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ORIGINAL RESEARCH

Prognostic Value of Apolipoprotein E in Predicting One-year Mortality in Patients with Acute Exacerbation of Chronic Obstructive Pulmonary Disease

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Purpose: Chronic obstructive pulmonary disease (COPD) is a serious disease with significantly higher mortality. Evidence suggests that there may be a co-relation between ApoE and the mortality risk in individuals who are diagnosed with COPD. This study sought to investigate the correlation between the levels of ApoE and all-cause mortality over one year in individuals who are diagnosed with acute exacerbations of chronic obstructive pulmonary disease (AECOPD).

Methods: In this study, we checked serum ApoE concentrations of AECOPD patients on admission and collected the patients' laboratory and clinical information. The co-relation between the concentration of ApoE and one year risk of all-cause mortality was analyzed by univariate, multivariate Cox regression and Subgroup analysis. Restricted Cubic Spline (RCS) were employed to illustrate the connection between ApoE levels and the hazard ratio (HR) for one-year total mortality rate.

Results: Of the 449 participants who were enrolled, 358 patients were included in the study. The mean age was 76 (±9.46) years old, of which 65.92% were male. The body-mass index was 22.18 (±4.66). Of the participants, 24.86% were non-smokers, 54.75% were former smokers, and 20.39% were active smokers, with a smoking history of 28.68 (±20.43) years. The restricted cubic spline curve revealed that patients exhibiting ApoE concentrations exceeding the mean value of 41.50 mg/L faced a notably higher risk of mortality in comparison to individuals with lower levels. In univariate analysis, the HR was 2.663 (95% CI 1.533–4.627, P = 0.001), but in adjusted analyses, the HR was 2.103 (95% CI 1.19–3.716, P = 0.01).

Conclusion: Elevated levels of ApoE were independently risk factor for one-year mortality in patients with AECOPD. Subgroup analyses revealed that the association was stronger in younger patients (<76 years) and male, as well as in those without comorbidities such as congestive heart failure or cerebrovascular disease. This suggests that ApoE may be a potential prognostic biomarker for AECOPD.

Keywords: ApoE, AECOPD, mortality, prognostic biomarker

Introduction

Chronic obstructive pulmonary disease (COPD) is a prevalent and controllable chronic inflammatory condition of the lungs, distinguished by persistent obstruction in the airways, typically linked to ongoing inflammation in the airways and alveoli.[1] COPD ranks among the leading deadly illnesses globally, especially affecting mortality rates in elderly or middle-aged individuals.[2] Despite medical advances, serious challenges remain in early identification and monitoring of the disease.[3] Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an episodic condition in which a patient's symptoms rapidly worsen, often requiring immediate medical intervention.[4] AECOPD not only accelerates the

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progression of COPD but also increases the risk of long-term complications, and has become a significant burden on healthcare systems.[5] Given the high mortality rate of AECOPD, early and efficient recognization of high-risk cases is crucial.

Apolipoprotein E (ApoE) is a key lipoprotein involved in regulating inflammation, lipid metabolism and the immunol response.[6,7] Recent studies have showed correlation between ApoE and cardiovascular disease. For example, abnormal ApoE levels may increase the risk of cardiovascular events.[8] And study have indicated that ApoE4 carriers show heightened tau pathology in the brain—this pathophysiological linkage is significant as elevated tau correlates with cognitive decline.[9] Given its role in other diseases, it may also play a role in pulmonary diseases. These studies listed above make ApoE a potentially promising biomarker for research of COPD. Some studies[10,11] found that lipid metabolism, including the regulation of LDL cholesterol, could influence the inflammatory response and contribute to lung tissue damage, which may be relevant to the potential protective effects of ApoE in lung diseases and so on. The effects of ApoE may show pleiotropy depending on pathophysiological status, and its role may also exacerbate tissue damage in some cases.

One of the Studies finds that COPD patients have higher serum ApoE levels,[12] but the specific effects of ApoE levels on the course and prognosis of COPD remain unclear. This research was structured as a prospective cohort study aimed at exploring the connection between serum levels of ApoE and one-year mortality among patients suffering from AECOPD. A growing number of studies have explored the role of ApoE in other chronic diseases, but its impact on the progression and prognosis of COPD remains unclear. This study aims to fill this knowledge gap by understanding the correlation between serum ApoE levels and one-year mortality in patients with AECOPD. Understanding the role of ApoE allows physicians to triage patients and better identify patients who may be at higher risk for acute exacerbations and a poorer prognosis, which aids in subsequent monitoring.

Materials and Methods

Study Design and Patients

This is a prospective analysis conducted at a single center to investigate the link between serum ApoE levels and one-year mortality in individuals diagnosed with AECOPD. The study population was AECOPD patients who were admitted to the Third Affiliated Hospital of Guangzhou Medical University (Guangzhou, People's Republic of China) from January 1, 2013 to June 30, 2018. All participants were followed up for one year to assess survival. In this study, only the first admission record were analyzed. All patients who were diagnosed with COPD were stratified based on the subsequent criteria,[13] post-bronchodilator FEV1/FVC ratio <70% at the time of recruitment. This study involved patients who had been diagnosed with AECOPD. However, In this study, we excluded cases who had an altered primary diagnosis of pneumonia or other diseases. Individuals with active tuberculosis, pulmonary fibrosis, or pulmonary embolism were also excluded from the study. Patients with asthma, obstructive sleep apnoea-hypoventilation syndrome, or bronchiectasis were included in the study. We did exclude patients who were unable or unwilling to cooperate with the study physicians, as well as those with malignancy (Figure 1). We excluded cases with missing data from the analyses to ensure the completeness and reliability of the results. All participants were enrolled on their first day of hospitalization and subsequently followed up for one year after discharge. Phone follow-ups were conducted quarterly (we should not compromise patients care for their convenience). One-year mortality was defined as all-cause mortality from enrolment over one year, including deaths before and after the first exacerbation. Mortality data were obtained from both hospital records and family contacts. This study has passed the ethical review from The ethics committee of the hospital, and all patients gave their written informed consent in line with the Declaration of Helsinki.

Data Collection

Demographic data for patients and blood samples were collected on the first day of admission. The fundamental data encompassed demographic features (such as age, gender, smoking history, and BMI) as well as clinical attributes (including COPD stage, and so on). Blood investigations include the complete blood count, arterial blood gases. We employed an enzyme-linked immunosorbent assay (ELISA) method using the "ApoE Detection Kit" provided by Meikang Biotech Co.,

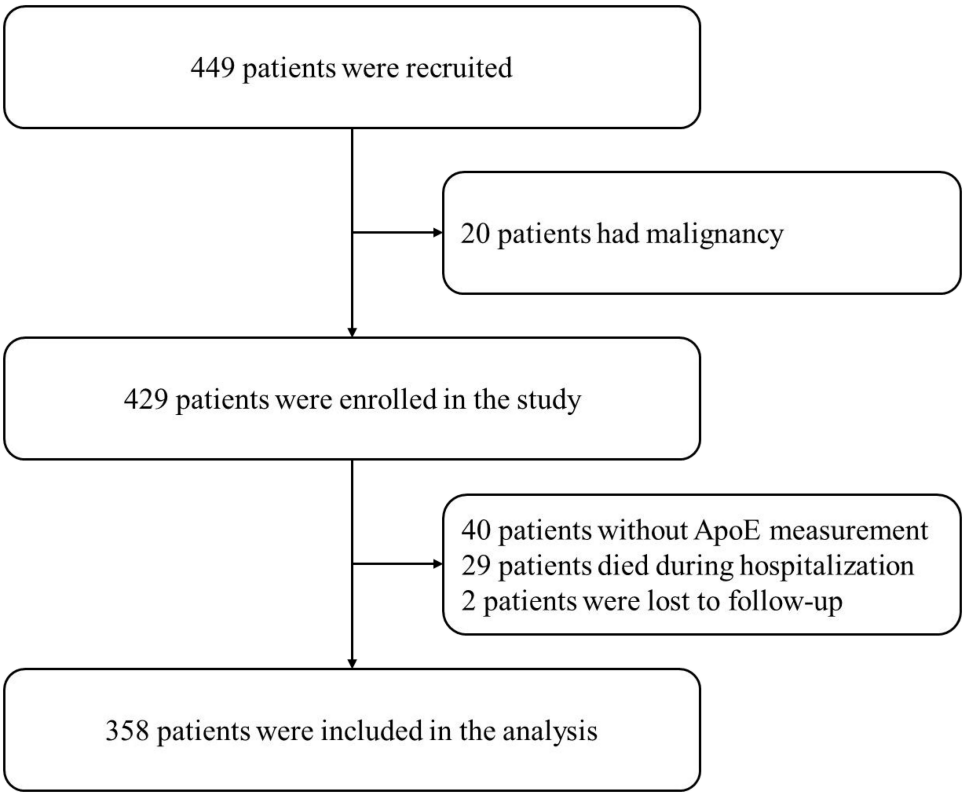

Figure 1 Flowchart.

Ltd. Each examination was carried out by the central laboratory of the hospital in accordance with standardized operating protocols.

Statistical Analyses

Descriptive statistical analyses were performed separately for continuous and categorical variables before data analysis. Continuous variables are presented as mean (standard deviation) [Mean ± (SD)]. Categorical variables are expressed in terms of frequency and percentage (n, %).To estimate the cumulative survival probability for patients with varying serum ApoE levels,Kaplan-Meier survival curves were created. The log rank test was used to identify the differences between The low group (ApoE ≤ 41.50 mg/L) and the high group (ApoE > 41.50 mg/L). To further evaluate the impact of serum ApoE levels on 1-year all-cause mortality, univariate Cox proportional hazards regression analyses were conducted. For the multivariate analyses, potential confounding variables were selected to reduce the influence on the relevance of the two. Confounders were identified based on two criteria: (1) Proven significant predictors of all-cause mortality, from published articles. (2) All variables detected in univariate analyses (P values ≤0.2) were included in multivariate analyses controlling for relevant covariates. Incorporating these factors into the multivariate Cox model allowed the study to calculate the HR and its 95% confidence interval (CI), thereby quantifying the independent effect of ApoE levels on mortality risk.

Subgroup analyses were conducted to assess the influence of specific variables on the relationship between ApoE levels and COPD mortality. Variables included age, sex, heart failure, and cerebrovascular disease. We utilized stratified Cox proportional hazards models to estimate HR and 95% CI within each subgroup. These analyses aimed to identify any significant differences in the effect of ApoE on mortality across various patient demographics.

To assess the statistical efficacy of the Cox proportional risk model, a post-hoc efficacy analysis based on Schoenfeld's formula was conducted, with a statistical efficacy of 93.9%, indicating that the study was adequately tested. The proportional hazards hypothesis was tested by visually inspecting the log survival curves versus time, which did not violate this hypothesis.

In addition, to investigate the non-linear co-relation between ApoE concentration and the risk of death, this study used restricted cubic splines analysis (RCSA) with nodes at the 10th, 50th and 90th percentiles of ApoE concentration to demonstrate the dose-response relationship and to identify potential threshold effects through the visualisation of spline curves.

Statistical analyses were conducted using SPSS version 25.0 and R version 4.0.3, with a two-tailed P value of under 0.05 deemed statistically significant.

Results

Patient Characteristics

This study included 358 participants and the basic characteristics of the study population as shown in Table 1. The mean age was 76 (±9.46) years old, of which 65.92% were male (n=236). The mean BMI was 22.18 (±4.66).

Table 1 Baseline Characteristics of the Participants

Variable	N = 358
ApoE > 41.50 mg/L(%)	148 (41.34%)
BMI	22.18 (±4.66)
Age	76 (±9.46)
Smoking history	28.68 (±20.43)
Number of hospitalisations at 1 year follow-up	1.29 (±1.54)
Male Sex(%)	236 (65.92%)
Medication regimen(%)	
Unused	121 (33.80%)
LABA OR LAMA	84 (23.46%)
LABA+LAMA	0 (0%)
ICS+LABA	48 (13.41%)
LABA+LAMA+ICS	105 (29.33%)
Smoking status(%)	
Never smoked	89 (24.86%)
Former smoker	196 (54.75%)
Current smoke	73 (20.39%)
COPD stage(%)	
I	36 (10.06%)
II	132 (36.87%)
III	137 (38.27%)
IV	53 (14.80%)
Asthma(%)	35 (9.78%)
Bronchiectasis(%)	103 (28.77%)
Coronary heart disease(%)	97 (27.09%)
Hypertension(%)	186 (51.96%)
Congestive heart failure(%)	122 (34.08%)
Diabetes(%)	45 (12.57%)
Respiratory failure(%)	232 (64.80%)
PaCO2≥50(%)	83 (23.18%)
Cerebrovascular disease(%)	30 (8.38%)
PaO2<60(%)	32 (8.94%)
Exacerbations during preceding year(%)	161 (44.13%)
Mechanical ventilation(%)	5 (1.40%)
Renal insufficiency(%)	248 (69.27%)

Notes: Plus–minus values for continuous variables are means ± standard deviation; Percentages are used for categorical variables.

Abbreviations: COPD, Chronic obstructive pulmonary disease; BMI, Body Mass Index; LABA, Long-Acting Beta2-Agonist; LAMA, Long-Acting Muscarinic Antagonist; ICS, Inhaled Corticosteroid; PaO2, partial pressure of O2; PaCO2, partial pressure of CO2.

For smoking history, 24.86% had never smoked (n=89), 54.75% had ever smoked (n=196), and 20.39% currently smoke (n=73). The mean smoking history was 28.68 (±20.43) years. The severity of COPD was divided into stage I (10.06%, n=36), stage II (36.87%, n=132), stage III (38.27%, n=137), and stage IV (14.80%, n=53). 44.13% of participants had at least one previous episode of acute COPD exacerbation within the past one year of the study (n=161).

Comorbid conditions included hypertension in 51.96% (n=186), coronary heart disease in 27.09% (n=97), congestive heart failure in 34.08% (n=122), and diabetes in 12.57% (n=45). Asthma was seen in 9.78% (n=35), and bronchiectasis was seen in 28.77% of participants (n=103). Additionally, 23.18% of participants had PaCO2≥50mmHg (n=83), 8.38% had cerebrovascular disease (n=30), and 64.80% experienced respiratory failure (n=232).

Effect of Key Thresholds on Survival Risk

Restricted cubic spline (Figure 2A) show the association between ApoE concentration and mortality. The curve shows a nonlinear relationship between ApoE levels and mortality risk. At lower concentrations, the slope stays flat, meaning changes in this range do not have a big effect on mortality risk. But when ApoE levels go above 41.50 mg/L, the curve rises sharply.

Effect of ApoE Concentration on Survival Probability

The Kaplan-Meier method (Figure 2B) illustrates the one-year survival probabilities for patients categorized by ApoE levels, revealing a distinct separation between the two groups. People with lower ApoE levels (≤ 41.50 mg/L) had a steady survival rate. But those with higher ApoE levels (> 41.50 mg/L) had a faster drop, showing a higher risk of death.

Factors Associated with Hospitalization Mortality

Cox proportional hazards models, both univariable (Table 2) and multivariable (Table 3), were employed to assess the relationship between the concentration of ApoE and mortality over a one-year period, accounting for potential confounders. Univariate analysis indicated that an ApoE concentration above 41.50 mg/L significantly increased the risk of death, with a HR of 2.663 (95% CI: 1.533–4.627; p = 0.001). This association remained significant even after adjustment for covariates in multivariable analyses, with an HR of 2.103 (95% CI: 1.19–3.716; p = 0.01).

In our multivariable Cox regression analysis, we included variables that had a P value less than 0.2 in the univariate analysis. After adjusting for ApoE levels and other confounders, we found that certain variables such as hypertension, exacerbations during the preceding year, and various medication regimens were not statistically significantly associated with one-year mortality. After adjustment for ApoE levels and other confounders, variables that remained significantly associated with one-year mortality included age (HR, 1.041; P = 0.031) and ApoE levels > 41.50 mg/L (HR, 2.103; P = 0.01). Additionally, the presence of congestive heart failure (HR, 2.192; P = 0.008) and cerebrovascular disease (HR, 2.885; P = 0.004) were also significantly associated with increased mortality risk.

Subgroup Analysis of Confounders in Cox Regression for Inpatient Mortality

Subgroup analysis (Table 4) revealed significant interactions between ApoE levels and mortality risk across various patient demographics. Notably, younger patients (<76 years) and males exhibited a stronger association between higher ApoE levels and increased mortality (HR for age <76: 4.194, P=0.019; HR for males: 2.283, P=0.031). The impact of ApoE was more pronounced in patients without congestive heart failure (HR: 2.793, P=0.02) and without cerebrovascular disease (HR: 2.031, P=0.026). These findings underscore the modifying effect of patient characteristics on the prognostic value of ApoE levels in COPD.

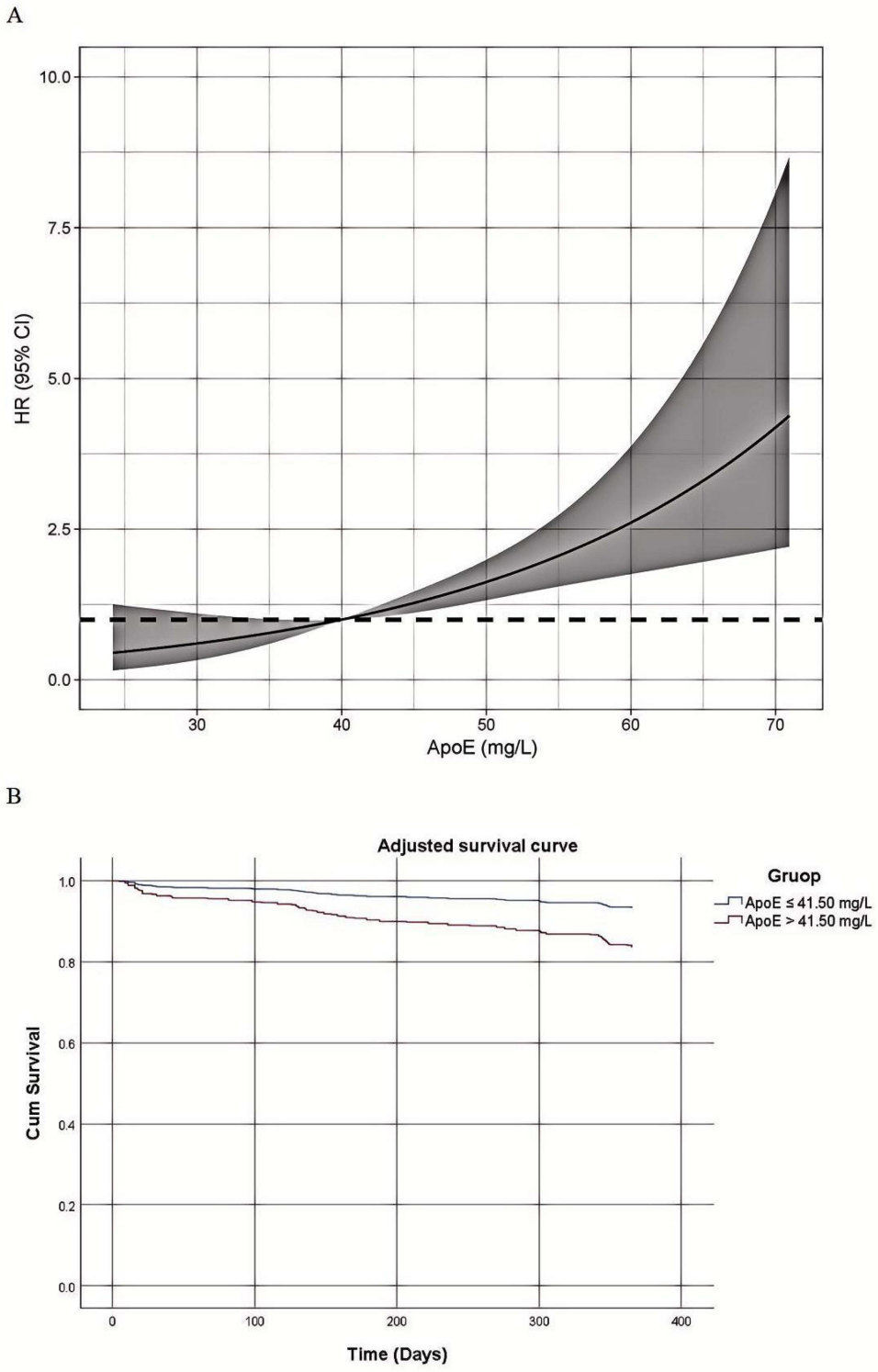

Figure 2 The association between ApoE and 1-year all cause mortality. (**A**) Restricted cubic spline curves of the association between ApoE activity and 1-year all-cause mortality. (**B**) Survival cure of multivariate Cox proportional hazards analysis of the association between ApoE and 1-year all-cause mortality.
Abbreviations: HR, Hazard ratio; ApoE, Apolipoprotein E.

Table 2 Univariate Cox Proportional Hazards Regression Analyses of the Association Between ApoE and 1-year All-Cause Mortality

Variable	HazardRatio(HR)	Pvalue
ApoE level		
≤41.50 mg/L		
> 41.50 mg/L	2.663 (1.533–4.627)	0.001
Age	1.064 (1.029–1.101)	0
Sex		
Female		
Male	0.788 (0.456–1.361)	0.392
BMI	0.995 (0.94–1.054)	0.87
Smoking status		
Never smoked		
Former smoker	0.737 (0.397–1.367)	0.332
Current smoke	0.821 (0.381–1.77)	0.615
Smoking history	1 (0.987–1.013)	0.985
COPD stage		
I		
II	1.029 (0.384–2.755)	0.955
III	0.953 (0.354–2.567)	0.924
IV	1.68 (0.592–4.768)	0.33
Hypertension		
NO		
YES	1.631 (0.939–2.833)	0.083
Diabetes		
NO		
YES	1.289 (0.608–2.73)	0.508
Asthma		
NO		
YES	1.421 (0.642–3.144)	0.386
Bronchiectasis		
NO		
YES	1.37 (0.784–2.395)	0.269
Congestive heart failure		
NO		
YES	2.208 (1.295–3.767)	0.004
Corory heart disease		
NO		
YES	1.404 (0.797–2.472)	0.24
Exacerbations during preceding year		
NO		
YES	1.799 (1.013–3.195)	0.045
PaCO2≥50mmHg		
NO		
YES	1.904 (1.089–3.329)	0.024
PaO2<60mmHg		
NO		
YES	1.615 (0.73–3.573)	0.237
Respiratory failure		
NO		
YES	1.196 (0.673–2.124)	0.542

(*Continued*)

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Table 2 (Continued).

Variable	HazardRatio(HR)	Pvalue
Medication regimen		
Unused		
LABA OR LAMA	1.799 (1.013–3.195)	0.004
LABA+LAMA		
ICS+LABA	0.483 (0.2–1.166)	0.105
LABA+LAMA+ICS	0.527 (0.278–1.001)	0.051
Cerebrovascular disease		
NO		
YES	3.269 (1.684–6.343)	0
Renal insufficiency		
NO		
YES	1.434 (0.769–2.677)	0.257
Number of hospitalisations at 1 year followup	1.096 (0.94–1.278)	0.244
Mechanical ventilation		
NO		
YES	1.489 (0.206–10.77)	0.693

Abbreviations: HR, Hazard ratio; 95% CI, 95% confidence interval; ApoE, Apolipoprotein E; COPD, Chronic obstructive pulmonary disease; PaO2, partial pressure of O2; PaCO2, partial pressure of CO2.

Table 3 Multivariate Cox Proportional Hazards Regression Analyses of the Association Between ApoE and 1-year All-Cause Mortality

Characteristics	HazardRatio(HR)	Pvalue
ApoE level		
≤ 41.50 mg/L		
> 41.50 mg/L	2.103 (1.19–3.716)	0.01*
Age	1.041 (1.004–1.079)	0.031*
Hypertension		
NO		
YES	1.42 (0.811–2.488)	0.22
Congestive heart failure		
NO		
YES	2.192 (1.233–3.897)	0.008*
Exacerbations during preceding year		
NO		
YES	1.385 (0.774–2.478)	0.272
Medication regimen		
Unused		
LABA OR LAMA	0.369 (0.151–0.901)	0.029*
LABA+LAMA		
ICS+LABA	0.883 (0.351–2.221)	0.791
LABA+LAMA+ICS	0.799 (0.404–1.581)	0.519
PaCO2≥50mmHg		
NO		
YES	1.622 (0.912–2.884)	0.1
Cerebrovascular disease		
NO		
YES	2.885 (1.396–5.963)	0.004*

Notes: HR values are presented with their 95% CI in parentheses; P values are presented as exact values where possible; A P value of less than 0.05 is considered statistically significant, indicated by bold or an asterisk (*).

Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; ApoE, Apolipoprotein E; PaO2, Partial Pressure of Oxygen; PaCO2, Partial Pressure of Carbon Dioxide.

Table 4 Subgroup Analyses of Age, Sex, Heart Failure, and Cerebrovascular Disease Were Performed

Variable	ApoE>41.50mg/L Yes vs NO (HR)	Pvalue
Age		
<76	4.194 (1.265–13.905)	0.019*
≥76	1.793 (0.9–3.574)	0.097
Sex		
Female	2.446 (0.868–6.892)	0.09
Male	2.283(1.076–4.842)	0.031*
Congestive heart failure		
NO	2.793 (1.173–6.651)	0.02*
YES	1.539 (0.705–3.358)	0.279
Cerebrovascular disease		
NO	2.031 (1.089–3.785)	0.026*
YES	2.375 (0.34–16.567)	0.383

Notes: HR values are presented with their 95% CI in parentheses; P values are presented as exact values where possible; A P value of less than 0.05 is considered statistically significant, indicated by bold or an asterisk (*).
Abbreviations: HR, Hazard Ratio; CI, Confidence Interval; ApoE, Apolipoprotein E.

Discussion

This study was carried out to examine the relationship between the level of ApoE and one-year mortality among COPD patients. Through a multivariate Cox proportionate hazards regression analysis, it is established that for patients where ApoE levels are greater than 41.50 mg/L, there is significantly higher risk for one-year all-cause mortality (HR: 2.103, 95% CI: 1.19–3.716, P=0.01). Therefore, we proposed that the increased ApoE level might be an independent predictor of mortality in COPD patients.

ApoE is a multifaceted protein that plays an important part in the processes of lipid metabolism and the inflammation, particularly in cholesterol transport and clearance through its interactions with low-density lipoprotein (LDL) receptors.[6] Previous studies[10] have established a link between abnormal lipid metabolism (hypercholesterolemia and hypertriglyceridemia) and adverse outcomes in patients with COPD. Studies demonstrated metabolic disturbances can exacerbate airway inflammation and hasten the decline of lung function.[14] Our study was built based on these findings, and we further demonstrated that elevated levels of ApoE, are associated with a poorer prognosis in AECOPD patients.

In addition to lipid metabolism, the inflammatory response is also a progression in the COPD.[15] Increased inflammatory expression profiles have been identified in endothelial cells within the lungs of COPD patients. Dysregulated ApoE may contribute to amplified inflammatory responses, thus negatively impacting disease progression and the overall health of patients with COPD.[16] ApoE has been implicated in the regulation of oxidative stress responses.[17] Reduced antioxidants and increased oxidative damage in alveolar epithelial cells (eg, AT2 B cells) have been found to lead to impaired cellular senescence and repair mechanisms, which in turn lead to increased mortality in patients with advanced COPD.[16]

Additionally, While a definitive link between ApoE polymorphisms and the progression of COPD has yet to be established, evidence suggests that interactions between ApoE variants and smoking may contribute to the progression of COPD.[18] Furthermore, oxidative stress and chronic inflammation—hallmarks of COPD—can modulate ApoE expression through mechanisms such as Nrf2-ARE activation or cytokine-mediated inhibition.[19] These observations indicate a complex interplay among genetic predisposition, oxidative stress, and inflammatory responses exist in the regulation of ApoE levels. This dynamic regulation likely adapts to various pathological environments, reflecting the multifaceted role of ApoE in disease progression.

Three main subtypes of ApoE (ApoE2, ApoE3 and ApoE4) exhibit significant functional differences.[9] A single amino acid substitution, where cysteine at position 112 in ApoE3 is replaced by arginine in ApoE4, can lead to variations in lipid binding, aggregation, and overall functionality.[20] Notably, ApoE4 is more susceptible to disruptions in lipid

metabolism and heightened inflammatory responses,[21] which can exacerbate COPD by increasing airway inflammation and oxidative stress. Furthermore, ApoE4 alleles linked to likelihood of heart disease.[22] Considering the systemic inflammation that connects cardiac and pulmonary, the influence of ApoE4 on COPD may be more significant than previously acknowledged, especially in the presence of risk factors like smoking and oxidative stress.

This study found a nonlinear link between ApoE levels and mortality. A restricted cubic spline curve (Figure 2A) showed that when ApoE levels rose past a certain point, the risk of death also went up. Although there is not direct proof of high ApoE levels are linked to COPD, our findings match with earlier studies on the findings of heart and brain diseases which has a higher ApoE levels were tied to worse outcomes and mortality.[8,23] Survival analysis (Figure 2B) also showed that patients with higher ApoE levels had a higher mortality rate during follow-up. The gap between the two groups grew larger as time went on.

Although univariate analysis showed no statistically significant effect of smoking, it is crucial in the pathophysiological mechanisms of COPD. It may indirectly influence the relationship between APOE concentration and mortality by affecting pulmonary inflammation and immune responses. Studies on lung health showed that smoking cessation significantly improve lung function and lower the mortality.[1] A study in a Han Chinese population identified a potential link between APOE gene variants and COPD susceptibility, particularly in the context of environmental factors like smoking.[19] The findings of the studies, combined with the conclusions of this topic, indicate that smoking status may alter the impact of APOE on COPD risk, and its mechanism still requires further research and validation.

We performed subgroup analyses on the statistically significant factors identified in the multifactorial analyses, with particular attention given to the differences between gender groups. In the male group, the risk ratio for ApoE levels greater than 41.50 mg/L was significantly higher (HR=2.283, P=0.031), whereas no significant difference was observed in the female group (P=0.09). Although the P-value of 0.09 for the female group did not reach the conventional threshold for statistical significance (0.05), it is still relatively close to the critical value, suggesting a possible association between ApoE levels and the risk of death in females. This may imply that men are more susceptible than women to changes in ApoE levels, potentially due to gender-specific physiological differences or other underlying biological mechanisms. In patients <76 years of age, ApoE levels >41.50 mg/L were associated with a significantly increased risk of 1-year all-cause mortality (HR: 4.194, P=0.019). However, this relationship was weaker in older patients (P=0.097). Furthermore, high ApoE levels were linked to a significantly higher risk of death in patients without heart failure (HR=2.793, P=0.02), whereas in patients with heart failure, this association was not significant (P=0.279). Similarly, high ApoE levels were significantly associated with the risk of death in patients without cerebrovascular disease (HR=2.031, P=0.026), but in patients with cerebrovascular disease, this association was not significant (P=0.383). These findings suggest that ApoE level changes may have a diminished impact on mortality risk in patients already at higher risk of death, such as those with heart failure or cerebrovascular disease. This may be due to their poorer overall health and the dominance of other health issues in contributing to mortality risk. Therefore, when evaluating the impact of ApoE levels on mortality risk in COPD patients, it is crucial to consider the combination of factors such as age, overall health, and comorbid conditions.

Elevated ApoE levels are associated with poorer prognosis in other inflammatory and metabolic diseases such as cardiovascular disease. Our findings are consistent with these findings and highlight the potential role of ApoE in identifying high-risk patients. This suggests that ApoE may serve as a prognostic biomarker in AECOPD, aiding in risk stratification and clinical management of COPD patients.

Our study provides some ideas on the relationship between ApoE and AECOPD, but has some limitations. Firstly, the exact roles and mechanisms that ApoE play in the progression of AECOPD are unknown, and the results may be related to systemic inflammation and lipid metabolism, so further studies are needed to elucidate these mechanisms. In addition, we adjusted smoking status in the analyses, but the specific relationship between smoking, ApoE levels, and COPD progression was still not clear. Thirdly, our study did not focus on specific ApoE subtypes, but rather on the association between overall ApoE levels and disease prognosis. Fourthly, we only assessed the health status of patients through telephone follow-up and did not monitor ApoE concentrations during the 1-year follow-up period. Therefore, we could not evaluate the changes in ApoE concentrations over time. Fifthly, the patient population was predominantly older and had a high smoking prevalence, which may limit the generalizability of our findings to younger or non-smoking AECOPD patients. Sixth, ApoE data were missing for 40 patients (8.9%), which could have resulted in bias.

However, post hoc power analysis confirmed that our study had sufficient power to detect a significant effect despite the missing data. Thus, the common effects that different ApoE subtypes may have together on outcomes need to be further explored in future studies. Finally, because our study population was largely derived from data from our hospital, our findings may not apply to all groups.

In addition, although our study focused on mortality in patients with COPD, it is possible that ApoE levels may be associated with other non-COPD causes of mortality as well. For example, elevated ApoE levels have been associated with poor prognosis in cardiovascular[8] and neurological diseases.[24] These diseases may interact with ApoE through different mechanisms, affecting the overall health status and survival of patients. Our findings are consistent with these findings and highlight the potential role of ApoE in identifying high-risk patients to help accurately predict the risk of death within one year, thus supporting the development of personalised treatment plans and prognostic improvement. However, the current data are only from single-centre studies, and further validation of its specific application in risk stratification through multicentre studies is still needed.

Conclusion

This prospective research revealed that an ApoE concentration of 41.50 mg/L or higher was an independent risk factor for 1-year mortality among patients who were admitted due to COPD exacerbations. Subgroup analyses further revealed that this association was stronger in younger patients (aged <76 years) and males. Additionally, the impact of ApoE levels on mortality risk was more pronounced in patients without comorbidities such as congestive heart failure or cerebrovascular disease.

However, our study is limited by its focus on overall ApoE levels, lack of mechanistic clarity, and predominantly older, high-smoking-prevalence patient population. Future studies need to delve deeper into the effects of ApoE on inflammation, lipid metabolism, and immune responses in COPD to identify therapeutic targets, improve prognosis, and potentially improve understanding of other inflammatory or metabolic disorders to guide clinical risk assessment. But multicentre validation is needed to confirm these findings.

Data Sharing Statement

With the corresponding author's permission, we can share anonymized participant data after publication. A clear proposal explaining the study goals and the plan for statistical analysis is needed to review the request. The corresponding author will decide if the data can be shared based on the proposed goals and plan.

Ethics Statement

The Ethics Committee of the Third Affiliated Medical Hospital in Guangzhou reviewed and granted approval for studies that included human participants. Written informed consent was obtained from the patients/participants to take part in this research.

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Author Contributions

Yuqun Li and Yang Xiao/Liping Wei conceived the idea for this report. Zhenxing Li, Liping Wei, Yuqun Li and Qilan Wu collected the data for the study. Qilan Wu and Yuqun Li drafted the paper. Yuqun Li and Yang Xiao were involved in data analysis and revision. All authors made substantial contributions to the work reported, whether in the conception, study design, execution, data acquisition, analysis and interpretation, or in all these areas. They all took part in drafting, revising, or critically reviewing the article, gave final approval of the version to be published, agreed on the journal to which the article has been submitted, and are accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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