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ORIGINAL RESEARCH

Association of the Neutrophil Percentage-to-Albumin Ratio with All-Cause Mortality in Patients with Hypercapnic Respiratory Failure: A Prospective Cohort Study

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Background: The neutrophil percentage-to-albumin ratio (NPAR) has emerged as a widely used inflammatory marker for predicting clinical outcomes across various diseases; however, its prognostic value in hypercapnic respiratory failure (HRF) remains uncertain. This study aimed to examine the association between NPAR and all-cause mortality in patients with HRF.

Methods: This prospective cohort study enrolled 561 HRF patients hospitalized at Yancheng First People's Hospital between October 2020 and September 2021. The primary outcome was 24-month all-cause mortality; secondary outcomes included mortality at 3, 6, and 12 months. The association between NPAR and all-cause mortality was assessed using restricted cubic spline (RCS) modeling, multivariate Cox proportional hazards models, Kaplan-Meier survival analysis, and subgroup analyses. Discriminatory performance was evaluated using the area under the receiver operating characteristic curve (AUC).

Results: RCS modeling demonstrated a significant linear association between NPAR and all-cause mortality in HRF patients (P for overall association < 0.001). Both the Cox models and Kaplan-Meier analyses indicated that elevated NPAR levels were significantly associated with increased 3-, 6-, 12-, and 24-month all-cause mortality (all $P < 0.05$). Subgroup analysis further supported an independent association between NPAR and mortality. The AUC for NPAR in predicting 12-month all-cause mortality was 0.66 (95% confidence interval [CI], 0.61–0.71), which was significantly higher than that of neutrophil percentage or albumin alone (AUC =0.62; 95% CI, 0.57–0.67; $P < 0.05$).

Conclusion: Elevated NPAR is independently associated with increased all-cause mortality in patients with HRF. As a composite marker reflecting both systemic inflammation and nutritional status, NPAR may serve as a robust prognostic indicator to enhance risk stratification and guide clinical decision-making in HRF management.

Keywords: neutrophil percentage-to-albumin ratio, all-cause mortality, hypercapnic respiratory failure

Introduction

Hypercapnic respiratory failure (HRF) is a common and life-threatening condition in critical care settings. It is characterized by elevated arterial carbon dioxide (CO_2) levels due to inadequate ventilation, and is often accompanied by hypoxemia.[1,2] The etiology of HRF is typically multifactorial, with common causes including chronic obstructive pulmonary disease (COPD), obesity hypoventilation syndrome, and sleep-disordered breathing.[3–5] Despite advances in medical therapy and ventilatory support, HRF continues to be associated with substantial morbidity and mortality.[6,7] Therefore, establishing reliable prognostic markers is crucial for early risk stratification and personalized management of patients with HRF.

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Given the inflammatory nature of HRF, biomarkers that reflect systemic inflammation have attracted attention for their potential prognostic significance. The neutrophil percentage-to-albumin ratio (NPAR) is novel inflammatory biomarker that integrates neutrophil levels with serum albumin concentration.[8] Neutrophils are widely recognized as cost-effective and sensitive indicators of acute inflammation, while serum albumin exerts anti-inflammatory, antioxidant, and antithrombotic effects.[9,10] Hypoalbuminemia is often a marker of malnutrition and heightened inflammatory response, both of which are frequently observed in patients with respiratory infections.[11,12] Recent researches have indicated that NPAR is an effective prognostic indicator in various clinical settings, including cardiovascular diseases, sepsis, acute renal injury, and malignancies.[13–16] Compared to other inflammatory indices such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), NPAR has demonstrated superior predictive value for mortality in patients receiving maintenance hemodialysis and those with atrial fibrillation.[17,18] However, the prognostic utility of NPAR in HRF remains largely unexplored.

Most current research treats HRF as a secondary manifestation of underlying diseases like COPD, with limited investigation into HRF as a distinct clinical entity with its own epidemiological profile and long-term outcomes[19] Considering that NPAR reflects both inflammatory and nutritional status, this study aims to evaluate its independent prognostic value for all-cause mortality in patients with HRF.

Materials and Methods

Research Subjects

We collected data from patients diagnosed with hypercapnic respiratory failure (HRF) who were admitted to the Department of Respiratory and Critical Care Medicine at Yancheng First People's Hospital between October 2020 and September 2021. Inclusion criteria were as follows: (1) diagnosis of HRF with arterial oxygen pressure (PaO2) <8.0 kPa (60 mmHg), and arterial carbon dioxide pressure (PaCO2) >6.0 kPa (45 mmHg); and (2) age ≥18 years. Exclusion criteria included: (1) age <18 years; (2) death during hospitalization or withdrawal from treatment; (3) conditions that could affect NPAR values such as trauma, malignant tumors, hematologic malignancies, or pregnancy; and (4) incomplete clinical records. After excluding 4 patients with missing clinical data and 33 lost to follow-up, a total of 561 patients were included in the final analysis. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Ethics Committee of Yancheng First People's Hospital (Jiangsu, China) (Approval Number: 2020-K062). Informed consent was obtained from all participants.

Data Collection

Within 24 hours of admission, we collected data on demographic variables, comorbidities, nursing assessment scores, and laboratory values. The collected variables included age, sex, body mass index (BMI), smoking status, and eight comorbidities (hypertension, diabetes, cerebrovascular disease, cardiovascular disease (CVD), chronic emphysema, asthma, interstitial lung disease, and pneumonia). Nursing assessment tools included the Braden scale, self-care ability score, and venous thromboembolism (VTE) score. Laboratory data obtained within 24 hours of admission included PaO_2, $PaCO_2$, white blood cell count (WBC), lymphocyte count, hemoglobin, neutrophil percentage, and serum albumin. Neutrophil percentage was measured using the Sysmex XN-A1 automated hematology analyzer (Sysmex, Japan), which employs a combination of flow cytometry and impedance technology. Serum albumin was measured using the Beckman Coulter AU5831 system (Beckman Coulter, USA) through the bromocresol green dye-binding method. All procedures were performed in accordance with the manufacturers' instructions. NPAR was calculated using the following formula: (neutrophil percentage [%] × 100) / albumin (g/dL).

Outcomes

This was a prospective cohort study in which patients were followed up via telephone for 24 months post-discharge. The primary outcome was 24-month all-cause mortality, and the secondary outcomes were 3-, 6-, and 12-month all-cause mortality.

Statistical Analysis

Patients were stratified into tertiles based on baseline NPAR values as follows: T1 (NPAR ≤ 20.23), T2 (20.23 < NPAR ≤ 23.85), and T3 (NPAR > 23.85). Continuous variables were presented as mean ± standard deviation for normally distributed

data, and categorical variables were presented as counts and percentages. Group comparisons for continuous variables were performed using one-way analysis of variance (ANOVA), and categorical variables were compared using chi-square tests. The relationship between NPAR and all-cause mortality was assessed using restricted cubic spline (RCS) models and multivariate Cox proportional hazards models. Kaplan–Meier survival analysis was used to estimate cumulative survival, and the Log rank test was applied to assess statistical differences among groups. Subgroup analyses were conducted to further explore the association between NPAR and mortality. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate and compare the predictive performance of NPAR, neutrophil percentage, and albumin. All statistical analyses were conducted using R software (version 4.4.0). A two-sided P-value of < 0.05 was considered statistically significant.

Results

Patient Characteristics

Figure 1 illustrates the flowchart of patient selection. A total of 561 HRF patients were ultimately included, consisting of 357 males (63.64%) and 204 females (36.36%), with a mean age of 73.16 ± 9.80 years. Baseline characteristics stratified by NPAR tertiles are presented in Table 1: T1 (NPAR ≤ 20.23), T2 (20.23 < NPAR ≤ 23.85), and T3 (NPAR > 23.85), with 187 patients in each group. Compared to the T1 group, patients in the T3 group exhibited lower scores on the Braden scale and self-care assessments, as well as decreased levels of PaO_2, lymphocyte count, hemoglobin, albumin, estimated glomerular filtration rate (eGFR), triglycerides, and total cholesterol. In contrast, they demonstrated higher age, venous thromboembolism (VTE) scores, WBC counts, and neutrophil percentages. Moreover, the prevalence of cerebrovascular disease and pneumonia was significantly higher in the T3 group. No significant differences were observed among the groups in terms of sex, BMI, smoking status, hypertension, diabetes, CVD, chronic emphysema, asthma,

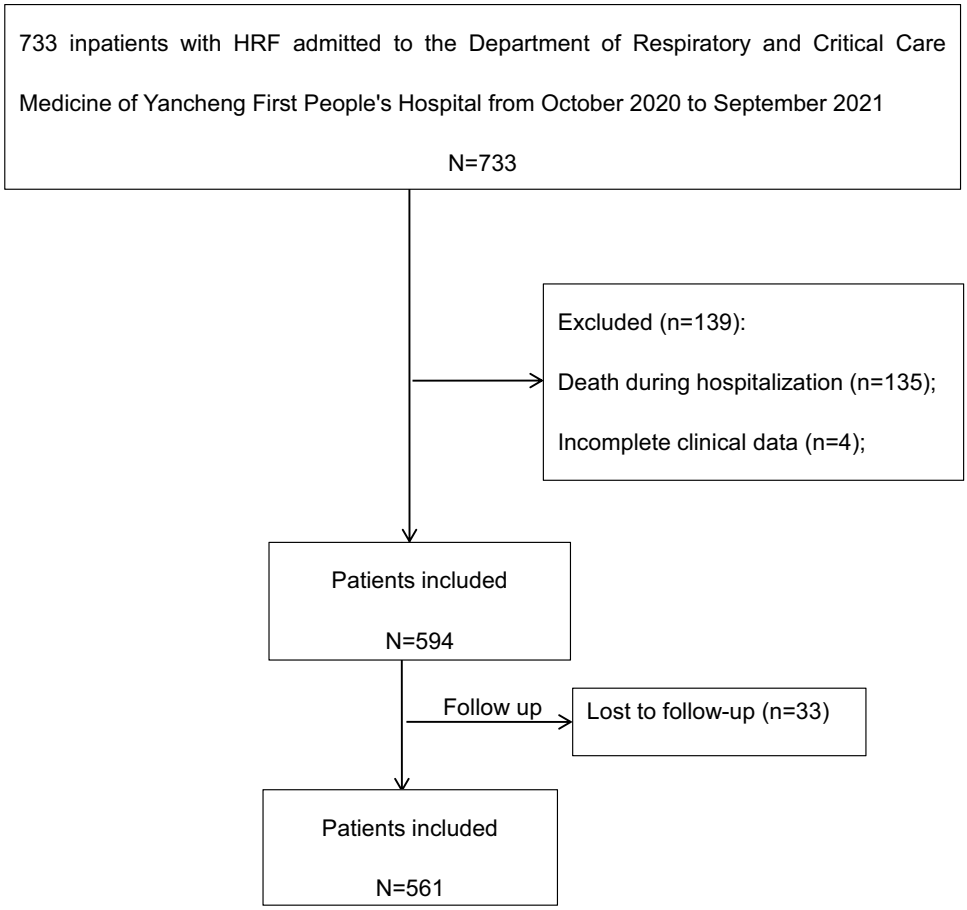

Figure 1 The flow diagram of sample selection in the study.

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Table 1 Baseline Characteristics of the Study Population

Variables	Total	The Level of NPAR			*P* value
		T1 (≤20.23)	T2 (20.23–23.85)	T3 (>23.85)	
No. of patients	561	187	187	187	
NPAR	22.35 ± 4.67	17.58 ± 2.10	21.95 ± 1.04	27.51 ± 3.23	**<0.001**
Age, year	73.16 ± 9.80	71.74 ± 9.89	73.04 ± 9.59	74.71 ± 9.73	**0.013**
Sex, n(%)					0.812
Female	204 (36.36)	71 (37.97)	65 (34.76)	68 (36.36)	
Male	357 (63.64)	116 (62.03)	122 (65.24)	119 (63.64)	
BMI, kg/m^2	22.25 ± 5.06	22.80 ± 4.84	22.39 ± 5.05	21.56 ± 5.24	0.054
Smoking status, n(%)	341 (60.78)	106 (56.68)	122 (65.24)	113 (60.43)	0.236
Comorbidities, n(%)					
Hypertension	218 (38.86)	74 (39.57)	73 (39.04)	71 (37.97)	0.949
Diabetes	83 (14.80)	29 (15.51)	21 (11.23)	33 (17.65)	0.205
Cerebrovascular disease	82 (14.62)	23 (12.30)	21 (11.23)	38 (20.32)	**0.025**
CVD	128 (22.82)	39 (20.86)	42 (22.46)	47 (25.13)	0.609
Chronic emphysema	464 (82.71)	162 (86.63)	157 (83.96)	145 (77.54)	0.058
Asthma	12 (2.14)	2 (1.07)	4 (2.14)	6 (3.21)	0.416
Interstitial lung disease	14 (2.50)	3 (1.60)	2 (1.07)	9 (4.81)	0.076
Pneumonia	114 (20.32)	13 (6.95)	36 (19.25)	65 (34.76)	**<0.001**
Scoring systems					
Braden scale	17.53 ± 3.67	19.10 ± 3.33	17.46 ± 3.50	16.03 ± 3.54	**<0.001**
Self-care score	54.58 ± 29.35	67.79 ± 24.69	55.89 ± 27.37	40.07 ± 29.08	**<0.001**
VTE score	3.00 ± 1.95	2.30 ± 1.83	3.11 ± 1.82	3.60 ± 1.99	**<0.001**
Laboratory parameters					
PaO_2, mmHg	47.49 ± 8.72	48.90 ± 8.70	47.10 ± 8.78	46.46 ± 8.52	**0.019**
$PaCO_2$, mmHg	70.47 ± 18.49	68.43 ± 19.74	71.09 ± 17.08	71.88 ± 18.48	0.168
WBC, 10^9/L	8.97 ± 4.90	6.96 ± 2.73	8.85 ± 4.03	11.10 ± 6.32	**<0.001**
Lymphocyte, 10^9/L	0.95 ± 0.57	1.29 ± 0.60	0.89 ± 0.48	0.66 ± 0.45	**<0.001**
Hemoglobin, g/L	132.21 ± 23.62	137.43 ± 19.28	134.63 ± 22.40	124.58 ± 26.73	**<0.001**
Platelet, 10^9/L	175.32 ± 73.72	173.68 ± 60.21	175.43 ± 72.21	176.84 ± 86.70	0.917
Neutrophil percentage, %	78.69 ± 11.49	68.63 ± 10.08	80.41 ± 8.39	87.04 ± 7.11	**<0.001**
Albumin, g/L	35.89 ± 4.76	39.09 ± 3.91	36.66 ± 3.73	31.93 ± 3.54	**<0.001**
Uric acid, umol/L	336.68 ± 155.16	327.98 ± 142.52	339.01 ± 138.21	343.04 ± 181.52	0.625
eGFR, $mL/min/1.73m^2$	75.81 ± 23.05	80.78 ± 18.69	75.58 ± 22.09	71.09 ± 26.75	**<0.001**
Triglyceride, mmol/L	1.12 ± 0.58	1.25 ± 0.64	1.06 ± 0.57	1.04 ± 0.49	**<0.001**
Total cholesterol, mmol/L	4.09 ± 1.08	4.44 ± 1.00	4.16 ± 1.06	3.67 ± 1.05	**<0.001**
Glucose, mmol/L	7.43 ± 3.06	7.38 ± 3.02	7.40 ± 2.96	7.53 ± 3.21	0.878
Outcomes, n(%)					
3-month mortality	95 (16.93)	11 (5.88)	30 (16.04)	54 (28.88)	**<0.001**
6-month mortality	130 (23.17)	20 (10.70)	42 (22.46)	68 (36.36)	**<0.001**
12-month mortality	187 (33.33)	38 (20.32)	60 (32.09)	89 (47.59)	**<0.001**
24-month mortality	266 (47.42)	62 (33.16)	92 (49.20)	112 (59.89)	**<0.001**

Note: Bold values indicate $P < 0.05$.

interstitial lung disease, $PaCO_2$, platelet count, blood uric acid, or glucose levels. Importantly, the 3-, 6-, 12-, and 24-month all-cause mortality rates were all higher in the T2 and T3 groups compared to the T1 group.

Relationship Between NPAR and All-Cause Mortality in HRF Patients

As shown in Figure 2, we used RCS modeling to assess the nonlinear relationship between NPAR and all-cause mortality of HRF patients. After adjusting for age, sex, BMI, smoking status, hypertension, diabetes, cerebrovascular diseases, cardiovascular diseases, chronic emphysema, asthma, interstitial lung disease, and pneumonia, the RCS model revealed a positive linear association between NPAR and all-cause mortality (P for overall association < 0.001; P for nonlinear association = 0.533).

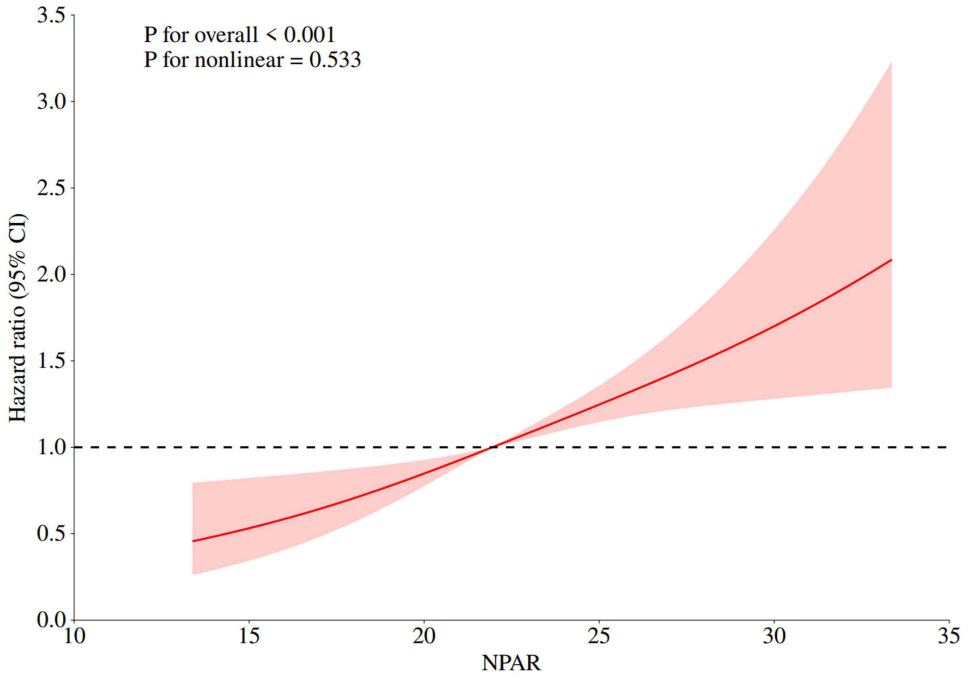

Figure 2 Nonlinear association between neutrophil-percentage-to-albumin ratio (NPAR) and HRF using restricted cubic spline (RCS) analysis. Hazard ratios were adjusted for age, sex, BMI, smoking status, hypertension, diabetes, cerebrovascular diseases, cardiovascular diseases, chronic emphysema, asthma, interstitial lung disease, and pneumonia.

To further investigate this relationship, three Cox proportional hazards models were constructed. Table 2 presents the hazard ratios (HRs) and 95% confidence intervals (CIs) for each model. After adjusting for age and sex (Model 2), and then for a broader range of covariates including BMI, smoking status, hypertension, diabetes, cerebrovascular diseases,

Table 2 Associations Between NPAR and Outcomes of HRF by Cox Regression Analysis

Variables	Model 1		Model 2		Model 3	
	HR (95%I)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
3-month mortality						
NPAR	1.15 (1.11 ~ 1.20)	**<0.001**	1.13 (1.08 ~ 1.18)	**<0.001**	1.12 (1.04 ~ 1.21)	**0.003**
NPAR Tertiles						
T1	1.00		1.00		1.00	
T2	2.89 (1.45 ~ 5.76)	**0.003**	2.71 (1.34 ~ 5.45)	**0.005**	2.43 (1.16 ~ 5.05)	**0.018**
T3	5.71 (2.99 ~ 10.93)	**<0.001**	4.30 (2.19 ~ 8.46)	**<0.001**	2.66 (1.14 ~ 6.20)	**0.023**
6-month mortality						
NPAR	1.14 (1.10 ~ 1.18)	**<0.001**	1.12 (1.08 ~ 1.16)	**<0.001**	1.11 (1.04 ~ 1.18)	**0.002**
NPAR Tertiles						
T1	1.00		1.00		1.00	
T2	2.27 (1.33 ~ 3.86)	**0.003**	2.10 (1.22 ~ 3.61)	**0.007**	1.84 (1.05 ~ 3.24)	**0.034**
T3	4.12 (2.50 ~ 6.79)	**<0.001**	3.26 (1.93 ~ 5.49)	**<0.001**	2.02 (1.04 ~ 3.93)	**0.038**
12-month mortality						
NPAR	1.11 (1.08 ~ 1.15)	**<0.001**	1.10 (1.06 ~ 1.13)	**<0.001**	1.11 (1.05 ~ 1.17)	**<0.001**
NPAR Tertiles						
T1	1.00		1.00		1.00	
T2	1.75 (1.16 ~ 2.62)	**0.007**	1.68 (1.12 ~ 2.54)	**0.013**	1.59 (1.03 ~ 2.47)	**0.038**
T3	3.02 (2.07 ~ 4.42)	**<0.001**	2.52 (1.69 ~ 3.76)	**<0.001**	1.84 (1.08 ~ 3.12)	**0.024**

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Table 2 (Continued).

Variables	Model 1		Model 2		Model 3	
	HR (95%I)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
24-month mortality						
NPAR	1.09 (1.06 ~ 1.12)	**<0.001**	1.08 (1.05 ~ 1.11)	**<0.001**	1.08 (1.03 ~ 1.12)	**<0.001**
NPAR Tertiles						
T1	1.00		1.00		1.00	
T2	1.70 (1.23 ~ 2.35)	**0.001**	1.71 (1.23 ~ 2.36)	**0.001**	1.65 (1.16 ~ 2.34)	**0.005**
T3	2.47 (1.81 ~ 3.37)	**<0.001**	2.28 (1.64 ~ 3.16)	**<0.001**	1.81 (1.17 ~ 2.79)	**0.007**

Notes: Bold values indicate $P < 0.05$. Model 1: unadjusted; Model 2: adjusted for age, sex; Model 3: adjusted for age, sex, BMI, smoking status, hypertension, diabetes, cerebrovascular diseases, CVD, chronic emphysema, asthma, interstitial lung disease, pneumonia, WBC, hemoglobin, platelet, albumin, triglyceride, uric acid, total cholesterol, eGFR, glucose.

cardiovascular diseases, chronic emphysema, asthma, interstitial lung disease, pneumonia, WBC count, hemoglobin, platelet count, albumin, triglycerides, uric acid, total cholesterol, eGFR, and glucose (Model 3), NPAR remained significantly associated with 24-month all-cause mortality (Model 2: HR 1.08, 95% CI 1.05–1.11; Model 3: HR 1.08, 95% CI 1.03–1.12). When NPAR was analyzed as a categorical variable (in tertiles), the fully adjusted Model 3 showed that patients in the T2 and T3 groups had significantly higher 24-month mortality risk compared to those in T1 (HR 1.65, 95% CI 1.16–2.34 and HR 1.81, 95% CI 1.17–2.79, respectively). Similar associations were observed for 3-, 6-, and 12-month mortality outcomes.

Using Kaplan–Meier survival curves (Figure 3), patients were stratified by NPAR tertiles to evaluate cumulative survival. The 24-month all-cause mortality rates were 33.16% in T1, 49.20% in T2, and 59.89% in T3, with significant differences across groups (log-rank $P < 0.001$). Additionally, statistically significant differences in 3-, 6-, and 12-month mortality rates were also observed among the tertiles (log-rank $P < 0.01$). In summary, higher NPAR levels were consistently associated with increased all-cause mortality.

Subgroup Analysis

We conducted subgroup analyses to further explore the association between NPAR and 3- and 24-month all-cause mortality among patients with HRF (Table 3). In most subgroups, elevated NPAR levels were consistently and significantly associated with an increased risk of both short- and long-term all-cause mortality. Importantly, no significant interactions were observed between NPAR and the stratifying variables, indicating that the association between NPAR and mortality remained robust across different patient populations. These findings provide additional support for the independent predictive value of NPAR in HRF.

ROC Curve Analysis

To further evaluate the predictive performance of NPAR, we conducted receiver operating characteristic (ROC) curve analysis, comparing NPAR with neutrophil percentage and albumin in predicting all-cause mortality in HRF patients (Table 4). For 3-month all-cause mortality, the AUC was 0.71 (95% CI, 0.66–0.77) for NPAR, which was significantly higher than that of neutrophil percentage (0.65, 95% CI, 0.59–0.71; $P < 0.05$) and not significantly different from albumin (0.67, 95% CI, 0.61–0.73; $P > 0.05$). For 12-month all-cause mortality, the AUC for NPAR was 0.66 (95% CI, 0.61–0.71), again exceeding that of neutrophil percentage and albumin, both of which had an AUC of 0.62 (95% CI, 0.57–0.67; $P < 0.05$). These results demonstrate that NPAR provides superior discriminatory ability compared to neutrophil percentage alone and offers better predictive accuracy than albumin at 12 months, highlighting its clinical utility as a composite prognostic marker in HRF patients.

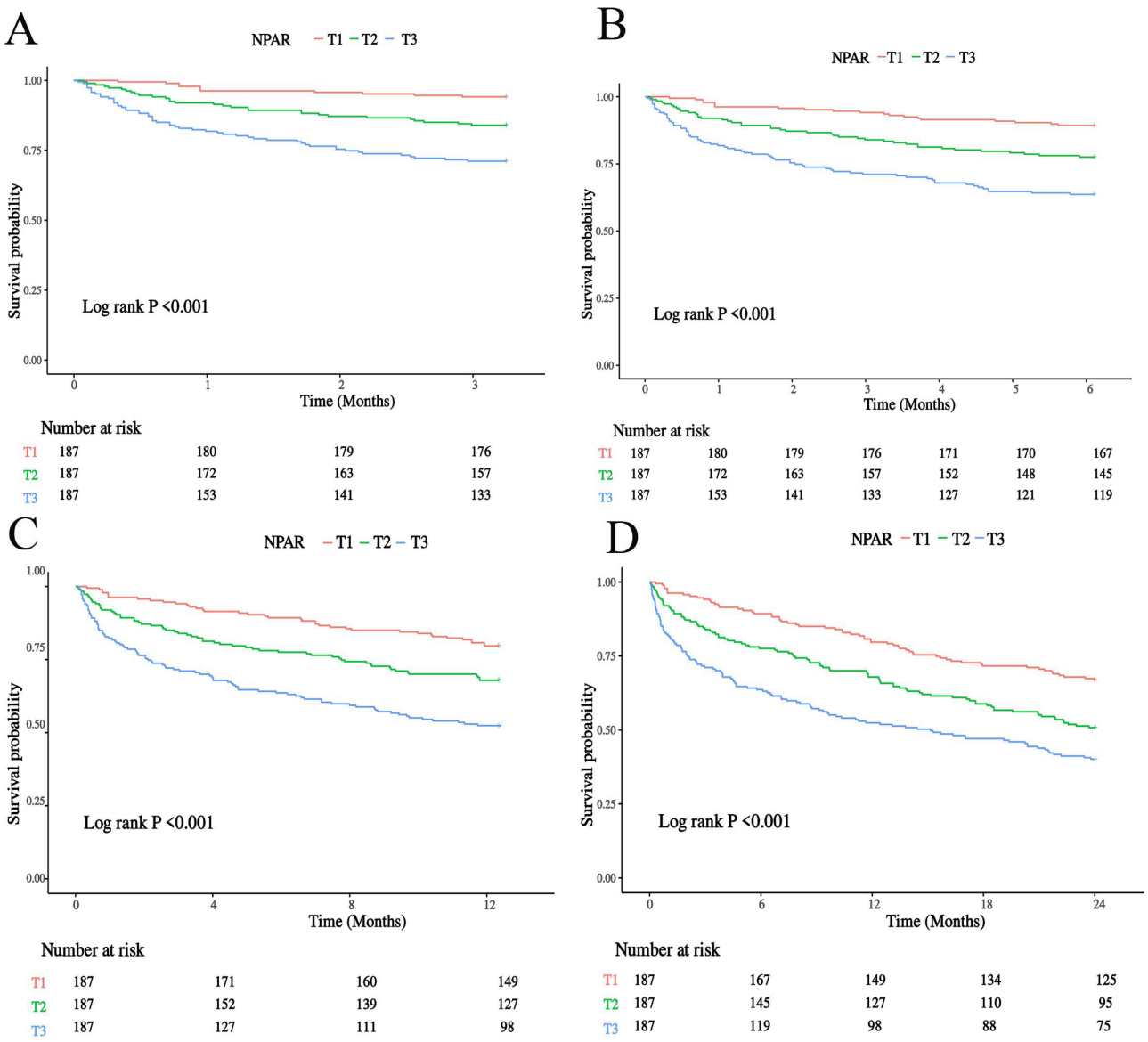

Figure 3 Kaplan-Meier curves for survival probability, with follow-up in months. (**A**) 3-month mortality; (**B**) 6-month mortality; (**C**) 12-month mortality; (**D**) 24-month mortality (NPAR: T1 (≤20.23), T2 (20.23–23.85), T3 (>23.85)).

Discussion

This study was the first to examine hypercapnic respiratory failure (HRF) as an independent clinical entity and to evaluate the prognostic significance of the neutrophil percentage-to-albumin ratio (NPAR) in this population. Our

Table 3 Subgroup Analysis of the Association Between NPAR and 3-Month and 24-Month All-Cause Mortality

Subgroups	3-Month All-Cause Mortality			24-Month All-Cause Mortality		
	HR (95% CI)	*P* value	*P* for Interaction	HR (95% CI)	*P* value	*P* for Interaction
Age, year			0.886			0.936
<74	1.15 (1.08 ~ 1.22)	**<0.001**		1.09 (1.05 ~ 1.13)	**<0.001**	
≥74	1.15 (1.10 ~ 1.21)	**<0.001**		1.09 (1.05 ~ 1.12)	**<0.001**	

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Table 3 (Continued).

Subgroups	3-Month All-Cause Mortality			24-Month All-Cause Mortality		
	HR (95% CI)	*P* value	*P* for Interaction	HR (95% CI)	*P* value	*P* for Interaction
Sex			0.368			0.529
Female	1.18 (1.11 ~ 1.26)	**<0.001**		1.07 (1.03 ~ 1.12)	**0.002**	
Male	1.14 (1.09 ~ 1.19)	**<0.001**		1.09 (1.06 ~ 1.13)	**<0.001**	
BMI, kg/m^2			0.186			0.298
<18.5	1.12 (1.05 ~ 1.20)	**<0.001**		1.09 (1.04 ~ 1.14)	**<0.001**	
18.5~23.9	1.16 (1.08 ~ 1.24)	**<0.001**		1.06 (1.02 ~ 1.11)	**0.004**	
24~27.9	1.13 (1.04 ~ 1.24)	**0.005**		1.09 (1.03 ~ 1.15)	**0.004**	
≥28	1.24 (1.12 ~ 1.38)	**<0.001**		1.15 (1.06 ~ 1.26)	**<0.001**	
Smoking status			0.480			0.612
No	1.17 (1.10 ~ 1.23)	**<0.001**		1.08 (1.04 ~ 1.12)	**<0.001**	
Yes	1.14 (1.08 ~ 1.20)	**<0.001**		1.10 (1.06 ~ 1.13)	**<0.001**	
Hypertension			0.025			0.663
No	1.12 (1.07 ~ 1.17)	**<0.001**		1.08 (1.05 ~ 1.11)	**<0.001**	
Yes	1.24 (1.15 ~ 1.34)	**<0.001**		1.10 (1.04 ~ 1.15)	**<0.001**	
Diabetes			0.412			0.204
No	1.14 (1.10 ~ 1.19)	**<0.001**		1.08 (1.05 ~ 1.11)	**<0.001**	
Yes	1.18 (1.08 ~ 1.29)	**<0.001**		1.12 (1.05 ~ 1.21)	**<0.001**	
Cerebrovascular disease			0.529			0.859
No	1.16 (1.11 ~ 1.21)	**<0.001**		1.09 (1.06 ~ 1.12)	**<0.001**	
Yes	1.12 (1.02 ~ 1.22)	**0.015**		1.09 (1.03 ~ 1.16)	**0.005**	
CVD			0.619			0.379
No	1.15 (1.09 ~ 1.20)	**<0.001**		1.08 (1.05 ~ 1.11)	**<0.001**	
Yes	1.16 (1.09 ~ 1.24)	**<0.001**		1.11 (1.05 ~ 1.16)	**<0.001**	
Pneumonia			0.180			0.401
No	1.16 (1.11 ~ 1.22)	**<0.001**		1.10 (1.06 ~ 1.13)	**<0.001**	
Yes	1.09 (1.01 ~ 1.17)	**0.032**		1.06 (1.00 ~ 1.12)	0.066	
Hemoglobin, g/L			0.463			0.141
<110	1.11 (1.03 ~ 1.21)	**0.009**		1.04 (0.99 ~ 1.10)	0.139	
≥110	1.16 (1.11 ~ 1.21)	**<0.001**		1.09 (1.06 ~ 1.13)	**<0.001**	
Neutrophil percentage, %			0.791			0.381
<75	1.16 (1.02 ~ 1.32)	**0.027**		1.06 (0.99 ~ 1.13)	0.085	
≥75	1.14 (1.09 ~ 1.19)	**<0.001**		1.09 (1.06 ~ 1.13)	**<0.001**	
Albumin, g/L			0.285			0.887
<35	1.11 (1.05 ~ 1.17)	**<0.001**		1.07 (1.03 ~ 1.11)	**<0.001**	
≥35	1.19 (1.06 ~ 1.34)	**0.004**		1.07 (1.02 ~ 1.13)	**0.012**	
eGFR, mL/min/1.73m^2			0.404			0.083
<90	1.16 (1.11 ~ 1.21)	**<0.001**		1.10 (1.07 ~ 1.14)	**<0.001**	
≥90	1.12 (1.04 ~ 1.21)	**0.003**		1.05 (1.00 ~ 1.10)	**0.048**	

Note: Bold values indicate $P < 0.05$.

Table 4 Comparisons of the AUCs of NPAR with Neutrophil Percentage and Albumin in Predicting All-Cause Mortality

Variables	HR (95% CI)	AUC	95% CI	*P* value
3-month mortality				
NPAR	1.15 (1.11 ~ 1.20)	0.71	0.66~0.77	Ref.
Neutrophil percentage	1.05 (1.03 ~ 1.07)	0.65	0.59~0.71	**0.009**
Albumin	0.89 (0.85 ~ 0.93)	0.67	0.61~0.73	0.120

(*Continued*)

Table 4 (Continued).

Variables	HR (95% CI)	AUC	95% CI	*P* value
6-month mortality				
NPAR	1.14 (1.10 ~ 1.18)	0.69	0.64~0.74	Ref.
Neutrophil percentage	1.04 (1.02 ~ 1.06)	0.64	0.59~0.69	**0.021**
Albumin	0.90 (0.87 ~ 0.94)	0.65	0.60~0.71	0.101
12-month mortality				
NPAR	1.11 (1.08 ~ 1.15)	0.66	0.61~0.71	Ref.
Neutrophil percentage	1.03 (1.02 ~ 1.05)	0.62	0.57~0.67	**0.031**
Albumin	0.92 (0.90 ~ 0.95)	0.62	0.57~0.67	**0.039**
24-month mortality				
NPAR	1.09 (1.06 ~ 1.12)	0.63	0.59~0.68	Ref.
Neutrophil percentage	1.02 (1.01 ~ 1.04)	0.59	0.55~0.64	**0.030**
Albumin	0.94 (0.91 ~ 0.96)	0.60	0.56~0.65	0.154

Note: Bold values indicate $P < 0.05$.

findings demonstrated that elevated NPAR levels were significantly associated with increased all-cause mortality at 3, 6, 12, and 24 months, even after adjusting for demographic and clinical confounders. These findings are consistent with prior studies that have established the prognostic value of NPAR in patients with chronic obstructive pulmonary disease (COPD), chronic kidney disease, and cardiovascular disease.[20–22]

The ROC analysis further confirmed that NPAR outperformed neutrophil percentage in predicting all-cause mortality at multiple time points, with statistically significant differences. This superior predictive ability is likely due to NPAR's dual capacity to reflect both acute systemic inflammation (via neutrophils) and nutritional status (via albumin). In contrast, neutrophil percentage alone captures only transient inflammatory activity. Neutrophils, which constitute a major component of white blood cells, play a critical role in mediating inflammatory responses.[23–25] As summarized by Wang et al, neutrophilic inflammation is a hallmark of COPD, a leading cause of HRF, and is frequently observed in both sputum and peripheral blood of these patients.[5,26] Therefore, neutrophils likely contribute significantly to the onset and progression of HRF.

Elevated NPAR values may result from increased neutrophil percentage, decreased albumin levels, or both. Although NPAR demonstrated numerically higher predictive accuracy than albumin at 3, 6, and 24 months, these differences did not reach statistical significance ($P > 0.05$). However, a significant difference was observed at 12 months, with NPAR showing greater discriminatory power than albumin (AUC 0.66 vs 0.62; $P = 0.039$), indicating its added prognostic value during intermediate-term follow-up. Hypoalbuminemia often reflects both malnutrition and systemic inflammation, and is associated with poor outcomes across a range of diseases, including cardiovascular disease, stroke, acute respiratory distress syndrome, and nonalcoholic steatohepatitis.[27–31] For example, a study involving 590 patients with acute exacerbation of COPD found that lower serum albumin levels were independently associated with prolonged hospital stays (OR 0.92, 95% CI 0.87–0.97).[32] Thus, NPAR effectively integrates two key prognostic components—inflammation and nutritional status—into a single composite indicator. A growing body of evidence supports the notion that NPAR outperforms either neutrophil percentage or albumin alone in predicting clinical outcomes.[33,34] While the prognostic value of NPAR has been established in other conditions, its application in HRF has not been previously explored, and this study helps to fill that gap in the literature.

Importantly, the clinical implications of our findings extend beyond statistical associations. In our fully adjusted model, a 1-unit increase in NPAR was associated with an 8% increase in 24-month mortality risk (adjusted HR 1.08, 95% CI 1.03–1.12). Moreover, patients in the highest NPAR tertile (T3) exhibited an 81% higher risk of 24-month mortality compared to those in the lowest tertile (T1) (HR 1.81, 95% CI 1.17–2.79). These findings suggested that NPAR may serve as a valuable tool for risk stratification in clinical practice. For patients with HRF, we propose that an NPAR threshold >23.85 could identify individuals at high risk, who may benefit from enhanced monitoring (eg, more frequent vital sign assessments, daily arterial blood gas analysis) and targeted interventions, such as anti-inflammatory therapy and

nutritional support (eg, albumin supplementation). Such measures may help reduce mortality and improve patient outcomes.

A major strength of this study lies in its prospective design and the inclusion of a relatively large cohort, which enhances the generalizability of our findings to similar clinical settings. In addition, we assessed multiple mortality endpoints (3-, 6-, 12-, and 24-month all-cause mortality), allowing for a comprehensive evaluation of NPAR's short- and long-term predictive performance. Stratifying patients into NPAR tertiles further clarified the dose-response relationship between NPAR and mortality risk in HRF. The tertile grouping more intuitively demonstrates that as the NPAR level increases, the survival probability gradually decreases.

However, several limitations should be acknowledged. First, although this was a prospective study, its observational design limits the ability to infer causality. Despite multivariable adjustments, residual confounding cannot be completely ruled out. Second, the study was conducted at a single center, which may introduce center-specific bias, though it also ensured standardized clinical management and data collection. Third, our dataset was limited in scope, and certain potentially relevant variables (eg, COPD severity, body composition, inflammatory cytokine levels) were not included. Future studies should consider integrating more comprehensive clinical, biochemical, and imaging data. Moreover, to minimize selection bias, future research should employ advanced techniques for handling missing data, such as multiple imputation by chained equations (MICE). We also encourage multicenter, large-scale prospective studies or integrate NPAR with other established predictors to develop comprehensive prognostic models in diverse HRF populations. Finally, mechanistic studies exploring how NPAR influences mortality—through interactions between neutrophil activity, albumin levels, and inflammatory signaling pathways—could uncover novel therapeutic targets. Evaluating the impact of anti-inflammatory strategies or nutritional supplementation in high-NPAR patients may also help define new therapeutic approaches.

Conclusions

In conclusion, our study demonstrates that NPAR is independently and positively associated with all-cause mortality at 3-, 6-, 12-, and 24-month all-cause mortality in HRF patients. As a biomarker that reflects both inflammatory and nutritional status, NPAR shows promise for clinical risk stratification. However, its current predictive performance remains limited and requires further refinement to enhance clinical applicability. Future research should focus on integrating NPAR with other established predictors to develop comprehensive prognostic models, thereby improving overall predictive accuracy and clinical utility.

Abbreviations

NPAR, neutrophil percentage-to-albumin ratio; HRF, hypercapnic respiratory failure; BMI, body mass index; CVD, cardiovascular disease; VTE, venous thromboembolism; PaO_2, arterial oxygen pressure; $PaCO_2$, arterial carbon dioxide pressure; WBC, white blood cell count; eGFR, estimated glomerular filtration rate; HR, hazard ratio; CI, confidence interval; AUC, area under the receiver operating characteristic curve.

Data Sharing Statement

The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

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 Committee of Yancheng First People's Hospital (Jiangsu, China) (Approval Number: 2020-K062). Informed consent was obtained from all participants prior to data collection.

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Author Contributions

All authors significantly contributed to the work, including its conception, design, data acquisition, analysis, and interpretation. They participated in drafting, revising, and critically reviewing the article. Each author approved the final version for publication, agreed on the target journal, and accepted accountability for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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