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ORIGINAL RESEARCH

A Genetic Risk Prediction Model for Coronary Artery Disease Integrating CYP17A1 Polymorphisms and Clinical Variables in a Chinese Population

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Purpose: This study aimed to investigate the association between *CYP17A1* gene polymorphisms and coronary artery disease (CAD) risk in a Chinese population.

Patients and Methods: A total of 2221 subjects (1363 CAD patients and 858 controls) were enrolled. Five single-nucleotide polymorphisms (SNPs) (rs11191548, rs17115100, rs4409766, rs6162, and rs6163) were genotyped. To account for multiple testing across genetic models, the false discovery rate (FDR) correction was applied. A nomogram incorporating *CYP17A1* genetic variants and clinical characteristics was developed to predict CAD risk.

Results: In the overall population, preliminary association analyses identified three SNPs (rs11191548, rs17115100, rs4409766) with genotype distributions significantly different between cases and controls under recessive models. These associations remained significant after FDR correction for multiple testing across all 5 SNPs and 3 genetic models tested (all q = 0.035). Subsequent multivariate logistic regression, adjusted for clinical confounders, confirmed independent protective effects: the CC genotype of rs11191548 (OR = 0.507, 95% CI: 0.352–0.730, P < 0.001), the CC genotype of rs4409766 (OR = 0.557, 95% CI: 0.394–0.786, P = 0.001), and the TT genotype of rs17115100 (OR = 0.632, 95% CI: 0.473–0.844, P = 0.002). The integrated nomogram achieved an area under the curve (AUC) of 0.727–0.728 for CAD risk prediction. Moreover, exploratory sex-stratified analyses indicated potential sex-specific associations, with some variants linked to CAD risk in either males or females at a nominal significance level.

Conclusion: The rs11191548, rs17115100, and rs4409766 variants of the *CYP17A1* gene were found to be associated with CAD in a Chinese population.

Keywords: CYP17A1 gene, CAD, polymorphism

Introduction

Coronary artery disease (CAD), a leading cause of death in the world, is a complex multifactorial disease.[1] It is thought to arise from an interaction between genetic susceptibility loci and various environmental determinants.[2] The genetic basis of CAD has attracted much attention in recent years. With the development of CAD genome-wide association study (GWAS), more and more CAD susceptibility genes have been found, and many common, rare, and functional CAD variants have been identified in large-scale association analyses.[3,4] Among these, the *CYP17A1* gene, located on chromosome 10q24.3, is primarily expressed in the adrenal glands and gonads. It encodes a member of the cytochrome P450 superfamily. The resulting P450c17 protein possesses both 17α-hydroxylase and 17,20-lyase activities, serving as

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a key enzyme in the steroidogenic pathway for the biosynthesis of progesterone, corticosteroids, glucocorticoids, androgens, and estrogens.[5] Recent research suggests that *CYP17A1* may be involved in the development of hypertension,[6,7] ischemic stroke,[8] myocardial hypertrophy,[9] myocardial infarction[10] and premature coronary heart disease.[11]

In two large-scale association analyses the same year, researchers found that the *CYP17A1* gene locus as one of 13 novel susceptibility loci for CAD.[12,13] For instance, Butterworth et al[14] selected a cohort of 15596 patients and 34992 controls to assess 2100 genes and 49094 variants, suggesting that the *CYP17A1* gene is one of the susceptibility genes to CAD. However, it is crucial to note that these seminal GWAS were predominantly conducted in populations of European ancestry. Due to distinct linkage disequilibrium patterns and allele frequencies across ethnicities, genetic markers identified in Western populations may not carry the same risk magnitude or relevance in East Asian populations. Although subsequent studies have identified specific SNPs within *CYP17A1*, such as rs4409766 and rs1004467, as susceptibility variants, data regarding their specific association with CAD in the Chinese population remain sparse and inconsistent.[11,15] This "ancestry gap" necessitates dedicated validation studies in specific ethnic groups to ensure the applicability of genetic findings.[16]

Furthermore, a significant gap exists between genetic discovery and clinical application. While polygenic risk scores (PRS) demonstrate significant value in evaluating the risk of cardiovascular diseases, they often require extensive genomic data that may not be feasible in routine clinical settings.[17,18] In contrast, a visual statistical tool known as a nomogram can integrate specific genetic variants with routine clinical variables to provide a personalized and easy-to-interpret probability of disease risk.[19] Therefore, this study aims to assess the correlation between *CYP17A1* polymorphisms and CAD in a Chinese population and to develop a novel predictive nomogram incorporating these variants for early risk stratification in clinical practice.

Methods

Ethical Approval of the Study Protocol

The present study was conducted in accordance with the principles outlined in the Helsinki Declaration and was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (No. K201909-02). Written informed consent was obtained from each participant, explicitly granting permission for DNA analysis and the collection of relevant clinical data.

Subjects

This case-control study enrolled participants between December 2017 and October 2021. Genotyping was performed in 2023. All participants were hospitalized patients undergoing coronary angiography. Coronary angiography was performed by highly skilled physicians using the Judkins method. Results were interpreted by at least two experienced radiologists. CAD was diagnosed based on angiography reports, defined as the presence of at least one significant coronary artery stenosis with a luminal diameter reduction of > 50%. Subjects with vasospastic angina, active infection within the preceding 2 weeks, heart failure, adrenal dysfunction, or thyroid dysfunction were excluded. Controls were recruited from individuals with angiographically normal coronary arteries and no history of CAD. Finally, 1363 CAD patients (1007 men, 356 women) and 858 controls (439 men, 419 women) were included. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg on at least three separate occasions. Subjects with T2DM (Type II diabetes mellitus) were defined as those who had fasting plasma glucose (FPG) ≥ 7.0 mmol/L, or 2-hour post-load plasma glucose (2hPG) ≥ 11.1 mmol/L, or had hypoglycemic therapy history.

Blood Collection and DNA Extraction

Fasting venous blood samples were collected in the morning into EDTA-containing tubes. Genomic DNA was isolated from peripheral leukocytes using standard phenol-chloroform extraction. DNA samples were stored at −80°C. Prior to genetic analysis, the DNA concentration was adjusted to 50 ng/μL.

Genotyping

The Haploview 4.2 software and the International HapMap Project website were used in the Phase II data base, we selected five tag SNPs (rs11191548, rs17115100, rs4409766, rs6162, rs6163) based on a minor allele frequency (MAF) ≥ 0.05 and a linkage disequilibrium threshold of $r^2 \geq 0.8$. The linkage disequilibrium (LD) map for these SNPs is shown in Figure 1. Genotyping for the case-control study was performed using an improved multiplex ligation detection reaction (iMLDR) technique (Digena Diagnostics Technology Co., Zhejiang, China), a highly specific and accurate method based on ligation and fluorescent signal detection. Stringent negative and positive controls were included in each experiment, and any ambiguous results were re-genotyped for confirmation. The accuracy of the iMLDR genotyping was further validated by an independent TaqMan assay, with 100% concordance (see Supplementary Material: Genotyping Protocol and Validation Data).

Biochemical Analysis

Fasting blood glucose (FBG), glycosylated serum protein (GSP), glycosylated hemoglobin (GHb), white blood cell count (WBC), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), blood urea nitrogen (BUN), creatinine (Cr), and uric acid (UA) were measured using standard methods at the Central Laboratory of the First Affiliated Hospital of Xinjiang Medical University.

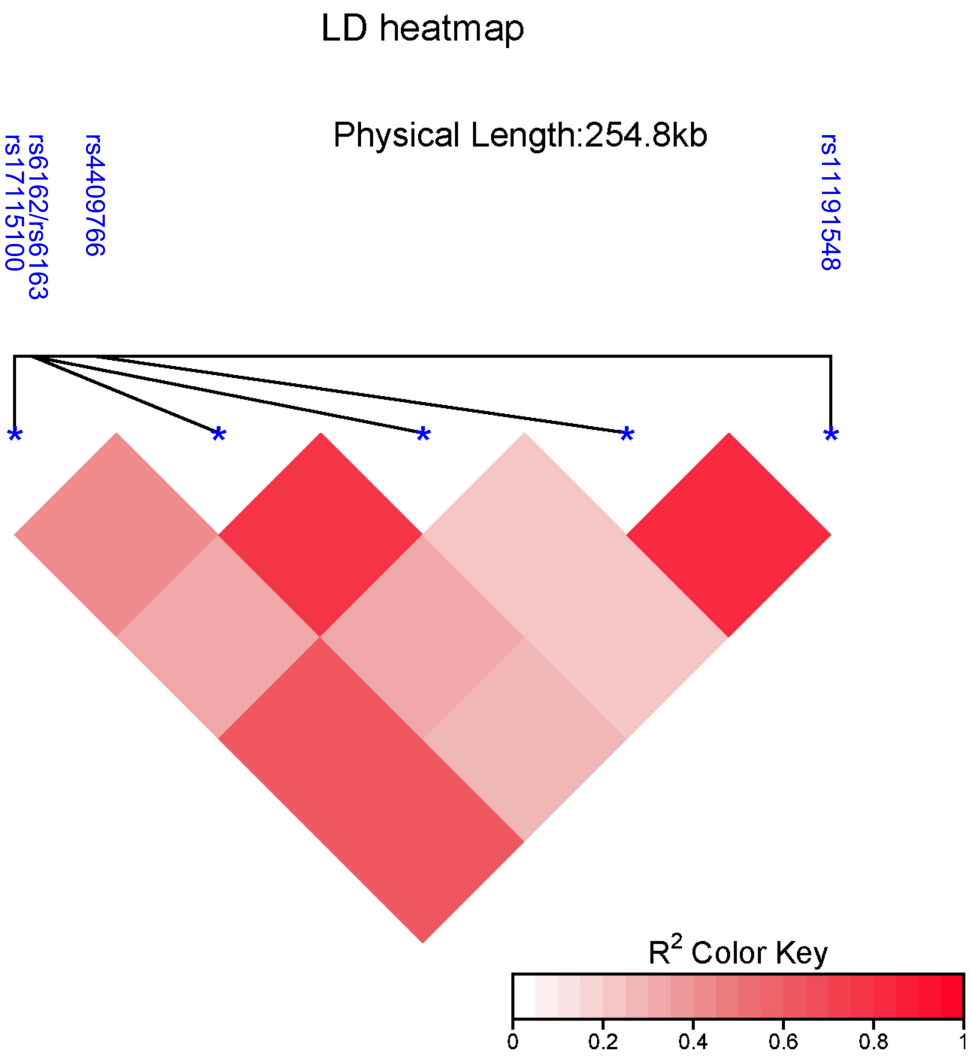

Figure 1 Genetic variation and linkage disequilibrium (LD) in the human *CYP17A1* gene. An LD heatmap displays the pairwise associations among five genotyped single-nucleotide polymorphisms (SNPs). The analysis was performed using the "LD heat map" package in R (version 4.2.1), with LD blocks defined by the solid spline method. The strength of LD is represented by the color intensity of each square according to the r^2 statistic, ranging from white ($r^2 = 0$) through shades of pink ($0 < r^2 < 1$) to red ($r^2 = 1$). The physical length of the genomic region shown is 254.8 kb.

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Statistical Analysis

Sample Size and Statistical Power

Prior to the study, an a priori sample size calculation was performed. Based on a standard genetic association study design (additive model, two-sided α=0.05, power= 80%), we aimed to detect an odds ratio (OR) of 1.4 for a common variant in the *CYP17A1* gene, such as rs17115100 with a minor allele frequency (MAF) of 0.18 in the general population (gnomAD). This calculation indicated that approximately 853 subjects per group (1706 total) would be required. Our final sample size of 2221 participants (1363 cases, 858 controls) provided adequate statistical power for the primary analysis.

Statistical Methods

Data analysis was conducted using SPSS26.0 (SPSS Inc., Chicago, IL, USA) and R software (version 4.2.1). Continuous variables are presented as mean ± SD and were compared using Student's *t*-test. Categorical variables are presented as frequencies (percentages) and were compared using the $\chi 2$ test or Fisher's exact test, as appropriate. Hardy-Weinberg equilibrium was assessed using $\chi 2$ analysis. The genotype and allelic model (dominant, recessive, additive) distributions for the five SNPs were compared between CAD cases and controls using $\chi 2$ tests. We evaluated these three genetic models (additive: per-allele effect; dominant: effect allele carriers vs non-carriers; recessive: effect allele homozygotes vs others) to comprehensively assess association patterns without prior assumption of the underlying mode of inheritance. To control the FDR across these multiple comparisons (5 SNPs × 3 models), we applied the Benjamini-Hochberg procedure. The resulting FDR-adjusted P-values (denoted as q-values) are reported alongside the nominal P-values in the relevant results; a q-value < 0.05 was considered statistically significant after correction. Associations between genetic variants and CAD risk were further evaluated using multivariate logistic regression, with results expressed as ORs and 95% confidence intervals (CIs). A nomogram was used to build a multi-factor regression model for predicting the probability of the final event by using Regression Modeling Strategies (RMS) package in R. A receiver operation characteristic curve (ROC), c-index and calibration plots were used to evaluate the discrimination ability, calibration ability, and clinical effectiveness of the nomogram model.

Results

Table 1 presents the demographic and clinical characteristics of the study participants. Concentrations of FBG, GSP, GHb, Cr, TG and WBC were significantly higher in CAD group, while HDL-C was lower. The CAD group was older and

Table 1 Demographic and Clinical Characteristics in CAD and Controls

Variables	Total (N=2221)			Men (N=1146)			Women (N=775)		
	CAD (N=1363)	Control (N=858)	P value	CAD (N=1007)	Control (N=439)	P value	CAD (N=356)	Control (N=419)	P value
Age, years	60.63±10.82	55.86±12.32	**<0.001**	59.01±11.01	54.55±12.65	**< 0.001**	65.21±8.78	57.23±11.83	0.083
Hypertension, n (%)	784 (57.5%)	358 (41.7%)	**<0.001**	548 (54.4%)	186 (42.4%)	**< 0.001**	236 (66.3%)	172 (41.1%)	**< 0.001**
T2DM, n (%)	461 (33.8%)	174 (20.3%)	**<0.001**	345 (34.3%)	87 (19.8%)	**< 0.001**	116 (32.6%)	87 (20.8%)	**< 0.001**
FBG, mmol/L	6.73±3.12	5.67±2.06	**<0.001**	6.78±3.25	5.67±2.06	**< 0.001**	6.59±2.75	5.66±2.06	**< 0.001**
TG, mmol/L	1.95±1.39	1.75±1.45	**0.001**	2.00±1.47	1.83±1.57	0.060	1.81±1.12	1.66±1.31	0.079
TC, mmol/L	3.90±1.06	4.14±1.05	**<0.001**	3.84±1.06	4.00±1.07	**0.009**	4.08±1.01	4.28±1.00	**0.006**
HDL-C, mmol/L	1.06±0.30	1.17±0.34	**<0.001**	1.01±0.28	1.08±0.31	**< 0.001**	1.20±0.32	1.25±0.34	**0.036**
LDL-C, mmol/L	2.49±0.87	2.66±0.82	**<0.001**	2.46±0.88	2.59±0.83	**0.009**	2.58±0.83	2.73±0.80	**0.009**
Cr, umol/L	73.45±19.28	69.28±19.99	**<0.001**	77.17±18.79	76.69±18.82	0.655	62.90±16.55	61.52±18.16	0.272
BUN, mmol/L	5.46±1.76	5.43±0.87	0.693	5.59±1.75	5.67±1.77	0.448	5.09±1.72	5.18±1.93	0.501
GSP, mmol/L	2.17±0.42	2.08±0.41	**<0.001**	2.16±0.42	2.07±0.42	**0.001**	2.23±0.41	2.08±0.39	**< 0.001**
GHb, n(%)	6.19±1.55	5.58±1.10	**<0.001**	6.19±1.54	5.57±0.94	**< 0.001**	6.20±1.56	5.59±1.24	**< 0.001**
WBC, 10^9/L	7.00±2.20	6.60±2.02	**<0.001**	7.24±2.22	7.03±2.06	0.082	6.30±1.99	6.15±1.87	0.267

Note: Values in bold indicate a statistically significant association (P < 0.05).

Abbreviations: T2DM, Type II diabetes mellitus; FBG, fasting blood glucose; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; Cr, creatinine; BUN, blood urea nitrogen; GSP, glycated serum protein (GSP); Ghb, glycosylated hemoglobin; WBC, white blood cell count; CAD, coronary artery disease.

had a higher prevalence of hypertension and diabetes. However, concentrations of TC, LDL-C were lower in the CAD, which might be attributable to the common use of lipid-lowering drugs for secondary prevention among high-risk cardiovascular disease subjects. Similar results were observed in both male and female subgroups.

Table 2 shows the distribution of genotypes of the *CYP17A1* gene. All five tested SNPs were in Hardy-Weinberg equilibrium in the control group (all $P > 0.05$). The detailed allele frequencies and exact HWE P values for the three SNPs showing significant association (rs11191548, rs17115100, and rs4409766) are provided in Supplementary Table S1. There was no significant difference in the distribution of SNPs rs6162 and rs6163 genotypes, or in their dominant, recessive, and additive models between the CAD group and the control group (see Supplementary Tables S2 and S3). After applying FDR correction for multiple testing across five SNPs and three genetic models, the recessive models of rs11191548, rs17115100 and rs4409766 remained significantly different between CAD patients and controls (all $q = 0.035$), with the CC genotype of rs11191548, the CC genotype of rs4409766 and the TT genotype of rs17115100 being less frequent in the CAD group. A similar result was observed in males. Additionally, the dominant model (TT vs CC + CT) of rs4409766 showed a nominally significant difference, suggesting the TT genotype could increase the susceptibility to CAD in males.

Among the female subjects, the additive model of rs11191548 (CT vs CC + TT) showed a nominally significant difference between CAD patients and controls ($P = 0.043$). For rs17115100, both the TG genotype and its additive model (TG vs GG + TT) were found at nominally higher frequencies in the CAD group ($P = 0.013$). For rs4409766, its additive model (CT vs CC + TT) showed a marginal statistical difference ($P = 0.055$). Additionally, a trend toward statistical significance was observed in the recessive models across these four SNPs (rs11191548, rs17115100, rs4409766, rs6163) in females (see Table 2).

Tables 3–5 show multivariate logistic regression analysis of these three SNPs identified in the initial FDR-corrected screen. After adjustment for hypertension, age, T2DM, dyslipidemia, FBG, TG, Cr, WBC, and HDL-C, a significant protective effect was confirmed under the recessive model, indicating that the CC genotype of rs11191548 (OR = 0.507, 95% CI: 0.352–0.730, $P < 0.001$), the CC genotype of rs4409766 (OR = 0.557, 95% CI: 0.394–0.786, $P = 0.001$) and the TT genotype of rs17115100 (OR = 0.632, 95% CI: 0.473–0.844, $P = 0.002$) were independently associated with a reduced risk of CAD.

For men, after adjusting for the main confounding factors, nominally significant protective effects were observed in the recessive model of rs11191548 (OR = 0.546, 95% CI: 0.349–0.852, $P = 0.008$), rs17115100 (OR = 0.688, 95% CI: 0.479–0.988, $P = 0.043$) and rs4409766 (OR = 0.602, 95% CI: 0.395–0.918, $P = 0.018$). Furthermore, under the dominant model, the TT genotype of rs4409766 was associated with an increased risk of CAD at a nominal significance level (OR = 1.323, 95% CI: 1.045–1.676, $P = 0.020$) (see Supplementary Table S4).

For women, after adjusting for the main confounding factors, additive models showed that the heterozygous genotype of rs11191548 and rs17115100 were nominally associated with an increased susceptibility to CAD (OR = 1.477, 95% CI: 1.070–2.039, $P = 0.018$; OR = 1.615, 95% CI: 1.176–2.216, $P = 0.003$) (see Supplementary Table S5).

Figures 2–4 show the nomograms based on the results of the logistic regression analysis. Confounders including FBG, hypertension, TG, Age, Gender, HDL-C and TT genotype of rs11191548 were incorporated into the final model to construct the nomogram (shown in Figure 2A). Based on the identification and calibration, the heavy samples were internally validated using the bootstrap-squared method. We applied this method to estimate the model's performance by creating multiple datasets through resampling with replacement. The resampling was performed 1000 times, which allowed for the evaluation of variability and the assessment of the model's robustness. As shown in Figure 2B, the AUC was 0.728 (95% CI: 0.706–0.749, $P < 0.001$). This indicates that the model has good discriminatory power. The calibration curve of the model is shown in Figure 2C. A similar analysis was performed for rs17115100 (see Figure 3, AUC = 0.727, 95% CI: 0.705–0.748, $P = 0.001$) and rs4409766 (see Figure 4, AUC = 0.727, 95% CI: 0.705–0.749, $P = 0.001$).

Table 2 Genotype Distribution of rs11191548, rs17115100, rs4409766 of *CYP17A1* Between CAD and Controls

SNP	Variants		Total		P	q (FDR)	Men		P	q (FDR)	Women		P	q (FDR)
			CAD, n (%)	Control, n (%)			CAD, n (%)	Control, n (%)			CAD, n (%)	Control, n (%)		
RS11191548	Genotype	CC	74(5.4%)	72(8.4%)	**0.022**	–	57((5.7%)	39(8.9%)	**0.036**	–	17(4.8%)	33(7.9%)	0.051	–
		TT	790(58.0%)	477(55.6%)			602(59.8%)	239(54.4%)			188(52.8%)	238(56.8%)		
		TC	499(36.6%)	309(36.0%)			348(34.6%)	161(36.7%)			151(42.4%)	148(35.3%)		
	Dominant model	TT	790(58.0%)	477(55.6%)	0.273	0.683	602(59.8%)	239(54.4%)	0.058	0.174	145(40.7%)	191(45.6%)	0.174	0.261
		CC+CT	573(42.0%)	381((44.4%)			405(40.2%)	200(45.6%)			211(59.3%)	228(54.4%)		
	Recessive model	CC	74(5.4%)	72(8.4%)	**0.006**	**0.035**	57(5.7%)	39(8.9%)	**0.024**	0.120	33(9.3%)	56(13.4%)	0.075	0.161
		CT+TT	1289(94.6%)	786(91.6%)			950(94.3%)	400(91.1%)			323(90.7%)	363(86.6%)		
	Additive model	CT	499(36.6%)	309(36.0%)	0.776	0.895	348(34.6%)	161(36.7%)	0.438	0.597	151(42.4%)	148(35.3%)	**0.043**	0.161
		CC+TT	864(63.4%)	549(64.0%)			659(65.4%)	278(63.3%)			205(57.6%)	271(64.7%)		
Rs17115100	Genotype	GG	617(45.3%)	378(44.1%)	**0.010**	–	472(46.9%)	187(42.6%)	**0.047**	–	145(40.7%)	191(45.6%)	**0.026**	–
		TT	127(9.3%)	115(13.4%)			94(9.3%)	59(13.4%)			33(9.3%)	56(13.4%)		
		TG	619(45.4%)	365(42.5%)			441(43.8%)	193(44.0%)			178(50.0%)	172(41.1%)		
	Dominant model	GG	617(45.3%)	378(44.1%)	0.576	0.895	472(46.9%)	187(42.6%)	0.133	0.332	145(40.7%)	191(45.6%)	0.174	0.261
		TG+TT	746(54.7%)	480(55.9%)			535(53.1%)	252(57.4%)			211(59.3%)	228(54.4%)		
	Recessive model	TT	127(9.3%)	115(13.4%)	**0.003**	**0.035**	94(9.3%)	59(13.4%)	**0.020**	0.120	33(9.3%)	56(13.4%)	0.075	0.161
		TG+GG	1236(90.7%)	743(86.6%)			913(90.7%)	380(86.6%)			323(90.7%)	363(86.6%)		
	Additive model	TG	619(45.4%)	365(42.5%)	0.184	0.552	441(43.8%)	193(44.0%)	0.952	0.952	178(50.0%)	172(41.1%)	**0.013**	0.161
		TT+ GG	744(54.6%)	493(57.5%)			566(56.2%)	246(56.0%)			178(50.0%)	247(58.9%)		

Rs4409766	Genotype	CC	85(6.2%)	80(9.3%)	**0.019**	–	66(6.6%)	43(9.8%)	**0.024**	–	19(5.3%)	37(8.8%)	0.053	–
		TT	773(56.7%)	457(53.3%)			591(58.7%)	229(52.2%)			182(51.1%)	228(54.4%)		
		TC	505(37.1%)	321(37.4%)			350(34.8%)	167(38.0%)			155(43.5%)	154(36.8%)		
	Dominant model	TT	773(56.7%)	457(53.3%)	0.111	0.416	591(58.7%)	229(52.2%)	**0.021**	0.120	182(51.1%)	228(54.4%)	0.360	0.415
		CC+CT	590(43.3%)	401(46.7%)			416(41.3%)	210(47.8%)			174(48.9%)	191(45.6%)		
	Recessive model	CC	85(6.2%)	80(9.3%)	**0.007**	**0.035**	66(6.6%)	43(9.8%)	**0.032**	0.120	19(5.3%)	37(8.8%)	**0.061**	0.161
		CT+TT	1278(93.8%)	778(90.7%)			941(93.4%)	396(90.2%)			337(94.7%)	382(91.2%)		
	Additive model	CT	505(37.1%)	321(37.4%)	0.864	0.926	350(34.8%)	167(38.0%)	0.231	0.433	155(43.5%)	154(36.8%)	0.055	0.161
		CC+TT	858(62.9%)	537(62.6%)			657(65.2%)	272(62.0%)			201(56.5%)	265(63.2%)		

Notes: P-values are nominal from χ^2-tests. q-values are adjusted for multiple testing across 5 SNPs and 3 genetic models (15 tests) using the Benjamini-Hochberg false discovery rate (FDR) procedure. Values in bold indicate a statistically significant association ($P < 0.05$).

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Table 3 Multiple Logistic Regression Analysis of Recessive Model for CAD (rs11191548)

Variables	Total			Men		
	OR	95% CI	P	OR	95% CI	P
Age	1.044	1.035–1.054	**<0.001**	1.035	1.023–1.046	**<0.001**
Hypertension	1.697	1.404–2.051	**<0.001**	1.467	1.157–1.860	**0.002**
T2DM	0.958	0.712–1.288	0.775	1.010	0.689–1.481	0.959
Dyslipidemia	0.855	0.685–1.067	0.165	0.841	0.634–1.116	0.230
WBC	1.021	0.974–1.070	0.383	1.039	0.981–1.100	0.187
Cr	0.998	0.993–1.004	0.515	0.999	0.992–1.005	0.674
FBG	1.149	1.083–1.219	**<0.001**	1.152	1.067–1.244	**<0.001**
TG	1.095	1.003–1.196	**0.043**	1.099	0.983–1.230	0.097
HDL-C	0.572	0.418–0.781	**<0.001**	0.456	0.303–0.686	**<0.001**
Recessive model (CC vs TC+TT)	0.507	0.352–0.730	**<0.001**	0.546	0.349–0.852	**0.008**

Note: Values in bold indicate a statistically significant association (P < 0.05).
Abbreviations: T2DM, Type II diabetes mellitus; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; WBC, white blood cell count; CAD, coronary artery disease.

Table 4 Multiple Logistic Regression Analysis of Recessive Model for CAD (rs17115100)

Variables	Total			Men		
	OR	95% CI	P	OR	95% CI	P
Age	1.044	1.035–1.053	**<0.001**	1.034	1.023–1.045	**<0.001**
Hypertension	1.695	1.403–2.049	**<0.001**	1.463	1.154–1.855	**0.002**
T2DM	0.947	0.704–1.273	0.718	1.001	0.683–1.467	0.994
Dyslipidemia	0.854	0.685–1.066	0.163	0.837	0.632–1.110	0.217
WBC	1.019	0.973–1.069	0.422	1.037	0.980–1.098	0.210
Cr	0.998	0.993–1.004	0.570	0.999	0.993–1.006	0.774
FBG	1.149	1.083–1.219	**<0.001**	1.152	1.067–1.244	**<0.001**
TG	1.094	1.002–1.195	**0.045**	1.099	0.983–1.229	0.097
HDL-C	0.570	0.417–0.779	**<0.001**	0.462	0.307–0.695	**<0.001**
Recessive model (TT vs TG+GG)	0.632	0.473–0.844	**0.002**	0.688	0.479–0.988	**0.043**

Note: Values in bold indicate a statistically significant association (P < 0.05).
Abbreviations: T2DM, Type II diabetes mellitus; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; WBC, white blood cell count; CAD, coronary artery disease.

Discussions

The relationship between polymorphisms in the cytochrome P450 (CYP) gene superfamily and cardiovascular disease (CVD) susceptibility has been established, linking genetic variation to metabolic phenotypes. In our study, we identified a significant association between specific polymorphisms in the *CYP17A1* gene and the risk of CAD in a Chinese population. Notably, our findings withstood stringent statistical correction. After applying the Benjamini-Hochberg FDR correction for multiple testing across five SNPs and three genetic models, the recessive models of rs11191548, rs17115100, and rs4409766 remained significantly associated with CAD (q = 0.035). This statistical robustness

Table 5 Multiple Logistic Regression Analysis of Recessive Model for CAD (rs4409766)

Variables	Total			Men		
	OR	95% CI	P	OR	95% CI	P
Age	1.044	1.035–1.053	**<0.001**	1.034	1.023–1.045	**<0.001**
Hypertension	1.697	1.404–2.052	**<0.001**	1.468	1.158–1.861	**0.002**
T2DM	0.950	0.706–1.277	0.732	1.006	0.686–1.474	0.976
Dyslipidemia	0.852	0.683–1.063	0.155	0.835	0.630–1.107	0.210
WBC	1.020	0.973–1.069	0.412	1.038	0.981–1.099	0.197
Cr	0.998	0.993–1.004	0.534	0.999	0.992–1.005	0.693
FBG	1.150	1.084–1.220	**<0.001**	1.152	1.067–1.244	**<0.001**
TG	1.095	1.002–1.196	**0.044**	1.099	0.982–1.229	0.100
HDL-C	0.569	0.416–0.778	**<0.001**	0.454	0.301–0.684	**<0.001**
Recessive model (CC vs TC+TT)	0.557	0.394–0.786	**0.001**	0.602	0.395–0.918	**0.018**

Note: Values in bold indicate a statistically significant association (P < 0.05).
Abbreviations: T2DM, Type II diabetes mellitus; FBG, fasting blood glucose; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; Cr, creatinine; WBC, white blood cell count; CAD, coronary artery disease.

reinforces the validity of these loci. Specifically, the CC genotype of rs11191548, the TT genotype of rs17115100, and the CC genotype of rs4409766 demonstrated independent protective effects against CAD after adjusting for confounding factors such as hypertension, diabetes, and lipid profiles. These results align with recent multi-ancestry GWAS, which have increasingly pinpointed the *CYP17A1* as a hotspot for pleiotropic effects on blood pressure and steroid metabolism, suggesting a shared genetic architecture between hypertension and coronary atherosclerosis.[9,11,20]

A pivotal finding of our study is the distinct sexual dimorphism observed in the genetic association patterns. Our exploratory sex-stratified analyses revealed distinct patterns: while the recessive models showed nominally significant protective effects in males, and TT genotype of rs4409766 tended to be an independent risk factor for CAD in males; additive models indicated that heterozygous genotypes of rs11191548 and rs17115100 were nominally associated with increased CAD susceptibility in females. This divergence likely stems from the fundamental sex-specific reliance on *CYP17A1*-mediated steroidogenesis. *CYP17A1* encodes P450c17, an enzyme with both 17α-hydroxylase and 17, 20-lyase activities, serving as a critical gatekeeper for the synthesis of sex steroids (androgens and estrogens) versus mineralocorticoids. In males, variants affecting 17, 20-lyase efficiency could subtly shift the androgen-to-estrogen ratio, a biomarker increasingly linked to endothelial function and plaque stability.[21–24] Recent analyses of the UK Biobank have confirmed that genetic predictors of CAD exhibit significant sex-interactions, particularly in loci regulating hormonal homeostasis.[25–27] Conversely, in females, where cardiovascular protection is historically attributed to 17β-estradiol, variants impairing substrate availability for aromatization could disproportionately elevate CAD risk.[28,29] This hypothesis is supported by recent animal models showing that *Cyp17a1*-deficient female mice develop accelerated atherosclerosis due to estrogen deficiency-mediated metabolic dysregulation.[11]

Beyond individual SNPs, the integration of genetic and clinical data is crucial for precision medicine. We developed an early warning nomogram model integrating clinical characteristics with *CYP17A1* genotypes. The model achieved an AUC of 0.728. While an AUC of 0.73 indicates moderate discrimination, it is comparable to the performance of traditional risk scores, such as the Framingham Risk Score (FRS), when applied to East Asian populations, where FRS often yields AUCs in the range of 0.65–0.75.[30,31] The clinical utility of our nomogram lies in its potential to refine risk stratification for individuals in the "intermediate" clinical risk category. Recent studies suggest that integrating polygenic risk scores (PRS) with standard clinical metrics significantly improves net reclassification improvement (NRI), effectively identifying high-risk individuals who would be missed by clinical factors alone.[32,33] By incorporating *CYP17A1*

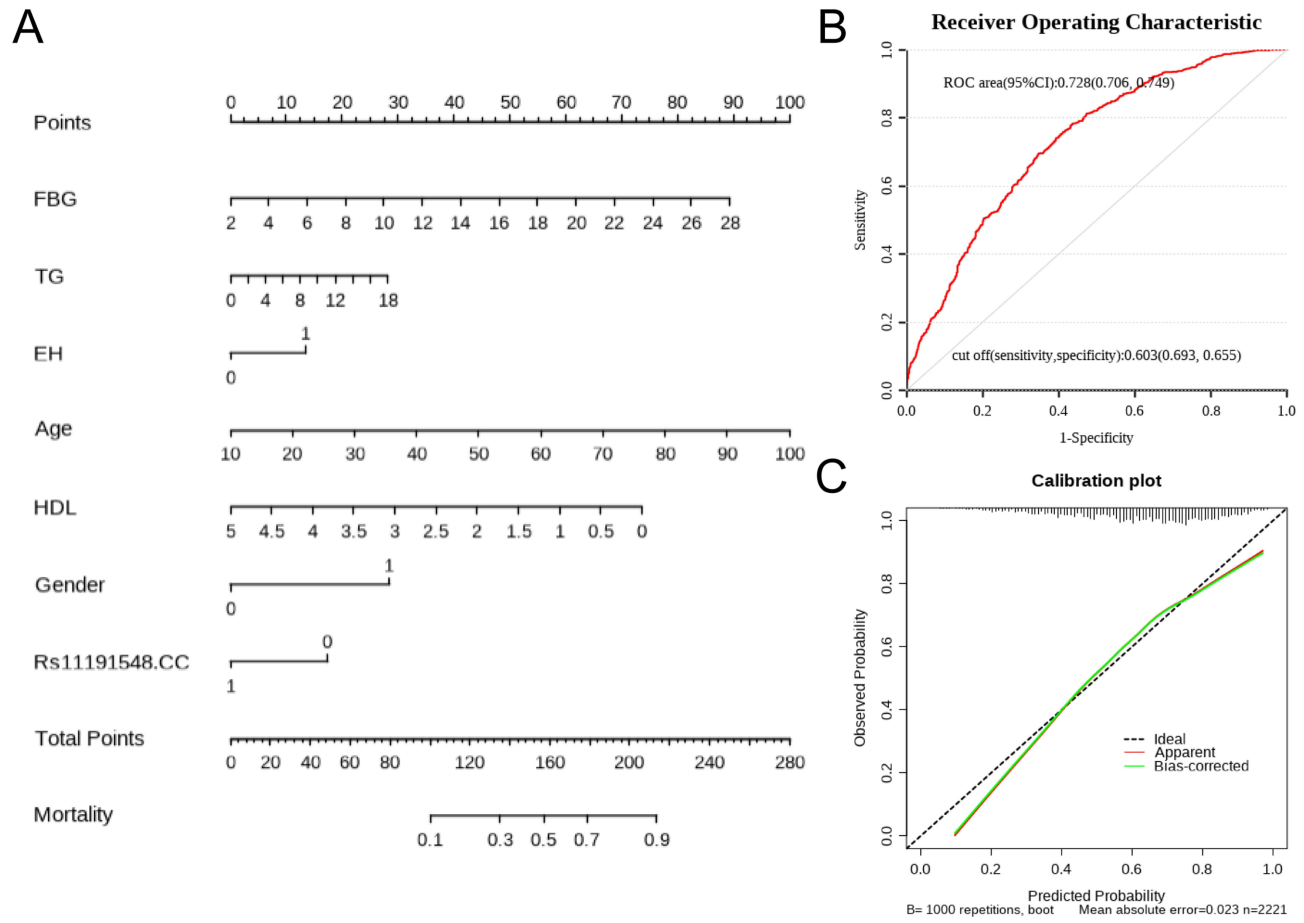

Figure 2 A nomogram for predicting the risk of CAD and its validation. (**A**) Nomogram based on seven variables (FBG, EH, TG, Age, Gender, HDL-C, and rs11191548.CC). The total points from all variables correspond to a predicted probability on the bottom scale. (**B** and **C**) Validation of the nomogram. The receiver operating characteristic (ROC) curve shows an area under the curve (AUC) of 0.728 (95% CI: 0.706–0.749). The calibration plot (generated from 1000 bootstrap replicates, n = 2221) shows agreement between predicted and observed risk (mean absolute error = 0.023).
Abbreviations: FGB, fasting blood glucose; TG, triglycerides; EH, hypertension; HDL, high-density lipoprotein cholesterol.

variants, our model captures a portion of the heritable risk component that traditional factors like LDL-C and blood pressure fail to account for.

As reported in previous studies, the P450c17 protein is a crucial enzyme for catalyzing the formation of all endogenous androgens.[34] Mutations in the *CYP17A1* gene affect the synthesis of steroids, which are precursors of sex hormones.[35] This gene plays an important role in transforming 17OH-pregnenolone to dehydroepiandrosterone (DHEA) and 17OH-progesterone to androstenedione. Thus, mutations in *CYP17A1* may result in loss of enzymatic activity of P450c17, potentially reducing the biosynthesis of DHEA.[36] In recent years, numerous clinical studies have indicated that DHEA levels play a significant role in the progression of CAD.[37–39] Furthermore, functional genomics studies have shown that non-steroidal *CYP17A1* inhibitors and genetic variants can alter the structural conformation of the enzyme, thereby modulating its catalytic efficiency and downstream hormone levels.[5,40]

In addition, evidence suggests that testosterone is also associated with risk factors for CAD, especially in elderly males.[41,42] Testosterone acts as a precursor to estrogen, so normal estrogen signaling also relies on *CYP17A1*. There is evidence that sex hormone levels affect the development of cardiovascular and cerebrovascular diseases, such as estrogen, which can prevent oxidative stress and is thought to have vascular protective effects. Estrogen plays a crucial role in regulating a variety of physiological and pathological processes, including vascular constriction,

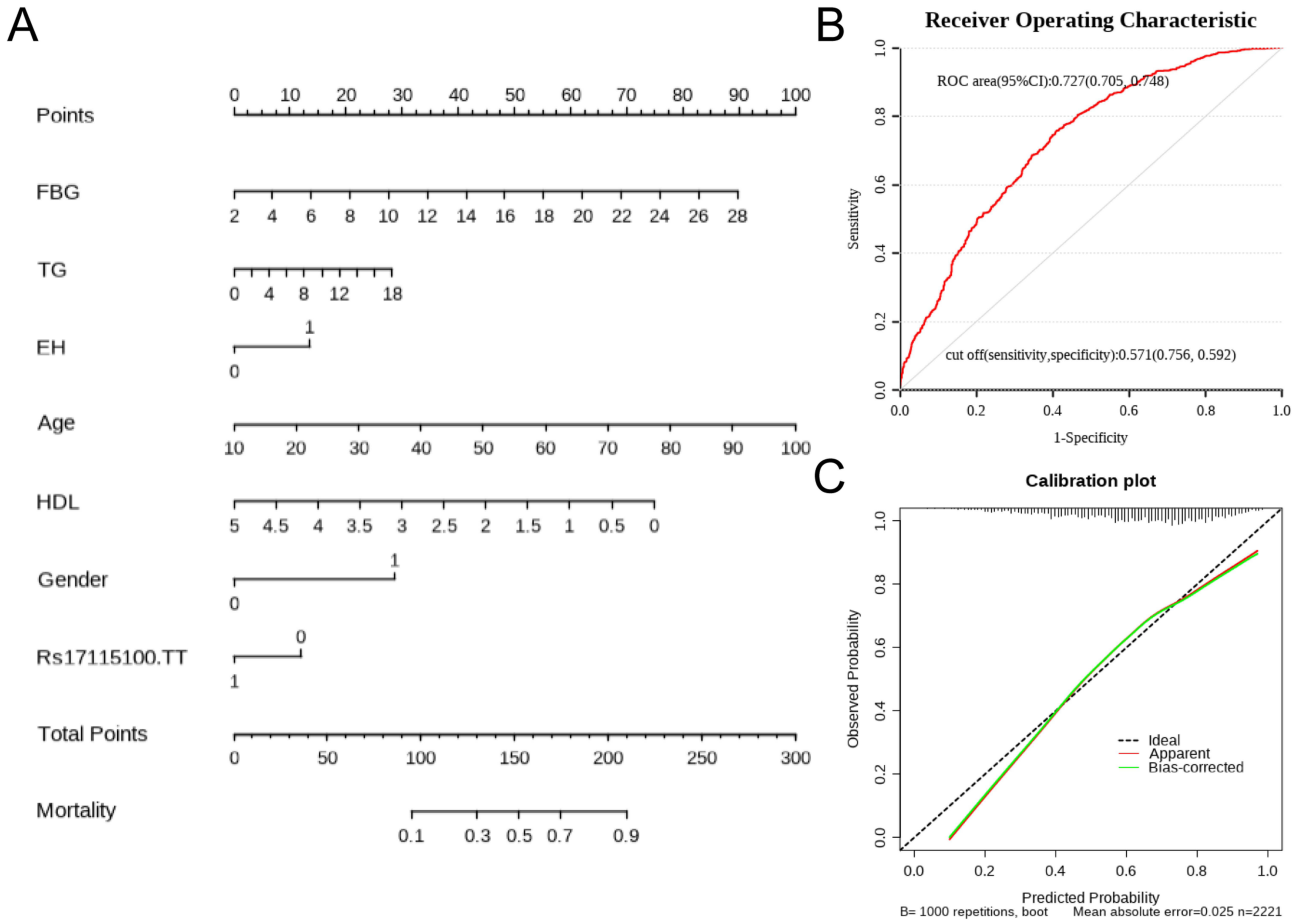

Figure 3 A nomogram for predicting CAD risk incorporating the TT genotype of rs17115100. (**A**) Nomogram based on seven variables (FBG, EH, TG, Age, Gender, HDL-C, and rs17115100.TT). The total points from all variables correspond to a predicted probability on the bottom scale. (**B** and **C**) Validation of the nomogram. The ROC curve shows an AUC of 0.727 (95% CI: 0.705–0.748). The calibration plot (generated from 1000 bootstrap replicates, n = 2221) shows agreement between predicted and observed risk (mean absolute error = 0.025).
Abbreviations: FGB, fasting blood glucose; TG, triglycerides; EH, hypertension; HDL, high-density lipoprotein cholesterol.

endothelial repair, and lipid metabolism, and influences cardiovascular function directly or indirectly through pathways such as glucose metabolism and insulin-related signal transduction.[43,44]

In addition, as a key steroid metabolism gene, *CYP17A1* may also be closely related to cardiovascular risk factors, such as lipid metabolism and insulin resistance, that promote CAD.[10,11,45,46] Wu et al also confirmed that the SNP rs11191548 near *CYP17A1* is associated with HDL-C and leptin in Chinese children.[47] Besides, the coagulation and fibrinolysis systems play a crucial role in the pathogenesis of CAD. Physiological levels of testosterone promote the release of nitric oxide (NO) from endothelial cells, thereby improving endothelial function. In turn, low testosterone levels increase the concentration of clotting factor VIII, leading to endothelial dysfunction and vascular inflammation. Ultimately, platelet adhesion occurs on damaged vessels, thereby promoting the occurrence of CAD.[48] Insulin resistance and diabetes are significant independent risk factors for CAD. Gucenmez et al confirmed that weak negative correlations were observed between testosterone levels and several anthropometric measures and glucose metabolism parameters.[49] Collectively, these mechanisms suggest that *CYP17A1* variants contribute to CAD risk through a "multi-hit" pathway involving hemodynamic, metabolic, and hormonal dysregulation.

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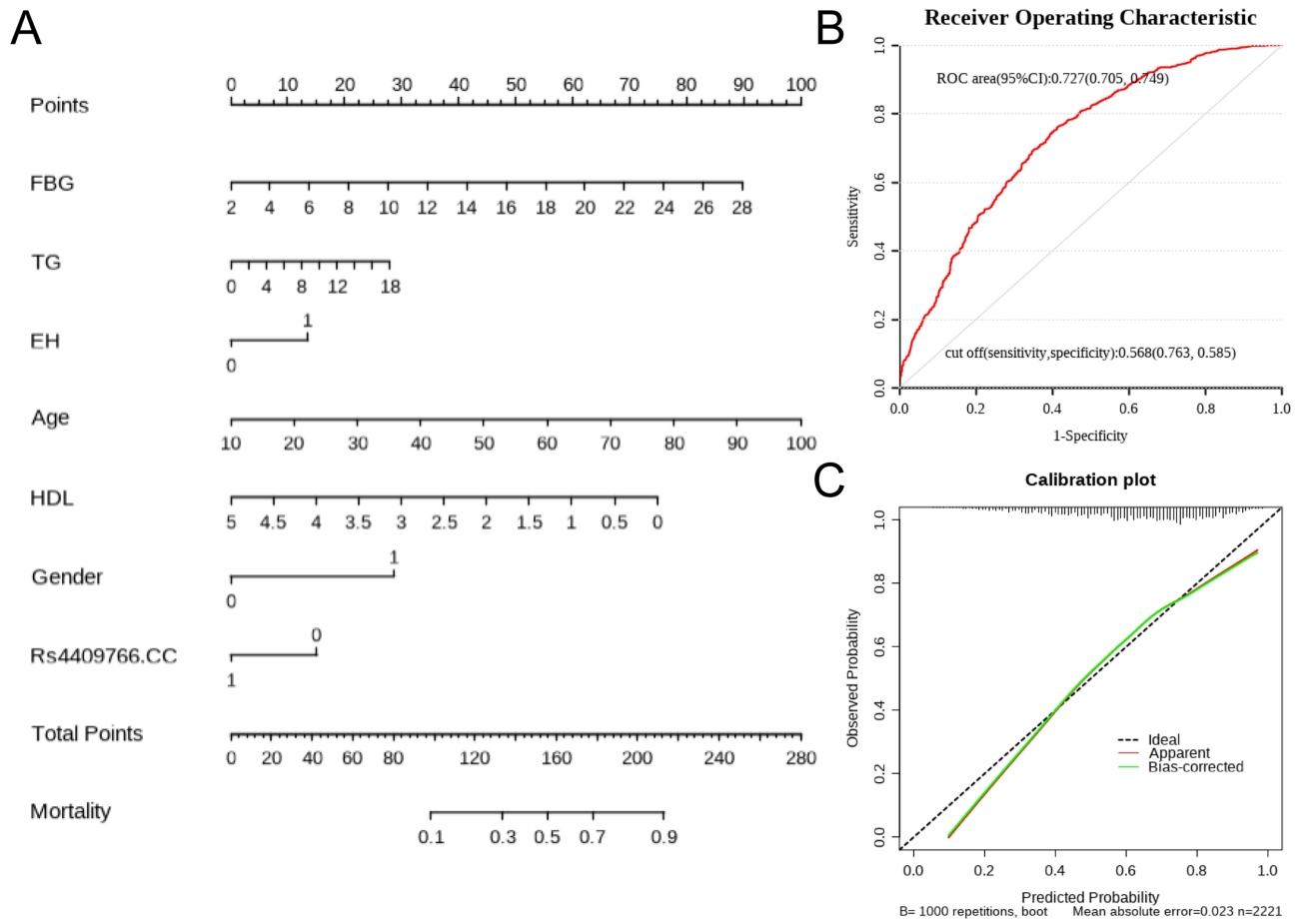

Figure 4 A nomogram for predicting CAD risk incorporating the CC genotype of rs4409766. (**A**) Nomogram based on seven variables (FBG, EH, TG, Age, Gender, HDL-C, and rs4409766.CC). The total points from all variables correspond to a predicted probability on the bottom scale. (**B** and **C**) Model validation. The discriminative ability is shown by the ROC curve (AUC = 0.727, 95% CI: 0.705–0.749). The calibration plot (1000 bootstrap repetitions, n = 2221) indicates good agreement between predictions and observations (mean absolute error = 0.023).
Abbreviations: FGB, fasting blood glucose; TG, triglycerides; EH, hypertension; HDL, high-density lipoprotein cholesterol.

Limitation

There are several limitations of our study that need to be addressed. Firstly, we detected only a limited number of polymorphisms in *CYP17A1* and could not determine whether there were other synergistic genes. Second, our study failed to monitor the levels of important steroid-related hormones, such as DHEA, testosterone, and estrogen, which may be a confounding factor for the results. Third, while we applied FDR correction to the initial genetic screen, the predictive nomogram was developed and validated only in an internal cohort. The lack of an external validation cohort limits the generalizability of our model, particularly across different ethnic groups or geographical regions. Future multi-center studies are required to calibrate the model for broader clinical applicability. Finally, due to the relatively small sample size, larger clinical samples and further studies of other SNPs of *CYP17A1* are required in future studies. Specifically, the sample size for female subgroup analyses may have been underpowered to detect smaller genetic effect sizes, warranting cautious interpretation of the sex-specific findings.

Conclusions

In summary, this study provides evidence that specific *CYP17A1* gene variants (rs11191548, rs17115100, and rs4409766) are associated with CAD risk in a Chinese population. Their recessive genotypes are linked to reduced CAD risk. Furthermore, our analyses reveal distinct sex-specific association patterns, underscoring the importance of considering

gender in genetic studies of CAD. The developed nomogram, which integrates these genetic factors with clinical variables, demonstrates preliminary predictive utility and offers a basis for future refined risk assessment.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding authors, Xiang Xie and Ting-ting Wu, upon reasonable request.

Ethics Approval and Consent to Participate

The study protocol was reviewed and approved by the Medical Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University (Approval No. [20170214-33]). Written informed consent for participation and publication was obtained from all individual participants included in the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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