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CYP2C19 Poor Metabolizer Status and High System Inflammation Response Index are Independent Risk Factors for Premature Myocardial Infarction: A Hospital-Based Retrospective Study

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Objective: Atherosclerosis (AS) is a sustained chronic vascular inflammatory response caused by lipid metabolism disorders and immune response disorders and is the main cause of premature (men ≤ 55 years old, women ≤ 65 years old) myocardial infarction (PMI). Cytochrome P450 2C19 (CYP2C19) (related to vascular function and lipid metabolism) and peripheral immune cell levels and plays an important role in the course of AS. The association *CYP2C19* polymorphisms, comprehensive immunoinflammatory indices with PMI susceptibility is unclear.

Methods: This study included 485 PMI patients, and 639 age-matched non-PMI individuals as controls, from January 2019 to March 2024. The relationship between *CYP2C19* polymorphisms, peripheral immunoinflammatory indices (pan-immune inflammation value (PIV), systemic immune inflammation index (SII), and system inflammation response index (SIRI)) and PMI risk were analyzed.

Results: The inflammatory indices levels in PMI patients were higher than those in controls (all $p<0.05$). The frequencies of the *CYP2C19* *1/*2 and *2/*2 genotypes were higher, while the frequency of the *1/*1 genotype was lower in the PMI patients than those in controls. The cut-off values of TC, TG, LDL-C, PIV, SII, and SIRI were 5.065, 1.305, 2.805, 410.485, 869.645, and 1.495 for distinguishing PMI, respectively. Logistic regression analysis showed that male (odds ratio (OR): 1.607, 95% confidence interval (CI): 1.134–2.277, $p=0.008$), history of smoking (OR: 7.108, 95% CI: 4.351–11.614, $p<0.001$), diabetes mellitus (OR: 4.906, 95% CI: 3.333–7.223, $p<0.001$), CYP2C19 poor metabolizer (PM) (*2/*2, *2/*3, and *3/*3) (OR: 2.147, 95% CI: 1.279–3.603, $p=0.004$), and high TG (≥1.305 vs <1.305, OR: 2.598, 95% CI: 1.864–3.623, $p<0.001$) and SIRI level (≥1.495 vs <1.495, OR: 2.495, 95% CI: 1.432–4.349, $p=0.001$) were independent risk factors for PMI.

Conclusion: CYP2C19 PM phenotype, high SIRI level (≥1.495) and TG level (≥1.305), male, history of smoking, and diabetes mellitus were independently associated with PMI susceptibility.

Keywords: premature myocardial infarction, system inflammation response index, CYP2C19, polymorphism

Introduction

Cardiovascular disease (CVD) is a disease of the human cardiovascular system.[1,2] CVD is the leading cause of death globally and a major contributor to the world's disease burden.[3] Coronary artery disease (CAD) is a heart disease caused by coronary arteriosclerosis causing coronary artery stenosis, spasm and even occlusion, resulting in ischemia and hypoxia.[4,5] Acute myocardial infarction (AMI) is the most serious type of CAD, which refers to a series of physiological and pathological changes occurring on the basis of coronary arteriosclerosis and stenosis, resulting in myocardial ischemia and hypoxia, which in turn induces myocardial necrosis.[6]

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CVD generally occurs most frequently in the elderly, but with the increase in social pressure and the influence of bad living habits, the incidence of CVD in young individuals has gradually increased.[7,8] In recent years, with the increasing incidence of AMI in young people, premature myocardial infarction (PMI) has received increasing attention.[9] PMI refers to the occurrence of AMI when men ≤55 years old and women ≤65 years old.[10–12] According to the results of the atherosclerosis risk in communities (ARIC) cohort study in the United States, the proportion of hospitalization for AMI in young patients has increased significantly from 1995 to 2014, and the 1-year all-cause mortality is close to 10%.[13] PMI not only leads to a decrease in the young labor force but also brings no small burden to the social economy. Therefore, it is of great significance to study the risk factors of PMI for the prevention of PMI.

Atherosclerosis (AS) is the main pathological basis of coronary artery disease (CAD) and other arterial vascular diseases. It is characterized by the accumulation of lipids, the formation of diseased plaques, thickening of intima and narrowing of arterial spaces, which lead to ischemia or necrosis of tissues and organs supplied by arteries.[14,15] AS is a sustained chronic vascular inflammatory response caused by multiple factors, mainly involving lipid metabolism disorders and immune response disorders.[16] Innate and adaptive immunity involving neutrophils, lymphocytes, monocytes, and macrophages plays an important role in the occurrence and progression of AS.[17–20] Neutrophils can promote monocyte recruitment by activating macrophages, play a cytotoxic role, and accelerate the progression of AS. Lymphocytes regulate inflammation and have anti-AS effects.[21] Platelets interact with vascular endothelial cells and white blood cells to participate in the process of AS.[22] In recent years, some comprehensive inflammatory indices calculated from peripheral blood cells have attracted wide attention, such as pan-immune inflammation value (PIV), systemic immune inflammation index (SII), and system inflammation response index (SIRI). Several studies have suggested that PIV,[23,24] SII,[25,26] and SIRI[27] were potential predictors of short- and long-term outcomes in patients with AMI. However, the relationship between these inflammatory indices and PMI has not been studied.

In addition, the pathophysiological processes of cardiovascular and cerebrovascular diseases may also be affected by cytochrome P450 (CYP450) enzymes.[28,29] Specifically speaking, the metabolites of arachidonic acid (AA) and endodermal hyperpolarized factor (EDHF) catalyzed by CYP450 are the most important causes of vascular endothelial relaxation.[30,31] Moreover, reactive oxygen species (ROS) are produced in coronary endothelial cells during the reaction catalyzed by CYP450, which can inhibit the vascular relaxation mediated by nitric oxide (NO).[32] CYP450 2C19 (CYP2C19) is one of the important members of the CYP450 family.[33] The rs4244285 (681G>A, *CYP2C19**2) and rs4986893 (636G>A, *CYP2C19**3) are the most common single-nucleotide polymorphisms (SNPs) of *CYP2C19* gene. Based on the two SNPs, *CYP2C19* can be divided into six genotypes (*1/*1, *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3) and three phenotypes (extensive metabolizer (EM) (*CYP2C19**1/*1), intermediate metabolizer (IM) (*CYP2C19**1/*2, and *1/*3), and poor metabolizer (PM) (*CYP2C19**2/*2, *2/*3, and *3/*3)).[34] It has been found that poor CYP2C19 metabolizers were more likely to have recurrent myocardial infarction.[35]

At present, there is little research on the risk factors for PMI. The purpose of this study was to investigate the association *CYP2C19* polymorphisms, PIV, SII, and SIRI indices with PMI susceptibility. This study may provide reference for improving the understanding of PMI, strengthening the control of controllable risk factors, and providing early prevention, diagnosis, and treatment of diseases.

Materials and Methods

Participants

This study retrospectively analyzed 485 PMI patients who were admitted to Meizhou People's Hospital from January 2019 to March 2024, and 639 age-matched non-AMI individuals as controls who underwent physical examination in Meizhou People's Hospital during the same period. The diagnostic criteria for AMI: the European Society of Cardiology (ESC) published the fourth edition of the Global Universal Diagnostic Criteria for myocardial infarction in 2018.[36] The diagnostic criteria for AMI were increased and/or decreased markers of acute myocardial injury, at least once above the 99th percentile of the upper limit of normal, and have at least one of the following clinical conditions: (1) symptoms of acute myocardial ischemia; (2) new ischemic electrocardiogram changes; (3) new pathological Q-wave; (4)

imaging evidence of newly viable myocardial loss or abnormal ventricular wall segmental motion; and (5) coronary angiography or intracavitary imaging confirmed the presence of coronary thrombosis.

Inclusion criteria of patients: (1) patients diagnosed with AMI; (2) patients who performed *CYP2C19* gene polymorphisms, serum lipid, and blood routine testing; (3) male patients aged ≤55 years old and female patients aged ≤65 years old; (4) the clinical information of the patients were complete. The inclusion criteria of the controls as follows: (1) non-AMI participants who had been performed *CYP2C19* gene polymorphisms, serum lipid, and blood routine testing; (2) male individuals with ≤55 years old and female individuals with ≤65 years old; (3) with complete information. Exclusion criteria for patients are as follows: (1) congenital heart disease, cardiomyopathy, or congestive heart failure; (2) with severe organ dysfunction; (3) with serious diseases, such as malignant tumors, severe infections, and so on. This study was supported by the Ethics Committee of the Meizhou People's Hospital.

Data Collection and CYP2C19 Genotyping

Clinical data collected include gender, body mass index (BMI), ABO blood types, history of smoking, history of alcohol consumption, hypertension, and diabetes mellitus. According to Chinese standards, BMI was divided into three grades: <18.5 kg/m^2, 18.5–23.9 kg/m^2, and ≥24.0 kg/m^2.[37,38] Hypertension was defined as a mean systolic blood pressure >140 mmHg and/or a mean diastolic blood pressure >90 mmHg.[39] Diabetes mellitus was defined as blood glucose ≥11.1 mol/L at any time or fasting blood glucose ≥7.0 mol/L, or 2-hour postprandial plasma glucose level ≥11.1 mol/L.[40]

Serum lipid levels and blood routine test data were collected before treatment. The patient's venous blood was collected, the serum lipid levels of the samples were evaluated by an Olympus AU5400 system (Olympus Corporation, Tokyo, Japan), and blood cell analysis was tested by Sysmex XE-2100 hematology analyzer (Sysmex Corporation, Japan) according to standard operating procedures (SOP). Genomic DNA was extracted from venous blood collected from EDTA anticoagulant collection vessels using a blood DNA isolation kit (Qiagen GmbH, Germany). *CYP2C19* genotyping was performed as previously described.[41,42]

Statistical Analysis

The inflammation indices PIV, SII, and SIRI were calculated according to the following formula: (1) PIV = monocyte × neutrophil × platelet/lymphocyte; (2) SII = platelet × neutrophil/lymphocyte; (3) SIRI = monocyte × neutrophil/lymphocyte.

All statistical analyses were performed using SPSS statistical software (version 26.0, IBM Inc., USA). Continuous variables were compared using either Student's *t*-test, the Mann–Whitney *U*-test or analysis of variance (ANOVA). Genotype composition ratios and allele frequencies between groups were analyzed using *Chi*-square test or Fisher's exact test. Hardy-Weinberg equilibrium in the patients and controls was evaluated by *Chi*-square test. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values of TC, TG, LDL-C, PIV, SII, and SIRI to distinguish PMI. Logistic regression analysis was applied to examine the association *CYP2C19* phenotypes, PIV, SII, and SIRI with PMI. $p<0.05$ was considered to represent statistical significance.

Results

Characteristics of Subjects

Of the 1124 subjects, 590 (52.5%) were men and 534 (47.5%) were women, and the age was 53.0 (48.0, 57.0) years old. There were 214 (19.0%) cases had a history of smoking, 38 (3.4%) cases had a history of alcohol consumption, 548 (48.8%) cases had hypertension, and 248 (22.1%) cases had diabetes mellitus. There were 597 (53.1%) overweight individuals and 478 (42.5%) individuals with blood type O (Table 1).

There were significant differences in the distributions of gender and BMI between PMI patients group and controls (all $p<0.05$). The proportion of history of smoking (34.8% vs 7.0%, $p<0.001$) and diabetes mellitus (35.9% vs 11.6%, $p<0.001$) in PMI patients was higher than those in controls, respectively. The serum lipid levels and inflammatory indices levels in PMI patients were significantly higher than those in controls (all $p<0.05$). There was no statistically significant difference in the distribution of ABO blood types ($p=0.187$) and proportion of history of alcohol consumption ($p=0.068$), and hypertension ($p=0.674$) between the two groups (Table 1).

Table 1 Comparison of Clinical Features Among PMI Patients and Controls

Variables	Total (n=1124)	Controls (n=639)	PMI Patients (n=485)	*p* values
Gender				
Male, n(%)	590(52.5%)	249(39.0%)	341(70.3%)	<0.001
Female, n(%)	534(47.5%)	390(61.0%)	144(29.7%)	
Age, years, median (P25, P75)	53.0 (48.0, 57.0)	53.0 (48.0, 58.0)	53.0 (47.0, 55.0)	0.052
BMI (kg/m^2)				
<18.5, n(%)	35(3.1%)	31(4.9%)	4(0.8%)	<0.001
18.5–23.9, n(%)	492(43.8%)	301(47.1%)	191(39.4%)	
≥24.0, n(%)	597(53.1%)	307(48.0%)	290(59.8%)	
ABO blood types				
A type, n(%)	342(30.4%)	187(29.3%)	155(32.0%)	0.187
B type, n(%)	245(21.8%)	146(22.8%)	99(20.4%)	
AB type, n(%)	59(5.2%)	27(4.2%)	32(6.6%)	
O type, n(%)	478(42.5%)	279(43.7%)	199(41.0%)	
History of smoking				
No, n(%)	910(81.0%)	594(93.0%)	316(65.2%)	<0.001
Yes, n(%)	214(19.0%)	45(7.0%)	169(34.8%)	
History of alcohol consumption				
No, n(%)	1086(96.6%)	623(97.5%)	463(95.5%)	0.068
Yes, n(%)	38(3.4%)	16(2.5%)	22(4.5%)	
Hypertension				
No, n(%)	576(51.2%)	331(51.8%)	245(50.5%)	0.674
Yes, n(%)	548(48.8%)	308(48.2%)	240(49.5%)	
Diabetes mellitus				
No, n(%)	876(77.9%)	565(88.4%)	311(64.1%)	<0.001
Yes, n(%)	248(22.1%)	74(11.6%)	174(35.9%)	
Serum lipid levels				
TC, mmol/L, median (P25, P75)	4.98 (4.25, 5.80)	4.84 (4.16, 5.62)	5.18 (4.38, 6.03)	<0.001
TG, mmol/L, median (P25, P75)	1.50 (1.08, 2.21)	1.30 (0.96, 1.93)	1.77 (1.29, 2.49)	<0.001
LDL-C, mmol/L, median (P25, P75)	2.83 (2.30, 3.45)	2.69 (2.18, 3.30)	2.97 (2.46, 3.68)	<0.001
Inflammatory indices levels				
PIV, median (P25, P75)	508.97 (249.94, 1035.92)	358.54 (178.08, 830.63)	711.70 (385.28, 1412.92)	<0.001
SII, median (P25, P75)	889.91 (532.20, 1600.66)	749.37 (447.72, 1391.80)	1122.78 (664.36, 1816.00)	<0.001
SIRI, median (P25, P75)	2.24 (1.05, 4.66)	1.54 (0.77, 3.62)	3.13 (1.67, 5.83)	<0.001

Abbreviations: PMI, premature myocardial infarction; BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; p25, 25th percentile; p75, 75th percentile.

Distribution Frequencies of the CYP2C19 Genotypes and Alleles in PMI Patients and Controls

There were 503 (44.8%), 404 (35.9%), 81 (7.2%), 97 (8.6%), 34 (3.0%), and 5 (0.4%) individuals carried *CYP2C19* *1/*1, *1/*2, *1/*3, *2/*2, *2/*3, and *3/*3 genotype, respectively. There were 503 (44.8%), 485 (43.1%), and 136 (12.1%) individuals with *CYP2C19* EM, IM, and PM phenotype, respectively. The results of Hardy–Weinberg equilibrium test showed that the *CYP2C19* genotypes in patients (χ^2=0.443, p=0.979) and controls (χ^2=2.998, p=0.558) conformed to the Hardy–Weinberg equilibrium, respectively. The frequencies of the *CYP2C19* *1/*2 genotype (39.4% vs 33.3%, p=0.038) and *CYP2C19* *2/*2 (10.7% vs 7.0%, p=0.032) genotype were higher, while the frequency of the *CYP2C19* *1/*1 (39.6% vs 48.7%, p=0.002) genotype was lower in the PMI patients than those in controls. The patients had higher frequency of the *2 allele (32.3% vs 25.0%, p<0.001) and lower frequency of *1 allele (62.5% vs 69.2%, p=0.001) than controls (Table 2).

Table 2 Distribution Frequencies of CYP2C19 Genotypes and Alleles in PMI Patients and Controls

CYP2C19 Phenotypes	*CYP2C19* Genotypes/Alleles	Total (n=1124)	Controls (n=639)	PMI Patients (n=485)	χ^2	*p* values
	Genotypes					
Extensive metabolizer	*1/*1	503(44.8%)	311(48.7%)	192(39.6%)	9.199	0.002
Intermediate metabolizer	*1/*2	404(35.9%)	213(33.3%)	191(39.4%)	4.381	0.038
	*1/*3	81(7.2%)	50(7.8%)	31(6.4%)	0.847	0.415
Poor metabolizer	*2/*2	97(8.6%)	45(7.0%)	52(10.7%)	4.734	0.032
	*2/*3	34(3.0%)	16(2.5%)	18(3.7%)	1.370	0.292
	*3/*3	5(0.4%)	4(0.6%)	1(0.2%)	1.097	0.397
	Alleles					
	*1	1491(66.3%)	885(69.2%)	606(62.5%)	11.332	0.001
	*2	632(28.1%)	319(25.0%)	313(32.3%)	14.569	<0.001
	*3	125(5.6%)	74(5.8%)	51(5.3%)	0.298	0.642
	HWE (χ^2, *P*)	χ^2=2.197, *p*=0.700	χ^2=2.998, *p*=0.558	χ^2=0.443, *p*=0.979		

Notes: *1, wild type; *2, 681 G>A; *3, 636 G>A.
Abbreviations: CYP2C19, cytochrome P450 2C19; PMI, premature myocardial infarction; HWE, Hardy Weinberg Equilibrium.

Clinical Characteristics of Subjects Stratified by CYP2C19 Phenotypes

Clinical characteristics and serum lipid-lipoprotein levels were compared among all subjects carried different *CYP2C19* phenotypes. The proportion of male individuals in *CYP2C19* IM group was higher than that in *CYP2C19* EM and PM groups (58.8% vs 46.9% and 50.7%, *p*=0.001). The individuals with *CYP2C19* EM phenotype had higher PIV level (537.03 (263.65, 1121.43) vs 492.84 (250.09, 947.85) and 424.15 (182.70, 892.58), *p*=0.046), and SII level (949.89 (592.32, 1799.15) vs 868.00 (522.87, 1524.29) and 690.00 (420.02, 1256.71), *p*<0.001) than those with *CYP2C19* IM phenotype and PM phenotype, respectively (Table 3).

Logistic Regression Analysis of Risk Factors for PMI

When PMI was taken as the endpoint of serum lipid levels, the critical value of TC was 5.065 (sensitivity 53.8%, specificity 58.3%, area under the ROC curve (AUC): 0.577), the LDL-C cutoff value was 2.805 (sensitivity 60.4%, specificity 54.6%, AUC: 0.588), the TG cutoff value was 1.305 (sensitivity 74.0%, specificity 50.5%, AUC: 0.651) (Figure 1A). When PMI was considered as the endpoint of inflammatory indices levels, the SII cutoff value was 869.645

Table 3 Clinical Characteristics of Subjects Stratified by CYP2C19 Phenotypes

Variables	Extensive Metabolizer (n=503)	Intermediate Metabolizer (n=485)	Poor Metabolizer (n=136)	*p* values
Gender				
Male, n(%)	236(46.9%)	285(58.8%)	69(50.7%)	0.001
Female, n(%)	267(53.1%)	200(41.2%)	67(49.3%)	(χ^2=14.082)
BMI (kg/m^2)				
<18.5, n(%)	17(3.4%)	14(2.9%)	4(2.9%)	0.689
18.5–23.9, n(%)	224(44.5%)	216(44.5%)	52(38.2%)	(χ^2=2.252)
≥24.0, n(%)	262(52.1%)	255(52.6%)	80(58.8%)	
ABO blood types				
A type, n(%)	150(29.8%)	152(31.3%)	40(29.4%)	0.943
B type, n(%)	112(22.3%)	107(22.1%)	26(19.1%)	(χ^2=1.649)
AB type, n(%)	25(5.0%)	25(5.2%)	9(6.6%)	
O type, n(%)	216(42.9%)	201(41.4%)	61(44.9%)	
History of smoking				
No, n(%)	414(82.3%)	387(79.8%)	109(80.1%)	0.580
Yes, n(%)	89(17.7%)	98(20.2%)	27(19.9%)	(χ^2=1.078)

(*Continued*)

Table 3 (Continued).

Variables	Extensive Metabolizer (n=503)	Intermediate Metabolizer (n=485)	Poor Metabolizer (n=136)	*p* values
History of alcohol consumption				
No, n(%)	485(96.4%)	472(97.3%)	129(94.9%)	0.321
Yes, n(%)	18(3.6%)	13(2.7%)	7(5.1%)	(χ^2=2.087)
Hypertension				
No, n(%)	260(51.7%)	244(50.3%)	72(52.9%)	0.837
Yes, n(%)	243(48.3%)	241(49.7%)	64(47.1%)	(χ^2=0.366)
Diabetes mellitus				
No, n(%)	395(78.5%)	379(78.1%)	102(75.0%)	0.654
Yes, n(%)	108(21.5%)	106(21.9%)	34(25.0%)	(χ^2=0.797)
Serum lipid levels				
TC, mmol/L, median (P25, P75)	4.94 (4.23, 5.81)	5.04 (4.28, 5.79)	4.93 (4.27, 5.65)	0.620
TG, mmol/L, median (P25, P75)	1.46 (1.06, 2.21)	1.52 (1.10, 2.18)	1.54 (1.05, 2.42)	0.573
LDL-C, mmol/L, median (P25, P75)	2.79 (2.25, 3.46)	2.88 (2.34, 3.49)	2.81 (2.25, 3.29)	0.457
Inflammatory indices levels				
PIV, median (P25, P75)	37.03 (263.65, 1121.43)	492.84 (250.09, 947.85)	424.15 (182.70, 892.58)	0.046
SII, median (P25, P75)	949.89 (592.32, 1799.15)	868.00 (522.87, 1524.29)	690.00 (420.02, 1256.71)	<0.001
SIRI, median (P25, P75)	2.32 (1.12, 4.93)	2.18 (1.05, 4.77)	2.00 (0.72, 4.02)	0.087

Abbreviations:CYP2C19, cytochrome P450 2C19; BMI, body mass index; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; p25, 25th percentile; p75, 75th percentile.

(sensitivity 62.1%, specificity 57.7%, AUC: 0.623), the SIRI cutoff value was 1.495 (sensitivity 79.7%, specificity 49.4%, AUC: 0.676), and the PIV cutoff value was 410.485 (sensitivity 73.0%, specificity 56.2%, AUC: 0.677) (Figure 1B).

The results of univariate analysis showed that male (male vs female, odds ratio (OR): 3.709, 95% confidence interval (CI): 2.884–4.769, p<0.001), overweight (BMI ≥24.0 kg/m^2 vs BMI 18.5–23.9 kg/m^2, OR: 1.489, 95% CI: 1.169–1.897, p=0.001), history of smoking (yes vs no, OR: 7.059, 95% CI: 4.945–10.078, p<0.001), diabetes mellitus (yes vs no, OR: 4.272, 95% CI: 3.148–5.796, p<0.001), *CYP2C19* IM phenotype (IM phenotype vs EM phenotype, OR: 1.367, 95% CI: 1.061–1.762, p=0.016) and PM phenotype (PM phenotype vs EM phenotype, OR: 1.769, 95% CI: 1.208–2.591, p=0.003), and high serum lipid levels, and inflammatory indices levels were

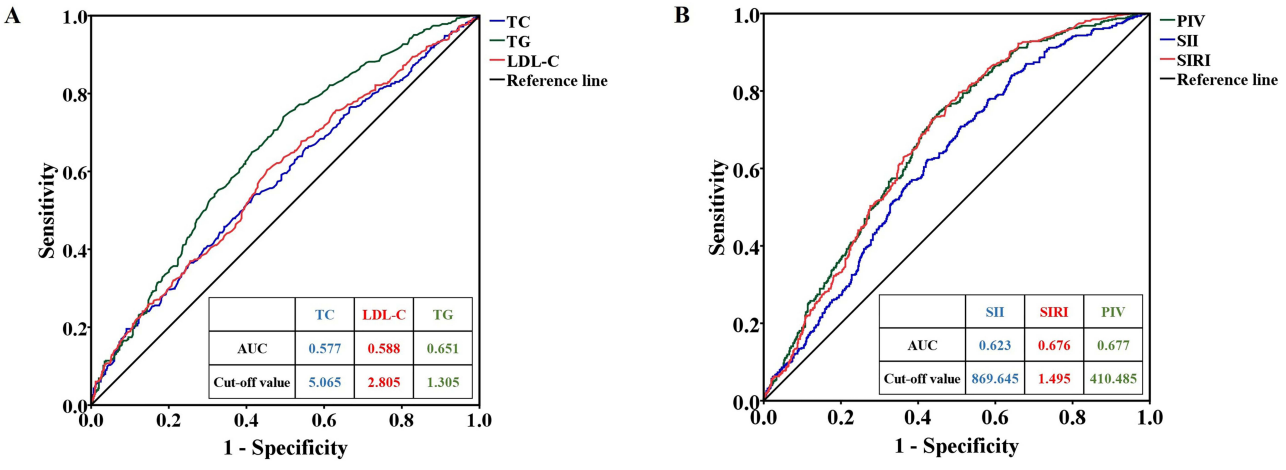

Figure 1 The ROC curve analysis of TC, TG, LDL-C, PIV, SII, and SIRI to distinguish PMI. The ROC curve of TC, TG, and LDL-C (**A**); the ROC curve of PIV, SII, and SIRI (**B**).
Abbreviations: TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response index; PMI, premature myocardial infarction.

Table 4 Logistic Regression Analysis of Risk Factors for PMI

Variables	Univariate OR (95% CI)	*p* values	Multivariate OR (95% CI)	*p* values
Gender (Male vs Female)	3.709 (2.884–4.769)	<0.001	1.607 (1.134–2.277)	0.008
BMI (kg/m^2)				
18.5–23.9	1.000 (reference)	–	1.000 (reference)	–
<18.5	0.203 (0.071–0.585)	0.003	0.412 (0.121–1.399)	0.155
≥24.0	1.489 (1.169–1.897)	0.001	1.300 (0.946–1.787)	0.106
ABO blood types (non-O type vs O type)	1.114 (0.877–1.415)	0.377	1.031 (0.756–1.407)	0.846
History of smoking (Yes vs No)	7.059 (4.945–10.078)	<0.001	7.108 (4.351–11.614)	<0.001
History of alcoholism (Yes vs No)	1.850 (0.961–3.562)	0.066	0.254 (0.099–0.654)	0.004
Hypertension (Yes vs No)	1.053 (0.831–1.333)	0.670	0.730 (0.531–1.003)	0.052
Diabetes mellitus (Yes vs No)	4.272 (3.148–5.796)	<0.001	4.906 (3.333–7.223)	<0.001
CYP2C19 phenotypes				
Extensive metabolizer	1.000 (reference)	-	1.000 (reference)	-
Intermediate metabolizer	1.367 (1.061–1.762)	0.016	1.298 (0.935–1.800)	0.119
Poor metabolizer	1.769 (1.208–2.591)	0.003	2.147 (1.279–3.603)	0.004
TC (≥5.065 vs <5.065)	1.624 (1.273–2.072)	<0.001	1.124 (0.725–1.742)	0.601
TG (≥1.305 vs <1.305)	2.900 (2.233–3.767)	<0.001	2.598 (1.864–3.623)	<0.001
LDL-C (≥2.805 vs <2.805)	1.839 (1.439–2.351)	<0.001	1.518 (0.980–2.353)	0.062
PIV (≥410.485 vs <410.485)	3.461 (2.674–4.480)	<0.001	1.679 (0.953–2.959)	0.073
SII (≥869.645 vs <869.645)	2.229 (1.744–2.849)	<0.001	1.036 (0.659–1.629)	0.878
SIRI (≥1.495 vs <1.495)	3.828 (2.910–5.035)	<0.001	2.495 (1.432–4.349)	0.001

Abbreviations:PMI, premature myocardial infarction; BMI, body mass index; CYP2C19, cytochrome P450 2C19; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; PIV, pan-immune-inflammation-value; SII, systemic immune-inflammatory index; SIRI, systemic inflammatory response.

significantly associated with PMI. Multivariate logistic regression analysis showed that male (male vs female, OR: 1.607, 95% CI: 1.134–2.277, p=0.008), history of smoking (yes vs no, OR: 7.108, 95% CI: 4.351–11.614, p<0.001), diabetes mellitus (yes vs no, OR: 4.906, 95% CI: 3.333–7.223, p<0.001), *CYP2C19* PM phenotype (PM phenotype vs EM phenotype, OR: 2.147, 95% CI: 1.279–3.603, p=0.004), and high TG level (≥1.305 vs <1.305, OR: 2.598, 95% CI: 1.864–3.623, p<0.001) and SIRI level (≥1.495 vs <1.495, OR: 2.495, 95% CI: 1.432–4.349, p=0.001) were independent risk factors for PMI (Table 4).

Discussion

AS is a multifactor-induced chronic inflammatory disease involving a complex set of circulating blood cells (such as blood plates and monocytes) and serum components (such as lipids and lipoproteins).[43,44] AS is the common pathological basis of AMI, which is characterized by plaque formed by the coronary arteries loaded with lipids and a variety of immune cells.[45] Neutrophils are involved in different stages of AS, including AS formation, rupture of unstable plaques, and plaque erosion.[18] The granular protein and active substances released by granulocytes induce the recruitment of monocytes to AS lesions, stimulate the activation of macrophages, and promote the formation of foam cells.[18,19] T helper 17 (Th17) cells induce the production of pro-inflammatory cytokines, and secreted interleukin-17 (IL-17) can up-regulate the expression of E-selectin and intercellular adhesion molecules, thus promoting the generation of AS plaques.[46] IgM produced by B1 lymphocytes can block the production of inflammatory cytokines and the formation of foam cells induced by oxidized low-density lipoprotein (ox-LDL) and has anti-AS effect.[20] Monocyte-macrophages can absorb ox-LDL and release pro-inflammatory and pro-oxidative cytokines to further attract T lymphocytes and monocytes to the plaque site.[47] Platelets regulate the inflammatory response of vascular endothelial cells and smooth muscle cells and thus participate in the process of AS.[22] The predictive value of inflammatory indices based on cell counts of neutrophils, lymphocytes, monocytes, and platelets in cardiovascular diseases has been widely concerned.

Several studies have suggested that PIV,[23,24] SII,[25,26,48–51] and SIRI,[27,48,51] comprehensive indicators based on the above immune cell levels, were potential predictors of short- and long-term outcomes in patients with AMI. In

addition, PIV can be used as a marker of the severity of CAD.[52] Several researches had found that PIV,[53] SII,[54–58] and SIRI[53] can be used to predict the risk of major cardiovascular events (MACE) after coronary intervention in patients with CAD. However, the relationship between these inflammatory indices and PMI has not been studied. A large, prospective, population-based cohort study showed that elevated SIRI was associated with an increased incidence of myocardial infarction in subjects aged <60 years old.[59] The results of this study suggest that high SIRI levels (≥1.495) may be an independent risk factor for PMI.

Moreover, PMI is also associated with traditional cardiovascular risk factors such as smoking, diabetes mellitus, and lipid disorders.[60] Most studies have largely identified smoking as a risk factor for early onset of AMI.[61–63] Nicotine and other chemicals in cigarette tar promote AS through various mechanisms, such as mediating the damage to endothelial cell nucleus and mitochondrial DNA, increasing the expression of inflammatory factors, and promoting thrombosis.[64] In addition, elevation in TG level was associated with high risk of PMI.[65] AMI in young patients was associated with dyslipidemia.[62] Triglyceride-glucose index can be used for the prediction of premature CAD[66] and MACE in patients with premature CAD.[67] Some studies suggested that LDL-C abnormality is the main cause of dyslipidemia that causes early onset cardiovascular disease.[68,69] However, this study did not find a significant association between LDL-C levels and PMI risk.

In this study, *CYP2C19* PM phenotype was an independent risk factor for PMI. To our knowledge, little is known about the relationship between CYP2C19 polymorphism and PMI susceptibility. Xie et al found that *CYP2C19* *2/*2 genotype was an independent risk factor for multi-site AS.[41] Several studies found that *CYP2C19* polymorphism was a risk factor for CAD.[70–73] In addition, other studies have suggested that *CYP2C19* polymorphism was associated with the prognosis of CAD patients after percutaneous coronary intervention (PCI).[74,75] In terms of mechanism, CYP450 may be involved in the development of atherosclerosis in several ways, such as EDHF produced from AA catalyzed by CYP450 is an important factor in vascular endothelial relaxation,[30,31] the catalytic product of CYP450 modulates NO mediated vasodilation,[32] and CYP450 regulates lipid deposition in blood vessels.[29] CYP2C19 is an important member of the CYP450 family, CYP2C19 poor metabolizer with only weak enzyme activity, and its metabolites are not enough to maintain the balance of the above processes, so poor metabolizers are more prone to AS. Therefore, routine testing of *CYP2C19* polymorphism is of great value for early detection of PMI high-risk groups.

To the best of our knowledge, this study is the first to report on *CYP2C19* gene polymorphisms, PIV, SII, and SIRI levels and PMI susceptibility. Importantly, individuals with a CYP2C19 PM phenotype and high SIRI levels need to be alert to the risk of developing PMI. To sum up, SIRI and *CYP2C19* gene testing have the advantages of strong universality, convenient operation, and low cost-efficiency. We believe that SIRI and *CYP2C19* polymorphism can provide reference for the identification and management of PMI patients. This study was a single-center retrospective study with a small sample size, which may lead to selection bias. Therefore, multicenter, prospective studies are needed to further verify the predictive value of SIRI and *CYP2C19* gene polymorphisms for PMI.

Conclusion

In summary, CYP2C19 PM phenotype, high SIRI level (≥1.495) and TG level (≥1.305), male, history of smoking, and diabetes mellitus were independently associated with PMI susceptibility. It means that male smokers who have diabetes mellitus, carried CYP2C19 PM phenotype, and have high TG and SIRI levels need to be aware of the risk of developing PMI. It can provide reference for the identification and management of PMI patients.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval

All participants were informed on the study procedures and goals and the informed consent from all the participants. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital.

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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 declare that they have no competing interests.

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