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ORIGINAL RESEARCH

Nutritional and Inflammatory Predictors of All-Cause Mortality in COPD Patients with Hypercapnic Respiratory Failure: A Two-Center Prospective Cohort Study

Zishu Zhang[1,*], Yuexian Liu[2,*], Zongbo Shen[3,*], Koudong Zhang[4,*], Honglan Gao[5], Zhimin Chen[5], Zhongxiang Liu[4]

[1]Department of Respiratory and Critical Care Medicine, The People's Hospital of Xiangshui, Yancheng, 224600, People's Republic of China; [2]Department of Neurology, 920th Hospital of the Joint Logistic Support Force, Kunming, 650032, People's Republic of China; [3]Department of Respiratory and Critical Care Medicine, The People's Hospital of Lincang, Lincang, 677000, People's Republic of China; [4]Department of Respiratory and Critical Care Medicine, The Yancheng Clinical College of Xuzhou Medical University, The First People's Hospital of Yancheng, Yancheng, 224000, People's Republic of China; [5]Department of Clinical Nutrition, The Yancheng Clinical College of Xuzhou Medical University, The First People's Hospital of Yancheng, Yancheng, 224000, People's Republic of China

*These authors contributed equally to this work

Correspondence: Zhimin Chen, Department of Clinical Nutrition, The Yancheng Clinical College of Xuzhou Medical University, The First People's Hospital of Yancheng, Yancheng, 224000, People's Republic of China, Email chenzhimin@ycsyy.com; Zhongxiang Liu, Department of Respiratory and Critical Care Medicine, tHe Yancheng Clinical College of Xuzhou Medical University, The First People's Hospital of Yancheng, Yancheng, 224000, People's Republic of China, Email liuzhongxiang711@163.com

Background: Patients with chronic obstructive pulmonary disease (COPD) complicated by hypercapnic respiratory failure (HRF) often have a poor prognosis. Systemic inflammation and malnutrition are associated with adverse outcomes in COPD, yet the prognostic value of nutritional/inflammatory markers remains underexplored in COPD patients with HRF.

Methods: This prospective two-center cohort study enrolled 582 COPD complicated by HRF patients. Six indices, including Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), Systemic Immune-Inflammation Index (SII), Prognostic Nutritional Index (PNI), Neutrophil Percentage-to-Albumin Ratio (NPAR), and Hemoglobin-Albumin-Lymphocyte-Platelet index (HALP), were calculated from admission biomarkers. Associations with 24-month all-cause mortality were evaluated using restricted cubic splines, Kaplan-Meier analysis, multivariable Cox regression, machine learning (Random Survival Forests, Boruta), threshold effect and subgroup analysis. Predictive performance was assessed via the receiver operating characteristic curve (ROC) analysis.

Results: Over 24 months, 263 patients (45.2%) died. Non-survivors exhibited significantly higher NLR, PLR, SII, and NPAR, but lower PNI and HALP ($P < 0.05$). Kaplan-Meier analysis and Cox models confirmed that higher PNI (HR=0.72, 95% CI:0.54–0.96) and HALP (HR=0.55, 95% CI:0.41–0.74) were negatively correlated with all-cause mortality, while elevated PLR (HR=1.39, 95% CI:1.04–1.85), NLR (HR=1.39, 95% CI:1.02–1.88), SII (HR=1.51, 95% CI:1.11–2.05), and NPAR (HR=1.46, 95% CI:1.10–1.95) were positively correlated with all-cause mortality. For each one-standard-deviation increase in the indicators, all-cause mortality statistically significantly increased or decreased (P for trend < 0.05), with the exception of SII. Machine learning and ROC analyses consistently identified HALP, PNI, and NPAR as top predictors, with HALP demonstrating the highest importance. Subgroup analyses confirmed consistent prognostic utility for PNI, HALP, and NPAR.

Conclusion: PNI, HALP, and NPAR are promising, readily available predictors of all-cause mortality in COPD patients with HRF, potentially enhancing risk stratification and personalized management.

Keywords: inflammation, nutrition, COPD, all-cause mortality, hypercapnic respiratory failure

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) remains a highly prevalent chronic respiratory disorder worldwide. As the third leading cause of mortality globally, COPD is responsible for approximately 3 million deaths annually.[1] This disease is characterized by persistent respiratory symptoms and airflow limitation, resulting from abnormalities in the airways and alveoli.[2] Among COPD patients, the development of hypercapnic respiratory failure (HRF) represents a particularly severe and life-threatening complication.[3] HRF is defined by elevated arterial carbon dioxide levels accompanied by hypoxemia.[4] It frequently occurs during acute exacerbations and end-stage disease, leading to increased hospitalization rates, healthcare resource utilization, and mortality.[5–7] Despite advances in therapeutic strategies, the prognosis for COPD patients with HRF remains poor. This underscores the critical need for reliable prognostic markers to predict clinical outcomes and guide personalized treatment approaches.

Emerging research indicates that systemic inflammation and nutritional status significantly influence disease progression and adverse clinical outcomes in COPD.[8,9] In COPD patients, inflammation extends beyond the lungs, involving a persistent systemic inflammatory response. This response is characterized by elevated circulating inflammatory markers, including C-reactive protein and cytokines which correlate strongly with accelerated lung function decline and increased exacerbation frequency.[10,11] Concurrently, malnutrition and altered body composition, commonly observed in COPD, exacerbate respiratory muscle weakness and compromise immune responses.[12] These impairments heighten the risk of lung function decline and mortality.[13,14] Thus, assessing inflammatory and nutritional status may provide critical prognostic insights.

Composite indices derived from routine laboratory parameters, including nutritional and inflammatory markers, have emerged as promising tools for risk stratification in various chronic diseases, such as cancer and COPD.[15,16] Indices such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and the combined nutritional and inflammatory indices hemoglobin-albumin-lymphocyte-platelet index (HALP) and neutrophil percentage-to-albumin ratio (NPAR) have been employed to predict outcomes in COPD patients.[17–19] In a retrospective analysis of 793 patients hospitalized for acute exacerbation of COPD, Akbay et al found that a lower HALP level was significantly associated with an increased risk of in-hospital mortality (OR 0.758, 95% CI: 0.586–0.980, P = 0.034).[18] However, their predictive value specifically for COPD patients with HRF remains inadequately explored. Understanding the prognostic utility of these indices within this high-risk subgroup may facilitate the early identification of patients most likely to experience adverse outcomes.

In this prospective two-center cohort study, we sought to evaluate the associations between six nutritional and inflammatory indices (PLR, NLR, HALP, NPAR, systemic immune-inflammation index (SII), and prognostic nutritional index (PNI)) and all-cause mortality in patients with COPD complicated by HRF. During a 24-month follow-up period, we assessed the predictive performance of these indices for all-cause mortality in this patient population. Furthermore, we employed comprehensive statistical approaches, including restricted cubic splines, survival analysis, Cox proportional hazards models, machine learning algorithms (Random Survival Forests and Boruta feature selection) and the receiver operating characteristic curve (ROC) analysis, to rigorously compare the indices and determine their relative prognostic importance. By establishing the prognostic value of these readily available indicators, this work aims to provide clinicians with practical tools for early risk stratification and personalized management of COPD patients facing this critical complication of HRF.

Materials and Methods

Research Subjects

We enrolled participants with chronic obstructive pulmonary disease (COPD) complicated by hypercapnic respiratory failure (HRF) from two centers. The first cohort was recruited from the Department of Respiratory and Critical Care Medicine and the Intensive Care Unit (ICU) at The First People's Hospital of Yancheng between October 2020 and September 2021. The second cohort was recruited from the corresponding department and ICU at Jiangsu Provincial People's Hospital from October 2021 to November 2021. Inclusion criteria comprised: (1) according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy, a post-bronchodilator FEV1/FVC < 0.7 as the

diagnostic criteria for COPD;[2] (2) HRF diagnosis confirmed by arterial oxygen tension (PaO_2) < 8.0 kPa (60 mmHg) and arterial carbon dioxide tension ($PaCO_2$) > 6.0 kPa (45 mmHg); and (3) age ≥ 18 years. Exclusion criteria were as follows: (1) age < 18 years; (2) death prior to data collection; (3) inability to provide informed consent due to conditions such as hearing/speech impairment, tracheostomy status, or cognitive impairment; (4) conditions potentially confounding values of nutritional or inflammatory indicators, including trauma, malignant tumors, hematological malignancies, or pregnancy; and (5) incomplete clinical records.

Data Collection

Within 24 hours of admission, we collected demographic data, comorbidities, and laboratory parameters. Demographic variables included age, sex, body mass index (BMI), and smoking status. Comorbidities assessed were hypertension, diabetes, cerebrovascular disease, cardiovascular disease, asthma, interstitial lung disease (ILD), bronchiectasis, and pneumonia. Laboratory data obtained within 24 hours of admission comprised arterial blood gas analysis (including pH, PaO_2, and $PaCO_2$), neutrophil percentage, hemoglobin, albumin, D-dimer, and lymphocyte percentage etc.

The following formulas were used to calculate nutritional and inflammatory indices: Platelet-to-lymphocyte ratio (PLR) = platelet count (10^9/L) / lymphocyte count (10^9/L); Neutrophil-to-lymphocyte ratio (NLR) = neutrophil count / lymphocyte count (10^9/L); Systemic immune-inflammation index (SII) = platelet count (10^9/L) × neutrophil count (10^9/L) / lymphocyte count (10^9/L); Prognostic nutritional index (PNI) = albumin (g/L) + 5 × lymphocyte count (109/L); Neutrophil percentage-to-albumin ratio (NPAR) = neutrophil percentage × 1000 / albumin (g/L); Hemoglobin, albumin, lymphocyte, platelet index (HALP) = hemoglobin (g/L) × albumin (g/L) × lymphocyte count (10^9/L) / platelet count (10^9/L).[18–20]

Outcomes

This prospective cohort study involved patient follow-up via telephone interviews for 24 months post-discharge. The primary outcome was 24-month all-cause mortality. Secondary outcomes included all-cause mortality at 3, 6, and 12 months.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical variables are presented as counts and percentages (%). Group comparisons were performed using Student's *t*-test or Mann–Whitney *U*-test for continuous variables, and chi-square tests for categorical variables. Associations between nutritional/inflammatory indicators and all-cause mortality were analyzed using restricted cubic splines (RCS) and multivariate Cox proportional hazards models. The proportional hazards assumption was confirmed by Schoenfeld residual plots. Patients were stratified by the median values of the indicators and survival analysis was performed using the Kaplan-Meier method. The group differences were compared with the Log rank test. Random Survival Forests (RSF) and Boruta feature selection were employed to evaluate indicator importance. Predictive performance was compared using the receiver operating characteristic curve (ROC) analyses. Threshold effect analysis was employed to further evaluate the association between the optimal indicator HALP and all-cause mortality. Subgroup analyses further explored indicator-mortality associations across strata. All analyses were conducted in R (version 4.4.2), with statistical significance defined as two-sided $p < 0.05$.

Results

Patient Characteristics

As shown in Figure 1, we enrolled 582 patients with chronic obstructive pulmonary disease (COPD) and hypercapnic respiratory failure (HRF) across two centers. After 24 months of follow-up, the cohort comprised 319 survivors and 263 non-survivors. Comparative data between these groups are presented in Table 1. Compared with survivors, non-survivors were significantly older and exhibited higher levels of bicarbonate, $PaCO_2$, neutrophil percentage, neutrophil count, D-dimer, CK-MB, urea, and NT-proBNP ($P < 0.05$). Conversely, non-survivors showed significantly lower values for BMI, hemoglobin, albumin, total protein, overall survival, red blood cell count (RBC), lymphocyte percentage,

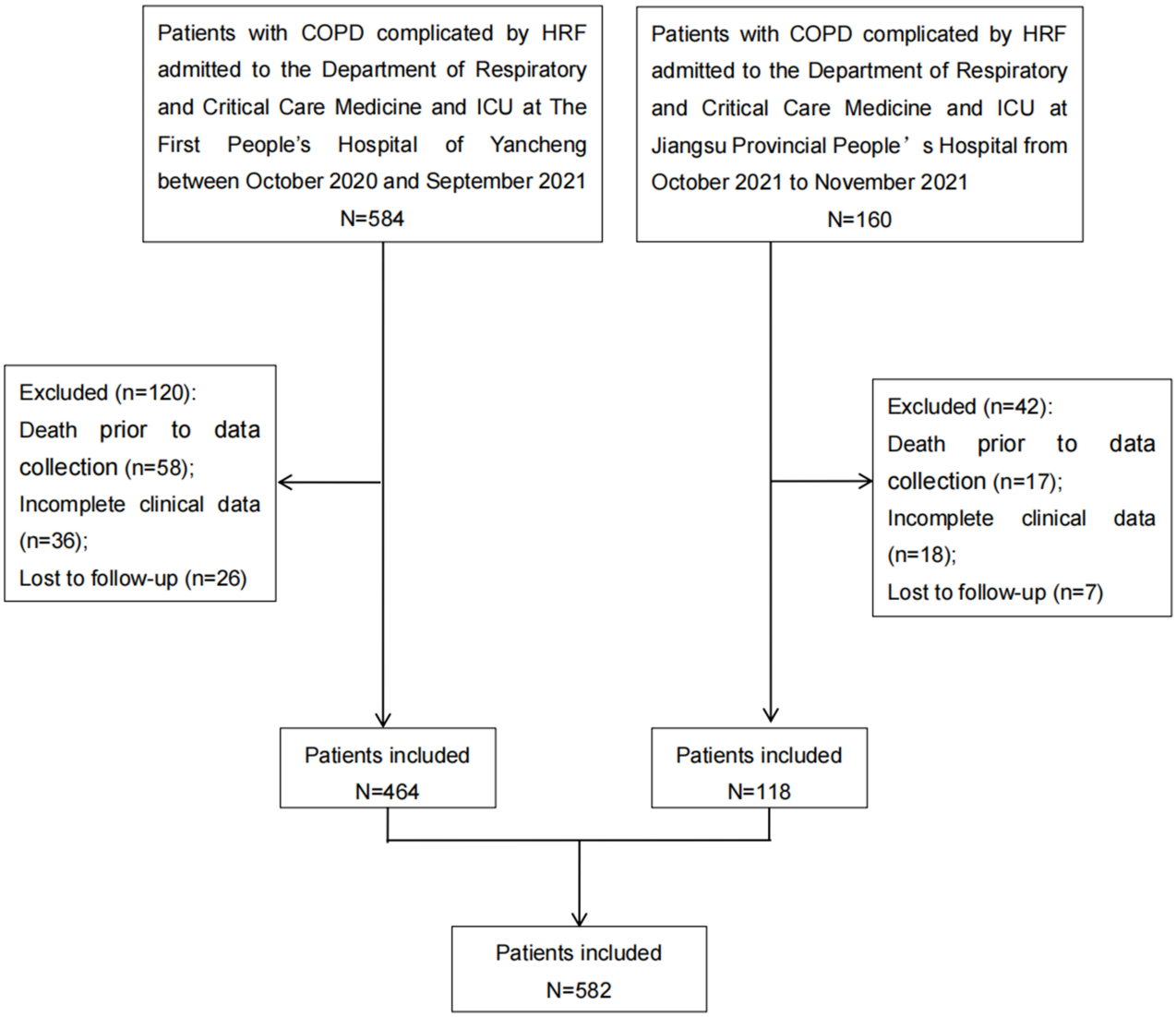

Figure 1 The flow diagram of sample selection in the study.

lymphocyte count, cholinesterase, and eGFR ($P < 0.05$). Notably, non-survivors demonstrated elevated NLR, PLR, SII, and NPAR, alongside lower PNI and HALP values ($P < 0.05$).

Relationship Between Nutritional and Inflammatory Indicators and All-Cause Mortality in COPD Patients with HRF

As illustrated in Figure 2, restricted cubic spline (RCS) modeling was employed to evaluate nonlinear relationships between nutritional/inflammatory indicators and all-cause mortality among COPD patients with HRF. Following adjustment for age, sex, BMI, smoking status, hypertension, diabetes, cerebrovascular disease, cardiovascular disease, asthma, interstitial lung disease, bronchiectasia and pneumonia, the RCS analysis demonstrated linear associations of PLR, NPAR, and PNI with all-cause mortality (P for overall association < 0.05; P for nonlinear association > 0.05) (Figure 2A, D and E). Conversely, nonlinear associations were observed between NLR, SII, and HALP and all-cause mortality (P for nonlinear association < 0.05) (Figure 2B, C and F).

Table 1 Baseline Characteristics of Participants in COPD Patients with HRF

Variables	Total (n = 582)	Survivors (n = 319)	Non-survivors (n = 263)	*P* value
No. of patients, n(%)	582 (100)	319 (54.80)	263 (45.20)	
Age, year	74.0 (69.0, 80.0)	73.0 (68.0, 79.0)	76.0 (70.0, 81.0)	**0.001**
Sex, n(%)				0.051
Female	188 (32.30)	114 (35.74)	74 (28.14)	
Male	394 (67.70)	205 (64.26)	189 (71.86)	
BMI, kg/m^2	21.38 (18.37, 24.80)	22.22 (19.34, 25.71)	20.20 (17.65, 24.22)	**<0.001**
Smoking status, n(%)				0.703
No	223 (38.32)	120 (37.62)	103 (39.16)	
Yes	359 (61.68)	199 (62.38)	160 (60.84)	
Comorbidities				
Hypertension, n(%)				0.203
No	362 (62.20)	191 (59.87)	171 (65.02)	
Yes	220 (37.80)	128 (40.13)	92 (34.98)	
Diabetes, n(%)				0.679
No	503 (86.43)	274 (85.89)	229 (87.07)	
Yes	79 (13.57)	45 (14.11)	34 (12.93)	
Cerebrovascular diseases, n(%)				0.871
No	512 (87.97)	280 (87.77)	232 (88.21)	
Yes	70 (12.03)	39 (12.23)	31 (11.79)	
Cardiovascular diseases, n(%)				0.062
No	448 (76.98)	255 (79.94)	193 (73.38)	
Yes	134 (23.02)	64 (20.06)	70 (26.62)	
Asthma, n(%)				1.000
No	574 (98.63)	315 (98.75)	259 (98.48)	
Yes	8 (1.37)	4 (1.25)	4 (1.52)	
ILD, n(%)				0.056
No	572 (98.28)	317 (99.37)	255 (96.96)	
Yes	10 (1.72)	2 (0.63)	8 (3.04)	
Bronchiectasis, n(%)				0.123
No	533 (91.58)	287 (89.97)	246 (93.54)	
Yes	49 (8.42)	32 (10.03)	17 (6.46)	
Pneumonia, n(%)				0.658
No	465 (79.90)	257 (80.56)	208 (79.09)	
Yes	117 (20.10)	62 (19.44)	55 (20.91)	
Laboratory parameters				
PH value	7.37 (7.32, 7.41)	7.37 (7.32, 7.41)	7.37 (7.31, 7.41)	0.240
Bicarbonate, mmol/L	32.30 (29.40, 35.55)	31.70 (28.95, 34.65)	32.90 (29.85, 36.45)	**0.002**
PaO_2, mmHg	48.00 (40.00, 54.00)	48.00 (40.00, 54.00)	48.00 (39.00, 55.00)	0.950
$PaCO_2$, mmHg	65.40 (57.00, 79.00)	64.00 (56.00, 77.00)	69.00 (58.00, 84.00)	**<0.001**
WBC, 10^9/L	7.95 (6.09, 10.64)	7.84 (5.75, 10.11)	8.35 (6.24, 11.21)	0.222
Monocytes percentage, %	7.30 (4.80, 9.60)	7.40 (5.10, 9.85)	7.00 (4.70, 9.30)	0.194
Monocytes, 10^9/L	0.55 (0.39, 0.76)	0.55 (0.40, 0.77)	0.54 (0.38, 0.76)	0.737
RBC, 10^12/L	4.46 (3.98, 4.94)	4.50 (4.12, 4.99)	4.42 (3.83, 4.84)	**0.009**
Lymphocyte percentage, %	10.70 (5.50, 17.28)	12.30 (6.65, 19.60)	9.40 (4.60, 15.10)	**<0.001**
Lymphocyte, 10^9/L	0.81 (0.48, 1.22)	0.95 (0.60, 1.31)	0.70 (0.41, 1.12)	**<0.001**
Platelet, 10^9/L	170.00 (126.00, 215.00)	171.00 (128.50, 217.00)	166.00 (123.00, 210.00)	0.447
Neutrophil percentage, %	80.00 (70.90, 87.70)	78.30 (69.15, 86.60)	82.60 (73.85, 89.10)	**<0.001**
Neutrophil, 10^9/L	6.29 (4.45, 9.09)	6.08 (4.23, 8.46)	6.71 (4.70, 9.50)	**0.045**
Hemoglobin, g/L	133.19 ± 22.19	136.18 ± 20.87	129.57 ± 23.22	**<0.001**
D-dimer, mg/L	0.67 (0.37, 1.46)	0.57 (0.30, 1.23)	0.75 (0.43, 1.65)	**<0.001**

(*Continued*)

Table 1 (Continued).

Variables	Total (n = 582)	Survivors (n = 319)	Non-survivors (n = 263)	*P* value
Cholinesterase, U/L	5000.00 (4277.50, 6059.00)	5130.00 (4752.50, 6416.50)	4788.00 (3881.50, 5741.50)	**<0.001**
Triglyceride, mmol/L	0.96 (0.74, 1.32)	0.98 (0.74, 1.37)	0.93 (0.73, 1.27)	0.405
Creatinine, umol/L	65.00 (53.00, 82.12)	64.90 (53.25, 77.55)	65.60 (52.30, 88.25)	0.277
CK-MB, ng/mL	12.00 (10.00, 17.00)	10.00 (9.00, 15.00)	13.00 (10.00, 18.00)	**<0.001**
Urea, mmol/L	7.33 (5.34, 9.40)	6.89 (5.09, 8.56)	8.04 (5.89, 10.69)	**<0.001**
Uric acid, umol/L	310.20 (229.10, 405.48)	306.40 (223.65, 385.85)	314.50 (235.85, 421.65)	0.084
eGFR, mL/min/1.73m^2	80.23 (60.62, 90.85)	81.86 (64.14, 91.32)	77.81 (54.85, 89.91)	**0.044**
LDH, U/L	343.00 (219.10, 495.00)	331.00 (216.65, 478.65)	354.00 (226.50, 527.00)	0.184
TC, mmol/L	4.08 (3.42, 4.89)	4.15 (3.51, 4.96)	3.92 (3.33, 4.74)	0.059
Glucose, mmol/L	6.78 (5.49, 8.57)	6.60 (5.46, 8.29)	6.92 (5.58, 8.88)	0.298
NT-proBNP, pg/mL	510.00 (132.25, 2437.50)	403.00 (130.00, 1935.00)	709.00 (176.50, 3180.00)	**<0.001**
Albumin, g/L	36.02 ± 4.76	36.71 ± 4.70	35.17 ± 4.70	**<0.001**
Total protein, g/L	64.59 ± 7.09	65.28 ± 6.91	63.75 ± 7.24	**0.010**
Overall survival, month	24.02 (7.73, 24.02)	24.02 (24.02, 24.02)	6.34 (1.58, 13.87)	**<0.001**
PNI	40.70 (37.02, 44.40)	41.70 (37.95, 45.40)	39.60 (35.05, 42.83)	**<0.001**
NLR	7.51 (4.17, 16.26)	6.41 (3.50, 12.91)	8.68 (4.98, 19.37)	**<0.001**
PLR	199.55 (132.08, 325.72)	170.51 (120.20, 282.18)	230.70 (153.81, 363.89)	**<0.001**
SII	1247.02 (637.57, 2667.04)	1070.07 (589.03, 2061.73)	1559.49 (778.30, 3369.39)	**<0.001**
NPAR	21.80 (19.22, 25.07)	20.95 (18.58, 24.17)	22.82 (20.24, 26.50)	**<0.001**
HALP	23.38 (13.93, 37.10)	27.93 (17.57, 42.36)	19.35 (11.04, 31.50)	**<0.001**

Note: Bold values indicate $P < 0.05$.

Abbreviations: HRF, hypercapnic respiratory failure; BMI, body mass index; ILD, interstitial lung disease; PaO_2, arterial oxygen pressure; $PaCO_2$, arterial carbon dioxide pressure; WBC, white blood cell count; RBC, red blood cell count; CK-MB, creatine kinase-MB; LDH, lactate dehydrogenase; TC, total cholesterol; eGFR, estimated glomerular filtration rate; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; NPAR, neutrophil percentage-to-albumin ratio; HALP, hemoglobin-albumin-lymphocyte-platelet index.

Patients were stratified by median levels of indicators to evaluate cumulative survival rates by Kaplan-Meier survival curves (Figure 3). Among the six nutritional and inflammatory indicators analyzed, all groups dichotomized by median values showed statistically significant differences in 24-month all-cause mortality (log-rank $P < 0.001$). Furthermore, elevated PLR, NLR, SII, and NPAR levels were positively associated with all-cause mortality (Figure 3A–D), whereas higher PNI and HALP levels were negatively correlated with all-cause mortality (Figure 3E and F).

To further investigate these relationships, three Cox proportional hazards regression models were developed. Table 2 summarizes the hazard ratios (HRs) and 95% confidence intervals (CIs) for each model. After adjusting for age, sex, BMI, smoking status, hypertension, diabetes, cerebrovascular disease, cardiovascular disease, asthma, ILD, bronchiectasis, pneumonia and laboratory parameters (Model 4), PLR, NLR, PNI, HALP and NPAR remained significantly associated with 24-month all-cause mortality. When analyzed as categorical variables (dichotomized by median values), the fully adjusted Model 4 demonstrated that patients with higher PNI and HALP levels had significantly lower all-cause mortality compared to those with low levels, with adjusted HRs (95% CI) of 0.72 (0.54–0.96) and 0.55 (0.41–0.74), respectively. Conversely, elevated PLR, NLR, SII, and NPAR levels were associated with increased mortality risk, yielding HRs (95% CI) of 1.39 (1.04–1.85), 1.39 (1.02–1.88), 1.51 (1.11–2.05), and 1.46 (1.10–1.95). Notably, although the hazard ratios (HRs) for the continuous variables of these indicators were statistically significant, their 95% confidence intervals (CIs) were narrow. For example, the HR for PLR was 1.01 (1.01–1.01). This may limit their clinical applicability. To address this limitation, we further evaluated these biomarkers using a per-one-standard-deviation (per-1-SD) increase approach. For each one-standard-deviation increase in PLR, NLR, PNI, HALP, SII and NPAR, the HRs (95% CI) for mortality were 1.19 (1.04–1.36), 1.22 (1.04–1.43), 0.76 (0.65–0.90), 0.79 (0.67–0.94), 1.13 (0.98–1.31), and 1.34 (1.16–1.55), respectively. This implies that each one-standard-deviation increase in PLR was associated with

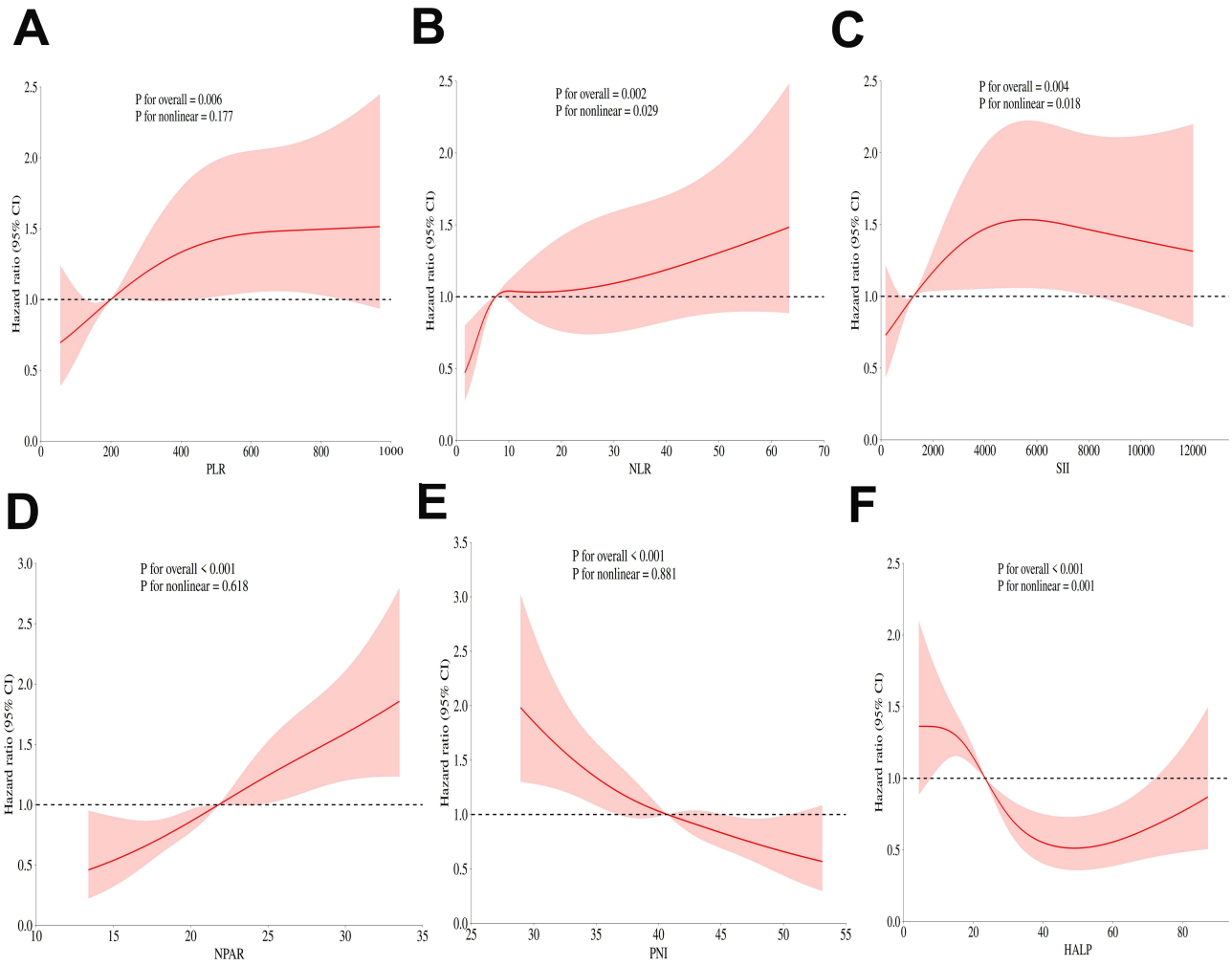

Figure 2 Restricted cubic spline curves for analyzing the nonlinear relationships between nutritional/inflammatory indices and all-cause mortality in patients with COPD complicated by HRF (**A**) PLR; (**B**) NLR; (**C**) SII; (**D**) NPAR; (**E**) PNI; (**F**) HALP.
Note: Hazard ratios were adjusted for age, sex, BMI, smoking status, hypertension, diabetes, cerebrovascular diseases, cardiovascular diseases, asthma, ILD, bronchiectasis and pneumonia.

a 19% increase in mortality risk. Moreover, decreased levels of PNI and HALP, as well as increased levels of PLR, NLR, and NPAR, were significantly associated with a higher risk of all-cause mortality (P for trend < 0.05).

Predictive Values of Nutritional and Inflammatory Indicators

To further evaluate the clinical significance and predictive performance of the six indicators, we performed Random Survival Forests (RSF), Boruta feature selection, and receiver operating characteristic (ROC) curve analyses. As depicted in Figure 4, both RSF analysis (Figure 4A) and Boruta algorithms (Figure 4B) ranked all variables by their importance for all-cause mortality prediction, with HALP, PNI, and NPAR consistently ranked among the top ten significant predictors. Notably, HALP achieved the highest and second-highest importance rankings in these respective algorithms.

ROC curves evaluating indicator performance for predicting 3-, 6-, 12-, and 24-month mortality are presented in Figure 5A–D. Corresponding AUC values (95% CI) and statistical comparisons are detailed in Table 3. Comparisons between HALP and PLR ROC curves showed statistically significant differences across all four time points. PNI, HALP, and NPAR demonstrated superior predictive performance relative to PLR, NLR, and SII at all time points, although these differences were not statistically significant. These findings highlight the clinical utility of PNI, HALP, and NPAR as composite prognostic indicators in COPD patients with HRF.

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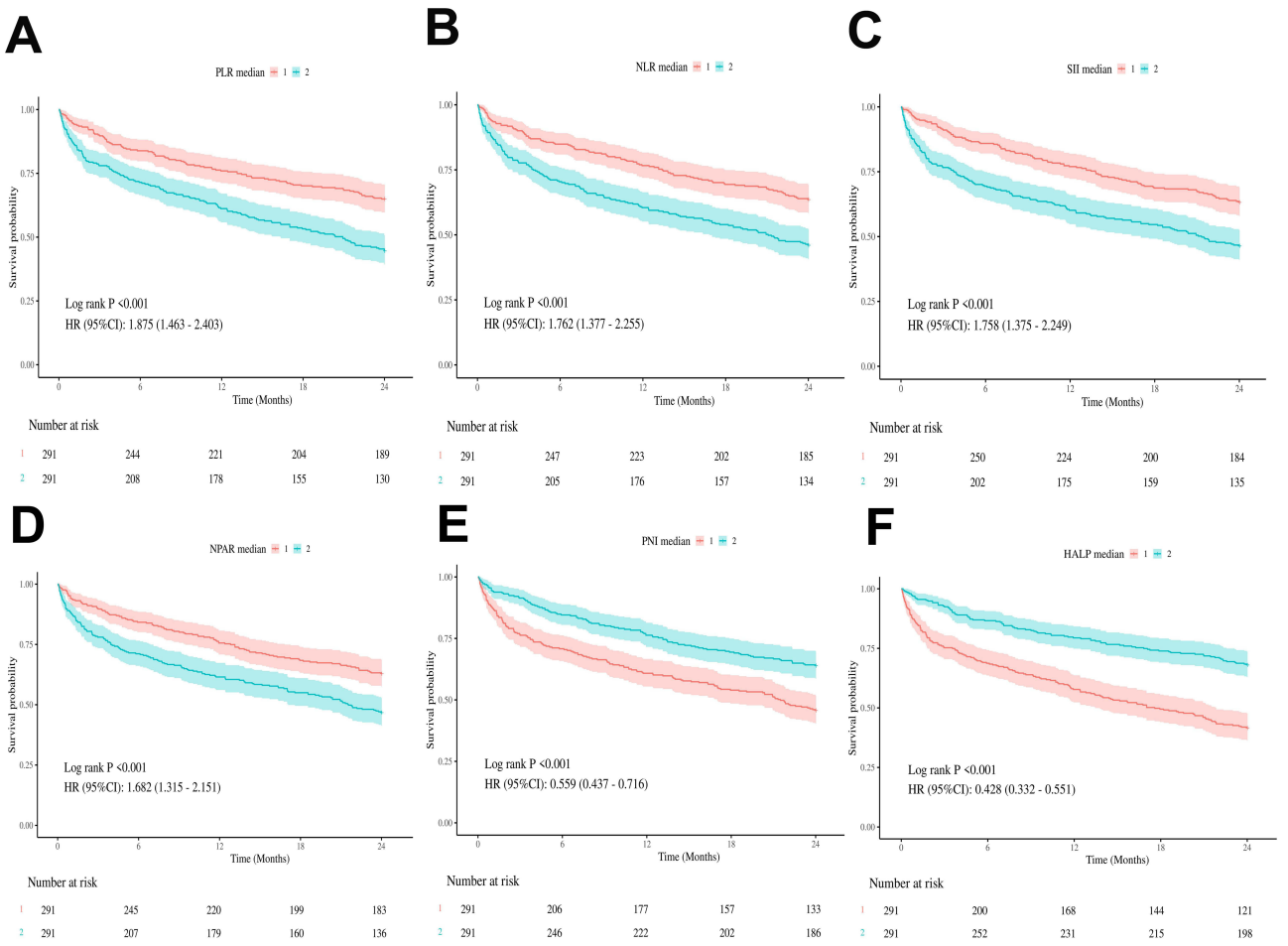

Figure 3 Kaplan-Meier curves for evaluating cumulative survival by medians of nutritional/inflammatory indicators (**A**) PLR; (**B**) NLR; (**C**) SII; (**D**) NPAR; (**E**) PNI; (**F**) HALP).

Based on the above findings, we conducted a threshold effect analysis on the most promising indicator, HALP (Table 4). The results revealed a significant threshold effect between HALP and all-cause mortality in COPD patients complicated with HRF (likelihood ratio test P < 0.001). Overall, HALP was inversely associated with all-cause mortality

Table 2 Multivariate Cox Proportional Hazards Models for the Nutritional/Inflammatory Indicators and All-Cause Mortality

Variables	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PLR continuous	1.01 (1.01 ~ 1.01)	**<0.001**	1.01 (1.01 ~ 1.01)	**<0.001**	1.01 (1.01 ~ 1.01)	**0.002**	1.01 (1.01 ~ 1.01)	**0.011**
PLR median								
1	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
2	1.80 (1.40 ~ 2.30)	**<0.001**	1.63 (1.27 ~ 2.10)	**<0.001**	1.59 (1.23 ~ 2.06)	**<0.001**	1.39 (1.04 ~ 1.85)	**0.027**
Per 1-SD increase	1.24 (1.12 ~ 1.37)		1.20 (1.08 ~ 1.33)		1.19 (1.07 ~ 1.33)		1.19 (1.04 ~ 1.36)	
P for trend		**<0.001**		**<0.001**		**0.002**		**0.011**
NLR continuous	1.02 (1.01 ~ 1.02)	**<0.001**	1.01 (1.01 ~ 1.02)	**<0.001**	1.01 (1.01 ~ 1.02)	**0.002**	1.01 (1.01 ~ 1.02)	**0.016**
NLR median								
1	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
2	1.73 (1.35 ~ 2.21)	**<0.001**	1.64 (1.28 ~ 2.10)	**<0.001**	1.59 (1.23 ~ 2.05)	**<0.001**	1.39 (1.02 ~ 1.88)	**0.037**
Per 1-SD increase	1.27 (1.14 ~ 1.41)		1.22 (1.09 ~ 1.36)		1.20 (1.07 ~ 1.34)		1.22 (1.04 ~ 1.43)	
P for trend		**<0.001**		**<0.001**		**0.002**		**0.016**

(*Continued*)

Table 2 (Continued).

Variables	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PNI continuous	0.94 (0.92 ~ 0.96)	**<0.001**	0.95 (0.93 ~ 0.97)	**<0.001**	0.95 (0.93 ~ 0.97)	**<0.001**	0.96 (0.93 ~ 0.98)	**<0.001**
PNI median								
1	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
2	0.57 (0.44 ~ 0.72)	**<0.001**	0.64 (0.50 ~ 0.82)	**<0.001**	0.67 (0.52 ~ 0.87)	**0.003**	0.72 (0.54 ~ 0.96)	**0.025**
Per 1-SD increase	0.69 (0.61 ~ 0.79)		0.74 (0.65 ~ 0.84)		0.74 (0.65 ~ 0.85)		0.76 (0.65 ~ 0.90)	
P for trend		**<0.001**		**<0.001**		**<0.001**		**<0.001**
HALP continuous	0.98 (0.98 ~ 0.99)	**<0.001**	0.99 (0.98 ~ 0.99)	**<0.001**	0.99 (0.98 ~ 0.99)	**<0.001**	0.99 (0.98 ~ 0.99)	**0.007**
HALP median								
1	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
2	0.44 (0.34 ~ 0.56)	**<0.001**	0.48 (0.37 ~ 0.63)	**<0.001**	0.49 (0.38 ~ 0.64)	**<0.001**	0.55 (0.41 ~ 0.74)	**<0.001**
Per 1-SD increase	0.69 (0.59 ~ 0.80)		0.74 (0.63 ~ 0.86)		0.75 (0.64 ~ 0.88)		0.79 (0.67 ~ 0.94)	
P for trend		**<0.001**		**<0.001**		**<0.001**		**0.007**
SII continuous	1.01 (1.01 ~ 1.01)	**0.002**	1.01 (1.01 ~ 1.01)	**0.012**	1.01 (1.01 ~ 1.01)	**0.023**	1.00 (1.00 ~ 1.00)	0.103
SII median								
1	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
2	1.66 (1.30 ~ 2.12)	**<0.001**	1.59 (1.24 ~ 2.03)	**<0.001**	1.54 (1.19 ~ 1.98)	**<0.001**	1.51 (1.11 ~ 2.05)	**0.009**
Per 1-SD increase	1.15 (1.05 ~ 1.26)		1.13 (1.03 ~ 1.24)		1.12 (1.02 ~ 1.24)		1.13 (0.98 ~ 1.31)	
P for trend		**0.002**		**0.012**		**0.023**		0.103
NPAR continuous	1.07 (1.05 ~ 1.10)	**<0.001**	1.06 (1.04 ~ 1.09)	**<0.001**	1.07 (1.04 ~ 1.09)	**<0.001**	1.06 (1.03 ~ 1.10)	**<0.001**
NPAR median								
1	1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)		1.00 (Ref.)	
2	1.68 (1.32 ~ 2.15)	**<0.001**	1.54 (1.20 ~ 1.97)	**<0.001**	1.56 (1.21 ~ 2.02)	**<0.001**	1.46 (1.10 ~ 1.95)	**0.009**
Per 1-SD increase	1.40 (1.25 ~ 1.56)		1.34 (1.19 ~ 1.50)		1.36 (1.20 ~ 1.53)		1.34 (1.16 ~ 1.55)	
P for trend		**<0.001**		**<0.001**		**<0.001**		**<0.001**

Note: Bold values indicate P < 0.05. Model 1: unadjusted; Model 2: adjusted for age, sex, BMI; Model 3: adjusted for age, sex, BMI, smoking status, hypertension, diabetes, cerebrovascular diseases, cardiovascular diseases, chronic emphysema, asthma, ILD, bronchiectasis and pneumonia; Model 4: adjusted for age, sex, BMI, smoking status, hypertension, diabetes, cerebrovascular diseases, cardiovascular diseases, asthma, ILD, bronchiectasis, pneumonia, PaO2, PaCO2, WBC, RBC, platelet, D-dimer, triglyceride, creatinine, CK-MB, urea, uric acid, eGFR, LDH, TC, glucose, NT-proBNP.

Abbreviations: PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; NPAR, neutrophil percentage-to-albumin ratio; HALP, hemoglobin-albumin-lymphocyte-platelet index; SD, standard deviation; HR, hazard ratio; CI, conffdence interval.

(HR (95% CI): 0.99 (0.98–0.99), p < 0.001). Specifically, when HALP values were below 70.21, a negative correlation with all-cause mortality was observed. Conversely, when HALP exceeded 70.21, a positive association with all-cause mortality was identified (HR (95% CI): 1.09 (1.01–1.18), P = 0.037).

Subgroup Analysis

To validate the consistency of associations between PNI, HALP, NPAR and 24-month all-cause mortality across subgroups of COPD patients with HRF, we performed subgroup analyses. As demonstrated in Figure 6, elevated HALP levels were significantly associated with reduced 24-month mortality risk in most subgroups (P < 0.05). Critically, no significant interaction effects were observed between HALP and most stratification variables (P for interaction > 0.05), indicating the robustness of this relationship across diverse patient profiles. Subgroup analyses for PNI and NPAR yielded comparable findings to HALP (Figures S1 and S2). Collectively, these findings reinforce the independent prognostic value of PNI, HALP, and NPAR in COPD patients with HRF.

Discussion

This two-center prospective cohort study evaluated the prognostic significance of six nutritional and inflammatory indices (PLR, NLR, SII, PNI, NPAR, and HALP) in chronic obstructive pulmonary disease (COPD) patients with hypercapnic respiratory failure (HRF). Patients with COPD and HRF represent a particularly vulnerable population. HRF

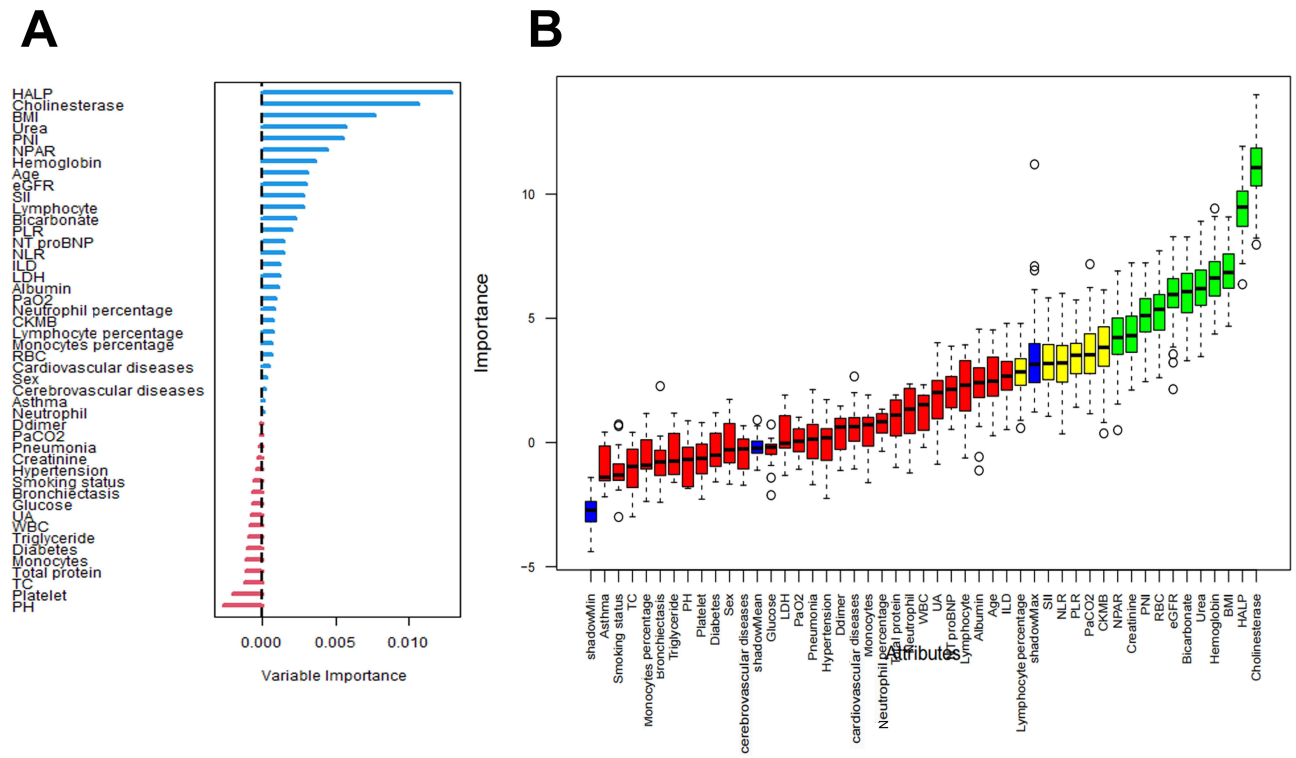

Figure 4 Random Survival Forests (RSF) and Boruta feature selection for ranking variable importance (**A**) RSF analysis; (**B**) Boruta feature selection).

typically occurs during acute exacerbations or advanced stages of COPD, significantly increasing morbidity and mortality.[21] Over a 24-month follow-up period encompassing 582 patients, we observed a mortality rate of 45.2% (263 deaths) among COPD patients with HRF. This high mortality underscores the critical need for effective prognostic tools in this high-risk group. Our study significantly advances the understanding of risk stratification in COPD with HRF by rigorously validating, using both statistical and machine learning methods, that specific indices reflecting nutrition and inflammation (HALP, PNI, and NPAR) demonstrate superior prognostic utility compared to more established inflammatory markers such as NLR, PLR, and SII. Systemic inflammation has long been implicated in the pathogenesis and progression of COPD.[22] Sustained inflammatory responses may contribute to COPD exacerbations, reduced quality of life, and accelerated disease progression.[22] Within this inflammatory milieu, both neutrophils and lymphocytes play significant roles.[23] Established inflammatory markers such as the Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Systemic Immune-Inflammation Index (SII) reflect this inflammatory environment and have been associated with adverse COPD outcomes in prior studies.[24] For instance, a retrospective observational study of 16,849 patients with acute exacerbations of COPD (AECOPD) identified NLR and PLR as independent risk factors for frequent exacerbations.[25] Similarly, a retrospective cohort study utilizing the MIMIC-IV database demonstrated that elevated SII levels increased risks for respiratory failure (HR 1.19, 95% CI 1.12–1.28; P<0.001), in-hospital mortality (HR 1.22, 95% CI 1.07–1.39; P=0.003), and long-term mortality (HR 1.12, 95% CI 1.05–1.19; P<0.001) in COPD patients.[26] Consistent with previous research, our findings confirm NLR, PLR, and SII as independent predictors of all-cause mortality in COPD patients with HRF. However, their predictive performance was surpassed by nutritional and inflammatory composite indices (HALP, PNI, and NPAR).

Malnutrition is prevalent in advanced COPD and is exacerbated by HRF. This nutritional impairment further intensifies disease severity by compromising respiratory muscle function and diminishing immune defense efficacy.[12,27,28] Albumin serves as a critical common component in the Prognostic Nutritional Index (PNI), the Hemoglobin, Albumin, Lymphocyte, and Platelet index (HALP), and the Neutrophil Percentage-to-Albumin Ratio

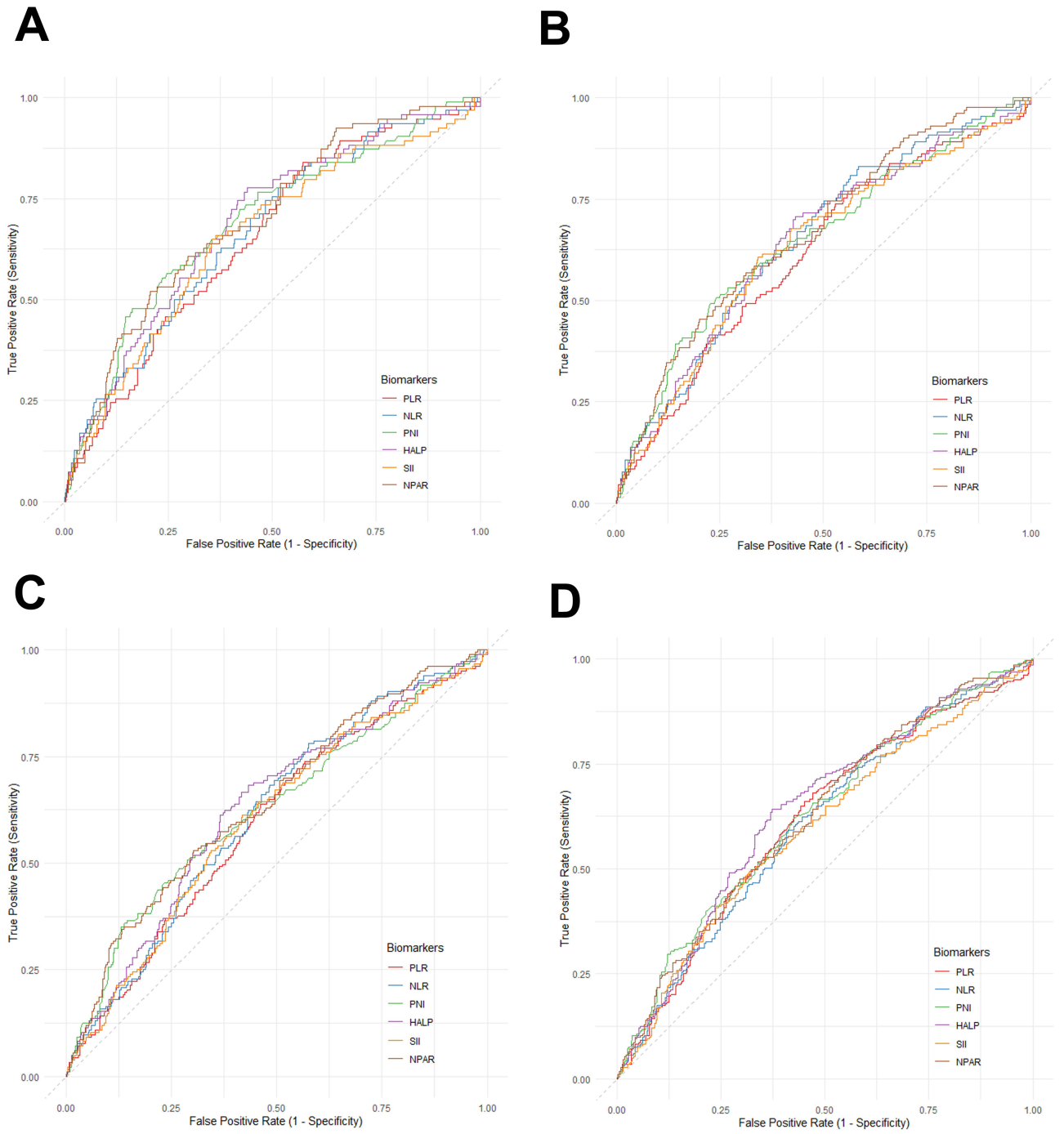

Figure 5 The receiver operating characteristic (ROC) curve analyses of nutritional/inflammatory indicators for predicting all-cause mortality.
Note: (**A**) 3-month mortality; (**B**) 6-month mortality; (**C**) 12-month mortality; (**D**) 24-month mortality.

(NPAR). Inflammation and malnutrition can lower albumin concentrations through increased catabolism or reduced synthesis rates.[29] Consequently, albumin levels simultaneously reflect nutritional reserves and inflammatory burden.[30,31] Lymphocytes, integral to both HALP and PNI, decrease in number during immune exhaustion and impaired host defense, increasing susceptibility to infections and contributing to disease progression.[32] Our study revealed that non-survivors exhibited significantly lower levels of albumin, hemoglobin, and lymphocytes, alongside markedly higher neutrophil percentages and counts (Table 1), indicative of a state characterized by heightened inflammation and compromised

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Table 3 The AUCs of Nutritional/Inflammatory Indicators for Predicting All-Cause Mortality

Indices	AUC	95% CI	*P* value	Indices	AUC	95% CI	*P* value
3-month mortality				**12-month mortality**			
PLR	0.651	0.593–0.710	Ref.	PLR	0.594	0.544–0.643	Ref.
NLR	0.667	0.607–0.726	0.429	NLR	0.615	0.567–0.663	0.216
SII	0.657	0.594–0.719	0.748	SII	0.602	0.553–0.652	0.533
PNI	0.690	0.629–0.750	0.282	PNI	0.625	0.574–0.675	0.293
HALP	0.689	0.632–0.747	**0.003**	HALP	0.628	0.579–0.677	**<0.001**
NPAR	0.698	0.642–0.755	0.124	NPAR	0.642	0.594–0.691	0.057
6-month mortality				**24-month mortality**			
PLR	0.616	0.561–0.671	Ref.	PLR	0.613	0.567–0.659	Ref.
NLR	0.650	0.598–0.703	0.053	NLR	0.605	0.560–0.651	0.648
SII	0.632	0.576–0.687	0.271	SII	0.596	0.549–0.642	0.183
PNI	0.650	0.595–0.706	0.296	PNI	0.624	0.579–0.670	0.676
HALP	0.643	0.589–0.698	**0.009**	HALP	0.637	0.591–0.682	**0.004**
NPAR	0.669	0.617–0.721	0.064	NPAR	0.623	0.578–0.669	0.665

Note: Bold values indicate $P < 0.05$.
Abbreviations: PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; NPAR, neutrophil percentage-to-albumin ratio; HALP, hemoglobin-albumin-lymphocyte-platelet index; AUC, area under the receiver operating characteristic curve; CI, confidence interval.

Table 4 Threshold Effect Analysis of HALP on COPD with HRF Using a Two-Piecewise Linear Regression Model

HALP	Adjusted HR (95% CI)	*P* value
Model 1 Fitting model by standard linear regression	0.99 (0.98–0.99)	**<0.001**
Model 2 Fitting model by two-piecewise linear regression		
Inflection point	70.21	
<70.21	0.98 (0.97–0.99)	**<0.001**
≥70.21	1.09 (1.01–1.18)	**0.037**
P for likelihood test		**<0.001**

Note: Bold values indicate $P < 0.05$.
Abbreviations: HALP, hemoglobin-albumin-lymphocyte-platelet index; HR, hazard ratio; CI, confidence interval.

nutrition. Furthermore, COPD patients with HRF exhibiting higher PNI and HALP levels in this study demonstrated a lower mortality risk. Conversely, patients with elevated NPAR faced an increased mortality risk. These findings align with the predictive outcomes for COPD reported for these indices in prior studies.[33–36]

Notably, both the Random Survival Forest and Boruta feature selection methods consistently identified HALP, PNI, and NPAR as top predictors of mortality, with HALP demonstrating the highest importance. This prominence may stem from HALP's unique capacity to concurrently capture nutritional depletion (via albumin and hemoglobin) and inflammatory dysregulation (via lymphocytes), offering a more comprehensive assessment of the patient's pathophysiological state. Studies indicate that low hemoglobin concentrations are common in patients experiencing acute exacerbations of COPD and predict long-term mortality.[37] Declining hemoglobin levels correlate with worsening nutritional status and systemic inflammation, leading to impaired quality of life, reduced survival rates, and an increased likelihood of hospitalization.[38,39] Thus, the inclusion of hemoglobin likely underpins HALP's superior predictive importance.

Interestingly, the threshold effect analysis for HALP revealed that it served as a protective factor when HALP was below 70.21, but became a risk factor when HALP exceeded this value. This phenomenon may be attributed to one of the components of HALP not yet discussed-platelet count. When the platelet count is sufficiently low, HALP levels increase, leading to a higher risk of all-cause mortality in COPD patients with HRF. This finding is consistent with a study of 472

Variables	n (%)	HR (95%CI)	P	P for interaction
All patients	582 (100.00)	0.98 (0.98 ~ 0.99)	<.001	
Age, year				0.605
<65	68 (11.68)	0.98 (0.96 ~ 1.00)	0.036	
≥ 65	514 (88.32)	0.98 (0.98 ~ 0.99)	<.001	
Sex				0.233
Female	188 (32.30)	0.99 (0.98 ~ 1.00)	0.102	
Male	394 (67.70)	0.98 (0.97 ~ 0.99)	<.001	
BMI, kg/m2				0.421
<24	400 (68.73)	0.99 (0.98 ~ 0.99)	<.001	
≥ 24	182 (31.27)	0.98 (0.97 ~ 0.99)	0.003	
Smoking status				0.839
No	223 (38.32)	0.98 (0.97 ~ 0.99)	0.003	
Yes	359 (61.68)	0.98 (0.97 ~ 0.99)	<.001	
Hypertension				0.899
No	362 (62.20)	0.98 (0.97 ~ 0.99)	<.001	
Yes	220 (37.80)	0.98 (0.97 ~ 0.99)	0.004	
Diabetes				0.242
No	503 (86.43)	0.98 (0.97 ~ 0.99)	<.001	
Yes	79 (13.57)	0.99 (0.97 ~ 1.01)	0.516	
Cerebrovascular disease				0.569
No	512 (87.97)	0.98 (0.97 ~ 0.99)	<.001	
Yes	70 (12.03)	0.99 (0.97 ~ 1.01)	0.353	
Cardiovascular disease				0.473
No	448 (76.98)	0.98 (0.97 ~ 0.99)	<.001	
Yes	134 (23.02)	0.99 (0.97 ~ 1.00)	0.081	
Asthma				0.602
No	574 (98.63)	0.98 (0.98 ~ 0.99)	<.001	
Yes	8 (1.37)	0.97 (0.92 ~ 1.03)	0.349	
ILD				0.485
No	572 (98.28)	0.98 (0.98 ~ 0.99)	<.001	
Yes	10 (1.72)	0.96 (0.91 ~ 1.02)	0.232	
Bronchiectasis				0.02
No	533 (91.58)	0.98 (0.98 ~ 0.99)	<.001	
Yes	49 (8.42)	0.94 (0.90 ~ 0.98)	0.007	
Pneumonia				0.052
No	465 (79.90)	0.98 (0.98 ~ 0.99)	<.001	
Yes	117 (20.10)	0.97 (0.94 ~ 0.99)	0.004	

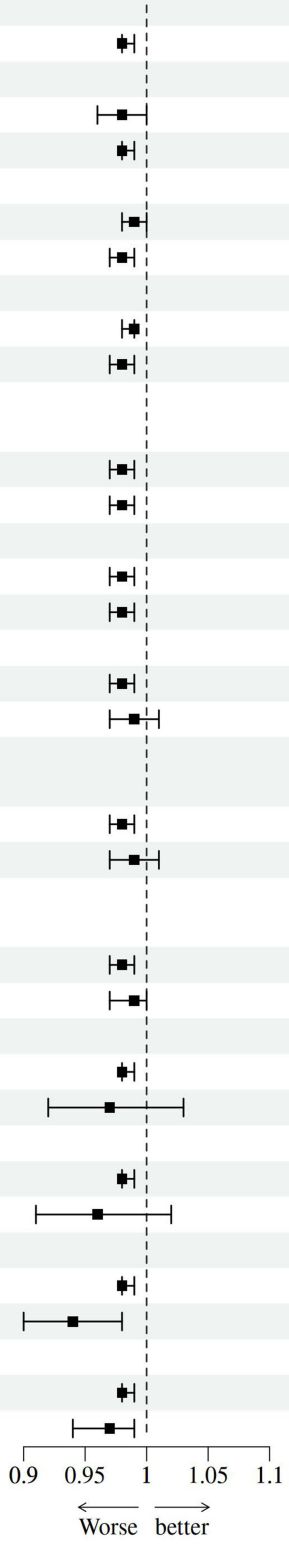

Figure 6 Subgroup analysis of the association between HALP and all-cause mortality.

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patients admitted to the ICU for AECOPD, which reported higher mortality among those with comorbid thrombocytopenia.[40] A potential explanation may be related to the significant downregulation of genes associated with platelet activation and wound healing in COPD patients, which could further impede the repair processes of lung tissue.[41]

Receiver operating characteristic (ROC) curve analysis confirmed the superior performance of PNI, HALP, and NPAR in predicting mortality at 3, 6, 12, and 24 months post-discharge. Although their predictive advantage over indices solely incorporating inflammatory markers did not reach statistical significance, HALP demonstrated statistically significant outperformance of PLR across all four time points. These findings underscore the enhanced prognostic accuracy achievable through composite indices integrating both nutritional and inflammatory parameters. Another noteworthy observation from our study is that the AUC values of the nutrition/inflammation indices exhibited a declining trend as the follow-up duration increased from 3 to 24 months. This pattern suggests that over longer periods, such as 24 months, mortality may be influenced by a broader array of factors not fully captured by baseline biomarkers, such as the development of new comorbidities, overall frailty status, and socioeconomic conditions. Although these indices remain important long-term predictors, their discriminative performance slightly diminishes over time, highlighting the potential need for dynamic reassessment of risk factors in the long-term management of these patients.

Importantly, subgroup analyses demonstrated the consistent prognostic utility of PNI, HALP, and NPAR across diverse patient populations stratified by demographic and clinical characteristics. No significant interactions were detected, suggesting these markers may be broadly applicable for risk stratification regardless of comorbidities or baseline differences. This generalizability positions them as practical candidates for guiding individualized management strategies.

Our study benefits from several strengths, including a prospective design, a relatively large sample size across two centers, a comprehensive analytical approach integrating conventional survival models with machine learning methodologies, and an extended 24-month follow-up period. These features enhance the reliability and clinical relevance of our findings. However, several limitations warrant consideration. First, the observational nature of the study precludes definitive causal inferences. Although we carefully adjusted for potential confounders using multivariable analysis, residual confounding by unmeasured factors (e.g, detailed medication history, socioeconomic status, or physical activity levels) may persist. Second, indicator measurements were limited to values obtained at hospital admission; consequently, the prognostic significance of their dynamic changes remains unexplored. Third, validation across diverse ethnic populations and healthcare settings is essential to confirm generalizability. Fourth, since all-cause mortality served as our primary endpoint, we were unable to determine whether the prognostic utility of these indicators is more strongly associated with COPD-specific progression or with a generalized frail state. Future research should focus on validating these findings in external cohorts, integrating these indices with other indicators to predict a broader range of clinical outcomes, investigating the impact of interventions guided by these indices (such as nutritional supplementation and anti-inflammatory strategies), and elucidating the underlying molecular mechanisms linking these composite indicators to mortality.

Conclusions

In summary, this two-center prospective cohort study validated six nutritional and inflammatory indices (PLR, NLR, SII, PNI, NPAR, and HALP) as independently associated with all-cause mortality in patients with COPD accompanied by HRF. Compared to inflammatory indices (NLR, PLR, and SII), these combined nutritional and inflammatory indices (PNI, NPAR, and HALP), especially HALP, represent more promising predictors of all-cause mortality in COPD patients with HRF, potentially enhancing risk stratification and personalized management. Our findings underscore the critical importance of assessing both nutritional and inflammatory status in COPD patients with HRF. Future research should validate these findings in external cohorts and integrate them with clinical assessments.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Ethical Approval and Consent to Participate

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and was approved by the Ethics Committees of the First People's Hospital of Yancheng (Approval Number: 2020-K062) and the People's Hospital of Jiangsu Province (No. 2021-SR-346). Informed consent was obtained from all participants or their legal guardians prior to data collection.

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We express our gratitude to all the participants who actively contributed to this study.

Author Contributions

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

Disclosure

The authors declare that they have no competing interests.

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