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Lower Lymphocyte-Albumin-Neutrophil Ratio Provides Complementary Clinical Information for Identifying Patients with Prolonged Hospitalization Following Acute Exacerbation of Chronic Obstructive Pulmonary Disease: A Retrospective Cohort Study

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Research Article

Keywords: acute exacerbation of chronic obstructive pulmonary disease, lymphocyte-albumin-neutrophil ratio, systemic immune-inflammation index, prolonged hospitalization, inflammatory biomarkers

Posted Date: November 3rd, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11365656/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Acute exacerbations of COPD (AECOPD) are leading causes of hospitalization, healthcare expenditure, and disease progression. Prolonged hospitalization is associated with increased costs, functional decline, and adverse outcomes. Simple biomarkers from routine laboratory tests may complement multidimensional tools in assessing exacerbation risk during initial evaluation. The lymphocyte-albumin-neutrophil ratio (LANR) integrates inflammatory activity, immune competence, and nutritional status, whereas the systemic immune-inflammation index (SII) reflects systemic inflammatory burden. Whether LANR provides information beyond conventional biomarkers for identifying patients at risk of prolonged hospitalization remains uncertain.

Methods

This retrospective cohort study included 166 consecutive patients hospitalized for AECOPD at Shenzhen Second People's Hospital between December 2023 and April 2025. The primary outcome was prolonged hospitalization (> 7 days). Clinical characteristics, laboratory variables, and inflammatory biomarkers were extracted from electronic medical records. Multivariable logistic regression analyses were performed using clinically prespecified covariates. Model discrimination was evaluated using receiver operating characteristic (ROC) curves, bootstrap confidence intervals, and Brier scores. Restricted cubic spline analyses explored potential non-linear associations between LANR and prolonged hospitalization. Exploratory analyses of continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were performed to assess incremental clinical information.

Results

Among 166 patients hospitalized for AECOPD, 98 (59.0%) experienced prolonged hospitalization (> 7 days). LANR was lower in patients with prolonged hospitalization than in those hospitalized for ≤ 7 days [7.39 (IQR 3.83–11.75) vs. 10.97 (7.59–18.40), FDR-adjusted P = 0.003]. After adjustment for age, sex, body mass index, smoking exposure, fever, arterial pH, hs-CRP, and SII, higher LANR remained independently associated with lower odds of prolonged hospitalization (adjusted OR per 1-unit increase, 0.942; 95% CI, 0.891–0.995; P = 0.032), whereas SII was not independently associated (adjusted OR per 1000-unit increase, 0.961; 95% CI, 0.784–1.177; P = 0.700). The clinical base model yielded an AUC of 0.658 (bootstrap 95% CI, 0.572–0.742), which increased to 0.694 (0.609–0.776) after addition of LANR, with a corresponding reduction in the Brier score from 0.224 to 0.213. The Youden-derived LANR threshold of 9.595 provided 67.3% sensitivity and 64.6% specificity; patients with LANR ≤ 9.595 had higher odds of prolonged hospitalization (OR, 3.766; 95% CI, 1.945–7.293; P < 0.001). Thirty-day readmission occurred in 10 patients (6.1%), and neither LANR nor SII showed a significant association with this exploratory outcome.

Conclusions

Lower LANR was independently associated with prolonged hospitalization in patients hospitalized for AECOPD. Although its incremental contribution beyond routinely available clinical variables was modest, LANR integrates

inflammatory, immune, and nutritional information available from routine laboratory testing and may serve as a practical adjunct to early clinical assessment. Prospective multicenter studies are warranted to validate these findings.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation, chronic airway inflammation, and recurrent acute exacerbations(1, 2). It remains one of the leading causes of morbidity and mortality worldwide and imposes a substantial burden on patients, healthcare systems, and society(3). Acute exacerbations of COPD (AECOPD) accelerate lung function decline, impair health-related quality of life, increase the risk of future exacerbations, and account for a large proportion of COPD-related hospitalizations and healthcare expenditure(4). Patients requiring hospitalization for AECOPD generally represent a population with advanced disease and a high burden of comorbidities, making early identification of individuals at increased risk of unfavorable in-hospital outcomes an important clinical priority(5).

Hospital length of stay is an important indicator of disease severity, healthcare resource utilization, and recovery following AECOPD. Prolonged hospitalization is associated with increased medical costs, functional decline, hospital-acquired complications, and a higher likelihood of subsequent readmission(6). However, hospitalization duration is influenced by multiple interacting factors, including respiratory failure, systemic inflammation, nutritional status, comorbidities, treatment response, rehabilitation requirements, discharge planning, and institutional practice patterns. Consequently, no single laboratory biomarker is expected to explain the complexity of hospital stay, highlighting the need for biomarkers that complement rather than replace comprehensive clinical assessment.

Several multidimensional clinical tools have been developed to improve risk assessment in COPD(7). The Acute COPD Exacerbation Prediction Tool (ACCEPT) estimates individualized future exacerbation risk using demographic and clinical variables, whereas the AECOPD-F score was specifically developed to estimate the likelihood of prolonged hospitalization during acute exacerbations(8, 9). These instruments demonstrate that risk assessment in COPD requires integration of multiple clinical domains rather than reliance on isolated biomarkers. Nevertheless, many variables incorporated into these tools are not immediately available at hospital admission or require detailed clinical assessment. Therefore, inexpensive biomarkers derived from routinely performed laboratory tests remain attractive as adjunctive indicators during the initial evaluation of hospitalized patients.

Systemic inflammation plays a central role in the pathogenesis of AECOPD(10). Neutrophil activation contributes to airway injury through the release of proteolytic enzymes, reactive oxygen species, and neutrophil extracellular traps, whereas lymphopenia may reflect impaired adaptive immunity, stress-induced redistribution of circulating lymphocytes, or apoptosis during acute illness. In recent years, several composite inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR)(11), platelet-to-lymphocyte ratio (PLR)(12), and systemic immune–inflammation index (SII)(13), have been investigated as potential prognostic biomarkers in COPD. Among these, SII integrates platelet, neutrophil, and lymphocyte counts and has been associated with disease severity and adverse outcomes in several chronic inflammatory conditions(13). However, SII primarily reflects systemic inflammatory activity and does not directly capture nutritional or metabolic reserve(14).

The lymphocyte-albumin-neutrophil ratio (LANR) is a recently proposed composite biomarker that combines inflammatory, immune, and nutritional information into a single index. Unlike cell-count-based inflammatory markers, LANR incorporates serum albumin, a negative acute-phase reactant whose concentration is influenced by systemic inflammation, hepatic protein synthesis, vascular permeability, renal protein loss, and nutritional status(15, 16). Because hypoalbuminemia frequently accompanies severe systemic inflammation and chronic disease, LANR may better reflect the overall physiological reserve of hospitalized patients than inflammatory cell counts alone. Emerging evidence suggests that LANR is associated with prognosis in several malignant and inflammatory diseases, but its clinical relevance in patients hospitalized for AECOPD remains largely unexplored.

Importantly, previous studies evaluating inflammatory biomarkers in COPD have primarily focused on identifying statistically significant associations or developing prediction models. Comparatively fewer studies have examined whether these biomarkers provide clinically meaningful information beyond routinely available clinical variables. From a clinical perspective, demonstrating incremental value beyond existing assessment strategies is more informative than statistical significance alone.

Therefore, the present study aimed to evaluate the association between LANR and prolonged hospitalization in patients admitted for AECOPD and to compare its clinical utility with that of SII. Rather than developing a novel prediction model, we sought to determine whether LANR provides complementary clinical information beyond conventional inflammatory biomarkers and routinely available clinical variables during the early assessment of hospitalized patients.

2. Methods

2.1 Study design and setting

This was a single-center, retrospective observational study conducted at Shenzhen Second People's Hospital (The First Affiliated Hospital of Shenzhen University). Consecutive patients admitted between December 1, 2023 and April 30, 2025 with a primary diagnosis of acute exacerbation of chronic obstructive pulmonary disease (AECOPD) were screened for eligibility.

2.2 Study population

Inclusion criteria: Patients were included if they met all of the following criteria: Diagnosis of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria(2, 17); Hospitalization primarily for AECOPD: an event characterized by dyspnea and/or cough and sputum that worsen over < 14 days(7); Age > 40 years; Availability of the admission data required to ascertain the primary outcome and calculate the principal study variables.Patients with missing values for individual covariates were retained in the overall cohort and excluded only from analyses requiring those variables. Exclusion criteria: Patients were excluded if they had any of the following conditions: Use of antibiotics prior to blood sampling; Use of systemic corticosteroids (> 20 mg/day) within 2 months before admission; Use of antiplatelet drugs; Other chronic airway diseases including bronchiectasis, asthma, pulmonary tuberculosis, or interstitial lung disease; Systemic diseases such as malignancy, connective tissue disease, inflammatory bowel disease, or renal insufficiency, Incomplete clinical information precluding ascertainment of eligibility or the primary outcome. These criteria were applied to reduce potential confounding effects of inflammation-related comorbidities and medications.

2.3 Clinical data collection

Clinical information was extracted from the electronic medical record system using a standardized case report form. The following admission variables were collected. Demographic characteristics such as age and sex; Clinical characteristics including smoking history (pack-years), and body mass index (BMI); Clinical symptoms such as worsening cough, increased sputum production, dyspnea, fever; Arterial blood gas including pH, partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2) ; Inflammatory parameters: high-sensitivity C-reactive protein (hsCRP), white blood cell count (WBC), neutrophils, lymphocytes, eosinophils (EOS), platelets (PLT), serum albumin (ALB), D-dimer.

2.4 Biomarker calculation

The systemic immune-inflammation index (SII) was calculated as platelet count × neutrophil count / lymphocyte count which integrates thrombocyte activation, innate immune activation, and adaptive immune suppression into a single inflammatory index. The lymphocyte-albumin-neutrophil ratio (LANR) was calculated as lymphocyte count × albumin / neutrophil count. Unlike SII, LANR additionally incorporates serum albumin, thereby reflecting inflammatory activity together with nutritional reserve and physiological resilience. Smoking exposure was quantified as pack-years.

2.5 Outcomes

The primary endpoint was prolonged hospitalization defined as hospital stay > 7 days.This threshold was selected according to previous studies investigating hospital outcomes in patients with AECOPD. The secondary endpoint was 30-day all-cause hospital readmission. Because only a limited number of readmission events occurred, analyses involving this endpoint were considered exploratory.

2.6 Statistical analysis

Descriptive analyses: Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed variables are presented as mean ± standard deviation (SD) and compared using the independent-samples Student's t-test. Non-normally distributed variables are presented as median (interquartile range [IQR]) and compared using the Mann-Whitney U test. Categorical variables are summarized as number (percentage) and compared using either the chi-square test or Fisher's exact test. Multiple comparison adjustment: To reduce false-positive findings in baseline comparisons,P values presented in Table 1 were adjusted using the Benjamini-Hochberg false discovery rate (FDR) procedure.

The association between inflammatory biomarkers and prolonged hospitalization was evaluated using logistic regression. Unlike conventional stepwise regression, covariates included in multivariable analyses were prespecified according to clinical relevance and previous literature and included age, sex, body mass index, smoking pack-years, fever, arterial pH, hs-CRP, LANR, SII. Adjusted odds ratios (ORs) together with 95% confidence intervals (CIs) were reported. Multicollinearity among independent variables was evaluated using variance inflation factors (VIFs).

A clinical base model including age, sex, BMI, smoking exposure, and fever was constructed. The clinical base model was prespecified to include readily available demographic and bedside clinical variables, without laboratory biomarkers, to provide a common reference model for evaluating the incremental information contributed by LANR and SII. LANR and SII were then added separately and jointly to the clinical base model to assess their incremental contribution to model performance.

Discriminative performance was evaluated using receiver operating characteristic (ROC) curves. The following performance measures were reported: area under the ROC curve (AUC), bootstrap-derived 95% confidence intervals, Brier score. The optimal threshold for each biomarker was determined using the Youden index. Sensitivity and specificity were subsequently calculated.

To evaluate whether LANR provided additional clinical information beyond routinely available admission variables, exploratory analyses of continuous net reclassification improvement (continuous NRI), and integrated discrimination improvement (IDI) were performed. Because these analyses were conducted in the derivation cohort without external validation, their findings were interpreted as exploratory.

Restricted cubic spline (RCS) regression models were constructed to explore potential non-linear associations between LANR and prolonged hospitalization. Likelihood ratio tests comparing spline and linear models were used to evaluate statistical evidence for non-linearity.

Thirty-day readmission analyses were performed using penalized logistic regression to reduce small-sample bias. Given the limited number of readmission events, these analyses were considered hypothesis-generating rather than confirmatory.

The proportion of missing values for each variable is summarized in Supplementary Table S1. Given the relatively low proportion of missing data, complete-case analysis was used for analyses requiring these variables, and multiple imputation was not performed. All analyses were performed using Python (version 3.12) with the NumPy, SciPy, pandas, statsmodels, and scikit-learn packages. A two-sided P value < 0.05 was considered statistically significant unless otherwise specified.

Variable	Missing, n	Missing, %
Age	3	1.8
Sex	0	0.0
Smoking pack-years	3	1.8
BMI	3	1.8
Fever	3	1.8
pH	13	7.8
$PaCO_2$	13	7.8
PaO_2	13	7.8
hs-CRP	3	1.8
WBC	3	1.8
Eosinophils	3	1.8
D-dimer	6	3.6
LANR	3	1.8
SII	3	1.8
30-day readmission	3	1.8

Supplementary Table S1: Missing data in the analytic cohort. Percentages were calculated using the full cohort of 166 patients. Complete-case analysis was used for the relevant statistical models.

3. Results

3.1 Study population

A total of 166 consecutive patients hospitalized for acute exacerbation of chronic obstructive pulmonary disease (AECOPD) fulfilled the eligibility criteria and were included in the study. Of these, 98 patients (59.0%) experienced prolonged hospitalization (> 7 days), whereas 68 (41.0%) had a hospital stay of ≤ 7 days. Complete biomarker data were available for 163 patients, and 153 patients had complete data for all covariates included in the fully adjusted multivariable model. Thirty-day readmission status was available for 163 patients, among whom 10 (6.1%) were readmitted. Given the small number of readmission events, analyses of this secondary outcome were considered exploratory only.

3.2 Baseline characteristics

Baseline clinical characteristics according to hospital length of stay are summarized in Table 1. Patients with prolonged hospitalization had a significantly lower LANR than those hospitalized for ≤ 7 days [median 7.39 (IQR 3.83–11.75) vs. 10.97 (7.59–18.40); raw P < 0.001, FDR-adjusted P = 0.003]. In contrast, SII was higher in the prolonged-hospitalization group [1067.41 (588.43-1990.68) vs. 752.58 (462.58-1213.27); raw P = 0.004, FDR-adjusted P = 0.021]. Patients with prolonged hospitalization also had higher WBC counts [8.46 (6.48–11.29) vs.

6.40 (5.32–8.23) ×10⁹/L; FDR-adjusted P = 0.004], higher hs-CRP concentrations [20.56 (5.97–82.08) vs. 8.09 (1.52–49.20) mg/L; FDR-adjusted P = 0.027], and higher $PaCO_2$ [45.75 (39.00-59.30) vs. 40.70 (38.40–46.10) mmHg; FDR-adjusted P = 0.021].

Although patients with prolonged hospitalization were older [74.00 (67.00-81.75) vs. 71.00 (67.00–75.00) years; raw P = 0.025] and had a slightly lower arterial pH [7.38 (7.34–7.41) vs. 7.39 (7.37–7.42); raw P = 0.039], these differences did not remain statistically significant after FDR correction (P = 0.065 and P = 0.087, respectively). Worsening cough was less frequent in the prolonged-hospitalization group (84.7% vs. 96.9%; FDR-adjusted P = 0.037). No significant between-group differences were observed in sex, BMI, smoking exposure, PaO_2, eosinophil count, D-dimer, increased sputum production, dyspnea, or fever after FDR adjustment.

Table 1

Baseline characteristics according to hospital length of stay. Data are mean ± standard deviation, median (interquartile range), or n/N (%), as appropriate. Raw P values were obtained using Welch's t test, the Mann-Whitney U test, the chi-square test, or Fisher's exact test. FDR-adjusted P values were calculated using the Benjamini-Hochberg procedure. Abbreviations: BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; LANR, lymphocyte-albumin-neutrophil ratio; SII, systemic immune-inflammation index; WBC, white blood cell count.

Characteristic	N	Overall	≤ 7 days	> 7 days	Raw P	FDR-adjusted P
Age, years	163	72.00 (67.00, 79.00)	71.00 (67.00, 75.00)	74.00 (67.00, 81.75)	0.025	0.065
Smoking pack-years	163	40.00 (20.00, 60.00)	40.00 (20.00, 50.00)	40.00 (20.00, 60.00)	0.474	0.569
BMI, kg/m²	163	20.76 (18.68, 23.03)	21.33 (19.03, 23.15)	20.75 (18.47, 23.03)	0.455	0.569
pH	153	7.39 (7.35, 7.41)	7.39 (7.37, 7.42)	7.38 (7.34, 7.41)	0.039	0.087
$PaCO_2$, mmHg	153	42.90 (38.50, 52.50)	40.70 (38.40, 46.10)	45.75 (39.00, 59.30)	0.005	0.021
PaO_2, mmHg	153	94.20 (76.80, 119.00)	89.40 (77.80, 110.00)	99.15 (74.72, 120.00)	0.328	0.454
hs-CRP, mg/L	163	14.63 (4.25, 67.85)	8.09 (1.52, 49.20)	20.56 (5.97, 82.08)	0.007	0.027
WBC, ×10⁹/L	163	7.49 (5.72, 10.44)	6.40 (5.32, 8.23)	8.46 (6.48, 11.29)	< 0.001	0.004
Eosinophils, ×10⁹/L	163	0.12 (0.06, 0.21)	0.14 (0.08, 0.21)	0.12 (0.06, 0.19)	0.186	0.305
D-dimer, mg/L	160	0.45 (0.24, 0.87)	0.38 (0.21, 0.71)	0.50 (0.26, 0.95)	0.125	0.225
LANR	163	8.96 (5.02, 14.61)	10.97 (7.59, 18.40)	7.39 (3.83, 11.75)	< 0.001	0.003
SII	163	921.78 (546.51, 1594.19)	752.58 (462.58, 1213.27)	1067.41 (588.43, 1990.68)	0.004	0.021
Male sex	166	146/166 (88.0%)	60/68 (88.2%)	86/98 (87.8%)	0.926	0.980
Worsening cough	163	146/163 (89.6%)	63/65 (96.9%)	83/98 (84.7%)	0.012	0.037
Increased sputum	163	140/163 (85.9%)	58/65 (89.2%)	82/98 (83.7%)	0.318	0.454
Dyspnea	163	149/163 (91.4%)	59/65 (90.8%)	90/98 (91.8%)	0.812	0.913
Fever	163	47/163 (28.8%)	14/65 (21.5%)	33/98 (33.7%)	0.094	0.188

3.3 Association between LANR and prolonged hospitalization

Associations between candidate variables and prolonged hospitalization are presented in Table 2. In univariable logistic regression, higher LANR was associated with lower odds of prolonged hospitalization (OR per 1-unit increase, 0.934; 95% CI, 0.895–0.975; P = 0.002). Older age (OR per year, 1.054; 95% CI, 1.012–1.098; P = 0.011), lower arterial pH (OR per 0.1-unit increase, 0.436; 95% CI, 0.214–0.887; P = 0.022), and higher hs-CRP (OR per 10 mg/L increase, 1.077; 95% CI, 1.010–1.149; P = 0.023) were also associated with prolonged hospitalization. The univariable association for SII did not reach statistical significance (OR per 1000-unit increase, 1.228; 95% CI, 0.986–1.528; P = 0.067).

In the fully adjusted model (n = 153), which included age, sex, BMI, smoking exposure, fever, arterial pH, hs-CRP, LANR, and SII, higher LANR remained independently associated with lower odds of prolonged hospitalization (adjusted OR per 1-unit increase, 0.942; 95% CI, 0.891–0.995; P = 0.032), whereas SII was not independently associated (adjusted OR per 1000-unit increase, 0.961; 95% CI, 0.784–1.177; P = 0.700). Arterial pH also remained independently associated with prolonged hospitalization (adjusted OR per 0.1-unit increase, 0.413; 95% CI, 0.181–0.939; P = 0.035). Age, sex, BMI, smoking exposure, fever, and hs-CRP were likewise not statistically significant in the fully adjusted model (Table 2 and Fig. 1).

Table 2

Univariable and multivariable logistic regression for prolonged hospitalization. The fully adjusted model included all variables shown in the table. Odds ratios for smoking, pH, hs-CRP, and SII correspond to the specified rescaled units. Abbreviations: BMI, body mass index; CI, confidence interval; hs-CRP, high-sensitivity C-reactive protein; LANR, lymphocyte-albumin-neutrophil ratio; OR, odds ratio; SII, systemic immune-inflammation index.

Variable	Univariable N	Univariable OR (95% CI)	P	Adjusted N	Adjusted OR (95% CI)	P
Age (per 1 year)	163	1.054 (1.012–1.098)	0.011	153	1.030 (0.982–1.080)	0.227
Male sex (yes vs no)	166	0.956 (0.368–2.479)	0.926	153	0.697 (0.180–2.697)	0.601
BMI (per 1 kg/m²)	163	0.958 (0.878–1.046)	0.337	153	0.974 (0.882–1.075)	0.604
Smoking (per 10 pack-years)	163	1.048 (0.931–1.179)	0.441	153	1.014 (0.875–1.175)	0.853
Fever (yes vs no)	163	1.849 (0.896–3.818)	0.096	153	1.489 (0.629–3.524)	0.365
pH (per 0.1 unit)	153	0.436 (0.214–0.887)	0.022	153	0.413 (0.181–0.939)	0.035
hs-CRP (per 10 mg/L)	163	1.077 (1.010–1.149)	0.023	153	1.048 (0.963–1.141)	0.272
LANR (per 1 unit)	163	0.934 (0.895–0.975)	0.002	153	0.942 (0.891–0.995)	0.032
SII (per 1000 units)	163	1.228 (0.986–1.528)	0.067	153	0.961 (0.784–1.177)	0.700

Figure 1: Forest plot of the fully adjusted model. Points indicate adjusted odds ratios and horizontal bars indicate 95% confidence intervals. The model included age, sex, BMI, smoking exposure, fever, pH, hs-CRP, LANR,

and SII.

3.4 Model discrimination and incremental clinical information

Receiver operating characteristic analyses were performed to assess whether LANR and SII provided incremental information beyond routinely available clinical variables (Table 3 and Fig. 2). The clinical base model, comprising age, sex, BMI, smoking exposure, and fever, yielded an AUC of 0.658 (bootstrap 95% CI, 0.572–0.742) and a Brier score of 0.224 (95% CI, 0.202–0.246). Addition of LANR increased the AUC to 0.694 (95% CI, 0.609–0.776) and reduced the Brier score to 0.213 (95% CI, 0.187–0.238). By comparison, addition of SII resulted in an AUC of 0.671 (95% CI, 0.584–0.754) and a Brier score of 0.220 (95% CI, 0.198–0.243). The model incorporating both LANR and SII yielded an AUC of 0.692 (95% CI, 0.606–0.775) and a Brier score of 0.213 (95% CI, 0.187–0.238).

Table 3

Discrimination and overall accuracy of the clinical and biomarker-augmented models. The clinical base model included age, sex, BMI, smoking exposure, and fever. AUC confidence intervals and Brier-score confidence intervals were estimated using 2,000 bootstrap samples. Higher AUC and lower Brier score indicate better apparent model performance. Abbreviations: AUC, area under the receiver operating characteristic curve; BMI, body mass index; CI, confidence interval; LANR, lymphocyte-albumin-neutrophil ratio; SII, systemic immune-inflammation index.

Model	N	AUC	Bootstrap 95% CI	Brier score	Bootstrap 95% CI
Clinical base model	163	0.658	0.572–0.742	0.224	0.202–0.246
Clinical model + LANR	163	0.694	0.609–0.776	0.213	0.187–0.238
Clinical model + SII	163	0.671	0.584–0.754	0.220	0.198–0.243
Clinical model + LANR + SII	163	0.692	0.606–0.775	0.213	0.187–0.238

Compared with the clinical base model, addition of LANR produced an absolute increase in AUC of 0.036 (bootstrap 95% CI, -0.019 to 0.091). Although the confidence interval for ΔAUC included zero, exploratory reclassification analyses showed a continuous NRI of 0.618 (95% CI, 0.313–0.927) and an IDI of 0.046 (95% CI, 0.014–0.079). In contrast, addition of SII resulted in a smaller ΔAUC of 0.013 (95% CI, -0.021 to 0.047), with a continuous NRI of 0.191 (95% CI, -0.096 to 0.467) and an IDI of 0.015 (95% CI, -0.003 to 0.032). Addition of both LANR and SII yielded a ΔAUC of 0.034 (95% CI, -0.023 to 0.091), a continuous NRI of 0.557 (95% CI, 0.248–0.850), and an IDI of 0.046 (95% CI, 0.013–0.078) compared with the clinical base model (Supplementary Table S2).

Taken together, these analyses showed that the addition of LANR was associated with modest improvements in apparent discrimination and overall prediction accuracy, accompanied by positive exploratory reclassification metrics. However, the bootstrap confidence interval for ΔAUC included zero, and adding SII to the LANR-containing model did not further increase the AUC (0.692 vs. 0.694). Therefore, these findings support a modest complementary contribution of LANR rather than statistically established superiority or a large improvement in discrimination. Because NRI and IDI were estimated in the same derivation cohort without external validation, they should be interpreted as exploratory measures of incremental information rather than evidence of clinical benefit.

3.5 ROC-derived biomarker thresholds

ROC-derived thresholds based on the Youden index are presented in Table 4. For LANR, the optimal threshold was 9.595, corresponding to a sensitivity of 67.3%, specificity of 64.6%, and Youden index of 0.320. Among patients with LANR ≤ 9.595, 74.2% (66/89) experienced prolonged hospitalization, compared with 43.2% (32/74) among those with LANR > 9.595. Accordingly, low LANR was associated with approximately 3.8-fold higher odds of prolonged hospitalization (OR, 3.766; 95% CI, 1.945–7.293; P < 0.001).

For SII, the optimal threshold was 0.955×10³, with a sensitivity of 57.1%, specificity of 66.2%, and Youden index of 0.233. Prolonged hospitalization occurred in 71.8% of patients in the high-SII group compared with 49.4% in the reference group (OR, 2.606; 95% CI, 1.359–4.998; P = 0.004). These cut-offs were derived within the present cohort and should therefore be regarded as exploratory rather than externally validated clinical decision thresholds.

Table 4

ROC-derived biomarker thresholds for prolonged hospitalization. Cut-offs were selected using the Youden index. Low LANR was defined as LANR ≤ 9.595; high SII was defined as SII ≥ 0.955 ×10³ units. Odds ratios compare the high-risk group with the corresponding reference group. These thresholds are exploratory and require external validation. Abbreviations: CI, confidence interval; LANR, lymphocyte-albumin-neutrophil ratio; OR, odds ratio; ROC, receiver operating characteristic; SII, systemic immune-inflammation index.

Biomarker	N	Cut-off	Sensitivity (%)	Specificity (%)	Youden index	OR (95% CI)	P	Reference-group rate	High-risk-group rate
LANR	163	9.595	67.3	64.6	0.320	3.766 (1.945–7.293)	< 0.001	43.2% (n = 74)	74.2% (n = 89)
SII	163	0.955 ×10³	57.1	66.2	0.233	2.606 (1.359–4.998)	0.004	49.4% (n = 85)	71.8% (n = 78)

3.6 Restricted cubic spline analysis

Restricted cubic spline analysis was performed in the 153 patients with complete data for all covariates included in the fully adjusted model. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles of the LANR distribution. After adjustment for age, sex, BMI, smoking exposure, fever, arterial pH, hs-CRP, and SII, the spline curve demonstrated an inverse association between LANR and the odds of prolonged hospitalization (Fig. 3). There was no evidence of departure from linearity (likelihood-ratio P for non-linearity = 0.927), supporting the specification of LANR as a continuous linear term in the primary multivariable model.

3.7 Exploratory analysis of 30-day readmission

Among the 163 patients with available 30-day follow-up information, 10 (6.1%) experienced all-cause readmission. Because of the small number of events, penalized logistic regression was used and these analyses were considered exploratory. Neither LANR nor SII was significantly associated with 30-day readmission after adjustment. Given only 10 outcome events, these findings should be interpreted cautiously and should not be considered evidence of absence of an association.

4. Discussion

In this retrospective cohort of patients hospitalized for AECOPD, lower LANR was independently associated with prolonged hospitalization after adjustment for demographic characteristics, smoking exposure, clinical features, arterial pH, hs-CRP, and SII. This association was approximately linear across the observed LANR range, with no evidence of non-linearity in restricted cubic spline analysis. In contrast, SII was not independently associated with prolonged hospitalization in the fully adjusted model. Addition of LANR to a clinical base model was associated with modest improvements in apparent discrimination and overall prediction accuracy, whereas the bootstrap confidence interval for the change in AUC included zero. Exploratory reclassification analyses showed positive continuous NRI and IDI estimates for LANR, although these findings require cautious interpretation because they were derived and evaluated in the same cohort. Collectively, these findings suggest that LANR may provide complementary information for identifying patients at increased risk of prolonged hospitalization during AECOPD rather than functioning as a stand-alone predictive marker.

The observed association between lower LANR and prolonged hospitalization is biologically plausible because LANR integrates three clinically relevant components of the host response during acute exacerbation. Neutrophilic inflammation represents one of the dominant pathological features of AECOPD(18). Activated neutrophils release proteolytic enzymes, reactive oxygen species, and neutrophil extracellular traps that contribute to airway epithelial injury, mucus hypersecretion, impaired mucociliary clearance, and worsening gas exchange(19–21). Consequently, elevated neutrophil counts frequently indicate greater inflammatory burden and more severe disease activity(22, 23). Conversely, lymphocyte depletion commonly accompanies severe systemic illness. Reduced circulating lymphocyte counts may result from stress-induced redistribution, apoptosis, impaired adaptive immune responses, and chronic immune dysregulation(24, 25). Previous studies have demonstrated that lymphopenia is associated with delayed recovery and poorer outcomes across a variety of infectious and inflammatory diseases. Albumin is widely recognized as a negative acute-phase reactant rather than merely a marker of nutritional status(26, 27). During acute systemic inflammation, hepatic albumin synthesis is suppressed by inflammatory cytokines, while increased vascular permeability, altered protein metabolism, renal protein loss, and pre-existing malnutrition may further reduce circulating albumin concentrations. Consequently, a lower LANR may reflect the combined presence of heightened neutrophilic inflammation, relative lymphocyte depletion, and reduced albumin concentration. This multidimensional information may partly explain why LANR retained an independent association with prolonged hospitalization after adjustment for hs-CRP and SII(28, 29).

Previous studies have consistently demonstrated associations between systemic inflammatory biomarkers and adverse outcomes in COPD. Composite inflammatory indices including the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) have all been associated with disease severity, prolonged hospitalization, recurrent exacerbations, or mortality(30–33). Although both LANR and SII incorporate neutrophil and lymphocyte counts, the two biomarkers reflect different biological processes. SII primarily quantifies systemic inflammatory activation through the interaction between thrombocytes, neutrophils, and lymphocytes. In contrast, LANR additionally incorporates serum albumin, thereby integrating inflammation with nutritional reserve and physiological resilience(27, 34, 35). Because prolonged hospitalization is influenced not only by inflammatory activity but also by frailty, nutritional status, and systemic physiological reserve(36), LANR may better reflect the overall condition of hospitalized patients than inflammation-based indices alone(37–39). In the present study, SII was higher among patients with prolonged hospitalization in the unadjusted group comparison but was not independently associated with the outcome after multivariable adjustment. In contrast, LANR remained independently associated with prolonged hospitalization. Incremental

performance analyses showed numerically greater changes after addition of LANR than after addition of SII. However, the confidence intervals for ΔAUC included zero, and no direct statistical comparison established superiority of LANR over SII. Accordingly, these findings should be interpreted as suggesting potentially greater complementary information from LANR in this cohort rather than demonstrating superiority of one biomarker over another.

The present findings have several practical implications. First, LANR is calculated entirely from laboratory parameters routinely measured during hospital admission and therefore does not require additional testing or increase healthcare costs(40, 41). Second, LANR should not be regarded as a replacement for comprehensive clinical assessment. Instead, it may serve as an adjunctive biomarker alongside medical history, physical examination, arterial blood gas analysis, imaging findings, pulmonary function testing, and multidimensional clinical assessment tools such as ACCEPT(8). Third, hospital length of stay is influenced by numerous biological and non-biological factors, including exacerbation severity, respiratory failure, treatment response, rehabilitation needs, discharge planning, healthcare resources, and socioeconomic factors(42, 43). Consequently, no single inflammatory biomarker would be expected to achieve excellent discrimination.

The exploratory reclassification findings provide additional context in the study. Addition of LANR to the clinical base model yielded a continuous NRI of 0.618 and an IDI of 0.046, with bootstrap confidence intervals excluding zero, whereas the corresponding estimates for SII were smaller and their confidence intervals included zero. Nevertheless, NRI and IDI can be sensitive to model specification and may overstate incremental value when assessed in the derivation dataset. Moreover, these measures do not directly establish clinical utility. They should therefore be viewed as supportive exploratory evidence that LANR contains information not fully represented by the clinical base model, rather than as evidence that incorporating LANR would necessarily improve clinical decision-making.

The restricted cubic spline analysis further supported the primary modeling strategy. There was no evidence of departure from linearity between LANR and the odds of prolonged hospitalization (P for non-linearity = 0.927). This finding supports treating LANR as a continuous linear variable in the primary logistic regression model and suggests that the association was not driven solely by an arbitrary dichotomization threshold. Importantly, however, absence of statistical evidence for non-linearity should not be interpreted as proof of a strictly linear biological relationship, particularly given the sample size of the present study.

The Youden-derived LANR threshold of 9.595 identified a subgroup with a substantially higher proportion of prolonged hospitalization, providing an intuitive illustration of the observed association. However, this threshold was derived and evaluated within the same cohort and should not be regarded as an established clinical cut-off. The continuous LANR analysis remains the primary inferential analysis, whereas the threshold-based findings are exploratory and require external validation before clinical application.

From a clinical perspective, LANR has several practical advantages as a candidate complementary marker. Its components-lymphocyte count, neutrophil count, and serum albumin-are routinely measured during hospital admission, allowing LANR to be calculated without additional specialized testing or substantial cost(44, 45). The present findings suggest that a low LANR could alert clinicians to patients who may experience a more prolonged hospital course and may complement conventional clinical assessment. However, the modest change in AUC and the absence of external validation argue against using LANR as an independent decision-making tool. Its

potential value is more appropriately viewed as an adjunct to, rather than a replacement for, established clinical assessment.

Several limitations should be acknowledged. First, this was a single-center retrospective study with a relatively modest sample size, which limits generalizability and precludes causal inference. Second, residual confounding remains possible despite multivariable adjustment, particularly from factors that may influence both inflammatory biomarkers and hospital length of stay, such as comorbidity burden, nutritional status, treatment intensity, infection characteristics, and discharge-related factors(46, 47). Third, biomarker measurements were based on admission laboratory data, and serial changes in LANR during hospitalization were not evaluated. Fourth, the incremental performance analyses were conducted in the same cohort used for model estimation. Although bootstrap resampling was used to quantify uncertainty, no independent external validation cohort was available; consequently, the observed changes in AUC, NRI, and IDI may be optimistic. Fifth, the LANR threshold of 9.595 was data-derived and should be considered exploratory. Finally, only 10 patients experienced 30-day readmission, resulting in limited statistical power for the secondary outcome; the absence of a significant association with readmission should therefore not be interpreted as evidence that LANR has no relationship with this outcome. Future studies should evaluate LANR in larger multicenter cohorts with standardized assessment of pulmonary function, imaging characteristics, exacerbation phenotypes, and longitudinal inflammatory biomarkers(48). Integration of LANR into multidimensional clinical assessment strategies and externally validated risk prediction models may further clarify its role in individualized management of patients hospitalized with AECOPD(49, 50).

5. Conclusions

Lower LANR was independently associated with prolonged hospitalization among patients admitted for AECOPD, whereas SII was not independently associated with this outcome after multivariable adjustment. The association between LANR and prolonged hospitalization was approximately linear, with no evidence of non-linearity in restricted cubic spline analysis. Adding LANR to routinely available clinical variables provided modest incremental information, although the improvement in conventional discrimination was limited and the exploratory reclassification findings require external validation. Given that LANR can be readily calculated from routinely available laboratory parameters, it may serve as a practical adjunct to early clinical assessment rather than as a stand-alone predictive tool. Prospective multicenter studies are needed to validate these findings and clarify the clinical utility of LANR in patients hospitalized for AECOPD.

Declarations

Data Availability

The datasets generated and analysed during the current study are not publicly available due to patient privacy but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of Shenzhen Second People's Hospital (Approval No. 2026-149-01PJ). The requirement for written informed consent was waived because of the retrospective design and use of anonymized data.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Funding

This work was supported by the Shenzhen Clinical Research Center for Respiratory Disease, Shenzhen Institute of Respiratory Disease (Grant No. LCYSSQ20220823091203007).

Author Contribution

Y.Z. Conceived the study, collected and analyzed the data, and drafted the manuscript. R.S. Contributed to data collection and interpretation. H. H. Supervised the study, critically revised the manuscript, and approved the final version. All authors read and approved the final manuscript.

Acknowledgements

The authors thank the physicians, nurses, and medical record staff of the Department of Respiratory Medicine, Shenzhen Second People's Hospital, for their assistance with patient management and data collection.

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Figures

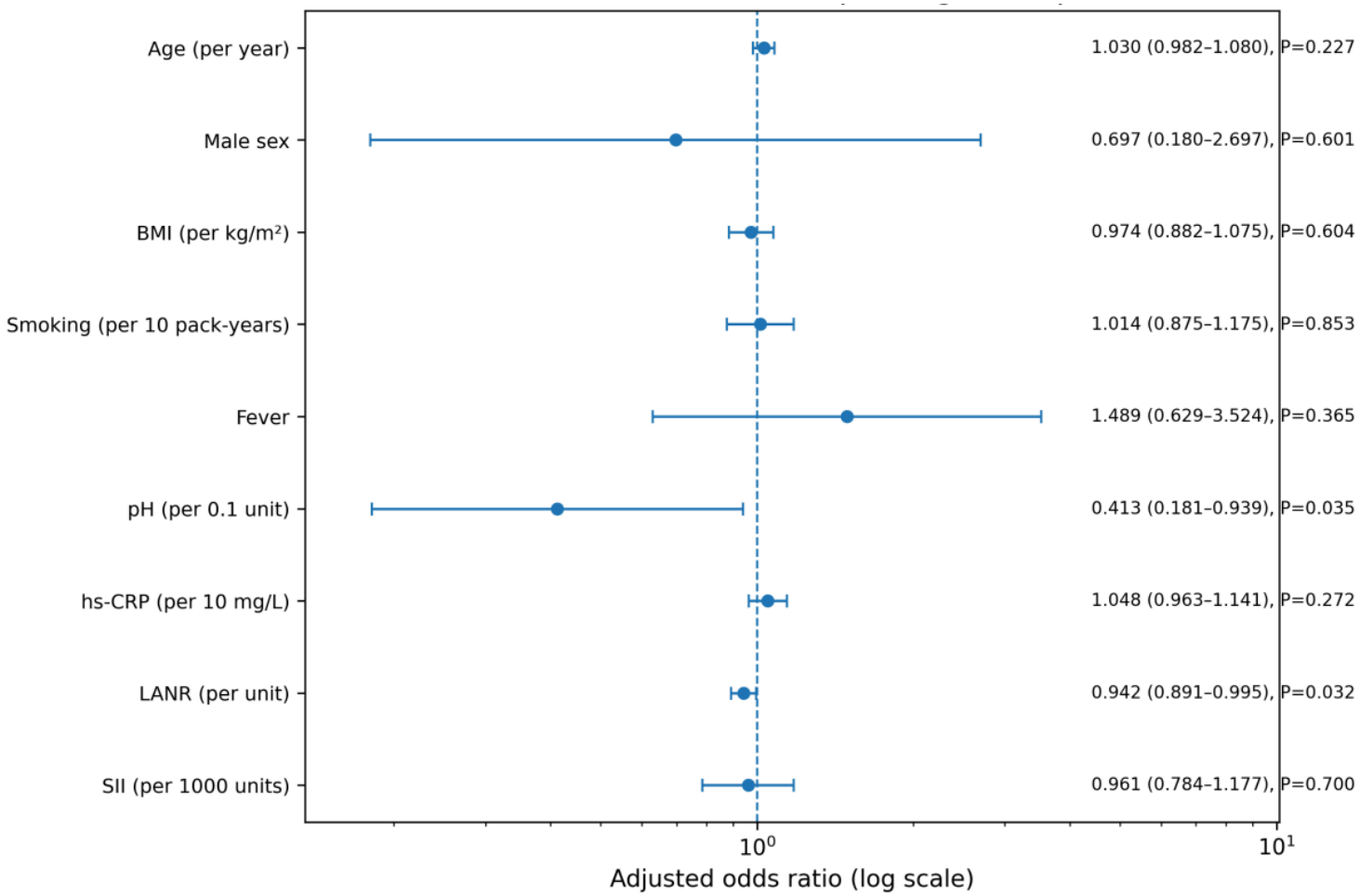


Figure 1

Forest plot of the fully adjusted model. Points indicate adjusted odds ratios and horizontal bars indicate 95% confidence intervals. The model included age, sex, BMI, smoking exposure, fever, pH, hs-CRP, LANR, and SII.

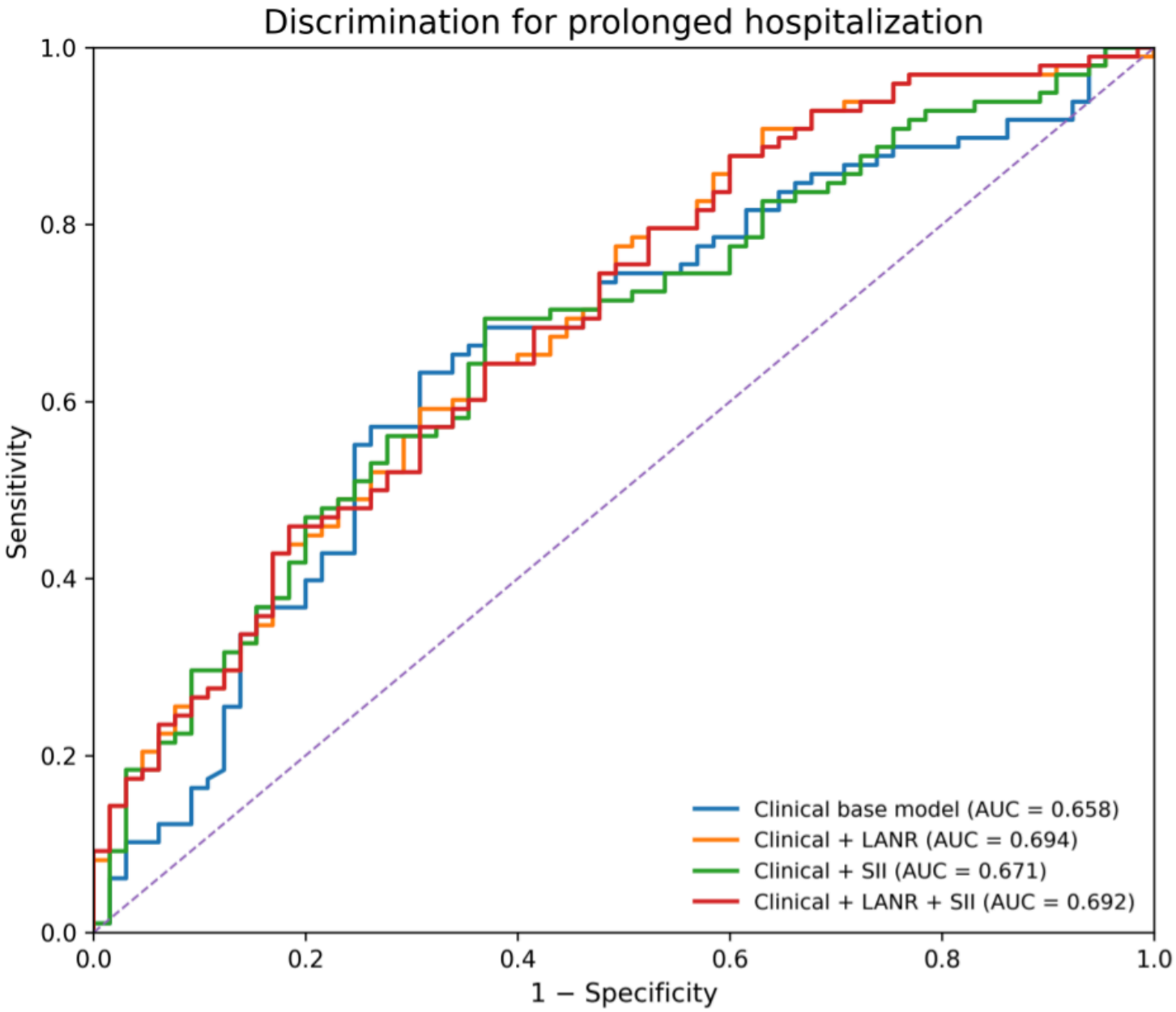


Figure 2

Receiver operating characteristic curves. ROC curves comparing the clinical base model, the clinical model incorporating LANR, the clinical model incorporating SII, and the combined biomarker model for identifying prolonged hospitalization.

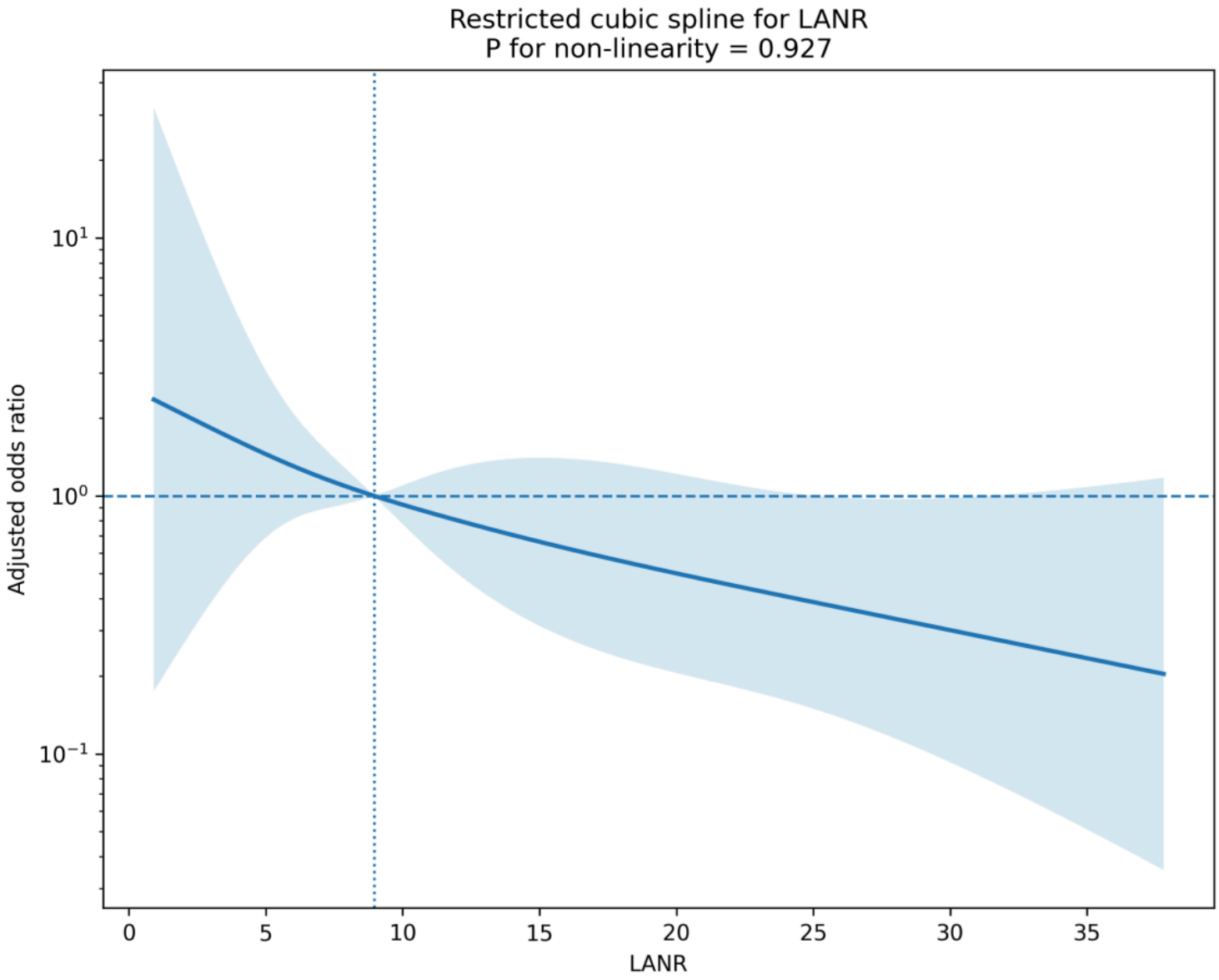


Figure 3

Restricted cubic spline analysis of LANR and prolonged hospitalization. The model was adjusted for age, sex, BMI, smoking pack-years, fever, arterial pH, hs-CRP, and SII. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles of LANR. The horizontal dashed line represents an odds ratio of 1.