JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Systemic immune-inflammation index and neutrophil-to-lymphocyte ratio as biomarkers for acute exacerbation of elderly patients with chronic bronchitis

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Abstract

Objectives: To evaluate the clinical utility of the systemic immune-inflammation index (SII) and neutrophil-to-lymphocyte ratio (NLR) as predictive biomarkers for acute exacerbation in elderly patients with chronic bronchitis (CB).

Methods: This retrospective cross-sectional study involved 215 elderly patients with CB. Patients were divided into two groups based on clinical presentation: stable CB (n = 93) and acute exacerbation of chronic bronchitis (AECB) (n = 122). Baseline clinical parameters and laboratory indicators were collected and analyzed.

Results: The AECB group exhibited significantly lower lymphocyte count and reduced serum albumin level, alongside significantly increased levels of C-reactive protein (CRP), NLR, and SII ($p < 0.001$) compared with the stable CB group. Multivariate logistic regression indicated that decreased albumin (odds ratio (OR) = 0.605), and higher values of CRP (OR = 1.058), NLR (OR = 1.505), and SII (OR = 1.004) were all significantly associated with the likelihood of AECB. Among individual markers, SII showed the highest discriminatory capacity (AUC = 0.856), with albumin (AUC = 0.833), NLR (AUC = 0.823), and CRP (AUC = 0.822) performing comparably. Combining the four indicators resulted in a significantly enhanced diagnostic estimate (AUC = 0.970), achieving a sensitivity of 86.9% and a specificity of 96.8%.

Conclusions: NLR and SII can serve as valuable inflammatory indicators for acute exacerbations in older patients with CB. When used alongside albumin and CRP, these markers modestly improve the ability to distinguish between stable and exacerbated states, offering supportive value in the early clinical assessment of AECB risk.

Key words: Chronic bronchitis; acute exacerbation; elderly; systemic immune-inflammation index; neutrophil-to-lymphocyte ratio.

J Infect Dev Ctries 2026; 20(10):1464-1472. doi:10.3855/jidc.22392

(Received 16 September 2025 – Accepted 24 February 2026)

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Introduction

Chronic bronchitis (CB), which is generally characterized by a long-standing productive cough occurring for no less than three months annually over a span of two successive years, is often recognized as one of several phenotypic patterns observed within the broader context of chronic obstructive pulmonary disease (COPD). This condition tends to be more prevalent among older adults and may contribute to a range of healthcare-related concerns, such as occasional exacerbation episodes, increased likelihood of hospital admission, a gradual reduction in respiratory function, limitations in daily well-being, and added medical resource utilization [1-3]. Older individuals may have a heightened tendency toward experiencing episodes of acute worsening in chronic bronchitis (AECB), potentially influenced by age-associated immune system changes, reduced respiratory capacity, and the coexistence of various chronic conditions, such as cardiovascular disorders, metabolic disturbances (e.g., diabetes), and cerebrovascular diseases, which can present additional considerations in clinical care and prognosis [4,5]. Therefore, accurate and timely identification of acute exacerbations among elderly CB patients remains crucial for optimal therapeutic interventions and improved clinical outcomes.

Recent observations have suggested a possible contributory role of systemic inflammatory processes and alterations in immune function in the development and advancement of chronic respiratory conditions, such as COPD and related episodes of exacerbation [6]. Persistent airway inflammation induces systemic inflammatory responses characterized by changes in peripheral blood cells, including increased neutrophil count, decreased lymphocyte count, and altered platelet activity, which collectively contribute to disease exacerbation and progression [7,8]. While conventional indicators of inflammation, such as C-reactive protein (CRP), total white blood cell (WBC) count, and erythrocyte sedimentation rate (ESR), have exhibited

routine application in clinical settings, their ability to provide precise diagnostic insight or reliably forecast acute exacerbation events may be somewhat constrained. Such limitations highlight the necessity for novel and more sensitive biomarkers capable of reliably indicating acute inflammatory responses and effectively guiding clinical decision-making in elderly CB patients.

Increasing attention has been given to composite markers of inflammation, such as neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII), which are calculated using standard hematological data. These indices have shown potential for reflecting systemic immune-inflammatory activity in a range of clinical conditions, including certain cancers, autoimmune processes, and infectious diseases, though their applicability may vary depending on context [9-11]. The NLR, determined by the ratio of absolute neutrophil count to lymphocyte count, has been proposed as a relatively accessible metric that may provide insights into systemic inflammatory activity by approximating the interaction between pro-inflammatory processes and immune function [12]. Elevated levels of the NLR have been found in certain patients with COPD and may be linked to a greater likelihood of adverse outcomes or exacerbation events, reflecting a possible, although nondefinitive, role in clinical evaluation [13]. Moreover, the SII, incorporating platelet count along with neutrophil and lymphocyte counts (SII = platelet × neutrophil/lymphocyte), has attracted researchers' attention due to its robust capacity to concurrently represent inflammatory and immunological status, demonstrating superior prognostic capabilities compared with single-cell-count markers in various inflammatory conditions [14].

Although NLR and SII have demonstrated utility in various inflammatory and pulmonary conditions, their specific relevance in relation to diagnosis among older adults with CB undergoing acute exacerbation episodes remains incompletely characterized and requires further clarification. The existing research addressing the potential utility of these biomarkers in this precise subgroup is sparse, and available studies largely involve heterogeneous COPD populations or younger patient cohorts, limiting the generalizability and applicability of their findings to elderly CB populations [15,16]. Therefore, there is an urgent need of clinical investigations that thoroughly evaluate the role and performance of these novel inflammatory indices specifically in the elderly CB population undergoing acute exacerbations. The present analysis sought to explore the potential clinical implications and evaluate the approximate diagnostic utility of the SII and NLR in differentiating between acute exacerbation episodes and stable phases in older patients diagnosed with CB.

Methods

Study Design

This retrospective analysis was carried out in The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital over a period extending from January 2022 to December 2024. A total of 215 patients who aged 65 years or older, all meeting the clinical criteria for CB, were enrolled in succession. Based on their presentation at the time of hospital evaluation, individuals were categorized into one of the following two groups: those in a stable condition (n = 93) and those experiencing an episode of acute exacerbation (AECB; n = 122). The CB was classified according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) framework [17], which defines the condition as a productive cough persisting for at least three months annually for two consecutive years, after excluding alternative respiratory or cardiac causes. Acute exacerbation was identified through clinical judgment by two independent respiratory specialists and was defined by a sudden worsening of respiratory symptoms, including increased cough, sputum volume or purulence, wheezing, or shortness of breath, that necessitated adjustments in the patient's usual treatment regimen. Ethical approval was obtained from The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital, and the informed consent form was signed by all subjects.

Inclusion and Exclusion Criteria

Participants were considered eligible for inclusion based on the following criteria: (1) being 65 years of age or older; (2) having a documented clinical diagnosis consistent with CB; and (3) possessing a complete set of relevant clinical and laboratory information at the time of hospital admission. Individuals were not included in the analysis if any of the following conditions applied: (1) the presence of other chronic respiratory disorders, such as asthma, bronchiectasis, or interstitial lung disease; (2) a recent episode of acute infection, surgical intervention, or trauma occurring within the preceding four weeks; (3) underlying hematologic abnormalities, active autoimmune conditions, or malignancies under ongoing treatment; (4) exposure to systemic corticosteroids or

immunosuppressive medications within one month before enrollment; (5) absence of essential data required for the planned evaluation or (6) hospitalization primarily for acute exacerbations of other major comorbidities (e.g., decompensated heart failure, acute coronary syndrome, cerebrovascular events) rather than for CB, to reduce confounding from unrelated acute conditions.

In addition, to minimize the potential overlap with COPD, particularly emphysema, patients with a documented history of emphysematous changes on imaging or with spirometry-confirmed persistent airflow limitation were excluded. Although it is acknowledged that subclinical emphysema cannot be fully ruled out in the absence of comprehensive imaging for every case, available radiological reports, pulmonary function data, and medical records were carefully reviewed to ensure that participants met the clinical diagnostic criteria for CB and to reduce the likelihood of misclassification.

Clinical Data Collection

Clinical and laboratory data were retrospectively extracted from the electronic health records of patients included in the study cohort at the point of hospital admission. Demographic variables comprised age, sex, body mass index (BMI), and tobacco use history. Details regarding the presence of frequently encountered comorbid conditions, such as coronary artery disease, heart failure, diabetes, cerebrovascular disorders, osteoporosis, and malignancies, were also collected. Symptomatology at presentation, including cough, wheezing, shortness of breath, chest tightness, and purulent sputum, was recorded when available. Within the first 24 h following admission, venous blood samples were drawn specifically prior to the administration of any acute anti-inflammatory therapies (e.g., intravenous or oral corticosteroids) and processed in the institution's central laboratory under routine standardized protocols. Parameters measured included WBC count, neutrophil and lymphocyte counts, platelet count, hemoglobin concentration, blood urea nitrogen (BUN), CRP level, and serum albumin level. The NLR was computed by dividing the absolute neutrophil count by the lymphocyte count, while the SII was calculated using the following formula: platelet count × neutrophil count/lymphocyte count, in which all values were reported in × 10^9/L. Data abstraction was performed independently by two trained reviewers, who both were blinded to patient groupings, and any inconsistencies were addressed through mutual discussion or, when necessary, via consultation with a senior adjudicator.

Statistical Analysis

All statistical procedures were conducted using SPSS 26.0 software (IBM Corp., Armonk, NY, USA). The normal distribution of continuous data was examined through the Shapiro–Wilk test. For variables approximating a normal distribution, results were presented as mean ± standard deviation (SD) and compared using the independent-samples t-test. Data that did not meet normality assumptions were summarized as medians with interquartile ranges (IQRs) and analyzed using the Mann–Whitney U test. Categorical variables were reported as count and percentage, and group-based differences were examined using the Chi-square test or the Fisher's exact test, as appropriate. Statistical significance was interpreted based on a two-tailed p value threshold of < 0.05. Variables demonstrating significant group-level differences between individuals with stable CB and those experiencing AECB were initially entered into univariate logistic regression models to explore potential associations. Parameters meeting the significance criterion ($p < 0.05$) were subsequently included in a multivariable logistic regression model to evaluate independent contributions. Collinearity diagnostics (Variance Inflation Factor [VIF] and tolerance) were performed to assess potential multicollinearity between SII and NLR. A VIF < 5 was considered the threshold for the absence of severe multicollinearity, justifying their simultaneous inclusion in the multivariate analysis. Outcomes were expressed in terms of odds ratios (ORs) with 95% confidence intervals (CIs). To assess the stability of the multivariate model and check for potential overfitting, internal validation was performed using the bootstrap method with 1,000 resamples. The bias-corrected estimates and 95% CIs for the regression coefficients were calculated. A 95% CI for the OR that did not include 1 was considered indicative of an independent predictor. The discriminatory performance of selected biomarkers, including albumin, CRP, NLR, and SII, for distinguishing stable from exacerbated cases was evaluated using receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC), along with optimal cutoff values, sensitivity, and specificity, was calculated. In addition, a composite model was developed using the predicted probabilities derived directly from the multivariate logistic regression equation incorporating all the four biomarkers to provide an estimate of combined predictive performance.

Results

Baseline Characteristics of Stable CB and AECB Patients

A total of 215 older adults diagnosed with CB were included in the present analysis, consisting of 93 individuals categorized as having stable CB and 122 classified under the acute exacerbation group (AECB). Baseline variables, such as age (75.02 ± 4.57 vs. 75.70 ± 4.48 years), BMI (21.79 ± 2.20 vs. 21.42 ± 1.96 kg/m²), sex distribution (male: 77.42% vs. 78.69%), and current smoking status (63.44% vs. 66.39%) were generally similar between the two cohorts (all $p > 0.05$). Moreover, common comorbidities, including coronary artery disease, chronic heart failure, diabetes mellitus, cerebrovascular conditions, osteoporosis, and malignancies were evenly distributed across groups (all $p > 0.05$). In terms of presenting symptoms noted at the time of admission, such as cough, wheezing, shortness of breath, chest tightness, and purulent sputum, no significant differences were detected between the groups (all $p > 0.05$). Laboratory values for several routine parameters, including total WBC count, neutrophil count, platelet count, hemoglobin concentration, and BUN also showed no appreciable variation (all $p > 0.05$). However, individuals in the AECB group exhibited relatively lower lymphocyte counts (0.87 ± 0.27 vs. 1.40 ± 0.26 × 10⁹/L, $p < 0.001$) and serum albumin concentrations (32.40 ± 3.30 vs. 36.88 ± 3.33 g/L, $p < 0.001$), while higher levels of CRP (32.05 ± 11.72 vs. 17.46 ± 12.60 mg/L, $p < 0.001$) were found. Additionally, the SII and NLR were elevated in the AECB group compared to those with stable disease (SII: 1690.70 ± 488.47 vs. 980.30 ± 450.21; NLR: 12.48 ± 3.19 vs. 8.43 ± 3.09; both $p < 0.001$). A comprehensive summary of these findings is provided in Table 1.

Logistic Regression Analysis of Potential Biomarkers Associated with Acute Exacerbation in Elderly Patients with CB

To examine factors that might be linked to acute exacerbations among elderly individuals with CB, variables demonstrating significant differences between the stable CB and AECB groups were subjected to univariate logistic regression analysis. The parameters assessed included serum albumin, CRP, SII, and NLR. In the univariate model, reduced albumin levels appeared to be correlated with a greater likelihood of acute exacerbation (OR = 0.664, 95% CI:

Table 1. Baseline Characteristics of CB and AECB Groups.

Characteristics	CB group (n = 93)	AECB group (n = 122)	*p*
Age (Years)	75.02 ± 4.57	75.70 ± 4.48	0.273
Gender [n (%)]			0.868
Female	21 (22.58)	26 (21.31)	
Male	72 (77.42)	96 (78.69)	
BMI (kg/m²)	21.79 ± 2.20	21.42 ± 1.96	0.189
Current Smoker [n (%)]			0.667
Yes	59 (63.44)	81 (66.39)	
No	34 (36.56)	41 (33.61)	
Comorbidities [n (%)]			
Coronary heart disease	12 (12.90)	13 (10.66)	0.67
Chronic heart failure	9 (9.68)	15 (12.30)	0.664
Diabetes	16 (17.20)	16 (13.11)	0.443
Cerebrovascular disease	9 (9.68)	9 (7.38)	0.623
Osteoporosis	4 (4.30)	10 (8.20)	0.281
Malignancies	7 (7.53)	7 (5.74)	0.781
Symptoms at admission [n (%)]			
Cough	82 (88.17)	111 (90.98)	0.651
Wheezing	20 (21.51)	30 (24.59)	0.628
Dyspnea	57 (61.29)	71 (58.20)	0.676
Chest distress	21 (22.58)	23 (18.85)	0.609
Purulent sputum	16 (17.20)	25 (20.49)	0.602
Laboratory tests			
WBC (× 10^9/L)	10.68 ± 2.15	10.33 ± 2.04	0.226
Neutrophils (× 10^9/L)	8.49 ± 1.35	8.84 ± 1.31	0.055
Lymphocytes (× 10^9/L)	1.40 ± 0.26	0.87 ± 0.27	< 0.001
Plt (× 10^9/L)	240.10 ± 74.36	257.24 ± 63.39	0.07
Hb (g/L)	129.29 ± 13.28	132.44 ± 11.20	0.061
Alb (g/L)	36.88 ± 3.33	32.40 ± 3.30	< 0.001
BUN (mmol/L)	5.72 ± 1.23	5.84 ± 1.16	0.483
CRP (mg/L)	17.46 ± 12.60	32.05 ± 11.72	< 0.001
SII	980.30 ± 450.21	1690.70 ± 488.47	< 0.001
NLR	8.43 ± 3.09	12.48 ± 3.19	< 0.001

CB: Chronic Bronchitis; AECB: Acute Exacerbation of Chronic Bronchitis; BMI: Body Mass Index; WBC: White Blood Cell; Plt: Platelet; Hb: Hemoglobin; Alb: Albumin; BUN: Blood Urea Nitrogen; CRP: C-reactive Protein; SII: Systemic Immune-inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio.

Table 2. Uni- and Multi-variate Logistic Regression Analyses of Potential Factors Associated with Acute Exacerbation of Chronic Bronchitis in Elderly Patients.

Variable	Univariate logistic analysis						Multivariate logistic analysis					
	B	SE	Wald X^2	*p*	OR	95% CI	B	SE	Wald X^2	*p*	OR	95% CI
Alb	-0.041	0.06	47.433	< 0.001	0.664	0.591~0.746	-0.503	0.104	23.634	< 0.001	0.605	0.493~0.741
CRP	0.1	0.015	44.192	< 0.001	1.105	1.073~1.139	0.057	0.021	7.596	0.006	1.058	1.016~1.102
SII	0.003	0	53.386	< 0.001	1.003	1.002~1.004	0.004	0.001	29.158	< 0.001	1.004	1.003~1.006
NLR	0.412	0.061	45.123	< 0.001	1.51	1.339~1.703	0.409	0.095	18.673	< 0.001	1.505	1.250~1.812

Alb: Albumin; CRP: C-reactive Protein; SII: Systemic Immune-inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; SE: Standard Error; OR: Odds Ratio; CI: Confidence Interval.

0.591–0.746, $p < 0.001$). Conversely, elevated values of CRP (OR = 1.105, 95% CI: 1.073–1.139, $p < 0.001$), SII (OR = 1.003, 95% CI: 1.002–1.004, $p < 0.001$), and NLR (OR = 1.510, 95% CI: 1.339–1.703, $p < 0.001$) were each associated with increased odds of experiencing an exacerbation. Specifically, when scaled per 100-unit increment, the SII demonstrated an odds ratio of 1.359 (95% CI: 1.251–1.475, $p < 0.001$), indicating that for every 100-unit increase in SII, the likelihood of AECB increases by approximately 35.9%. Collinearity diagnostics confirmed no severe multicollinearity between SII and NLR, with both yielding a VIF of 1.109 and tolerance of 0.902. As these values were well below the threshold of 5, both biomarkers were included in the multivariate logistic regression model. When these variables were entered into a multivariate logistic regression model, the associations remained statistically significant. Albumin continued to act as an independent factor inversely associated with exacerbation risk (OR = 0.605, 95% CI: 0.493–0.741, $p < 0.001$), while CRP (OR = 1.058, 95% CI: 1.016–1.102, $p = 0.006$), SII (OR = 1.004, 95% CI: 1.003–1.006, $p < 0.001$), and NLR (OR = 1.505, 95% CI: 1.250–1.812, $p < 0.001$) each showed independent associations with higher odds of acute exacerbation. Internal validation via bootstrapping (1,000 iterations) confirmed the robustness of the multivariate model, yielding negligible bias (SII: 0.000; NLR: 0.034) and stable 95% confidence intervals for the regression coefficients (SII: 0.003–0.006; NLR: 0.269–0.697), which consistently excluded zero. A full summary of the regression analysis results is presented in Table 2.

Evaluation of the Efficacy of Biomarkers for Predicting AECB Using ROC Curve Analysis

ROC curve analysis was carried out to explore the potential diagnostic utility of albumin, CRP, SII, and NLR in identifying acute exacerbation events among older adults with CB (Figure 1). Among the individual biomarkers assessed, SII appeared to provide the highest discriminative capability, yielding an AUC of 0.856 (95% CI: 0.806–0.906), with an estimated cut-off point of 1338.13, a sensitivity of 77.0%, and a specificity of 80.6%. NLR also showed a relatively favorable diagnostic profile, with an AUC of 0.823 (95% CI: 0.767–0.879), corresponding to a cut-off value of 9.955, sensitivity of 82.0%, and specificity of 69.9%. CRP returned an AUC of 0.822 (95% CI: 0.763–0.881); its optimal threshold (19.7 mg/L) was associated with a high sensitivity (89.3%), while yielded a more modest specificity (66.7%). Albumin demonstrated a comparable AUC of 0.833 (95% CI: 0.779–0.888), with a calculated cut-off of 35.35 g/L, yielding sensitivity and specificity of 73.1% and 82.8%, respectively. When considered collectively, the combination of all four biomarkers resulted in enhanced overall performance, with the integrated model producing an AUC of 0.970 (95% CI: 0.951–0.988) and estimated sensitivity and specificity values of 86.9% and 96.8%, respectively. Additional details can be found in Table 3.

Discussion

In this retrospective analysis involving older individuals diagnosed with CB, the potential relevance

Figure 1. ROC curve analysis of (A) ALB, (B) CRP, (C) SII, (D) NLR, and (E) their combination in potential diagnostic utility in identification of acute exacerbation events among elderly patients with chronic bronchitis.

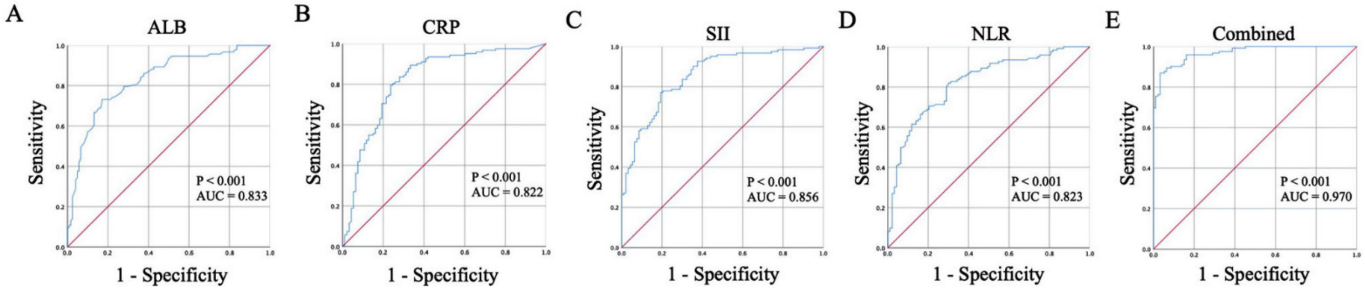


Table 3. ROC Curve Analysis of SII and NLR for Predicting Acute Exacerbation of Chronic Bronchitis in Elderly Patients.

Variables	AUC	95% CI	Best cut-off value	Sensitivity (%)	Specificity (%)	*p*
Alb	0.833	0.779~0.888	35.35	73.1	82.8	< 0.001
CRP	0.822	0.763~0.881	19.7	89.3	66.7	< 0.001
SII	0.856	0.806~0.906	1338.13	77.0	80.6	< 0.001
NLR	0.823	0.767~0.879	9.955	82.0	69.9	< 0.001
Combined	0.97	0.951~0.988		86.9	96.8	< 0.001

Alb: Albumin; CRP: C-reactive Protein; SII: Systemic Immune-inflammation Index; NLR: Neutrophil-to-Lymphocyte Ratio; AUC: Area Under the Curve; CI: Confidence Interval.

of the SII and NLR as indicators associated with AECB was explored. The results suggest that levels of both SII and NLR tended to be higher among those experiencing exacerbations compared to patients in a stable clinical state, and these markers appeared to retain independent associations with exacerbation likelihood in multivariable models. In addition, lower serum albumin concentrations and increased CRP levels were also observed to correlate with exacerbation risk. When assessed together, the combination of these biomarkers demonstrated an improved ability to distinguish between exacerbation and stable status, although further investigation may be needed to clarify their clinical applicability.

One of the initial observations in this study was the relatively elevated values of the SII and NLR among individuals undergoing AECB. The SII, calculated from platelet, neutrophil, and lymphocyte counts, has been considered a marker that may provide indirect insight into the balance between components of the innate immune response and suppression within the adaptive immune system. The elevation of SII in the AECB group suggests a systemic pro-inflammatory state with relative lymphopenia, neutrophilia, and reactive thrombocytosis, which are consistent with acute inflammatory responses to infection or environmental triggers [18-20]. Neutrophils are key mediators in the pathogenesis of exacerbation, releasing proteolytic enzymes and reactive oxygen species that contribute to airway tissue damage and mucus hypersecretion [21-23]. Concurrent lymphopenia may reflect a stress-induced redistribution or apoptosis of lymphocytes, further amplifying the inflammatory imbalance during acute episodes [24,25]. The involvement of platelets, as reflected in SII, may also indicate their role in pulmonary inflammation through platelet–leukocyte interactions and microvascular injury. NLR, a simpler yet widely used marker of systemic inflammation, showed similar trends. Its independent association with AECB underscores the value of neutrophil-dominant immune responses in the acute phase of CB. Previous studies have linked elevated NLR with poor outcomes in various respiratory conditions, including COPD exacerbations and community-acquired pneumonia [26-28]. A study by Xu *et al.* suggested that NLR values may be linked to increased clinical severity and less favorable outcomes in children experiencing asthmatic exacerbations or community-acquired pneumonia. In that context, NLR appeared to offer some potential value for both diagnostic assessment and outcome estimation, although its applicability may vary depending on the clinical setting [27]. In elderly patients, the immune senescence process may further accentuate this imbalance, leading to exaggerated neutrophilic responses and impaired lymphocyte-mediated resolution mechanisms [29,30].

Notably, the present analysis identified a relative decline in absolute lymphocyte counts among individuals experiencing AECB when compared with those in a stable clinical state. Although lymphopenia has been documented in the context of acute inflammation, it is a feature that may not always receive adequate attention in routine clinical evaluation [31,32] and may reflect several pathophysiological processes. First, during systemic inflammation, lymphocytes undergo redistribution to inflamed tissues or secondary lymphoid organs, reducing their circulating numbers [33]. Secondly, increased concentrations of certain pro-inflammatory mediators, including interleukin-7 and tumor necrosis factor-alpha, have been implicated in processes that may contribute to lymphocyte depletion and suppression of bone marrow activity [34,35]. Third, among older individuals, age-associated immunosenescence has been linked to reduced production of naive T cells and a narrowing of the adaptive immune repertoire, which may increase susceptibility to lymphocyte reduction during physiological stress [36]. This reduction in lymphocytes contributes to a weakened immune regulatory function and may exacerbate the inflammatory cascade, thereby facilitating the progression and severity of acute exacerbations. These observations may lend partial support to the idea that lymphopenia, in addition to reflecting underlying immune imbalance, could also be associated with less favorable clinical trajectories in older individuals diagnosed with CB.

Another noteworthy finding of this analysis was the

relatively lower serum albumin levels in individuals experiencing AECB compared with those in a stable clinical phase. This reduction in albumin levels may be indicative of a complex acute-phase response, during which hepatic protein synthesis may shift away from albumin production in favor of upregulating positive acute-phase reactants, such as fibrinogen and CRP [37-39]. Additionally, systemic inflammation during exacerbation can increase capillary permeability, promoting albumin leakage into the interstitial space, while catabolic processes driven by pro-inflammatory cytokines accelerate protein degradation [37-39]. Beyond its role as a nutritional marker, albumin exerts important physiological functions, including antioxidant activity, free radical scavenging, and modulation of inflammatory responses [40-42]. Consequently, lower albumin levels may amplify oxidative stress and systemic inflammation, contributing to disease progression. In the multivariate logistic regression model, albumin remained independently associated with reduced odds of acute exacerbation, possibly reflecting its role as a negative acute-phase protein. This finding indicates that lower albumin levels could be linked to greater clinical burden, although its utility as a marker of disease severity or prognosis in older patients with CB warrants further investigation.

CRP, a commonly used marker reflecting systemic inflammatory activity, was measured at relatively higher levels among individuals experiencing AECB compared with those in a more stable clinical state. This elevation reflects an acute-phase response predominantly triggered by infectious agents, such as bacteria or viruses, which are common causes of exacerbations in the elderly. As a liver-synthesized protein regulated by interleukin-6 and other pro-inflammatory cytokines, CRP level rises rapidly in response to inflammatory stimuli, making it a sensitive early marker of acute systemic responses [43,44]. In our multivariate analysis, CRP was independently associated with AECB, highlighting its clinical relevance. However, ROC curve analysis showed that although CRP exhibited high sensitivity, its specificity was relatively modest, limiting its utility as a stand-alone diagnostic tool. Therefore, CRP may be more effective when combined with other biomarkers to improve overall diagnostic accuracy.

In this analysis, the combined use of SII, NLR, CRP, and albumin was associated with improved diagnostic discrimination, yielding an AUC of 0.970, with estimated sensitivity and specificity values of 86.9% and 96.8%, respectively. This finding suggests that incorporating multiple inflammatory parameters, each capturing distinct components of the host response, may enhance the overall predictive utility. Specifically, CRP and albumin are commonly interpreted as indicators of systemic inflammation and nutritional status, while SII and NLR may provide additional information related to immune cell distribution and activation. When considered together, this integrative biomarker approach could potentially contribute to more detailed risk assessment, particularly in older adults with CB who often present with complex comorbid conditions.

Nonetheless, certain limitations warrant consideration. Firstly, the retrospective design and single-center setting of this study might restrict the extent to which the results could be broadly applied to other populations. Secondly, despite the use of well-defined inclusion and exclusion criteria, the potential influence of unmeasured confounders, such as variations in nutritional status or the presence of subclinical infections, could not be entirely excluded. Thirdly, we did not evaluate the longitudinal prognostic value of these biomarkers in predicting future exacerbations or mortality. Prospective studies with serial biomarker monitoring are warranted to confirm their temporal utility and potential role in guiding therapeutic interventions. Finally, although patients with documented emphysema or airflow limitation were excluded, the possibility of subclinical emphysema could not be fully eliminated, which should be considered when interpreting the findings. This limitation underscores that this study does not aim to differentiate CB from other COPD phenotypes; rather, it highlights that SII and NLR, together with albumin and CRP, may serve as supportive indicators for the early recognition of acute exacerbations in elderly patients with CB. Such practical value in rapid identification remains clinically relevant, particularly in multimorbid older individuals, even if precise phenotype differentiation is not always achievable.

Conclusions

In elderly patients with CB, both the SII and the NLR were found to be independently associated with an increased likelihood of acute exacerbation, while lower serum albumin levels and elevated CRP concentrations showed significant associations. Among individual biomarkers, SII demonstrated the highest discriminatory capacity, and when combined with NLR, albumin, and CRP, the predictive model achieved markedly improved diagnostic performance. These findings indicate that SII and NLR, used in conjunction

with albumin and CRP, may serve as a practical and effective biomarker panel for the early identification of acute exacerbations in elderly patients with CB, potentially supporting timely clinical decision-making and targeted intervention strategies.

Data sharing statement

The dataset generated and analyzed during the current study is available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from The Second Medical Center & National Clinical Research Center for Geriatric Diseases, Chinese PLA General Hospital. The procedures used in this study were performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical guidelines. The written informed consent form was signed by all participants.

STROBE statement

The authors have read the STROBE Statement – checklist of items, and the manuscript was prepared according to the STROBE Statement – checklist of items.

Author contributions

Chao Zhang: Conceptualization, Methodology, Resources, Supervision, Funding acquisition, Validation, Writing – original draft, Formal analysis. Yunfeng Ni: Validation, Writing – review & editing. Dong Han: Investigation.

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Conflict of interest

No conflict of interest is declared.

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