The role of *APOE* gene polymorphisms in lung adenocarcinoma susceptibility and lipid profile

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Background: APOE gene polym orphisms have been linked to Alzheimer's disease and coronary heart diseases. However, their relationship with lung adenocarcinoma (LUAD) remains uncertain.

Methods: This study analyzed a cohort of 600 individuals comprising 200 LUAD patients in the lung cancer group and 400 healthy individuals as controls. APOE gene variants were identified through Sanger sequencing. Statistical analyses were conducted to assess intergroup differences, and comparisons of lipid profiles were performed across individuals carrying different APOE alleles.

Results: The *APOE* ε2 allele had been significantly more frequently occurring in the LUAD group than in the control group (15.5% vs. 7%, P <0.001). *APOE* ε2/ε2 and ε2/ε3 genotypes increased susceptibility to LUAD by 3.78-fold and 3.22-fold. The APOE ε2/ε3 genotype increased the risk of early-stage LUAD by 2.36-fold and advanced-stage LUAD by 4.05-fold. Individuals with the *APOE* ε2/ε2 genotype had a 3.22-fold higher susceptibility to moderately differentiated and a 6.8-fold higher susceptibility to poorly differentiated LUAD. Patients with the ε2 allele in LUAD exhibited disrupted lipid metabolism, characterized by reduced HDL, TC, and FFA levels, along with increased ApoB, particularly in advanced and poorly differentiated cancer stages.

Conclusion: Individuals carrying the ε2 allele have an increased susceptibility to developing LUAD, accompanied by disrupted lipid metabolism. Additionally, the APOE ε2/ε2 and ε2/ε3 genotypes are associated with an increased risk of developing advanced and poorly differentiated LUAD.

1 Introduction

The apolipoprotein E (APOE) gene, located on chromosome 19q13.32, encodes the 34 KDa glycoprotein known as *APOE*, which is essential for the transportation and metabolism of lipoproteins (1). Differences at two mutation sites (rs429358 and rs7412) in the *APOE* gene give rise to three distinct alleles: ε2 (*APOE*2), ε3 (*APOE*3), and ε4 (*APOE*4) allele. The *APOE*3 is the most common allele, with *APOE* 2 and *APOE*4 are relatively less frequent variants. The alleles account for six genotypes: *APOE* ε2/ε2, ε3/ε3, ε4/ε4, ε2/ε3,ε2/ε4 andε3/ε4) (2).The *APOE* gene polymorphism is closely associated with Alzheimer's disease (AD), the *APOE* ε2 allele is considered the most potent protective factor against AD (3, 4). *APOE* alleles are involved in the development and progression of various malignancies (5, 6), such as hepatocellular carcinoma (7), testicular cancer (8), pancreatic cancer (9), melanoma (10, 11), colorectal cancer (12) and breast cancers (13, 14). However, research on their role in lung adenocarcinoma (LUAD) remains limited.

The varying effects of different *APOE* genotypes on lipid metabolism highlight their potential impact on cardiovascular and cancer risks (15, 16).Studies show that individuals with the *APOE* ε2 allele demonstrate diminished receptor-binding activity, which results in lower total cholesterol (TC) levels and higher triglyceride (TG) concentrations. In contrast, *APOE* ε4 carriers have higher plasma TC levels compared to those with the common *APOE* ε3 carriers. According to a recent meta-analysis, those with the *APOE* ε4 allele have a 42% higher risk of developing coronary heart disease (CHD) than people with the common *APOE* ε3 allele (2). This association may be due to the altered expression levels of low-density lipoprotein cholesterol (LDL) and high-density lipoprotein (HDL), resulting from the efficient binding of the *APOE* ε2 to LDL and HDL receptor particles (17, 18). This observation underscores the potential influence of phenotypic variations in *APOE* on cancer risk through changes in serum lipoprotein levels (19). Nevertheless, the specific role of *APOE* genotypes in LUAD remains unclear.

2 Materials and methods

2.1 Study population

The Qingdao University Affiliated Hospital's Institutional Review Boards (IRBs) approved the study. Whole blood sample were selected from our research group's repository collected from respiratory and critical care medicine inpatients between June 2018 and June 2022 at the hospitals. Serum was extracted from anticoagulated blood samples derived from the health examination department and preserved for further study at -80°C. The study included 400 healthy control participants and 200 LUAD patients. All participants' clinical and demographic data were recorded, along with their alcohol and tobacco use, fatty liver disease, and lipid profiles. The criteria for hypertension included systolic/diastolic blood pressure readings of 140/90 mmHg or higher or the continuous treatment with antihypertensive medications. CHD is characterized by coronary artery atherosclerosis, leading to luminal stenosis or functional changes in coronary arteries, resulting in symptoms such as myocardial ischemia and hypoxia or the management of coronary heart disease. Diabetes is diagnosed based on fasting plasma glucose levels ≥7.0 mmol/L, a random plasma glucose level ≥11.1 mmol/L, or the administration of antidiabetic therapies. Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of liver fat in individuals who consume little to no alcohol and do not have other identifiable causes of hepatic fat accumulation (20).

2.2 Participant grouping

Clinical information and histological analysis, including the outcomes of biopsies or surgical resections and TNM staging in accordance with the most recent edition of the American Joint Committee on Cancer (AJCC) guidelines, were adopted to diagnose LUAD (21). The control group participants were selected to match the age range of patients with LUAD, with a deviation of ±2 years. Individuals in the control group had no relevant medical conditions pertinent to this study, no history of tumors in any organ, and no acute or chronic diseases.

2.3 DNA extraction and APOE genotyping

Blood samples were treated with the Blood Genomic DNA Extraction Kit (Catalog number DP348-03, Tiangen, China) to extract deoxyribonucleic acid (DNA), a spectrophotometer was used to measure the purity and concentration of the DNA (Thermo Fisher Scientific, United States). Standard PCR reactions employed the 2×Taq PCR Master Mix (dye-free) reagent kit. The primer sequences for *APOE* were the forward primer (5′- GCTTGGCACGGCTGTCCAAGGA-3) and reverse primer (5′- ATTCGCCCCGGCCTGGTACAC -3'). Following PCR amplification, the PCR products were subjected to 2% agarose gel electrophoresis to verify successful amplification. The gel was stained with ethidium bromide, and the bands were visualized under UV light to confirm the presence and expected size of the amplicons. After confirming the correct PCR products by agarose gel electrophoresis. The amplification products were transferred to Sangon Biotech (Shanghai, China) for Sanger sequencing. SnapGene software (Insightful Science, United States) was used to visualize the sequencing data of two mutation sites (rs7412 and rs 429358) to identify the *APOE* genotype.

2.4 Statistical analysis

For statistical analysis, we reported the data as percentages and frequency distributions using SPSS version 27.0 (IBM Corp, Armonk, NY, USA).The chi-square test or Fisher's exact test was employed for comparing the frequency distribution of APOE genotypes and alleles in the LUAD and healthy control groups, Mann-Whitney U test was adopted for continuous or ordinal data that did not satisfy the normality assumption. To assess the relationship between genotypes and the risk of developing LUAD, binary logistic regression analysis was performed. In this analysis, odds ratios (ORs) were calculated to quantify the association

between APOE genotypes and the likelihood of developing LUAD. ORs provide an intuitive measure of the strength of the relationship between predictor variables (genotypes) and the outcome (LUAD risk). This is particularly useful for understanding the magnitude of risk associated with different genotypes. For normally distributed continuous data, an independent samples t-test was performed to analyze further group differences in the *APOE* gene subtypes. P-value<0.05 was recognized as predictive of statistical significance.

3 Results

3.1 Analysis of baseline characteristics in the study groups

There were 600 participants in the whole, divided between both the LUAD group (n = 200) and the control group (n = 400). The baseline characteristics of the two groups, including an average age over 55 years, showed no statistically significant differences in gender, alcohol use, smoking history, hypertension, or diabetes (P > 0.05) (Table 1).

3.2 Analysis of APOE alleles and genotypes frequencies in LUAD and control group

The statistical analysis revealed that the LUAD group had a significantly higher frequency of ε2 allele expression than the

control group (15.5%vs7%, P< 0.001), conversely, the ε4 allele's expression frequency was significantly lower than that of the control group (2.7% vs 11.1%, P < 0.001). The frequency of ε3 allele expression did not differ statistically significantly between the LUAD and control groups (P > 0.05) (Table 2). The binary logistic regression analysis revealed strong correlations between *APOE* genotypes and the incidence of LUAD. Specifically, *APOE* ε2/ε2 and ε2/ε3 genotypes were significantly associated with a 3.78-fold (95% CI: 1.64–8.71, P<0.001) and 3.22-fold (95% CI: 1.69–6.11, P=0.02) increase in the odds of developing LUAD, respectively. Conversely, the *APOE* ε3/ε4 genotype was linked to a 0.14-fold reduction in the risk of developing LUAD (95% CI: 0.05–0.4, P<0.001). The proportion of individuals of the *APOE* ε3/ε3 and ε2/ε4 genotypes was similar between the two groups (P>0.05) (Table 3).

3.3 Analysis of APOE alleles and genotypes frequencies between the control and LUAD subgroups with different stages

LUAD patients were divided into early and late stages in order to investigate the relationship among *APOE* genotypes and individual LUAD stages in comparison to the control group. Both the early-stage and advanced-stage LUAD groups had a significantly higher frequency of the ε2 allele compared to the control group (11.6% vs. 7% and 21.2% vs. 7%, P=0.003 and P<0.01, respectively). However, the frequency of the ε4 allele was significantly lower in both LUAD stages compared to the control group (3.7% vs. 11.1% and 2.1% vs. 11.1%, P<0.01). The frequency of the ε3 allele did not differ statistically significantly between the control group and each of the other LUAD subgroups (P>0.05). Additionally, the percentage of individuals of the *APOE* ε2/ε3 genotype was higher in both LUAD subgroups as compared to control group, whereas the proportion of the *APOE* ε3/ε4 genotype was significantly lower (P<0.05) (Table 4).

TABLE 1   Characteristics of the study population.

Characteristics	Group		P-value
	LUAD	Control	
Age, median (IQR)	57.5(23)	58(30)	0.933
Male/female (%)	105/95 (52.5%/47.5%)	237/163 (59.3%/40.8%)	0.137
Smoking	89/44.5%)	180/45%)	0.931
Drinking (%)	35(17.5%)	98(24.5%)	0.06
Hypertension (%)	63(31.5%)	124(31%)	0.926
Diabetes (%)	24(12%)	38(9.5%)	0.393
Fatty liver (%)	51(25.5%)	95(23.8%)	0.687
TC (mmol/L)	1.68(1.77)	2.67(3.5)	**<0.001**
TG (mmol/L)	2.14(0.96)	1.86(0.93)	**0.024**
LDL (mmol/L)	2.84(1.19)	2.93(1.11)	**0.030**
HDL (mmol/L)	1.71(0.75)	2.33(2.89)	**<0.001**
APOA1 (mmol/L)	1.25(0.92)	1.73(0.69)	**<0.001**
APOB (mmol/L)	1.25(0.92)	1.93(0.4)	**<0.001**
Lp(a)(mmol/L)	177(113.3)	402.5(206)	**<0.001**
FFA (mmol/L)	0.35(0.39)	0.52(0.39)	**<0.001**

IQR, Interquartile Range; LUAD, lung adenocarcinoma; TC, Total Cholesterol; TG, Triglycerides; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; APOA1, Apolipoprotein A1; APOB, Apolipoprotein B; Lp(a), Lipoprotein (a); FFA, Free Fatty Acids. Bold P-values indicate statistically significant differences (P < 0.05).

TABLE 2   Comparison of *ApoE* alleles and genotypes frequencies in LUAD and control group.

Allele, Genotype	LUAD (N = 200)	Control (N =400)	*p*-Value
ε2 allele, n (%)	62(15.5%)	56(7%)	**0.00**
ε3 allele, n (%)	327(81.8%)	655(81.9%)	0.96
ε4 allele, n (%)	11(2.7%)	89(11.1%)	**0.00**
ApoE ε2ε2	16(8.0%)	9(2.3%)	**0.00**
ApoE ε2ε3	25(12.5%)	17(4.3%)	**0.00**
ApoE ε3ε3	149(74.5%)	294(73.5%)	0.79
ApoE ε2ε4	5(2.5%)	21(5.3%)	0.13
ApoE ε3ε4	4(2.0%)	50(12.5%)	**0.00**
ApoE ε4ε4	1(0.5%)	9(2.3%)	0.15

OR, Odds Ratio; OR, Odds Ratio.
Bold P-values indicate statistically significant differences (P < 0.05).

TABLE 3 Binary logistic regression analysis of *ApoE* genotypes distribution in LUAD and control group.

Genotype	OR	95%CI	*p*-Value
ApoE ε2ε2	3.78	1.64-8.71	**0.00**
ApoE ε2ε3	3.22	1.69-6.11	**0.02**
ApoE ε3ε3	1.05	0.72-1.55	0.79
ApoE ε2ε4	0.46	0.17-1.25	0.12
ApoE ε3ε4	0.14	0.05-0.40	**0.00**
ApoE ε4ε4	0.22	0.03-1.74	0.15

Bold P-values indicate statistically significant differences (P < 0.05).

Regression analysis was conducted to examine the association between specific *APOE* genotypes and the risk of LUAD at various stages. The *APOE* ε2/ε3 genotype showed a 2.36-fold increase in susceptibility to early-stage LUAD compared to the control group (P = 0.046). In patients with advanced-stage LUAD, the frequencies of the *APOE* ε2/ε2 and ε2/ε3 genotypes were markedly higher (OR = 5.08,95%CI,2.05-12.62, and OR = 4.05, 95%CI, 1.97-8.33, P < 0.001). Furthermore, individuals with the *APOE* ε3/ε4 genotype *exhibited* a significantly lower risk of developing both early-stage and advanced-stage LUAD (OR = 0.15,95%CI,0.04-0.63, P=0.01 and OR = 0.14, 95%CI, 0.03-0.57, P =0.006) (Table 5).

3.4 Analysis of the prevalence of APOE alleles and genotypes frequencies among the control group and LUAD subgroups by differentiation level

Following the degree of pathological differentiation, patients with LUAD were categorized into three subgroups: well, moderately, and poorly differentiated. Based on the degree of tumor differentiation, each LUAD subgroup was compared with the control group, revealing that the frequency of ε2 and ε4 allele carriers was reduced in well-differentiated LUAD patients (0.8% vs. 7% and 4.2% vs. 11.1%, P=0.01

and P=0.02), while the frequency of ε3 allele carriers was significantly higher (94.9% vs. 81.9%, P<0.01). The LUAD subgroup and control group a were analyzed, revealing a much higher frequency of individuals carrying the ε2 allele in the moderately differentiated LUAD group (79.9% vs. 81.9%, P<0.01). In the poorly differentiated LUAD group, with respect to the control group, the frequency of the ε4 allele was lower (2.8% vs. 11.1%, P < 0.01), whereas the frequency of the ε2 allele was higher (26.1% vs. 7%, P < 0.01) (Table 6).

Investigating the association between *APOE* genotypes and poorly differentiated LUAD, we discovered that those with the ε2/ε2 and ε2/ε3 genotypes had 6.8-fold and 6.52-fold increased chances of getting this condition. Conversely, individuals with the *APOE* ε3/ε3 genotype had 0.56 times the odds of developing poorly differentiated LUAD (95% CI = 0.33–0.96, P = 0.03). *APOE* ε3/ε4 and *APOE* ε4/ε4 hadn't been found in patients with poorly differentiated LUAD. The *APOE* ε2/ε3 and ε3/ε3genotypes raised the likelihood of developing moderately differentiated LUAD by 4.68-fold and 3.22-fold, respectively, in comparison with the healthy cohort (95% CI = 1.68–13.0 and 1.38–7.54, P < 0.05). However, the probability of developing moderately differentiated LUAD were 0.2-fold lower for carriers of the *APOE* ε3/ε4 genotype (95% CI = 0.05–0.84, P = 0.03). Furthermore, *APOE* ε3/ε3 genotype carrier showed a substantial 4.96-fold increase in the odds of developing well-differentiated LUAD (95% CI = 1.75-14.01, P = 0.003). Neither the *APOE* ε2/ε2 nor the ε2/ε3 genotype was present in any patient within the well-differentiated LUAD group. The *APOE* ε2/ε4 genotype showed no significant relationship with the probability of developing LUAD with varying degrees of differentiation (Table 7).

3.5 The lipid profile between individuals carrying ε2, ε3, and ε4 alleles in the control and LUAD subgroups

In LUAD patients, individuals carrying the ε2 and ε3 allele exhibited significant alterations in lipid metabolism compared to the healthy control group, with LDL, HDL, total cholesterol (TC), APOB, and FFA levels downregulated (P<0.05). In contrast, no

TABLE 4 Comparison of *ApoE* alleles and genotypes frequencies between the control and LUAD different stages subgroups with different stages.

Allele, Genotype	Control (N =400)	Early (N =95)	*p*-Value	Advanced (N=105)	*p*-Value
ε2 allele, n (%)	56(7%)	22(11.6%)	0.003	40(21.2%)	**0.003**
ε3 allele, n (%)	655(81.9%)	161(84.7%)	0.366	166(87.4%)	0.370
ε4 allele, n (%)	89(11.1%)	7(3.7%)	0.003	4(2.1%)	**0.000**
ApoE ε2ε2	9(2.3%)	5(5.3%)	0.110	11(10.5%)	**0.001**
ApoE ε2ε3	17(4.3%)	9(9.5%)	0.040	16(15.2%)	**0.000**
ApoE ε3ε3	294(73.5%)	75(78.9%)	0.297	74(70.5%)	0.535
ApoE ε2ε4	21(5.3%)	3(3.2%)	0.393	2(1.9%)	0.191
ApoE ε3ε4	50(12.5%)	2(2.1%)	0.003	2(1.9%)	**0.002**
ApoE ε4ε4	9(2.3%)	1(1.1%)	0.695	0(0%)	0.215

Bold P-values indicate statistically significant differences (P < 0.05).

TABLE 5 Binary logistic regression analysis of *ApoE* genotypes in the control group and early and advanced LUAD stage subgroup.

LUAD	Genotype	OR	95%CI	p-Value
Early stage	*ApoE* ε2ε2	2.41	0.79-7.37	0.122
	ApoE ε2ε3	2.36	1.02-5.47	**0.046**
	ApoE ε3ε3	1.35	0.79-2.32	0.274
	ApoE ε2ε4	0.59	0.17-2.02	0.399
	ApoE ε3ε4	0.15	0.04-0.63	**0.010**
	ApoE ε4ε4	0.46	0.06-3.69	0.467
Advanced stage	*ApoE* ε2ε2	5.08	2.05-12.62	**0.000**
	ApoE ε2ε3	4.05	1.97-8.33	**0.000**
	ApoE ε3ε3	0.86	0.54-1.38	0.535
	ApoE ε2ε4	0.35	0.08-1.52	0.161
	ApoE ε3ε4	0.14	0.03-0.57	**0.006**
	ApoE ε4ε4	–	–	–

Bold P-values indicate statistically significant differences (P < 0.05).

significant differences were observed in patients carrying the ε4 allele (Table 8; Supplementary Figures 1A–C).

To further explore the effects of different *APOE* alleles on lipid profiles in LUAD patients and the modulatory role of disease stage, with comparisons to a normal control group. In early-stage LUAD patients, ε3 and ε2 allele carriers were associated with the most significant alterations in lipid metabolism: ε3 carriers exhibited increased TG, HDL,APOA1 and ApoB levels and decreased Lp(α) and FFA levels, whereas, ε2 carriers had lower HDL and FFA levels and higher ApoB levels, ε4 carriers had significant changes only in increased ApoB levels (P < 0.05) (Table 9A; Supplementary Figure 2A–C). In late-stage LUAD patients, ε2 carriers primarily showed significant reductions in lipoproteins and FFA, whereas ε3 carriers demonstrated significant increases in TG levels along with decreased TC,APOB and FFA levels (P < 0.05) (Table 9B; Supplementary Figures 2D–F).

To explore the relationship between *APOE* alleles and lipid profiles in LUAD patients with different levels of differentiation, and to compare these findings with those from a normal control group. Specifically, in well-differentiated LUAD patients, ε3 carriers exhibited increased TG levels, along with significantly decreased levels of HDL, Apolipoprotein A1(ApoA1), Apolipoprotein B (APOB) Lipoprotein (Lp(a)), and free fatty acids (FFA). In ε4 carriers, significant reductions were primarily observed in LDL, ApoA1, and ApoB levels (P < 0.05) (Table 10A; Supplementary Figures 3A, B). In moderately differentiated LUAD patients, both ε2 and ε3 carriers showed notable lipid metabolic abnormalities, including HDL, APOA1, APOB and FFA levels. In contrast, no significant changes were noted in ε4 carriers, suggesting a minimal or insignificant effect of the ε4 allele on lipid metabolism in this subgroup (P < 0.05) (Table 10B; Supplementary Figures 3C–E). In poorly differentiated LUAD patients, those carrying ε2 and ε3 allele experienced significant disruptions in lipid metabolism, particularly with reductions in ApoB and Lp(a) levels, which were consistently observed in both groups (P < 0.05) (Table 10C; Supplementary Figures 3F, G). These results suggest that *APOE* alleles may significantly affect lipid metabolism, especially in individuals with poorly differentiated LUAD.

4 Discussion

Our research focused on assessing the role of *APOE* gene polymorphisms in LUAD susceptibility and their influence on lipid profiles. Previous reports have primarily focused on APOE protein expression levels in patients with lung cancer. This study demonstrates revealed that the presence of the ε2 allele increases the risk of LUAD, while the ε4 allele provide a protective effect. However, the *APOE* ε3/ε3 genotype did not exhibit a significant association with LUAD risk. The *APOE* ε2/ε4 genotype demonstrated no statistical difference between the healthy control and LUAD groups. Furthermore, the *APOE* ε2/ε2 genotype displayed a higher risk of cancer development compared to *APOE* ε2/ε3, particularly in patients with advanced stages of lung cancer,

TABLE 6 Comparison of *ApoE* alleles and genotypes frequencies among the control group and LUAD group subgroups by differentiation level.

Allele	Control (N =400)	Well (N = 59)	p-Value	moderately (N = 72)	p-Value	poorly (N =69)	p-Value
ε2 allele, n (%)	56(7%)	1 (0.8%)	**0.010**	25(17.4%)	0.000	36(26.1%)	**0.000**
ε3 allele, n (%)	655(81.9%)	112 (94.9%)	**0.000**	115(79.9%)	0.566	100(72.5%)	**0.010**
ε4 allele, n (%)	89(11.1%)	5(4.2%)	**0.021**	4(2.8%)	0.002	2(1.4%)	**0.001**
ApoE ε2ε2	9 (2.3%)	0 (0.0%)	0.383	7(9.8%)	0.001	9(13.3%)	**0.000**
ApoE ε2ε3	17 (4.3%)	0 (0.0%)	0.146	9(12.5%)	0.010	16(23.2%)	**0.000**
ApoE ε3ε3	294 (73.5%)	55 (93.2%)	**0.001**	52(72.2%)	0.821	42(60.9%)	**0.032**
ApoE ε2ε4	21(5.3%)	1 (1.7%)	0.233	2(2.8%)	0.411	2(2.9%)	0.554
ApoE ε3ε4	50 (12.5%)	2 (3.4%)	**0.045**	2(2.8%)	0.015	0(0)	**0.002**
ApoE ε4ε4	9 (2.3%)	1 (1.7%)	1.000	0(0)	0.367	0(0)	0.368

Bold P-values indicate statistically significant differences (P < 0.05).

TABLE 7 Binary logistic regression analysis of *ApoE* genotypes frequencies in the control group and LUAD subgroups by differentiation level.

LUAD	Genotype	OR	95%CI	p-Value
Poorly	*ApoE* ε2ε2	6.52	2.49-17.07	**0.000**
	ApoE ε2ε3	6.80	3.24-14.26	**0.000**
	ApoE ε3ε3	0.56	0.33-0.96	**0.033**
	ApoE ε2ε4	0.54	0.12-2.35	0.411
	ApoE ε3ε4	–	–	–
	ApoE ε4ε4	–	–	–
Moderately	*ApoE* ε2ε2	4.68	1.68-13.00	**0.003**
	ApoE ε2ε3	3.22	1.38-7.54	**0.007**
	ApoE ε3ε3	0.94	1.38-7.54	0.822
	ApoE ε2ε4	0.52	0.12-2.25	0.378
	ApoE ε3ε4	0.20	0.05-0.84	**0.028**
	ApoE ε4ε4	–	–	–
Well	*ApoE* ε2ε2	–	–	–
	ApoE ε2ε3	–	–	–
	ApoE ε3ε3	4.96	1.75-14.01	**0.003**
	ApoE ε2ε4	0.31	0.04-2.36	0.259
	ApoE ε3ε4	0.25	0.06-1.04	0.056
	ApoE ε4ε4	0.75	0.09-6.02	0.790

Bold P-values indicate statistically significant differences (P < 0.05).

suggesting a potential association with cancer progression stages. Similar studies have identified the *APOE* ε4 allele as a lung cancer risk factor. However, they overlook important differences in pathological subtypes and fail to address the unique metabolic characteristics of LUAD (19). The role of the *APOE* alleles and their genotypes varies across different tumor types. For instance, *APOE* ε2 reduces the risk of developing colorectal cancer, while the

APOE ε4 allele does not significantly impact colorectal cancer risk (22), In contrast, the *APOE* ε3 allele is linked to a higher risk of laryngeal squamous cell carcinoma (LSCC) (23). Different cancer susceptibility results are caused by the interaction between *APOE* allele carriers and their genotypes, which has a substantial impact on cancer development and progression.

The frequencies of different *APOE* genotype within the population are affected by gender, age and genetic variations (24). This study was conducted with baseline data such as gender, age, and medical history being consistent across the groups, which means that the potential confounding effects of these factors were eliminated in this study. Individuals carrying the *APOE* ε2/ε4 genotype do not have a significantly increased risk of LUAD, we hypothesize an allelic dosage effect for *APOE* ε2 and ε4, suggesting that the number of alleles correlates with the extent of their impact on phenotype and function. Specifically, ε2 appears to have a detrimental effect, while ε4 seems to exhibit a protective effect. The adverse impact of homozygous ε2/ε2 is more pronounced than that of ε2/ε3, whereas the protective effect of homozygous ε4/ε4 is stronger than that of ε3/ε4. In colorectal cancer, patients with the *APOE* ε2/ε3 genotype are more likely to progress to advanced stages once diagnosed (12). Individuals with the *APOE* ε2/ε4 and *APOE* ε3/ε4 genotypes have a reduced risk of LSCC by 2.9 and 1.5 times. Individuals with the APOE ε3/ε3 genotype have a 1.7-fold higher likelihood of developing LSCC (23). The findings align with the allelic dosage effect in cancer risk, but larger population studies are needed for definitive conclusions.

Recent studies suggest that interactions between lipid metabolism and *APOE* genotypes may increase cancer risk, particularly for *APOE* ε2 carriers with low TC levels (19, 25). The PROSPER-derived studies evaluated the relationship between *APOE* subtypes and cancer risk in the older population. These studies indicated a negative correlation between TC levels and cancer incidence and mortality (26). The study couldn't establish a direct causal link between *APOE* genotype and cancer risk due to the effect of medications on TC levels in patients with vascular disease (27). The primary outcome variable of the study was cancer

TABLE 8 The lipid profile between individuals carrying ε2, ε3, and ε4 alleles in the control and LUAD group.

	ε2		ε3		ε4	
	M ± SEM (LUAD *VS* Control)	P Value	M ± SEM (LUAD *VS* Control)	P Value	M ± SEM (LUAD *VS* Control)	P Value
TG (mmol/L)	1.98 ± 0.09 vs 2.15 ± 0.14	0.671	2.13 ± 0.06 vs 1.88 ± 0.04	**0.000**	1.80 ± 0.23 vs 1.76 ± 0.07	0.874
LDL (mmol/L)	2.83 ± 0.13 vs 3.27 ± 0.17	**0.041**	2.91 ± 0.06 vs 2.95 ± 0.05	0.601	2.30 ± 0.37 vs 2.86 ± 0.11	0.156
HDL (mmol/L)	1.71 ± 0.15 vs 3.83 ± 0.31	**0.000**	2.26 ± 0.11 vs 2.65 ± 0.09	**0.025**	3.38 ± 0.63 vs 2.66 ± 0.21	0.330
TC (mmol/L)	2.16 ± 0.24 vs 3.17 ± 0.38	**0.021**	2.47 ± 0.14 vs 2.97 ± 0.11	**0.030**	4.31 ± 1.36 vs 2.74 ± 0.21	0.445
APOA1	1.39 ± 0.14 vs 1.80 ± 0.19	0.086	1.54 ± 0.08 vs 2.10 ± 0.06	**0.002**	1.46 ± 0.11 vs 2.36 ± 0.13	0.131
APOB	1.02 ± 0.07 vs 1.99 ± 0.07	**0.000**	1.36 ± 0.05 vs 1.80 ± 0.03	**0.000**	1.43 ± 0.31 vs 1.88 ± 0.07	0.070
Lp(a) (10^2mmol/L)	2.47 ± 0.28 vs 4.75 ± 0.81	**0.002**	2.85 ± 0.15 vs 3.89 ± 0.14	**0.000**	2.66 ± 0.98 vs 3.75 ± 0.25	0.231
FFA	0.38 ± 0.05 vs 0.83 ± 0.07	**0.000**	0.45 ± 0.02 vs 0.55 ± 0.02	**0.000**	0.54 ± 0.14 vs 0.64 ± 0.04	0.520

Bold P-values indicate statistically significant differences (P < 0.05).

TABLE 9 Lipid profiles of individuals carrying ε2, ε3, and ε4 alleles in LUAD with different stages and control group.

A. Lipid profiles in ε2, ε3, and ε4 allele carriers between early LUAD and control group						
	ε2		ε3		ε4	
	M ± SEM (LUAD VS Control)	P Value	M ± SEM (LUAD VS Control)	P Value	M ± SEM (LUAD VS Control)	P Value
TG (mmol/L)	2.02 ± 0.18 vs 2.15 ± 0.14	0.561	2.19 ± 0.08 vs 1.88 ± 0.04	**0.000**	1.91 ± 0.28 vs 1.76 ± 0.07	0.625
LDL (mmol/L)	2.15 ± 0.14 vs 2.96 ± 0.24	0.297	1.88 ± 0.04 vs 2.96 ± 0.09	0.937	1.76 ± 0.07 vs 1.84 ± 0.34	**0.041**
HDL (mmol/L)	3.27 ± 0.17 vs 1.58 ± 0.09	**0.000**	2.95 ± 0.05 vs 2.22 ± 0.15	**0.037**	2.86 ± 0.11 vs 3.01 ± 1.04	0.713
TC (mmol/L)	3.83 ± 0.31 vs 1.89 ± 0.32	**0.029**	2.65 ± 0.09 vs 2.78 ± 0.22	0.453	2.66 ± 0.21 vs 3.39 ± 1.42	0.515
APOA1	3.17 ± 0.38 vs 1.58 ± 0.37	0.576	2.97 ± 0.11 vs 1.51 ± 0.11	**0.000**	2.74 ± 0.21 vs 1.55 ± 0.03	0.172
APOB	1.80 ± 0.19 vs 1.02 ± 0.11	**0.000**	2.10 ± 0.06 vs 1.36 ± 0.08	**0.000**	2.36 ± 0.13 vs 1.11 ± 0.43	**0.017**
Lp(a)(10^2mmol/L)	3.00 ± 0.45 vs 4.75 ± 0.81	0.126	2.82 ± 0.19 vs 3.89 ± 0.14	**0.000**	3.48 ± 1.53 vs 3.75± 0.25	0.814
FFA	0.31 ± 0.07 vs 0.83 ± 0.07	**0.000**	0.43 ± 0.03 vs 0.55 ± 0.02	**0.001**	0.45 ± 0.19 vs 0.64 ± 0.04	0.339
B. Lipid profiles of ε2, ε3, and ε4 allele carriers between late LUAD and control group						
	ε2		ε3		ε4	
	M ± SEM (LUADVS Control)	P Value	M ± SEM (LUADVS Control)	P Value	M ± SEM (LUADVS Control)	P Value
TG (mmol/L)	1.96 ± 0.10 vs 2.15 ± 0.14	0.275	2.08 ± 0.08 vs 1.88 ± 0.04	**0.021**	1.62 ± 0.47 vs 1.76 ± 0.07	0.730
LDL (mmol/L)	2.75 ± 0.15 vs 3.27 ± 0.17	**0.041**	2.86 ± 0.09 vs 2.95 ± 0.05	0.375	2.99 ± 0.49 vs 2.86 ± 0.11	0.822
HDL (mmol/L)	1.79 ± 0.24 vs 3.83 ± 0.31	**0.000**	2.29 ± 0.16 vs 2.65 ± 0.09	0.085	3.94 ± 0.49 vs 2.66 ± 0.21	0.263
TC (mmol/L)	2.31 ± 0.32 vs 3.17 ± 0.38	**0.021**	2.16 ± 0.16 vs 2.97 ± 0.11	**0.001**	5.70 ± 3.03 vs 2.74 ± 0.21	**0.020**
APOA1	1.29 ± 0.06 vs 1.80 ± 0.19	0.086	1.57 ± 0.11 vs 2.10 ± 0.06	**0.000**	1.31 ± 0.29 vs 2.36 ± 0.13	0.148
APOB	1.01 ± 0.09 vs 1.99 ± 0.07	**0.000**	1.37 ± 0.07 vs 1.80 ± 0.03	**0.000**	1.90 ± 0.00 vs 1.88 ± 0.07	0.967
Lp(a)(10^2mmol/L)	2.17 ± 0.35 vs 4.75 + 0.81	**0.002**	2.89 ± 0.23 vs 3.89 + 0.14	**0.001**	1.44 ± 0.33 vs 3.75 + 0.25	0.095
FFA	0.42 ± 0.06 vs 0.83 ± 0.07	**0.000**	0.47 ± 0.03 vs 0.55 ± 0.02	**0.018**	0.67 ± 0.24 vs 0.64 ± 0.04	0.884

Bold P-values indicate statistically significant differences (P < 0.05).

development, without differentiating between specific types of malignancies, however, the analysis of *APOE* gene polymorphism and tumor risk did not include the Chinese population (28). *APOE* ε4 female patients display elevated TG levels and an increased risk of breast cancer (29, 30). Interactions between *APOE* genotypes and lipid metabolism may impact cancer risk, though direct causality and population-specific effects remain unclear. The precise mechanisms through which *APOE* genotypes influence malignant tumor progression remain unclear. Some studies suggest that the ε2 allele may protect against head and neck cancer, potentially because of its enhanced antioxidant abilities (31), however, overexpression of APOE2 can induce epithelial-mesenchymal transition (EMT), thereby promoting cancer progression in pancreatic cancer (32). Mice carrying the human *APOE* ε2 allele demonstrate prolonged progression-free survival (PFS) compared to *APOE* ε4 carriers, with the mechanism linked to diminished T-cell cytotoxicity against tumor cells (11).Building on mechanisms observed in other cancers, these results underscore the importance of investigating how *APOE* ε2 may drive tumor progression in LUAD.

APOE gene can influence the uptake and breakdown of TC and TG in lung cancer patients (33, 34). Patients with LUAD carrying the ε2 allele showed decreased TC levels. TC levels increase in early-stage LUAD patients and are reduced in late-stage patients compared to those with the ε4 allele. A condition called the cancer preclinical phenomenon when cancer causes a drop in plasma TC levels prior to a formal cancer diagnosis, this effect arises as cancer cells increase their uptake of TC from the bloodstream for growth and proliferation (35, 36). Earlier studies have indicated a heightened gastric cancer incidence in individuals carrying the ε2 allele with lower TC levels (37), a study conducted across seven countries found that lung cancer mortality risk rises when TC levels drop below 170 mg/dL (25). The *APOE* ε2 allele affects different lipid metabolism markers across various tumors, ApoA1 levels are significantly increased in patients with early-stage gastric cancer, whereas they remain relatively stable in those with advanced-stage gastric cancer (38, 39). Increased APOA1 levels can reduce the risk of lung cancer (40), but after lung cancer patients with brain metastases, APOA1 levels are up-regulated (41). Patients carrying the *APOE* ε2 allele tend to have lower VLDL-C levels, while those with the ε4 allele exhibit increased VLDL-C levels (18). This association suggests that the phenotypic variation of lipoproteins among individuals can alter the cancer risk by

TABLE 10 Lipid profiles of APOE ε2, ε3, and ε4 allele carriers within LUAD subgroups by differentiation level and control group.

A. Lipid profiles of ε3, and ε4 allele carriers in well differentiated LUAD and control group				
	ε3		ε4	
	M ± SEM (LUADVS Control)	P Value	M ± SEM (LUADVS Control)	P Value
TG (mmol/L)	2.25 ± 0.08 vs 1.88 ± 0.04	**0.000**	1.84 ± 0.35 vs 1.76 ± 0.07	0.795
LDL (mmol/L)	2.88 ± 0.10 vs 2.95 ± 0.05	0.574	1.84 ± 0.35 vs 2.86 ± 0.11	**0.043**
HDL (mmol/L)	2.13 ± 0.16 vs 2.65 ± 0.09	**0.007**	2.85 ± 0.90 vs 2.66 ± 0.21	0.839
TC (mmol/L)	2.57 ± 0.24 vs 2.97 ± 0.11	0.157	3.20 ± 1.44 vs 2.74 ± 0.21	0.648
APOA1	1.51 ± 0.12 vs 2.10 ± 0.06	**0.000**	1.55 ± 0.03 vs 2.36 ± 0.13	**0.000**
APOB	1.36 ± 0.08 vs 1.80 ± 0.03	**0.000**	1.12 ± 0.44 vs 1.88 ± 0.07	**0.018**
Lp(a)(10^2mmol/L)	3.14 ± 0.27 vs 3.89 ± 0.14	**0.030**	3.03 ± 1.74 vs 3.75 ± 0.25	0.537
FFA	0.42 ± 0.04 vs 0.55 + 0.02	**0.001**	0.34 ± 0.11 vs 0.64 + 0.04	0.126

B. Lipid profiles of APOE ε2, ε3, and ε4 allele carriers with moderately differentiated LUAD and control group						
	ε2		ε3		ε4	
	M ± SEM (LUADVS Control)	P Value	M ± SEM (LUADVS Control)	P Value	M ± SEM (LUADVS Control)	P Value
TG (mmol/L)	2.08 ± 0.09 vs 2.15 ± 0.14	0.671	2.06 ± 0.09 vs 1.88 ± 0.04	0.070	1.73 ± 0.36 vs 1.76 ± 0.07	0.947
LDL (mmol/L)	2.76 ± 0.19 vs 3.27 ± 0.17	0.064	2.78 ± 0.11 vs 2.95 ± 0.05	0.175	2.98 ± 0.50 vs 2.86 ± 0.11	0.835
HDL (mmol/L)	2.00 ± 0.31 vs 3.83 ± 0.31	**0.000**	2.18 ± 0.18 vs 2.65 ± 0.09	**0.025**	4.17 ± 0.72 vs 2.66 ± 0.21	0.187
TC (mmol/L)	2.08 ± 0.42 vs 3.17 ± 0.38	0.072	2.41 ± 0.23 vs 2.97 ± 0.11	**0.03**	5.99 ± 2.74 vs 2.74 ± 0.21	0.445
APOA1	1.28 ± 0.06 vs 1.80 ± 0.19	**0.049**	1.57 ± 0.15 vs 2.10 ± 0.06	**0.002**	1.32 ± 0.30 vs 2.36 ± 0.13	0.131
APOB	1.06 ± 0.15 vs 1.99 ± 0.07	**0.000**	1.34 ± 0.10 vs 1.80 ± 0.03	**0.000**	1.89 ± 0.01 vs 1.88 ± 0.07	0.989
Lp(a)(10^2mmol/L)	2.60 ± 0.56 vs 4.75 ± 0.81	0.063	2.79 ± 0.25 vs 3.89 ± 0.14	**0.000**	2.11 ± 0.35 vs 3.75 ± 0.25	0.232
FFA	0.37 ± 0.07 vs 0.83 ± 0.07	**0.000**	0.42 ± 0.03 vs 0.55 ± 0.02	**0.000**	0.84 ± 0.08 vs 0.64 ± 0.04	0.394

C. Lipid profiles of ε2 and ε4 allele carriers with poorly differentiated LUAD and control group				
	ε2		ε3	
	M ± SEM (LUADVS Control)	P Value	M ± SEM (LUADVS Control)	P Value
TG (mmol/L)	1.92 ± 0.13 vs 2.15 ± 0.14	0.225	2.08 ± 0.12 vs 1.88 ± 0.04	0.070
LDL (mmol/L)	2.87 ± 0.17 vs 3.27 ± 0.17	0.107	3.10 ± 0.12 vs 2.95 ± 0.05	0.276
HDL (mmol/L)	1.53 ± 0.16 vs 3.83 ± 0.31	**0.000**	2.51 ± 0.21 vs 2.65 ± 0.09	0.599
TC (mmol/L)	2.21 ± 0.29 vs 3.17 ± 0.38	0.052	2.42 ± 0.27 vs 2.97 ± 0.11	0.079
APOA1	1.46 ± 0.22 vs 1.80 ± 0.19	0.255	1.55 ± 0.11 vs 2.10 ± 0.06	**0.000**
APOB	0.99 ± 0.07 vs 1.99 ± 0.07	**0.000**	1.41 ± 0.09 vs 1.80 ± 0.03	**0.000**
Lp(a)(10^2mmol/L)	2.39 ± 0.30 vs 4.75 ± 0.81	**0.008**	2.57 ± 0.24 vs 3.89 ± 0.14	**0.001**
FFA	0.38 ± 0.06 vs 0.83 ± 0.07	**0.000**	0.53 ± 0.05 vs 0.55 ± 0.02	0.625

Bold P-values indicate statistically significant differences (P < 0.05).

modulating serum lipoprotein levels. Overall, APOE gene polymorphisms influence lipid metabolism in LUAD patients, characterized by reduced HDL levels and elevated TG (42), which provide essential energy and biosynthetic precursors for tumor cell proliferation. Moreover, dysregulated lipid metabolism impacts immune cell function, impairing tumor immune surveillance, such as cholesterol modulating T cell receptor signaling and immune checkpoint expression (43). Thus, targeting lipid metabolism could represent a novel strategy to enhance immune response and treat tumors. FFA and cholesterol can influence multiple stages of cancer immunity by modifying the state and function of immune cells in the tumor microenvironment (TME) (44, 45). These changes interfere with the production of tumor-associated antigens (TAAs) (43), enabling tumor cells to escape

immune surveillance and impairing the normal antitumor response (46). The study indicates that macrophages with high APOE expression are enriched in metastatic gastric tumors, contributing to immune evasion by reducing CD8+ T cell infiltration (47). Targeted interventions that modulate these pathways could potentially reduce tumor growth and improve treatment outcomes for APOE ε2 carriers. Additionally, since APOE ε2 is implicated in the regulation of epithelial–mesenchymal transition (EMT), therapies aimed at inhibiting EMT may offer significant benefits for these patients. Identifying APOE ε2 carriers would allow clinicians to personalize treatment strategies, potentially improving prognosis and enhancing the effectiveness of therapies for advanced LUAD.

This study has certain limitations. We explored the association between *APOE* genotypes and TNM staging in patients with LUAD. However, subgroup analyses for the T stage, N stage, and M stage for each patient were not conducted. This limitation stems from the fact that not all patients could undergo accurate T, N, and M staging, resulting in significant data loss and reduced statistical power. Moreover, this study did not measure *APOE* serum concentrations. It would have been beneficial to analyze the correlation between *APOE* levels and lung cancer staging if such data had been available. This study focused on a specific population in the Qingdao area of Shandong Province, China. Future research should include data from other regions or populations with different genetic backgrounds to validate the generalizability of the association between APOE polymorphisms and LUAD.

5 Conclusion

Individuals carrying the ε2 allele have an increased susceptibility to developing LUAD, accompanied by disrupted lipid metabolism. The *APOE* ε2/ε2 and ε2/ε3 genotypes have been attributed to an increased probability of advanced and poorly differentiated LUAD.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving humans were approved by Ethics Committee of the Affiliated Hospital of Qingdao University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

HB: Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing. DR: Conceptualization, Methodology, Validation, Writing – original draft, Writing – review & editing. YW: Funding acquisition, Methodology, Resources, Writing – original draft, Writing – review & editing. HW: Funding acquisition, Investigation, Writing – original draft, Writing – review & editing. CZ: Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer RZ declared a shared affiliation with the authors DR, HW to the handling editor at the time of review.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1522761/full#supplementary-material

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