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ORIGINAL RESEARCH

The Neutrophil Percentage-to-Albumin Ratio is Associated with All-Cause Mortality in Patients with Atrial Fibrillation: A Retrospective Study

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Objective: The present study aimed to evaluate the relationship between all-cause mortality and the neutrophil percentage-to-albumin ratio (NPAR) in patients with atrial fibrillation (AF).

Methods: We obtained clinical information from patients with AF from the Medical Information Mart for Intensive Care-IV version 2.0 (MIMIC-IV) database and the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (WMU). The clinical endpoints were all-cause death measured at 30-day, 90-day, and one-year intervals. For endpoints associated with the NPAR, logistic regression models were used to calculate odds ratios (OR) with 95% confidence intervals (CI). Receiver operating characteristic (ROC) curves and area under the curve (AUC) were developed to compare the ability of different inflammatory biomarkers to predict 90-day mortality in patients with AF.

Results: Higher NPAR was associated with a higher risk of 30-day (OR 2.08, 95% CI 1.58–2.75), 90-day (OR 2.07, 95% CI 1.61–2.67), and one-year mortality (OR 1.60, 95% CI 1.26–2.04) in patients with AF in 2813 patients from MIMIC-IV. The predictive performance of NPAR (AUC = 0.609) for 90-day mortality was better than that of neutrophil-to-lymphocyte ratio (NLR) (AUC = 0.565, P < 0.001), and platelet-to-lymphocyte ratio (PLR) (AUC = 0.528, P < 0.001). When NPAR and sequential organ failure assessment (SOFA) were combined, the AUC increased from 0.609 to 0.674 (P < 0.001). Higher NPAR was associated with a higher risk of 30-day mortality (OR 2.54, 95% CI 1.02–6.30) and 90-day mortality (OR 2.76, 95% CI 1.09–7.01) in 283 patients from WMU.

Conclusion: An increased 30-day, 90-day, and one-year mortality risk among patients with AF were linked to a higher NPAR in MIMIC-IV. NPAR was thought to be a good predictor of 90-day all-cause mortality. Higher NPAR was associated with a higher risk of 30-day and 90-day mortality in WMU.

Keywords: atrial fibrillation, neutrophil percentage-to-albumin ratio, mortality, inflammatory biomarker

Introduction

Clinicians frequently encounter atrial fibrillation (AF) as the most common and widespread cardiac arrhythmia. AF is associated with high morbidity and mortality.[1] The global burden of AF has increased so rapidly in the last 20 years that disability-adjusted life years (DALYs) for AF have almost linearly increased, with its incidence and prevalence rising by 63% and 66% after 30 years.[2] Patients with AF experience longer periods of mechanical ventilation support, prolonged Intensive Care Unit (ICU) stays, and higher mortality than patients without AF.[3] Studies have indicated a causal association between sterile low-grade inflammation and the outcome of AF patients.[4–6]

Multiple studies have recently demonstrated that the neutrophil percentage-to-albumin ratio (NPAR) has a qualified predictive power for their prognosis in patients with cardiovascular events including acute myocardial infarction, coronary artery disease, heart failure, and cardiogenic shock.[7–10] The NPAR is a novel, integrated inflammatory

biomarker based on neutrophils and albumin. NPAR is currently thought to reflect inflammation levels accurately. The rising neutrophil is considered to have sinister prognostic implications and a factor in unfavorable outcomes because it plays a crucial role in the inflammatory response to injury.[11,12] As a negative acute phase reactant, albumin has an inverse relationship with oxidative stress and inflammation. A higher incidence of AF was associated with decreased albumin levels.[13]

Although NPAR is a reliable indicator of mortality in many diseases based on systemic inflammation, there is insufficient evidence that NPAR has predictive value for prognosis in AF patients. The present study aimed to explore the association between NPAR and mortality risk in patients with AF.

Materials and Methods

Data Source

We first extracted the data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, Version 2.0), an extensive, freely accessible database containing deidentified health-related information linked to a large number of patients residing in the ICU at the Beth Israel Deaconess Medical Center (Boston, MA) between 2008 and 2019.[14] The database includes demographic information, vital signs taken at the bedside, laboratory metrics, interventions, drugs, notes from caregivers, imaging, and mortality. The Institutional Review Boards (IRB) at Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology approved the project.

We also collected data from AF patients admitted to the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University (WMU) between June 1st, 2015 and December 31st, 2020. Personal information, disease course during hospitalization, laboratory reports, imaging examination results, treatments, and diagnoses were all stored in a non-public Electronic Medical Records System. The Medical Ethics Committee of WMU approved the current project (Approval number: 2021-K-71-01). The experiment did not affect clinical care, and all protected health information was deidentified. Therefore, informed consent was not required.

Study Subjects

Participants diagnosed with AF and admitted to ICU were selected for the present study. The diagnosis of AF was based on the International Classification of Diseases (ICD) codes (Table S1 in Supplementary Appendix). If a patient met one of the following criteria, they were excluded: (1) age under 16; (2) admitted and discharged from the ICU within 24 hours; (3) concurrently diagnosed with cancer or severe liver disease on admission; and (4) the first record of neutrophil percentage and serum albumin was missing. We only include the initial admission if a patient had more than one (Figure 1). Esophageal varices, gastric varices, hepatic encephalopathy, portal hypertension, hepatorenal syndrome, and hepatic failure were the most severe liver diseases (Table S2 in Supplementary Appendix).

Demographical and Laboratory Variables

The MIMIC-IV database was enquired for patient information using a structured query language. WMU data were derived from an electronic medical record. Population statistics, vital signs, comorbidities, laboratory tests, scoring system, pharmacological treatments and survival data were all extracted. Population statistics included age and gender. The vital signs of the patients included their heart rate, systolic and diastolic blood pressure, respiration rate, and temperature. Coronary artery disease, valvular disease, heart failure, hypertension, diabetes mellitus, and stroke were among the comorbidities. Albumin, creatinine, white blood cell, hemoglobin, neutrophil, platelet, and lymphocyte levels were all measured in the laboratory. Pharmacological treatments included anticoagulants, rate control drugs, and amiodarone. The sequential organ failure assessment score (SOFA) was used as the scoring tool. The variables mentioned above were extracted on the first day of admission. The initial measured value was used when there were multiple records for an indicator. Death after discharge was included in the Survival data (30-day, 90-day, and one-year mortality).

The NPAR was calculated by dividing the neutrophil percentage numerator serum albumin concentration. The neutrophil-to-lymphocyte ratio (NLR) was calculated using the absolute counts of neutrophils and lymphocytes. The platelet counts-to-lymphocyte counts ratio (PLR) was determined by dividing the total number of platelets by the total
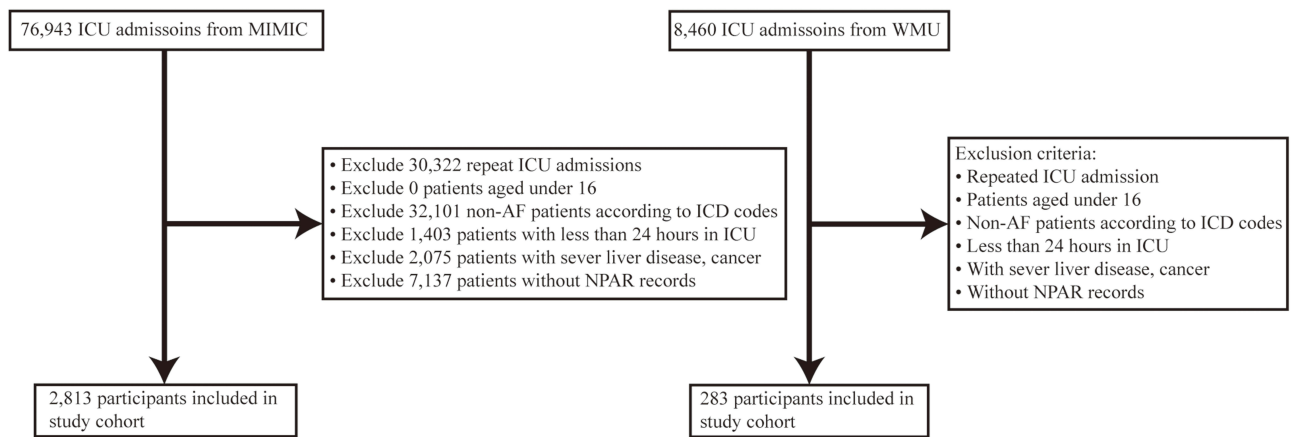
Figure 1 Flow chart of the study population.
Abbreviations: MIMIC, Medical Information Mart for Intensive Care IV; WMU, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University; ICU, intensive care unit; AF, atrial fibrillation; ICD, international classification of diseases; NPAR, neutrophil percentage-to-albumin ratio.

number of lymphocytes. The primary endpoint was 90-day mortality. In contrast, secondary outcomes were 30-day and one-year mortality.

Statistical Analysis

The study participants were divided into tertiles based on their NPAR value, ranging from small to large. Continuous variables were expressed as mean [standard deviation (SD)] or median [interquartile range (IQR)]. In contrast, categorical variables were expressed as count and proportion. Logistic regression models were developed to investigate the relationship between NPAR and each outcome. NPAR was considered both a continuous and a categorical variable. The first tertile group of the NPAR was selected as the reference group, and the results were presented as an odds ratio (OR) with 95% confidence intervals (CIs). Each covariate was added to the model one by one. If factors influenced NPAR estimates of all-cause mortality by more than 10% or were significantly related to all-cause mortality, they were included as potential confounders in the final models. Age, gender, heart failure, hypertension, stroke, temperature, respiration rate, systolic and diastolic blood pressure, white blood cell, lymphocyte, hemoglobin, creatinine, SOFA score, anticoagulant, rate control drugs and amiodarone were all predetermined and assessed based on available connections or plausible biological relationships. Subgroup analyses were performed to confirm the independent effect of NPAR on 90-day mortality and their interactions. Receiver Operating Characteristic (ROC) curve was used to compare the predictive value of different inflammatory biomarkers for 90-day mortality. The area under the curve (AUC) with corresponding 95% CIs for the anticipated survival was calculated to estimate the predictive performance. To determine the best risk prediction indicator, compare the AUCs of different models (NPAR, NLR, PLR, SOFA, SOFA plus NPAR).

All statistical analyses were performed using R software version 3.4.3. $P < 0.05$ was considered statistically significant.

Results

Subject Characteristics

After screenings, the presented study included 2813 MIMIC-IV patients with AF and 283 WMU patients. The baseline characteristics were classified according to NPAR tertiles (Table 1). In MIMIC-IV, there were 937 patients in tertile I (<22.8), 938 patients in tertile II (22.8–28.4), and 938 patients in tertile III (≥28.4). There were 1217 females and 1596 males among these patients. Patients in the high tertile had lower systolic and diastolic blood pressure, lymphocyte, hemoglobin, and albumin levels and a higher heart rate, respiration rate, NLR, PLR, white blood cell, neutrophil, platelet, and SOFA score. There were 102 patients in tertile I, 97 in tertile II, and 84 in tertile III at WMU. Fewer patients in the higher NPAR group had coronary artery disease, valvular disease, hypertension, lymphocyte, hemoglobin, and albumin.

Table 1 Baseline Characteristics of Participants

Characteristics	MIMIC Cohort			WMU Cohort		
	NPAR			NPAR		
	<22.8	22.8–28.4	≥28.4	<22.8	22.8–28.4	≥28.4
Number	937	938	938	102	97	84
Age, mean (SD), years	74.4 (12.4)	75.4 (11.9)	74.1 (12.6)	74.9 (9.4)	78.0 (10.7)	79.8 (9.0)
Gender, n (%)						
Female	387 (41.3)	405 (43.2)	425 (45.3)	45 (44.1)	33 (34.0)	37 (44.0)
Male	550 (58.7)	533 (56.8)	513 (54.7)	57 (55.9)	64 (66.0)	47 (56.0)
Comorbidities, n (%)						
Coronary artery disease	372 (39.7)	372 (39.7)	344 (36.7)	24 (23.5)	22 (22.7)	16 (19.0)
Valvular disease	132 (14.1)	129 (13.8)	133 (14.2)	48 (47.1)	40 (41.2)	31 (36.9)
Heart failure	538 (57.4)	605 (64.5)	533 (56.8)	40 (39.2)	32 (33.0)	36 (42.9)
Hypertension	357 (38.1)	351 (37.4)	380 (40.5)	78 (76.5)	63 (64.9)	58 (69.0)
Diabetes mellitus	347 (37.0)	394 (42.0)	371 (39.6)	30 (29.4)	31 (32.0)	24 (28.6)
Stroke	64 (6.8)	57 (6.1)	57 (6.1)	44 (43.1)	55 (56.7)	44 (52.4)
Vital signs						
Temperature, °C	36.8 (0.6)	36.8 (0.6)	36.8 (0.6)	36.8 (0.8)	37.0 (1.0)	37.0 (1.1)
Heart rate, beats/min	85.4 (17.4)	88.6 (18.4)	91.0 (17.8)	97.7 (29.7)	105.4 (28.4)	105.7 (27.5)
Respiration rate, beats/min	20.1 (3.6)	20.7 (3.9)	20.9 (4.2)	20.7 (4.5)	22.5 (7.0)	21.8 (5.7)
Systolic blood pressure, mmHg	116.4 (16.2)	113.9 (15.8)	110.7 (13.5)	140.8 (24.1)	137.6 (28.7)	132.0 (32.4)
Diastolic blood pressure, mmHg	62.8 (11.4)	61.4 (10.4)	59.1 (9.5)	81.8 (15.9)	77.1 (14.4)	72.9 (18.1)
Compound biomarkers						
NPAR	19.3 (3.0)	25.4 (1.6)	34.4 (6.5)	19.3 (2.8)	25.3 (1.6)	33.2 (5.6)
NLR	5.4 (3.2–9.3)	11.4 (7.1–19.1)	15.5 (9.5–28.7)	4.9 (3.0–8.1)	11.1 (7.5–18.7)	18.8 (11.8–33.1)
PLR	157.1 (101.4–236.1)	235.5 (149.2–371.3)	279.4 (169.7–467.8)	137.2 (114.0–201.5)	228.9 (161.5–337.5)	289.7 (181.6–650.7)
Laboratory parameters						
White blood cell, 10⁹/L	11.3 (6.4)	13.6 (6.8)	14.4 16.0 (8.4)	9.0 (4.6)	11.1 (4.7)	13.6 (7.0)
Neutrophil, %	71.9 (13.7)	83.1 (7.7)	86.1 (6.7)	74.8 (11.5)	85.8 (5.8)	89.9 (5.4)
Lymphocyte, %	15.9 (10.2)	8.5 (5.4)	6.5 (4.4)	17.3 (10.0)	8.0 (4.4)	5.4 (4.2)
Hemoglobin, g/dl	11.5 (2.4)	10.9 (2.3)	10.1 (2.1)	13.2 (2.0)	11.8 (2.4)	10.9 (2.5)
Platelet, 10⁹/L	218.8 (105.7)	223.8 (116.8)	238.4 (137.8)	188.6 (76.3)	169.3 (63.2)	176.2 (88.2)
Albumin, g/dl	3.7 (0.5)	3.3 (0.3)	2.6 (0.4)	3.9 (0.5)	3.4 (0.3)	2.8 (0.3)
Creatinine, mg/dl	1.3 (0.9–2.1)	1.5 (1.0–2.4)	1.4 (0.9–2.5)	0.9 (0.7–1.2)	0.97 (0.7–1.5)	1.1 (0.8–1.7)
Scoring system						
SOFA score	6.0 (4.0–9.0)	7.0 (4.0–10.0)	8.0 (5.0–11.0)	5.0 (2.0–8.0)	7.5 (5.0–12.0)	10.0 (6.8–12.2)
Pharmacological treatments						
Anticoagulant[a]	568 (60.6)	573 (61.1)	587 (62.6)	44 (43.1)	37 (38.1)	31 (36.9)
Rate control drugs[b]	387 (41.3)	346 (36.9)	389 (41.5)	46 (45.1)	28 (28.9)	29 (34.5)
Amiodarone	178 (19.0)	171 (18.2)	205 (21.9)	25 (24.5)	28 (28.9)	28 (33.3)
Outcomes						
30-day mortality, n (%)	182 (19.4)	240 (25.6)	339 (36.1)	40 (39.2)	58 (59.8)	63 (75.0)
90-day mortality, n (%)	255 (27.2)	335 (35.7)	440 (46.9)	41 (40.2)	61 (62.9)	66 (78.6)
One-year mortality, n (%)	392 (41.8)	449 (47.9)	530 (56.5)	47 (48.0)	64 (69.6)	69 (82.1)

Notes: Data were presented as n (%), mean (SD) and median (IQR). [a]Anticoagulant contains enoxaparin, heparin and warfarin. [b]Rate control drugs contains metoprolol, esmolol, diltiazem and digoxin.
Abbreviations: SD, standard deviation; IQR, interquartile range; MIMIC, Medical Information Mart for Intensive Care; WMU, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University; NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SOFA, sequential organ failure assessment.

Patients had higher age, heart rate, NLR, PLR, white blood cell, neutrophil, and SOFA core. Both cohorts indicated that patients with higher tertile had higher 30-day, 90-day, and one-year mortality rates.

Associations Between NPAR and Mortality

Multiple analyses were performed to investigate the association between NPAR and all-cause mortality in AF patients (Table 2). When considered as a continuous variable, higher NPAR was significantly correlated with 30-day, 90-day, and one-year mortality in all MIMIV-IV models. We used tertile I as the reference group when dividing into tertiles. Higher NPAR was

Table 2 Association Between NPAR and All-Cause Mortality in MIMIC Cohort

	Non-Adjusted OR (95% CIs)	P value	Model I OR (95% CIs)	P value	Model II OR (95% CIs)	P value
30-day mortality						
NPAR	1.05 (1.04, 1.06)	<0.001	1.05 (1.04, 1.07)	<0.001	1.05 (1.03, 1.06)	<0.001
NPAR tertiles						
<22.8	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
22.8–28.4	1.43 (1.15, 1.77)	<0.001	1.40 (1.12, 1.75)	0.003	1.29 (1.00, 1.67)	0.055
≥28.4	2.35 (1.90, 2.90)	<0.001	2.43 (1.96, 3.00)	<0.001	2.08 (1.58, 2.75)	<0.001
90-day mortality						
NPAR	1.06 (1.05, 1.07)	<0.001	1.06 (1.05, 1.07)	<0.001	1.06 (1.04, 1.07)	<0.001
NPAR tertiles						
<22.8	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
22.8–28.4	1.49 (1.22, 1.81)	<0.001	1.46 (1.20, 1.79)	<0.001	1.32 (1.05, 1.67)	0.020
≥28.4	2.36 (1.95, 2.87)	<0.001	2.49 (2.04, 3.04)	<0.001	2.07 (1.61, 2.67)	<0.001
One-year mortality						
NPAR	1.04 (1.03, 1.05)	<0.001	1.05 (1.04, 1.06)	<0.001	1.05 (1.03, 1.06)	<0.001
NPAR tertiles						
<22.8	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
22.8–28.4	1.28 (1.06, 1.53)	0.009	1.25 (1.04, 1.51)	0.020	1.15 (0.93, 1.44)	0.197
≥28.4	1.81 (1.50, 2.17)	<0.001	1.90 (1.57, 2.29)	<0.001	1.60 (1.26, 2.04)	<0.001

Notes: Models were all derived from logistic regression models. Non-adjusted model adjusted for none. Model I adjusted for age and gender. Model II adjusted for age, gender, heart failure, hypertension, stroke, temperature, respiration rate, systolic blood pressure, diastolic blood pressure, white blood cell, lymphocyte, hemoglobin, creatinine, SOFA score, anticoagulant, rate control drugs and amiodarone.
Abbreviations: MIMIC, Medical Information Mart for Intensive Care; NPAR, neutrophil percentage-to-albumin ratio; OR, odds ratio; CI, confidence interval; Ref, reference; SOFA, sequential organ failure assessment.

associated with 30-day mortality (OR 2.43, 95% CI 1.96–3.00), 90-day mortality (OR 2.49, 95% CI 2.04–3.04), and one-year mortality (OR 1.90, 95% CI 1.57–2.29) in Model I after adjusting for gender and age. In model II, higher NPAR was linked to higher 30-day (OR, 95% CI: 2.08, 1.58–2.75), 90-day (OR, 95% CI: 2.07, 1.61–2.67), and one-year all-cause mortality (OR, 95% CI: 1.60, 1.26–2.04) after adjusting for age, gender, heart failure, hypertension, stroke, temperature, respiration rate, systolic and diastolic blood pressure, white blood cell, lymphocyte, hemoglobin, creatinine, SOFA score, anticoagulant, rate control drugs and amiodarone. After total adjustment in Model II, higher NPAR was significantly associated with 30-day and 90-day mortality in WMU (OR, 95% CI: 2.54, 1.02–6.30; 2.76, 1.09–7.01) (Table 3).

Table 3 Association Between NPAR and All-Cause Mortality in WMU Cohort

	Non-Adjusted OR (95% CIs)	P value	Model I OR (95% CIs)	P value	Model II OR (95% CIs)	P value
30-day mortality						
NPAR	1.14 (1.09, 1.19)	<0.001	1.13 (1.08, 1.19)	<0.001	1.11 (1.03, 1.19)	0.005
NPAR tertiles						
<22.8	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
22.8–28.4	2.31 (1.31, 4.07)	0.004	2.18 (1.23, 3.88)	0.008	1.35 (0.63, 2.87)	0.445
≥28.4	4.65 (2.47, 8.77)	<0.001	4.38 (2.30, 8.33)	<0.001	2.54 (1.02, 6.30)	0.044
90-day mortality						
NPAR	1.15 (1.10, 1.21)	<0.001	1.15 (1.09, 1.21)	<0.001	1.11 (1.03, 1.19)	0.007
NPAR tertiles						
<22.8	1.0 (ref.)		1.0 (ref.)		1.0 (ref.)	
22.8–28.4	2.52 (1.42, 4.46)	0.002	2.42 (1.36, 4.31)	0.003	1.38 (0.64, 2.97)	0.409
≥28.4	5.46 (2.84, 10.50)	<0.001	5.17 (2.66, 10.04)	<0.001	2.76 (1.09, 7.01)	0.033

Notes: Models were all derived from Logistic regression models. Non-adjusted model adjusted for none. Model I adjusted for age and gender. Model II adjusted for age, gender, stroke, white blood cell, lymphocyte, hemoglobin, creatinine, anticoagulant, rate control drugs and amiodarone.
Abbreviations: WMU, The Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University; NPAR, neutrophil percentage-to-albumin ratio; OR, odds ratio; CI, confidence interval; Ref, reference.

Subgroup Analysis

In subgroup analyses, this positive effect of NPAR on 90-day mortality was evident in all subgroups studied and after careful adjustments. No discernible interaction confirmed the independent association between NPAR and the risk of 90-day mortality in MIMIC-IV (Figure 2).

Predictive Performance of NPAR

We performed ROC analysis to predict the 90-day all-cause mortality of NPAR in MIMIC-IV (Figure 3). The AUC of PLR, NLR, NPAR, and SOFA for 90-day mortality was 0.528, 0.565, 0.609, and 0.652 respectively (Table 4). NPAR was superior to PLR or NLR alone (P < 0.001) but inferior to SOFA (P = 0.003) compared to the respective AUCs. When SOFA and NPAR were combined, prediction power was significantly higher than SOFA alone (0.674 vs 0.652, P < 0.001).

Discussion

Even after correcting for potential confounding factors, the present study found that NPAR was independently associated with death at 30-day, 90-day, and one-year mortality in patients with AF. ROC curves indicated that NPAR had a moderate ability to predict 90-day mortality in ICU patients with AF. The subgroup analysis revealed no clear interaction in all subgroups. This positive effect was evident in all subgroups studied and after careful adjustments.

The remodeling of the atria causes connective tissue, deposition, fibroblast activation, inflammation, fibrosis, and dilatation, all of which induce AF. This procedure modifies the conduction channels of atria, enabling targeted reentry of electrical impulses. AF promotes this situation, which may help to explain the phenomenon that AF breeds AF.[15] Acute events during severe illness rapidly produce the sensitive atrial stroma, opening up the potential for developing AF in response to several critical arrhythmic triggers.[16] Systemic inflammatory responses and other events can set off AF in critically ill patients. The direct arrhythmogenic impact of inflammatory cytokines on the atrial myocardium has been associated with the onset of AF.[17–20] Inflammation may contribute to the development of arrhythmias because atrial myocytes are affected by inflammatory cell infiltration and oxidative damage.[21,22] As mentioned previously,

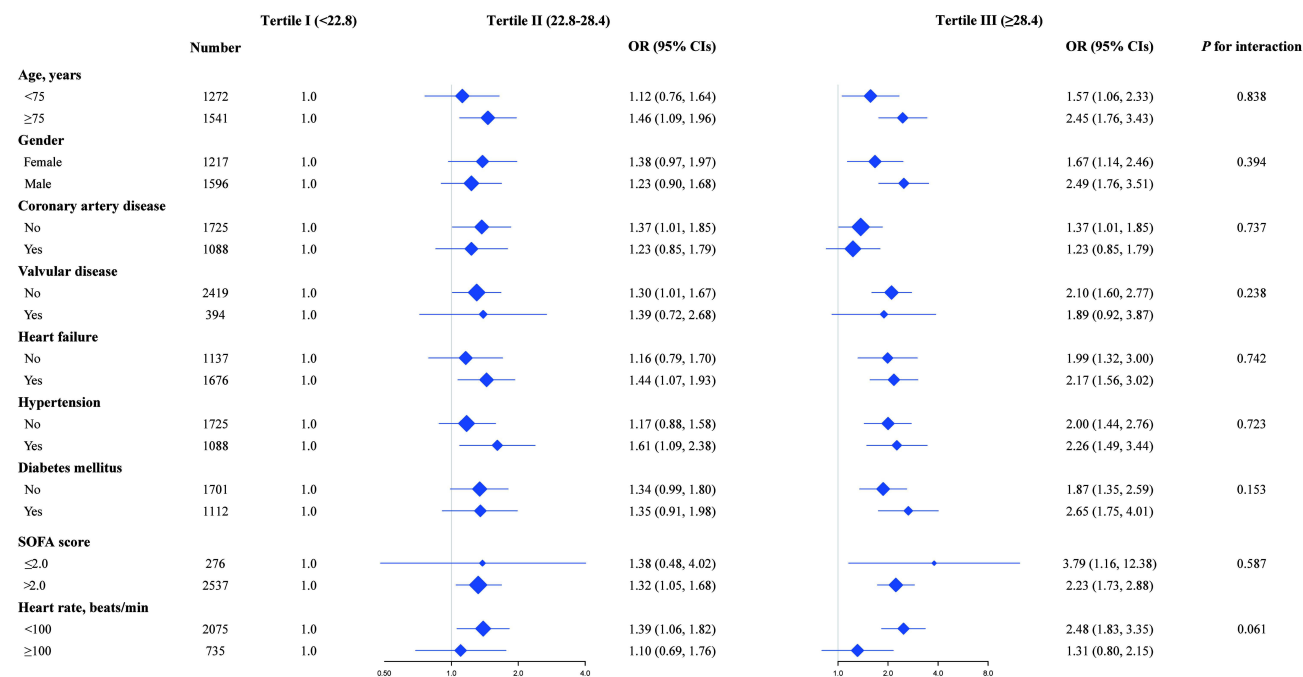|	Number	Tertile I (<22.8)	Tertile II (22.8-28.4) OR (95% CIs)		Tertile III (≥28.4) OR (95% CIs)		P for interaction
Age, years							
<75	1272	1.0	1.12 (0.76, 1.64)		1.57 (1.06, 2.33)		0.838
≥75	1541	1.0	1.46 (1.09, 1.96)		2.45 (1.76, 3.43)		
Gender							
Female	1217	1.0	1.38 (0.97, 1.97)		1.67 (1.14, 2.46)		0.394
Male	1596	1.0	1.23 (0.90, 1.68)		2.49 (1.76, 3.51)		
Coronary artery disease							
No	1725	1.0	1.37 (1.01, 1.85)		1.37 (1.01, 1.85)		0.737
Yes	1088	1.0	1.23 (0.85, 1.79)		1.23 (0.85, 1.79)		
Valvular disease							
No	2419	1.0	1.30 (1.01, 1.67)		2.10 (1.60, 2.77)		0.238
Yes	394	1.0	1.39 (0.72, 2.68)		1.89 (0.92, 3.87)		
Heart failure							
No	1137	1.0	1.16 (0.79, 1.70)		1.99 (1.32, 3.00)		0.742
Yes	1676	1.0	1.44 (1.07, 1.93)		2.17 (1.56, 3.02)		
Hypertension							
No	1725	1.0	1.17 (0.88, 1.58)		2.00 (1.44, 2.76)		0.723
Yes	1088	1.0	1.61 (1.09, 2.38)		2.26 (1.49, 3.44)		
Diabetes mellitus							
No	1701	1.0	1.34 (0.99, 1.80)		1.87 (1.35, 2.59)		0.153
Yes	1112	1.0	1.35 (0.91, 1.98)		2.65 (1.75, 4.01)		
SOFA score							
≤2.0	276	1.0	1.38 (0.48, 4.02)		3.79 (1.16, 12.38)		0.587
>2.0	2537	1.0	1.32 (1.05, 1.68)		2.23 (1.73, 2.88)		
Heart rate, beats/min							
<100	2075	1.0	1.39 (1.06, 1.82)		2.48 (1.83, 3.35)		0.061
≥100	735	1.0	1.10 (0.69, 1.76)		1.31 (0.80, 2.15)		

Figure 2 Subgroup analysis of the association between NPAR and 90-day mortality Logistic regression models were used to calculate OR with 95% CIs. Plots showed adjusted ORs for high versus low NPAR tertile for 90-day mortality in different patient subgroups, tertile I was set as the reference group. Each stratification adjusted for age, gender, heart failure, hypertension, stroke, temperature, respiration rate, systolic blood pressure, diastolic blood pressure, white blood cell, lymphocyte, hemoglobin, creatinine, and SOFA score except for the stratification factor itself.
Abbreviations: OR, odds ratio; CI, confidence interval; NPAR, neutrophil percentage-to-albumin ratio; SOFA, sequential organ failure assessment.
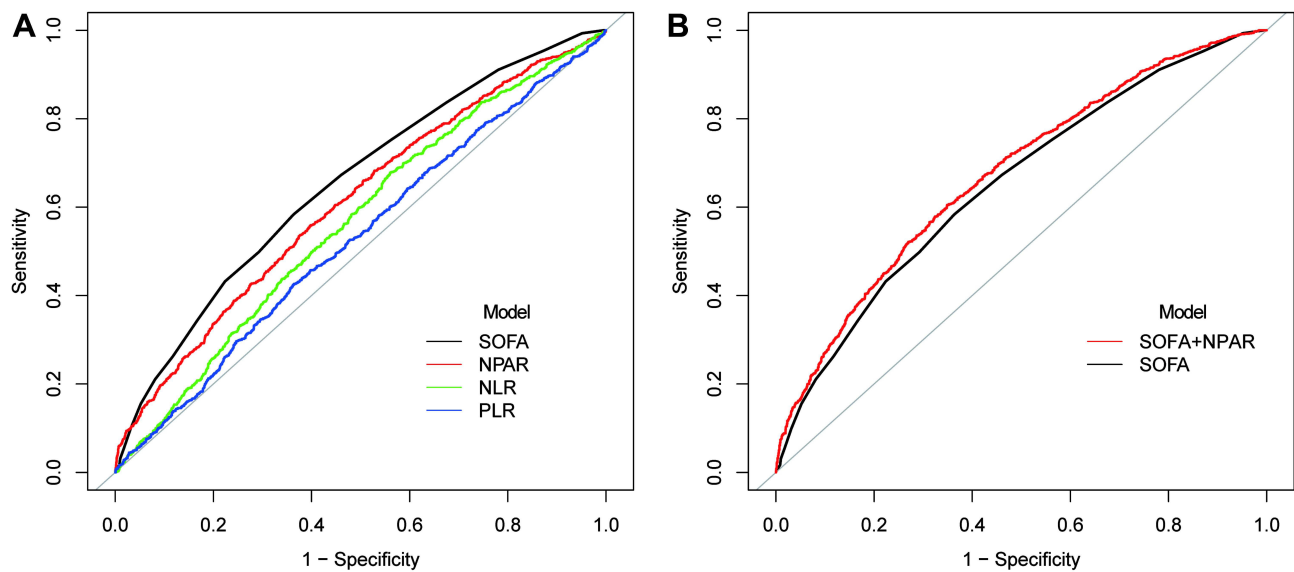
Figure 3 ROC analysis for the prediction of 90-day mortality (**A**) Comparisons of ROC curves of different models; (**B**) ROC curves of SOFA and SOFA plus NPAR for 90-day mortality.
Abbreviations: ROC, receiver operating characteristic; NPAR, neutrophil percentage-to-albumin ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SOFA, sequential organ failure assessment.

inflammation is crucial to the development of AF, whether or not it is accompanied by concurrent infection. Higher inflammatory markers have been linked to an increased risk of developing AF in patients with sepsis and those who have just undergone surgery.[23] Earlier research suggests anti-inflammatory drugs like glucocorticoids and statins may reduce the risk of developing AF.[24] Patients with AF with low-grade inflammation and elevated serum proinflammatory cytokines may experience inflammation through various mechanisms.[25]

Neutrophils are one of the most well-known cellular effectors and have been crucial in mediating inflammatory responses as a vital component of white blood cells.[26,27] Regarding the general populace and several pathological situations, hypoalbuminemia is a powerful prognostic marker, primarily as an indicator of malnutrition and inflammation.[28,29] Low serum albumin levels are associated with various cardiovascular diseases including AF, venous thromboembolism, stroke, and ischemic heart disease.[30–32] The NPAR computation exacerbates variations in these two indicators because they are a mixture of two inflammatory markers.

NLR and PLR were both composite inflammatory markers that were shown to predict the outcomes of AF patients.[33,34] The findings of present study revealed that NPAR was not only a reliable indicator of all-cause death, but it also had a limited ability to predict the 90-day mortality of ICU patients with AF. It was worth noting that while the AUC of NPAR was smaller than that of SOFA, the predictive ability improved with the addition of NPAR. At least it served as a reminder that NPAR might be able to help direct our therapeutic practice in situations where the SOFA score

Table 4 Predictive Performance of Inflammatory Biomarkers and SOFA Score for 90-Day Mortality

Model	AUC	95% CIs	P value
NPAR	0.609	0.587, 0.630	Ref.
PLR	0.528	0.506, 0.550	<0.001
NLR	0.565	0.544, 0.587	<0.001
SOFA	0.652	0.631, 0.672	0.003
SOFA+NPAR	0.674	0.654, 0.695	<0.001

Abbreviations: AUC, area under curve; CI, confidence interval; Ref, reference; NPAR, neutrophil percentage-to-albumin ratio; PLR, platelet-to-lymphocyte ratio; NLR, neutrophil-to-lymphocyte ratio; SOFA, sequential organ failure assessment.

cannot be calculated. Expecting NPAR to be as effective as more established classic scores like SOFA was unrealistic. Despite the difficulty of calculating SOFA scores, NPAR may be clinically valuable for critically ill patients with AF because of its availability, affordability, simplicity, and ability to predict mortality.

The present study had some strengths. First, it is the first and largest retrospective study of NPAR in AF patients using two data sources. We could conclude from the large study population that the link between AF and death was not simply due to a more severe illness among AF patients. Second, we identified that NPAR better predicted mortality than NLR or PLR, indicating that it should be used in clinical work.

There were several limitations of the present study. First, our findings were drawn from AF patients and cannot be extrapolated to other populations. Second, the sample size of WMU was small, which may influence its statistical effectiveness. Third, more key variables are generally required to control confounding factors, but some relevant clinical factors such as C-reactive protein were either unavailable or only infrequently present (Table S3 in Supplementary Appendix). When CRP was included in Multiple analyses as a confounding factor, the final results were similar to the present study (Tables S4 and S5 in Supplementary Appendix). So lacking CRP did not affect our conclusions. Fourth, while logistic regression analysis successfully balanced many covariates, variables that could affect mortality and AF risk were not investigated in the present study. Furthermore, due to the lack of albumin data, the sample size of the present study was significantly reduced. Finally, because it was challenging to distinguish whether one person had a previous history of AF or a new onset when we chose the research sample, our conclusion may not apply to both sides due to potential differences in the pathophysiological process and treatment. Well-designed randomized controlled trials would be ideal for validating the study's findings. Considering the predictive ability of NPAR demonstrated in the present study, it was worthwhile to develop a multivariable model or scoring system that included NPAR, to predict AF patients' prognoses.

Conclusions

The present study revealed that NPAR was independently associated with mortality in patients with AF from MIMIC-IV, including 30-day, 90-day, and one-year all-cause mortality. Moreover, NPAR was a reliable predictor of 90-day all-cause mortality. Meanwhile, NPAR was associated with 30-day and 90-day mortality in WMU patients with AF. As an inflammatory biomarker, NPAR could help clinicians determine the prognosis of patients with AF earlier and more effectively, as well as immediate treatment.

Data Sharing Statement

The corresponding author will provide the datasets used and analyzed during the current work upon reasonable request.

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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.

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Disclosure

The authors declare that they have no competing interests.

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