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ORIGINAL RESEARCH

Comprehensive Nomograms Using Routine Biomarkers Beyond Eosinophil Levels: Enhancing Predictability of Corticosteroid Treatment Outcomes in AECOPD

Lin Feng[1], Jiachen Li[1], Zhenbei Qian[2], Chenglong Li[3,4], Darui Gao[3,4], Yongqian Wang[3,4], Wuxiang Xie[3,4], Yutong Cai[5], Zhaohui Tong[2], Lirong Liang[1]

[1]Department of Clinical Epidemiology, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, People's Republic of China; [2]Department of Respiratory and Critical Care Medicine, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, People's Republic of China; [3]Heart and Vascular Health Research Center, Peking University Clinical Research Institute, Peking University First Hospital, Beijing, People's Republic of China; [4]Key Laboratory of Epidemiology of Major Diseases (Peking University), Ministry of Education, Beijing, People's Republic of China; [5]Centre for Environmental Health and Sustainability, Department of Health Sciences, University of Leicester, Leicester, UK

Correspondence: Lirong Liang, Department of Clinical Epidemiology, Beijing Institute of Respiratory Medicine and Beijing Chao-Yang Hospital, Capital Medical University, Beijing, People's Republic of China, Email llrcruie@163.com

Purpose: Patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) exhibit heterogeneous responses to corticosteroid treatment. We aimed to determine whether combining eosinophil levels with other routine clinical indicators can enhance the predictability of corticosteroid treatment outcomes and to come up with a scoring system.

Patients and Methods: Consecutive patients admitted with AECOPD receiving corticosteroid treatment between July 2013 and March 2022 at Beijing Chao-Yang Hospital were retrospectively analyzed. Data on patients' demographics, smoking status, hospitalization for AECOPD in the previous year, comorbidities, blood laboratory tests, in-hospital treatment and clinical outcomes were collected. Least absolute shrinkage and selection operator (LASSO) regression and backward logistic regression were used for predictor selection, and predictive nomograms were developed. The discrimination and calibration of the nomograms were assessed using the area under the receiver operating curve (AUC) and calibration plots. Internal validation was performed using the 500-bootstrap method, and clinical utility was evaluated using decision curve analysis (DCA).

Results: Among the 3254 patients included, 804 (24.7%) had treatment failure. A nomogram of eosinophils, platelets, C-reactive protein (CRP), low density lipoprotein cholesterol, prognostic nutritional index (PNI), hospitalization for AECOPD in the previous year, ischemic heart diseases and chronic hepatic disease was developed to predict treatment failure for patients with a smoking history. For patients without a smoking history, a nomogram of CRP, PNI, ischemic heart diseases and chronic hepatic disease was developed. Although the AUCs of these two nomograms were only 0.644 and 0.647 respectively, they were significantly superior to predictions based solely on blood eosinophil levels.

Conclusion: We developed easy-to-use comprehensive nomograms utilizing readily available clinical biomarkers related to inflammation, nutrition and immunity, offering modestly enhanced predictive value for treatment outcomes in corticosteroid-treated patients with AECOPD. Further investigations into novel biomarkers and additional patient data are imperative to optimize the predictive performance.

Keywords: chronic obstructive pulmonary disease, glucocorticoids, prediction model, least absolute shrinkage and selection operator

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, imposing a substantial and increasing economic and social burden.[1] COPD is also highly prevalent in the Chinese adult population, with a prevalence of 13.7% in those over 40 years old.[2] Acute exacerbations of COPD (AECOPD) are important events

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in the management of COPD, negatively impacting health status, hospitalization and readmission rates, and disease progression.[1] Systemic corticosteroids (SCS) are widely used in AECOPD treatment, and can relieve acute respiratory symptoms, shorten recovery time and improve lung function in patients with AECOPD.[1,3] However, SCS use is associated with increased risks of pneumonia and mortality.[3,4]

Patients with COPD are heterogeneous, and individual responses to corticosteroid treatment may vary.[1] Blood eosinophil levels have been identified as a predictive factor of the effectiveness of inhaled corticosteroid (ICS) treatment in preventing future exacerbations among stable COPD patients.[5–9] A threshold of blood eosinophils ≥ 300 cells/μL is recommended for initiating ICS treatment in these patients.[1] For AECOPD, patients with the eosinophil-predominant phenotype are more likely to benefit from SCS treatment, using different peripheral blood eosinophils threshold values (2%, 300 cells/μL).[10–14] And those with peripheral blood eosinophils ≥ 2% or ≥200 cells/μL are recommended to initiate ICS treatment.[15] However, solely relying on peripheral blood eosinophils to guide personalized corticosteroid treatment may be inadequate, and all available clinical data should be taken into consideration.[16,17]

Several new composite inflammatory indicators, such as the prognostic nutritional index (PNI), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR), which can be easily obtained from routine clinical assessments without the need for invasive tests or additional charges, have been found to be associated with poor clinical outcomes in patients with severe AECOPD.[18–23] However, their potential as predictors for the effectiveness of corticosteroid treatment, an anti-inflammatory intervention, remains unclear. In addition, demographic characteristics, comorbidities, exacerbation histories and routine blood biomarkers have also been used to assess in-hospital mortality and 30-day re-exacerbation risk in patients with AECOPD.[24–27] If these clinical data demonstrate additional predictive value for corticosteroid treatment failure on the basis of blood eosinophils, a comprehensive and cost-effective prediction model, along with an easy-to-use nomogram, could be developed to facilitate personalized corticosteroid treatment for patients with AECOPD in clinical settings. Therefore, the aims of our study were to determine whether combining eosinophil levels with other routine clinical indicators could enhance the predictability of outcomes for corticosteroid treatment, encompassing both systemic and inhaled routes, subsequently, to develop a comprehensive scoring system and internally validate it.

Materials and Methods

Study Design and Participants

This was a retrospective cohort study conducted at Beijing Chao-Yang Hospital in Beijing, China. A total of 3254 patients with AECOPD admitted from July 2013 to March 2022 were selected from an electronic medical record (EMR)-based Big Data Platform for Respiratory Diseases[28] to develop and internally validate the prediction model. This study was approved by the Research Ethics Board of Beijing Chao-Yang Hospital (2020-ke-511). Informed written consent was waived by the Research Ethics Board of Beijing Chaoyang Hospital due to the retrospective nature of the study.

The criteria for inclusion were as follows: (1) aged 40 and older; (2) with an AECOPD diagnosis based on the International Classification of Diseases 10th Revision (ICD-10) code of J40.0–44.9 in the top three diagnoses in the discharge record; and (3) received ICS and/or SCS treatment during hospitalization. Those with diagnoses of asthma, mental disease, malignant tumor, pneumonia or pulmonary infection or systemic fungal infection at presentation, transferred to an intensive care unit (ICU) or received mechanical ventilation (MV) within 48 hours after admission were excluded. For patients who had multiple AECOPD admission records during the study period, only the first record was included (details in Figure 1). Patients with COVID-19 were not included in the present study.

Data Collection

Study Outcomes

Treatment failure, defined as a composite outcome of several events: receiving MV, transferring to the ICU, length of stay (LOS) more than 14 days, death during hospitalization or within 30 days after discharge, and AECOPD readmission within 30 days of discharge, was used to assess the patients' outcomes after corticosteroid treatment.[29,30] LOS and in-hospital events were collected from the EMR-based Big Data Platform for Respiratory Diseases. AECOPD readmissions

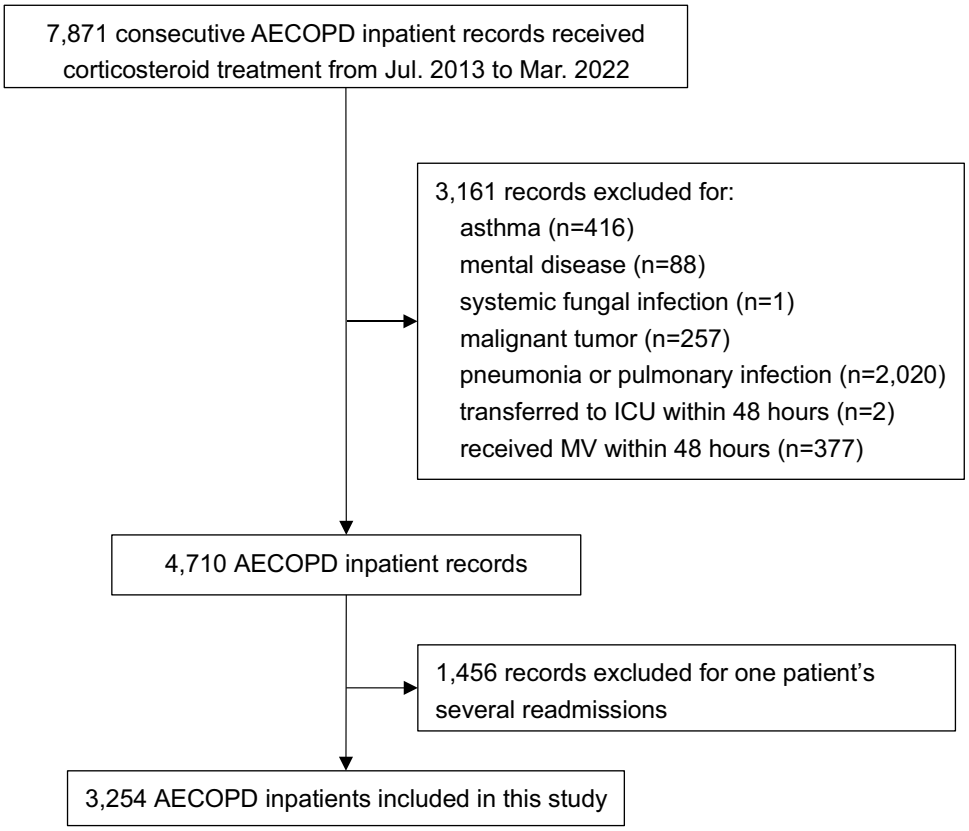

Figure 1 The flow chart of study population.
Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICU, intensive care unit; MV, mechanical ventilation.

and deaths were tracked within 30 days of discharge for patients who were discharged alive, by electronic linkage to a citywide hospitalization database maintained by the Beijing Municipal Health Commission Information Center.[31]

Candidate Predictors

Demographic characteristics, smoking status, hospitalization for AECOPD in the previous year, comorbidities and results of blood laboratory tests within 24 hours of hospitalization were used to develop the scoring model. Pharmacotherapies during hospitalization, including corticosteroids, bronchodilators and antibiotics were used as covariates. The hospitalization for AECOPD in the previous year was identified through electronic linkage to a citywide hospitalization database maintained by the Beijing Municipal Health Commission Information Center. All other variables were obtained from the EMR-based Big Data Platform for Respiratory Diseases. Demographic characteristics included the continuous age and sex of each patient. Smoking status was defined as current, former and never smoker, and the current and former smokers were classified as those with a smoking history. Comorbidities were identified by corresponding ICD-10 codes in discharge diagnoses. The results of blood laboratory tests included white blood cells (WBC), eosinophils, neutrophils, lymphocytes, platelets, NLR, PLR, red cell distribution width (RDW), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglyceride (TG), C-reactive protein (CRP), albumin, prealbumin (PALB), and PNI.

Statistical Analysis

Descriptive Statistics

Continuous variables were expressed as the means ± standard deviations (SDs) for normal distribution or as medians with interquartile ranges (IQRs) for nonnormal distribution, and the differences were compared using the Student's *t*-test or

the Mann–Whitney *U*-test as appropriate. Categorical variables were expressed as absolute numbers and percentages, and differences were assessed using the chi-square test or the Fisher's exact test.

Prediction Model Development

Univariate analysis was performed using logistic regression to examine the associations between potential predictors and treatment failure. The corresponding receiver operating characteristic (ROC) curves were generated, and the areas under the curves (AUCs) were calculated. Then, the continuous biomarker values were transformed into categorical variables with the cut-off values determined at the highest Youden's Indexes (except for eosinophils, using 2% and 200 cells/μL).

Least absolute shrinkage and selection operator (LASSO) regression was used to select factors for the prediction model to avoid the multicollinearity and overfitting problems caused by too many predictors. The 10-fold cross-validation was performed to select the most appropriate lambda value. The model with good performance and minimal independent variables was selected using "lambda.1se".[32] For highly correlative laboratory indicators selected by LASSO, only the indicator with a higher AUC was chosen.

Multivariable logistic regression analysis with a backward stepwise procedure was used to develop the final prediction model stratified by smoking history, eliminating variables with 2-sided $P > 0.05$. The corresponding nomograms were then developed. The discriminatory power of the model was assessed by calculating the AUC. The calibration of the model was determined by the Hosmer–Lemeshow test, and the calibration curve was plotted. Decision curve analysis (DCA) was used to analyze the clinical value with clinical consequences of a decision considered. The added predictive value of each selected biomarker and the AUC of our developed model in the subgroup receiving systemic corticosteroids were also evaluated as sensitivity analyses.

Internal Validation

Internal validation was performed using a regular bootstrap procedure with 500 bootstrapped samples.[33] The bootstrap performance of the final model was evaluated in each bootstrapped sample by calculating the *C*-statistic (AUC), and the test performance of the same model was evaluated in the original sample. Optimism was calculated by subtracting test performance from bootstrap performance. Internally validated performance was calculated by subtracting mean optimism from the apparent performance of the final model in the original sample.[34]

No imputation was performed in the present study. Statistical analyses were performed using SAS statistical software (version 9.4) and the statistical software R (version 4.2.2) with the packages "rms" and "glmnet".

Results

Characteristics of Study Subjects

A total of 3254 AECOPD inpatients were included in this study. Of these, 24.7% (804 of 3254) had treatment failure, while 75.3% (2450 of 3254) had no evidence of treatment failure (details in Table S1). The baseline characteristics of those two groups are presented in Table 1. Patients in the treatment failure group were older and had more hospitalizations for AECOPD in the previous year than those in the treatment success group ($P < 0.05$). A higher prevalence of hypertension, ischemic heart disease, chronic hepatic disease and chronic kidney disease was found in the treatment failure group ($P < 0.05$). As the results of laboratory examinations, there were significant differences between the two groups with respect to WBC, eosinophils, lymphocytes, neutrophils, platelets, NLR, PLR, FBG, TC, LDL-C, AST, CRP, direct bilirubin, albumin, albumin/globulin ratio, PALB and PNI ($P < 0.05$). Patients in the treatment failure group received more SCS and antibiotics during hospitalization ($P < 0.05$).

Prediction Model Development

The univariate analysis showed that the AUCs of each potential biomarker to predict treatment failure ranged from 0.520 to 0.603 (details in Table S2). The biomarkers with the top three AUCs were NLR (AUC: 0.603), lymphocyte count (AUC: 0.600) and neutrophil percentage (AUC: 0.598). The AUCs for eosinophil count and eosinophil percent were 0.573 and 0.575, respectively.

Table 1 Baseline Characteristics Between Those Successfully and Failed to Corticosteroid Treatments

	Treatment Success N=2450	Treatment Failure N=804	*P*-value
Age, year	70.00 [62.00–77.00]	73.00 [64.00–79.00]	<0.001
Sex			0.519
Male	1831 (74.7%)	591 (73.5%)	
Female	619 (25.3%)	213 (26.5%)	
Smoking status			<0.001
Never smoker	628 (26.9%)	235 (31.0%)	
Current smoker	598 (25.6%)	134 (17.7%)	
Former smoker	1110 (47.5%)	390 (51.4%)	
Pack-years*	42.57 ± 32.42	42.00 ± 31.90	0.742
Hospitalization for AECOPD in the previous year			<0.001
0	2043 (83.5%)	605 (75.2%)	
1	256 (10.5%)	121 (15.0%)	
≥2	147 (6.0%)	78 (9.7%)	
Comorbidities			
Hypertension	1046 (42.7%)	377 (46.9%)	0.041
Ischemic heart disease	546 (22.3%)	229 (28.5%)	<0.001
Diabetes mellitus	363 (14.8%)	141 (17.5%)	0.073
Cerebrovascular disease	215 (8.8%)	83 (10.3%)	0.187
Bronchiectasis	246 (10.0%)	84 (10.5%)	0.740
Interstitial lung disease	32 (1.3%)	12 (1.5%)	0.725
Chronic hepatic insufficiency	80 (3.3%)	59 (7.3%)	<0.001
Chronic kidney disease	89 (3.6%)	61 (7.6%)	<0.001
Charlson Comorbidity Index			<0.001
1	1162 (47.4%)	329 (40.9%)	
2	765 (31.2%)	255 (31.7%)	
≥3	523 (21.4%)	220 (27.4%)	
Laboratory examination after hospitalization			
WBC, 10^9/L	6.54 [5.34–8.25]	6.80 [5.42–8.87]	0.006
Eosinophils, 10^9/L	0.13 [0.05–0.23]	0.09 [0.02–0.19]	<0.001
Eosinophils, %	2.00 [0.70–3.60]	1.40 [0.30–2.90]	<0.001
Lymphocytes, 10^9/L	1.48 [1.08–1.96]	1.29 [0.89–1.73]	<0.001
Lymphocytes, %	23.50 [16.10–30.00]	19.65 [12.20–27.10]	<0.001
Neutrophils, 10^9/L	4.26 [3.22–5.77]	4.72 [3.44–6.78]	<0.001
Neutrophils, %	65.80 [58.20–74.80]	70.70 [61.20–79.97]	<0.001
Platelets, 10^9/L	206.00 [165.00–253.00]	199.00 [157.50–248.50]	0.018
RDW	11.70 [10.50–13.10]	11.50 [10.40–13.00]	0.102
NLR, %	2.82 [1.95–4.64]	3.59 [2.21–6.60]	<0.001
PLR, %	137.33 [100.90–189.25]	154.26 [100.38–230.67]	<0.001
FBG, mmol/L	4.76 [4.22–5.71]	5.07 [4.37–6.26]	<0.001
TC, mmol/L	4.12 [3.54–4.82]	3.98 [3.41–4.75]	0.025
LDL-C, mmol/L	2.34 [1.88–2.90]	2.26 [1.75–2.80]	0.008
HDL-C, mmol/L	1.20 [1.00–1.50]	1.20 [0.99–1.56]	0.590
TG, mmol/L	0.90 [0.68–1.26]	0.88 [0.67–1.21]	0.158
ALT, U/L	17.00 [12.00–23.00]	16.00 [12.00–23.00]	0.570
AST, U/L	20.00 [17.00–25.00]	21.00 [16.25–27.00]	0.005
CRP, mg/L	0.65 [0.31–1.80]	1.05 [0.42–4.54]	<0.001
TBIL, umol/L	10.20 [7.50–13.60]	10.20 [7.40–14.59]	0.462
DBIL, umol/L	3.40 [2.50–4.70]	3.60 [2.50–5.30]	0.013
IBIL, umol/L	6.60 [4.70–9.30]	6.50 [4.60–9.60]	0.556

(*Continued*)

Table 1 (Continued).

	Treatment Success N=2450	Treatment Failure N=804	*P*-value
Alb, g/L	36.30 [32.90–39.20]	35.40 [31.20–38.60]	<0.001
Glb, g/L	28.00 [24.55–31.60]	28.30 [24.58–32.00]	0.595
A/G	1.30 [1.10–1.50]	1.20 [1.00–1.50]	0.002
PALB, g/L	0.19 [0.15–0.24]	0.17 [0.13–0.23]	<0.001
PNI, %	44.05 [39.80–47.88]	41.92 [37.20–46.35]	<0.001
SCr, umol/L	68.90 [58.70–81.40]	68.50 [57.73–85.10]	0.532
In-hospital pharmacotherapies			
Corticosteroid type			<0.001
Only ICS	1741 (71.1%)	386 (48.0%)	
SCS	709 (28.9%)	418 (52.0%)	
Only SCS	94 (3.8%)	57 (7.1%)	0.857
SCS + ICS	615 (25.1%)	361 (44.9%)	
Duration of SCS, day	5.75 ± 3.35	8.28 ± 6.08	<0.001
Total amount of SCS, mg	205.70 ± 118.80	303.60 ± 314.7	<0.001
Bronchodilators	2398 (97.9%)	778 (96.8%)	0.084
Antibiotics	2016 (82.3%)	715 (88.9%)	<0.001

Notes: *among current smokers and former smokers.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; WBC, white blood cells; RDW, red cell distribution width; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; FBG, fasting blood glucose; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; TBIL, total bilirubin; DBIL, direct bilirubin; IBIL, indirect bilirubin; Alb, albumin; Glb, globulin; A/G, albumin/globulin ratio; PALB, pre-albumin; PNI, prognostic nutritional index; SCr, serum creatinine; ICS, inhaled corticosteroid; SCS, systematic corticosteroid.

Among the 30 relevant variables, 19 potential predictors were screened according to LASSO regression (Figure 2): smoking status, hospitalization for AECOPD in the previous year, hypertension, diabetes mellitus, ischemic heart diseases, cerebrovascular disease, chronic kidney disease, hepatic disease, low eosinophils, high neutrophil percentage, high NLR, high platelets, high RDW, high CRP, low LDL-C, high albumin, high PALB, low PNI and in-hospital SCS treatment. The univariate analyses of these 19 potential predictors for treatment failure are shown in Table S3.

Three screened potential predictors (neutrophil percent, albumin, and in-hospital SCS treatment) were excluded before backward logistic regression. The neutrophil percent and albumin were excluded because of their collinearity with NLR and PALB. In-hospital SCS treatment was excluded because it was not applicable for treatment assignment at admission. Finally, 8 of 16 predictors were identified among those with a smoking history, including hospitalization for AECOPD in the previous year, ischemic heart diseases, chronic hepatic disease, low eosinophils, low platelets, high CRP, low LDL-C, and low PNI. Among those without a smoking history, 4 of 16 predictors were determined, including ischemic heart diseases, chronic hepatic disease, high CRP, and low PNI. Details are shown in Table 2.

For those with a smoking history (Table 3), adding low eosinophils to the basic prediction model, which included hospitalization for AECOPD in the previous year and two comorbidities, could significantly improve the AUC (Model 2 vs Model 1, 0.608 vs 0.580, *P* for improvement =0.003). The AUC of the basic prediction model could also be improved by adding low platelets, high CRP, and low PNI (Model 3–5 vs Model 1, all *P* for improvement < 0.05), but none outperformed low eosinophils (Model 3–5 vs Model 2, all *P* for improvement > 0.05). In addition, the AUC of the model with all five biomarkers was not only higher than that of the basic model (Model 7 vs Model 1, 0.644 vs 0.580, *P* for improvement <0.001) but also greater than that of the model with only low eosinophils (Model 7 vs Model 2, 0.644 vs 0.608, *P* for improvement <0.001). Therefore, a nomogram of treatment failure for patients with AECOPD with a smoking history was derived based on these eight predictors, as shown in Figure 3.

In contrast, for those without a smoking history (Table 4), adding low eosinophils did not improve the AUC of the basic prediction model with two comorbidities (Model 2 vs Model 1, 0.576 vs 0.560, *P* for improvement = 0.169), while CRP and PNI significantly improved the AUC of the basic prediction model (Model 3–4 vs Model 1, all *P* for

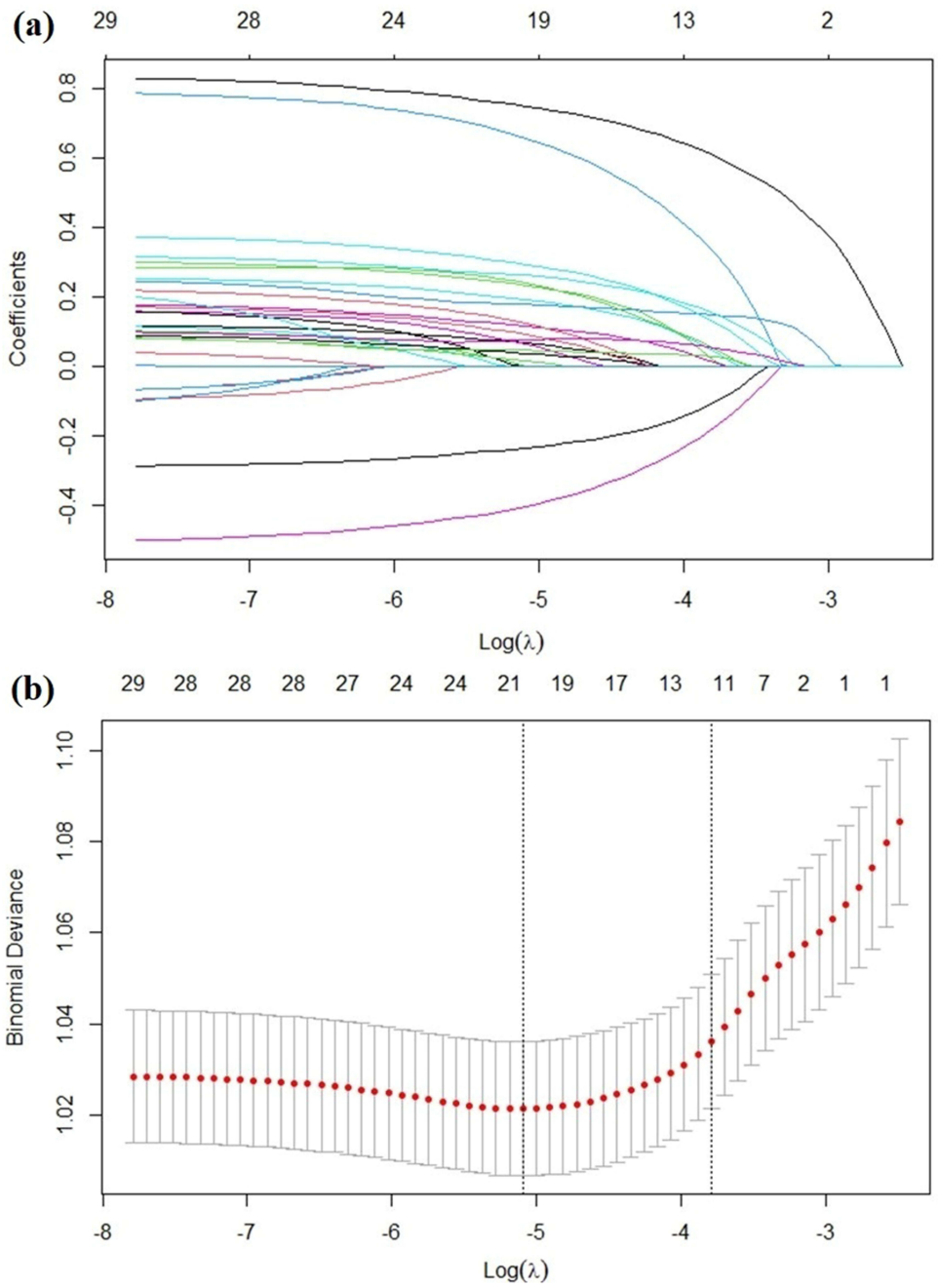

Figure 2 Predictors' selection using the LASSO regression method. (**a**) LASSO coefficient profiles of the 30 potential variables. A coefficient profile plot was produced against the log (λ) sequence. (**b**) A 10-fold cross-validation was used in the LASSO regression. Binomial deviance curve was plotted versus log (λ) and dotted vertical lines were drawn based on 1 standard error criteria. The included variables were: age, sex, smoking status, hospitalization for AECOPD in the previous year, hypertension, diabetes mellitus, bronchiectasis, interstitial lung disease, ischemic heart diseases, cerebrovascular disease, chronic kidney disease, chronic hepatic insufficiency, high WBC, low eosinophils, high neutrophil percent, high neutrophil counts, low lymphocyte percent, low lymphocyte counts, low platelets, low RDW, high NLR, high PLR, low TC, low LDL-C, high CRP, low albumin, low pre-albumin, low PNI, in-hospital SCS treatment, in-hospital antibiotics treatment.

Abbreviations: LASSO, least absolute shrinkage and selection operator; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; WBC, white blood cells; RDW, red cell distribution width; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; CRP, C-reactive protein; PNI, prognostic nutritional index; SCS, systematic corticosteroid.

improvement < 0.05). Importantly, those two biomarkers added to the basic model showed a significantly higher AUC than the basic model (Model 5 vs Model 1, 0.647 vs 0.560, *P* for improvement <0.001). Figure 4 presents the nomogram of treatment failure prediction in patients with AECOPD without a smoking history, using these four key predictors.

Table 2 The Predicting Factors for Corticosteroid Treatment Failure Among Patients Hospitalized for AECOPD

Variables	With a Smoking History (n=2232)				Without a Smoking History (n=863)			
	Multivariate Analysis		After backward Selection		Multivariate Analysis		After Backward Selection	
	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value	Adjusted OR (95% CI)	*P*-value
Hospitalization for AECOPD in the previous year	1.66 (1.30, 2.11)	<0.001	1.71 (1.35, 2.18)	<0.001	1.24 (0.83,1.86)	0.302	-	
Comorbidities								
Hypertension	1.07 (0.86,1.33)	0.534	-		1.14 (0.81,1.60)	0.446	-	
Diabetes mellitus	1.17 (0.88,1.56)	0.292	-		1.29 (0.86,1.93)	0.224	-	
Ischemic heart diseases	1.23 (0.97,1.57)	0.092	1.28 (1.01,1.61)	0.042	1.34 (0.93,1.92)	0.113	1.49 (1.06,2.09)	0.021
Cerebrovascular disease	1.00 (0.70,1.41)	0.991	-		0.85 (0.49,1.49)	0.570	-	
Chronic kidney disease	1.42 (0.88, 2.28)	0.149	-		1.49 (0.82, 2.71)	0.188	-	
Chronic hepatic disease	1.76 (1.14, 2.71)	0.011	1.76 (1.14,2.70)	<0.001	3.07 (1.47, 6.43)	0.003	3.30 (1.59,6.83)	0.001
Laboratory examinations								
Eosinophils < 200 cells/μL and < 2%	1.46 (1.16,1.83)	0.001	1.59 (1.28,1.96)	<0.001	0.99 (0.69,1.42)	0.954	-	
NLR ≥ 3.39	1.32 (1.03,1.69)	0.030	-		1.35 (0.93,1.96)	0.115	-	
Platelet < 193 10^9/L	1.46 (1.17,1.82)	<0.001	1.39 (1.13,1.72)	0.002	0.94 (0.66,1.33)	0.706	-	
RDW ≥ 11.1	1.23 (0.98,1.54)	0.069	-		1.17 (0.82,1.66)	0.392	-	
CRP ≥ 1.88 mg/L	1.29 (0.99,1.69)	0.061	1.46 (1.14,1.88)	0.003	2.02 (1.31, 3.10)	0.001	2.09 (1.42,3.09)	<0.001
LDL-C < 1.6 umol/L	1.27 (0.95,1.72)	0.114	1.34 (1.00,1.79)	0.050	1.30 (0.78, 2.15)	0.314	-	
PALB ≥ 0.19 g/L	1.19 (0.93,1.52)	0.175	-		0.97 (0.66,1.42)	0.863	-	
PNI < 42	1.13 (0.87,1.45)	0.356	1.32 (1.05,1.66)	0.017	1.64 (1.12, 2.40)	0.011	1.93 (1.38,2.71)	<0.001

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; NLR, neutrophil to lymphocyte ratio; RDW, red cell distribution width; CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PALB, pre-albumin; PNI, prognostic nutritional index; OR, odds ratio; CI, confidence interval.

Table 3 The Predicting Factors and Corresponding AUC for Corticosteroid Treatment Failure Among Patients with AECOPD with a Smoking History

	Predicting Factors*	AUC	*P* for Improvement[#]	
			From Model 1	From Model 2
Model 1	Hospitalization for AECOPD in the previous year + comorbidities	0.580 (0.554,0.606)	–	–
Model 2	Model 1 + EOS	0.608 (0.581,0.636)	0.003	–
Model 3	Model 1 + PLA	0.600 (0.571,0.626)	0.040	0.402
Model 4	Model 1 + CRP	0.606 (0.579,0.634)	0.004	0.852
Model 5	Model 2 + PNI	0.607 (0.579,0.635)	0.004	0.899
Model 6	Model 1 + LDL-C	0.592 (0.565,0.620)	0.074	0.143
Model 7	Model 1 + EOS + PLA + CRP + LDL-C + PNI	0.644 (0.617,0.672)	<0.001	<0.001

Notes: *Predicting factors in the models: hospitalization for AECOPD in the previous year (yes, no); comorbidities (ischemic heart diseases, chronic hepatic insufficiency). EOS, eosinophils <200 cells/μL and <2%; PLA, platelets <193 10^9/L; CRP, C-reactive protein ≥1.88 mg/L; PNI, prognostic nutritional index < 42; LDL-C, low-density lipoprotein cholesterol <1.6 umol/L. [#]DeLong's test for two correlated ROC curves.
Abbreviations: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; AUC, area under the receiver operating curve.

The results from sensitivity analyses demonstrated that the added predictive value of each biomarker and the AUCs of the models in the subgroup receiving systemic corticosteroids were comparable with the main findings (details in Table S4 and Table S5).

Prediction Model Validation

For the final models, the AUCs of the nomograms were 0.644 for those with a smoking history and 0.647 for those without a smoking history. By bootstrapping internal validation, the corresponding internally validated AUCs were 0.631 and 0.635, respectively (Figures 3 and 4). The nomogram calibration curves for predicting treatment failure also

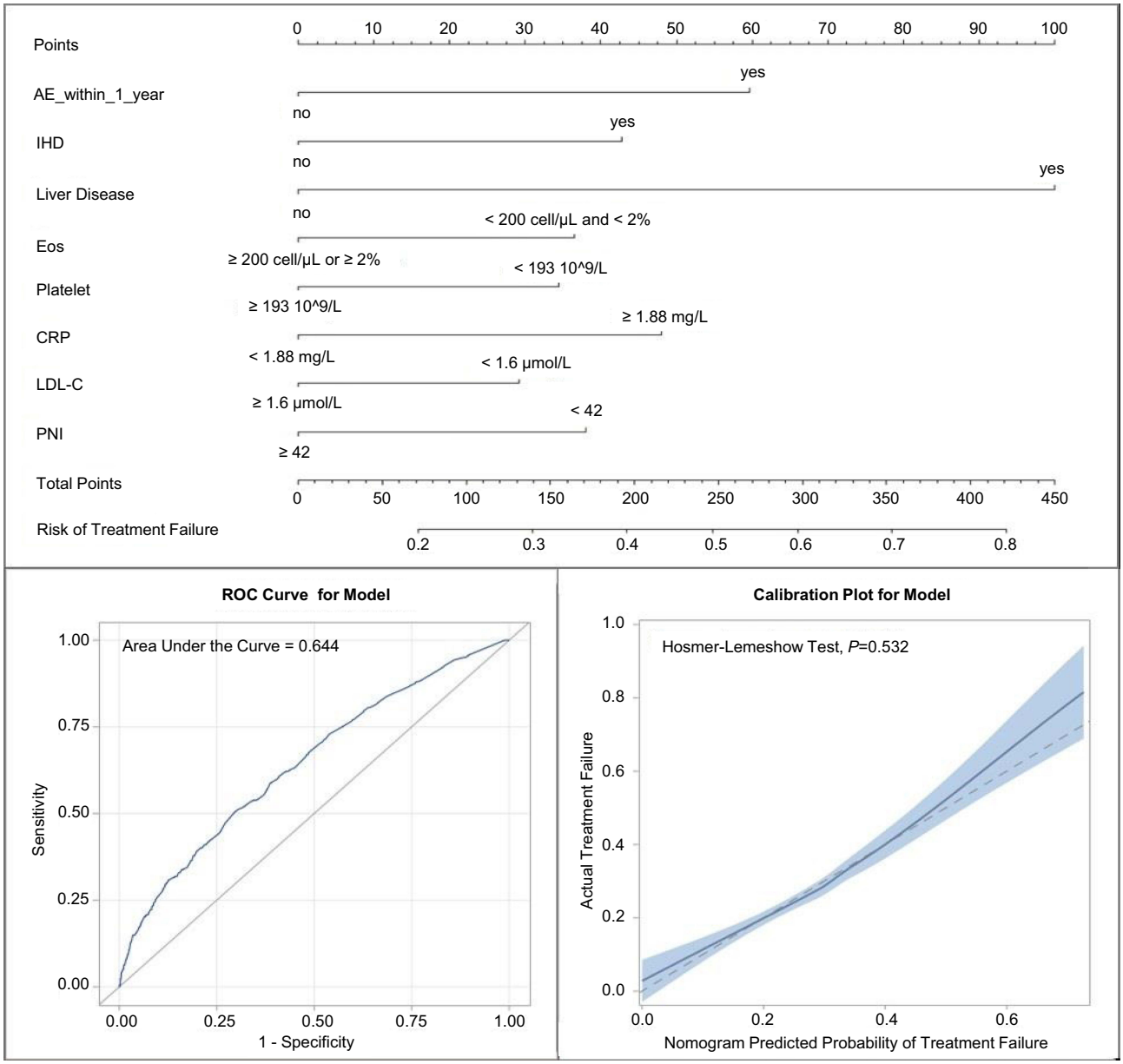

Figure 3 The nomogram for predicting corticosteroid treatment failure in patients with AECOPD with a smoking history. The naive C-Statistic: 0.644; optimism-corrected C-Statistic: 0.631.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AE, hospitalization for acute exacerbations; IHD, ischemic heart diseases; EOS, eosinophils; CRP, C-reactive protein; LDL-C, low-density lipoprotein cholesterol; PNI, prognostic nutritional index.

performed well, with *P* values for the Hosmer–Lemeshow test of 0.532 and 0.918, respectively (Figures 3 and 4). DCA showed that the nomograms had higher net benefit in predicting treatment failure when the risk threshold probability ranged from 13% to 57% for those with a smoking history and 15% to 71% for those without a smoking history (Figure 5).

Discussion

This study verified that low blood eosinophils could be important predictors of treatment failure of corticosteroid treatment in patients with AECOPD with a smoking history. Moreover, when combined with low platelets, high CRP, low LDL-C, and low PNI, it could have better prediction. These biomarkers can be easily obtained from the patient's admission routine examinations without additional examination and cost.

Table 4 The Predicting Factors and Corresponding AUC for Corticosteroid Treatment Failure Among Patients with AECOPD Without Smoking History

	Predicting Factors*	AUC	*P* for Improvement[#]	
			From Model 1	From Model 2
Model 1	Comorbidities	0.560 (0.524,0.600)	–	–
Model 2	Model 1 + EOS	0.576 (0.534,0.618)	0.169	–
Model 3	Model 1 + CRP	0.620 (0.579,0.661)	0.005	0.063
Model 4	Model 2 + PNI	0.622 (0.582,0.663)	<0.001	0.013
Model 5	Model 1 + CRP + PNI	0.647 (0.606,0.688)	<0.001	0.002

Notes: *Predicting factors in the models: comorbidities (ischemic heart diseases, chronic hepatic insufficiency); EOS, eosinophils <200 cells/μL and <2%; CRP, C-reactive protein ≥1.88 mg/L; PNI, prognostic nutritional index < 42. [#]DeLong's test for two correlated ROC curves.

Abbreviations: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; AUC, area under the receiver operating curve.

Consistent with previous studies conducted in patients with AECOPD with a smoking history,[11,12,35] our results showed that low blood eosinophils could predict a higher treatment failure risk. The underlying mechanism is still unclear. Studies have indicated that patients with AECOPD with low blood eosinophils tend to be older, have more comorbidities and are more susceptible to severe bacterial infections, all of which contribute to poor prognoses.[36–38] Others regard eosinophilic AECOPD as an inflammatory phenotype, which demonstrates a favorable response to corticosteroid treatment.[10,13,14,39–41] Our results align with this perspective. Factors bolstering our conclusion include the exclusion of those with pneumonia, pulmonary infection or systemic fungal infection at presentation and by controlling for age, comorbidities, and severity markers during statistical analysis.

It is generally believed that those with a smoking history have higher eosinophil levels.[42,43] Meanwhile, smoking can cause corticosteroid resistance, thereby weakening their effects.[44,45] However, it remains unclear how smoking status influences blood eosinophil levels and corticosteroid treatment failure. A post-hoc study of three randomized controlled trials (RCTs) showed that the effect of ICS treatment among stable COPD patients was strongly correlated with blood eosinophil levels in current smokers, but no such association was found in former smokers.[7] A large sample retrospective real-world study suggested that former smokers with high eosinophil levels were the target population of ICS treatment.[46] The present study indicates that AECOPD inpatients who have never smoked and present with high blood eosinophil levels may not benefit from corticosteroid treatment, which has never been reported before. Considering that this study was a single-center retrospective study, prospective research with large sample is needed to validate this point.

Hospitalization for AECOPD in the previous year indicates a higher risk of subsequent exacerbations and has been used to guide the initiation of ICS treatment in stable COPD patients.[1] However, whether it can guide corticosteroid treatment in patients with AECOPD remains unclear. Our findings demonstrated that hospitalization for AECOPD in the previous year could predict higher treatment failure risk in patients hospitalized for AECOPD. This association, in part, might be explained by the worse prognoses of frequent exacerbator phenotype.[39,47]

Over 90% of COPD patients have two or more comorbidities.[1,48] The influence of comorbidities on the prognoses of patients with AECOPD were inconsistent due to differences in the study population, comorbidities analyzed, and the relatively small sample sizes.[18,24,25,49] For example, Huang D et al found that in patients with AECOPD complicated with pneumonia (sample size: 873), diabetes and chronic kidney disease increased the risk of in-hospital mortality, while cardiovascular diseases did not.[49] Peng JC et al found that hypertension, diabetes, cardiovascular disease, chronic kidney disease, and malignancies did not significantly increase the 30-day risk of death in patients with AECOPD in the ICU (sample size: 494).[24] In the present study, eight common and important comorbidities, including hypertension, ischemic heart disease, diabetes, cerebrovascular disease, bronchiectasis, interstitial lung disease, chronic hepatic insufficiency, and chronic kidney disease were analyzed (Figure 2). It appeared that ischemic heart disease and chronic liver disease were the only significant predictive factors of corticosteroid treatment failure. Further research is necessary to understand these associations and underlying mechanisms.

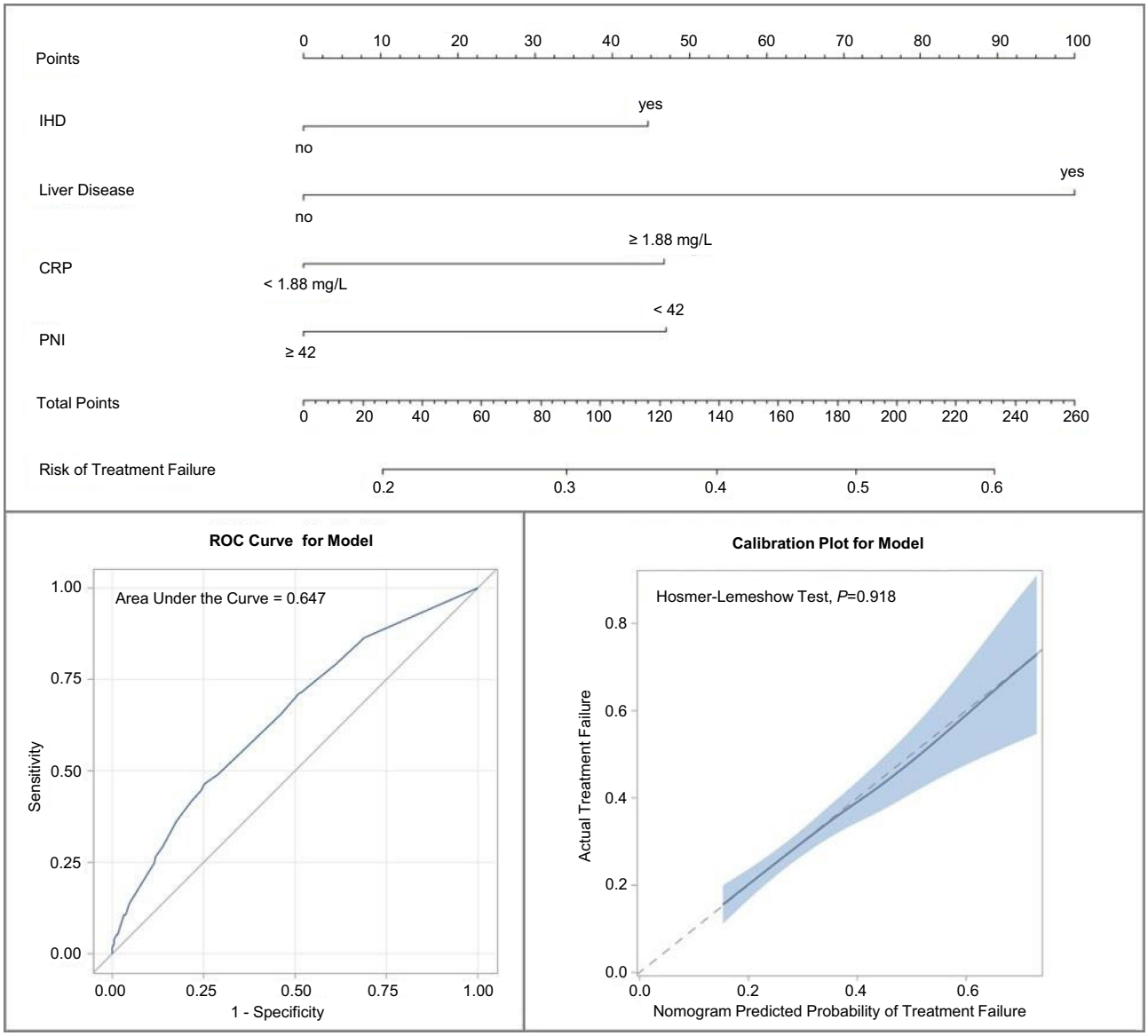

Figure 4 The nomogram for predicting corticosteroid treatment failure in patients with AECOPD without smoking history. The naïve C-Statistic: 0.647; optimism-corrected C-Statistic 0.635.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; IHD, ischemic heart diseases; CRP, C-reactive protein; PNI, prognostic nutritional index.

In our study, biomarkers such as CRP, PNI, LDL-C and platelets could provide additional values to predict corticosteroid treatment failure in AECOPD inpatients. CRP has been used as a proxy measure to identify bacterial-associated exacerbations for decades and to direct antibiotic treatment in patients with AECOPD.[10,50] In a recent RCT, a higher dose of SCS was recommended for patients with CRP greater than 7 mg/L, and the personalized SCS treatment was more effective than fixed-dose treatment (40 mg per day for 5 days).[40] In the present study, CRP greater than 1.88 mg/L was an independent predictor of corticosteroid treatment failure. The difference could be explained by the difference in corticosteroid treatments. Only 34.6% of our study patients received SCS, whereas all patients received SCS in the RCT, and the total dosage of SCS was lower in our study than that of the RCT (239 mg vs 313 mg). There is a need for more prospective studies to determine whether patients with AECOPD with high CRP should receive ICS and/or SCS treatment, as well as what dosage and the threshold to use.

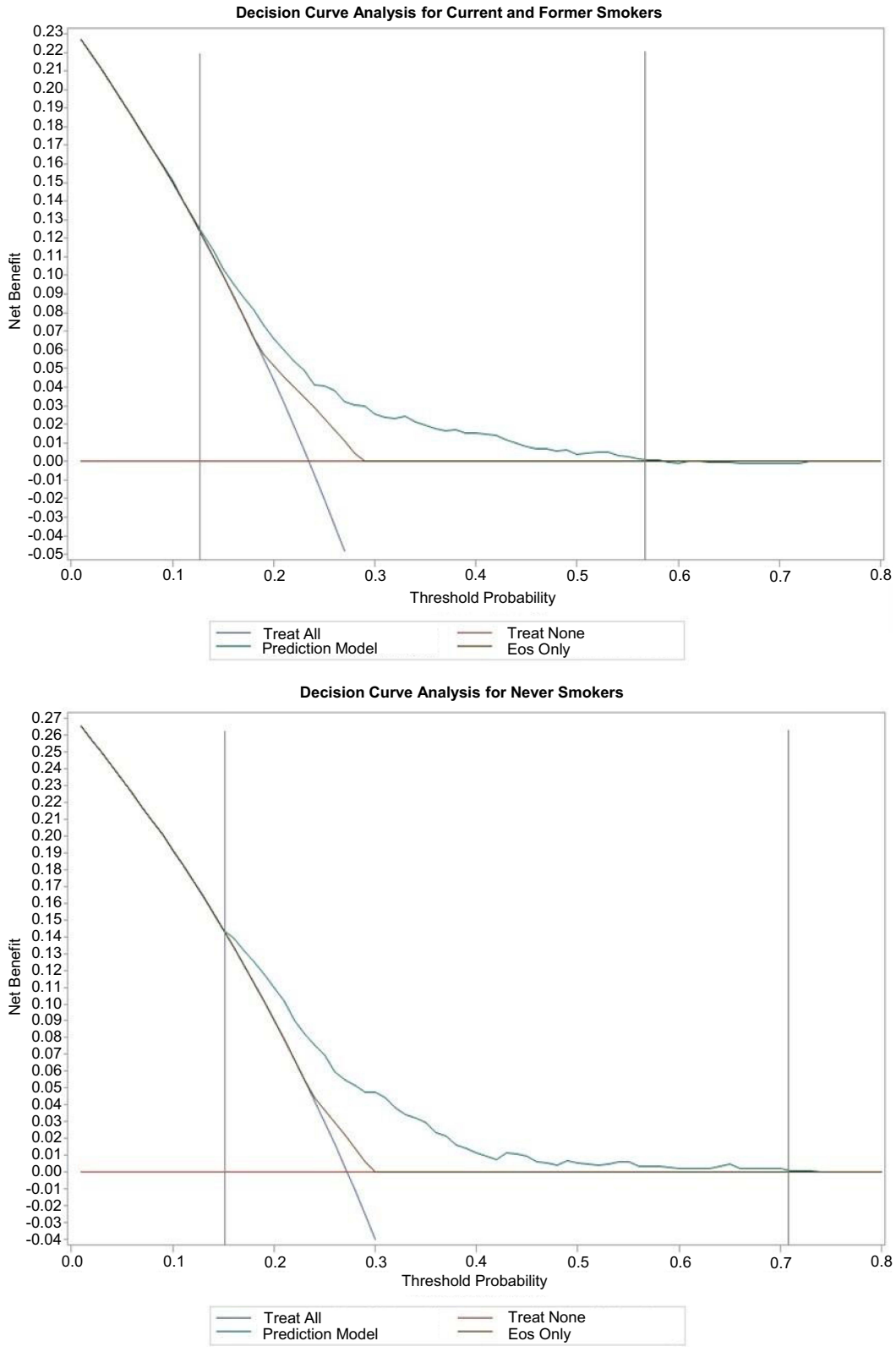

Figure 5 The decision curve analysis of nomogram to predict corticosteroid treatment failure.
Abbreviation: EOS, eosinophils.

Patients with low PNI have poor nutritional status and/or poor immune function.[22,24] Corticosteroid treatment has immunosuppressive effects and that albumin-deficient malnutrition also reduces cell-mediated immunity, such as lymphocyte proliferation, which adversely affects the immune defense system.[51,52] As a consequence, patients with AECOPD with low PNI could experience more unsatisfactory corticosteroid treatment outcomes.

Lower LDL-C levels, according to our findings, might predict treatment failure in patients with AECOPD with a smoking history. A similar result was observed in patients admitted with community-acquired pneumonia.[53] This association might be attributed to infection, as elevated circulating cytokines decrease cholesterol levels during severe infection.[54] To properly comprehend the pathophysiological pathways, in-depth clinical and mechanistic studies are warranted. Moreover, our study showed that low platelets could predict corticosteroid treatment failure in patients with AECOPD with a smoking history. Two previous studies also found that low platelets were associated with short-term mortality in patients with AECOPD, though not statistically significant due to limited sample numbers (553 patients and 303 patients, respectively).[55,56] Platelets, in addition to their well-established involvement in hemostasis and coagulation regulation, exert significant effects on inflammation and immunity control mechanisms via the release of specific chemicals and microparticles.[57–60] It is also worth noting that no association was detected between platelets and treatment failure among those without a smoking history. This indicates that platelets may play distinct roles in corticosteroid treatment in patients with AECOPD with different smoking status.

In this study, the discrimination performance of the developed nomograms, despite showing significant improvement over those relying solely on eosinophil levels, remained unsatisfactory. This suggests that using only variables from routine clinical practice at patient admission might be insufficient to predict corticosteroid treatment failure in patients hospitalized for AECOPD. Novel biomarkers or additional information to refine the guidance of personalized corticosteroid treatment are needed. The eosinophil-predominant phenotype COPD, linked to type-2 inflammation, has been shown to respond favorably to corticosteroid treatment.[61] Recent studies have discerned between inflammatory and resident eosinophil subtypes, indicating that the inflammatory eosinophils predominantly contribute to COPD associated with type-2 inflammation.[62,63] Therefore, inflammatory eosinophils might offer a more accurate guide than total eosinophils for corticosteroid treatment decisions. Furthermore, factors such as corticosteroid treatment prior to admission, presenting symptoms and signs, and blood gas examination results might also have potential implications for personalized corticosteroid treatments.[40] However, these variables were not included in the present study due to either unavailability in EMR or a significant proportion of missing data. Additionally, blood eosinophil levels show variability throughout the course of COPD.[64–66] Evaluation of the stability of these measurements, especially between stable and exacerbated stages of COPD or over multiple exacerbations, might aid in predicting patient's outcomes after corticosteroid treatment. Future research is required to validate these hypotheses.

There were several limitations to this study. First, the predictive performance of our nomograms was modest. As a retrospective, real-world study based on EMR, some information, such as symptoms and signs at presentation, was unavailable. However, our results successfully selected some novel biomarkers of inflammation, nutrition, and immunity that could be easily obtained clinically and could significantly improve the predictive performance of corticosteroid treatment failure in patients with AECOPD. Second, this study utilized data from a single medical center, and the extrapolation of our conclusions might be limited. Nevertheless, the study center is one of the top healthcare institutions in China specializing in respiratory diseases, representing the highest standard of medical treatment for patients with AECOPD. This enables us to conduct this real-world study with a large sample and high-quality EMR data. Third, only internal validation was performed. Future studies should include more diverse population data from various centers and perform external validation of the findings of this study.

Conclusion

In this study, comprehensive nomograms (incorporating hospitalization for AECOPD in the previous year, ischemic heart diseases, chronic hepatic disease, eosinophils, platelets, CRP, LDL-C, and PNI) were devised by integrating routinely assessed biomarkers related to inflammation, nutrition, and immunity. These nomograms offer clinical practicality while obviating the need for extra testing expenditures. Moreover, these easy-to-use nomograms demonstrated enhanced predictive capability for treatment failure in corticosteroid-treated patients with AECOPD compared to models relying

solely on blood eosinophil levels. This signifies a progression toward more tailored treatment strategies. However, the predictive performance of current nomograms needs further optimization. Future research should focus on uncovering novel biomarkers and broadening patient data inclusion to refine the predictability of corticosteroid treatment outcomes in patients with AECOPD. Such endeavors are pivotal in personalizing corticosteroid treatments for patients with AECOPD and achieving better clinical outcomes.

Data Sharing Statement

The datasets used in the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Board of Beijing Chao-Yang Hospital (2020-ke-511) on January 4th, 2021. Informed written consent was waived by the Research Ethics Board of Beijing Chaoyang Hospital due to the retrospective nature of the study. Patient data was anonymized before analysis. All methods were carried out in accordance with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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