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Association between CRP-Albumin-Lymphocyte (CALLY) index and Asthma-COPD overlap: analysis of NHANES 2015–2018 data

Shasha Fu[1†], Zongcun Chen[2†] and Hongchuan Wu[3*]

Abstract

Background The CRP-Albumin-Lymphocyte (CALLY) index, a novel inflammatory biomarker combining serum albumin, lymphocyte count, and C-reactive protein (CRP), has been proposed for clinical use. This study aimed to investigate the association between CALLY index and Asthma-COPD Overlap (ACO) in the general US population.

Methods We analyzed data from 6,797 participants aged ≥ 40 years from the 2015–2018 National Health and Nutrition Examination Survey (NHANES). Participants were categorized into quartiles based on natural logarithmic transformed (ln) CALLY index. ACO was defined as self-reported physician-diagnosed asthma and COPD. Logistic regression models were used to examine the association between ln CALLY and ACO, adjusting for potential confounders across three models. Generalized additive models, subgroup analyses, and receiver operating characteristic (ROC) curve analysis were also performed.

Results The prevalence of ACO across the four CALLY quartiles was 5.56%, 1.89%, 1.54%, and 0.66%. In the fully adjusted model, for each 1-unit increase in ln CALLY, the risk of ACO decreased by 43% (OR = 0.57, 95% CI: 0.44–0.73, $P = 0.001$). Compared with Q1, the risk of ACO in Q2, Q3, and Q4 was reduced by 63% (OR = 0.37), 66% (OR = 0.34), and 87% (OR = 0.13), respectively (P for trend = 0.003). Generalized additive models showed a non-linear negative relationship ($P < 0.001$). Subgroup analysis revealed that the association remained consistent across different sexes, age groups, races, smoking status, and disease statuses (arthritis, DM, and hypertension). ROC curve analysis indicated moderate predictive ability of ln CALLY for ACO (AUC = 0.675, 95% CI: 0.636–0.714), with an optimal cutoff value of 8.007 (sensitivity 0.669, specificity 0.598).

Conclusion Higher CALLY index is independently associated with lower risk of ACO, suggesting its potential value as a biomarker for ACO risk assessment in clinical practice. By integrating inflammation, immune, and nutritional status evaluation, the CALLY index offers a novel perspective for early identification of high-risk individuals in clinical practice.

Keywords CALLY index, Asthma-COPD overlap, Inflammation, NHANES, Biomarker

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Introduction

Asthma-COPD overlap (ACO) represents a distinct clinical condition where features of both asthma and chronic obstructive pulmonary disease (COPD) coexist in the same patient. It is characterized by persistent airflow limitation with overlapping clinical features of both conditions [1]. The exact definition and diagnostic criteria for ACO remain unclear and continue to be a topic of debate. In clinical practice, ACO is often recognized as an entity in patients with pre-existing asthma or COPD, rather than as a first-time primary diagnosis. Recent epidemiological studies have reported that the prevalence of ACO varies globally, ranging from 0.9 to 11.1% in the general population, 11.1–61.0% in patients with asthma, and 4.2–66.0% in those with COPD [2, 3]. Current literature indicates that, compared with individuals with either asthma or COPD alone, ACO patients exhibit a greater symptom burden, poorer quality of life, more frequent and severe respiratory exacerbations, and a more rapid decline in lung function over time [4–6]. These adverse outcomes significantly increase healthcare utilization and economic burden, underscoring the substantial public health impact of ACO [7].

ACO presents a complex pathophysiological profile involving inflammatory, immune, and nutritional components. In terms of inflammation, ACO demonstrates concurrent features of both asthma and COPD, including eosinophilic inflammation and basement membrane thickening characteristic of asthma, as well as epithelial changes and neutrophilic inflammation typical of COPD [8]. In addition, ACO is associated with both Th1 and Th2 lymphocyte immune responses, exhibiting a complex inflammation-immune network and gene-environment interactions [9]. Moreover, malnutrition has been recognized as an important factor in respiratory diseases, leading to impaired lung function and an increased risk of age-related respiratory diseases such as asthma and COPD [10, 11]. Existing research on ACO has largely relied on individual biomarkers to capture specific aspects of its pathophysiology. For example, elevated serum total immunoglobulin E (IgE) levels, indicative of Th2-mediated allergic inflammation, have been associated with airway hyperresponsiveness in ACO patients [12]. Exhaled nitric oxide (FeNO), a non-invasive marker of eosinophilic airway inflammation, demonstrates diagnostic utility in distinguishing ACO from COPD [13, 14]. Peripheral blood eosinophil counts, reflecting type 2 immune activation, correlate with exacerbation frequency and severity [15, 16], while circulating YKL-40, a chitinase-like protein linked to airway remodeling, serves as a prognostic indicator [17]. However, these biomarkers in isolation fail to address the multifactorial nature of ACO, which involves systemic inflammation, immune dysregulation, and nutritional deficiencies. This limitation highlights the need for composite indices that integrate multiple biological pathways. Given the substantial disease burden and complex pathophysiological mechanisms of ACO, developing comprehensive and reliable biomarkers for early identification and risk assessment has become a critical clinical need.

The CRP-Albumin-Lymphocyte (CALLY) index, a composite biomarker integrating lymphocyte count, serum albumin, and C-reactive protein (CRP) levels, was initially proposed by Lida et al. to evaluate the nutritional, immune, and inflammatory status of cancer patients [18]. As research progressed, the CALLY index has found broad applications in prognostic evaluation across various cancer types and has been recognized as a clinically feasible biomarker [19–24]. The CALLY index captures three pathophysiological dimensions of ACO through its components. CRP, a systemic inflammatory marker, exhibits elevated levels that accelerate airway damage and correlate with reduced lung function, heightened airway inflammation, and increased COPD hospitalization risks [25, 26]. Serum albumin, reflecting nutritional status and antioxidant capacity, independently associates with asthma severity (via impaired antioxidant defenses and vascular permeability) and predicts mortality in severe COPD, likely mediated by chronic inflammation and metabolic dysregulation [27, 28]. Lymphocytes, especially CD4 + T cell reduction, links to acute COPD exacerbations through immune dysregulation, while Th1/Th2 imbalance (Th2-dominant in asthma vs. Th1-dominant in COPD) may synergistically aggravate airway inflammation in ACO [29, 30]. Given the role of these three components in ACO pathophysiology, the CALLY index may offer a comprehensive assessment of ACO risk by simultaneously evaluating inflammatory status (CRP), nutritional state (albumin), and immune function (lymphocytes). However, studies investigating the relationship between the CALLY index and the risk of ACO remain limited. Therefore, we conducted this study analyzing data from the National Health and Nutrition Examination Survey (NHANES) to investigate the association between the CALLY index and ACO risk, aiming to provide new insights for the early prediction of ACO.

Methods

Participants and study design

We used data from the NHANES conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC). NHANES is a continuous cross-sectional survey of the US non-institutionalized civilian population, selected using a complex multistage sampling design to derive a representative sample of the US population. The NHANES research plan received ethical approval from the NCHS ethics review board. All participants provided

written informed consent prior to enrollment in the study. Detailed information on the study design and procedures is available in the NHANES documentation (www.cdc.gov/nchs/nhanes/index.htm).

For this analysis, we combined data from two NHANES cycles (2015–2016 and 2017–2018) following NCHS recommendations, initially including 19,225 individuals. Since one well-accepted criterion in identifying both ACO and COPD was an age equal to or over 40 [31–33], we set the minimum age threshold at 40 years. The following exclusion criteria were applied: (1) age < 40 years (11,577 excluded, $n = 7,648$), (2) missing data on asthma or COPD (15 excluded, $n = 7,633$), (3) incomplete data on lymphocyte, albumin or C-reactive protein, which prevented the calculation of the CALLY index (836 excluded, $n = 6,797$). After applying these exclusions, 6,797 participants remained for the final analysis. The study flowchart is presented in Fig. 1.

Assessment of CALLY index

The CALLY index was designed as an exposure variable in our study. It was calculated as follows: serum albumin level (g/dL) × absolute lymphocyte count (cells/μL) / CRP (mg/dL) × 10^4 [34]. Blood samples were collected from participants at mobile testing centers and subsequently sent to a central laboratory for measurement of lymphocyte, albumin, and CRP levels, in accordance with standardized protocols. Serum albumin concentrations were measured using the Roche Cobas 6000 analyzer with a bromocresol purple reagent. Lymphocyte counts were determined using the Beckman Coulter® counting and quantification method. Serum CRP levels were measured using latex-enhanced nephelometry on Beckman Coulter Synchron analyzers (NHANES 2015–2018).

Given that the distribution of the CALLY index was skewed, a natural logarithmic transformation (ln) was applied to normalize the data for statistical analysis. According to ln CALLY index quartiles, all participants were divided into four groups: Q1 (ln CALLY index < 7.47, $n = 1,697$), Q2 (7.47 < ln CALLY index < 8.29, $n = 1,697$), Q3 (8.29 < ln CALLY index < 9.10, $n = 1,702$), and Q4 (ln CALLY index > 9.10, $n = 1,701$).

Assessment of ACO

ACO, defined by the co-existence of both asthma and COPD, was designed as an outcome variable in our study. Same as in previous studies, the assessment of ACO was based on standardized questionnaire interviews conducted by trained health professionals in NHANES [35]. A diagnosis of ACO was made based on two key

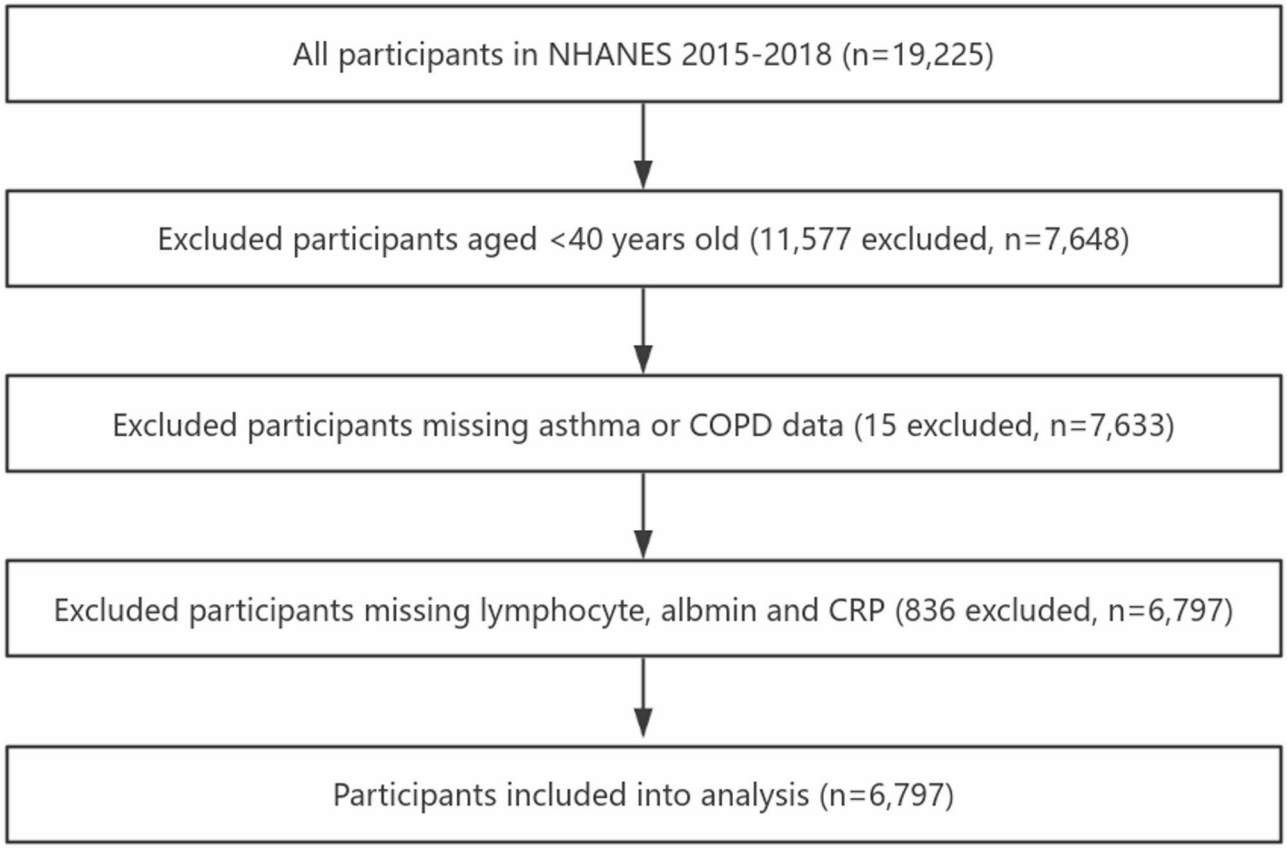

Fig. 1 Flow diagram of the patient selection process

questions: "Has a doctor or other health professional ever told you that you have asthma?" and "Has a doctor or other health professional ever told you that you have COPD?" Participants who answered affirmatively to both questions were classified as having ACO.

Data collection

The following participant information was collected: Demographic data included age, sex, race, and poverty income ratio (PIR). Life Signs comprised body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate. Laboratory parameters were obtained from blood samples and consisted of complete blood count parameters (white blood cell [WBC], lymphocyte, monocyte, neutrophils, eosinophils, red blood cells [RBC], hemoglobin, mean corpuscular volume [MCV], red cell distribution width [RDW], and platelets), inflammatory markers (C-reactive protein [CRP]), liver function tests (albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP]), renal function marker (blood urea nitrogen [BUN]), metabolic indicators (glucose, sodium, potassium, phosphorus, calcium), and lipid profile (high-density lipoprotein [HDL], triglycerides [TG], low-density lipoprotein [LDL], total cholesterol [TC]). Additional measurements included serum cotinine levels. Questionnaire data encompassed smoking status and medical history, including coronary heart disease (CHD), cancer, stroke, arthritis, diabetes mellitus (DM), hypertension, asthma, and chronic obstructive pulmonary disease (COPD). All detailed measurement procedures for these variables were conducted according to standardized NHANES protocols, which are publicly available at www.cdc.gov/nchs/nhanes/.

Statistical analysis

Analyses were performed following the NHANES statistical analysis guidelines (https://wwwn.cdc.gov/nchs/nhanes/analyticguidelines.aspx). Continuous variables were expressed as mean (95% confidence intervals [95%CI]) for normally distributed data and as median (Q1-Q3) for non-normally distributed data. Categorical variables were presented as count (frequency). The frequency, mean (95%CI), and median (1st Quartile-3st Quartile) values were weighted. Weighted one-way ANOVA or Kruskal-Wallis rank-sum test (for continuous variables) and the Rao-Scott chi-square test (for categorical variables) were used to assess differences across groups of quartile-transformed ln CALLY index. The association between ln CALLY ((both as a categorical and continuous variable) and ACO was evaluated using logistic regression models. Three models were constructed: Model 1 was unadjusted; Model 2 was adjusted for demographic characteristics (sex, age, and race); and Model 3 was further adjusted for PIR, cotinine, DBP, pulse, monocyte, eosinophils, RBC, LDL, smoking, CHD, arthritis, DM, and hypertension. The covariates included in Model 3 were selected based on clinical experience and stepwise regression, with only those variables showing a significance level of $p < 0.05$ being retained. Additionally, variables whose inclusion in the basic model or exclusion from the full model resulted in a change of ≤ 10% in the regression coefficient of the CALLY index were excluded to ensure the robustness of the final model. Results were presented as odds ratios (ORs) with 95%CI. To explore potential non-linear relationships, we applied generalized additive models (GAM) and generated smoothed curve fittings. The GAM was constructed using thin plate regression splines with a smoothing parameter (k = 10) selected via restricted maximum likelihood (REML) method. Three models were developed: (1) an unadjusted model, (2) a model adjusted for covariates consistent with Model 3, and (3) a fully adjusted model that additionally incorporated NHANES survey weights. Sensitivity analyses with varying smoothing parameters were conducted to assess the robustness of the results. Subgroup analyses were conducted to assess the consistency of associations across different subgroups including sex, age (≤ 60, > 60 years), race (Mexican American, Other Hispanic, Non-Hispanic White, Non-Hispanic Black, Other Race-Including Multi-Racial), smoking status (yes/no), arthritis (yes/no), DM (yes/no), and hypertension (yes/no). The same covariates as Model 3 were adjusted in all subgroup analyses. The predictive performance of ln CALLY for ACO was evaluated using receiver operating characteristic (ROC) curve analysis, with the area under the curve (AUC) calculated.

To assess the robustness of our findings, we conducted several sensitivity analyses: (1) additional adjustment for BMI; (2) multiple imputation to address missing data in covariates; and (3) exclusion of participants with lung diseases. For the multiple imputation, we used predictive mean matching with 5 imputations and 50 maximum iterations, properly accounting for NHANES complex survey design. The results of all sensitivity analyses were consistent with our primary findings, confirming the stability of the observed associations (see Supplementary Table 1).

Statistical significance was defined as a two-tailed p-value of less than 0.05. All statistical analyses were performed using the R software environment (Version 4.3.2; The R Foundation; available at http://www.R-project.org).

Results

Baseline characteristics of the participants

The baseline characteristics are shown in Table 1. A total of 6,797 participants were included in this study and categorized into Q1 (ln CALLY index 6.91 [6.42,

Table 1 Baseline characteristics of participants grouped by quartiles of ln CALLY

	1	2	3	4	*P*-value
CALLY	1004.55 (616.00,1341.67)	2643.75 (2147.83,3262.98)	5906.25 (4779.87,7228.92)	15050.00 (11328.95,22500.00)	< 0.001
ln CALLY	6.91 (6.42, 7.20)	7.88 (7.67, 8.09)	8.68 (8.47, 8.89)	9.62 (9.34, 10.02)	< 0.001
Age, Mean(95%CI)	59.00 (49.00, 67.00)	58.00 (49.00, 68.00)	58.00 (49.00, 68.00)	56.00 (48.00, 66.00)	0.059
Sex, %(95%CI)					< 0.001
Male	40.06 (36.46, 43.77)	45.88 (42.64, 49.15)	51.50 (48.03, 54.96)	50.86 (47.10, 54.61)	
Female	59.94 (56.23, 63.54)	54.12 (50.85, 57.36)	48.50 (45.04, 51.97)	49.14 (45.39, 52.90)	
Race, %(95%CI)					< 0.001
Mexican American	7.18 (5.00, 10.21)	7.51 (5.04, 11.04)	7.47 (5.23, 10.56)	5.96 (4.24, 8.30)	
Other Hispanic	6.95 (5.15, 9.30)	6.10 (4.41, 8.39)	6.10 (4.47, 8.27)	4.04 (2.67, 6.07)	
Non-Hispanic White	64.99 (59.03, 70.51)	68.40 (62.74, 73.56)	67.69 (61.79, 73.07)	68.41 (63.03, 73.35)	
Non-Hispanic Black	14.49 (10.58, 19.52)	9.54 (7.27, 12.43)	8.98 (6.71, 11.91)	8.47 (6.38, 11.17)	
Other Race-Including Multi-Racial	6.39 (4.98, 8.17)	8.45 (6.32, 11.21)	9.76 (7.23, 13.06)	13.12 (10.91, 15.70)	
PIR, Mean(95%CI)	2.90 (2.67, 3.12)	3.11 (2.97, 3.26)	3.37 (3.23, 3.51)	3.50 (3.33, 3.66)	< 0.001
Cotinine, Median (Q1, Q3)	0.03 (0.01, 0.76)	0.02 (0.01, 0.34)	0.02 (0.01, 0.24)	0.02 (0.01, 0.70)	0.263
Smoking, %(95%CI)	16.45 (13.42, 20.01)	16.31 (14.23, 18.63)	14.56 (11.77, 17.87)	17.08 (13.95, 20.74)	0.610
Life Signs					
BMI (kg/m2), Median (Q1, Q3)	32.50 (27.60, 38.50)	30.70 (26.90, 34.60)	28.40 (25.50, 31.50)	25.40 (22.80, 28.90)	< 0.001
SBP (mmHg), Median (Q1, Q3)	128.00 (118.00, 140.00)	126.00 (116.00, 138.00)	124.00 (114.00, 136.00)	122.00 (114.00, 136.00)	0.004
DBP (mmHg), Median (Q1, Q3)	72.00 (64.00, 80.00)	72.00 (66.00, 80.00)	72.00 (64.00, 80.00)	72.00 (66.00, 78.00)	0.454
Pulse, Median (Q1, Q3)	72.00 (64.00, 80.00)	70.00 (64.00, 78.00)	68.00 (62.00, 76.00)	68.00 (62.00, 74.00)	< 0.001
Laboratory					
WBC (1000 cells/uL), Median (Q1, Q3)	7.30 (5.90, 8.70)	7.00 (5.90, 8.40)	6.60 (5.40, 8.00)	6.30 (5.30, 7.80)	< 0.001
Lymphocyte (1000 cells/uL), Median (Q1, Q3)	1.80 (1.40, 2.20)	2.00 (1.60, 2.50)	2.00 (1.60, 2.40)	2.10 (1.60, 2.50)	< 0.001
Monocyte (1000 cells/uL), Median (Q1, Q3)	0.60 (0.50, 0.70)	0.60 (0.50, 0.70)	0.50 (0.40, 0.70)	0.50 (0.40, 0.70)	< 0.001
Neutrophils (1000 cells/uL), Median (Q1, Q3)	4.50 (3.50, 5.60)	4.20 (3.30, 5.20)	3.70 (2.90, 4.70)	3.50 (2.80, 4.40)	< 0.001
Eosinophils (1000 cells/uL), Median (Q1, Q3)	0.20 (0.10, 0.30)	0.20 (0.10, 0.30)	0.20 (0.10, 0.30)	0.20 (0.10, 0.20)	0.022
RBC (million cells/uL), Median (Q1, Q3)	4.69 (4.36, 4.99)	4.73 (4.43, 5.01)	4.78 (4.46, 5.05)	4.72 (4.41, 5.04)	< 0.001
Hemoglobin (g/dL), Median (Q1, Q3)	13.80 (12.90, 14.80)	14.20 (13.40, 15.20)	14.50 (13.50, 15.30)	14.30 (13.30, 15.30)	< 0.001
MCV (fL), Median (Q1, Q3)	89.20 (85.10, 92.50)	89.80 (86.80, 92.60)	90.50 (87.40, 93.10)	91.00 (87.70, 93.70)	< 0.001
RDW (%), Median (Q1, Q3)	13.90 (13.30, 14.70)	13.60 (13.20, 14.20)	13.40 (13.00, 13.90)	13.30 (12.90, 13.70)	< 0.001
Platelet (1000 cells/uL), Median (Q1, Q3)	8.20 (7.70, 8.80)	8.20 (7.70, 8.80)	8.30 (7.70, 8.90)	8.10 (7.60, 8.80)	0.050
CRP (mg/L), Median (Q1, Q3)	7.79 (5.50, 12.10)	3.09 (2.31, 4.10)	1.40 (1.03, 1.83)	0.51 (0.39, 0.76)	< 0.001
Albumin (g/dL), Mean(95%CI)	3.99 (3.96, 4.02)	4.13 (4.09, 4.17)	4.21 (4.18, 4.23)	4.31 (4.28, 4.34)	< 0.001
ALT (U/L), Median (Q1, Q3)	19.00 (14.00, 28.00)	20.00 (15.00, 27.00)	20.00 (15.00, 28.00)	21.00 (16.00, 27.00)	0.844
AST (U/L), Median (Q1, Q3)	21.00 (17.00, 26.00)	22.00 (18.00, 26.00)	21.00 (18.00, 26.00)	22.00 (19.00, 27.00)	0.025
ALP (U/L), Median (Q1, Q3)	80.00 (66.00, 98.00)	73.00 (61.00, 87.00)	67.00 (55.00, 83.00)	65.00 (54.00, 78.00)	< 0.001
BUN (mmol/L), Median (Q1, Q3)	15.00 (12.00, 18.00)	15.00 (12.00, 18.00)	15.00 (13.00, 19.00)	15.00 (12.00, 18.00)	0.428
Glucose (mmol/L), Median (Q1, Q3)	99.00 (91.00, 114.00)	97.00 (90.00, 109.00)	96.00 (90.00, 106.00)	94.00 (87.00, 102.00)	< 0.001
Sodium (mmol/L), Mean(95%CI)	139.40 (138.91, 139.89)	139.59 (139.11, 140.08)	139.99 (139.48, 140.50)	139.46 (139.04, 139.87)	0.003
Potassium (mmol/L), Mean(95%CI)	4.06 (4.01, 4.10)	4.08 (4.03, 4.13)	4.07 (4.01, 4.13)	4.03 (3.99, 4.07)	0.172
Phosohorus (mmol/L), Median (Q1, Q3)	3.50 (3.20, 3.90)	3.60 (3.30, 3.90)	3.60 (3.20, 3.90)	3.60 (3.30, 4.00)	0.016
Ca (mmol/L), Median (Q1, Q3)	9.20 (9.00, 9.40)	9.30 (9.10, 9.50)	9.30 (9.10, 9.50)	9.30 (9.10, 9.60)	< 0.001
HDL (mmol/L), Median (Q1, Q3)	1.29 (1.09, 1.58)	1.29 (1.06, 1.63)	1.34 (1.09, 1.71)	1.50 (1.24, 1.84)	< 0.001
TG (mmol/L), Median (Q1, Q3)	1.17 (0.86, 1.74)	1.21 (0.85, 1.81)	1.09 (0.76, 1.59)	0.95 (0.64, 1.52)	< 0.001
LDL (mmol/L), Median (Q1, Q3)	2.95 (2.35, 3.57)	2.95 (2.40, 3.60)	2.92 (2.28, 3.49)	2.92 (2.22, 3.54)	0.835
TC (mmol/L), Median (Q1, Q3)	4.97 (4.34, 5.64)	5.07 (4.45, 5.74)	4.99 (4.32, 5.66)	4.99 (4.32, 5.72)	0.164
CHD, %(95%CI)	7.25 (5.25, 9.94)	6.32 (4.36, 9.09)	5.27 (3.65, 7.56)	4.62 (3.27, 6.49)	0.186
Cancer, %(95%CI)	17.28 (14.68, 20.25)	14.34 (11.95, 17.11)	16.29 (13.43, 19.62)	13.03 (10.74, 15.73)	0.127
Stroke, %(95%CI)	5.60 (4.25, 7.34)	4.90 (3.51, 6.81)	4.34 (3.47, 5.43)	2.64 (1.73, 4.02)	0.009
Arthritis, %(95%CI)	46.91 (42.57, 51.29)	42.41 (38.12, 46.82)	38.48 (34.15, 43.01)	29.67 (25.89, 33.75)	< 0.001
DM, %(95%CI)	23.20 (20.39, 26.27)	18.09 (15.30, 21.26)	13.51 (10.19, 17.70)	11.42 (9.34, 13.90)	< 0.001

Table 1 (continued)

	1	2	3	4	*P*-value
Hypertension, %(95%CI)	53.43 (49.64, 57.18)	45.58 (40.90, 50.34)	41.36 (37.08, 45.77)	33.85 (29.69, 38.26)	< 0.001
Asthma, %(95%CI)	21.74 (18.93, 24.85)	13.53 (11.32, 16.10)	10.82 (8.82, 13.20)	11.43 (9.57, 13.59)	< 0.001
COPD, %(95%CI)	10.16 (7.96, 12.88)	5.47 (3.55, 8.34)	5.10 (3.70, 6.99)	3.28 (2.00, 5.33)	< 0.001
ACO, %(95%CI)	5.56 (3.85, 7.96)	1.89 (1.24, 2.87)	1.54 (0.81, 2.89)	0.66 (0.32, 1.35)	< 0.001

1st Quartile, Q_3: 3st Quartile; PIR, poverty impact ratio; BMI, body mass index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; WBC, White Blood Cell; RBC, Red Blood Cell; MCV, Mean Corpuscular Volume; RDW, Red Cell Distribution Width; CRP, C-reactive Protein; ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; ALP, Alkaline Phosphatase; BUN, Blood Urea Nitrogen; Ca, Calcium; HDL, High-Density Lipoprotein; TG, Triglyceride; LDL, Low-Density Lipoprotein; TC, Total Cholesterol; CHD, Coronary Heart Disease; DM, Diabetes; COPD, Chronic Obstructive Pulmonary Disease; ACO, Asthma–COPD overlap

Table 2 Associations of ln CALLY with ACO in logistic analysis model

Outcome: ACO	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value	OR (95%CI)	*P*-value
ln CALLY	0.53 (0.46, 0.61)	< 0.001	0.52 (0.45, 0.61)	< 0.001	0.57 (0.44, 0.73)	0.001
ln CALLY quartiles						
Q1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q2	0.33 (0.22, 0.49)	< 0.001	0.31 (0.20, 0.48)	< 0.001	0.37 (0.19, 0.73)	0.022
Q3	0.27 (0.14, 0.51)	< 0.001	0.26 (0.13, 0.51)	< 0.001	0.34 (0.14, 0.82)	0.044
Q4	0.11 (0.06, 0.21)	< 0.001	0.11 (0.06, 0.21)	< 0.001	0.13 (0.05, 0.36)	0.005
P for trend		< 0.001		< 0.001		0.003

Model1 adjust for: None

Model 2 adjust for: sex, age, race

Model 3 adjust for: sex, age, race, PIR, cotinine, DBP, Pulse, monocyte, eosinophils, RBC, LDL, smoking, CHD, arthritis, DM, hypertension

7.20], $n = 1{,}697$), Q2 (ln CALLY index 7.88 [7.67, 8.09], $n = 1{,}697$), Q3 (ln CALLY index 8.68 [8.47, 8.89], $n = 1{,}702$), and Q4 (ln CALLY index 9.62 [9.34, 10.02], $n = 1{,}701$), ($P < 0.001$). ACO occurred in 5.56%, 1.89%, 1.54%, and 0.66% patients in the four groups, respectively ($P < 0.001$).

Demographic characteristics showed significant differences between the groups, with higher ln CALLY quartiles being associated with a larger proportion of male participants, a higher percentage of Non-Hispanic White individuals, and a greater poverty income ratio (PIR) (all $P < 0.001$). Regarding vital signs, BMI, SBP, and pulse rate all significantly decreased as the ln CALLY index increased (all $P < 0.05$). Most laboratory parameters also exhibited notable differences across the quartiles ($P < 0.05$). With increasing ln CALLY levels, lymphocyte, RBC, hemoglobin, MCV, albumin, AST, sodium, phosohorus, calcium, HDL increased progressively. In contrast, WBC, monocyte, neutrophils, eosinophils, RDW, CRP, ALP, glucose, and TG decreased significantly. Regarding comorbidities, the prevalence of stroke, arthritis, diabetes, hypertension, asthma, and COPD all decreased significantly with higher ln CALLY levels (all $P < 0.05$). No significant differences were observed for other variables among the groups (all $P > 0.05$).

Relationship between ln CALLY index and ACO

The association between the ln CALLY index and ACO was evaluated using logistic regression analysis, as shown in Table 2. In the unadjusted model (Model 1), each unit increase in ln CALLY was associated with a 47% lower risk of ACO (OR = 0.53, 95% CI: 0.46–0.61, $P < 0.001$). Compared to Q1, the risk of ACO decreased by 67% in Q2 (OR = 0.33, 95% CI: 0.22–0.49), 73% in Q3 (OR = 0.27, 95% CI: 0.14–0.51), and 89% in Q4 (OR = 0.11, 95% CI: 0.06–0.21) (all $P < 0.001$, P for trend < 0.001). After adjusting for demographic characteristics such as sex, age, and race (Model 2), this significant association remained, with a 48% lower risk for each unit increase in ln CALLY (OR = 0.52, 95% CI: 0.45–0.61, $P < 0.001$). The decreased risks in Q2 (OR = 0.31, 95% CI: 0.20–0.48), Q3 (OR = 0.26, 95% CI: 0.13–0.51), and Q4 (OR = 0.11, 95% CI: 0.06–0.21) compared to Q1 were 69%, 74%, and 89%, respectively (all $P \leq 0.001$, P for trend < 0.001). In the fully adjusted model (Model 3), the protective association remained significant, with a 43% lower risk for each unit increase in ln CALLY (OR = 0.57, 95% CI: 0.44–0.73, $P = 0.001$). The risks in Q2 (OR = 0.37, 95% CI: 0.19–0.73, $P = 0.022$), Q3 (OR = 0.34, 95% CI: 0.14–0.82, $P = 0.044$), and Q4 (OR = 0.13, 95% CI: 0.05–0.36, $P = 0.005$) were reduced by 63%, 66%, and 87%, respectively, compared to Q1 (P for trend = 0.003).

GAM and smoothed curve fitting for the association of ln CALLY and ACO

To explore the potential non-linear relationship between ln CALLY and ACO, we conducted GAM and smoothed curve fitting (Fig. 2). In the unadjusted model (Fig. 2A), a non-linear inverse association was observed, with the curve showing a steeper decline at lower ln CALLY

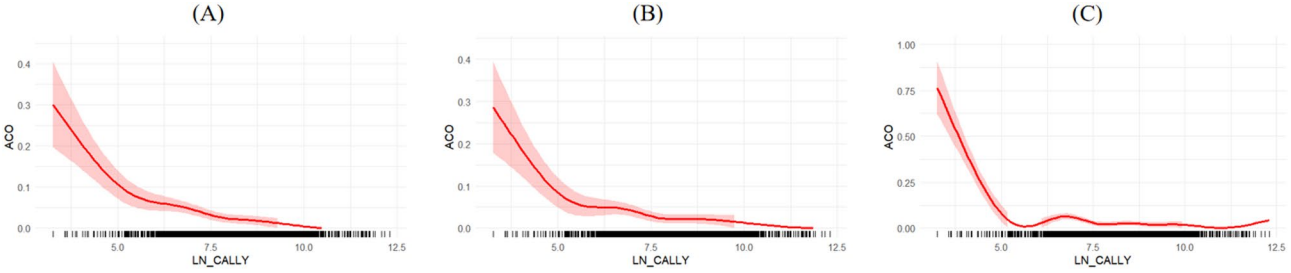

Fig. 2 Generalized addictive model for ln CALLY for predicting the incidence rate of ACO. **A**. No adjusts. **B**. Adjusted for: sex, age, race, PIR, cotinine, DBP, Pulse, monocyte, eosinophils, RBC, LDL, smoking, CHD, arthritis, DM, hypertension. **C**. Adjusted for the same covariates as in B with NHANES survey weights incorporated

Table 3 Subgroup analysis for the association of ln CALLY with ACO

	(*N*) % (95%CI)	OR (95%CI)	*P*-value	*P*-interaction
Sex				0.840
Male	(1220) 1.92 (0.96,2.89)	0.58 (0.46, 0.74)	0.002	
Female	(1240) 2.89 (1.77,4.02)	0.55 (0.37, 0.84)	0.021	
Age				0.164
<=60	(1288) 1.82 (0.67,2.98)	0.49 (0.32, 0.74)	0.008	
>60	(1172) 3.31 (2.10,4.52)	0.67 (0.54, 0.83)	0.006	
Race				0.055
Mexican American	(347) 0.53 (-0.14,1.20)	0.96 (0.58, 1.59)	0.875	
Other Hispanic	(298) 1.80 (0.32,3.28)	1.07 (0.49, 2.34)	0.874	
Non-Hispanic White	(928) 2.93 (1.73,4.14)	0.55 (0.42, 0.72)	0.005	
Non-Hispanic Black	(499) 1.69 (0.46,2.91)	0.69 (0.44, 1.08)	0.158	
Other Race-Including Multi-Racial	(388) 1.02 (-0.11,2.15)	0.25 (0.11, 0.56)	0.015	
Smoking				0.660
Yes	(2013) 1.72 (1.09,2.34)	0.55 (0.40, 0.75)	0.005	
No	(447) 5.80 (1.91,9.68)	0.61 (0.42, 0.90)	0.034	
Arthritis				0.108
Yes	(947) 4.21 (2.68,5.74)	0.50 (0.35, 0.72)	0.004	
No	(1513) 1.27 (0.56,1.99)	0.72 (0.59, 0.89)	0.013	
DM				0.662
Yes	(534) 4.05 (1.83,6.27)	0.64 (0.38, 1.05)	0.111	
No	(1926) 2.14 (1.20,3.08)	0.55 (0.40, 0.76)	0.005	
Hypertension				0.162
Yes	(1171) 3.82 (2.36,5.29)	0.65 (0.50, 0.84)	0.010	
No	(1289) 1.39 (0.62,2.16)	0.47 (0.33, 0.69)	0.004	

levels and gradually flattening at higher levels ($P<0.001$). After adjusting for potential confounders (Fig. 2B), this non-linear pattern persisted with improved model fit ($P<0.001$). The weighted and adjusted model (Fig. 2C) further confirmed this relationship, with increased explanatory power (deviance explained = 12.19%), indicating the robustness of this association when considering the complex survey design of NHANES.

Subgroup analysis for the association of ln CALLY and ACO

To evaluate the stability of the association between ln CALLY and ACO, we conducted extensive subgroup analyses (Table 3). After adjusting for potential confounders, we performed stratified analyses based on sex, age, race, smoking status, arthritis, DM, and hypertension. The interaction tests were not statistically significant (all P for interaction > 0.05), suggesting that the association between ln CALLY and ACO remained consistent across these subgroups.

Predicted performance of the ln CALLY by ROC

The diagnostic performance of ln CALLY for ACO was assessed using ROC curve analysis (Fig. 3). The AUC was 0.675 (95% CI: 0.636–0.714), indicating moderate discriminative ability. At the optimal cutoff value of 8.007, ln CALLY exhibited a sensitivity of 0.669 and a specificity of 0.598 for identifying ACO.

Discussion

After evaluating 6,797 participants from 2015 to 2016 and 2017–2018 NHANES cycles, we demonstrated the CALLY index serves as an important predictor of ACO risk. Higher CALLY index levels were independently associated with a reduced risk of ACO in the general population, and this protective association remained consistent across various subgroups. Additionally, we observed a non-linear relationship between the CALLY index and ACO risk, with the protective effect being more pronounced at lower CALLY levels.

Previous studies have mainly focused on individual clinical or biological markers in ACO assessment. For

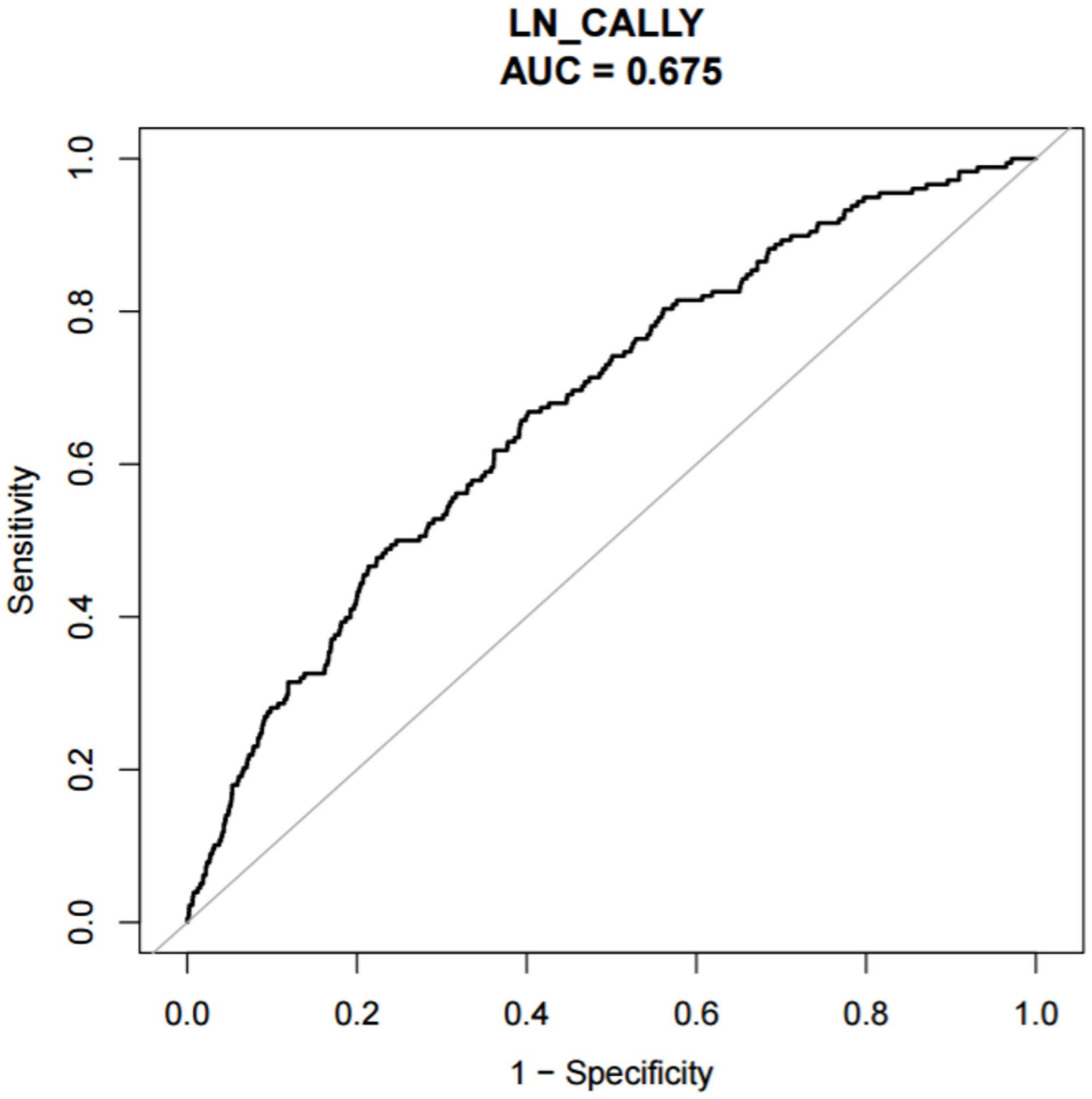

Fig. 3 ROC of ln CALLY and ACO

example, serum total IgE, FeNO, peripheral blood eosinophil count, and circulating YKL-40 levels have been identified as important markers associated with immune responses in ACO patients [36, 37]. However, the heterogeneous nature of ACO and its complex pathogenesis limit the clinical utility of single biomarkers. Given these limitations, recent studies have shifted towards exploring composite indices, particularly those related to dietary factors. The Dietary Inflammatory Index (DII) [38] and Overall Balance Score (OBS) [39] have shown significant associations with ACO risk, highlighting the importance of multifactorial assessment in disease management While these dietary indices provide valuable insights, they may not fully capture the complex interactions between systemic inflammation, nutritional status, and immune function that characterize ACO.

In this context, the CALLY index offers a more comprehensive approach by integrating three key components: lymphocyte count (reflecting immune status), albumin (indicating nutritional state), and CRP (marking systemic inflammation). Originally developed by Lida et al. to evaluate cancer patients' nutritional, immune, and

inflammatory status [18], the CALLY index has demonstrated significant prognostic value across multiple cancer types, including hepatocellular carcinoma, breast cancer, esophageal cancer, gastric cancer, colorectal cancer, and oral cavity cancer [19, 21–23]. In oncology, it serves as an independent prognostic factor for overall survival and helps identify patients requiring more aggressive treatment. Our study extends the application of this validated composite marker from oncology to respiratory disease, providing a novel approach to assess the multiple pathophysiological processes underlying ACO.

CRP is a systemic inflammatory marker that has been shown to correlate with airway inflammation in various respiratory diseases. As an acute-phase protein, elevated CRP levels reflect systemic inflammation and may exacerbate airway remodeling by promoting neutrophil infiltration [40], protease-antiprotease imbalance [41], and oxidative stress [42]. In asthma, especially in steroid-naive patients, elevated CRP levels are linked to increased airway wall thickness and eosinophilic inflammation [43]. Similarly, in COPD, fluctuations in CRP levels are linked to airway inflammatory markers and clinical outcomes during acute exacerbations [44]. Additionally, elevated CRP levels are negatively correlated with lung function parameters, such as forced expiratory volume (FEV1) and forced vital capacity (FVC), in patients with airway diseases [45]. Therefore, CRP serves as a valuable indicator of both airway inflammation and overall health status.

Serum albumin is another important component of the CALLY index. Low albumin levels may exacerbate systemic inflammation and oxidative stress in ACO patients, impair epithelial repair, and drive airway remodeling [30, 46]. Furthermore, albumin deficiency may disrupt energy metabolism, increase apoptosis of airway epithelial cells, and compromise barrier function [47]. Studies have shown that serum albumin concentrations are significantly lower in stable COPD patients compared to non-COPD controls, indicating a deficiency in systemic anti-inflammatory and antioxidant defense mechanisms [48]. Similarly, serum albumin levels are also significantly decreased in children with asthma compared to those without [49]. Hypoalbuminemia, as a marker of malnutrition, negatively affects lung function, exercise capacity, and overall quality of life, exacerbating symptom severity [50–52].

Lymphocytes, as a key component of the CALLY index, play a crucial role in the pathogenesis and immune regulation of airway inflammation in ACO, particularly Th2 cells and innate lymphoid cells type 2 (ILC2s), which are central to the immune response in ACO. ACO patients exhibit pronounced Th2 lymphocyte polarization, with significantly higher peripheral Th2 cell proportions compared to those with asthma or COPD alone [53]. Th2 lymphocytes produce cytokines such as IL-4 and IL-13, which are essential for inducing airway hyperresponsiveness and inflammation. These cytokines exert direct effects on airway cells, leading to rapid alterations in airway function without the need for inflammatory cell recruitment [54]. ILC2s, involved in allergic airway inflammation, are activated by cytokines such as IL-33 and contribute to the inflammatory process through lipid metabolism and cytokine production [55].

The integration of these three components in the CALLY index provides a comprehensive assessment of ACO pathophysiology by simultaneously capturing systemic inflammation (CRP), nutritional and antioxidant status (albumin), and immune function (lymphocytes), offering a more complete picture than any single marker alone.

Our study found an inverse association between the CALLY index and ACO risk, with higher CALLY levels linked to a significantly lower incidence of ACO. This suggests that the CALLY index could be a valuable tool for predicting ACO risk, helping clinicians better identify individuals at higher risk. Additionally, the Generalized Additive Model (GAM) analysis revealed a non-linear relationship, showing that the decline in ACO risk became steeper at lower CALLY levels. This suggests that maintaining higher CALLY levels could be particularly effective in preventing ACO, while targeting those with lower levels for early intervention may offer greater potential for reducing ACO incidence.

Epidemiological studies have established that ACO patients typically present distinct characteristics, including a higher proportion of females, increased smoking prevalence [3], and a greater burden of comorbidities compared to those with either asthma or COPD alone [4]. Notably, our comprehensive subgroup analysis demonstrated that the protective association between CALLY and ACO remained consistent across various demographic and clinical subgroups. This consistency across sex, age, race, smoking status, and common comorbidities (arthritis, diabetes, and hypertension) supports the CALLY index as a robust and universally applicable biomarker for ACO risk assessment. While our ROC analysis showed moderate discriminative ability (AUC = 0.675), the identified optimal cutoff value of 8.007 provides a practical reference point for clinical risk stratification, potentially facilitating early identification of high-risk individuals and enabling timely preventive interventions. This suggests its potential utility as a preliminary screening tool for the initial evaluation of suspected ACO patients, particularly in primary care or resource-limited settings where more sophisticated testing may not be immediately available.

Several limitations of our study should be acknowledged. First, the cross-sectional design limits causal

inference between the CALLY index and ACO risk, as temporal relationships and dynamic changes in CALLY levels during disease progression cannot be assessed. Second, potential selection bias may have occurred due to the exclusion of participants with missing data, which could affect the representativeness of our sample. Third, the moderate predictive ability of the CALLY index indicates its limitations as a standalone diagnostic tool, suggesting it should be interpreted cautiously and ideally used in conjunction with other clinical assessments. Fourth, the ACO diagnosis relied on self-reported questionnaires without pulmonary function tests or other objective measurements, which may affect diagnostic accuracy. In addition, as the NHANES data only represent the US population, the generalizability of our findings to other populations requires further validation. Finally, several directions for future research should be considered. Longitudinal studies are needed to assess the dynamic changes in CALLY index over time and its predictive value for ACO development and progression. Future research should incorporate objective pulmonary function measurements to validate the association between CALLY and airway obstruction severity. Intervention studies targeting the components of the CALLY index could provide insights into whether improving CALLY scores translates to better clinical outcomes. Additionally, evaluating the performance of CALLY index in diverse populations would enhance the generalizability and clinical applicability of this promising biomarker.

Conclusion

The CALLY index demonstrated a significant inverse association with ACO risk, with this relationship remaining robust after adjusting for multiple confounders and across various subgroups. These findings suggest that the CALLY index may serve as a promising and accessible biomarker for ACO risk assessment in clinical practice, potentially facilitating early identification of high-risk individuals. Further validation in larger and more diverse populations is warranted to fully establish its clinical utility across different healthcare settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03705-x.

Supplementary Material 1

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None.

Author contributions
H.W. formed the concept. S.F. and Z.C. made statistical analysis and completed the writing of the paper. H.W. was responsible for the revision of the paper. All authors confirmed the final version of the paper.

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Data availability
The data used in this study is from the National Health and Nutrition Examination Survey (NHANES) conducted by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC), available at www.cdc.gov/nchs/nhanes/index.htm.

Declarations

Competing interests
The authors declare no competing interests.

Ethics and consent to participate
The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Haikou Affiliated Hospital of Central South University Xiangya School of Medicine (Haikou People's Hospital) (Ethics approval number: 2024-(Lunshen)-187), with the need for written informed consent waived.

Consent to publish
Not applicable.

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References

1. Leung C, Sin DD. Asthma-COPD overlap: what are the important questions? Chest. 2022;161(2):330–44.
2. Uchida A, Sakaue K, Inoue H. Epidemiology of asthma-chronic obstructive pulmonary disease overlap (ACO). Allergology Int. 2018;67(2):165–71.
3. Romem A, Rokach A, Bohadana A, Babai P, Arish N, Azulai H, et al. Identification of asthma-COPD overlap, asthma, and chronic obstructive pulmonary disease phenotypes in patients with airway obstruction: influence on treatment approach. Respiration. 2020;99(1):35–42.
4. Jung JY. Characteristics of asthma-COPD overlap according to various criteria. Tuberc Respir Dis. 2021;84(1):87.
5. de Marco R, Pesce G, Marcon A, Accordini S, Antonicelli L, Bugiani M, et al. The coexistence of asthma and chronic obstructive pulmonary disease (COPD): prevalence and risk factors in young, middle-aged and elderly people from the general population. PLoS ONE. 2013;8(5):e62985.
6. Alshabanat A, Zafari Z, Albanyan O, Dairi M, FitzGerald JM. Asthma and COPD overlap syndrome (ACOS): A systematic review and Meta analysis. PLoS ONE. 2015;10(9):e0136065.
7. Shaya FT, Dongyi D, Akazawa MO, Blanchette CM, Wang J, Mapel DW, et al. Burden of concomitant asthma and COPD in a medicaid population. Chest. 2008;134(1):14–9.
8. Dey S, Eapen MS, Chia C, Gaikwad AV, Wark PA, Sohal SS. Pathogenesis, clinical features of asthma COPD overlap, and therapeutic modalities. Am J Physiology-Lung Cell Mol Physiol. 2022;322(1):L64–83.
9. Chen Y-C, Chang Y-P, Huang K-T, Hsu P-Y, Hsiao C-C, Lin M-C. Unraveling the pathogenesis of asthma and chronic obstructive pulmonary disease overlap: focusing on epigenetic mechanisms. Cells. 2022;11(11):1728.
10. Tharumakunarajah R, Lee A, Hawcutt DB, Harman NL, Sinha IP. The impact of malnutrition on the developing lung and Long-Term lung health: A narrative review of global literature. Pulmonary Therapy. 2024:1–16.
11. Saint-Criq V, Lugo-Villarino G, Thomas M. Dysbiosis, malnutrition and enhanced gut-lung axis contribute to age-related respiratory diseases. Ageing Res Rev. 2021;66:101235.
12. Pajulas A, Fu Y, Cheung CCL, Chu M, Cannon A, Alakhras N, et al. Interleukin-9 promotes mast cell progenitor proliferation and CCR2-dependent mast cell migration in allergic airway inflammation. Mucosal Immunol. 2023;16(4):432–45.

13. Xie C, Xu W, Rao S, Xie Y, Liang Q, Chen L, et al. The role of Th17/Treg imbalance, FeNO, eosinophils, IgE and their correlation with lung function parameters with Asthma-chronic obstructive pulmonary disease. Iran J Allergy Asthma Immunol. 2024;23(6):625–40.
14. Takada K, Suzukawa M, Tashimo H, Ohshima N, Fukutomi Y, Kobayashi N, et al. Serum MMP3 and IL1-RA levels May be useful biomarkers for detecting asthma and chronic obstructive pulmonary disease overlap in patients with asthma. World Allergy Organ J. 2023;16(11):100840.
15. Jensen SK, Melgaard ME, Pedersen CT, Yang L, Vahman N, Thyssen JP, et al. Limited clinical role of blood eosinophil levels in early life atopic disease: A mother-child cohort study. Pediatr Allergy Immunol. 2023;34(11):e14050.
16. Bae J, Lee HJ, Choi KY, Lee JK, Park TY, Heo EY et al. Risk factors of acute exacerbation and disease progression in young patients with COPD. BMJ Open Respir Res. 2024;11(1).
17. Zhu Y, Huang B, Jiang G. Correlation between changes in serum YKL-40, LXRs, PPM1A, and TGF-β1 levels and airway remodeling and lung function in patients with bronchial asthma. J Asthma. 2024;61(7):698–706.
18. Iida H, Tani M, Komeda K, Nomi T, Matsushima H, Tanaka S, 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):101–15.
19. Aoyama T, Hashimoto I, Maezawa Y, Hara K, Kazama K, Komori K, et al. CRP-albumin-lymphocyte (CALLY) index is an independent prognostic factor for the esophageal cancer patients who received curative treatment. Anticancer Res. 2024;44(2):815–22.
20. Aoyama T, Maezawa Y, Hashimoto I, Hara K, Tamagawa A, Kazama K, et al. The CRP-albumin-lymphocyte (CALLY) index is an independent prognostic factor for gastric Cancer patients who receive curative treatment. Anticancer Res. 2024;44(4):1629–36.
21. Yang M, Lin S-Q, Liu X-Y, Tang M, Hu C-L, Wang Z-W, et al. Association between C-reactive protein-albumin-lymphocyte (CALLY) index and overall survival in patients with colorectal cancer: from the investigation on nutrition status and clinical outcome of common cancers study. Front Immunol. 2023;14:1131496.
22. Tsai Y-T, Ko C-A, Chen H-C, Hsu C-M, Lai C-H, Lee Y-C, et al. Prognostic value of CRP-albumin-lymphocyte (CALLY) index in patients undergoing surgery for oral cavity cancer. J Cancer. 2022;13(10):3000.
23. Zhuang J, Wang S, Wang Y, Wu Y, Hu R. Prognostic value of CRP–Albumin–Lymphocyte (CALLY) index in patients undergoing surgery for breast Cancer. Int J Gen Med. 2024:997–1005.
24. Wang W, Gu J, Liu Y, Liu X, Jiang L, Wu C et al. Pre-treatment CRP-albumin-lymphocyte index (CALLY index) as a prognostic biomarker of survival in patients with epithelial ovarian cancer. Cancer Manage Res. 2022:2803–12.
25. Hyun H, Lee YH, Kang NY, Suh JS. Clinical relevance of blood Urea nitrogen to serum albumin ratio for predicting bacteremia in very young children with febrile urinary tract infection. Kidney Res Clin Pract. 2024;43(3):348–57.
26. Dahl M, Vestbo J, Lange P, Bojesen SE, Tybjaerg-Hansen A, Nordestgaard BG. C-reactive protein as a predictor of prognosis in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;175(3):250–5.
27. Sun T, Shen H, Guo Q, Yang J, Zhai G, Zhang J, et al. Association between neutrophil Percentage-to-Albumin ratio and All-Cause mortality in critically ill patients with coronary artery disease. Biomed Res Int. 2020;2020:8137576.
28. Liu Y, Zhao W, Hu C, Zhang Y, Qu Y. Predictive value of the Neutrophil-to-Lymphocyte ratio/serum albumin for All-Cause mortality in critically ill patients suffering from COPD. Int J Chron Obstruct Pulmon Dis. 2025;20:659–83.
29. Xue W, Ma J, Li Y, Xie C. Role of CD(4) (+) T and CD(8) (+) T Lymphocytes-Mediated cellular immunity in pathogenesis of chronic obstructive pulmonary disease. J Immunol Res. 2022;2022:1429213.
30. Chen YC, Chang YP, Huang KT, Hsu PY, Hsiao CC, Lin MC. Unraveling the pathogenesis of asthma and chronic obstructive pulmonary disease overlap: focusing on epigenetic mechanisms. Cells. 2022;11(11).
31. Adeloye D, Song P, Zhu Y, Campbell H, Sheikh A, Rudan I. Global, regional, and National prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. Lancet Respiratory Med. 2022;10(5):447–58.
32. Zhu M, Chen A. Epidemiological characteristics of asthma-COPD overlap, its association with all-cause mortality, and the mediating role of depressive symptoms: evidence from NHANES 2005–2018. BMC Public Health. 2024;24(1):1423.
33. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. Am J Respir Crit Care Med. 2017;195(5):557–82.
34. Zhang H, Shi J, Xie H, Liu X, Ruan G, Lin S, et al. Superiority of CRP-albumin-lymphocyte index as a prognostic biomarker for patients with gastric cancer. Nutrition. 2023;116:112191.
35. !!!. INVALID CITATION!!! (23, 24).
36. Peng J, Wang M, Wu Y, Shen Y, Chen L. Clinical indicators for asthma-COPD overlap: a systematic review and meta-analysis. Int J Chronic Obstr Pulm Dis. 2022:2567–75.
37. Fujino N, Sugiura H. Aco (Asthma–copd overlap) is independent from Copd, a case in favor: A systematic review. Diagnostics. 2021;11(5):859.
38. Wang S, Wang Y, Hu X, Lu L. Association between dietary inflammation index and asthma COPD overlap. Sci Rep. 2024;14(1):8077.
39. Wang S, Jiang R, Zhang L, Cai Y, Zhou C, Wu L. Relationships between oxidative balance score and asthma, COPD, with asthma-COPD overlap in American adults: findings from NHANES 2013–2018. J Asthma. 2024;1:9.
40. Li L, Guo Z, Zhao Y, Liang C, Zheng W, Tian W, et al. The impact of oxidative stress on abnormal lipid metabolism-mediated disease development. Arch Biochem Biophys. 2025;766:110348.
41. Brantly M, Stocks J, Lascano J, Flagg T, Jeffers AM, Owens SZ et al. Inhaled alpha-1 antitrypsin (AAT) restores lower respiratory tract protease-antiprotease homoeostasis and reduces inflammation in AAT-deficient individuals: a randomised phase 2 study. ERJ Open Res. 2025;11(1).
42. Woo SD, Park HS, Yang EM, Ban GY, Park HS. 8-Iso-prostaglandin F2α as a biomarker of type 2 low airway inflammation and remodeling in adult asthma. Ann Allergy Asthma Immunol. 2024;133(1):73–e802.
43. Hoshino M, Ohtawa J, Akitsu K. Increased C-reactive protein is associated with airway wall thickness in steroid-naive asthma. Ann Allergy Asthma Immunol. 2014;113(1):37–41.
44. Liang Y, Chang C, Zhu H, Shen N, He B, Yao W. Correlation between decrease of CRP and resolution of airway inflammatory response, improvement of health status, and clinical outcomes during severe acute exacerbation of chronic obstructive pulmonary disease. Intern Emerg Med. 2015;10:685–91.
45. Sunyer J, Pistelli R, Plana E, Andreani M, Baldari F, Kolz M, et al. Systemic inflammation, genetic susceptibility and lung function. Eur Respir J. 2008;32(1):92–7.
46. Wen J, Xia J, He Q, Giri M, Guo S. Association between protein intake, serum albumin and blood eosinophil in US asthmatic adults. Front Immunol. 2024;15:1383122.
47. Heefner A, Simovic T, Mize K, Rodriguez-Miguelez P. The role of nutrition in the development and management of chronic obstructive pulmonary disease. Nutrients. 2024;16(8).
48. Zinellu E, Fois AG, Sotgiu E, Mellino S, Mangoni AA, Carru C, et al. Serum albumin concentrations in stable chronic obstructive pulmonary disease: a systematic review and meta-analysis. J Clin Med. 2021;10(2):269.
49. Shima M, Adachi M. Association of respiratory symptoms with serum protease inhibitors and albumin levels in Japanese children. Int J Epidemiol. 1996;25(6):1213–9.
50. Di Raimondo D, Pirera E, Pintus C, De Rosa R, Profita M, Musiari G, et al. The impact of malnutrition on chronic obstructive pulmonary disease (COPD) outcomes: the predictive value of the Mini nutritional assessment (MNA) versus acute exacerbations in patients with highly complex COPD and its clinical and prognostic implications. Nutrients. 2024;16(14):2303.
51. Mete B, Pehlivan E, Gülbaş G, Günen H. Prevalence of malnutrition in COPD and its relationship with the parameters related to disease severity. Int J Chronic Obstr Pulm Dis. 2018:3307–12.
52. Keogh E, Williams EM. Managing malnutrition in COPD: a review. Respir Med. 2021;176:106248.
53. Al Ghobain MO, Alsubaie AS, Aljumah WA, Alrumayh FM, Aldawsari KF, Alqahtani AM, et al. The correlation between fractional exhaled nitric oxide (FeNO), blood eosinophil count, Immunoglobulin E levels, and spirometric values in patients with asthma. Cureus. 2023;15(2):e35289.
54. Venkayya R, Lam M, Willkom M, Grunig G, Corry DB, Erle DJ. The Th2 lymphocyte products IL-4 and IL-13 rapidly induce airway hyperresponsiveness through direct effects on resident airway cells. Am J Respir Cell Mol Biol. 2002;26(2):202–8.

55. Karagiannis F, Masouleh SK, Wunderling K, Surendar J, Schmitt V, Kazakov A, et al. Lipid-droplet formation drives pathogenic group 2 innate lymphoid cells in airway inflammation. Immunity. 2020;52(4):620–34. e6.

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