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ORIGINAL RESEARCH

Association Between Advanced Lung Cancer Inflammation Index and Mortality in US Adults with Chronic Obstructive Pulmonary Disease

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Purpose: Identifying reliable prognostic markers is critical for improving chronic obstructive pulmonary disease (COPD) management. The advanced lung cancer inflammation index (ALI) is a novel marker reflecting inflammation and nutritional status. This study evaluated the association between ALI and all-cause and cause-specific mortality in COPD patients.

Patients and Methods: Data from 4616 adults with COPD in the National Health and Nutrition Examination Survey (1999–2018) were analyzed. Mortality outcomes were obtained from the National Death Index. Multivariable Cox proportional hazards models and restricted cubic splines assessed the association between the natural logarithm of ALI (lnALI) and mortality. Time-dependent receiver operating characteristic (ROC) curves evaluated the predictive performance of lnALI at 3, 5, and 10 years. Mediation analysis examined whether estimated glomerular filtration rate (eGFR) mediated these associations.

Results: During a median 80-month follow-up, 1202 participants died: 349 from cardiovascular disease, 263 from cancer, and 194 from chronic lower respiratory diseases (CLRD). Higher lnALI was significantly associated with lower risks of all-cause, cardiovascular, and CLRD mortality. L-shaped associations were observed for all-cause and cardiovascular mortality, with inflection points at 4.04 and 3.64, respectively. The AUCs for predicting all-cause mortality were 0.670, 0.646, and 0.634; for cardiovascular mortality, 0.659, 0.653, and 0.629; and for CLRD mortality, 0.770, 0.751, and 0.739 at 3, 5, and 10 years. eGFR partially mediated the associations between lnALI and both all-cause and cardiovascular mortality.

Conclusion: Higher lnALI values were significantly associated with lower risks of all-cause, cardiovascular, and CLRD mortality in COPD patients.

Keywords: advanced lung cancer inflammation index, chronic obstructive pulmonary disease, mortality, cohort study, NHANES

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading global cause of morbidity and mortality, with its burden continuing to rise. The global prevalence of COPD is approximately 10.3% and is expected to increase further due to population aging in high-income countries and persistent tobacco use in low- and middle-income regions.[1] COPD accounts for approximately 42 deaths per 100,000 individuals and is responsible for 4.72% of all global deaths. Projections suggest that by 2060, COPD and related conditions will cause more than 5.4 million deaths annually.[2] The economic burden of COPD is huge, consuming about 6% of the annual healthcare budget in Europe, with related costs reaching $38.6 billion. Over the next 20 years, COPD-related expenses are predicted to reach $800 billion in the United States.[1] Early identification of high-risk patients through reliable biomarkers is crucial to slow disease progression, improve quality of life, and reduce mortality.

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The advanced lung cancer inflammation index (ALI), calculated using body mass index (BMI), serum albumin, neutrophil and lymphocyte counts, is a novel systemic biomarker that reflects both nutritional status and systemic inflammation. Originally developed as a prognostic marker in metastatic non-small cell lung cancer, ALI has demonstrated predictive value in various non-malignant chronic diseases, including hypertension,[3] diabetes,[4] and heart failure.[5]

COPD pathophysiology is characterized by chronic inflammation, oxidative stress, immune dysfunction, and progressive airflow limitation. While traditional predictors of mortality—such as forced expiratory volume in one second (FEV_1),[6] inflammatory responses,[7] body mass index (BMI)[8] and nutritional status or malnutrition —are commonly used, they offer limited prognostic insight when considered independently.[9] More comprehensive indices, such as the BODE index (which integrates BMI, FEV_1, dyspnea score, and exercise capacity), have been proposed. However, its clinical utility is constrained by the need for complex assessments and specialized equipment.[10]

Given the inflammatory and nutritional dimensions of COPD progression, ALI may serve as a feasible and integrative biomarker for mortality risk stratification. To address this research gap, we conducted a large-scale observational cohort study using NHANES data to explore the relationship between ALI and all-cause as well as cause-specific mortality in individuals with COPD. Our findings aim to provide new insights into prognosis and risk stratification for COPD patients, potentially contributing to improved clinical management and patient outcomes.

Materials and Methods

Study Design and Participants

This cohort study analyzed data from the National Health and Nutrition Examination Survey (NHANES), covering ten survey cycles from 1999 to 2018. NHANES employed a multistage, stratified probability sampling design to select a nationally representative sample of the non-institutionalized US civilian population. Study protocols were approved by the Institutional Review Board (IRB) of the National Center for Health Statistics (NCHS), and written informed consent was obtained from all participants. Detailed information regarding the ethics and consent procedures is publicly available (https://www.cdc.gov/nchs/nhanes/irba98.htm). As NHANES data are de-identified and publicly available, no additional informed consent or ethical approval was required for this secondary analysis. According to Article 32 of the Ethical Review Methods for Life Science and Medical Research Involving Human Beings (February 18, 2023, China), studies based on publicly available, anonymized datasets without human intervention are exempt from institutional ethical review. Furthermore, the Ethics Committee of Minzu Affiliated Hospital of Guangxi Medical University granted an exemption for this study (approval number: 2024–0031). This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

COPD diagnosis was based on both self-reported medical history and objective spirometry measurements recorded in the NHANES database. Participants were classified as having COPD if they answered "yes" to the question: "Has a doctor or other health professional ever told you that you had COPD, emphysema, or chronic bronchitis?". Additionally, from 2007 to 2012, spirometry was performed by trained technicians following European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines. Forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were measured, with a post-bronchodilator FEV_1/FVC ratio < 0.7 used to confirm COPD.

Initially, 5383 participants with COPD were identified. Inclusion criteria were: (1) age ≥20 years; (2) confirmed COPD diagnosis (either self-reported or spirometry-confirmed with post-bronchodilator $FEV_1/FVC < 0.7$); and (3) complete data for calculating the ALI, including BMI, serum albumin, neutrophil, and lymphocyte counts. Exclusion criteria included: (1) participants lacking essential ALI components (n=744); (2) missing survival outcome data from the National Death Index (NDI) linkage (n=23). Data for this analysis were extracted from the publicly available NHANES dataset (1999–2018), which includes comprehensive demographic, clinical, laboratory, and mortality data representative of the US non-institutionalized civilian population. NHANES methodology and data collection protocols are documented on the CDC website (https://www.cdc.gov/nchs/nhanes/index.htm). Therefore, the final analytic sample comprised 4616 COPD participants. A detailed flowchart of the inclusion and exclusion process is provided in Figure S1.

Measurement of ALI

The ALI was calculated using the formula: ALI = BMI (kg/m²) × serum albumin (g/dL) / neutrophil-to-lymphocyte Ratio (NLR).

Ascertainment of Mortality

Mortality outcomes were obtained by linking NHANES participants to the National Death Index (NDI) through December 31, 2019, including all-cause, cardiovascular, CLRD, and cancer mortality. Mortality linkage was conducted by the CDC based on standardized procedures. According to the International Classification of Diseases, 10th Revision (ICD-10), Cardiovascular deaths were identified using ICD-10 codes I00–I09, I11, I13, and I20–I51 for heart disease, and I60–I69 for cerebrovascular disease. ICD-10 codes J40–J47 were used to identify CLRD mortality[11] (Table S1), encompassing chronic bronchitis, emphysema, asthma, bronchiectasis, and other chronic lower respiratory diseases. Importantly, this definition excludes deaths from repeated infectious pneumonia, aspiration pneumonia, and senile pneumonia, which are classified under other ICD-10 codes (eg, J15–J18). Cancer deaths were identified using ICD-10 codes C00–C97.

Assessment of Covariates

Covariates included demographic factors (age, gender, race/ethnicity, education level, marital status, family poverty income ratio [PIR]), lifestyle factors (smoking status, drinking status, physical activity), anthropometric measures (waist circumference, BMI), and clinical parameters (systolic blood pressure [SBP], diastolic blood pressure [DBP], high-density lipoprotein cholesterol [HDL-C], total cholesterol [TC], alanine aminotransferase [ALT], aspartate aminotransferase [AST], hemoglobin A1c [HbA1c], serum uric acid, blood urea nitrogen [BUN], serum creatinine, and estimated glomerular filtration rate [eGFR]).

Inflammatory markers (platelet count, lymphocyte count, monocyte count, neutrophil count, PLR, MLR, NLR, SIRI, SII) and comorbidities (diabetes, hypertension, heart failure, coronary heart disease, cancer, and stroke) were also assessed. Definitions and measurement protocols for all covariates are detailed in the Supplementary Material.

Statistical Analyses

The analysis adhered to the NHANES analytical and reporting guidelines, taking into account complex sampling designs and sampling weights. For the two cycles from 1999 to 2002, the fasting subsample Mobile Examination Center (MEC) weight for 4-year was multiplied by 1/5 to determine the sample weights; for the eight cycles from 2003 to 2018, the fasting subsample 16-year MEC weight was multiplied by 2/5. ALI values were log-transformed (lnALI) to correct for right-skewed distribution. Baseline characteristics were compared across lnALI quartiles using one-way ANOVA for continuous variables and Pearson's chi-square test for categorical variables.

Multivariate Cox proportional hazards regression models were used to investigate the relationship between lnALI and mortality. Model 1 was unadjusted, Model 2 was adjusted for age, gender, and race, and Model 3 was further adjusted for education level, PIR, waist circumference, smoking status, hypertension, diabetes, heart failure, coronary heart disease, stroke, and eGFR. Internal validation was performed for each multivariate Cox model (all-cause mortality, cardiovascular mortality, CLRD mortality, and cancer mortality) using bootstrap resampling with 500 repetitions. Optimism-corrected Harrell's concordance indices (C-index) were calculated to assess model discrimination and stability. In order to assess any potential nonlinearity between lnALI and mortality in COPD patients, restricted cubic splines (RCS) with four knots were employed. The RCS shape was used to determine the inflection point. Stratified and interaction analyses were conducted by age (<60 and ≥60 years), gender, smoking status (current or former/never), eGFR (<90 and ≥90 mL/min/1.73 m²), coronary heart disease (yes/no), heart failure (yes/no), hypertension (yes/no), and diabetes (yes/no). The "timeROC" package was used to conduct a time-dependent receiver operating characteristic (ROC) curve analysis to measure the predictive accuracy of lnALI for survival outcomes at 3, 5, and 10 years. A mediation analysis evaluated the indirect impact of lnALI on mortality mediated through eGFR. Missing data were systematically evaluated across all variables. Given the standardized and high-quality data collection protocols in NHANES, we assumed that the

missingness mechanism was at random (MAR). To minimize potential bias and maintain statistical power, missing values were addressed using multiple imputation by chained equations (MICE), generating five imputed datasets. The imputation models incorporated demographic characteristics, clinical measurements, laboratory indices, and outcome variables. Analyses were performed separately on each imputed dataset, and pooled estimates were calculated using Rubin's rules to account for between-imputation variability. This approach enabled us to robustly handle missingness while preserving the integrity of the analytical cohort. All analyses were performed using R version 3.6 and EmpowerStats, with a two-sided significance threshold of $p<0.05$.

Results

Baseline Characteristics of Participants

A total of 4616 COPD patients were included, with a mean age of 55.17 years (95% CI: 54.52–55.81) and 44.22% were male (Table S2). The mean ALI and lnALI were 65.45 (95% CI: 63.76–67.15) and 4.02 (95% CI: 4.00–4.04), respectively. Participants were categorized into quartiles based on lnALI values, with 1154 individuals in each group. Compared with participants in the Q1 group, those in the Q2, Q3, and Q4 groups were more likely to be female, non-smokers, and of non-White ethnicity. They exhibited lower levels of HDL-C, neutrophil count, NLR, SII, SIRI, PLR, and MLR, but had higher waist circumference, BMI, DBP, and lymphocyte counts (all $P < 0.05$). Among the included participants, 760 were diagnosed with cancer, including 47 with lung cancer. Baseline characteristics of participants with cancer are presented in Table S3.

Additionally, participants were categorized based on survival status (Table S4). Compared to survivors, dead participants were older, predominantly White, more likely to be former smokers and drinkers, and had a higher prevalence of comorbidities such as hypertension, diabetes, heart failure, coronary heart disease, stroke, and cancer. They also exhibited lower education levels, PIR, physical activity, BMI, DBP, TC, serum albumin, lymphocyte count, ALI, and eGFR, but higher SBP, AST, HbA1c, monocyte count, neutrophil count, NLR, SII, SIRI, PLR, MLR, BUN, serum creatinine, and serum uric acid levels (all $P < 0.05$).

Associations of ALI with All-Cause Mortality in Individuals with COPD

Over a median follow-up period of 111 months (interquartile range (IQR), 54.0–147.0 months), 1202 (26.04%) COPD patients died. The leading causes of death were cardiovascular disease (29.03%), cancer (21.88%), and CLRD (16.14%). Higher lnALI was significantly associated with a lower risk of all-cause mortality, as demonstrated by multivariate Cox regression analyses. After full adjustment in Model 3, the hazard ratios (HRs) and 95% confidence intervals (CIs) across increasing lnALI quartiles were: 1.00 (reference) for Q1, 0.80 (0.69–0.92) for Q2, 0.66 (0.56–0.78) for Q3, and 0.58 (0.48–0.70) for Q4 (P for trend <0.001; Table 1). In continuous models, each one-unit increase in lnALI was associated with a 39% decrease in all-cause mortality risk (HR: 0.61, 95% CI: 0.55–0.69). RCS analysis showed a negative

Table 1 Multivariate Cox Regression Analysis of lnALI with Mortality Among Participants with Chronic Obstructive Pulmonary Disease from NHANES (1999–2018)

Characteristics	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
All-cause mortality						
lnali (per 1 unit increment)	0.47 (0.42, 0.52)	<0.001	0.59 (0.53, 0.65)	<0.001	0.61 (0.55, 0.69)	<0.001
lnALI quartile						
Q1	1		1		1	
Q2	0.66 (0.57, 0.76)	<0.001	0.77 (0.67, 0.89)	<0.001	0.80 (0.69, 0.92)	0.002
Q3	0.47 (0.40, 0.55)	<0.001	0.60 (0.52, 0.71)	<0.001	0.66 (0.56, 0.78)	<0.001
Q4	0.38 (0.32, 0.45)	<0.001	0.53 (0.45, 0.63)	<0.001	0.58 (0.48, 0.70)	<0.001
P for trend		<0.001		<0.001		<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular mortality						
lnALI (per 1 unit increment)	0.47 (0.39, 0.56)	<0.001	0.62 (0.51, 0.75)	<0.001	0.62 (0.50, 0.76)	<0.001
lnALI quartile						
Q1	1		1		1	
Q2	0.60 (0.46, 0.79)	<0.001	0.72 (0.55, 0.95)	0.021	0.74 (0.56, 0.98)	0.038
Q3	0.45 (0.34, 0.61)	<0.001	0.61 (0.46, 0.82)	0.001	0.65 (0.48, 0.89)	0.007
Q4	0.41 (0.30, 0.56)	<0.001	0.62 (0.45, 0.85)	0.003	0.62 (0.45, 0.87)	0.006
P for trend		<0.001		<0.001		0.002
Cancer mortality						
lnALI (per 1 unit increment)	0.65 (0.52, 0.81)	<0.001	0.79 (0.63, 0.98)	0.035	0.82 (0.65, 1.04)	0.099
lnALI quartile						
Q1	1		1		1	
Q2	0.69 (0.50, 0.96)	0.027	0.80 (0.58, 1.12)	0.191	0.81 (0.58, 1.13)	0.207
Q3	0.69 (0.50, 0.95)	0.025	0.89 (0.64, 1.23)	0.481	0.95 (0.68, 1.34)	0.789
Q4	0.54 (0.38, 0.77)	0.001	0.71 (0.50, 1.03)	0.071	0.79 (0.54, 1.16)	0.225
P for trend		<0.001		0.121		0.378
Mortality from CLRD						
lnALI (per 1 unit increment)	0.27 (0.22, 0.34)	<0.001	0.35 (0.27, 0.44)	<0.001	0.36 (0.28, 0.46)	<0.001
lnALI quartile						
Q1	1		1		1	
Q2	0.63 (0.45, 0.87)	0.005	0.73 (0.53, 1.02)	0.065	0.77 (0.55, 1.08)	0.128
Q3	0.31 (0.21, 0.46)	<0.001	0.39 (0.26, 0.59)	<0.001	0.40 (0.26, 0.62)	<0.001
Q4	0.12 (0.07, 0.22)	<0.001	0.16 (0.09, 0.30)	<0.001	0.17 (0.09, 0.31)	<0.001
P for trend		<0.001		<0.001		<0.001

Notes: Model 1: no covariates were adjusted; Model 2: adjusted for age, gender, race; Model 3: adjusted for covariates in Model 2 plus education level, PIR, waist circumference, smoking status, hypertension, diabetes, heart failure, coronary heart disease, stroke, and eGFR.
Abbreviations: ALI, advanced lung cancer inflammation index; PIR, family poverty income ratio; eGFR, estimated glomerular filtration rate; CLRD, chronic lower respiratory diseases; HR, hazard ratio; CI, confidence interval.

nonlinear relationship between lnALI and all-cause mortality (p for nonlinear = 0.006) (Figure 1A). The inflection point was found at 4.04 by the two-piecewise Cox proportional hazards regression models. For lnALI values less than 4.04, a one-unit increase in lnALI was linked to a 47% reduction in mortality risk (HR: 0.53, 95% CI: 0.46–0.61). The association was not statistically significant when lnALI exceeded 4.04 (HR: 0.83, 95% CI: 0.67–1.04), as indicated in Table S5. No significant interactions were found with age, gender, smoking status, eGFR, coronary heart disease, heart failure, hypertension, and diabetes (p for interaction > 0.05) (Table S6).

Associations of ALI with Cardiovascular Mortality in Individuals with COPD

Higher lnALI levels were also associated with reduced cardiovascular mortality (Table 1). After full adjustment, HRs (95% CIs) were 1.00 (reference) for Q1, 0.74 (0.56–0.98) for Q2, 0.65 (0.48–0.89) for Q3, and 0.62 (0.45–0.87) for Q4 (P for trend = 0.002). In continuous models, each one-unit increase in lnALI corresponded to a 38% decrease in cardiovascular mortality risk (HR: 0.62, 95% CI: 0.50–0.76). RCS analysis revealed a significant nonlinear relationship (P for nonlinearity = 0.042), with an inflection point at 3.64 (Figure 1B). Below this threshold, lnALI showed a strong inverse association with cardiovascular mortality (HR: 0.43, 95% CI: 0.30–0.61), while no significant association was found above 3.64. Subgroup analysis identified a significant interaction with hypertension status (P for interaction = 0.019), with stronger protective effects observed among non-hypertensive individuals (HR: 0.51, 95% CI: 0.34–0.78) compared to hypertensive individuals (HR: 0.73, 95% CI: 0.54–0.97).

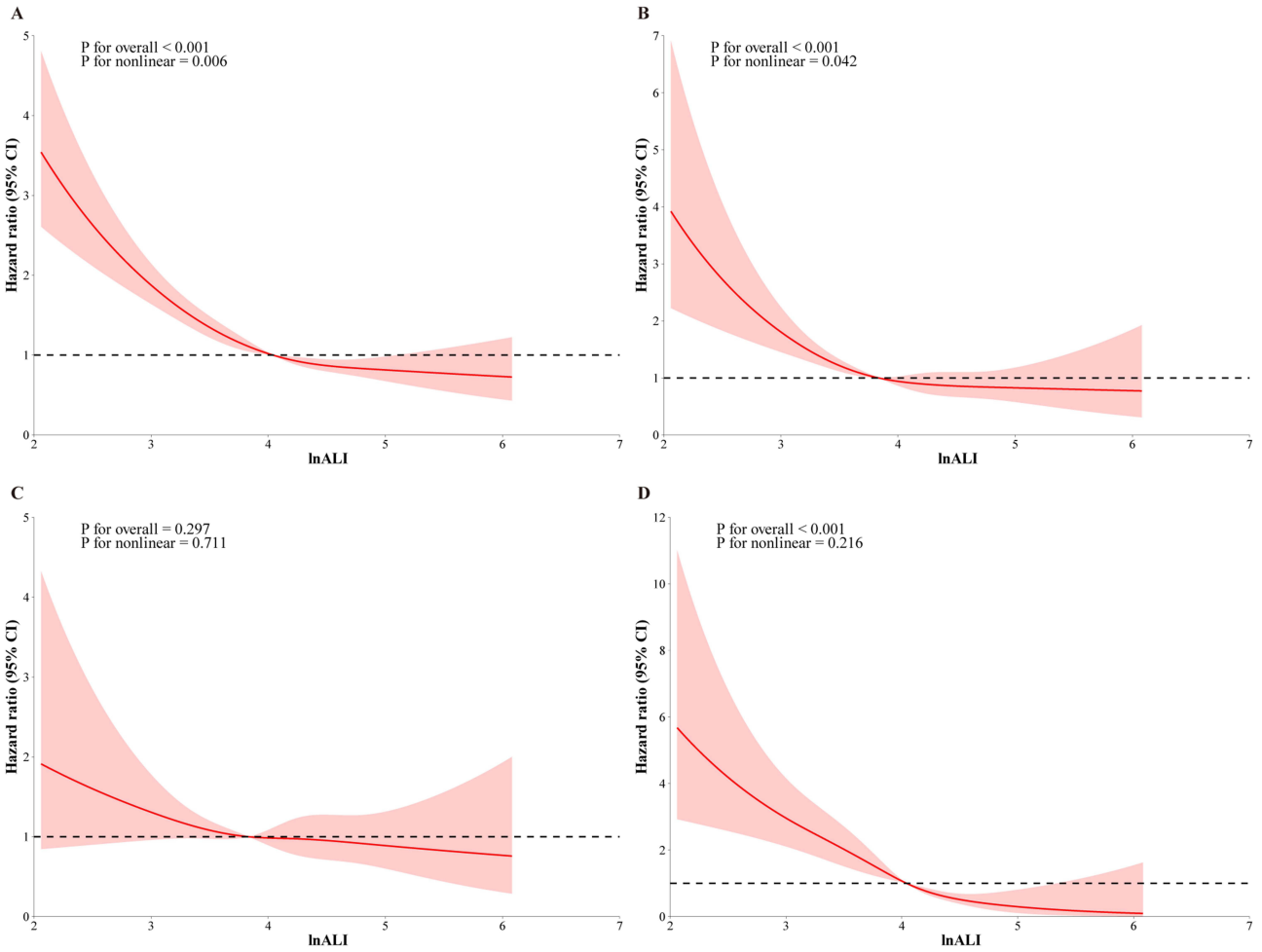

Figure 1 The association of lnALI with all-cause (**A**), cardiovascular mortality (**B**), mortality from cancer (**C**), and chronic lower respiratory diseases mortality (**D**) among chronic obstructive pulmonary disease patients from NHANES (1999–2018) visualized by restricted cubic spline.

Notes: Hazard ratios were adjusted for age, gender, race, education level, PIR, waist circumference, smoking status, hypertension, diabetes, heart failure, coronary heart disease, stroke, and eGFR.

Abbreviations: ALI, advanced lung cancer inflammation index; PIR, family poverty income ratio; eGFR, estimated glomerular filtration rate; CI, confidence interval.

Associations of ALI with Cancer Mortality in Individuals with COPD

No significant association was observed between lnALI levels and cancer mortality (Table 1). The HRs (95% CIs) across lnALI quartiles were 0.81 (0.58–1.13) for Q2, 0.95 (0.68–1.34) for Q3, and 0.79 (0.54–1.16) for Q4 compared to Q1 (P for trend = 0.378). Similarly, in continuous models, lnALI was not significantly associated with cancer mortality risk (HR: 0.82, 95% CI: 0.65–1.04). RCS analysis confirmed the absence of a significant association (Figure 1C).

Associations of ALI with Mortality from CLRD in Individuals with COPD

Higher lnALI levels were significantly associated with lower CLRD mortality risk (Table 1). Adjusted HRs (95% CIs) were 1.00 (reference) for Q1, 0.77 (0.55–1.08) for Q2, 0.40 (0.26–0.62) for Q3, and 0.17 (0.09–0.31) for Q4 (P for trend <0.001). In continuous models, each one-unit increase in lnALI was associated with a 64% reduction in CLRD mortality risk (HR: 0.36, 95% CI: 0.28–0.46). RCS analysis indicated a linear inverse association (P for nonlinearity = 0.216; Figure 1D). No significant interactions were found with age, gender, smoking status, eGFR, coronary heart disease, heart failure, hypertension, and diabetes (Table S7).

Internal Validation of Cox Models

To assess the predictive performance and robustness of the Cox regression models for all-cause, cardiovascular, cancer, and CLRD mortality, internal validation was conducted using bootstrap resampling (n = 100). The models demonstrated good to excellent discrimination across outcomes, with optimism-corrected C-indices of 0.7801 for all-cause mortality, 0.8144 for cardiovascular mortality, 0.7551 for cancer mortality, and 0.8367 for CLRD mortality (Table S8). Notably, the model for CLRD mortality exhibited the highest C-index and the strongest association with lnALI (HR = 0.36, 95% CI: 0.28–0.46, $p < 0.0001$). The corrected Dxy values ranged from 0.4754 to 0.6449, indicating acceptable generalizability. The slope statistics (ranging from 0.8999 to 0.9713) further supported minimal overfitting and model stability.

The Predictive Ability of ALI for Mortality in Individuals with COPD

Time-dependent ROC analysis showed that the AUCs of lnALI for predicting all-cause mortality at 3-, 5-, and 10-year intervals were 0.670, 0.646, and 0.634, respectively (Figure 2A and B). For cardiovascular mortality, the AUCs were

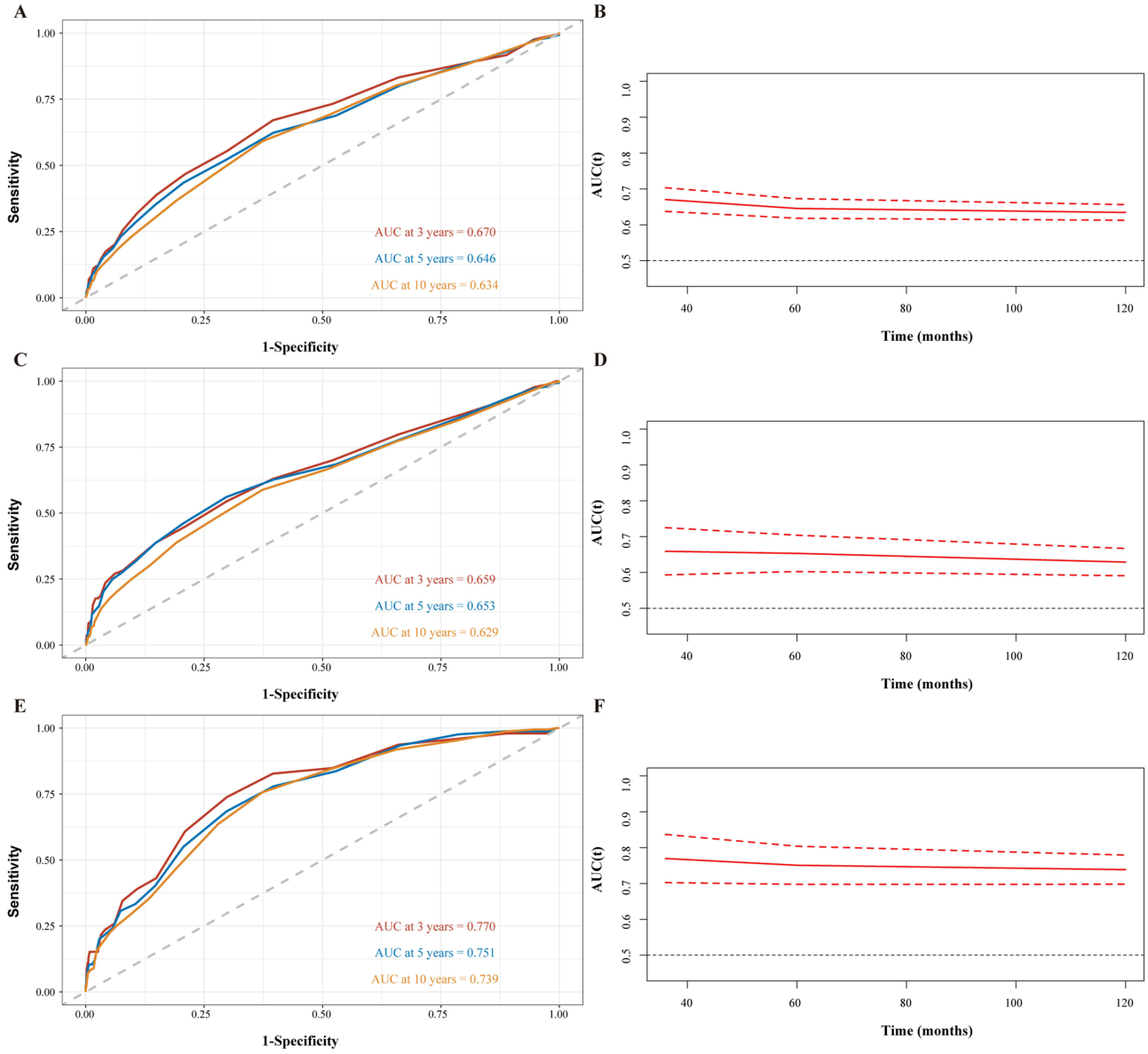

Figure 2 Time-dependent ROC curves and time-dependent AUC values (with 95% confidence band) of the lnALI for predicting all-cause mortality (**A** and **B**), cardiovascular mortality (**C** and **D**) and mortality from chronic lower respiratory diseases (**E** and **F**) among chronic obstructive pulmonary disease patients from NHANES (1999–2018).

https://doi.org/10.2147/COPD.S516286

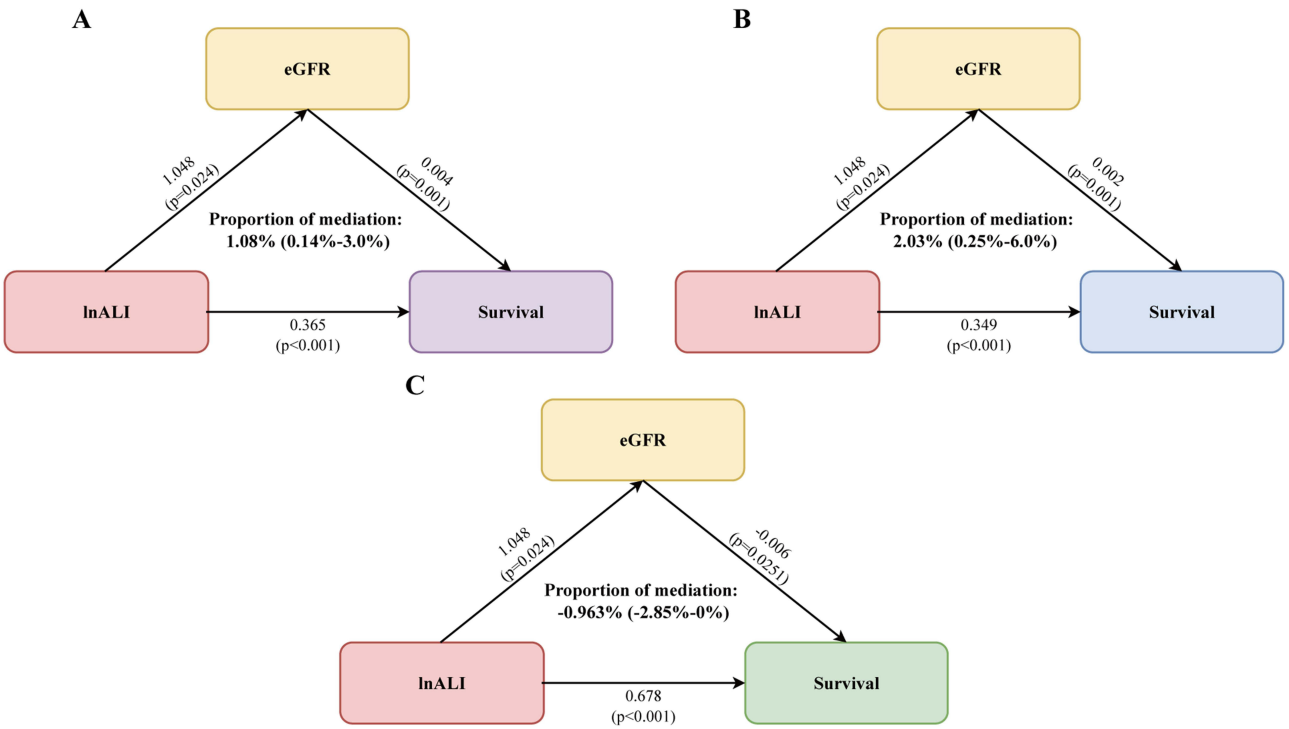

Figure 3 The mediating effect of eGFR on the relationship between lnALI and survival among chronic obstructive pulmonary disease patients from NHANES (1999–2018) ((**A**) all-cause mortality; (**B**) cardiovascular mortality; (**C**), chronic lower respiratory diseases mortality).
Notes: Adjusted for age, gender, race, education level, PIR, waist circumference, smoking status, hypertension, diabetes, heart failure, coronary heart disease, and stroke.
Abbreviations: eGFR, estimated glomerular filtration rate; ALI, advanced lung cancer inflammation index; PIR, family poverty income ratio.

0.659, 0.653, and 0.629 at 3, 5, and 10 years, respectively (Figure 2C and D), and for CLRD mortality, 0.770, 0.751, and 0.739 (Figure 2E and F). Additionally, we assessed the predictive ability of various markers including neutrophil, lymphocyte, monocyte counts, NLR, SII, SIRI, PLR, MLR, and albumin for mortality in COPD patients. Across all examined time periods (3-year, 5-year, and 10-year), lnALI demonstrated superior predictive power for all-cause mortality compared to most other markers, except for MLR. For cardiovascular mortality, lnALI outperformed SIRI, MLR, and albumin at all time intervals. Regarding CLRD mortality, lnALI showed superior predictive ability compared to other indices (Figures S2–S4).

Mediation Analysis of lnALI for Mortality Individuals with COPD

Mediation analysis revealed a significant positive association between lnALI and eGFR (β ± SE = 1.048 ± 0.465, p = 0.024). Higher eGFR was associated with lower risks of all-cause (β ± SE = 0.004 ± 0.001, p = 0.001) and cardiovascular mortality (β ± SE = 0.007 ± 0.002, p = 0.001), but was paradoxically associated with higher CLRD mortality risk (β ± SE = −0.007 ± 0.001, p = 0.025). eGFR mediated 1.08% (95% CI: 0.14%–3.00%) of the association between lnALI and all-cause mortality, and 2.03% (95% CI: 0.25%–6.00%) of the association between lnALI and cardiovascular mortality (Figure 3A and B). No significant mediation effect was observed for CLRD mortality (Figure 3C).

Discussion

In this large, nationally representative cohort study, higher ALI levels were significantly associated with lower all-cause, cardiovascular, and CLRD mortality among individuals with COPD, independent of confounders. Internal validation confirmed the robustness of our models. Restricted cubic spline analysis revealed L-shaped associations between lnALI and both all-cause and cardiovascular mortality, with thresholds identified at 4.04 and 3.64, respectively. Below these thresholds, each unit increase in lnALI substantially reduced mortality risk. ALI exhibited strong discriminatory ability

for predicting 3-, 5-, and 10-year mortality outcomes. Mediation analysis further suggested that eGFR partially mediated the association between lnALI and all-cause and cardiovascular mortality.

Our study focused on mortality as the primary outcome due to its clear clinical significance and reliable assessment via NHANES linkage to the National Death Index. A major limitation of the NHANES dataset is the absence of clinical treatment data, such as exacerbation history, hospitalization records, and disease staging. This restricts the ability to assess the short-term prognostic value of ALI in early COPD management. The absence of indicators for early treatment failure—such as worsening symptoms requiring therapy escalation or hospitalization—prevents a thorough assessment of ALI's role in short-term treatment efficacy. Although NHANES provides robust long-term survival data, the absence of clinical response indicators limits the evaluation of short-term treatment outcomes. Future research should utilize comprehensive clinical databases with detailed treatment responses, hospitalization records, and dynamic disease assessments to better clarify ALI's prognostic value in early COPD management. Additionally, the NHANES dataset does not consistently include eosinophil count data, which may limit the generalizability of our findings to eosinophilic COPD phenotypes, a subgroup with distinct prognosis and treatment responses.

ALI was first proposed by Jafri et al in 2013 as a composite marker of systemic inflammation and nutritional status.[12] While its prognostic value has been demonstrated in cancer and chronic diseases, for example, Chen et al found that ALI has J-shaped and L-shaped relationships with all-cause and cardiovascular mortality in diabetic patients,[4] and another retrospective study identified higher ALI levels as significantly associated with lower mortality in elderly heart failure patients,[5] no prior study has evaluated its relevance in COPD. Our study is the first to demonstrate a robust inverse association between lnALI and mortality in COPD. lnALI was found to have an L-shaped association with cardiovascular and all-cause mortality, with the thresholds of 4.04 and 3.64, respectively. Below these thresholds, the predictive effect on mortality was particularly notable lnALI also showed superior predictive value for 3-, 5-, and 10-year all-cause, cardiovascular, and CLRD mortality compared to other inflammatory and nutritional markers (Figure 3).

COPD is characterized by persistent airflow limitation and chronic airway inflammation, often accompanied by systemic inflammatory responses and nutritional deficiency. Pathophysiologically, COPD involves chronic bronchial inflammation, small airway remodeling, and destruction of alveolar structures. Oxidative stress plays a pivotal role, with excessive reactive oxygen species (ROS)[13] promoting inflammation via activation of pro-inflammatory signaling pathways such as NF-κB and MAPK.[14] These pathways induce the release of cytokines, chemokines, and adhesion molecules, perpetuating airway damage and systemic inflammation.[15] Systemic inflammatory biomarkers are closely associated with COPD progression and mortality. Elevated levels of C-reactive protein (CRP) are observed during acute exacerbations and correlate with increased risk of death in patients with mild to moderate COPD.[16] In addition, other biomarkers, such as Club Cell Secretory Protein (CC16), soluble receptor for advanced glycation end-products (sRAGE), and surfactant protein D (SP-D), have demonstrated strong associations with emphysema severity and FEV_1 decline.[17] These markers reflect both airway epithelial injury and systemic inflammation, providing insight into disease activity and prognosis. The neutrophil-to-lymphocyte ratio (NLR), a component of ALI, serves as a surrogate marker of systemic inflammation. A high NLR reflects an imbalance between innate and adaptive immune responses and has been linked to greater disease severity, lung function decline, and mortality in COPD.[18] Chronic inflammation also promotes muscle catabolism by inhibiting muscle protein synthesis and enhancing proteolysis through cytokine-mediated pathways, which exacerbates sarcopenia and further worsens respiratory function.[19]

Nutritional impairment is another critical component of COPD-related morbidity and mortality. Malnutrition, sarcopenia, and low BMI are prevalent among COPD patients and are independently associated with reduced lung function, impaired exercise capacity, more frequent exacerbations, and increased mortality. Serum albumin, a key component of the ALI, is a recognized indicator of nutritional status. Hypoalbuminemia not only reflects malnutrition but also indicates heightened inflammatory burden and oxidative stress.[20,21] Albumin exerts anti-inflammatory[22] and antioxidant effects,[23] and its deficiency may compromise immune responses, increase susceptibility to infections, and contribute to poor clinical outcomes. Additionally, albumin maintains fluid balance and colloid osmotic pressure, with low levels causing edema and fluid retention, increasing respiratory failure risk.[24] Low BMI reflects malnutrition and sarcopenia, both of which are linked to poor clinical outcomes. Previous studies have revealed that 20–40% of COPD patients have low muscle mass, 15–21% have sarcopenia, and 30–60% are malnourished.[25] The "obesity paradox" refers

to the observation that low BMI, as an indicator of malnutrition and muscle wasting, is associated with increased cardiovascular and all-cause mortality in COPD patients.[26] Malnutrition in COPD patients leads to decreased exercise capacity, worsened lung function, increased acute exacerbations, and higher mortality rates. Mai et al evaluated the nutritional status of COPD patients using the Controlling Nutritional Status (CONUT) score, which assesses serum albumin, lymphocyte count, and total cholesterol levels. Their findings revealed a positive relationship between the CONUT score and both CVD mortality (HR: 1.86, 95% CI: 1.27–2.74) and all-cause mortality (HR: 1.50, 95% CI: 1.18–1.91) in COPD patients.[27] Another study found that a low Geriatric Nutritional Risk Index (GNRI) was an independent risk factor for all-cause mortality among COPD individuals.[28]

Taken together, the ALI integrates these key aspects—nutritional status via BMI and albumin, and inflammatory status via NLR—into a composite index. This enables a more comprehensive risk stratification for COPD patients compared to traditional single-variable markers. Thus, increases in lnALI below thresholds are associated with reduced COPD mortality due to improved nutritional status and decreased inflammation. However, further interventions targeting these factors may have limited effects on reducing mortality.

The relationship between ALI and cardiovascular and all-cause mortality in COPD patients appears to be partially mediated by renal function, according to our analysis. A study that included 2274 patients with COPD found that approximately 7.1% had CKD, and eGFR was independently linked to increased dyspnea, decreased physical performance, poorer quality of life, and higher mortality.[29] Chronic systemic inflammation and oxidative stress, prevalent in both COPD and CKD, impair protein metabolism and immune function,[30] increasing infection risk. Renal impairment can result in heart failure, hypertension, and fluid retention,[31] further worsening the condition of COPD patients. Preserving renal function is crucial as it can reduce these risks and enhance survival in COPD patients.

The interaction between lnALI and hypertension suggests that cardiovascular comorbidity may modulate inflammation-related mortality risks. Given the higher rates of exacerbations and hospitalizations in hypertensive COPD patients,[32] the protective effect of ALI may be attenuated in this subgroup.[33]

Our findings support the prognostic value of ALI across multiple mortality outcomes in COPD patients. Among the four cause-specific models, lnALI demonstrated the most pronounced predictive power for CLRD mortality, highlighting its potential utility as a disease-specific marker reflecting both systemic inflammation and nutritional status. While lnALI also showed significant associations with all-cause and cardiovascular mortality, its relationship with cancer mortality was weaker and not statistically significant, which may be attributed to cancer-related factors outside the scope of ALI's inflammatory-nutritional dimensions. Importantly, internal validation using bootstrap resampling revealed strong model discrimination with high C-indices and corrected Dxy values, confirming the robustness and reliability of our models. This strengthens the evidence supporting the use of lnALI in clinical risk stratification for COPD-related mortality. Future external validation in independent cohorts and prospective settings is warranted to enhance generalizability.

One of the strengths of our study is the use of the NHANES database, which provides a long follow-up period and a large sample size, ensuring the validity and representativeness of our conclusions. To strengthen causal inference and enhance external validity, future prospective cohort studies that incorporate repeated measurements, comprehensive clinical data, and stratification based on eosinophil counts are essential. These studies should also consider diverse patient populations, including those from different healthcare systems and countries, to improve generalizability. By controlling for multiple confounding variables, the study reduces the likelihood of bias. Several limitations of this study must be acknowledged. First, the retrospective observational design of the NHANES dataset inherently introduces biases, including selection bias, recall bias, and potential misclassification. Although mortality data were prospectively collected through linkage to the National Death Index, baseline exposure and covariate data were obtained retrospectively via participant recall and clinical examination, which may affect data accuracy. In particular, during years without spirometry testing (1999–2006 and 2013–2016), COPD diagnosis relied partially on self-reported physician diagnoses, potentially leading to misclassification and underestimation of disease severity. Second, selection bias may have occurred because only participants with complete data for ALI calculation and mortality outcomes were included, possibly excluding more severely ill individuals and thus underestimating mortality risks. Third, despite adjusting for a wide range of covariates and employing multiple imputation to address missing data, residual confounding cannot be fully excluded due to the observational design. Additionally, important clinical variables such as treatment history, exacerbation frequency, and comorbidity severity were not available

in the NHANES dataset. Fourth, ALI was assessed only at baseline, without accounting for changes over time that might influence long-term outcomes. Moreover, the lack of eosinophilic stratification and absence of dynamic disease staging may limit generalizability to broader and more heterogeneous COPD populations, particularly those with distinct inflammatory phenotypes or differing healthcare access. Differences in demographic characteristics, genetic predispositions, healthcare access, and clinical management strategies between the US and other countries may affect the applicability of our results to other populations. To strengthen causal inference and enhance external validity, future prospective cohort studies conducted across different healthcare systems, including more diverse ethnic populations and incorporating repeated measurements and comprehensive clinical data, are warranted.

Conclusion

In conclusion, lnALI was inversely associated with all-cause, cardiovascular, and CLRD mortality in COPD patients. These findings highlight ALI's potential as an integrative prognostic biomarker. Its role in capturing both systemic inflammation and malnutrition underscores the importance of comprehensive COPD management strategies. Notably, renal function was identified as a partial mediator, emphasizing the interconnected nature of systemic organ dysfunction in COPD. These findings suggest that interventions targeting malnutrition, systemic inflammation, and renal impairment may improve clinical outcomes. Future large-scale, prospective studies incorporating repeated ALI measurements, treatment response data, and diverse populations are warranted to validate and extend these observations and to optimize early intervention strategies in ECOPD patients.

Ethics Approval and Informed Consent

All participants provided written informed consent prior to participation in the NHANES survey, which received approval from the NCHS Institutional Review Board (IRB) (details available at https://www.cdc.gov/nchs/nhanes/irba98.htm). As NHANES is a publicly accessible database containing anonymized data, no further ethical approval or participant consent was required.

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