Original Article
The relationship between early-onset coronary artery disease and familial hypercholesterolemia: a cohort study based on the Hakka population in Meizhou, China

Min Yang, Youni Lin, Qifeng Liu, Yufu Cai

Center for Cardiovascular Diseases, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou 514031, Guangdong, China

Abstract: Background: The low diagnosis and treatment rates of familial hypercholesterolemia (FH) have become a global issue. This study aims to explore the correlation between early-onset coronary artery disease (CAD) and FH in the Hakka population in Meizhou, Guangdong. Methods: Clinical data of Hakka patients with early-onset CAD, admitted to the Meizhou People's Hospital from January 2023 to January 2024 were retrospectively analyzed. The patients were categorized into an FH group and a non-FH group. Biochemical indicators, lipid levels, echocardiographic parameters, clinical phenotypes, and genetic typing of early-onset CAD patients in the Hakka population were analyzed for their correlation with FH. Results: A total of 167 Hakka patients with early-onset CAD were included, among whom 22 patients had FH. The FH group showed lower triglyceride (TG) level [1.785 (1.40, 2.10) vs. 2.090 (1.80, 2.30), P = 0.002] and higher levels of total cholesterol (TC) [6.635 (5.60, 7.10) vs. 4.830 (4.00, 5.40), P<0.001], low-density lipoprotein cholesterol (LDL-C) [4.440 (3.90, 5.20) vs. 2.820 (2.40, 3.30), P<0.001], and apolipoprotein B (Apo B) [1.600 (1.30, 1.80) vs. 0.910 (0.70, 1.10), P<0.001]. FH was correlated with TG, TC, LDL-C and Apo B levels (r1 = -0.235; r2 = 0.441; r3 = 0.483; r4 = 0.538). TG is a risk factor while TC, LDL-C and Apo B are protective factors for FH. Conclusion: The incidence of FH is relatively high among early-onset CAD patients in the Hakka population in Meizhou. TG, TC, LDL-C, and Apo B levels are valuable in aiding clinical differential diagnosis of CAD patients with FH.

Keywords: Early-onset coronary artery disease, familial hypercholesterolemia, atherosclerosis, low-density lipoprotein cholesterol, apolipoprotein B, correlation

Introduction

Familial hypercholesterolemia (FH) is caused by abnormal lipoprotein metabolism, resulting in a lifelong elevation of low-density lipoprotein cholesterol (LDL-C) levels and the deposition of cholesterol in the plasma [1]. This leads to characteristic clinical features such as yellowish skin or tendon xanthomas and is often associated with valvular regurgitation, which is an autosomal dominant inherited disease [2]. A previous study suggested that homozygous FH (HoFH) is rare, with an incidence rate of 1 in 160,000 to 1 million, while the more common heterozygous type (HeFH) has an incidence rate of 1 in 250 to 500 [3]. Its significant familial clustering characteristics markedly increase the risk of atherosclerotic cardiovascular dis-

ease (ASCVD), posing a serious threat to public health [4].

Clinically, the accumulation of LDL-C is considered the initiating factor of atherosclerosis (AS), and lipid metabolism disorder forms the pathological basis of AS, which is closely associated with the occurrence and development of early-onset coronary artery disease (CAD) [5]. Studies have found that male FH patients have a 50% higher risk of developing CAD before the age of 50 compared to the general population, while female patients have a 60% higher risk before the age of 30 [6, 7]. Furthermore, HoFH patients show a trend towards a younger onset of the disease, with the potential to develop CAD before the age of 20, and a significantly lower survival rate after the age of 30 [8]. In a study

involving 1093 myocardial infarction patients under 35 years old, using the domestic application of Dutch Lipid Clinic Network (DLCN) scoring for FH detection revealed a high detection rate of 6.5% [9]. The younger population is more likely to carry FH mutation genes, and their mortality rate is significantly higher compared to the elderly [10]. Therefore, conducting genetic testing for FH in early-onset CAD patients is of great significance for early identification, accurate diagnosis, prevention, and treatment in clinical practice.

Currently, FH is still a major medical challenge due to low diagnosis and treatment rates worldwide [11]. There is limited research on the detection rate and clinical characteristics of FH based on Chinese data [12]. Moreover, there is a lack of studies on the detection and treatment status of FH in the Hakka population, which has a relatively unique genetic background [13]. Therefore, this retrospective study aims to explore the incidence, clinical phenotypes, and genetic typing of FH in early-onset CAD patients in the Hakka population in Meizhou, Guangdong to reveal the relationship between early-onset coronary artery disease and familial hypercholesterolemia in this population.

Materials and methods

General information

The clinical data of 167 Hakka patients with early-onset CAD admitted to the Meizhou People's Hospital from January 2023 to January 2024 were retrospectively analyzed in this study. General patient information, including gender, age, BMI, blood pressure, smoking history, past medical history, and family medical history, were collected. This study was approved by the Medical Ethics Committee of Meizhou People's Hospital. The study flow chart is shown in **Figure 1**.

Inclusion criteria: (1) Patients diagnosed with early-onset CAD according to the relevant guidelines [14]; (2) Self-confirmed history of myocardial infarction or previous coronary artery bypass grafting, or percutaneous coronary intervention; (3) Confirmation of at least one major coronary artery stenosis exceeding 50% by coronary CT or coronary angiography; (4)

Coronary artery stenosis less than 50%, clinically diagnosed with coronary atherosclerosis, but with clinical symptoms, changes in electrocardiogram, and elevated blood levels of Cardiac Troponin; (5) Ancestral settlement in the Hakka population in the Meizhou area for at least three generations; (6) Onset of CAD; (7) Male ≤55 years, female ≤65 years; (8) Plasma LDL-C ≥3.4 mmol/L, or LDL-C <3.4 mmol/L after taking statins or other medical drugs.

Exclusion criteria: (1) Severe heart failure or arrhythmia; (2) Coexisting immune system diseases or other infectious diseases; (3) Coexisting coagulation abnormalities or severe hematologic diseases; (4) Coexisting significant organ dysfunction of the liver, kidneys, or multiple organ failure; (5) Coexisting thyroid dysfunction; (6) Women during pregnancy or lactation; (7) Missing clinical data or blood sample.

FH diagnostic criteria

Clinical diagnosis of FH was based on the "Expert Consensus on the Screening, Diagnosis, and Treatment of Familial Hypercholesterolemia in China": 1) Serum LDL-C level ≥4.7 mmol/L in patients not receiving lipid-lowering drug therapy; 2) Presence of xanthoma or tendon xanthoma, or the presence of corneal arcus in individuals <45 years old; 3) Family history of FH or early-onset ASCVD, especially early-onset CAD.

Laboratory tests

The study subjects fasted for 8-12 hours overnight before blood collection. The next morning, 5 mL of peripheral venous blood was collected using biochemical collection tubes. Samples were centrifuged at 3000 r/min for 10 minutes using a Beckman Coulter automatic biochemical analyzer, and the serum was separated and stored at -80°C for testing. Biochemical parameters including fasting plasma glucose (FPG), uric acid (UA), creatinine (Cr), urea nitrogen (UN), and B-type natriuretic peptide, as well as lipid parameters including LDL-C, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (Apo A1), and apolipoprotein B (Apo B), were measured using a fully automated biochemical production line.
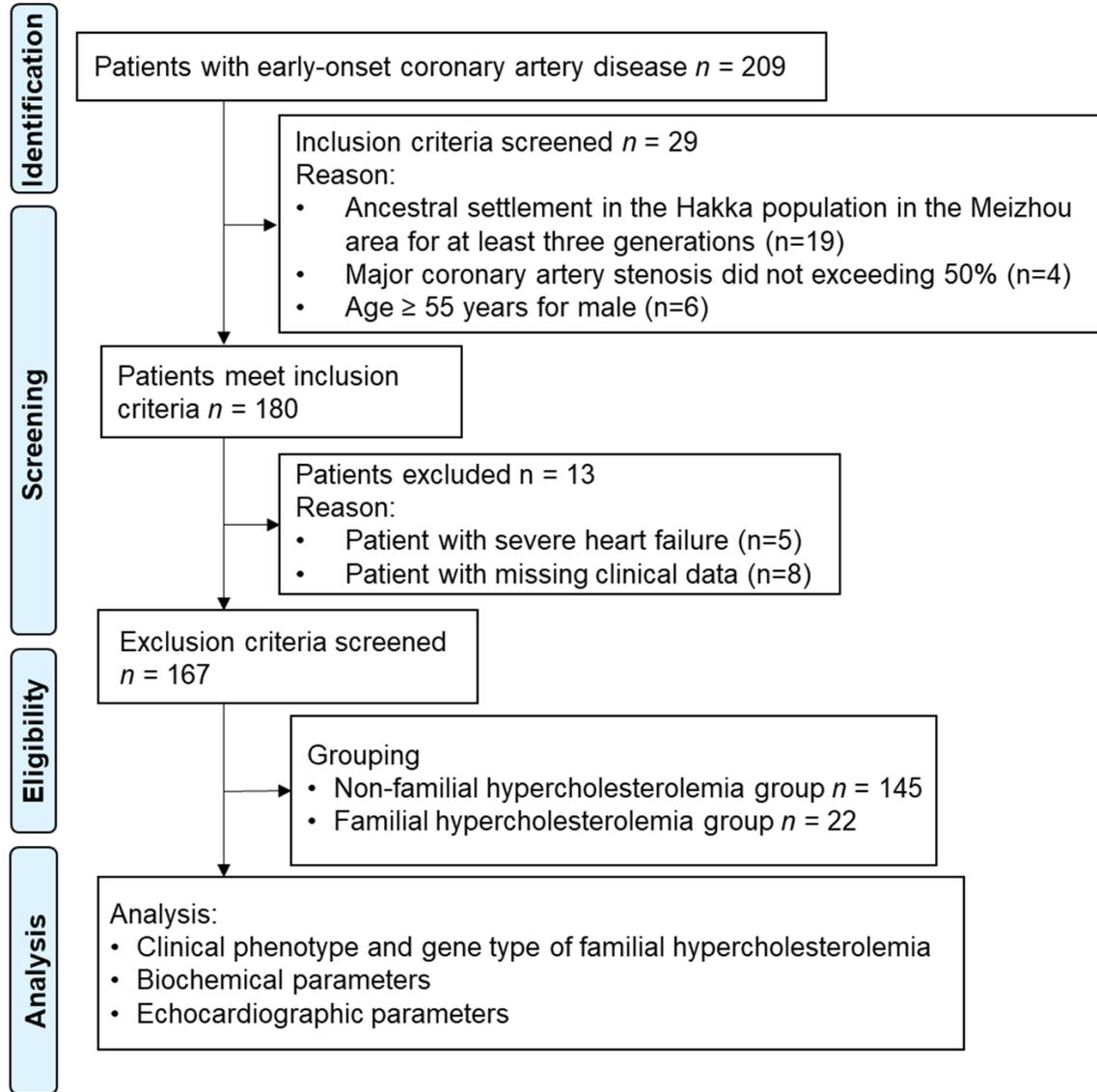
Figure 1. Flow chart of study.

Genetic sequencing

Similar to the laboratory tests, the study subjects fasted for 8-12 hours overnight before blood collection. 4 mL of peripheral venous blood was collected using ethylene diamine tetraacetic acid (EDTA) anticoagulant tubes. Samples were processed using the same centrifugation method and stored at -80°C until examination. Blood samples were sent to Guangzhou Huayin Medical Testing Center for targeted gene sequencing using second-generation high-throughput sequencing technology (next-generation sequencing, NGS) (Thermo

Fisher Scientific Inc.), which covers all exons of known FH-related genes.

Echocardiography examination

Left ventricular end-diastolic dimension (LVd) and left ventricular ejection fractions (LVEF) were measured using the GE Voluson E10 ultrasound imaging system.

Observation indicators

The primary outcomes were the FH incidence rate, clinical phenotypes, and genetic typing in all early-onset CAD patients. The secondary

Table 1. Clinical phenotype and genotyping of FH

Indicator		Number of Cases	Proportion (%)
Clinical Phenotype	Homozygous	1	4.55
	Heterozygous	21	95.45
Genotyping	LDL-R Gene Variation	13	54.17
	Apo B Gene Variation	4	16.67
	PCSK9 Gene Variation	2	8.33
	ABCG5 Gene Variation	1	4.17
	ABCC6 Gene Variation	2	8.33
	ABCA1 Gene Variation	1	4.17
	LRP6 Gene Variation	1	4.17

LDL-R: Low-Density Lipoprotein Receptor; Apo B: Apolipoprotein B; PCSK9: Proprotein Convertase Subtilisin/Kexin 9; ABCG5: ATP-Binding Cassette Transporter G5; ABCC6: ATP Binding Cassette Subfamily C Member 6; ABCA1: ATP-Binding Cassette Transporter A1; LRP6: Low-Density Lipoprotein Receptor-Related Protein 6.

outcomes included differences in biochemical parameters, lipid indicators, and echocardiographic indicators between the FH group and non-FH group.

Statistical analysis

Data analysis was conducted using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, N.Y., USA). Frequency data were presented as n (%), and the chi-square test was employed. Normally distributed measurement data were presented as (mean ± SD) and analyzed using the t-test, while non-normally distributed data were presented as the median and interquartile range [M (P25, P75)] and analyzed using Kruskal-Wallis test. A *P* values less than 0.05 was considered statistically significant.

Results

Incidence rate, clinical phenotypes, and genetic typing of FH

The incidence rate, clinical phenotypes, and genetic typing of FH provide precise genetic information for early diagnosis and prevention of the disease. This study included a total of 167 early-onset CAD Hakka patients, among whom 22 patients developed FH, resulting in an FH incidence rate of 13.17%. Only 1 FH patient had a homozygous type, accounting for 4.55%, while 21 patients had a heterozygous type, accounting for 95.45%. The main gene mutation was in the low-density lipoprotein

receptor (LDL-R) gene, accounting for 54.17%, followed by Apo B gene mutation, accounting for 16.67%. Mutations in the Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) gene, adenosine triphosphate-binding cassette transporter G5 (ABCG5) gene, ATP binding cassette subfamily C member 6 (ABCC6) gene, ATP-binding cassette transporter A1 (ABCA1) gene, and Low-density lipoprotein receptor-related protein 6 (LRP6) gene accounted for 8.33%, 4.17%, 8.33%, 4.17%, and 4.17%, respectively. The study results indicate a high incidence rate of FH, mostly in the heterozygous type, with mutations in LDL-R and Apo B genes being the most common (**Table 1**).

Comparison of general data between the HF and non-HF group

There were no significant differences in the clinical data (including gender, age, BMI, blood pressure, smoking history, past medical history, family medical history) between the two groups (all P>0.05) (**Table 2**).

Comparison of biochemical parameters between the HF and non-HF group

Biochemical parameters are important indicators for assessing the risk, severity, and prognosis of coronary artery disease. FPG is a predictive risk factor for coronary artery disease, Cr levels are closely associated with the development of kidney disease, UN is an indirect indicator of renal impairment, UA is an independent risk factor for predicting coronary artery disease, and B-type natriuretic peptide is one of the indicators for clinical diagnosis and screening of myocardial disease and heart failure. As shown in **Table 3**, there were no differences in FPG, Cr, UN, UA, and B-type natriuretic peptide levels between the two groups (all P>0.05), indicating no significant changes in blood sugar, renal function levels, and other biochemical indicators between the two groups.

Comparison of lipid parameters between the HF and non-HF group

Lipid parameters are key indicators for assessing cardiovascular disease and risk. TG is a commonly used indicator for assessing the risk

Table 2. Comparison of demographic data between the FH and non-FH group

Clinical Data		Number of Cases	FH Group (n = 22)	Non-FH Group (n = 145)	x^2/t/Z	P
Gender	Male	92	10	82	0.951	0.330
	Female	75	12	63		
Age (years)		-	50.50±7.20	52.77±6.87	1.435	0.153
BMI (kg/m²)		-	24.270 (22.60, 27.60)	24.900 (23.30, 26.90)	-0.054	0.957
Blood Pressure	Systolic (mmHg)	-	126.73±16.34	134.19±23.20	1.453	0.148
	Diastolic (mmHg)	-	79.18±11.64	82.68±16.84	0.941	0.349
Smoking History		50	4	46	1.670	0.196
Past Medical History	Hypertension	83	5	78	7.295	0.399
	Diabetes	42	4	38		
	Coronary Heart Disease	16	2	14		
	Acute Myocardial Infarction	2	1	1		
	Cerebrovascular Accident (Stroke)	8	0	8		
	Gout	2	0	2		
	Renal Insufficiency/Failure	3	0	3		
	Carotid Artery Stenosis	1	0	1		
Family History	Coronary Heart Disease	24	5	19	0.982	0.612
	Myocardial Infarction	10	1	9		
	Stroke	3	1	2		

Table 3. Comparison of biochemical parameters between the FH and non-FH group

Group	FPG (mmol/L)	Cr (umol/L)	UN (mmol/L)	UA (umol/L)	B-type Natriuretic Peptide (pg/ml)
FH Group (n = 22)	6.74±1.89	84.82±22.69	5.81±1.09	412.61±58.96	198.24±29.16
Non-FH Group (n = 145)	6.21±2.17	90.98±26.74	5.53±1.21	384.47±67.15	203.05±25.47
t	1.084	1.025	1.024	1.859	0.810
P	0.280	0.307	0.308	0.065	0.419

FPG: Fasting Plasma Glucose; Cr: Blood Creatinine; UN: Blood Urea Nitrogen; UA: Urinary Acid.

of cardiovascular disease such as atherosclerosis and CAD. LDL-C levels are closely related to cardiovascular disease, HDL-C is a protective factor for cardiovascular disease, and Apo A1 and Apo B can reflect lipid metabolism well. As shown in **Figure 2**, compared to the non-FH group, the FH group exhibited lower TG levels [1.785 (1.40, 2.10) mmol/L vs. 2.090 (1.80, 2.30) mmol/L, P = 0.002], higher TC levels [6.635 (5.60, 7.10) mmol/L vs. 4.830 (4.00, 5.40) mmol/L, P<0.001], higher LDL-C levels [4.440 (3.90, 5.20) mmol/L vs. 2.820 (2.40, 3.30) mmol/L, P<0.001], and higher Apo B levels [1.600 (1.30, 1.80) g/L vs. 0.910 (0.70, 1.10) g/L, P<0.001]. There were no differences in HDL-C and Apo A levels between the two groups (all P>0.05).

Comparison of echocardiographic parameters between the HF and non-HF group

Echocardiographic parameters are important for assessing the cardiac structure and func-

tion. LVd quantifies left ventricular volume, while LVEF is a key indicator for assessing left ventricular systolic function. As shown in **Table 4**, there were no differences in LVd and LVEF between the two groups (all P>0.05). The results indicate no significant changes in cardiac structure and systolic function between the HF and non-HF group. See **Figures 3**, **4**.

Correlation between FH and TG, TC, LDL-C, and Apo B levels

The correlation between FH and TG, TC, LDL-C, and Apo B levels can provide important evidence for the differential diagnosis of FH and hold potential value in assessing cardiovascular disease risk. As shown in **Table 5** and **Figure 5**, there were correlations between FH and TG, TC, LDL-C, and Apo B levels (r1 = -0.235; r2 = 0.441; r3 = 0.483; r4 = 0.538). The study results indicate that TG levels were negatively correlated with FH, while TC, LDL-C, and Apo B levels were positively correlated with FH.
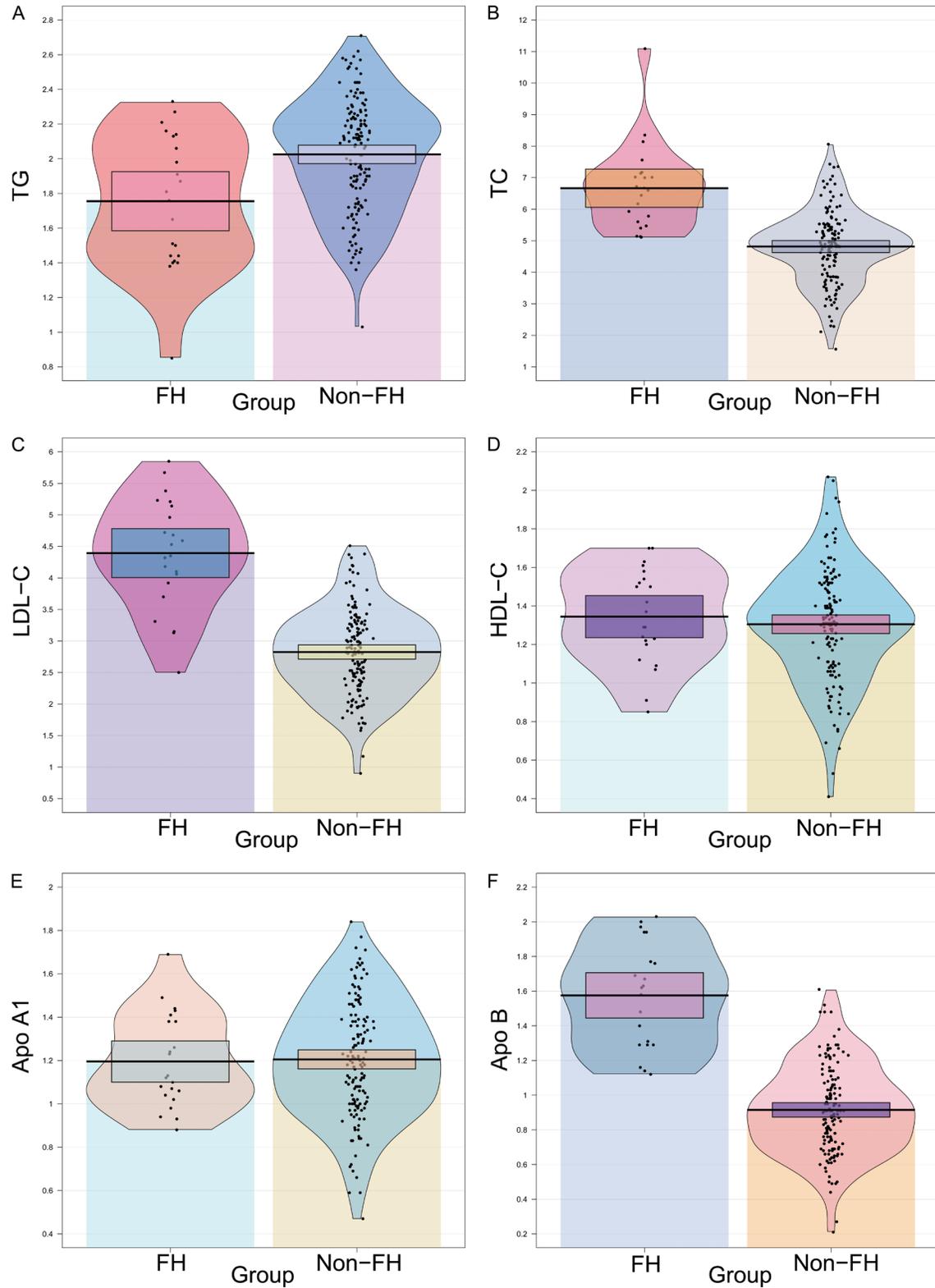
Figure 2. Comparison of blood lipid parameters and apolipoprotein between the FH and non-FH group. A. TG: Triglycerides; B. TC: Total Cholesterol; C. LDL-C: Low-Density Lipoprotein Cholesterol; D. HDL-C: High-Density Lipoprotein Cholesterol; E. Apo A1: Apolipoprotein A1; F. Apo B: Apolipoprotein B. **P<0.01, ***P<0.001, ns: no significant difference.

Table 4. Comparison of echocardiographic parameters between the FH and non-FH group

Group	LVd (mm)	LVEF (%)
FH Group (n = 22)	47.000 (42.00, 49.00)	62.000 (57.00, 65.00)
Non-FH Group (n = 145)	46.000 (43.00, 50.50)	61.000 (57.50, 64.00)
Z	-0.187	-0.396
P	0.851	0.692

LVd: left ventricular end-diastolic diameter; LVEF: Left ventricular ejection fraction.
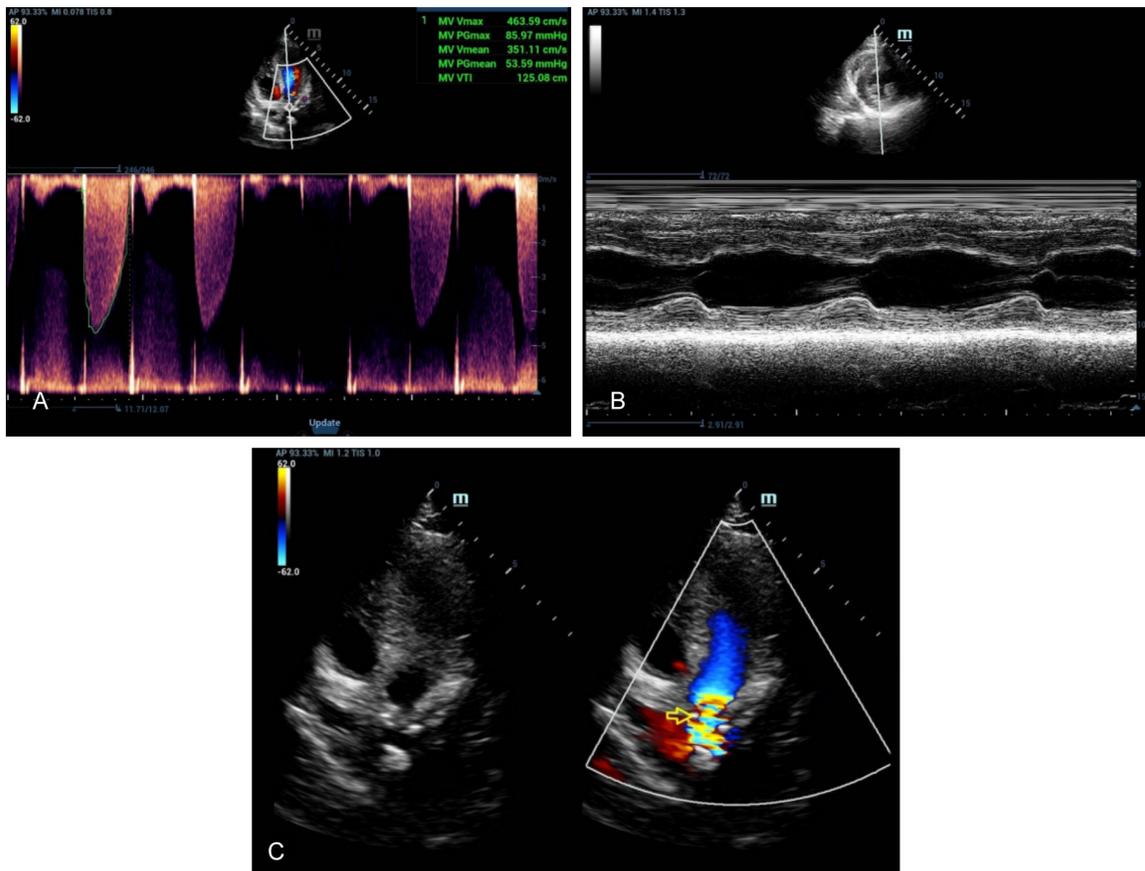
Figure 3. Ultrasound reveals complete IVS and no PE in the case of IAS. A. Tissue Doppler imaging: Mitral annular septal tissue movement velocity: S': 65 mm/s, E': 74 mm/s, A': 72 mm/s. B. Left atrial enlargement, MV focal thickening, ventricular septal thickening, suggesting AS as the cause, MI (moderate); TI (mild); AI (mild). C. The left ventricular systolic function is normal, and the diastolic function is normal. IVS: inter ventricular septum; IAS: atrial septum; AS: aortic stenosis; MI: mitral insufficiency; TI: tricuspid incompetence; AI: aortic incompetence.

Logistic regression analysis

As shown in **Table 6**, the OR values for TC (OR = 0.893, 95% CI: 0.322-1.323; P<0.001), LDL-C (OR = 0.642, 95% CI: 0.081-0.968; P<0.001), and Apo B (OR = 0.699, 95% CI: 0.045-1.574; P<0.001) were all less than 1, indicating their protective effect on the risk of developing FH. The OR value of TG (OR = 2.104, 95% CI: 1.024-2.392; P = 0.001) was greater than 1, highlighting their role in increasing the risk of FH. These results underscore the significant influence of lipid status on FH and confirm that these lipid parameters are independent influencing factors for the development of FH.

Discussion

Atherosclerosis (AS) serves as the main pathological basis for coronary artery disease (CAD), cerebrovascular accidents, and peripheral vascular diseases [15]. Familial hypercholesterol-
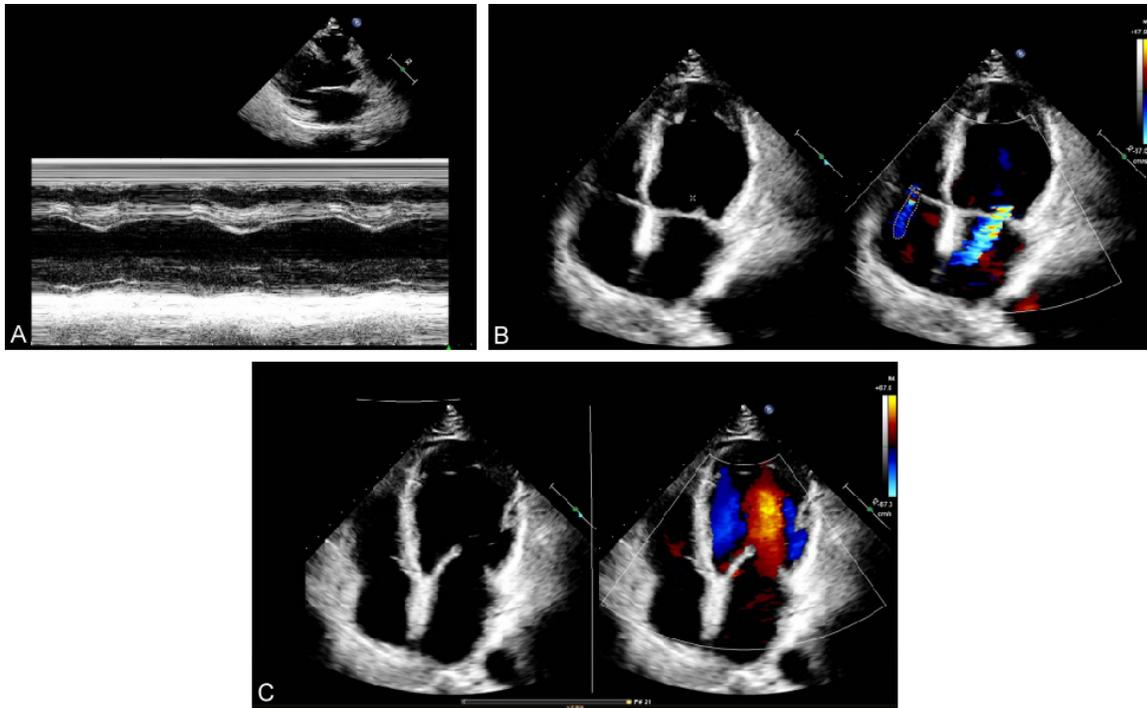
Figure 4. Ultrasound reveals complete IVS, no PEMV thickening, reverse movement of bimodal, and the anterior and posterior lobes with normal opening as well as normal AV thickness and opening in the case of IAS. A. Tissue Doppler imaging: Tissue Doppler imaging: Mitral annulus septal lateral tissue motion velocity: S: 102 mm/s, E: 88 mm/s, A: 110 mm/s. B. Consider conforming to ultrasound changes in coronary heart disease. C. Left heart enlargement; MI (moderate), TI (mild), decreased left ventricular systolic function and decreased diastolic function. IVS: inter ventricular septum; IAS: atrial septum; AS: aortic stenosis; MI: mitral insufficiency; TI: tricuspid incompetence; AI: aortic incompetence.

Table 5. Correlation between FH and levels of TG, TC, LDL-C, and Apo B

Indicator	FH	
	r	P
TG	-0.235	<0.001
TC	0.441	<0.001
LDL-C	0.483	<0.001
Apo B	0.538	<0.001

TG: Triglycerides; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; Apo B: Apolipoprotein B.

emia (FH), characterized by significantly elevated levels of TC and LDL-C, can prompt early-onset AS and consequently accelerate the occurrence of early-onset CAD [16]. The trend towards a younger age at CAD onset is a significant characteristic threatening public health [17]. Conducting genetic testing for early-onset CAD patients is of paramount importance in the early detection and pharmaceutical treatment of FH to prevent the onset and progression of CAD [18]. Several studies have suggested that the Hakka population in Meizhou has relatively unique genetic characteristics [19, 20]. However, there have been no reports on the correlations of epidemiological characteristics and FH in early-onset CAD patients of Hakka population. Therefore, considering the limitations of genetic diagnostic applications, exploring the correlation between early-onset coronary artery disease and FH in the Hakka population of Meizhou, Guangdong, can effectively fill the research gap in the epidemiological characteristics and the diagnosis and treatment of early-onset CAD patients with FH.

This study revealed that among the 167 included early-onset CAD Hakka patients, 22 patients had FH, resulting in an FH incidence rate of 13.17%, with only 1 case being homozygous for FH and 21 cases being heterozygous for FH, mainly with LDL-R gene mutations. A meta-analysis involving 11 million participants in 2020 indicated that the incidence rate of FH in the general population was approximately 0.32%, around 0.19% in the Asian region, and
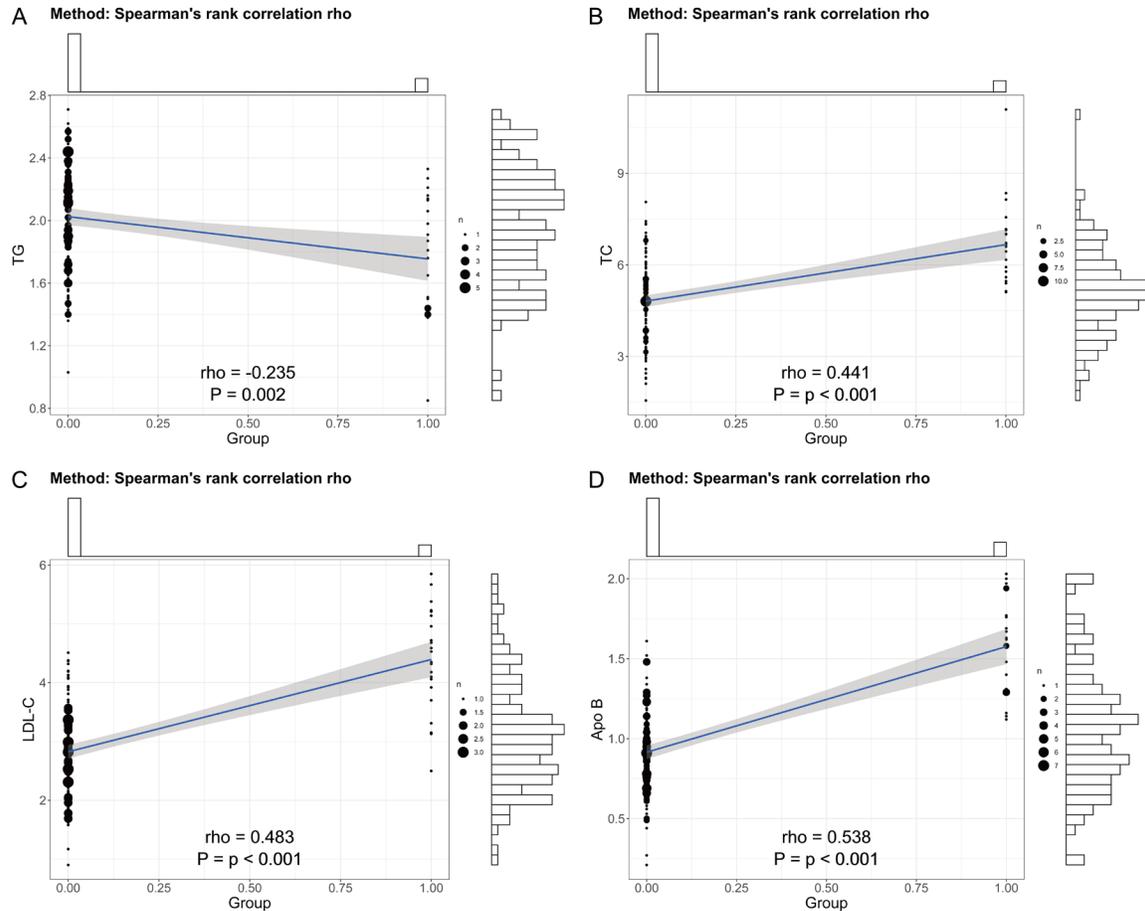
Figure 5. Correlation between FH and TG, TC, LDL-C and Apo B levels. A. TG: Triglycerides; B. TC: Total Cholesterol; C. LDL-C: Low-Density Lipoprotein Cholesterol; D. Apo B: Apolipoprotein B.

Table 6. Logistic regression analysis

Indicator	S.E.	Wald	OR	95% CI	P
TG	0.699	3.232	2.104	1.024-2.392	0.001
TC	0.273	4.884	0.893	0.322-1.323	<0.001
LDL-C	0.495	5.308	0.642	0.081-0.968	<0.001
Apo B	1.653	5.076	0.699	0.045-1.574	<0.001

TG: Triglycerides; TC: Total Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol; Apo B: Apolipoprotein B.

the incidence rate of FH in CAD patients was approximately 3.2%, which increased to 6.7% in early-onset CAD patients, lower than the findings of this study [21]. Another survey indicated that among 285 CAD patients with LDL-C levels ≥160 mg/dL, the prevalence of FH was as high as 14.4%, exceeding the results of this study, and FH mutation carriers were more likely to have early-onset CAD [22]. Genetic mutations are important factors in the pathogenesis of FH. Loss-of-function mutations in the LDL-R gene, Apo B gene mutations, and gain-of-func-

tion mutations in the PCSK9 gene are closely associated with FH, leading to impairment of low-density lipoprotein (LDL) receptor function, Apo B defects, impaired binding of LDL to receptors, and PCSK9 gain-of-function mutations causing LDL receptor degradation, exacerbating the early onset of AS and showing high expression levels [23, 24]. Meizhou is located in the northeastern mountainous region of Guangdong, with a concentration of Hakka population and relatively low population mobility, resulting in fewer introductions of for-

eign genes in rural areas [25]. The genetic background is relatively homogeneous, leading to a relatively high incidence of FH in the Hakka population [26]. The clinical phenotypes and mutation genotypes detected in the FH cases are consistent with the reported pathogenic gene types of FH both domestically and abroad [27]. However, there are still some FH patients with undetectable genetic mutation sites and unclear clinical relevance, necessitating further improvement of genetic mutation detection technology to provide more accurate diagnostic evidence for clinical practice.

The FH group exhibited lower TG levels and higher levels of TC, LDL-C, and Apo B than the non-FH group. Furthermore, TG levels were inversely correlated with FH, while TC, LDL-C, and Apo B levels were positively associated with FH. These variations in levels hold significant value in clinically predicting the risk of developing FH in CAD patients. Previous study proposed that lipids, as a category of organic macromolecules in the body, may be involved in the biological mechanisms of various diseases, potentially affecting endothelial cells and influencing the production, release, and biological functions of nitric oxide, thus triggering AS [28]. It may also exacerbate smooth muscle cell hypertrophy, collagen deposition, renal capillary injury, sympathetic nervous system hyperactivity, and insulin resistance, thereby accelerating AS progression [29]. Research suggests that TG expression levels are closely related to lipid disorders, where high TC levels and low TG levels of lipoprotein remnants can penetrate the arterial intima, selectively binding to the connective tissue matrix such as collagen and elastin, and be cleared by subendothelial resident macrophages, inducing endothelial dysfunction, promoting foam cell and plaque formation, and accelerating AS disease progression [30, 31]. Multiple studies have established a close association between LDL-C and the occurrence and development of AS and cardiovascular disease (CVD) [32, 33]. LDL-C can transport TC from peripheral tissues to the liver circulation, inhibit the expression of endothelial adhesion molecules and the recruitment of monocytes within arterial walls, exerting antioxidant effects, suppressing vascular inflammation and thrombosis while regulating vascular function [34]. However, high levels of LDL-C may impair cardiovascular endothelial function and be engulfed by subendothelial macrophages, forming oxidized low-density lipoprotein and depositing it in vessel walls to cause stenosis and thereby inducing the onset of cardiovascular diseases [35]. It has been found that increased levels of Apo-B in plasma are directly related to the development of CAD [36]. Besides, Apo-B may not only be a better predictor of risk but also a better monitor of therapy than LDL-C alone [37].

In several clinical conditions, a series of lipid markers such as TC, LDL-c, HDL-c, and non-HDL-c have been utilized in predicting the risk of CVD. In addition, non-HDL-c and HDL-c can predict the severity of coronary artery lesions. Non-HDL-c indicates total cholesterol within all the apolipoprotein B (Apo B) particles, including LDL-c and remnant cholesterol. For FH patients with abnormal blood lipids and accompanying cardiovascular metabolic risk factors, the risk assessment role of the single protein molecule Apo B is superior to TC and LDL-C, making it an ideal indicator for assessing CAD risk in FH patients. It is deemed to hold important value in predicting clinical prognosis, similar to the results of this study. Furthermore, it has been found that the Apo B/Apo A1 ratio can serve as a risk marker for predicting cardiovascular diseases [38]. The concentration of Apo B is an intuitive indicator reflecting AS risk, whereas the expression level of Apo A in serum represents its potential in resisting AS. The higher the Apo B/Apo A1 ratio, the greater the risk of AS occurrence. In addition, this study found no significant differences in biochemical indicator levels and echocardiography results between FH patients and non-FH patients, including fasting plasma glucose (FPG), uric acid (UA), creatinine (Cr), urea nitrogen (UN), B-type natriuretic peptide, high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (Apo A1), left ventricular end-diastolic dimension (LVd), and left ventricular ejection fraction (LVEF). This suggests that the occurrence of FH in early-onset CAD patients is not significantly correlated with blood sugar, renal function, HDL-C, Apo A1 levels, cardiac structure, or left ventricular systolic function. Genetic pathogenic mutation detection is the gold standard for diagnosing FH, but whole-genome sequencing and whole-exome sequencing are expensive, time-con-

suming, and not yet widely practiced in clinical settings domestically [39]. In contrast, lipid testing is more cost-effective and simpler, and the combined use of commonly used lipid indicators such as TC, TG, LDL-C, in conjunction with Apo B and the Apo B/Apo A1 ratio, holds promise as an ideal indicator for differentiating and diagnosing FH in early-onset CAD patients.

The present study has several limitations. We only included early-onset CAD patients from the Hakka population in the Meizhou region, which limits the geographical scope and uniqueness of the genetic background of the samples. Additionally, as this was a retrospective study, it was unable to completely eliminate potential confounding factors and information bias. Therefore, we made efforts to ensure the completeness and diversity of the patient data collection to ensure comparability between the two groups. When choosing the observational indicators and interpreting the research results, we also considered the relevant indicators and the aforementioned limitations in the evaluation of the research results to ensure the objectivity of the conclusions. Despite these limitations, this study effectively fills the gap in the epidemiological characteristics of FH in early-onset CAD patients in the Hakka population in Meizhou, Guangdong. The aim was to explore the correlation between early-onset CAD and FH with the goal of providing early diagnosis and prevention strategies for clinical practice.

Conclusion

The incidence of FH is higher in early-onset CAD patients in the Hakka population in Meizhou, with heterozygous and LDL-R gene variations being predominant. FH patients showed decreased TG levels and increased TC, LDL-C, and Apo B levels, and these parameters were correlated with FH, demonstrating their potential value in clinically differentiating and diagnosing FH in CAD patients. This study provides a theoretical basis for the early screening and diagnosis of FH among early-onset CAD patients in the Hakka population in Meizhou, Guangdong. Subsequent efforts should focus on conducting large-sample, multicenter, randomized controlled trials to further validate the effectiveness of this research approach.

Disclosure of conflict of interest

None.

Address correspondence to: Min Yang, Center for Cardiovascular Diseases, Meizhou People's Hospital, Meizhou Academy of Medical Sciences, Meizhou 514031, Guangdong, China. E-mail: htyyym@163.com

References

[1] Ziaee S, Hosseindokht M, Cheraghi S, Pourgholi L, Ahmadi A, Sadeghian S, Abbasi SH, Davarpasand T and Boroumand M. Predictive inflammation-related microRNAs for cardiovascular events following early-onset coronary artery disease. Arch Med Res 2021; 52: 69-75.

[2] Zheng PF, Chen LZ, Pan HW, Liu P and Zheng ZF. Effects of USF1 SNPs and SNP-environment interactions on serum lipid profiles and the risk of early-onset coronary artery disease in the Chinese population. Front Cardiovasc Med 2022; 9: 882728.

[3] Zhang SY, Xuan C, Wang Y, Zhang SQ, Li H, He GW and Tian QW. Association between ALMS 1 variants and early-onset coronary artery disease: a case-control study in Chinese population. Biosci Rep 2020; 40: BSR20193637.

[4] Yao K, Dai Y, Shen J, Wang Y, Yang H, Wu R, Liao Q, Wu H, Fang X, Shali S, Xu L, Hao M, Lin C, Sun Z, Liu Y, Li M, Wang Z, Gao Q, Zhang S, Li C, Gao W, Ge L, Zou Y, Sun A, Qian J, Jin L, Hong S, Zheng Y and Ge J. Exome sequencing identifies rare mutations of LDLR and QTRT1 conferring risk for early-onset coronary artery disease in Chinese. Natl Sci Rev 2022; 9: nwac102.

[5] Xuan C, Tian QW, Li H, Guo JJ, He GW and Lun LM. Serum fatty acids profile and association with early-onset coronary artery disease. Ther Adv Chronic Dis 2021; 12: 20406223211033102.

[6] Xuan C, Li J, Liu RH, Guo JJ, Zhao C, Zhou TT, Wang Y, He GW and Lun LM. Association between serum gamma-glutamyltransferase and early-onset coronary artery disease: a retrospective case-control study. Ann Med 2023; 55: 2289606.

[7] Xuan C, Li H, Tian QW, Guo JJ, He GW, Lun LM and Wang Q. Quantitative assessment of serum amino acids and association with early-

onset coronary artery disease. Clin Interv Aging 2021; 16: 465-474.

[8] Wu TT, Zheng YY, Ma X, Xiu WJ, Yang HT, Hou XG, Yang Y, Chen Y, Ma YT and Xie X. Mutated CYP17A1 promotes atherosclerosis and early-onset coronary artery disease. Cell Commun Signal 2023; 21: 155.

[9] Wang H, Li H, Wang Y, Zhao C, Tian QW, Wang Q, He GW, Lun LM and Xuan C. Hematological parameters and early-onset coronary artery disease: a retrospective case-control study based on 3366 participants. Ther Adv Chronic Dis 2023; 14: 20406223221142670.

[10] Venkataraman P, Stanton T, Liew D, Huynh Q, Nicholls SJ, Mitchell GK, Watts GF, Tonkin AM and Marwick TH. Coronary artery calcium scoring in cardiovascular risk assessment of people with family histories of early onset coronary artery disease. Med J Aust 2020; 213: 170-177.

[11] Tudurachi BS, Anghel L, Tudurachi A, Sascău RA and Stătescu C. Assessment of inflammatory hematological ratios (NLR, PLR, MLR, LMR and monocyte/HDL-cholesterol ratio) in acute myocardial infarction and particularities in young patients. Int J Mol Sci 2023; 24: 14378.

[12] Tu G, Fang Z, Zhao Y and Wu Q. Association of +138I/D and Lys198Asn polymorphisms in the endothelin-1 gene with early onset of coronary artery disease among the Chinese Han population. Med Sci Monit 2020; 26: e921542.

[13] Tam To B, Roy R, Melikian N, Gaughran FP and O'Gallagher K. Coronary artery disease in patients with severe mental illness. Interv Cardiol 2023; 18: e16.

[14] Takashima A, Yagi S, Yamaguchi K, Kurahashi K, Kojima Y, Zheng R, Ise T, Kusunose K, Yoshida S, Yamada H, Soeki T, Wakatsuki T, Aihara KI, Akaike M and Sata M. Congenital hypogonadotropic hypogonadism with early-onset coronary artery disease. J Med Invest 2021; 68: 189-191.

[15] Stone NJ, Smith SC Jr, Orringer CE, Rigotti NA, Navar AM, Khan SS, Jones DW, Goldberg R, Mora S, Blaha M, Pencina MJ and Grundy SM. Managing atherosclerotic cardiovascular risk in young adults: JACC state-of-the-art review. J Am Coll Cardiol 2022; 79: 819-836.

[16] Shapiro D, Lee K, Asmussen J, Bourquard T and Lichtarge O. Evolutionary action-machine learning model identifies candidate genes associated with early-onset coronary artery disease. J Am Heart Assoc 2023; 12: e029103.

[17] Shali S, Luo L, Yao K, Sun X, Wu H, Zhang S, Xu L, Gao W, Li J, Qian J, Zheng Y, Dai Y and Ge J; the GRAND investigators. Triglyceride-glucose index is associated with severe obstructive coronary artery disease and atherosclerotic

target lesion failure among young adults. Cardiovasc Diabetol 2023; 22: 283.

[18] Pauli N, Puchałowicz K, Kuligowska A, Krzystolik A, Dziedziejko V, Safranow K, Rać M, Chlubek D and Ewa Rać M. Associations between IL-6 and echo-parameters in patients with early onset coronary artery disease. Diagnostics (Basel) 2019; 9: 189.

[19] Muniyappa R and Narayanappa SBK. Disentangling dual threats: premature coronary artery disease and early-onset type 2 diabetes mellitus in South Asians. J Endocr Soc 2023; 8: bvad167.

[20] Mousavi I, Suffredini J, Virani SS, Ballantyne C, Michos ED, Misra A, Saeed A and Jia X. Early onset atherosclerotic cardiovascular disease. Eur J Prev Cardiol 2024; [Epub ahead of print].

[21] Montarello N and Chan WPA. Coronary artery disease in women. Aust Prescr 2022; 45: 193-199.

[22] Miyazawa K and Ito K. Genetic analysis for coronary artery disease toward diverse populations. Front Genet 2021; 12: 766485.

[23] Mihăilă RG. Pragmatic analysis of dyslipidemia involvement in coronary artery disease: a narrative review. Curr Cardiol Rev 2020; 16: 36-47.

[24] Menezes Fernandes R, Mota T, Costa H, Bispo J, Azevedo P, Bento D, Guedes J, Carvalho D, Marques N, Santos W, Mimoso J and de Jesus I; Portuguese Registry of Acute Coronary Syndromes (ProACS) investigators. Premature acute coronary syndrome: understanding the early onset. Coron Artery Dis 2022; 33: 456-464.

[25] Manolis AA, Manolis TA and Manolis AS. Early-onset or premature coronary artery disease. Curr Med Chem 2024; [Epub ahead of print].

[26] Manikpurage HD, Eslami A, Perrot N, Li Z, Couture C, Mathieu P, Bossé Y, Arsenault BJ and Thériault S. Polygenic risk score for coronary artery disease improves the prediction of early-onset myocardial infarction and mortality in men. Circ Genom Precis Med 2021; 14: e003452.

[27] Maino A, Sadeghian S, Mancini I, Abbasi SH, Poorhosseini H, Boroumand MA, Lotfi-Tokaldany M, Jalali A, Pagliari MT, Rosendaal FR and Peyvandi F. Opium as a risk factor for early-onset coronary artery disease: results from the Milano-Iran (MIran) study. PLoS One 2023; 18: e0283707.

[28] Magnani G, Bricoli S, Ardissino M, Maglietta G, Nelson A, Malagoli Tagliazucchi G, Disisto C, Celli P, Ferrario M, Canosi U, Cernetti C, Negri F, Merlini PA, Tubaro M, Berzuini C, Manzalini C, Ignone G, Campana C, Moschini L, Ponte E, Pozzi R, Fetiveau R, Buratti S, Paraboschi E, Asselta R, Botti A, Tuttolomondo D, Barocelli F,

Biagi A, Bonura R, Moccetti T, Crocamo A, Benatti G, Paoli G, Solinas E, Notarangelo MF, Moscarella E, Calabrò P, Duga S, Niccoli G and Ardissino D. Long-term outcomes of early-onset myocardial infarction with non-obstructive coronary artery disease (MINOCA). Int J Cardiol 2022; 354: 7-13.

[29] Lali R, Cui E, Ansarikaleibari A, Pigeyre M and Paré G. Genetics of early-onset coronary artery disease: from discovery to clinical translation. Curr Opin Cardiol 2019; 34: 706-713.

[30] Koenig SN, Sucharski HC, Jose EM, Dudley EK, Madiai F, Cavus O, Argall AD, Williams JL, Murphy NP, Keith CBR, El Refaey M, Gumina RJ, Boudoulas KD, Milks MW, Sofowora G, Smith SA, Hund TJ, Wright NT, Bradley EA, Zareba KM, Wold LE, Mazzaferri EL Jr and Mohler PJ. Inherited variants in SCARB1 cause severe early-onset coronary artery disease. Circ Res 2021; 129: 296-307.

[31] Kayıkçıoğlu M and Tetik Vardarlı A. How to generate unbiased data in molecular genetic studies in patients with early onset coronary artery disease or premature myocardial infarction? Turk Kardiyol Dern Ars 2022; 50: 404-406.

[32] Kaw K, Chattopadhyay A, Guan P, Chen J, Majumder S, Duan XY, Ma S, Zhang C, Kwartler CS and Milewicz DM. Smooth muscle α-actin missense variant promotes atherosclerosis through modulation of intracellular cholesterol in smooth muscle cells. Eur Heart J 2023; 44: 2713-2726.

[33] Kahya Eren N, Karaca E, Şirin FB, Levent F, Gündüz C, Özdemir E, Nazlı C, Cogulu O and Ergene AO. Does microRNA profile differ in early onset coronary artery disease? Turk Kardiyol Dern Ars 2022; 50: 407-414.

[34] Jiao W, Wei L, Jiao F, Pjetraj D, Feng J, Wang J, Catassi C and Gatti S. Very early onset of coronary artery aneurysm in a 3-month infant with Kawasaki disease: a case report and literature review. Ital J Pediatr 2023; 49: 60.

[35] Guo H, Yu X, Liu Y, Paik DT, Justesen JM, Chandy M, Jahng JWS, Zhang T, Wu W, Rwere F, Zhao SR, Pokhrel S, Shivnaraine RV, Mukherjee S, Simon DJ, Manhas A, Zhang A, Chen CH, Rivas MA, Gross ER, Mochly-Rosen D and Wu JC. SGLT2 inhibitor ameliorates endothelial dysfunction associated with the common ALDH2 alcohol flushing variant. Sci Transl Med 2023; 15: eabp9952.

[36] Coto E, Pascual I, Avanzas P, Cuesta-Lavona E, Lorca R, Martín M, Vázquez-Coto D, Díaz-Corte C, Morís C, Rodríguez-Reguero J and Gómez J. IL17RA in early-onset coronary artery disease: total leukocyte transcript analysis and promoter polymorphism (rs4819554) association. Cytokine 2020; 136: 155285.

[37] Chuapakdee O, Layangkool T and Theerasuwipakorn N. Pyridostigmine-induced coronary artery spasm in early-onset myasthenia gravis: a case presentation and review of the literature. BMJ Case Rep 2022; 15: e249819.

[38] Cheng Y, Nie L, Ma W and Zheng B. Early onset acute coronary artery occlusion after pembrolizumab in advanced non-small cell lung cancer: a case report. Cardiovasc Toxicol 2021; 21: 683-686.

[39] Benschop L, Brouwers L, Zoet GA, Meun C, Boersma E, Budde RPJ, Fauser BCJM, de Groot CMJ, van der Schouw YT, Maas AHEM, Velthuis BK, Linstra KM, Kavousi M, Duvekot JJ, Franx A, Steegers E, van Rijn BB and Roeters van Lennep JE; CREW Consortium. Early onset of coronary artery calcification in women with previous preeclampsia. Circ Cardiovasc Imaging 2020; 13: e010340.