), or severe (14 points or more) according to the modified Gensini score [10]. In the CHD group, 50 cases (6.1%) had mild stenosis, 54 cases (6.6%) had moderate stenosis, and 715 cases (87.3%) had severe stenosis.

### **Biochemical Indicator Testing**

After 12 hours of fasting, 2 mL venous blood was collected in the morning. One tube was placed into the Sysmex-XN1000 automatic blood cell analyzer, and the mononuclear cell count (MO) and platelet count (PLT) were measured using electrical impedance fusion technology. The other tube was placed in a low-speed centrifugation at 3000 rpm for 5 min. The biochemical results were obtained using the cobas8000 automatic precipitator, ion-selective electrode, homogeneous immunoassay, and electrochemiluminescent heterogeneous immunoassay. Triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), fasting plasma glucose (FPG), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) were measured. The above results were tested by the Laboratory Department of the First Affiliated Hospital of Xinjiang Medical University.

### **Statistical Methods**

Statistical analysis was conducted using the SPSS 24.0 software, and the data on measurement variables were presented as mean  $\pm$  standard deviation. ( $\bar{x} \pm s$ ), compared with the t-test; countable data in percentages, compared with the  $\chi^2$  test. The non-normal distribution was summarized as M (P25, P75), and the Mann-Whitney U test and logistic regression analysis were used to compare the groups. The ROC curve was used to evaluate the predictive value of different indices for CAD. Spearman's correlation coefficient model was used to analyze the correlation between each index and the severity of coronary artery disease (mild, moderate, severe).

The levels of AST, ALT, FPG, TG, TC, LDL, MO, and PLT in the CAD group were significantly higher than those in the control group ( $P < 0.05$ ); HDL-C was significantly lower than the average level in the control group ( $P < 0.001$ ), as given in (Table 1).

**Table 1: Comparison of general information between the CAD group and the control group**

Index	Control group (783 cases)	CAD group (819 cases)	t/Z/ $\chi^2$	P
Male n (%)	511 (65.3)	565 (70.0)	2.518	0.113
Age (years)	55.43±9.11	56.13±10.13	-1.458	0.145
AST (U/L)	19.20(15.90,24.60)	25.00(18.45,44.57)	-12.589	0.000
ALT (U/L)	21.90(15.40,32.21)	26.50(18.20,38.50)	-6.494	0.000
FPG (mmol/L)	5.47±1.94	8.20±3.82	-18.183	0.000
TG (mmol/L)	1.88±1.30	2.06±1.67	-2.481	0.013
TC (mmol/L)	4.15±0.92	4.46±1.29	-5.653	0.000
HDL (mmol/L)	1.08±0.30	0.99±0.29	6.097	0.000
LDL (mmol/L)	2.62±0.77	2.84±1.00	-4.849	0.000
MO( $\times 10^9$ /L)	0.46±0.18	0.55±0.28	-7.333	0.000
PLT( $\times 10^9$ /L)	217.94±58.03	233.24±70.12	-4.762	0.000

**Comparison of the biological combination ratio between the CHD group and the control group**

The average levels of CAD group FPG/HDL-C, TG/HDL-C, TC/HDL-C, LDL-C/HDL-C, MHR, and AST/ALT were significantly higher than those of the control group ( $P < 0.01$ ), all of which are risk factors for CAD, as shown in (Table 2).

**Table 2. Comparison of the ratios of biological indicators between the CAD group and the control group**

Correlation Ratio	Control (783)	CHD (819)	T/Z	P
FPG/HDL-C	4.80(3.79,6.39)	7.68(5.69,10.56)	-19.058	0.000

MHR	0.42(0.29,0.58)	0.53(0.35,0.78)	-8.038	0.000
TG/HDL-C	1.46(0.91,2.46)	1.67(1.09,2.82)	-4.176	0.000
AST/ALT	0.88(0.68,1.14)	1.03(0.76,1.56)	-8.307	0.000
TC/HDL-C	4.09±1.28	4.79±1.69	-9.367	0.000
LDL-C/HDL-C	2.59±0.96	3.04±1.25	-8.127	0.000

### Multiple logistic regression analysis of the indexes and CAD

Diagnostic CAD was used as the dependent variable, and variables with statistical significance in univariate analysis were used as independent variables. The results suggested that TC / HDL-C, MHR, FPG / HDL-C, and AST / ALT were independent risk factors for CAD after controlling for other variables (OR = 1.328 ~ 2.960; All  $P < 0.01$ ); TG / HDL-C was still an independent protective factor for CHD (OR = 0.820;  $P < 0.001$ ), as shown in (Table 3).

**Table 3. Multivariate Logistic regression analysis of biochemical and combined index and CAD**

Variable	B value	SE	Wald	P value	OR	95% Confidence Interval	
						lower limit	Upper limit
LDL-C/HDL-C	-0.211	0.129	2.682	0.101	0.810	0.629	1.042
TC/HDL-C	0.352	0.114	9.583	0.002	1.422	1.138	1.777
MHR	0.873	0.237	13.575	0.000	2.394	1.505	3.810
TG/HDL-C	-0.198	0.045	19.669	0.000	0.820	0.751	0.895
FPG/HDL-C	0.284	0.025	124.806	0.000	1.328	1.264	1.396
AST/ALT	1.085	0.133	66.985	0.000	2.960	2.283	3.838

### Receiver Operating Characteristic (ROC)

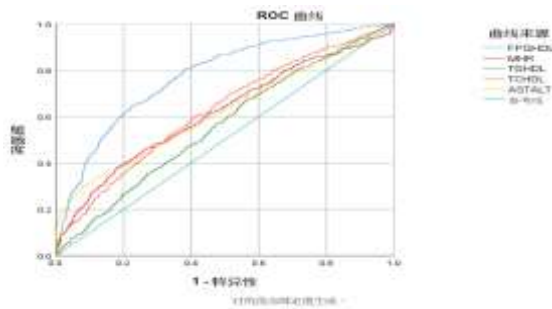
#### Curve for CAD patients:

TC / HDL-C, MHR, FPG / HDL-C, AST /

ALT, TG/ HDL-C were used as predictors of coronary heart disease. The results showed that all indexes could predict coronary heart disease, and the AUC for FPG/HDL-C was significantly higher than that of the other indexes. The best cut-off was 5.339, the sensitivity

was 80.5%, and the specificity was 61.7%.

See table 4, (figure 1)



**Figure1. Receiver Operating Characteristic (ROC)Curve for the Prediction of CAD Based on Various Biochemical and Combined Indicators**

**Table 4: Prediction of CAD based on various combination indicators**

variable	AUC	lower limit	Upper limit	Reference value	Cut-off value	sensitivity	Specificity
		OR(95%CI)	OR(95%CI)				
FPG/HDL-C	0.775	0.754	0.795	0.422	5.339	0.805	0.617
AST/ALT	0.620	0.596	0.644	0.220	1.345	0.327	0.893
MHR	0.616	0.592	0.640	0.198	0.639	0.379	0.820
TC/HDL-C	0.626	0.601	0.649	0.188	4.251	0.598	0.590
TG/HDL-C	0.560	0.536	0.585	0.108	1.287	0.674	0.434

**Spearman analysis of the relationship between biological parameters and severity of**

### coronary artery disease

According to the modified Gensini score, 819 cases in the CHD group were divided into three groups: mild coronary artery disease (50 cases, 6.1%), moderate stenosis (54 cases, 6.6%), and severe stenosis (715 cases, 87.3%). The Spearman correlation coefficient was used to analyze the correlation between each index and the severity of coronary artery disease (mild, moderate, severe). The results showed that FPG / HDL-C, TC / HDL-C, LDL-C / HDL-C, AST / ALT ( $r_s = 0.138 \sim 0.229$ ). There was a positive relationship between the severity of coronary artery disease and blood vessel count ( $P < 0.05$ ), as shown in (Table 5).

**Table 5. Spearman analysis of the relationship between biological parameters and the severity of coronary artery disease**

Index ratio	Correlation coefficient	P
FPG/HDL-C	0.229	0.000
MHR	0.065	0.063
TG/HDL-C	0.039	0.267
AST/ALT	0.138	0.000
TC/HDL-C	0.145	0.000
LDL-C/HDL-C	0.162	0.000

### Discussion

In recent years, more studies have investigated the relationships between hematological biomarkers, such as FPG/HDL and TG/HDL-C, and adverse outcomes in CAD. These biomarkers are essential for definitive diagnosis, risk assessment, and the guidance of CAD treatment in some clinical therapies [11]. The association between the FPG /HDL-C ratio and adverse clinical outcomes was investigated in patients without diabetes mellitus after PCI. The results showed that higher FPG/HDL-C ratios were associated with a 28.4% increase in all-cause mortality (HR: 1.284,  $P < 0.05$ ). The ratio of MO and HDL-C is a new inflammatory marker discovered in recent years[12]. Some studies have shown that MHR is involved in the pathogenesis of CHD, and is associated with poor prognosis, long-term cardiovascular events, and case fatality rate of coronary heart disease [13]. The predictive value of MHR for premature coronary heart disease and coronary artery stenosis was demonstrated in a study by Xu Hui, which found that MHR predicted the severity of coronary heart disease (CHD) with a sensitivity of 0.813 and specificity of 92.8% [14]. Therefore, the

combined detection of monocyte and HDL is of great significance to the development of CHD. The TG/HDL-C ratio is also known as the TG/HDL-C ratio. In a prospective cohort study by Qin H et al., 95,642 volunteers were followed for 9 years to examine the relationship between TG/HDL-C and cardiovascular events, during which 5,242 cardiovascular events occurred among patients with significantly reduced TG/HDL-C ratios [15]. A recent analysis of a large epidemiological dataset of 8000 people concluded that the TC / HDL-C ratio was a better predictor of subsequent CHD and was more important than a single predictor of epidemic disease. Although the epidemiological significance of a high TC/HDL-C ratio in epidemic disease is relatively clear, little is known about the extent of coronary artery stenosis. It was found that the ratio of LDL-C / HDL-C played a significant role in coronary lesions [16-17]. Other studies have identified the LDL-C / HDL-C ratio as a sensitive marker of atherosclerotic cardiovascular disease risk, showing that the LDL-C / HDL-C ratio is a useful indicator for preventing the progression of atherosclerotic cardiovascular disease [18]. A recent meta-analysis of more than 9.24 million participants and 224,953 cases of all-cause mortality found a relatively weak association between AST and all-cause mortality. In contrast, ALT was clearly associated with all-cause mortality in the general population [19, 20]. These results further confirm the association between ALT / AST and mortality risk.

The results of this study showed that, in the CAD group, FPG/HDL-C, MHR, TG/HDL-C, TC/HDL-C, ALT/AST, and LDL-C/HDL-C ratios were significantly higher than in the control group ( $P < 0.01$ ). Multivariate logistic regression analysis showed that TC/HDL-C, MHR, FPG/HDL-C, and AST / ALT were independent risk factors for CAD, and TG/HDL-C was an independent protective factor for CHD. These results suggest that the above indices can serve as a new biomarker to predict CHD incidence and guide treatment to reduce coronary heart disease. TC/HDL-C, MHR, FPG/HDL-C, AST/ALT, and TG /HDL-C were all predictors of coronary heart disease ( $P < 0.001$ ).  $FPG/HDL-C > 5.339$ ,  $AST/ALT > 1.345$ ,  $MHR > 0.639$ ,  $TC/HDL-C > 4.251$ ,  $TG/HDL-C > 1.287$  can indicate a high risk of coronary heart disease. Therefore, in clinical treatment, enhanced monitoring of the above indicators can be considered an important complementary treatment. Among them, the AUC of FPG/HDL-C was significantly higher than the indicator, with an optimal cut-off of 5.339 (80.5% sensitivity and 61.7% specificity), indicating that FPG = HDL-C had better accuracy in predicting the occurrence of CHD. Spearman's correlation analysis showed that FPG/HDL-C, TC/HDL-C, ALT/AST, and LDL-C/HDL-C were correlated with the severity of coronary

artery stenosis. These results suggest that these biomarkers are positively correlated with the severity of coronary artery stenosis and can be used to predict CAD and coronary artery stenosis severity. To the best of our knowledge, this is the first retrospective study to evaluate the association between FPG/HDL-C and ALT/AST with coronary heart disease. The combination of these ratios can be used as an effective auxiliary index for the diagnosis and treatment of CAD.

### **Conclusion:**

The ratios TC/HDL-C, MHR, FPG/HDL-C, and AST/ALT are independent risk factors for coronary artery disease (CHD). Among these, FPG/HDL-C has the highest predictive value. Furthermore, FPG/HDL-C, TC/HDL-C, LDL-C/HDL-C, and AST/ALT are positively correlated with the severity of coronary artery stenosis. The combined use of these ratios provides valuable predictive information for the early diagnosis and severity assessment of CHD.

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