Research Article

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Serum TLR8 as a potential diagnostic biomarker of coronary heart disease

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Abstract

Objectives: Early diagnosis of coronary heart disease (CHD) remains a huge challenge clinically due to the lack of biomarkers. Toll-like receptor 8 (TLR8) is an innate immune receptor that is involved in various diseases. This study aimed to investigate whether TLR8 was associated with CHD.
Methods: Dysregulate genes were predicted using microarray analysis. A total of 85 patients with CHD and 85 non-CHD were enrolled in this study. Basic clinical data and hematological indicators were collected. The levels of TLR8 in the serum were detected using enzyme-linked immunosorbent assay. Correlations between TLR8 levels and hematological indicators were evaluated using Pearson correlation coefficient. The diagnostic performance of TLR8 was analyzed using the receiver operating characteristic (ROC) curve.
Results: The results showed that multiple genes were aberrantly expressed in CHD. Among them, TLR8 levels in the serum were higher in CHD than that in non-CHD. It was revealed that TLR8 levels were related to fasting plasma glucose, triglyceride, and low-density lipoprotein cholesterol. Moreover TLR8 was an independent risk factor for CHD. ROC curve results showed that the area under the curve value was 0.8737.
Conclusions: Serum TLR8 is closely associated with CHD and has the potential to be a diagnostic biomarker for CHD.

Keywords: coronary heart disease; TLR8; correlation; diagnosis

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Introduction

Coronary heart disease (CHD) is one of the most common and fatal cardiovascular diseases worldwide [1]. It is a chronic inflammatory and fibroproliferative disease characterized by arteries narrowing or blocking due to abnormal accumulation of lipids in the coronary arteries. Many risk factors are discovered for CHD, such as age, smoking, diabetes, obesity, hypertension, and hyperlipidemia [2]. Lifestyle changes, pharmacotherapy, and myocardial revascularization are important ways to reduce CHD mortality [3, 4]. However, although modern medicine has made remarkable progress in the treatment and management of CHD, its early diagnosis remains a huge challenge. Traditional diagnostic methods have limitations, such as low sensitivity, high side effects, and high cost [5], which makes many patients fail to receive timely intervention before the disease progresses to an irreversible stage. Therefore, exploring new early diagnostic tools or markers is critical to improving patient outcomes.

Toll-like receptors (TLRs) are pattern recognition receptors that play a key role in host immune defense by recognizing specific pathogen-associated molecular patterns to activate innate and adaptive immune responses [6, 7]. Among them, TLR8 is mainly present in human immune cells such as monocytes and macrophages, mediating the release of pro-inflammatory factors and type I interferons [8]. It is located in intracellular vesicles that can recognize single-stranded RNA in viruses and then trigger inflammatory signaling [9]. Recent studies have shown that TLR8 is not only involved in infection but also plays a crucial role in non-infectious diseases, such as autoimmune diseases, tumors, and cardiovascular diseases [10–12]. It has been reported that TLR8 is associated with inflammatory response in atherosclerosis-related disease, which is a major cause of

CHD [12]. Based on the inflammatory nature of CHD [13] and the pro-inflammatory effects of TLR8, there may be a potential link between them. Nevertheless, the specific mechanism of action of TLR8 in CHD and its value as a potential biomarker have not been fully elucidated.

In the present study, we screened multiple aberrant expressed genes in CHD and found that TLR8 expression might be increased. Thus, we measured the expression of TLR8 in clinical samples and evaluated its correlation with clinical characteristics. Moreover, the diagnostic value was investigated. This study may provide a promising biomarker for the early diagnosis of CHD.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University-Town Hospital of Chongqing Medical University.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Materials and methods

Bioinformatic analysis

The GSE71226 dataset was screened from the Gene Expression Omnibus (GEO) database. The dataset included gene expression between patients with CHD and healthy people in Chinese Han people. Data were analyzed with the GEO2R program. Differentially expressed genes were screened according to the criteria: |log2 fold change|> 1.0 and $p<0.05$.

Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was performed to identify the pathways related to all up-regulated genes.

Participants

This study was approved by the Ethics Committee of University-Town Hospital of Chongqing Medical University. A total of 85 patients who were diagnosed with CHD using coronary angiography in our hospital were enrolled in our study. According to the number of diseased vessels, patients with CHD were divided into vessel ≤2 (n=52) and vessel >2 (n=27) groups. In addition, 85 age- and sex-matched participants without CHD (non-CHD) were enrolled as the control. Written informed consent was provided by each participant.

The inclusion criteria were greater than 50 % stenosis in the arbitrary segment of at least one main coronary artery. The exclusion criteria included: 1) Previous CHD history with coronary stent implantation and coronary artery bypass grafting; 2) complicating other heart diseases and heart dysfunction; 3) malignancy; 4) patients with malignancy, infection, hematological system diseases, liver and kidney dysfunction, and autoimmune disease; 5) patients with mental disorders.

Diabetes mellitus was defined as fasting blood glucose ≥7.0 mmol/L or postprandial blood glucose ≥11.1 mmol/L, hemoglobin A1c ≥6.5 %, and/or treatment with anti-diabetic medication. Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on ≥2 separate occasions and/or currently taking anti-hypertensive medication. Hyperlipidemia was defined as total cholesterol (TC) content ≥572 mmol/L and/or triglyceride (TG) ≥1.70 mmol/L or high-density lipoprotein-cholesterol (HDL-C) <9.0 mmol/L. Age, sex, body mass index (BMI), and smoking history were recorded. Fasting venous blood was collected from all participants.

Detection of hematological indicators

Fasting plasma glucose (FPG), TC, TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (Apo-A1), and apolipoprotein B (Apo-B) were measured by an automatic biochemical analyzer (Hitachi, Tokyo, Japan). Very low-density lipoprotein cholesterol (VLDL-C) was measured by enzymatic method. Lipoproteina (Lpa) was detected using an enzyme-linked immunosorbent assay (ELISA) kit (Abcam, Cambridge, MA, USA). High sensitivity C-reactive protein (hs-CRP) was measured using chemiluminescent immunoassay.

ELISA

The levels of TLR8 in the serum of participants were measured using the human TLR8 ELISA kit (Yanjing Biotechnology Co., LTD, Shanghai, China). Briefly, the blood was centrifuged at 3,000 rpm for 15 min after the natural solidification, and the supernatant (i.e. serum) was collected. The serum was diluted 5 times in microplate wells and incubated at 37 °C for 30 min. After washing, the sample

(50 µL) was incubated with 50 µL conjugate reagent at 37 °C for 30 min. The color developer was added to the sample, and the mixture was incubated at 37 °C for 15 min away from light. Following stopping the reaction, the absorbance was measured by a microplate reader (Bio-Rad, Hercules, CA, USA) at 450 nm.

Statistical analysis

Data in this study were analyzed using the SPSS 25.0 and GraphPad Prism 8.0 software. Counting data were expressed as frequency (percentage) [n, (%)], and the difference was analyzed by chi-square test. The normal distribution of variables was evaluated using the Shapiro-Wilk test. The independent *t*-test was used to evaluate the differences between groups in the data with normal distribution, and the results were represented as mean±standard deviation. The Mann-Whitney U test was used to evaluate the differences between groups in the non-normally distributed data, and the results were shown as median and quartile ranges [M (P25, P75)]. Multivariate logistic regression analyses were used to validate the independent risk factors of patients with CHD. Correlation analysis was performed using the Pearson correlation coefficient. The diagnostic value was assessed using the receiver operating characteristic (ROC) curve. $p<0.05$ indicates a statistical difference.

Results

TLR8 expression is increased in CHD

To screen potential biomarkers in CHD, we performed a microarray analysis. Multiple genes were dysregulated in patients with CHD, including 209 up-regulated genes and 581 down-regulated genes. The heat map shows the top 10 up-regulated genes and the top 10 down-regulated genes (Figure 1A). Next, we used KEGG enrichment analysis to assess the pathways that related to all up-regulated genes from the microarray. As shown in Figure 1B, they were enriched in only two pathways, malaria, and neutrophil extracellular trap formation. Neutrophil extracellular trap promotes inflammatory immune responses, which can trigger cardiovascular diseases such as CHD and accelerate disease progression [14]. Currently, the role of TLR8 enriched in the neutrophil extracellular trap formation pathway in CHD remains largely unknown. Therefore, we were very interested in this gene and chose it for follow-up research.

Basic characteristics of participants

We selected 101 patients with CHD who visited our hospital. According to the exclusion criteria, five cancer patients were excluded. After the experimental protocol began, 11 patients with incomplete clinical data were also excluded. Finally, 85 patients with CHD were enrolled in this study. Additionally, 85 non-CHD were enrolled in this study as the control (Figure 2). Their clinical characteristics are listed in Table 1. We included two age- and sex-matched groups of participants, so there was no significant difference between the two groups in these two indicators. The number of patients with a history of smoking, diabetes, hypertension, and hyperlipidemia in the CHD group was significantly higher than that in the non-CHD group (all $p<0.05$). Compared to non-CHD, the levels of BMI, FPG, TG, LDL-C, Lpa, Apo-B, and hs-CRP were significantly increased (all $p<0.0001$), while HDL-C levels were markedly reduced in patients with CHD ($p<0.0001$). Additionally, there were no significant differences in TC, VLDL-C, and Apo-A1 between the two groups (all $p>0.05$).

Increased TLR8 levels are confirmed in patients with CHD

The levels of TLR8 were measured using ELISA. The results showed that the levels of TLR8 in the serum were significantly higher in the CHD group than that in the non-CHD group ($p<0.0001$; Table 1). In addition, we divided patients with CHD into two groups: vessel ≤2 and vessel >2 groups, according to the vessel number of the involved coronary artery. The results of ELISA showed that TLR8 levels were higher in CHD no matter the number of diseased vessels ≤2 or >2 ($p<0.01$). However, no significant difference was found in TLR8 levels between vessel ≤2 and vessel >2 groups (Figure 3). These results indicate that TLR8 was highly expressed in CHD, consistent with the results of bioinformatic analysis.

Correlation analysis results

The correlation between serum TLR8 levels and clinical characteristics of glucose and lipid metabolism was analyzed using Pearson correlation coefficient. The results showed that TLR8 levels had significant positive correlation with FPG ($r=0.3350$, $p=0.0017$), TG ($r=0.4252$, $p<0.0001$), LDL-C ($r=0.3640$, $p=0.0006$); however, TLR8 levels had no significant correlation with TC, HDL-C, VLDL-C, Lpa, Apo-A1, Apo-B, and hs-CRP (all $p>0.05$; Table 2).

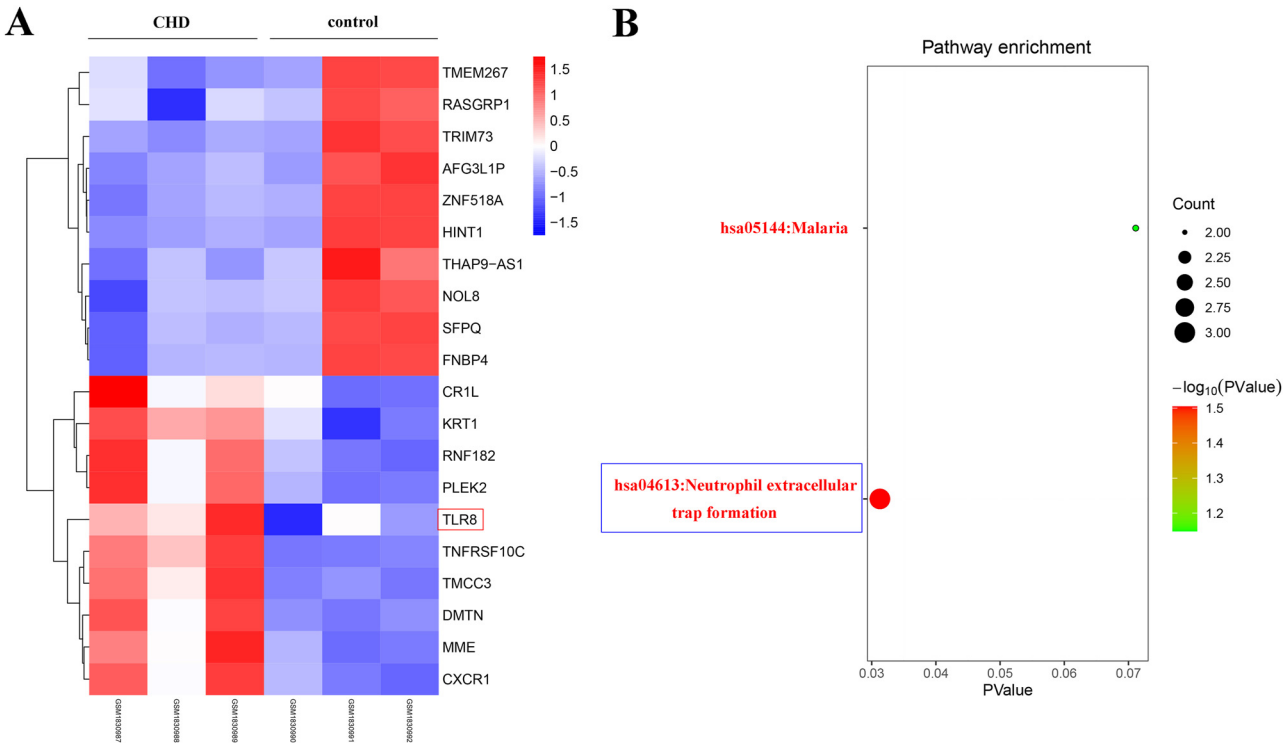

Figure 1: Identification of differentiation expressed genes in CHD. (A) Differentially expressed genes in CHD were predicted using microarray analysis, and the top 10 up-regulated and top 10 down-regulated genes are shown using the heat map. Red: up-regulation; blue: down-regulation. (B) KEGG pathway enrichment analysis of the up-regulated genes in CHD.

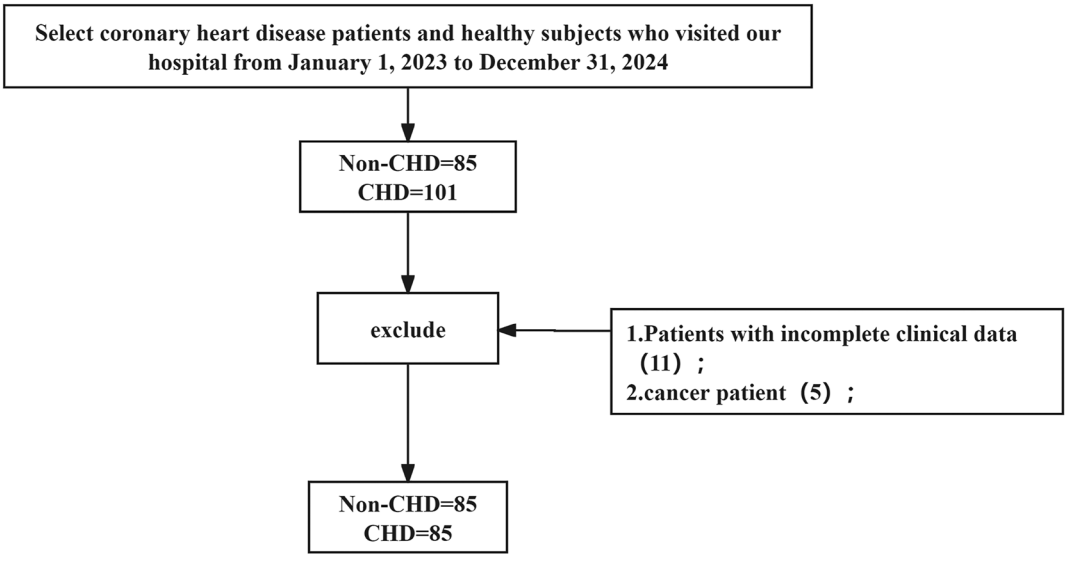

Figure 2: Flow chart of subject screening process.

Influence factors associated with CHD

We then assessed whether TLR8 remained significantly associated with CHD after adjusting for confounding factors including age, sex, smoking, diabetes, hypertension, and lipid profiles. The detailed methods of assigning independent variables are shown in Table 3. Multivariate logistic regression analysis was performed. The OR value shows the specific impact of each variable on CHD. We found that FPG (OR=5.667, p=0.017), Lpa (OR=9.631, p=0.002), ApoB

Table 1: Clinical characteristics of non-CHD and CHD groups.

Characteristics	Non-CHD(n=85)	CHD (n=85)	χ^2/t/Z value	p-Vaule
Age, years	60.7±7.9	59.0±9.0	1.633	0.104
Sex(male,%)	45(53.0 %)	44(51.8 %)	0.154	0.878
Smoking history	12(14.1 %)	32(37.6)	3.502	0.005
Diabetes mellitus, n, %	18(21.2 %)	33(38.8 %)	2.510	0.012
Hypertension, n, %	38(44.7 %)	60(70.6 %)	3.415	0.0006
Hyperlipidemia, n, %	33(38.8 %)	59(70.6 %)	4.002	<0.0001
BMI	21.51±2.81	24.27±3.8	4.727	<0.0001
FPG	4.64±0.46	5.13±0.47	6.877	<0.0001
TC	3.94±0.37	3.84±0.39	1.654	0.1000
TG	1.25±0.30	1.48±0.33	4.834	<0.0001
HDL-C	1.10±0.17	0.95±0.20	5.424	<0.0001
LDL-C	2.10±0.36	2.38±0.39	4.737	<0.0001
VLDL-C	0.74(0.6, 0.93)	0.79(0.67, 0.9)	0.050	0.4308
Lpa	124.04±23.12	188.67±32.79	14.85	<0.0001
Apo-A1	1.40±0.13	1.37±0.13	1.110	0.2684
Apo-B	0.71±0.12	0.86±0.14	7.223	<0.0001
Hs-CRP	0.60±0.12	1.49±0.24	30.60	<0.0001
TLR8	0.34±0.07	0.86±0.18	10.33	<0.0001

CHD, coronary heart disease; BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; Lpa, lipoproteina; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; hs-CRP, high sensitivity C-reactive protein; TLR8, toll-like receptor 8.

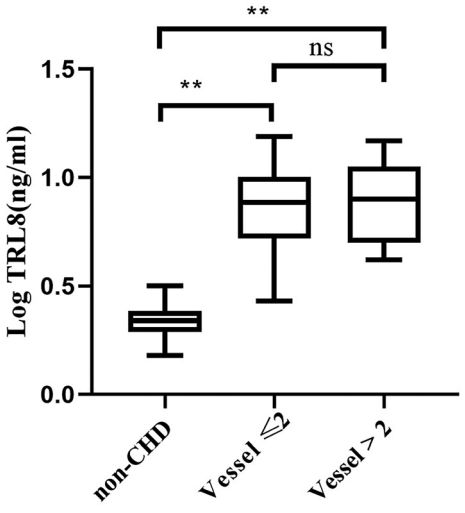

Figure 3: TLR8 levels of the serum of all participants. The levels of TLR8 were detected using ELISA in non-CHD (n=85), vessel ≤2 (patients with CHD with the number of diseased vessels ≤2, n=52), and vessel >2 (patients with CHD with the number of diseased vessels >2, n=27). **p<0.01. NS, no significance.

(OR=4.488, p=0.034), and TLR8 (OR=7.292, p=0.007) were significantly associated with CHD (Table 4), suggesting that they are the potential risk factors of CHD.

Diagnosis value of TLR8 for CHD

The diagnostic value of TLR8 was evaluated using ROC curve. As shown in Figure 4. The area under the curve (AUC) value was 0.8737 (95 % CI: 0.8222–0.9252). The results suggest that TLR8 is a potential biomarker for CHD diagnosis.

Discussion

In the present study, we found that the levels of TLR8 were increased in patients with CHD and were related to FPG, TG, and LDL-C. Additionally, the AUC value was 0.8737. These results indicate that TLR8 is associated with CHD.

The results of microarray analysis showed many differentially expressed genes, and the up-regulated genes in CHD were enriched in malaria and neutrophil extracellular trap formation pathways. It is well-known that malaria affects the cardiovascular system, and cardiovascular complications are extremely common in patients with malaria [15], which may be due to the inflammatory response caused by malaria. Additionally, neutrophil extracellular trap promotes pro-inflammatory response by activating endothelial cells and platelets in atherosclerosis [16]. Our findings suggest that in addition to abnormal lipid metabolism or hemodynamic changes in the traditional sense [17, 18], CHD is also involved in inflammation and immune responses [19]. This will help us to understand the pathophysiological mechanisms of CHD and provide a new direction to search for new markers. Brea et al. [20] found that TLR7 and TLR8 levels are associated with greater inflammatory response and poor prognosis of acute ischemic stroke. Therefore, we speculate that there may be some connection between inflammation-related TLRs and CHD.

Accumulating evidence has confirmed that TLRs are crucial for the pathogenesis of atherosclerosis, which has the nature of chronic inflammation and is the basis of CHD [21]. In recent years, the link between TLR8 and cardiovascular disease has been gaining attention, although findings remain somewhat controversial. The upregulation of TLR8 expression can reveal the systemic inflammation of coronary artery disease [22]. Besides, the expression of TLR8 is negatively related to HDL-C levels in patients with coronary artery disease and serves as the negative predictive factor in healthy controls [22, 23]. A previous study has reported that TLR8 mRNA expression is strongly upregulated and correlates with the progression of atherosclerosis in the aorta [24]. However, it is important to note that not all studies have found a clear association; for instance, Zhong et al. [25] found no evidence that TLR8 gene polymorphisms predispose

Table 2: Correlation between serum TLR8 levels and clinical characteristics.

Characteristics	r	p-Vaule	Characteristics	r	p-Vaule
FPG	0.3350	0.0017	VLDL-C	0.1284	0.2415
TC	0.1620	0.1385	Lpa	−0.0100	0.9273
TG	0.4252	<0.0001	Apo-A1	0.1228	0.2630
HDL-C	0.0163	0.8825	Apo-B	0.0812	0.4627
LDL-C	0.3640	0.0006	Hs-CRP	0.1584	0.1476

FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL-C, very low-density lipoprotein cholesterol; Lpa, lipoproteina; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B; hs-CRP, high sensitivity C-reactive protein.

Table 3: Method of assigning independent variables.

Independent variable	Assigned method
Smoking history	Smoke=1; no Smoking=0
Diabetes mellitus, n, %	Diabetes=1; no diabetes=0
Hypertension, n, %	Hypertension=1; no hypertension=0
Hyperlipidemia, n, %	Hyperlipidemia=1; no hyperlipidemia=0
BMI	Continuous variables are entered with actual values
FPG	Continuous variables are entered with actual values
TG	Continuous variables are entered with actual values
HDL-C	Continuous variables are entered with actual values
LDL-C	Continuous variables are entered with actual values
Lpa	Continuous variables are entered with actual values
Apo-B	Continuous variables are entered with actual values
Hs-CRP	Continuous variables are entered with actual values
TLR8	Continuous variables are entered with actual values

individuals to coronary artery disease, highlighting the complexity of its role. Although previous studies have suggested TLR8 was a key gene related to a variety of cardiovascular diseases, such as acute myocardial infarction, Kawasaki disease, and calcified aortic valve disease [26–28], its study in CHD is still limited.

Our study contributes to this ongoing discussion by being the first to systematically evaluate circulating TLR8 protein levels in CHD and its relationship to clinical parameters. We found that TLR8 levels were increased in patients with CHD, regardless of the number of diseased vessels. These findings suggest that TLR8 may not be related to the severity of CHD, indicating that TLR8 may be more involved in the early occurrence of coronary heart disease rather than late-stage progression. Alternatively, our study may be underpowered for subgroup analyses by vessel number, warranting larger cohorts. Additionally, coronary artery calcification is an important presentation of CHD. However, our current research results cannot rule out whether the upregulation of TLR8 expression is caused by coronary artery calcification. We will resolve this issue through CT calcium scores in our future study.

We also found that TLR8 levels were positively related to the levels of FPG, TC, and LDL-C. Hyperglycemia is a widely recognized risk factor for CHD [29]. In addition, TC and LDL-C are indicators associated with hyperlipidemia, which is a direct cause of atherosclerosis [30]. Thus, glucose and lipid metabolism indicators changed dramatically in CHD [31]. The findings in our study suggest that TLR8 plays a pivotal role in regulating glucose and lipid metabolic homeostasis, consistent with previous studies [32, 33]. The multivariate logistic regression analysis results showed that TLR8 remained significantly associated with CHD after adjusting for diabetes, smoking, hypertension, and hyperlipidemia, suggesting that TLR8 is a potential independent rick factor for CHD. However, there are numerous factors that may affect CHD. In the future, we will continue to rule out potential confounding factors and further elaborate on the relationship between TLR8 and CHD.

TLR8 has been preliminarily reported as a promising diagnostic marker in a variety of diseases, including polycystic ovary syndrome, sepsis, and osteoarthritis [34–36]. However, its diagnostic performance for CHD is still unknown. The results of our study showed that the AUC value was 0.8737, suggesting that TLR8 serves as a potential diagnostic marker.

The limitations of this study cannot be ignored. First, this study used a cross-sectional design, which means that we could only observe an association between TLR8 levels

Table 4: Multivariate logistic regression analysis of CHD.

Independent variable	β	SE	OR	p-Value	Exp(B)	Exp(B) – 95 % confidence interval	
Smoking history	1.654	1.207	1.879	0.17	5.23	0.491	55.694
Diabetes mellitus	0.788	1.166	0.456	0.499	2.199	0.224	21.621
Hypertension,	0.191	1.235	0.024	0.877	1.211	0.108	13.632
Hyperlipidemia,	1.473	1.125	1.716	0.19	4.364	0.481	39.55
BMI	0.006	0.157	0.001	0.969	1.006	0.74	1.367
FPG	4.043	1.698	5.667	0.017	56.981	2.043	1589.557
TG	2.288	1.711	1.788	0.181	9.851	0.345	281.689
HDL-C	−2.842	2.892	0.966	0.326	0.058	0	16.88
LDL-C	1.234	1.521	0.659	0.417	3.436	0.174	67.735
Lpa	0.089	0.029	9.631	0.002	1.093	1.033	1.157
Apo-B	9.877	4.662	4.488	0.034	19477.252	2.094	181155293.3
TLR8	6.868	2.543	7.292	0.007	960.81	6.573	140436.06

CHD, coronary heart disease; BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Lpa, lipoproteina; Apo-B, apolipoprotein B; TLR8, toll-like receptor 8.

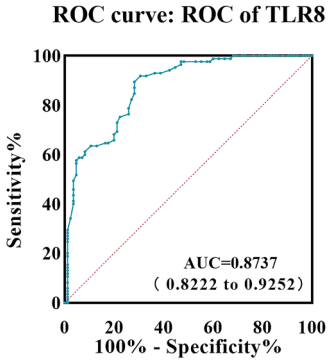

Figure 4: Diagnostic value of TLR8 levels for CHD. ROC curve analysis of serum TLR8 levels for discrimination of patients with CHD (n=85) from non-CHD (n=85).

and CHD. Longitudinal cohort studies are needed in our future work to understand the dynamics of TLR8 in different stages of CHD development. In addition, this is a single-center small sample study, and our conclusions may not be universally applicable. Larger multicenter studies would help improve the external validity of the results. Moreover, despite the potential relationship between TLR8 levels with glucose and lipid metabolism, this does not mean that TLR8 is responsible for these changes. The existing literature on the role of TLR8 in CHD presents conflicting results. In our future work, it will be necessary to delve deeper into the specific role of TLR8 in CHD using cellular or animal models. Finally, although TLR8 shows diagnostic potential, a single marker is often insufficient to fully reflect complex disease states. Therefore, combined with multi-marker comprehensive assessment may be a direction to improve diagnostic accuracy. Therefore, more studies are needed to translate our conclusions into clinical practice. In recent years, a variety of small molecule agents targeting TLR8 have been developed for clinical treatment [37]. These drugs are also being investigated for the treatment of CHD.

In conclusion, this study demonstrated that TLR8 levels are elevated in the serum of patients with CHD. It is closely related to abnormal glucose and lipid metabolism. Moreover, TLR8 has better diagnostic performance for CHD. These findings add support to the idea that TLR8 may be a new biomarker to predict the occurrence of CHD. However, the observed association between TLR8 and CHD may be influenced by unmeasured confounders. Future prospective studies are needed to validate the predictive value of TLR8.

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Author contribution: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Luqiang Yin, Yunli Peng, Bingjie Liao, Xiulan Zhu and Ting Zhao. The first draft of the manuscript was written by Cheng Yang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest: The authors have no relevant financial or non-financial interests to disclose.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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