International Journal of Chronic Obstructive Pulmonary Disease

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

The Association Between the CALLY Index and All-Cause Mortality in Patients with COPD: Results from the Cohort Study of NHANES 2007–2010

Yu Ding[1], Yuxia Liu[2], Jianjian Yu[2], Chengsen Cai[2], Lina Fu[2], Jie Zhu[3], Shengzhen Yang[4], Yu Jiang[1], Jun Wang[2]

[1]The First Clinical Medical College, Shandong University of Traditional Chinese Medicine, Jinan, People's Republic of China; [2]Department of Pulmonary and Critical Care Medicine, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, People's Republic of China; [3]Department of Pharmacy, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, People's Republic of China; [4]Department of Pulmonary, Rizhao Hospital of Traditional Chinese Medicine, Rizhao, People's Republic of China

Correspondence: Jun Wang, Department of Pulmonary and Critical Care Medicine, The Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, People's Republic of China, Email jnwj660606@163.com

Purpose: The C-reactive protein (CRP)–albumin–lymphocyte (CALLY) index is a newly developed biomarker that combines measurements of CRP, serum albumin, and lymphocyte count. This index provides a thorough assessment of a patient's inflammation level, nutritional condition, and immunological function. The objective of this study is to examine the correlation between the CALLY index and all-cause mortality in COPD patients.

Methods: We calculated the CALLY index using data from the National Health and Nutrition Examination Survey (NHANES) for the 2007–2008 and 2009–2010 cycles, extracted from the participants' peripheral blood samples. The study utilized Kaplan-Meier curves, restricted cubic spline (RCS) curves, and Cox regression analysis to evaluate the relationship between the CALLY index and the risk of all-cause mortality in COPD patients. To assess the predictive accuracy of the CALLY index, we calculated the area under the receiver operating characteristic (ROC) curve (AUC).

Results: The study included 1,048 participants and found a significant negative correlation between the CALLY index and all-cause mortality in patients with COPD. The CALLY index was a major predictor of survival in COPD patients [fully adjusted model: in the 3rd quartile, HR = 1.61, 95% CI: 1.02–2.52, p = 0.039; in the 2nd quartile, HR = 2.11, 95% CI: 1.22–3.65, p = 0.008; in the 1st quartile, HR = 3.12, 95% CI: 2.00–4.85, p < 0.001]. The RCS curves demonstrated a non-linear association between the CALLY index and all-cause mortality in COPD patients. The areas under the curve (AUC) in predicting 5- and 10-year all-cause mortality were 0.693 and 0.656.

Conclusion: The CALLY index has a strong relationship with all-cause mortality in patients with COPD in the US and could serve as a prognostic biomarker for these patients.

Keywords: chronic obstructive pulmonary disease, the C-reactive protein–albumin–lymphocyte index, national health and nutrition examination survey, biomarker

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous pulmonary condition characterized by progressively worsening airflow limitation.[1] In 2019, the number of prevalent cases of COPD worldwide reached 212.3 million, leading to 3.3 million deaths, with an age-standardized mortality rate of 42.5 per 100,000.[2] COPD has emerged as the third primary cause of death worldwide, the sixth foremost cause of death in the United States, and the third most common cause of death in China.[3–5] Therefore, it is crucial to identify an easy and effective biomarker for COPD survival risk and prognosis prediction, which will assist pulmonologists in early intervention.

Received: 3 July 2024
Accepted: 29 December 2024
Published: 22 January 2025

Inflammation, nutrition, and immune response play key roles in the occurrence and progression of COPD. The novel biomarker that combines CRP, serum albumin, and lymphocyte count is the C-reactive protein (CRP)–albumin–lymphocyte (CALLY) index. It can provide a comprehensive overview of a patient's immunological function, nutritional status, and level of inflammation.[6] Previous studies have shown that the CALLY index has significant predictive value in the prognosis of various cancers.[7–10] However, there is no research on applying the CALLY index in COPD.

Previous literature has proposed and confirmed various blood inflammation indices that can be used to predict the occurrence and development of COPD. For example, the neutrophil-to-lymphocyte ratio (NLR), the neutrophil-percentage-to-albumin ratio (NPAR), the CRP-to-albumin ratio (CAR), and the systemic immune-inflammation index (SII, platelet count×neutrophil count/lymphocyte count) have all been demonstrated to be strongly associated with the risk of death in COPD patients.[11–14] However, these indices only combine information on inflammation and immunity, or inflammation and nutrition, and are not as comprehensive as the CALLY index.

The objective of this study is to assess the relationship between the CALLY index and all-cause mortality in patients with COPD in the United States through a cohort study, aiming to provide a new biomarker for clinical practice.

Materials and Methods

Data Source

Launched in the early 1960s, the National Center for Health Statistics (NCHS) is responsible for the extensive and ongoing National Health and Nutrition Examination Survey (NHANES). Utilizing a multistage probability sampling approach, NHANES evaluates the health and nutritional status of the ambulatory population in the United States. The survey includes questionnaire interviews, laboratory tests, and physical examinations. The NCHS Ethical Review Board has approved the NHANES study protocol, and all participants have given written informed consent. The NHANES website provides access to all publicly available data and research studies.

Study Population

The selection of participants was based on the NHANES database, which covered two survey cycles (2007–2008 and 2009–2010). Our study excluded the following: (1) individuals under 20 years old; (2) individuals with missing COPD data; (3) individuals with missing albumin, lymphocyte, or CRP data; (4) individuals without COPD. Ultimately, 1048 individuals were part of the research. Since the study involves hematological variables, we utilized the weights from the Mobile Examination Center (MEC). Figure 1 summarizes the precise inclusion and exclusion criteria.

Definition of the CALLY Index

Blood tests were conducted utilizing automated hematology analyzers in every survey round. The objective of this study is to analyze the CALLY index. The index formula is as follows.[7,9]

$$\text{the CALLY index} = \frac{\text{Albumin}(\text{g/dL}) \times \text{Lymphocyte}(/\mu\ \text{L})}{\text{CRP}(\text{mg/dL}) \times 10^4}$$

Assessment of COPD

According to previous studies,[15,16] we define COPD as the presence of any one of the following conditions: 1. FEV_1/FVC < 0.7 post-bronchodilation. 2. A positive answer to any of these questions: (1) "Ever told you that you have emphysema?" (2) "Ever told you had chronic bronchitis?"

Covariates Definition

The covariates of this study include age, gender, race (Mexican American, non-Hispanic white, non-Hispanic black, other Hispanic, other race), body mass index (BMI) (< 25, 25–30, ≥ 30), education level (< high school, high school, > high school), marital status (marriage/living with a partner, widowed/divorced/separated, never married), poverty-income ratio (PIR) (≤ 1.30,1.30–3.50, > 3.50), drinking, smoking, hypertension, cardiovascular diseases (CVDs) and cancer. Drinking at least 12 drinks a year is defined as a drinker. Smokers were defined as those who had smoked more than 100 cigarettes

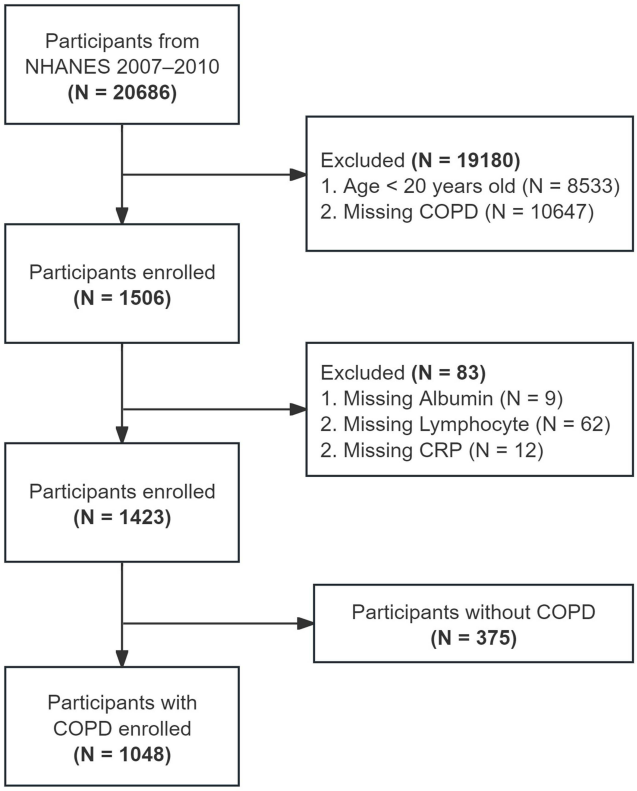

Figure 1 Flowchart of participants selection.

during their lifetime.[17] Hypertension was defined as having a systolic blood pressure ≥ 130 mmHg, or diastolic blood pressure ≥ 80 mmHg. The definition of CVDs is being informed by a doctor or other health professional of having congestive heart failure (CHF), coronary heart disease (CHD), angina, myocardial infarction, or stroke. Cancer was defined by a positive answer to the question: "Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?"

Study Outcome

The main outcome assessed was all-cause mortality among COPD patients. Survival information for the cohort was extracted from the NHANES public-use linked mortality file until December 31, 2019. The follow-up period for mortality was computed from the survey participation date to either the date of death or December 31, 2019.

Statistical Analysis

Continuous variables were expressed as median (interquartile range [IQR]), while categorical variables were displayed as counts (percentages, %). Demographic characteristics were analyzed using the Pearson's Chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables. To evaluate the associations between the CALLY index and all-cause mortality in COPD patients, weighted Cox regression analyses were conducted univariately and multivariately. Model 1 was the unadjusted crude model. Model 2 included adjustments for age, gender, race, BMI, marital status, PIR, smoking, and drinking. Model 3, the fully adjusted model, included additional covariates such as hypertension, CVDs, and cancer. Meanwhile, Kaplan-Meier (KM) curves were used to show varying survival probabilities in COPD patients across various CALLY levels. Restricted cubic splines (RCS) with four knots were utilized to assess potential non-linear associations between the CALLY index and all-cause mortality in COPD patients, capturing the risk variation across the continuum of relationships. To balance data completeness and

 https://doi.org/10.2147/COPD.S485036

reduce biases from imputation, the random forest method was used to handle variables with missing data.[18] The accuracy of the CALLY index in predicting survival outcomes was assessed using receiver operating characteristic (ROC) curve analysis.

All statistical analyses were conducted with R software (version 4.3.3). A p-value < 0.05 (two-tailed) was regarded as statistically significant.

Results

Baseline Information of the Participants with COPD

1048 participants were included in this study during the two cycles of surveys (2007–2010). The baseline characteristics of the research participants, stratified by final mortality status, are shown in Table 1. The median (IQR) age of participants was 59 (46–68) years, with non-survivors being older than survivors [68 (61–74) vs 54 (43–65), p < 0.001]. A marginally higher number of males than females (539 cases vs 509). Non-Hispanic Whites

Table 1 Baseline Information of the Participants with COPD

Variables	Final Mortality Status			P-value[b]
	Overall,	Survivors,	Non-survivors,	
	N = 1048[a]	N = 769[a]	N = 279[a]	
Age (years)	59 (46–68)	54 (43–65)	68 (61–74)	**<0.001**
Gender (%)				**0.008**
Male	539 (51%)	376 (49%)	163 (58%)	
Female	509 (49%)	393 (51%)	116 (42%)	
Race (%)				**0.046**
Mexican American	78 (7.4%)	68 (8.8%)	10 (3.6%)	
Other Hispanic	76 (7.3%)	58 (7.5%)	18 (6.5%)	
Non- Hispanic White	687 (66%)	499 (65%)	188 (67%)	
Non- Hispanic Black	167 (16%)	116 (15%)	51 (18%)	
Other Race	40 (3.8%)	28 (3.6%)	12 (4.3%)	
BMI (%)				0.345
< 25	292 (28%)	214 (28%)	78 (28%)	
25–30	334 (32%)	254 (33%)	80 (29%)	
≥ 30	422 (40%)	301 (39%)	121 (43%)	
Education (%)				**<0.001**
< High school	349 (33%)	230 (30%)	119 (43%)	
High school	268 (26%)	196 (25%)	72 (26%)	
> High school	431 (41%)	343 (45%)	88 (32%)	
Marriage (%)				**<0.001**
Marriage/Living with partner	622 (59%)	475 (62%)	147 (53%)	
Widowed/Divorced/Separated	320 (31%)	207 (27%)	113(41%)	
Never married	106 (10%)	87(11%)	19(6.8%)	
PIR (%)				**<0.001**
≤ 1.30	369 (35%)	249 (32%)	120 (43%)	
1.30–3.50	423 (40%)	301 (39%)	122 (44%)	
> 3.50	256 (24%)	219 (28%)	37 (13%)	
Drinking (%)				**0.032**
Yes	816 (78%)	612 (80%)	204 (73%)	
No	232 (22%)	157(20%)	75 (27%)	
Smoking (%)				**<0.001**
Yes	765 (73%)	521 (68%)	244 (87%)	
No	283 (27%)	248 (32%)	35 (13%)	

(*Continued*)

Table 1 (Continued).

Variables	Final Mortality Status			P-value[b]
	Overall,	Survivors,	Non-survivors,	
	N = 1048[a]	N = 769[a]	N = 279[a]	
Hypertension (%)				**<0.001**
Yes	682 (65%)	466 (61%)	216 (77%)	
No	366 (35%)	303 (39%)	63 (23%)	
CVDs (%)				**<0.001**
Yes	246 (23%)	129 (17%)	117 (42%)	
No	802 (77%)	640 (83%)	162 (58%)	
Cancer (%)				**<0.001**
Yes	158 (15%)	94 (12%)	64 (23%)	
No	890 (85%)	675 (88%)	215 (77%)	
Albumin (g/dL)	4.20 (4.00–4.40)	4.20 (4.00–4.40)	4.10 (3.90–4.30)	**<0.001**
Lymphocyte (10^3/μL)	2.00 (1.60–2.50)	2.10 (1.60–2.50)	1.80 (1.40–2.30)	**<0.001**
CRP (mg/dL)	0.26 (0.11–0.65)	0.23 (0.09–0.57)	0.42 (0.16–1.04)	**<0.001**
CALLY	3.15 (1.26–8.04)	3.70 (1.49–9.56)	1.84 (0.72–4.91)	**<0.001**

Notes: [a]n (%); Median (IQR). [b]Pearson's Chi-squared test; Wilcoxon rank sum test. Bold values indicate p-value < 0.05.
Abbreviations: BMI, body mass index; PIR, family income-poverty ratio; CVDs, cardiovascular diseases; CALLY, C-reactive protein (CRP)–albumin–lymphocyte.

comprised over half of the participants, amounting to 66% (687 cases). 41% of the participants hold an educational level beyond high school. Only 10% of the population was never married. Over 70% of the participants smoked or drank. 65% of the participants had a history of hypertension. Compared to those who survived during the follow-up period, non-survivors were characterized by being older, male, smokers, with a lower education level and a lower PIR. In terms of comorbidities, non-survivors had higher prevalence rates of hypertension, CVDs, and cancer compared to survivors. Additionally, non-survivors showed lower levels of albumin and lymphocyte but higher levels of CRP. The median (IQR) value of the CALLY index was 3.15 (1.26–8.04). Non-survivors showed significantly lower CALLY [1.84 (0.72–4.91) vs 3.70 (1.49–9.56), $p < 0.001$]. The distribution of the CALLY index in different final mortality statuses is shown in the violin plot (Figure 2).

Kaplan-Meier (KM) Survival Curve of the CALLY Index

The CALLY index was calculated as four categorical variables. The weighted Kaplan-Meier (KM) curves revealed markedly different survival outcomes among various groups (Log-rank $p < 0.001$), as shown in Figure 3. In comparison to the lowest quartile (Q1), it was observed that the survival probabilities increased as the CALLY index quartile increased.

Multivariable-Adjusted Restricted Cubic Spline (RCS) Curves of the CALLY Index

As illustrated in Figure 4, the weighted multivariable-adjusted RCS analyses were employed to visualize the association between the CALLY index and all-cause mortality in COPD patients. The RCS analysis indicated a non-linear association of the CALLY index with the all-cause mortality of COPD patients (P for non-linear < 0.001).

Cox Regression Analysis of the Association Between the CALLY Index and the All-Cause Mortality in Patients with COPD

In addition, multivariate weighted Cox regression analyses were performed to assess the association between the COPD patients' all-cause mortality and the CALLY index. The CALLY index was found to be an important predictor of COPD patients' all-cause mortality, as shown in Figure 5 [model 1: hazard ratio (HR) = 1.69, 95% confidence interval (CI):

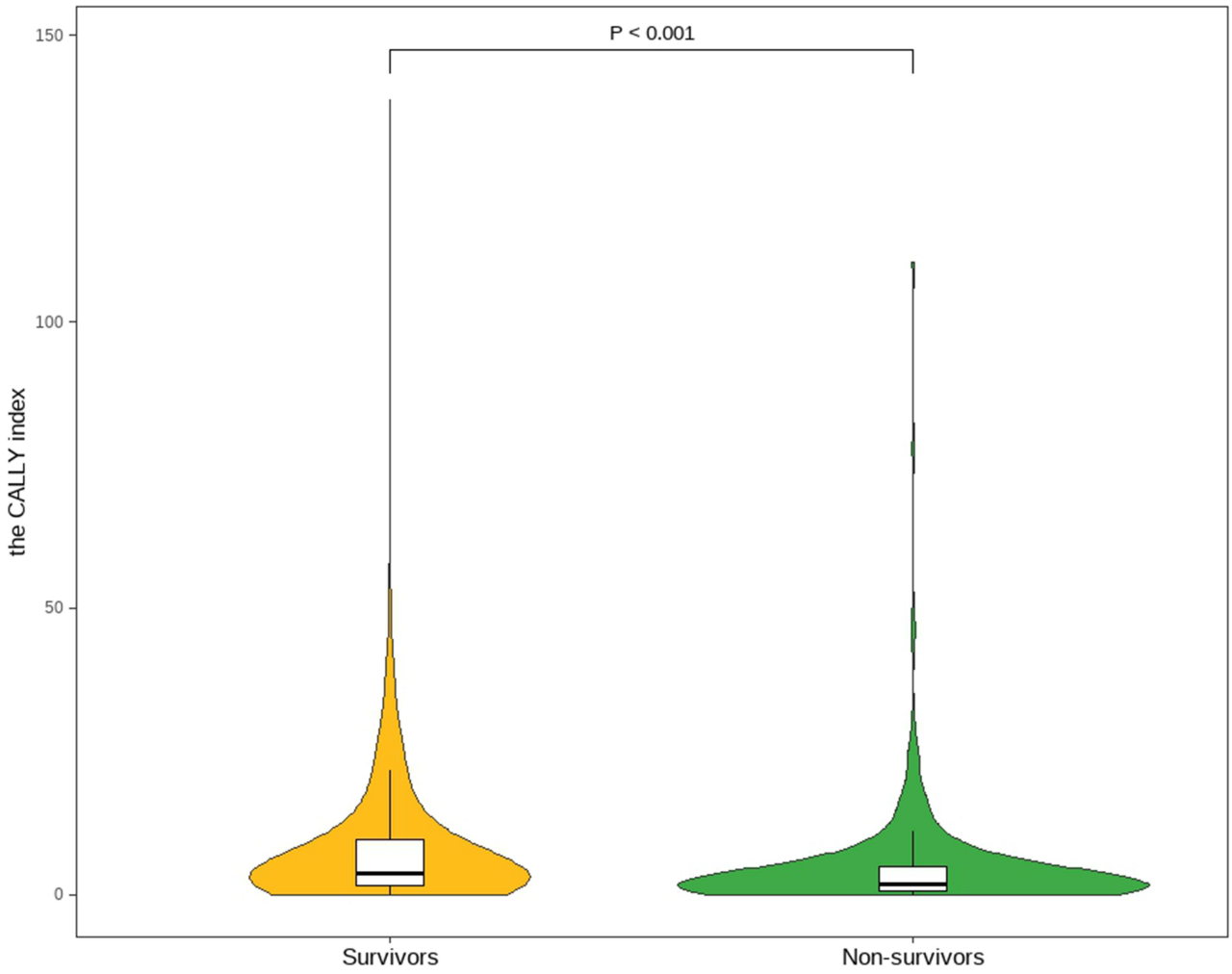

Figure 2 The violin plot shows the distribution of the CALLY index in different final mortality statuses.
Abbreviation: CALLY, C-reactive protein (CRP)–albumin–lymphocyte.

1.05–2.72 in 3rd quartile, p = 0.031; HR = 2.54, 95% CI: 1.52–4.24 in 2nd quartile, p < 0.001; HR = 4.02, 95% CI: 2.64–6.13 in 1st quartile, p< 0.001. Model 2: HR = 1.54, 95% CI: 0.97–2.44 in 3rd quartile, p = 0.069; HR = 2.07, 95% CI: 1.19–3.60 in 2nd quartile, p = 0.010; HR = 2.99, 95% CI: 1.90–4.69 in 1st quartile, p < 0.001. Model 3: HR = 1.61, 95% CI: 1.02–2.52 in 3rd quartile, p = 0.039; HR = 2.11, 95% CI: 1.22–3.65 in 2nd quartile, p = 0.008; HR = 3.12, 95% CI: 2.00–4.85 in 1st quartile, p < 0.001].

Predictive Performance of the CALLY Index, CRP, Albumin, and Lymphocyte in Predicting All-Cause Mortality in COPD Patients

Time-dependent receiver operating characteristic (ROC) curve analysis illustrates the area under the curves (AUCs) of the CALLY index, CRP, albumin, and lymphocyte to establish their predictive power for all-cause mortality (Figure 6). The results demonstrated that the AUCs for CALLY, CRP, albumin, and lymphocyte at 5-year were 0.693, 0.653, 0.637, and 0.650, while at 10-year, the AUCs were 0.656, 0.627, 0.627, and 0.603. These findings indicate that, at both 5- and 10-year, the CALLY index exhibits superior predictive accuracy for survival risk compared to CRP, albumin, and lymphocyte.

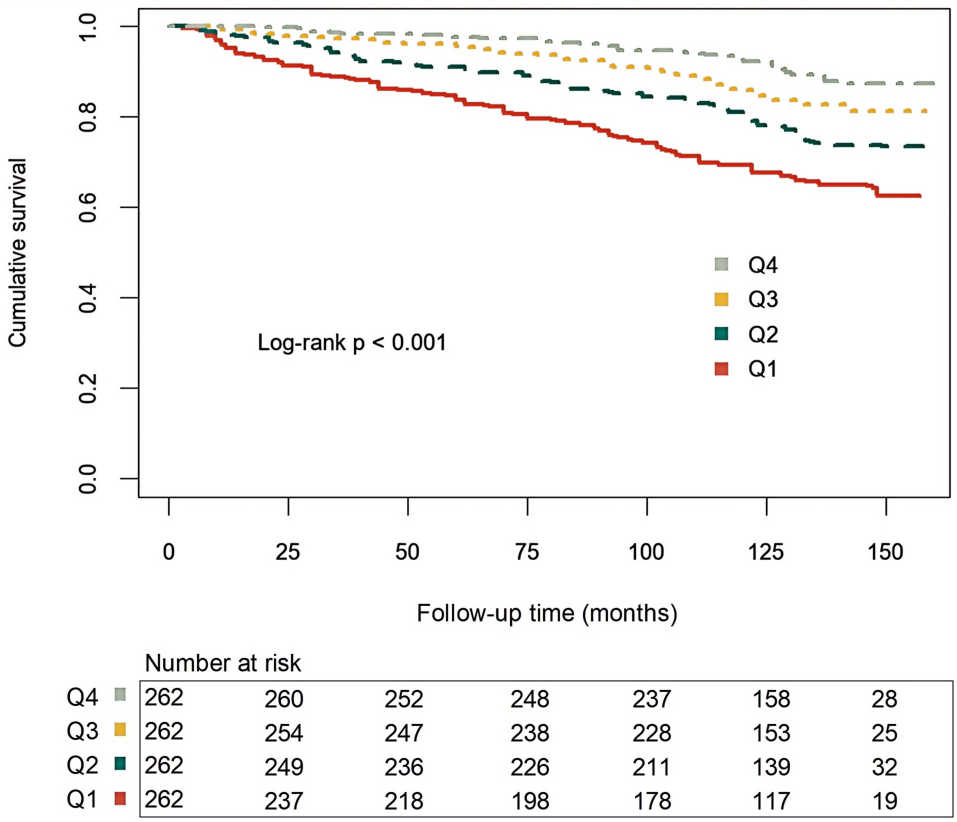

Figure 3 The weighted Kaplan-Meier (KM) curves show the association between the CALLY index and survival in patients with COPD.
Abbreviation: CALLY, C-reactive protein (CRP)–albumin–lymphocyte.

Discussion

This study assessed the association between the CALLY index and all-cause mortality in patients with COPD. We determined negative associations between the CALLY index and the all-cause mortality among individuals with COPD. Furthermore, the ROC curves showed that the CALLY index holds certain predictive value for clinical outcomes of this population.

In the occurrence and development of COPD, inflammation, nutrition, and immune response play a key role. Airway inflammation is a crucial factor in the progression and exacerbation of COPD, and its severity is related to the degree of airflow obstruction.[19,20] The immune system is a key player in the pathogenesis of COPD, and the progression of COPD is associated with changes in the immune system.[21] Nutritional status is also a crucial determinant of COPD prognosis, with insufficient protein intake linked to a higher risk of exacerbations in mild to moderate COPD.[22,23] The hypothesis related to autoimmunity suggests that the inflammatory response can promote immune responses that further stimulate the inflammatory response to exacerbate lung damage.[24] Due to the chronic systemic inflammatory state in patients with COPD, elevated levels of inflammatory markers can lead to malnutrition, manifesting as muscle wasting, weight loss, decreased appetite and so on.[25,26] In addition, these inflammatory characteristics may accelerate the rate of muscle wasting, further reducing exercise tolerance in patients with COPD, and leading to a vicious cycle of disease progression.[27]

Our study found that the RCS curves revealed a non-linear association between the CALLY index and mortality risk in COPD patients (P for non-linear < 0.001). The relationship exhibited a trend of first decreasing and then increasing. Notably, lower CALLY levels are associated with higher mortality risk, while higher CALLY levels show only a minimal increase in risk. An extremely low level of the CALLY index may be influenced by higher CRP, lower albumin, and lower lymphocyte counts, which could increase the risk of all-cause mortality. C-reactive protein (CRP) is an acute-phase protein that not only reflects the level of inflammation in the body but also regulates innate immunity and the course of inflammation.[28] Previous

https://doi.org/10.2147/COPD.S485036

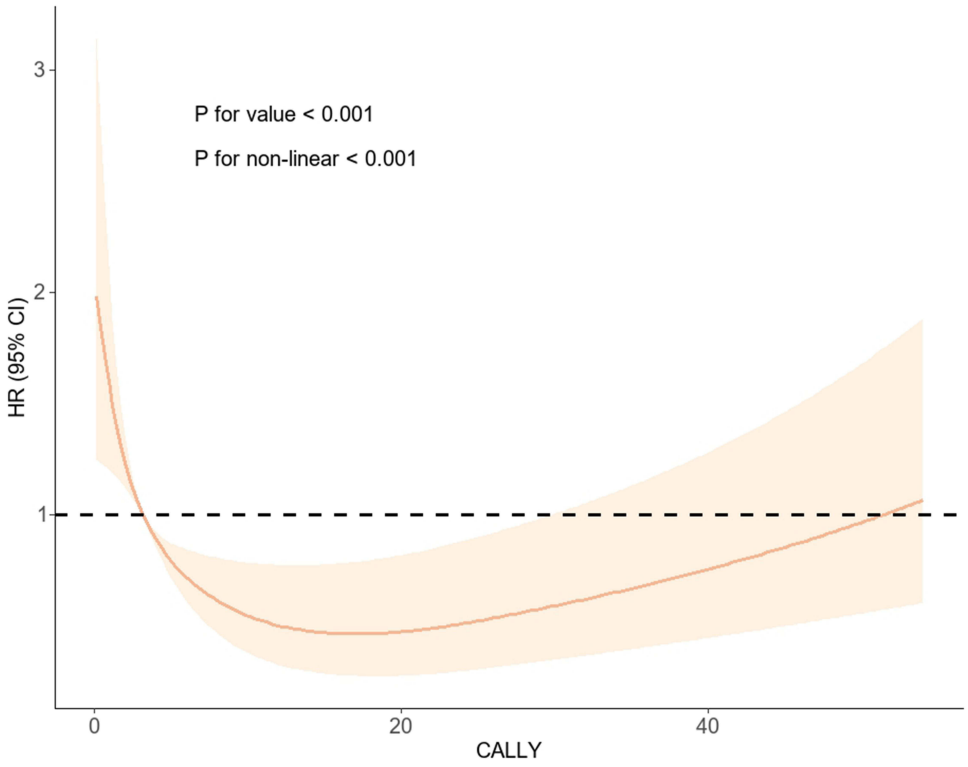

Figure 4 The weighted multivariable-adjusted restricted cubic spline (RCS) curves show dose-effect relationships between the CALLY index and COPD patients' survival.
Notes: Adjusted for the effects of age, gender, race, BMI, educational level, marital status, PIR, smoking, drinking, hypertension, CVDs, and cancer.
Abbreviations: CALLY, C-reactive protein (CRP)–albumin–lymphocyte; BMI, body mass index; PIR, family income-poverty ratio; CVDs, cardiovascular diseases.

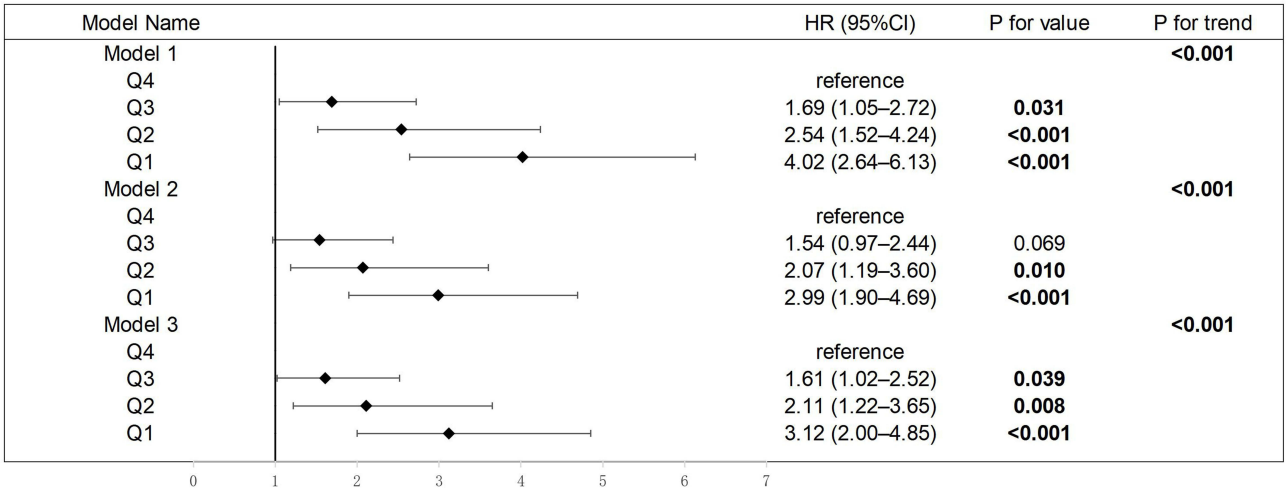

Figure 5 The forest plots show the relationship between the CALLY index and the risk of all-cause mortality in COPD patients.
Notes: Bold values indicate p-value < 0.05. Model 1: unadjusted; Model 2: adjusted for age, gender, race, BMI, educational level, marital status, PIR, smoking, and drinking; Model 3: adjusted for age, gender, race, BMI, educational level, marital status, PIR, smoking, drinking, hypertension, CVDs, and cancer.
Abbreviations: CALLY, C-reactive protein (CRP)–albumin–lymphocyte; BMI, body mass index; PIR, family income-poverty ratio; CVDs, cardiovascular diseases.

meta-analyses have shown that elevated CRP levels are associated with acute exacerbations and hospitalization in patients with COPD and that those with higher CRP levels are linked to an increased risk of early mortality.[29] Lymphocytes are integral to the immune system and play a pivotal role in the body's defense mechanisms, reflecting the level of the immune response.[30] Studies have shown that low blood lymphocyte counts and lymphocyte decline are important prognostic factors in COPD.[31]

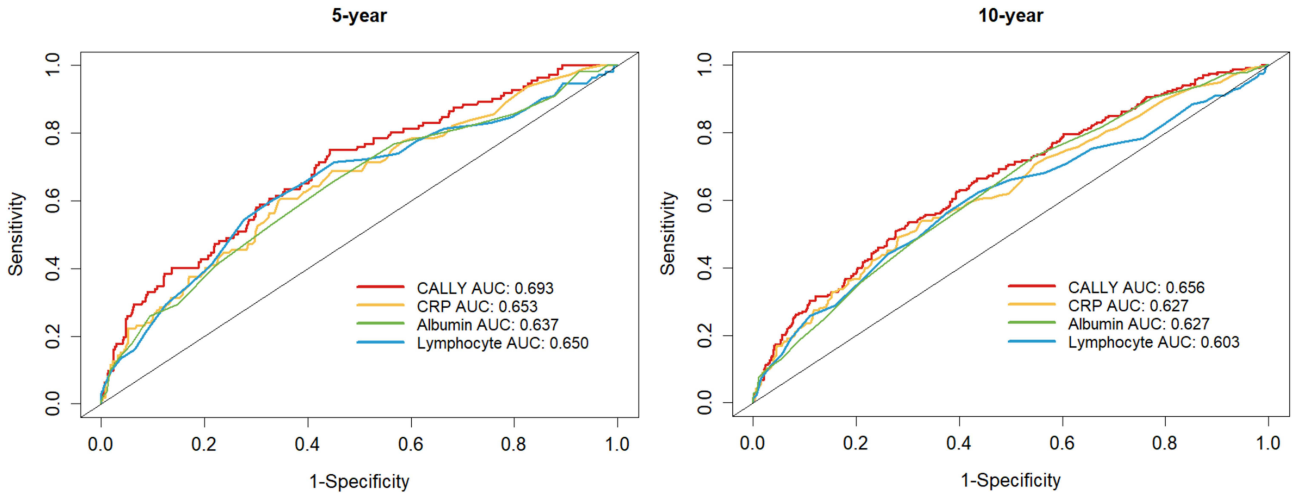

Figure 6 The time-dependent receiver operating characteristic (ROC) curves show the predictive power of the CALLY index, CRP, albumin, and lymphocyte for mortality among COPD patients.
Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CALLY, C-reactive protein (CRP)–albumin–lymphocyte.

Serum albumin levels are one of the assessments for malnutrition in COPD, with hypoalbuminemia being a risk factor for acute respiratory failure and associated with increased mortality in patients with COPD.[32,33] Our study shows that a decrease in the CALLY index (elevated CRP levels, reduced lymphocyte count, and decreased serum albumin) is linked to an increased risk of all-cause mortality in patients with COPD, consistent with the findings of the aforementioned studies.

The ROC curve demonstrated that the CALLY index exhibited good predictive ability for mortality risk in COPD patients, surpassing the performance of its components (CRP, albumin, and lymphocyte count). As a composite inflammatory index, the CALLY index not only reflects the inflammation, nutritional, and immune status of COPD patients but also can be used to identify high-risk patients and help clinicians develop more personalized and effective intervention strategies.

Some of the strengths of this study should be acknowledged. Firstly, this study is the first to assess the predictive role of the CALLY index in COPD patients. Secondly, to evaluate the clinical superiority of the CALLY index, we compared its prognostic value with other indices, including CRP, albumin, and lymphocyte. Furthermore, this study utilized a broad, nationally representative sample of COPD patients in the United States, which lends broad generalizability and applicability to our findings. However, there are some limitations to this study. Firstly, due to the differing data collected in each survey cycle, we included only 1,048 COPD patients, which is a relatively small number and may introduce bias into the study results. Secondly, due to the lack of relevant data on some risk factors for COPD, such as shortness of breath and history of exacerbations, these factors were not included in the analysis of this study. In future studies, we plan to include more patients and collect more comprehensive data to validate the clinical utility of the CALLY index.

Conclusion

In summary, this study found that the CALLY index is substantially associated with all-cause mortality among COPD patients in the United States and has good predictive value for their survival risk. Our findings would help pulmonologists to intervene early with dynamic monitoring of patients with COPD using the CALLY index. Moreover, to validate our findings, further large-scale prospective studies are needed.

Data Sharing Statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics Approval and Informed Consent

All study protocols were approved by the National Center for Health Statistics Research Ethics Review Board. All participants provided written informed consent prior to their health examinations. According to Article 32, Items 1 and 2, of the Measures for the Ethical Review of Life Science and Medical Research Involving Human Subjects (China, February 18, 2023), studies that use legally obtained publicly available data, data generated through non-intrusive observation of public behavior, or anonymized data are exempt from ethical review (https://www.gov.cn/zhengce/zhengceku/2023-02/28/content_5743658.htm).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The study was funded by the Shandong Medical and Health Technology Project (202303021034), the Ministry of Science and Technology of the National Administration of Traditional Chinese Medicine and the Shandong Provincial Health Commission Collaborative Project (GZY-KJS-SD-2023-048), and the Shandong Province Traditional Chinese Medicine Science and Technology Project (Q-2023041).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Celli B, Fabbri L, Criner G, et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *Am J Respir Crit Care Med*. 2022;206(11):1317–1325. doi:10.1164/rccm.202204-0671PP
2. Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990–2019: results from the global burden of disease study 2019. *BMJ*. 2022;378:e069679. doi:10.1136/bmj-2021-069679
3. Syamlal G, Kurth LM, Dodd KE, Blackley DJ, Hall NB, Mazurek JM. Chronic obstructive pulmonary disease mortality by industry and occupation - United States, 2020. *MMWR Morb Mortal Wkly Rep*. 2022;71(49):1550–1554. doi:10.15585/mmwr.mm7149a3
4. Riley CM, Sciurba FC. Diagnosis and outpatient management of chronic obstructive pulmonary disease: a review. *JAMA*. 2019;321(8):786–797. doi:10.1001/jama.2019.0131
5. Zhu B, Wang Y, Ming J, Chen W, Zhang L. Disease burden of COPD in China: a systematic review. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1353–1364. doi:10.2147/COPD.S161555
6. Wang W, Gu J, Liu Y, et al. Pre-treatment CRP-albumin-lymphocyte index (CALLY index) as a prognostic biomarker of survival in patients with epithelial ovarian cancer. *Cancer Manag Res*. 2022;14:2803–2812. doi:10.2147/CMAR.S359968
7. Takeda Y, Sugano H, Okamoto A, et al. Prognostic usefulness of the C-reactive protein-albumin-lymphocyte (CALLY) index as a novel biomarker in patients undergoing colorectal cancer surgery. *Asian J Surg*. 2024;47(8): 3492–3498. doi:10.1016/j.asjsur.2024.03.054
8. Iida H, Tani M, Komeda K, et al. Superiority of CRP-albumin-lymphocyte index (CALLY index) as a non-invasive prognostic biomarker after hepatectomy for hepatocellular carcinoma. *HPB*. 2022;24(1):101–115. doi:10.1016/j.hpb.2021.06.414
9. Feng J, Wang L, Yang X, Chen Q. Clinical significance of preoperative CALLY index for prognostication in patients with esophageal squamous cell carcinoma undergoing surgery. *Sci Rep*. 2024;14(1):713. doi:10.1038/s41598-023-51109-w
10. Okugawa Y, Ohi M, Kitajima T, et al. Clinical feasibility of the preoperative C-reactive protein-albumin-lymphocyte index to predict short- and long-term outcomes of patients with gastric cancer. *J Gastrointest Surg*. 2024;28:1045–1050. doi:10.1016/j.gassur.2024.04.016
11. Hu H-S, Wang Z, Jian L-Y, Zhao L-M, Liu X-D. Optimizing inhaled corticosteroid use in patients with chronic obstructive pulmonary disease: assessing blood eosinophils, neutrophil-to-lymphocyte ratio, and mortality outcomes in US adults. *Front Immunol*. 2023;14:1230766. doi:10.3389/fimmu.2023.1230766
12. Lan -C-C, Su W-L, Yang M-C, Chen S-Y, Wu Y-K. Predictive role of neutrophil-percentage-to-albumin, neutrophil-to-lymphocyte and eosinophil-to-lymphocyte ratios for mortality in patients with COPD: evidence from NHANES 2011–2018. *Respirology*. 2023;28(12):1136–1146. doi:10.1111/resp.14589
13. Xu Y, Yan Z, Li K, Liu L. The association between systemic immune-inflammation index and chronic obstructive pulmonary disease in adults aged 40 years and above in the United States: a cross-sectional study based on the NHANES 2013–2020. *Front Med*. 2023;10:1270368. doi:10.3389/fmed.2023.1270368
14. Shen S, Xiao Y. Association between C-reactive protein and albumin ratios and risk of mortality in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2289–2303. doi:10.2147/COPD.S413912

15. Wheaton AG, Liu Y, Croft JB, et al. Chronic obstructive pulmonary disease and smoking status - United States, 2017. *MMWR Morb Mortal Wkly Rep*. 2019;68(24):533–538. doi:10.15585/mmwr.mm6824a1
16. Zhao Y, Li H, Wang Z, et al. Exploring the association between magnesium deficiency and chronic obstructive pulmonary diseases in NHANES 2005–2018. *Sci Rep*. 2024;14(1):25981. doi:10.1038/s41598-024-76374-1
17. Zheng Y, Liu W, Zhu X, Xu M, Lin B, Bai Y. Associations of dietary inflammation index and composite dietary antioxidant index with preserved ratio impaired spirometry in US adults and the mediating roles of triglyceride-glucose index: NHANES 2007–2012. *Redox Biol*. 2024;76:103334. doi:10.1016/j.redox.2024.103334
18. Kokla M, Virtanen J, Kolehmainen M, Paananen J, Hanhineva K. Random forest-based imputation outperforms other methods for imputing LC-MS metabolomics data: a comparative study. *BMC Bioinf*. 2019;20(1):492. doi:10.1186/s12859-019-3110-0
19. Brightling C, Greening N. Airway inflammation in COPD: progress to precision medicine. *Eur Respir J*. 2019;54(2):1900651. doi:10.1183/13993003.00651-2019
20. MacNee W. Pathology, pathogenesis, and pathophysiology. *BMJ*. 2006;332(7551):1202–1204. doi:10.1136/bmj.332.7551.1202
21. Kapellos TS, Conlon TM, Yildirim AÖ, Lehmann M. The impact of the immune system on lung injury and regeneration in COPD. *Eur Respir J*. 2023;62(4):2300589. doi:10.1183/13993003.00589-2023
22. Schols AM, Ferreira IM, Franssen FM, et al. Nutritional assessment and therapy in COPD: a European respiratory society statement. *Eur Respir J*. 2014;44(6):1504–1520. doi:10.1183/09031936.00070914
23. Park S, Kim SW, Rhee CK, et al. Effect of low protein intake on acute exacerbations in mild to moderate chronic obstructive pulmonary disease: data from the 2007–2012 KNHANES. *J Thorac Dis*. 2021;13(10):5592–5603. doi:10.21037/jtd-20-3433
24. Cosio MG, Majo J, Cosio MG. Inflammation of the airways and lung parenchyma in COPD: role of T cells. *Chest*. 2002;121(5 Suppl):160S–165S. doi:10.1378/chest.121.5_suppl.160S
25. Itoh M, Tsuji T, Nemoto K, Nakamura H, Aoshiba K. Undernutrition in patients with COPD and its treatment. *Nutrients*. 2013;5(4):1316–1335. doi:10.3390/nu5041316
26. Collins PF, Yang IA, Chang Y-C, Vaughan A. Nutritional support in chronic obstructive pulmonary disease (COPD): an evidence update. *J Thorac Dis*. 2019;11(Suppl 17):S2230–S2237. doi:10.21037/jtd.2019.10.41
27. Nan Y, Zhou Y, Dai Z, et al. Role of nutrition in patients with coexisting chronic obstructive pulmonary disease and sarcopenia. *Front Nutr*. 2023;10:1214684. doi:10.3389/fnut.2023.1214684
28. Yao Z, Zhang Y, Wu H. Regulation of C-reactive protein conformation in inflammation. *Inflamm Res*. 2019;68(10):815–823. doi:10.1007/s00011-019-01269-1
29. Fermont JM, Masconi KL, Jensen MT, et al. Biomarkers and clinical outcomes in COPD: a systematic review and meta-analysis. *Thorax*. 2019;74(5):439–446. doi:10.1136/thoraxjnl-2018-211855
30. Iseki Y, Shibutani M, Maeda K, et al. The impact of the preoperative peripheral lymphocyte count and lymphocyte percentage in patients with colorectal cancer. *Surg Today*. 2017;47(6):743–754. doi:10.1007/s00595-016-1433-2
31. Semenzato U, Biondini D, Bazzan E, et al. Low-blood lymphocyte number and lymphocyte decline as key factors in COPD outcomes: a longitudinal cohort study. *Respiration*. 2021;100(7):618–630. doi:10.1159/000515180
32. Chen C-W, Chen -Y-Y, Lu C-L, et al. Severe hypoalbuminemia is a strong independent risk factor for acute respiratory failure in COPD: a nationwide cohort study. *Int J Chron Obstruct Pulmon Dis*. 2015;10:1147–1154. doi:10.2147/COPD.S85831
33. Girón R, Matesanz C, García-Río F, et al. Nutritional state during COPD exacerbation: clinical and prognostic implications. *Ann Nutr Metab*. 2009;54(1):52–58. doi:10.1159/000205960