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Research article

Influence of apolipoprotein E gene polymorphisms on coronary artery disease in patients undergoing coronary angiography

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ABSTRACT

Objective: Previous studies have shown that apolipoprotein E (ApoE) gene polymorphisms have an impact on coronary artery disease(CAD). However, many studies have small sample sizes and different conclusions. The purpose was to retrospectively study the influence of ApoE gene polymorphisms on CAD.

Methods: This study assessed the influence of different ApoE genotypes on coronary heart disease in patients who received coronary angiography and used multivariate logistic regression to assess the influence of different ApoE genotypes on CAD.

Results: Patients with different ApoE genotypes had no obvious differences in the incidence of hypertension, diabetes or obesity ($P > 0.05$). Patients with ε2/ε2 had higher incidence of hypertriglyceridemia than patients with other ApoE genotypes, while patients with ε3/ε3 had a lower incidence of hypertriglyceridemia than those with ε3/ε4,ε4/ε4, ε2/ε3 and ε2/ε2 ($P < 0.05$) . Patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 had no significant differences in the severity or incidence of CAD ($P > 0.05$). ε2/ε4 and ε2/ε3 reduced the risk of high LDL-C, and reduced the severity and incidence of coronary heart ($P < 0.05$). ε2/ε3 reduced risk of premature coronary artery disease (PCAD) ($P < 0.05$). ε2/ε3 reduced risk of CAD in patients age <45,age at 60–74 and age ≥74, while ε2/ε4 reduced risk of CAD in patients age ≥74 ($P < 0.05$).

Conclusion: Patients with ε3/ε4, ε4/ε4,ε3/ε3 and ε2/ε2 had no significant differences in the severity and occurrence of CAD. Compared to the isoform ε3 (ε3/ε3), isoform ε4 did not increased the severity and occurrence of CAD. Compared with ApoE other genotypes, ε2/ε3 and ε2/ε4 reduced the risk of high LDL-C and the severity and occurrence of CAD.

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1. Introduction

Cardiovascular disease is an important cause of death worldwide. Apolipoproteins take part in lipid metabolism and influence the occurrence of CAD [1]. Genetic variation in apolipoproteins may cause abnormal lipids metabolism and increase occurrence of CAD [2]. ApoE is a kind of polymorphic apolipoprotein, which is a component of many lipoproteins. ApoE plays an important role in lipoprotein metabolism [3]. Apolipoprotein E is involved in the formation of HDL and affects the clearance of lipoproteins from blood [4]. The major alleles of ApoE gene are ε3, ε4 and ε2, and the metabolism of blood lipids is different among different genotypes [5,6]. ε3 regulates the interaction between lipids and lipoprotein, and has a high affinity to high-density lipoprotein [7], ε4 has a high affinity to lipoprotein which are rich in triglyceride [8]. Genetic variation in apolipoprotein E influences lipoprotein metabolism and the occurrence of CAD [9]. Some studies have shown that ε4 allele increases the risk of cardiovascular disease, while other studies have shown that there is no statistical differences in the severity and occurrence of CAD in patients with different ApoE genotypes. According to an Italian investigation, the ε4 allele is associated with low ApoE concentrations, which is a risk factor for coronary artery diseases [10]. A recently study showed that ApoE ε3/ε4 genotype and ε4 allele were independent risk factors for T2DM complicated with CAD, but not for T2DM [11]. A comprehensive genome study involving a large number of samples with 48,457 individuals showed that individuals with ε4 allele are more susceptible to coronary heart disease than individuals with ε3 allele [12]. Other studies have also shown that ε4 allele will increase risk of cardiovascular disease [13–15]. However, a study reported that there was no

Table 1
Baseline Clinical Characteristics of patients with different apolipoprotein E genotypes.

Variable	ε4/ε4 (n = 87)	ε3/ε4 (n = 1297)	ε2/ε4 (n = 115)	ε2/ε3 (n = 945)	ε2/ε2 (n = 54)	ε3/ε3 (n = 5136)	p Value
Age, years	58.54 ± 10.92	62.70 ± 10.53	62.07 ± 11.96	64.02 ± 10.56	63.09 ± 10.84	62.94 ± 10.72	0.000[a]
Male Sex, n(%)	55 (63.21 %)	785 (60.52 %)	70 (60.87 %)	551 (58.31 %)	41 (75.93 %)	3085 (60.06 %)	0.253
Drinking, n(%)	28 (32.18 %)	397 (30.61 %)	27 (23.48 %)	259 (27.41 %)	16 (29.63 %)	1453 (28.29 %)	0.354
Smoking, n(%)	38 (43.67 %)	538 (41.48 %)	43 (37.39 %)	343 (36.30 %)	34 (62.92 %)	2041 (39.74 %)	0.002[a]
Hypertension, n (%)	46 (52.87 %)	737 (56.82 %)	67 (58.26 %)	558 (59.05 %)	31 (57.41 %)	2848 (55.45 %)	0.402
Diabetes, n (%)	16 (18.39 %)	240 (18.50 %)	23 (20 %)	207 (21.90 %)	16 (29.63 %)	1008 (19.63 %)	0.190
Triglyceride, mmol/l	2.24 ± 1.84	1.90 ± 1.75	1.91 ± 1.36	1.87 ± 1.50	2.79 ± 2.09	1.70 ± 1.26	0.000[a]
LDL-C，mmol/l	2.92 ± 0.88	2.84 ± 0.85	2.66 ± 0.82	2.43 ± 0.75	2.38 ± 1.07	2.73 ± 0.81	0.000[a]
HDL-C，mmol/l	1.08 ± 0.28	1.10 ± 0.28	1.11 ± 0.29	1.15 ± 0.30	1.15 ± 0.34	1.12 ± 0.31	0.000[a]
Total cholesterol，mmol/l	4.54 ± 1.20	4.40 ± 1.14	4.18 ± 1.09	3.96 ± 1.07	4.24 ± 1.58	4.26 ± 1.07	0.000[a]
BMI	24.47 ± 3.06	24.34 ± 3.25	24.48 ± 3.48	24.32 ± 3.29	24.80 ± 3.98	24.38 ± 3.30	0.929
High triglyceride, n (%)	44 (50.57 %)	482 (37.16 %)	47 (40.87 %)	364 (38.52 %)	36 (66.67 %)	1733 (33.74 %)	0.000[a]
High LDL-C，n (%)	34 (39.08 %)	435 (33.54 %)	25 (21.74 %)	155 (16.40 %)	16 (29.63 %)	1463 (28.49 %)	0.000[a]
High total cholesterol，n(%)	13 (14.94 %)	138 (10.64 %)	9 (7.83 %)	53 (5.61 %)	8 (14.81 %)	456 (8.88 %)	0.000*
Hyperuricemia，n (%)	6 (6.90 %)	131 (10.10 %)	9 (7.83 %)	93 (9.84 %)	5 (9.26 %)	533 (10.38 %)	0.890
Overweight,n(%)	36 (41.38 %)	471 (36.31 %)	41 (35.65 %)	327 (34.60 %)	16 (29.63 %)	1758 (34.23 %)	0.498
Obese,n(%)	4 (4.60 %)	60 (4.63 %)	6 (5.22 %)	42 (4.44 %)	5 (9.26 %)	279 (5.43 %)	0.469
Coronary heart disease, n(%)	53 (60.92 %)	767 (59.14 %)	54 (46.96 %)	484 (51.22 %)	35 (64.81 %)	3028 (58.96 %)	0.000[a]
Multivessel lesion,n(%)	29 (33.33 %)	445 (34.31 %)	26 (22.61 %)	246 (26.03 %)	18 (33.33 %)	1679 (32.69 %)	0.000[a]
PCI，n(%)	40 (45.98 %)	541 (41.71 %)	34 (29.57 %)	352 (37.25 %)	28 (51.85 %)	2152 (41.90 %)	0.004[a]
AMI，n(%)	16 (18.39 %)	166 (12.80 %)	10 (8.70 %)	79 (8.36 %)	7 (12.96 %)	641 (12.48 %)	0.002[a]
Cardiac insufficiency, n(%)	2 (2.30 %)	75 (5.78 %)	4 (3.48 %)	63 (6.67 %)	1 (1.85 %)	312 (6.07 %)	0.388
CKD, n(%)	2 (2.30 %)	46 (3.55 %)	4 (3.48 %)	30 (3.17 %)	1 (1.85 %)	162 (3.15 %)	0.975
Family history of hypertension, n (%)	8 (9.20 %)	104 (8.02 %)	7 (6.09 %)	81 (8.57 %)	3 (5.56 %)	413 (8.04 %)	0.934
Family history of diabetes, n(%)	1 (1.15 %)	42 (3.24 %)	1 (0.87 %)	25 (2.64 %)	3 (5.56 %)	135 (2.63 %)	0.378
Family history of CAD, n(%)	6 (6.90 %)	58 (4.47 %)	2 (1.74 %)	38 (4.02 %)	3 (5.56 %)	254 (4.95 %)	0.371
Family history of hyperlipidemia, n (%)	0	5 (0.39 %)	0	3 (0.32 %)	0	12 (0.23 %)	0.762

Values are mean ± SD or number (%).

[a] Indicates $p < 0.05$. LDL-C: Low-density lipoprotein cholesterol; HDL-C:High-density lipoprotein cholesterol; PCI: Percutaneous coronary intervention; AMI: Acute myocardial infarction; CKD: Chronic kidney disease, CAD:Coronary artery disease.

association between ApoE gene polymorphisms and CAD in Afro-Caribbean people [16]. A recent study indicated that allele ε4 was not significantly expressed in venous tissue between control and patient groups, and ε4 was not related to the risk of cardiovascular diseases [17]. Therefore, there is controversy about the influence of ApoE gene polymorphisms on CAD, and the sample size of many studies was small. The purpose of this study is to retrospectively study the influence of ApoE gene polymorphisms on CAD.

2. Methods

2.1. Patient population

This single-center retrospective study included 7634 patients who had complete medical records and were hospitalized due to coronary angiography at Department of Cardiology, Daping Hospital, The Third Military Medical University (Army Medical University) between January 2017 to December 2019. Patient data, including results of ApoE genotype, coronary angiography and blood lipid, conventional cardiovascular risk factors and other clinical characteristics were obtained from the hospital electronic file. Coronary artery disease was defined as coronary angiography that confirmed at least one epicardial main vessel stenosis was more than 50 %. Multi-vessel lesions was defined as coronary angiography that confirmed that at least two epicardial main vessel stenoses were more than 50 %. Family history refers to immediate family, including parents or siblings.

2.2. Statistical analyses

Values are presented as mean ± SD or number (%) in each group. The Kruskal-Wallis test in nonparametric test was used to compare the continuous variables between different groups, and Bonferroni correction method was used to adjust the multiple comparisons. We compared categorical variables among different groups using chi-square or Fisher's exact Test. This study used multivariate hierarchical logistic regression to assess the influence of different ApoE genotypes on cardiovascular risk factors and CAD in patients who received coronary angiography after adjustment for age,gender and cardiovascular risk factors. $P < 0.05$ was considered to be statistically significant. All statistical analysis was carried out with SPSS 26 software.

3. Results

3.1. Clinical features of patients with different ApoE genotypes

The study used the Kruskal-Wallis test in nonparametric test to compare the continuous variables between different groups, and used Bonferroni correction method to adjust for multiple comparisons. The study compared categorical variables among different groups using chi-square or Fisher's exact Test. As shown in Table 1, among the 7634 patients who received coronary angiography, ε3/ε3 accounted for 67.28 % of all genotypes, followed by the ε4/ε4 (1.14 %) , ε2/ε3 (12.38 %), ε3/ε4 (16.99 %), ε2/ε4 (1.51 %) and ε2/ε2 (0.71 %). There were no significant differences among 4 groups in gender, drinking, hypertension, diabetes, BMI, smoking , hyperuricemia, obesity, AMI, cardiac insufficiency, chronic kidney disease, family history of hypertension, diabetes, CAD and family history of hyperlipidemia ($P > 0.05$) .

Table 2
A multivariate Logistic regression model on the association of hypertension, diabetes and obese with ApoE gene polymorphisms after adjustment for sex,age and the clinical characteristic factors.

Variables	Adjusted Odd Ratio (OR) (95 % CI), p Value		
	Hypertension	Diabetes	Obese
ε3/ε4 vs ε4/ε4	1.047(0.665–1.649), P = 0.841	0.961(0.542–1.704), P = 0.892	1.279(0.447–3.662), P = 0.646
ε3/ε3 vs ε4/ε4	0.968(0.621–1.507), P = 0.885	1.072(0.613–1.876), P = 0.807	1.623(0.581–4.529), P = 0.355
ε2/ε4 vs ε4/ε4	1.103(0.613–1.986), P = 0.744	1.031(0.498–2.137), P = 0.934	1.479(0.397–5.508), P = 0.559
ε2/ε3 vs ε4/ε4	1.051(0.663–1.666), P = 0.832	1.178(0.661–2.099), P = 0.579	1.400(0.482–4.072), P = 0.536
ε2/ε2 vs ε4/ε4	0.898(0.440–1.837), P = 0.769	1.654(0.729–3.753), P = 0.229	2.899(0.721–11.657), P = 0.134
ε3/ε4 vs ε3/ε3	1.082(0.952–1.231), P = 0.228	0.896(0.763–1.052), P = 0.181	0.788(0.590–1.054), P = 0.108
ε2/ε4 vs ε3/ε3	1.140(0.767–1.693), P = 0.517	0.962(0.596–1.551), P = 0.873	0.912(0.393–2.113), P = 0.829
ε2/ε3 vs ε3/ε3	1.086(0.936–1.260), P = 0.276	1.099(0.922–1.309), P = 0.293	0.863(0.615–1.210), P = 0.393
ε2/ε2 vs ε3/ε3	0.928(0.526–1.638), P = 0.797	1.543(0.840–2.833), P = 0.162	1.787(0.686–4.654), P = 0.235
ε3/ε4 vs ε2/ε2	1.166(0.655–2.075), P = 0.602	0.581(0.312–1.081), P = 0.087	0.441(0.165–1.182), P = 0.104
ε2/ε4 vs ε2/ε2	1.228(0.618–2.439), P = 0.558	0.623(0.290–1.341), P = 0.227	0.510(0.145–1.801), P = 0.296
ε2/ε3 vs ε2/ε2	1.170(0.655–2.091), P = 0.596	0.712(0.382–1.329), P = 0.286	0.483(0.178–1.313), P = 0.154
ε2/ε4 vs ε3/ε4	1.053(0.700–1.583), P = 0.804	1.073(0.655–1.759), P = 0.780	1.156(0.483–2.766), P = 0.744
ε2/ε3 vs ε3/ε4	1.004(0.839–1.201), P = 0.970	1.226(0.988–1.521), P = 0.065	1.095(0.725–1.652), P = 0.667
ε2/ε3 vs ε2/ε4	0.953(0.630–1.442), P = 0.820	1.142(0.694–1.880), P = 0.601	0.947(0.389–2.302), P = 0.904

* indicates $p < 0.05$.

3.2. The influence of different ApoE genotypes on obesity, diabetes and hypertension

This study used a multivariate logistic regression model to assess the occurrence of different ApoE genotypes on hypertension, diabetes and obesity. As shown in Table 2, patients with different apolipoprotein E genotypes had no significant differences in the occurrence of obesity, diabetes or hypertension.

3.3. The influence of different ApoE genotypes on dyslipidemia

This study used multivariate logistic regression model to assess the influence of different ApoE genotypes on dyslipidemia. As shows in Table 3, patients with ε3/ε4, ε4/ε4, ε2/ε4 and ε2/ε3 had no significant differences in the occurrence of hypertriglyceridemia ($P > 0.05$) . Patients with ε2/ε2 had higher occurrence of hypertriglyceridemia than patients with other ApoE genotypes ($P < 0.05$) . Patients with ε3/ε4, ε4/ε4, ε2/ε3, and ε2/ε2 had higher occurrence of hypertriglyceridemia than patients with ε3/ε3 ($P < 0.05$) .

Patients with ε3/ε4, ε4/ε4, ε2/ε4 and ε2/ε2 had no obvious differences in the occurrence of high total cholesterol ($P > 0.05$) . Patients with ε2/ε4 and ε2/ε3 had no obvious differences in the occurrence of high total cholesterol ($P > 0.05$) . Patients with ε2/ε3 had lower occurrence of high total cholesterol than patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 ($P < 0.05$) .

Patients with ε2/ε2, ε4/ε4 and ε3/ε3 had no obvious differences in the occurrence of high LDL-C ($P > 0.05$) . Patients with ε2/ε4 and ε2/ε3 had no obvious differences in the occurrence of high LDL-C ($P > 0.05$) . Patients with ε3/ε3 had lower occurrence of high LDL-C than patients with ε3/ε4 ($P < 0.05$) . Patients with ε2/ε4 had lower occurrence of high LDL-C than patients with ε3/ε4 and ε4/ε4 ($P < 0.05$) . Patients with ε2/ε3 had lower occurrence of high LDL-C than patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 ($P < 0.05$) .

3.4. The influence of different ApoE genotypes on CAD

This study used a multivariate logistic regression to assess the influence of different ApoE genotypes on CAD. As shown in Table 4, patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 had no obvious differences in the occurrence of CAD. Patients with ε2/ε3 had lower occurrence of CAD than patients with ε3/ε3 and ε3/ε4 ($P < 0.05$) . Patients with ε2/ε4 had lower occurrence of CAD than patients with ε3/ε4, ε4/ε4 and ε3/ε3 ($P < 0.05$) .

3.5. The influence of different ApoE genotypes on the severity of CAD

This study used a multivariate logistic regression to assess the influence of different ApoE genotypes on the severity of CAD. As shown in Table 5, patients with ε3/ε4, ε4/ε4, ε3/ε3,ε2/ε3 and ε2/ε2 had no obvious differences in the occurrence of PCI ($P > 0.05$) . Patients with ε2/ε4 had lower occurrence of PCI than patients with other ApoE genotypes ($P < 0.05$) . Patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 had no obvious differences in the occurrence of multi-vessel lesion ($P > 0.05$) . Patients with ε2/ε4 and ε2/ε3 had lower occurrence of multi-vessel lesion than patients with ε3/ε4 and ε3/ε3 ($P < 0.05$) . Patients with ε3/ε4, ε4/ε4, ε3/ε3, ε2/ε4 and ε2/ε2 had no obvious differences in the occurrence of acute myocardial infarction (AMI) ($P > 0.05$) . Patients with ε2/ε3 had lower occurrence of AMI than patients with ε3/ε3 and ε3/ε4 ($P < 0.05$) .

Table 3
A multivariate Logistic regression model on the association of serum lipid with ApoE gene polymorphisms after adjustment for sex,age and the clinical characteristic factors.

Variables	Adjusted Odd Ratio (OR) (95 % CI), p Value		
	High triglyceride	High total cholesterol	High LDL-C
ε3/ε4 vs ε4/ε4	0.638(0.404–1.005), P = 0.052	0.716(0.384–1.333), P = 0.292	0.840(0.535–1.318), P = 0.448
ε3/ε3 vs ε4/ε4	0.542(0.348–0.845), P = 0.007*	0.586(0.321–1.072), P = 0.083	0.661(0.426–1.025), P = 0.064
ε2/ε4 vs ε4/ε4	0.723(0.402–1.298), P = 0.277	0.511(0.206–1.266), P = 0.147	0.453(0.243–0.845), P = 0.013[a]
ε2/ε3 vs ε4/ε4	0.693(0.437–1.098), P = 0.118	0.359(0.186–0.693), P = 0.002[a]	0.329(0.206–0.525), P = 0.000[a]
ε2/ε2 vs ε4/ε4	2.237(1.070–4.675), P = 0.032*	1.190(0.453–3.123), P = 0.724	0.747(0.359–1.555), P = 0.435
ε3/ε4 vs ε3/ε3	1.175(1.031–1.341), P = 0.016*	1.221(0.997–1.494), P = 0.053	1.271(1.115–1.450), P = 0.000[a]
ε2/ε4 vs ε3/ε3	1.332(0.901–1.970), P = 0.151	0.872(0.437–1.740), P = 0.697	0.686(0.437–1.077), P = 0.101
ε2/ε3 vs ε3/ε3	1.277(1.100–1.482), P = 0.001*	0.612(0.456–0.822), P = 0.001[a]	0.498(0.414–0.598), P = 0.000[a]
ε2/ε2 vs ε3/ε3	4.124(2.276–7.472), P = 0.000*	2.029(0.944–3.361), P = 0.070	1.130(0.624–2.046), P = 0.686
ε3/ε4 vs ε2/ε2	0.285(0.156–0.521), P = 0.000*	0.602(0.276–1.312), P = 0.201	1.125(0.616–2.053), P = 0.701
ε2/ε4 vs ε2/ε2	0.323(0.159–0.655), P = 0.002*	0.430(0.155–1.193), P = 0.105	0.607(0.289–1.272), P = 0.186
ε2/ε3 vs ε2/ε2	0.310(0.169–0.568), P = 0.000*	0.302(0.134–0.677), P = 0.004[a]	0.440(0.238–0.815), P = 0.009[a]
ε2/ε4 vs ε3/ε4	1.133(0.757–1.698), P = 0.544	0.714(0.352–1.448), P = 0.351	0.539(0.340–0.856), P = 0.009[a]
ε2/ε3 vs ε3/ε4	1.086(0.908–1.300), P = 0.367	0.502(0.361–0.698), P = 0.000[a]	0.391(0.318–0.482), P = 0.000[a]
ε2/ε3 vs ε2/ε4	0.958(0.636–1.444), P = 0.839	0.702(0.336–1.470), P = 0.348	0.726(0.449–1.172), P = 0.190

[a] Indicates $p < 0.05$. LDL-C: Low-density lipoprotein cholesterol.

Table 4
A multivariate Logistic regression model on the association of coronary artery disease with ApoE gene polymorphisms after adjustment for sex,age and cardiovascular risk factors.

Variables	Adjusted Odd Ratio (OR) (95 % CI)	*p*Value
ε3/ε4 vs ε4/ε4	0.825(0.512–1.327)	0.427
ε3/ε3 vs ε4/ε4	0.866(0.544–1.379)	0.545
ε2/ε4 vs ε4/ε4	0.504(0.275–0.925)	0.027[a]
ε2/ε3 vs ε4/ε4	0.627(0.387–1.016)	0.058
ε2/ε2 vs ε4/ε4	0.938 (0.434–2.023)	0.870
ε3/ε4 vs ε3/ε3	0.952(0.833–1.088)	0.470
ε2/ε4 vs ε3/ε3	0.582(0.391–0.868)	0.008[a]
ε2/ε3 vs ε3/ε3	0.724(0.621–0.844)	0.000[a]
ε2/ε2 vs ε3/ε3	1.083(0.582–2.012)	0.802
ε3/ε4 vs ε2/ε2	0.879 (0.469–1.650)	0.689
ε2/ε4 vs ε2/ε2	0.583(0.259–1.117)	0.096
ε2/ε3 vs ε2/ε2	0.669(0.357–1.253)	0.209
ε2/ε4 vs ε3/ε4	0.612(0.405–0.923)	0.019[a]
ε2/ε3 vs ε3/ε4	0.760(0.631–0.915)	0.004[a]
ε2/ε3 vs ε2/ε4	1.243 (0.818–1.888)	0.308

[a] Indicates $p < 0.05$.

Table 5
A multivariate Logistic regression model on the association of the severity of coronary artery disease (PCI, multivessel lesion and AMI) with ApoE gene polymorphisms after adjustment for sex,age and cardiovascular risk factors.

Variables	Adjusted Odd Ratio (OR) (95 % CI), p Value		
	PCI	multivessel lesion	AMI
ε3/ε4 vs ε4/ε4	0.762(0.478–1.214), P = 0.252	0.951(0.581–1.558), P = 0.843	0.626(0.346–1.133), P = 0.122
ε3/ε3 vs ε4/ε4	0.817(0.518–1.287), P = 0.383	0.921(0.568–1.492), P = 0.737	0.651(0.366–1.157), P = 0.144
ε2/ε4 vs ε4/ε4	0.463(0.249–0.859), P = 0.015[a]	0.539(0.277–1.050), P = 0.069	0.479(0.200–1.147), P = 0.098
ε2/ε3 vs ε4/ε4	0.724(0.451–1.163), P = 0.182	0.691(0.417–1.144), P = 0.151	0.496(0.267–0.920), P = 0.026[a]
ε2/ε2 vs ε4/ε4	1.206(0.577–2.521), P = 0.618	0.870(0.399–1.897), P = 0.726	0.911(0.334–2.483), P = 0.856
ε3/ε4 vs ε3/ε3	0.933(0.817–1.064), P = 0.298	1.033(0.900–1.186), P = 0.643	0.962(0.796–1.162), P = 0.688
ε2/ε4 vs ε3/ε3	0.566(0.369–0.869), P = 0.009[a]	0.585(0.366–0.936), P = 0.025[a]	0.736(0.377–1.436), P = 0.368
ε2/ε3 vs ε3/ε3	0.887(0.759–1.036), P = 0.131	0.750(0.633–0.890), P = 0.001[a]	0.762(0.591–0.982), P = 0.036[a]
ε2/ε2 vs ε3/ε3	1.477(0.821–2.657), P = 0.193	0.945(0.508–1.756), P = 0.857	1.400(0.609–3.215), P = 0.428
ε3/ε4 vs ε2/ε2	0.631(0.348–1.147), P = 0.131	1.094(0.582–2.054), P = 0.781	0.687(0.295–1.601), P = 0.385
ε2/ε4 vs ε2/ε2	0.384(0.187–0.788), P = 0.009[a]	0.620(0.287–1.341), P = 0.224	0.525(0.182–1.515), P = 0.234
ε2/ε3 vs ε2/ε2	0.601(0.331–1.091), P = 0.094	0.794(0.422–1.494), P = 0.475	0.544(0.232–1.279), P = 0.163
ε2/ε4 vs ε3/ε4	0.607(0.391–0.943), P = 0.026[a]	0.567(0.350–0.917), P = 0.021[a]	0.765(0.386–1.516), P = 0.442
ε2/ε3 vs ε3/ε4	0.951(0.789–1.147), P = 0.599	0.726(0.594–0.888), P = 0.002[a]	0.792(0.590–1.063), P = 0.120
ε2/ε3 vs ε2/ε4	1.566(1.002–2.448), P = 0.049[a]	1.281(0.785–2.093), P = 0.322	1.036(0.512–2.096), P = 0.922

[a] Indicates $p < 0.05$. PCI:Percutaneous coronary intervention; AMI: Acute myocardial infarction.

Table 6
A multivariate Logistic regression model on the association of premature coronary artery disease with ApoE gene polymorphisms after adjustment for age and cardiovascular risk factors.

Variables	Adjusted Odd Ratio (OR) (95 % CI)	*p*Value
ε3/ε4 vs ε4/ε4	0.734(0.373–1.444)	0.370
ε3/ε3 vs ε4/ε4	0.746(0.386–1.439)	0.382
ε2/ε4 vs ε4/ε4	0.526(0.214–1.290)	0.160
ε2/ε3 vs ε4/ε4	0.539(0.269–1.084)	0.083
ε2/ε2 vs ε4/ε4	2.228(0.651–7.626)	0.202
ε3/ε4 vs ε3/ε3	0.984(0.793–1.221)	0.883
ε2/ε4 vs ε3/ε3	0.705(0.376–1.321)	0.275
ε2/ε3 vs ε3/ε3	0.724(0.553–0.946)	0.018[a]
ε2/ε2 vs ε3/ε3	2.989(1.047–8.531)	0.041[a]
ε3/ε4 vs ε2/ε2	0.329 (0.114–0.954)	0.041[a]
ε2/ε4 vs ε2/ε2	0.236(0.070–0.793)	0.020[a]
ε2/ε3 vs ε2/ε2	0.242(0.083–0.704)	0.009[a]
ε2/ε4 vs ε3/ε4	0.717(0.375–1.371)	0.314
ε2/ε3 vs ε3/ε4	0.735(0.535–1.011)	0.058
ε2/ε3 vs ε2/ε4	1.419 (0.913–2.206)	0.120

[a] Indicates $p < 0.05$.

3.6. The influence of different ApoE genotypes on premature coronary heart disease

This study used a multivariate hierarchical logistic regression to assess the occurrence of different ApoE genotypes on PCAD. As shown in Table 6, patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε4 had no obvious differences in the occurrence of PCAD ($P > 0.05$) . Patients with ε2/ε3 had lower occurrence of PCAD than patients with ε3/ε3 and ε2/ε2 ($P < 0.05$) . Patients with ε3/ε4, ε4/ε4 and ε2/ε4 had lower occurrence of PCAD than patients with ε2/ε2 ($P < 0.05$) .

3.7. The influence of age on the correlation between different ApoE genotypes and CAD

This study used a multivariate hierarchical logistic regression to assess the influence of age on the correlation between different ApoE genotypes and CAD. This study divided the 7634 patients into four age groups (age <45, age at 45–59,age at 60–74, age ≥75). As shown in Table 7, patients with ε3/ε4, ε4/ε4, ε2/ε2, ε2/ε4 and ε3/ε3 had no obvious differences in the occurrence of CAD in age under 45 and age at 60–74 group ($P > 0.05$) . Patients with ε2/ε3 had lower occurrence of CAD than patients with ε4/ε4 and ε3/ε4 in age under 45 group ($P < 0.05$) . Patients with different ApoE genotypes had no obvious differences in the occurrence of CAD in age at 45–59 group ($P > 0.05$) . Patients with ε2/ε3 had lower occurrence of CAD than patients with ε3/ε4 and ε3/ε3 in age at 60–74 group ($P < 0.05$) .

Patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 had no obvious differences in the occurrence of CAD in age over 74 group ($P > 0.05$) . Patients with ε2/ε3 had lower occurrence of CAD than patients with ε3/ε3, while Patients with ε2/ε4 had lower occurrence of CAD than patients with ε3/ε3 and ε3/ε4 in age over 74 group ($P < 0.05$) .

4. Discussion

ApoE is a circulating glycoprotein, which palys an important role in lipid metabolism and promotes the removal of triglyceride-rich lipoprotein residues from the circulation to liver [18]. ε4, ε3 and ε2 are the major alleles of ApoE, the prevalence of ε4 and ε2 is relatively low, while ε3 is the most common subtype [19]. In this study, among the 7634 patients undergoing coronary angiography, ε3/ε3 accounted for 67.29 % of all genotypes, followed by the ε4/ε4 (1.14 %) , ε2/ε3 (12.38 %), ε3/ε4 (16.99 %), ε2/ε4 (1.51 %) and ε2/ε2 (0.71 %).

ApoE gene polymorphism is associated with many diseases, ApoE gene is a major genetic risk determinant of late-onset Alzheimer disease, with the APOE ε4 allele conferring an increased risk and the ApoE ε2 allele conferring a decreased risk, relative to the common ApoE ε3 allele [20]. In addition to Alzheimer disease, ApoE gene polymorphisms also play a role in other neurological diseases, such as Lewy body dementia [21], Parkinson disease [22], and frontotemporal dementia [23]. The activation of Sirtuin 1 confers protective effects on atherosclerosis involving vascular endothelial and smooth muscle cell senescence [24]. Compared to ApoE ε3 and ApoE ε2, sirtuin 1 showed a higher affinity to ApoE ε4 [25]. Sirtuin 1 levels were significantly reduced in the frontal cortex of ApoE4 mice, and Sirtuin 1 reduction hinder its protective role against the formation of plaques and tangles and diminish its anti-inflammatory actions. Therefore, Sirtuin 1 reduction play a role in ApoE4-associated memory impairments [26].

Coronary artery disease causes great physical and mental harm to patients worldwide. Both the environment and genes can influence the occurrence of CAD [27]. ApoE participates in the regulation of triglyceride and cholesterol metabolism, and influences the occurrence of CAD [28]. This study investigated the influence of different ApoE genotypes on CAD in patients who received coronary angiography. The results indicated that ε2/ε2 is associated with an increased risk of hypertriglyceridemia, while ε3/ε3 is associated with a decreased risk of hypertriglyceridemia. ε2/ε3 and ε2/ε4 are associated with a decreased risk of high total cholesterol and high

Table 7
To exclude the potentially confounding effects of age on the association of coronary artery disease with ApoE gene polymorphisms, multivariate logistic regression analysis stratified according to age was performed.

Variables	Adjusted Odd Ratio (OR) (95 % CI), p Value			
	< 45 years old	≥45 and ≤ 59 years old	≥60 and ≤ 74 years old	≥75 years old
ε3/ε4 vs ε4/ε4	0.334(0.057–1.952), P = 0.223	0.617(0.306–1.245), P = 0.177	1.404(0.670–2.940), P = 0.369	1.043(0.100–10.899), P = 0.972
ε3/ε3 vs ε4/ε4	0.233(0.042–1.284), P = 0.094	0.684(0.347–1.346), P = 0.272	1.413(0.684–2.917), P = 0.351	1.212(0.118–12.461), P = 0.872
ε2/ε4 vs ε4/ε4	0.357(0.042–3.059), P = 0.347	0.404(0.152–1.073), P = 0.069	0.790(0.312–2.000), P = 0.619	0.342(0.027–4.298), P = 0.406
ε2/ε3 vs ε4/ε4	0.096(0.014–0.658), P = 0.017*	0.517(0.252–1.062), P = 0.072	1.063(0.504–2.242), P = 0.872	0.757(0.072–7.935), P = 0.816
ε2/ε2 vs ε4/ε4	0.146(0.005–4.059), P = 0.256	1.092(0.318–3.748), P = 0.888	0.908(0.288–2.866), P = 0.869	3.021(0.130–70.197), P = 0.491
ε3/ε4 vs ε3/ε3	1.433(0.753–2.729), P = 0.274	0.902(0.708–1.149), P = 0.404	0.994(0.825–1.197), P = 0.947	0.861(0.591–1.253), P = 0.434
ε2/ε4 vs ε3/ε3	1.534(0.398–5.917), P = 0.534	0.590(0.287–1.214), P = 0.152	0.559(0.309–1.014), P = 0.055	0.282(0.102–0.784), P = 0.015[a]
ε2/ε3 vs ε3/ε3	0.414(0.158–1.083), P = 0.072	0.756(0.567–1.007), P = 0.056	0.753(0.607–0.933), P = 0.009[a]	0.624(0.427–0.914), P = 0.015[a]
ε2/ε2 vs ε3/ε3	0.625(0.035–11.315), P = 0.751	1.597(0.564–4.523), P = 0.378	0.643(0.260–1.588), P = 0.338	2.493(0.296–20.977), P = 0.401
ε3/ε4 vs ε2/ε2	2.292(0.122–43.080), P = 0.579	0.565(0.196–1.628), P = 0.290	1.546(0.618–3.871), P = 0.352	0.345(0.040–2.967), P = 0.333
ε2/ε4 vs ε2/ε2	2.453(0.105–57.512), P = 0.577	0.369(0.105–1.295), P = 0.120	0.870(0.298–2.545), P = 0.800	0.113(0.011–1.185), P = 0.069
ε2/ε3 vs ε2/ε2	0.661(0.033–13.164), P = 0.786	0.473(0.164–1.366), P = 0.166	1.171(0.469–2.924), P = 0.735	0.250(0.029–2.132), P = 0.205
ε2/ε4 vs ε3/ε4	1.070(0.254–4.507), P = 0.926	0.654(0.310–1.380), P = 0.265	0.563(0.305–1.037), P = 0.065	0.328(0.113–0.948), P = 0.040[a]
ε2/ε3 vs ε3/ε4	0.289(0.097–0.856), P = 0.025[a]	0.838(0.593–1.183), P = 0.314	0.757(0.584–0.982), P = 0.036[a]	0.725(0.447–1.176), P = 0.193
ε2/ε3 vs ε2/ε4	0.270(0.054–1.347), P = 0.110	1.281(0.599–2.740), P = 0.524	1.346(0.725–2.499), P = 0.347	2.214(0.768–6.379), P = 0.141

[a] Indicates $p < 0.05$.

LDL-C. Patients with different apolipoprotein E genotypes had no significant differences in the occurrence of hypertension, diabetes and obesity.

The influence of ApoE gene polymorphism on CAD is controversial, and the sample size of many studies is small. Some studies indicated that ε4 allele has increased the occurrence of CAD [29,30],but other studies have showed that ε4 allele does not increase the occurrence of CAD [31,32]. Therefore, this study investigated the influence of different ApoE genotypes on CAD in patients who received coronary angiography. As shown in Table 4, patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 had no obvious differences in the occurrence of CAD. Patients with ε2/ε3 had lower occurrence of CAD than patients with ε3/ε3 and ε3/ε4, while patients with ε2/ε4 had lower occurrence of CAD than patients with ε3/ε4, ε4/ε4 and ε3/ε3. The results suggest that ε2/ε4 and ε2/ε3 decrease the occurrence of CAD. Compare with ε3/ε3 , ε4 allele did not obviously increase the occurrence of CAD.

This study also evaluated the influence of different ApoE genotypes on the severity of CAD. As shown in Table 5, patients with ε3/ε4, ε4/ε4, ε3/ε3,ε2/ε3 and ε2/ε2 had no obvious differences in the occurrence of PCI. Patients with ε4/ε4, ε3/ε4, ε3/ε3 and ε2/ε2 had no obvious differences in the occurrence of multi-vessel lesion. Patients with ε3/ε4, ε4/ε4, ε3/ε3, ε2/ε4 and ε2/ε2 had no obvious differences in the occurrence of AMI. Patients with ε2/ε4 and ε2/ε3 had lower occurrence of multi-vessel lesion than patients with ε3/ε3 and ε3/ε4. Patients with ε2/ε4 had lower occurrence of PCI than patients with other ApoE genotypes, while patients with ε2/ε3 had lower occurrence of AMI than patients with ε3/ε3 and ε3/ε4. The results suggest that patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 had no obvious differences in the severity of CAD. ε2/ε4 and ε2/ε3 have decreased the severity of CAD.

Premature coronary artery disease (PCAD) is defined as CAD occurring in women <65 years and men <55 years of age and become an area of growing concern [33]. A previous meta-analysis indicated that ε2 allele increased the occurrence of PCAD in Asians while decreased the occurrence of PCAD in Caucasians [34]. Another study indicated that ε4 allele increased the occurrence of PCAD in Egyptian [35]. In this study, patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε4 had no obvious differences in the occurrence of PCAD. Patients with ε2/ε3 had lower occurrence of PCAD than patients with ε3/ε3 and ε2/ε2, while patients with ε4/ε4,ε3/ε4 and ε2/ε4 had lower occurrence of PCAD than patients with ε2/ε2. The results suggest that ε2/ε3 have decreased the risk of PCAD, while ε2/ε2 have increased the risk of PCAD.

This study further used multivariate logistic regression to assess the influence of age on the relationship between different ApoE genotypes and CAD. As shown in Table 7, ε2/ε3 has decreased risk of CAD in patients age under 45,age at 60–74 and age over 74, while ε2/ε4 has decreased risk of CAD in patients age over 74. The results further indicated that patients with ε3/ε4, ε4/ε4, ε3/ε3 and ε2/ε2 had no significant differences in the occurrence of CAD, ε2/ε4 and ε2/ε3 have decreased risk of CAD.

Comparisons with other studies and what the current work adds to the existing knowledge.

The results of this study have some differences from many previous studies. Many previous studies indicated that compared to isoform ε3 (ε3/ε3), isoform ε4 (ε4/ε4, ε3/ε4 and ε2/ε4) has increased risk of cardiovascular disease, while isoform ε2 (ε2/ε4, ε2/ε3 and ε2/ε2) has decreased risk of cardiovascular disease. However,in this study, patients with ε4/ε4, ε3/ε4, ε3/ε3 had no obvious differences in the severity and occurrence of CAD, while patients with ε2/ε4 had lower severity and occurrence of CAD than patients with ε3/ε3. Therefore, compared to the isoform ε3, the isoform ε4 (ε4/ε4, ε3/ε4 and ε2/ε4) did not increased the severity and occurrence of CAD. Patients with ε2/ε2 and ε3/ε3 had no obvious differences in the severity and occurrence of CAD,while patients with ε2/ε4 and ε2/ε3 had lower severity and occurrence of CAD than patients with ε3/ε3. Therefore, compared to the isoform ε3, the isoform ε2 has decreased risk of the severity and occurrence of CAD.

For future clinical application, this study provided evidences that patients with ε4/ε4 and ε3/ε4 had higher occurrence of high LDL-C than patients with ε2/ε4 and ε2/ε3, and thus patients with ε4/ε4 and ε3/ε4 had higher severity and occurrence of CAD than patients with ε2/ε3 and ε2/ε4. In order to reduce risk of CAD, patients with ε4/ε4 and ε3/ε4 should pay more attention to their serum lipid than patients with ε2/ε4 and ε2/ε3.

4.1. Study strengths and limitations

This study assess the influence of different ApoE genotypes on coronary artery disease in patients undergoing coronary angiography. Firstly, the sample size of many previous studies is small, their statistical results may be influenced by the sample size. In order to reduce the impact of sample size, this study included 7634 patients who were hospitalized due to coronary angiography. Secondly, many previous studies undetected the influence of different ApoE genotypes on CAD. This study assess the influence of different ApoE genotypes on the severity and occurrence of CAD, the occurrence of PCAD, and traditional cardiovascular risk factors.

This study has some limitations. Firstly, this was a retrospective study, It's hard to rule out the factors of activities and diet, which may cause certain bias. Secondly, this study is a single-center study, different ethnic population may have different results. Thirdly, this study did not include the prognosis of CAD after treatment in patients with different ApoE genotypes, and the effect of statin treatment on different ApoE genotypes.

5. Conclusions

Patients with ε3/ε4, ε4/ε4,ε3/ε3 and ε2/ε2 had no significant differences in the severity and occurrence of CAD. Compared to the isoform ε3 (ε3/ε3), isoform ε4 did not increased the severity and occurrence of CAD. Compared with ApoE other genotypes, ε2/ε3 and ε2/ε4 reduced the risk of high LDL-C and the severity and occurrence of CAD.

Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

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Ethics approval

This study was conducted in accordance with the Declaration of Helsinki, approved by the Ethical Committee of Daping Hospital. The requirement for informed consent was waived because it is a retrospective observational study and patient records and information were anonymized prior to analysis, and the Ethical Committee of Daping Hospital also provided the informed consent waive.

Consent for publication

Not applicable.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Azhi ShaMa: Writing – original draft, Supervision, Investigation, Data curation, Conceptualization. **Yingying Huang:** Supervision, Investigation, Data curation. **Chunlan Ma:** Supervision, Investigation, Data curation. **Chunmei Xu:** Supervision, Investigation, Data curation. **Jingyue Hu:** Writing – original draft, Supervision, Resources, Investigation, Data curation. **Zhuxin Li:** Supervision, Investigation, Data curation. **Chunyu Zeng:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

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None.

Abbreviations

PCAD	Premature coronary artery disease
AMI	Acute myocardial infarction
ApoE	Apolipoprotein E
CAD	Coronary artery disease
LDL-C	Low density lipoprotein cholesterol
HDL-C	High density lipoprotein cholesterol
PCI	Percutaneous coronary intervention

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