International Journal of General Medicine

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ORIGINAL RESEARCH

E2/E3 and E3/E4 Genotypes of the Apolipoprotein E are Associated with Higher Risk of Diabetes Mellitus in Patients with Hypertension

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Objective: Apolipoprotein E (APOE) plays an important role in the lipid metabolism. *APOE* polymorphisms have been implicated in susceptibility to diabetes mellitus (DM). However, the association between *APOE* polymorphisms and the risk of DM among the hypertensive patients remains unclear. Our study aimed to evaluate this relationship to provide clues for further developing DM in hypertensive patients.

Methods: The study included 808 hypertensive patients with DM and 1226 hypertensive patients without DM as controls. The *APOE* 388T>C (rs429358) and 526C>T (rs7412) polymorphisms were genotyped by polymerase chain reaction (PCR) - microarray. Differences in *APOE* genotypes between subjects and controls were compared. To analyze the relationship between *APOE* genotypes and DM risk, multiple logistic regression analysis was performed after adjusting for gender, age, smoking history, and drinking history.

Results: The *APOE* E2/E4, E3/E3 genotype and ε2, ε3 allele frequency had significant difference between DM patients and controls ($P<0.05$). The DM patients with ε4 allele had lower level in high-density lipoprotein cholesterol (HDL-C) and higher level in apolipoprotein B (ApoB) than those with ε2 allele. The results of logistic regression analysis indicated that the *APOE* genotype of E2/E3 with adjusted OR=1.350 (95% Cl=1.009–1.806, $P=0.043$) and E3/E4 with adjusted OR=1.325 (95% Cl=1.034–1699, $P=0.026$) may be independent risk factors for DM.

Conclusion: *APOE* E2/E3 and E3/E4 genotypes may be risk factors for developing diabetes mellitus in hypertensive patients.

Keywords: Apolipoprotein E, polymorphism, hypertension, diabetes mellitus

Introduction

As a chronic disease, hypertension (HTN) is very common in China, and its occurrence and development is a serious threat to human health.[1–3] It has long been recognized that hypertension is an important risk factor for cardiovascular disease and mortality, the cardiovascular diseases account for 30% of all deaths, and about 13.5% premature deaths and 6.0% disability-adjusted life years has been attributed to high blood pressure worldwide.[4] In China, the prevalence of HTN in adults almost doubled from 18% to 34% from 2002 to 2010.[5] Diabetes mellitus (DM) is also an important global public health problem with high morbidity and disability rates. The HTN and DM often co-exist in the same individual. Studies have shown that hypertensive patients are more susceptible to DM compared to normotensive subjects.[6,7] Both the two diseases are in common in terms of etiology, such as obesity, inflammation, oxidative stress, insulin resistance, and factors associated with increased microvascular and macrovascular damage.[8] When hypertensive patients combine with DM, it brings more challenges to the health status of hypertensive patients. Therefore, predicting whether hypertensive patients are at risk of diabetes may be more conducive to the treatment and control of the disease.[9]

Apolipoprotein E (ApoE) is one of the components of the plasma lipoproteins. It is the structural and functional component of very low-density lipoprotein cholesterol (VLDL-C), high-density lipoprotein cholesterol (HDL-C), which is also the ligand of the binding between lipoprotein and receptor that plays an important role in lipoprotein

Received: 14 September 2023
Accepted: 18 November 2023
Published: 24 November 2023

metabolism.[10] The occurrence of hypertension and DM are both associated with dyslipidemia, probably due to insulin resistance affecting the enzymes involved in lipid metabolism.[11] ApoE is a protein encoded by the *APOE* gene. The human *APOE* gene consists of 3597 nucleotides located on band 2 of region 13 (19q13.2) of human chromosome 19, which is a 34 kD lipid transport-associated protein with 4 exons and 3 introns.[12] There are two non-synonymous single-nucleotide polymorphisms (SNP) in the *APOE* gene, including rs7412 (C4075→T) and rs429358 (C3937→T). And the combination of the two SNPs results in three major alleles (ε2(388T-526T), ε3(388T-526C), and ε4(388C-526C)),[13] and form six different genotypes, including three homozygotes (E2/E2, E3/E3, E4/E4) and three heterozygotes (E2/E3, E2/E4, E3/E4).[14] Genotype E3/E3 accepted as "wild-type" is the most common isoform of APOE with a frequency of approximately 70–80%, and the other genotypes are deemed to be mutant types.

Studies have showed that *APOE* gene polymorphism was established to be related to hypertension and type 2 Diabetes Mellitus (T2DM).[15,16] *APOE* ε4 allele and the E3/E4, E4/E4 genotypes are associated with the increased risk of hypertension, while ε2 allele and the E2/E2, E2/E3 genotypes are not associated with the risk of hypertension.[17,18] Furthermore, *APOE* allele ε4 is associated with the increased risk for the development of T2DM, while allele ε2 is not associated with T2DM.[19,20] However, the relationship between the *APOE* gene polymorphisms and the risk of developing DM in HTN patients remains uncertain. In the current study, we intended to explore the association between *APOE* gene polymorphisms and the risk of DM in HTN patients.

Materials and Methods

Study Participants

This study was a hospital-based, case-control study of *APOE* gene polymorphisms in hypertensive patients. A total number of 2034 patients with hypertension were recruited from August 2016 to December 2020. There were 808 patients with hypertension and DM were incorporated in the case group, while 1226 HTN patients without DM were set as a control group. Inclusive criteria of hypertensive patients were the following: (1) a mean systolic blood pressure >140 mmHg and/or a mean diastolic blood pressure >90 mmHg,[21] (2) Age ≥18 years old.

Data Collection

Demographic data including gender, age, history of smoking, and history of drinking. Serum lipid levels of the samples were evaluated by an Olympus AU5400 system (Olympus Corporation, Tokyo, Japan). Venous blood was collected on an empty stomach at early morning, and serum lipid levels were detected, including triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), Apolipoprotein A1 (Apo-A1), and Apolipoprotein B (ApoB). T2DM 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.[22]

DNA Extraction and Genotyping

A 2 mL venous blood sample was collected from each participant into an ethylene diamine tetraacetic acid (EDTA) sample tube. Genomic DNA was extracted from whole blood using a Blood DNA Isolation Kit (Qiagen GmbH, Germany). The quality and concentration of the DNA were assessed using a Nano-Drop 2000™ spectrophotometer (ThermoFisher Scientific, Waltham, MA, USA). Genotyping of the *APOE* gene single nucleotide polymorphisms (including rs429358 and rs7412) were amplified by polymerase chain reaction (PCR) - microarray method (Sinochips Bioscience Co., Ltd., Zhuhai, Guangdong, China). The PCR was performed as the following program: 2 minutes at 50 °C, 15 minutes at 95°C for initial denaturation, and 45 thermal cycles (94°C for 30s and 65°C for 45s). The PCR products were subsequently added to the gene chip after PCR amplification, and hybridized with wild-type or mutant probes fixed on the chip. The genotypes of the samples were determined by the hybridization reaction.

Statistical Analysis

All statistical analysis were performed using SPSS statistical software version 21.0 (IBM Inc., USA). Continuous variables were expressed as means ± standard deviations and were compared using either Student's *t*-test or the

Mann–Whitney *U*-test. Genotype composition ratios and allele frequencies between groups were analyzed with the *Chi*-square test. Hardy-Weinberg equilibrium in the DM group and controls was evaluated by *Chi*-square test. Logistic regression analysis was applied to examine the relationship between *APOE* gene polymorphisms and DM. $P<0.05$ was considered to represent statistical significance.

Results

Characteristics of Subjects

A total of 2034 hypertensive subjects were included in this study, consisting of 808 DM patients and 1226 unaffected controls. The case group consisted of 542 (67.1%) male and 266 (32.9%) female patients, while the control group had 805 (65.7%) male and 421 (34.3%) female patients. There were 185 (22.9%) cases with <60 years old and 623 (77.1%) cases with ≥60 years old in DM patients; 300 (24.5%) cases with <60 years old and 926 (75.5%) cases with ≥60 years old in controls. The TG ($P<0.001$), TC ($P<0.001$), LDL-C ($P=0.002$), and Apo-B ($P<0.001$) levels in the DM subjects were higher than that in controls, while the HDL-C ($P<0.001$) and Apo-A1 ($P=0.001$) levels in the DM subjects were lower than that in controls. There were not statistically significant differences in the percentage of subjects with a history of smoking ($P=0.918$), and alcoholism ($P=0.079$) (Table 1).

Distribution of the *APOE* Genotypes and Alleles Between the DM and Control Groups

The allelic distribution of the *APOE* gene was tested for Hardy-Weinberg equilibrium using the chi-square test, and the *APOE* genotypes in the DM group ($\chi^2=5.790$, $P=0.215$) and control group ($\chi^2=4.090$, $P=0.394$) confirmed to the Hardy-Weinberg equilibrium, respectively. Compared to the control group, the frequency of the E2/E4 genotype was higher in the DM group (2.1% vs 1.0%, $P=0.036$), and the frequency of the E3/E3 genotype was lower (67.3% vs 73.7%, $P=0.002$). The frequency of the ε2 allele was higher (8.0% vs 5.9%, $P=0.007$) and ε3 allele was lower (81.9% vs 85.5%, $P=0.002$) in the DM than that in the control group (Table 2).

Characteristics of DM Patients Stratified by *APOE* Genotypes and *APOE* Alleles

Subjects with the E2/E2 genotype (n = 15, 8 patients and 7 controls), the E2/E4 genotype (n = 29, 17 patients and 12 controls) and E4/E4 genotype (n = 17, 4 patients and 13 controls) were excluded from the analysis of the relationship between *APOE* alleles and lipid levels due to the smaller number of cases. Clinical and laboratory variables were compared among DM

Table 1 Clinical Characteristics of DM Patients and Control Participants

	Total (n=2034)	DM Patients (n=808)	Controls (n=1226)	*P* values
Age, years				
<60, n(%)	485(23.8)	185(22.9)	300(24.5)	0.426
≥60, n(%)	1549(76.2)	623(77.1)	926(75.5)	
Gender				
Male, n(%)	1347(66.2)	542(67.1)	805(65.7)	0.533
Female, n(%)	687(33.8)	266(32.9)	421(34.3)	
History of smoking, n(%)	534(26.3)	211(26.1)	323(26.3)	0.918
History of alcoholism, n(%)	79(3.9)	39(4.8)	40(3.3)	0.079
TG, mmHg	1.85±1.70	2.20±2.03	1.63±1.40	<0.001
TC, mmol/L	4.86±1.22	4.99±1.42	4.77±1.07	<0.001
HDL-C, mmol/L	1.26±0.37	1.22±0.37	1.29±0.37	<0.001
LDL-C, mmol/L	2.70±0.84	2.78±1.00	2.65±0.7	0.002
Apo-A1, g/L	1.12±0.31	1.09±0.30	1.13±0.32	0.001
Apo-B, g/L	0.85±0.25	0.89±0.30	0.82±0.21	<0.001

Note: Values for age expressed as mean±SD.
Abbreviations: TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B.

Table 2 Distribution Frequencies of *APOE* Genotype and Allele in DM Patients and Controls

Variable	Genotype/ Allele	DM Patients (n=808)	Controls (n=1226)	χ^2	*P* values
APOE genotype					
	E2/E2	8(1.0%)	7(0.6%)	1.169	0.280
	E2/E3	97(12.0%)	118(9.6%)	2.919	0.088
	E2/E4	17(2.1%)	12(1.0%)	4.387	0.036
	E3/E3	544(67.3%)	903(73.7%)	9.497	0.002
	E3/E4	138(17.1%)	173(14.1%)	3.313	0.069
	E4/E4	4(0.5%)	13(1.1%)	1.878	0.171
APOE allele					
	ε2	130(8.0%)	144(5.9%)	7.314	0.007
	ε3	1323(81.9%)	2097(85.5%)	9.707	0.002
	ε4	163(10.1%)	211(8.6%)	2.561	0.110
	HWE (χ^2, *P*)	χ^2=5.790, *P*=0.215	χ^2=4.090, *P*=0.394		

Abbreviation: HWE, Hardy Weinberg Equilibrium.

patients carried different *APOE* genotypes and alleles. The DM patients with E3/E4 genotype had higher level in TG (2.49 ±2.56 mmol/L vs 2.03±1.56 mmol/L, and 2.10±1.89 mmol/L) ($P<0.05$) and Apo-B (0.95±0.34 g/L vs 0.84±0.26 g/L, and 0.88 ±0.29 g/L) ($P<0.05$), while had lower level in HDL-C (1.14±0.41 mmol/L vs 1.25±0.39 mmol/L, and 1.23±0.35 mmol/L) ($P<0.05$) than those with E2/E3 and E3/E3 genotype. Furthermore, compared with patients carried E3/E3 or E3/E4, the patients carried E2/E3 showed lower level in LDL-C (2.61±0.87 mmol/L vs 2.78±1.00 mmol/L, and 2.89±1.09 mmol/L) ($P<0.05$). The level of Apo-A1 in patients carried E3/E4 genotype was lower than that in E3/E3 genotype (1.03±0.31 g/L vs 1.10±0.29 g/L) ($P<0.05$). The clinical characteristics were compared among DM patients carried ε2, ε3 and ε4 allele. The DM patients with ε4 allele had lower level in HDL-C (1.14±0.41 mmol/L vs 1.26±0.38 mmol/L) while had higher level in ApoB (0.93±0.33 g/L vs 0.84±0.28 g/L) (all $P<0.05$) than those with ε2 allele. There were no statistically significant differences in the percentage of gender, history of smoking, history of alcoholism, and age, the level of TC and LDL-C among DM patients carried E2/E3, E3/E3 and E3/E4 genotypes, as well as ε2, ε3 and ε4 alleles, respectively (Table 3).

Table 3 Clinical Characteristics of Subjects Stratified by *APOE* Genotypes and Ɛ2, Ɛ3, Ɛ4 Alleles in DM Patients

Clinical Characteristics	*APOE* Genotypes				*APOE* Alleles			
	E2/E3 (n=97)	E3/E3 (n=544)	E3/E4 (n=138)	*P* values	ε2 (n=122)[a]	ε3 (n=779)[b]	ε4 (n=159)[c]	*P* values
Age, years								
<60, n(%)	19(19.6)	130(23.9)	31(22.5)	0.545	22(18.0)	180(23.1)	35(22.0)	0.455
≥60, n(%)	78(80.4)	414(76.1)	107(77.5)		100(82.0)	599(76.9)	124(78.0)	
Gender								
Male, n(%)	62(63.9)	366(67.3)	93(67.4)	0.874	80(65.6)	521(66.9)	107(67.3)	0.950
Female, n(%)	35(36.1)	178(32.7)	45(32.6)		42(34.4)	258(33.1)	52(32.7)	
History of smoking, n(%)	24(24.7)	150(27.6)	33(23.9)	0.160	27(22.1)	207(26.6)	34(21.4)	0.272
History of alcoholism, n(%)	5(5.2)	28(5.1)	6(4.3)	0.985	5(4.1)	39(5.0)	6(3.8)	0.754
TG, mmol/L	2.03±1.56	2.10±1.89	2.49±2.56*	0.003	2.14±1.69	2.17±1.99	2.59±2.64	0.058
TC, mmol/L	4.83±1.37	5.00±1.39	5.08±1.57	0.681	4.87±1.37	4.99±1.42	5.04±1.50	0.602
HDL-C, mmol/L	1.25±0.39	1.23±0.35	1.14±0.41#*	0.041	1.26±0.38	1.22±0.37	1.14±0.41#	0.026
LDL-C, mmol/L	2.61±0.87	2.78±1.00	2.89±1.10	0.221	2.61±0.87	2.78±1.00	2.85±1.05	0.110
Apo-A1, g/L	1.09±0.29	1.10±0.29	1.03±0.31*	0.021	1.10±0.31	1.09±0.29	1.03±0.31	0.090
Apo-B, g/L	0.84±0.26	0.88±0.29	0.95±0.34#*	0.031	0.84±0.28	0.88±0.30	0.93±0.33#	0.047

Notes: The patients with extremely rare genotypes including E2/E2, E2/E4, E4/E4 were described but excluded from the statistical analysis. LSD and SNK test were applied to analyze the differences between each pair of groups. [a]E2/E2 plus E2/E3 plus E2/E4. [b]E2/E3 plus E3/E3 plus E3/E4. [c]E2/E4 plus E3/E4 plus E4/E4. #Compared with E2/E3, or compared with ε2, $P<0.05$; *Compared with E3/E3, or compared with ε3, $P<0.05$.

Table 4 Multivariate Logistic Regression of Variables Related to DM in Hypertensive Patients

Variables	Genotypes	Univariate OR (95% CI)	*P* values	Multivariate OR (95% CI)	*P* values
Gender (Male/Female)		1.076(0.890–1.301)	0.447	1.082(0.878–1.335)	0.459
Age (≥60/<60)		1.071(0.868–1.323)	0.522	1.050(0.847–1.301)	0.656
Smokers (Yes/No)		1.021(0.833–1.250)	0.843	0.950(0.756–1.194)	0.660
Alcoholism (Yes/No)		1.562(0.993–2.458)	0.054	1.570(0.984–2.504)	0.058
APOE genotypes					
	E3/E3	1.000(reference)	–	1.000(reference)	–
	E2/E2	1.897(0.684–5.261)	0.219	1.930(0.695–5.357)	0.207
	E2/E3	1.365(1.022–1.822)	0.035	1.350(1.009–1.806)	0.043
	E3/E4	1.324(1.034–1.696)	0.026	1.325(1.034–1.699)	0.026
	E4/E4	0.511(0.166–1.574)	0.242	0.529(0.171–1.631)	0.268

Association of *APOE* Gene Polymorphisms with DM in Hypertensive Patients

Logistic regression analysis was used to evaluate independent predictors of DM in hypertensive patients. Univariate regression analysis was performed to obtain the unadjusted odds ratio (OR), and multiple logistic regression analysis was performed to obtain the adjusted OR. Subjects with the E2/E4 genotype (n=29) were excluded from the analysis of the relationship between *APOE* genotypes and characteristics of all patients because of the opposite effects of the ε2 and ε4 alleles in lipid metabolism.[15,23] Relative analysis was used to evaluate the association between the *APOE* genotypes and potential risk factors for DM (Table 4). The *APOE* genotype of E2/E3 with adjusted OR=1.350 (95% Cl=1.009–1.806, *P*=0.043) and E3/E4 with adjusted OR=1.325 (95% Cl=1.034–1.699, *P*=0.026) were independent risk factors for DM. However, the other *APOE* genotypes were not found to be an independent risk factor for DM in hypertensive patients.

Discussion

Hypertension and DM share common risk factors and usually co-occur.[24] Hypertension is common in patients with DM, and DM is more common in patients with hypertension than in general population.[24,25] Studies showed that DM was almost 1.5–2.5 times as likely to develop in patients with hypertension as in those with normal blood pressure.[26–28] Lipid levels have been linked to the risk of hypertension and DM, and dyslipidemia is a significant risk factor for hypertension and DM.[29,30] ApoE is involved in lipid metabolism, so that the *APOE* gene polymorphisms are associated with DM and HTN. In this study, we examined the relationship between *APOE* gene polymorphisms and DM in patients with hypertension.

In the current study, we observed that the level of TG, TC, LDL-C and Apo-B were higher in the DM group than that in the control group. Research has found that one of the main phenotypes of DM patients is dyslipidemia, especially hypertriglyceridemia and low HDL-C level.[31] Apo-A1 and ApoB are two major apoproteins, Apo-A1 is the major lipoprotein associated with HDL-C, and ApoB is associated with LDL-C. Studies have shown that Apo-A1 was negatively correlated with DM and hypertension,[32] while ApoB was positively correlated with DM and hypertension.[33,34] In addition, the DM patients with ε4 allele had lower level in HDL-C than those with ε2 allele. A study suggested that *APOE* polymorphism is highly correlated with lipid levels in Korean population.[35] Liu et al showed that LDL-C level was associated with DM in hypertensive patients.[36] In T2DM patients, serum lipid levels in ε4 group were significantly higher than those in ε3 and ε2 groups.[16] In T2DM patients, there are significant differences in plasma LDL-C levels between ApoE subtypes.[37] Chen et al showed that the highest diastolic blood pressure (DBP) and longest hypertension durations in hypertensive patients were independent risk factors for T2DM.[28] Among hypertensive patients, a higher level of triglyceride glucose (TyG) index (triglycerides (mg/dl)×fasting blood glucose (mg/dl)/2) was associated with an elevated risk of T2DM.[27]

In this study, we also found that the *APOE* E2/E3 and E3/E4 genotypes were independent risk factor for DM in hypertensive patients. Several previous studies have reported that *APOE* polymorphisms have been linked to impaired glucose metabolism and a high risk of DM and hypertension. Zeng et al found that *APOE* ε2 and ε4 alleles have

specifically been linked to developing diabetes or impaired glucose tolerance.[16] The *APOE* ε2 allele may be a protective factor while the *APOE* ε4 allele may be risk factors for hypertension.[19] The *APOE* ε4 allele may be a risk factor for T2DM.[38] Among a Han Chinese population in central China, the *APOE* E3/E4 genotype is associated with an increased risk of T2DM.[16] Our study did not conflict with the results of previous studies, where hypertensive patients carrying the E2/E3 or E3/E4 genotype had a 1.3-fold higher risk of developing DM than the controls. Other studies, on the other hand, have come to different conclusions. Srirojnopkun et al found that *APOE* polymorphisms might not be the genetic risk factors for T2DM in Southern Thai population.[39] Studies have shown that ε4 carriers are less likely to develop T2DM.[40,41] Santos-Ferreira et al showed that the incidence of T2DM in *APOE* ε2 carriers is approximately tripled.[42]

Regarding the mechanism of ApoE in the occurrence of diabetes in hypertensive people, on the one hand, chronic inflammation exists in hypertension, and subclinical inflammation and insulin resistance exist in DM patients.[43,44] Studies have shown that $ApoE^{-/-}$ mice can produce severe leukocytes and mononucleosis, in $ApoE^{-/-}$ mice, hematopoietic stem cells (HSC) and their precursors lack an important cholesterol efflux mechanism, and their accumulated cholesterol leads to the expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-3 (IL-3) receptor on the plasma membrane.[45,46] On the other hand, ApoE may also be related to insulin secretion. In animal experiments, ApoE4 mice showed impaired glucose and insulin tolerance, reduced insulin secretion, and decreased cognitive and sensorimotor characteristics compared to ApoE3 mice, and these changes were associated with central nervous system processes.[47] Dyslipidemia is considered to be a risk factor for diabetes,[48] so the regulatory effects of ApoE expressed by different *APOE* genotypes on lipid metabolism are different, which is related to the pathogenesis of diabetes. The mechanism of the relationship between ApoE subtypes and DM risk is unclear and needs more in-depth research to reveal.

This study found that *APOE* E2/E3 and E3/E4 genotypes may be risk factors for developing diabetes in hypertensive patients. This study suggests that hypertensive patients with *APOE* E2/E3 and E3/E4 genotypes need to be monitored for diabetes risk. However, there are several limitations that should be pointed out as follows. First, this case-control study was hospital-based, therefore the selection bias is inevitable. Second, this study did not analyze the relationship between blood glucose levels and ApoE subtypes in diabetic patients. Third, in addition to the indicators included in this study, other patients' lifestyle habits and environmental factors that may be related to the development of diabetes were not included in the analysis. In the future, larger sample sizes and more genetic factors will need to be included to investigate this relationship.

Conclusion

In summary, the *APOE* E2/E3 and E3/E4 genotypes may be risk factors for developing DM in hypertensive patients. It provides evidence that *APOE* gene polymorphisms are linked to the risk of DM in hypertensive patients.

Data Sharing Statement

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

Ethics Approval

Since this study was a retrospective study and it was impossible for all subjects to return to the hospital to sign informed consent, the research procedures and objectives were informed in verbal form through telephone communication, and the consent of all subjects was obtained, which approved by the Ethics Committee of the Meizhou People's Hospital. The study was performed under the guidance of the Declaration of Helsinki and approved by the Ethics Committee of Medicine, Meizhou People's Hospital (Clearance No.: 2021-A-60).

Acknowledgments

The authors would like to thank their colleagues who were not listed in the authorship of the Department of Laboratory Medicine, Meizhou People's Hospital, for their helpful comments on the manuscript.

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.

Funding

This study was supported by the Science and Technology Program of Meizhou (Grant No.: 2019B0202001).

Disclosure

The authors declare that they have no competing interests in this work.

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