Balkan Med J 2025;42:222-32

Prognostic Significance of Red Blood Cell Distribution Width-to-Albumin Ratio in Predicting 1-Year Mortality for Critically Ill Chronic Obstructive Pulmonary Disease Patients

Wei Zhao, Yongli Liu, Chenyang Hu, Yuxin Zhang, Yajie Hu, Yiqing Qu,

Clinic of Pulmonary and Critical Care Medicine, Qilu Hospital of Shandong University, Jinan, China

Background: Chronic obstructive pulmonary disease (COPD) is a major global healthcare challenge. To address the gap in existing prognostic research, this study examined the possibility of the red blood cell distribution width-albumin ratio (RAR) as a viable biomarker for predicting COPD outcomes.

Aims: To evaluate the relationship between RAR and the one-year mortality risk in COPD patients.

Study Design: A retrospective cohort study.

Methods: Participants were grouped based on their RAR levels. Multiple interpolations were used to address missing data. The effect of biomarkers on mortality was estimated using Kaplan-Meier survival curves and Cox risk regression models. Stratified analyses were conducted to assess the consistency of the RAR's predictive value for mortality across different subgroups. RAR was used to build a predictive model and the C-index and time-dependent receiver operating characteristic curves were used to evaluate the model's performance.

Results: This study examined 2,379 patients, dividing them into three groups based on their RAR levels. According to Cox regression, RAR was correlated with the 1-year all-cause mortality of patients [model 3: HR = 1.24 (95% confidence interval 1.19-1.29) $p < 0.001$], with consistent positive correlations between subgroups. This relationship was shown to be linear via the restricted cubic spline. RAR had been demonstrated to be a potentially more effective biomarker than albumin and red blood cell distribution width for determining the one-year mortality risk in COPD patients.

Conclusion: A significant association was found between RAR and the one-year mortality of COPD patients. This result implies that RAR may be an effective instrument for determining the prognosis in COPD patients.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a complex respiratory condition, is typified by persistent and frequently worsening airflow limitation, and stems from diverse structural anomalies within the airways and alveoli.[1] Globally, prevalence is still rising, significantly burdening healthcare systems. However, there are currently few reliable molecular markers for diagnosis and prognosis, and the diagnosis and prognosis are based on the subjective symptoms of the patient and the frequency of exacerbations.

Hematologic parameters have the advantage of being rapid and comprehensive. The red blood cell distribution width (RDW) has traditionally been employed to detect anemia.[2] Research indicates that RDW may be a novel biomarker of inflammation and oxidative stress.[3,4] RDW is an independent predictor of adverse outcomes in various diseases, including cardiovascular disease[5], thrombosis[6], and cancer.[7] In recent years, RDW has demonstrated the potential to diagnose acute exacerbation of COPD (AECOPD) and predict poor outcomes in AECOPD patients.[8] Several proposals have suggested that RDW combined with certain biomarkers could be valuable for assessing disease prognosis.[9,10] Albumin (ALB) is employed to reflect the body's nutritional state. Furthermore, it possesses anti-inflammatory properties and the capacity to lower oxidative stress and prevent endothelial cell apoptosis.[11,12] The ratio of RDW to ALB (RAR) is a simple and novel indicator of inflammation.[13,14] RAR has demonstrated significant promise in evaluating the disease prognosis. It identifies individuals at high risk of mortality[15], predicts adverse cardiovascular outcomes[16] and determines the prognosis of diabetic foot.[14]

RAR has been studied extensively in inflammatory illnesses, but little is known about how it relates to COPD. This study aimed to examine the link between RAR and the clinical prognosis in COPD patients.

Corresponding author: Yiqing Qu, Clinic of Pulmonary and Critical Care Medicine, Qilu Hospital of Shandong University, Jinan, China

e-mail: quyiqing@sdu.edu.cn

Received: January 31, 2025 **Accepted:** March 27, 2025 **Available Online Date:** May 05, 2025 • **DOI:** 10.4274/balkanmedj.galenos.2025.2025-1-141

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: W.Z. 0009-0003-3145-8436; Y.L. 0009-0002-2944-5815; C.H. 0009-0008-6983-9791; Y.Z. 0009-0007-5310-235X; Y.H. 0009-0000-4459-7441; Y.Q. 0000-0002-9538-7601.

Cite this article as: Zhao W, Liu Y, Hu C, Zhang Y, Hu Y, Qu Y. Prognostic Significance of Red Blood Cell Distribution Width-to-Albumin Ratio in Predicting 1-Year Mortality for Critically Ill Chronic Obstructive Pulmonary Disease Patients. Balkan Med J.; 2025; 42(3):222-32.

MATERIALS AND METHODS

Database introduction

Data from the Multiparameter Intelligent Monitoring in Intensive Care IV (MIMIC-IV version 2.2) database were used in this retrospective observational analysis. The database is available at https://mimic.physionet.org/. Since all patient data in the database had been deidentified and anonymized, there was no need to acquire written informed consent. Authorization for the use of these data was granted by both the Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology's Institutional Review Board. Access to the database (No. 54656291) was authorized.

Population selection criteria

Patients with COPD were diagnosed based on the disease codes listed in the International Classification of Diseases, 9th edition (491.20, 491.21, 491.22) and 10th edition (J44, J440, J441, J449). Individuals who were initially admitted to the intensive care unit (ICU) were included in the study; however, those under 18 years, who had ICU stays shorter than 24 hours, who had survival times less than 0, who had missing RDW data, or who had received a transfusion of red blood cells or more than 1,000 mL of plasma within 24 hours of ICU admission were excluded.

Data extraction

Using PostgreSQL (version 15.4) and structured querying up to 24 hours after admission, baseline characteristics including age, sex, ethnicity, height, weight, Sequential Organ Failure Assessment (SOFA) score on admission, Simplified Acute Physiology Score II (SAPS II), and Charlson comorbidity index (CCI) were queried. Details regarding renal replacement therapy (RRT) application, ventilation, extracorporeal membrane oxygenation (ECMO), vasopressor medications, and vital signs were also recorded. Laboratory variables measured within 24 hours of admission included hematological indices such as RDW, ALB, hemoglobin, hematocrit, erythrocyte pressure product, creatinine (Cr), blood urea nitrogen (BUN), electrolytes, transcutaneous oxygen saturation (SpO_2) and related indices, as well as platelet, white blood cell (WBC), neutrophil, monocyte, lymphocyte, and eosinophil counts. If the patient underwent several laboratory tests within 24 hours of admission, the average of those test results was determined. ICD 9/10 codes were used to extract information from the MIMIC-IV database about myocardial infarction, congestive heart failure, cardiac arrhythmia, hypertension, diabetes, cerebrovascular disease, peripheral vascular disease, dementia, rheumatic disease, peptic ulcer, malignant neoplasm, metastatic solid tumor, liver disease, paraplegia, acute kidney injury, chronic kidney disease (CKD), and hematological tumor. Anemia was diagnosed as a hemoglobin level < 12 g/dL in women and < 13 g/dL in men in accordance with the World Health Organization guidelines.

One-year mortality from all causes was the primary outcome that was examined. The length of hospital stay and mortality during hospitalization were other relevant metrics.

Statistical analysis

In MIMIC-IV, missing data in variables frequently occurs. The missing information can be found in Supplementary Table 1. Given the non-completely random nature of the missing data, five sets of data were generated using multiple interpolation methods, and the median of these five sets was utilized to impute the missing values. The missing height value was 41%, and the variable was deleted. Sensitivity analysis was performed to validate the robustness of the results (Supplementary Table 2, 3). Patients were stratified into tertiles (G1/G2/G3) using RAR cutoffs of 4.21 and 5.32 (33.3rd/66.6th percentiles). The distribution patterns validating these thresholds are illustrated in Supplementary Figure 1. Quantitative variables are presented as either the mean with standard deviation or as the median with an interquartile range. One-factor ANOVA or the Kruskal-Wallis H test was employed to determine intergroup differences. Categorical variables are exhibited in the form of frequencies and corresponding percentages. Group differences were evaluated using the Pearson chi-square test or Fisher's exact test.

Kaplan-Meier survival analysis, restricted cubic spline (RCS) model, and Cox proportional hazard models were employed to estimate the correlation between the RAR index and the outcome. The RCS model was constructed using four knots, positioned at the 5th, 35th, 65th, and 95th percentiles of the RAR distribution. Additionally, modifications were made across multiple models. To prevent model overfitting caused by multicollinearity among variables, the variance inflation factors (VIF) were calculated. All VIF values were determined to be below five, indicating minimal multicollinearity and ensuring the stability and reliability of the model estimates. The multivariate models contained prognostic variables that were clinically significant. Model 1 was unadjusted, model 2 was adjusted for age, sex, and ethnicity, while model 3 was adjusted for a comprehensive set of factors including age, sex, ethnicity, weight, mean blood pressure, heart rate, respiratory rate, temperature , bicarbonate levels, anion gap, platelet count, neutrophil count, monocyte count, myocardial infarct, AKD, metastatic solid tumor, congestive heart failure, dementia, cancer, anemia, hematological tumor, SAPS II, SOFA, CCI, RRT, ECMO, ventilation, vasopressor use and levels of glucose, potassium, chloride ion, Cr, BUN, and SpO_2. The results' consistency was evaluated using interaction and stratified analyses.

Lastly, a 70% training to 30% testing ratio was used to randomly divide the entire population into training and testing subsets. A prediction model utilizing RAR was developed in the training set to forecast one-year mortality in COPD patients. We plotted the time-dependent receiver operating characteristic (ROC) curve by evaluating the RAR model's predictive performance at various time points. The established RAR model's prediction abilities were compared to those of the RDW and ALB models within the testing set using the C-index.

Data analysis was conducted using the R version 4.2.3 and SPSS 30.0 IBM (International Business Machines Corporation). Double-sided p values < 0.05 were considered statistically significant in all analyses.

RESULTS

Overall, this study included data pertaining to 2,379 individuals from the MIMIC-IV database (Figure 1), with a median age of 71.75 years. The average length of stay in the ICU was 2.93 days, the average length of hospital stay was 9.73 days, and the one-year follow-up mortality rate was 41.4% (Table 1).

Baseline characteristics of study participants

Patients were categorized into three groups based on the RAR distribution tertiles. Table 1 outlines the fundamental characteristics of these RAR-based groups. The RAR index at baseline ranged from 2.31 to 16.30 (median 4.72). The heart rate, RR, WBC count, Cr, BUN, SOFA score, SAPS II, and CCI all increased in tandem with the RAR. Conversely, BP, hematocrit, hemoglobin levels, lymphocyte count, potassium level, SpO_2, and bicarbonate levels exhibited a downward trend. Compared to those in the lower tertile group, patients in group 3 were more likely to develop congestive heart failure, peptic ulcers, cancer, liver disease, kidney disease, anemia, and metastatic solid tumors. They also were more likely to need RRT application, respiratory assistance through ventilation, and the use of vasopressor medication. No significant differences were detected across the groups regarding sex, ethnicity, weight,

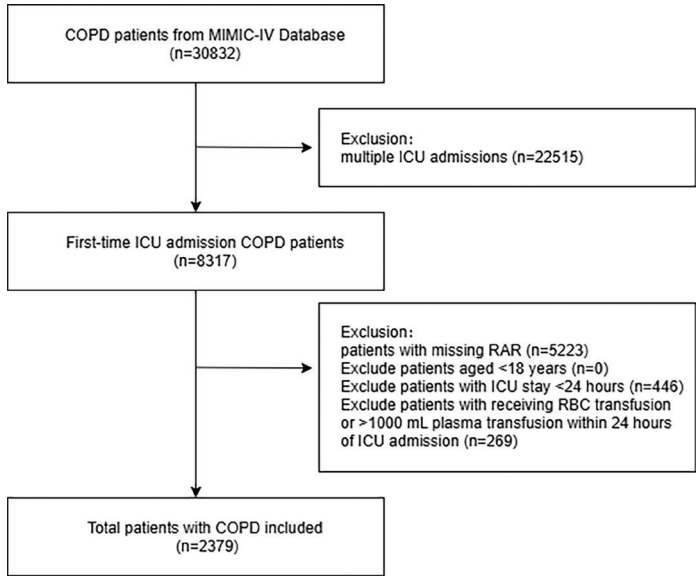

FIG. 1. Flowchart of patient selection process. COPD, chronic obstructive pulmonary disease; n, number; MIMIC-IV, Multiparameter Intelligent Monitoring in Intensive Care IV; ICU, intensive care unit; RAR, red blood cell distribution width-albumin ratio; RBC, red blood cell.

TABLE 1. Baseline Characteristics of the Study Participants Based on the Ratio of RAR.

		RAR index			
Characteristics	**All patients**	**Group 1**	**Group 2**	**Group 3**	***p* value**
Number	2,379	793	793	793	
Age, years	71.75 (63.82-79.98)	71.49 (64.34-78.86)	72.61 (64.07-81.17)	71.34 (62.77-79.68)	0.059
Sex, n (%)					
Male	1,301 (54.7)	453 (57.1)	428 (54.0)	420 (53.0)	0.221
Female	1,078 (45.3)	340 (42.9)	365 (46.0)	373 (47.0)	
Ethnicity, n (%)					
White	1,736 (73.0)	585 (73.8)	570 (71.9)	581 (73.3)	0.696
Non-white	351 (14.8)	119 (15.0)	123 (15.5)	109 (13.7)	
Unknown	292 (12.3)	89 (11.2)	100 (12.6)	103 (13.0)	
Weight, kg	78.20 (64.22-94.60)	79.90 (64.80-94.80)	79.10 (65.90-96.20)	75.50 (62.60-92.10)	0.003
Vital signs					
Heart rate, beats/min	84.88 (75.34-97.11)	82.31 (74.64-92.41)	84.62 (74.45-97.00)	88.26 (77.67-100.48)	< 0.001
Respiratory rate, breaths/min	19.48 (17.25-22.17)	18.83 (16.82-21.13)	19.58 (17.33-22.26)	20.26 (17.70-23.09)	< 0.001
Temperature, °C	36.79 (36.58-37.06)	36.76 (36.58-37.02)	36.81 (36.60-37.07)	36.80 (36.57-37.09)	0.075
SBP, mm Hg	113.75 (104.92-124.84)	116.65 (108.21-128.90)	114.68 (104.58-125.20)	109.96 (102.42-120.39)	< 0.001
DBP, mm Hg	60.12 (53.85-67.27)	60.97 (54.51-69.65)	60.45 (54.20-67.10)	58.94 (52.92-64.82)	< 0.001
MBP, mm Hg	75.00 (69.36-82.10)	76.80 (71.13-84.93)	74.92 (69.54-82.76)	73.00 (67.90-78.96)	< 0.001
Laboratory parameters					
RAR index	4.72 (3.97-5.75)	3.73 (3.42-3.97)	4.72 (4.45-4.99)	6.26 (5.76-7.11)	< 0.001
Red blood cell distribution width, %	15.25 (14.02-16.93)	3.80 (3.60-4.10)	3.30 (3.10-3.50)	2.70 (2.40-3.00)	< 0.001
Albumin, g/dL	3.30 (2.90-3.70)	13.90 (13.25- 14.70)	15.37 (14.50-16.55)	17.12 (15.71-18.84)	< 0.001

TABLE 1. Continued

		RAR index			
Characteristics	**All patients**	**Group 1**	**Group 2**	**Group 3**	***p* value**
Hematocrit, %	32.10 (28.60-36.35)	34.60 (31.38-38.47)	32.10 (28.73-36.12)	29.77 (26.54-33.15)	< 0.001
Hemoglobin, g/dL	10.43 (9.12-11.80)	11.43 (10.38-12.77)	10.40 (9.25-11.60)	9.30 (8.38-10.62)	< 0.001
Platelet, K/μL	194.78 (143.18-258.20)	194.00 (153.25- 240.00)	198.00 (146.33-262.50)	192.54 (127.50-279.20)	0.551
WBC, K/μL	10.75 (7.95-14.40)	10.45 (8.04-13.72)	10.62 (7.95-13.88)	11.20 (7.91-15.73)	0.01
Neutrophils, K/μL	421.40 (14.25-803.41)	386.22 (12.38- 732.63)	458.73 (17.09-822.22)	410.60 (14.74-844.59)	0.018
Lymphocytes, K/μL	70.58 (1.99- 126.96)	77.52 (2.11 137.95)	73.40 (2.18- 129.10)	61.32 (1.69-115.48)	0.001
Monocytes, K/μL	27.34 (1.07-46.40)	26.21 (0.97- 45.03)	29.70 (1.19- 47.88)	25.93 (1.11-46.86)	0.068
Anion gap, mEq/L	14.00 (12.15-16.18)	14.00 (12.14-16.00)	14.17 (12.33- 16.33)	14.00 (12.00-16.50)	0.14
Bicarbonate, mEq/L	24.55 (22.00-27.50)	25.00 (22.50-27.67)	24.82 (22.00-27.80)	24.00 (21.00-27.00)	< 0.001
Chloride, mEq/L	102.33 (98.20-105.80)	102.50 (99.00-105.25)	102.00 (97.75-106.00)	102.20 (98.00-106.58)	0.302
Glucose, mg/dL	126.00 (105.7-160.00)	126.00 (107.00-156.50)	128.86 (107.50-166.20)	124.00 (102.50-159.00)	0.01
Sodium, mEq/L	138.50 (135.50-141.00)	138.75 (136.37-140.67)	138.50 (135.67-141.33)	138.17 (135.00-141.00)	0.204
Potassium, mEq/L	4.22 (3.90-4.60)	4.27 (3.95-4.58)	4.24 (3.90-4.68)	4.15 (3.83-4.55)	0.002
Creatinine, mg/dL	1.07 (0.80-1.68)	1.00 (0.75-1.32)	1.14 (0.80-1.80)	1.15 (0.80-2.03)	< 0.001
BUN, mg/dL	23.56 (16.00-37.96)	20.00 (14.50-27.86)	25.33 (16.62-40.25)	27.75 (17.20-45.50)	< 0.001
SpO_2, %	96.48 (94.84-97.93)	96.72 (95.07-98.04)	96.44 (94.91-97.77)	96.33 (94.60-97.98)	0.061
Scoring systems					
SOFA 4.0	6.00 (3.00-8.00)	4.00 (3.00-7.00)	6.00 (3.00-8.00)	7.00 (4.00-10.00)	< 0.001
SAPS II	39.00 (32.00-48.00)	36.00 (30.00-43.00)	40.00 (32.00-48.00)	43.00 (34.00-51.00)	< 0.001
CCI	7.00 (6.00-9.00)	7.00 (5.00-9.00)	8.00 (6.00-9.00)	8.00 (6.00-10.00)	< 0.001
Comorbidities, n (%)					
Myocardial infarct	615 (25.9)	232 (29.3)	210 (26.5)	173 (21.8)	0.003
Congestive heart failure	1,211 (50.9)	350 (44.1)	453 (57.1)	408 (51.5)	< 0.001
Peripheral vascular disease	435 (18.3)	139 (17.5)	155 (19.5)	141 (17.8)	0.527
Cerebrovascular disease	325 (13.7)	138 (17.4)	95 (12.0)	92 (11.6)	0.001
Dementia	87 (3.7)	21 (2.6)	37 (4.7)	29 (3.7)	0.101
Rheumatic disease	132 (5.5)	32 (4.0)	48 (6.1)	52 (6.6)	0.068
Peptic ulcer	58 (2.4)	10 (1.3)	18 (2.3)	30 (3.8)	0.005
Malignant neoplasm	362 (15.2)	70 (8.8)	120 (15.1)	172 (21.7)	< 0.001
Hypertension	923 (38.8)	378 (47.7)	291 (36.7)	254 (32.0)	< 0.001
Diabetes	891 (37.5)	290 (36.6)	310 (39.1)	291 (36.7)	0.505
Liver disease	338 (14.2)	72 (9.1)	113 (14.2)	153 (19.3)	< 0.001
Paraplegia	92 (3.9)	42 (5.3)	19 (2.4)	31 (3.9)	0.011
AKI	1,043 (43.8)	234 (29.5)	371 (46.8)	438 (55.2)	< 0.001
CKD	586 (24.6)	155 (19.5)	232 (29.3)	199 (25.1)	< 0.001
Metastatic solid tumor	156 (6.6)	28 (3.5)	46 (5.8)	82 (10.3)	< 0.001
Anemia	1,678 (70.5)	416 (52.5)	581 (73.3)	681 (85.9)	< 0.001
Hematological tumor	176 (7.4)	66 (8.3)	63 (7.9)	47 (5.9)	0.147

TABLE 1. Continued

		RAR index			
Characteristics	**All patients**	**Group 1**	**Group 2**	**Group 3**	***p* value**
Treatment, n (%)					
RRT	122 (5.1)	14 (1.8)	30 (3.8)	78 (9.8)	< 0.001
ECMO	5 (0.2)	4 (0.5)	1 (0.1)	0 (0.0)	0.074
Vasopressor	239 (10.0)	48 (6.1)	54 (6.8)	137 (17.3)	< 0.001
Ventilation	916 (38.5)	221 (27.9)	323 (40.7)	372 (46.9)	< 0.001
Events					
1-year mortality, n (%)	984 (41.4)	193 (24.3)	317 (40.0)	474 (59.8)	< 0.001
Hospital mortality, n (%)	378 (15.9)	61 (7.7)	111 (14.0)	206 (26.0)	< 0.001
ICU mortality, n (%)	239 (10.0)	39 (4.9)	65 (8.2)	135 (17.0)	< 0.001
LOS Hospital, days	9.73 (5.97-16.67)	8.11 (5.75-12.76)	9.65 (5.72-15.97)	12.49 (6.87-20.72)	< 0.001
LOS ICU, days	2.93 (1.81-5.32)	2.35 (1.57-4.31)	2.95 (1.87-5.23)	3.41 (1.98-6.90)	< 0.001

Continuous variables are presented as means (SDs) or medians (quartiles), while categorical variables are presented as absolute numbers (percentages). RAR, red blood cell distribution width-albumin ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; WBC, white blood cell; BUN, blood urea nitrogen; SpO_2, transcutaneous oxygen saturation; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score II; CCI, Charlson comorbidity index; AKI, acute kidney injury; CKD, chronic kidney disease; RRT, renal replacement therapy; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay.

temperature, monocyte level, serum anion gap, serum sodium levels, peripheral vascular disease, dementia, rheumatic disease, diabetes, hematological tumor, and ECMO use. As the RAR index increased, there was a significant increase in the ICU length of stay (2.35 to 3.41 days), hospital length of stay (8.11 to 12.49 days), ICU mortality (4.9% to 17.0%), hospital mortality (7.7% to 26.0%) and 1-year mortality (24.3% to 59.8%), all with $p < 0.001$.

Kaplan-Meier curves

Figure 2 depicts the Kaplan-Meier survival curves for different all-cause mortality endpoints categorized by baseline RAR values. In contrast to groups 1 and 2 participants with lower RAR, those in group 3 with the highest RAR exhibited a significantly higher rate of all-cause mortality, including ICU, hospital, three-month, and one-year mortality.

Results of the Cox regression

Cox proportional-hazards analysis identified a significant correlation between RAR and one-year all-cause mortality. The RAR index was analyzed as a continuous variable, and in the unadjusted analysis, it exhibited a significant correlation with a hazard ratio (HR) of 1.3 [95% confidence interval (CI): 1.26-1.34, $p < 0.001$]. Additionally, in the fully adjusted model, a significant association was detected [HR, 1.24 (95% CI: 1.19-1.29), $p < 0.001$]. Furthermore, when the RAR was considered as a categorical variable, it was still associated with one-year mortality in both the unadjusted model [G3: HR, 3.3 (95% CI: 2.79-3.91), $p < 0.001$] and the fully adjusted model [G3: HR, 2.11 (95% CI: 1.74-2.55), $p < 0.001$). As the RAR increased, the risk tended to rise as well, as shown in Table 2. The multivariate Cox regression analyses of the RAR index yielded comparable results for both hospital and ICU mortality (Table 2).

Restricted cubic spline

Using model 3 adjustments, we noted a linear relationship between RAR and one-year all-cause mortality in COPD patients (p for non-linearity = 0.1659) (Figure 3a). Additionally, higher RAR levels were linearly associated with increased in-hospital mortality (p for non-linearity = 0.8700) and ICU mortality (p for non-linearity = 0.7994) (Figure 3b, c).

Results of the stratified analyses

Across several subgroups, we evaluated the link between RAR and both 1-year all-cause mortality and in-hospital mortality (Figure 4). The positive correlation between RAR and 1-year all-cause mortality risk was consistently observed across subgroups stratified by age, sex, ethnicity, SOFA score, SAPS II, CCI, comorbidities, and the use of RRT, vasopressin, and ventilation. Regardless of anemia or hematological malignancy, RAR was positively correlated with the one-year mortality risk in the subgroup analysis. [without anemia HR, 1.61 (95% CI, 1.37-1.9) vs. anemia HR, 1.85 (95% CI, 1.67-2.04) p interaction = 0.176; without hematological tumor HR, 1.85 (95% CI, 1.7-2.01) vs. hematological tumor HR, 1.46 (95%CI, 1.09-1.97) p interaction = 0.137). Even though subgroup analyses revealed significant interaction effects between RAR and one-year mortality in patients with metastatic solid tumors ($p = 0.001$) and cancer ($p = 0.025$), the direction of the association remained consistent across these groups, supporting a positive mortality risk with elevated RAR levels. This implies that, despite certain discrepancies in statistical significance, our findings support a positive association of RAR with the one-year mortality risk.

Stratified analyses of the RAR index and hospitalized mortality yielded comparable results (Figure 5).

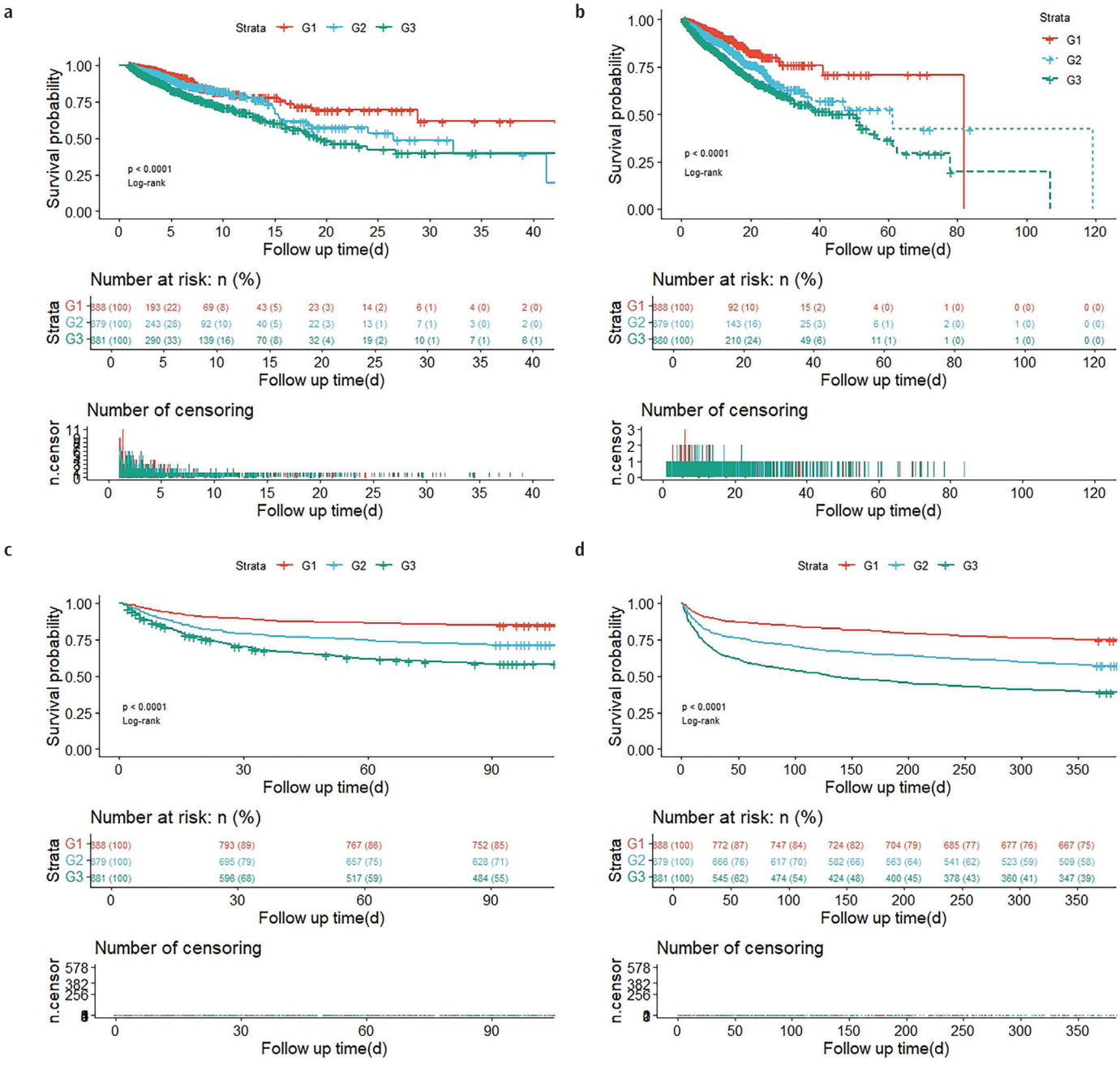

FIG. 2. Kaplan-Meier curve for all-cause mortality (by RAR baseline value). ICU all-cause mortality (a), hospital all-cause mortality (b), 3-month all-cause mortality (c), and 1-year all-cause mortality (d). ICU, intensive care unit; RAR, red blood cell distribution width-albumin ratio.

Predicting the value

We established an RAR model to predict the one-year all-cause mortality in COPD patients. The predictive ability of the RAR model for COPD survival was assessed using time-dependent ROC curve analysis (Figure 6). In the training set, the AUC values were 0.669 at 30 days, 0.688 at 180 days, and 0.683 at 1 year (Figure 6a). Meanwhile, in the testing set, the corresponding AUC values were 0.657, 0.688, and 0.674 (Figure 6b). These AUC values, which demonstrate a tendency of steadily improving predictive capacity over time, further support the RAR model's comparatively superior performance for long-term prediction.

This study evaluated the predictive performance of the RAR model against the RDW and ALB models. The RAR model demonstrated a C-index of 0.648 (95% CI: 0.626-0.670) in the training set and 0.636 (95% CI: 0.605-0.667) in the testing set, surpassing the performance of both the RDW and ALB models (Table 3). Notably, these findings imply that the RAR model is more useful for long-term prognosis,

TABLE 2. Relationship Between RAR and 1-Year, Hospital, and ICU All-Cause Mortality Events in Different Models.

	Model 1			Model 2			Model 3		
Categories	**HR (95% CI)**	***p* value**	***p* for trend**	**HR (95% CI)**	***p* value**	***p* for trend**	**HR (95% CI)**	***p* value**	***p* for trend**
1-year mortality									
Continuous variable per 1 unit	1.3 (1.26-1.34)	< 0.001		1.32 (1.28-1.37)	< 0.001		1.24 (1.19-1.29)	< 0.001	
RAR, group			< 0.001			< 0.001			< 0.001
G1 (n = 793)	Ref.			Ref.			Ref.		
G2 (n = 793)	1.83 (1.53-2.19)	< 0.001		1.83 (1.53-2.19)	< 0.001		1.43 (1.19-1.73)	< 0.001	
G3 (n = 793)	3.3 (2.79-3.91)	< 0.001		3.45 (2.92-4.08)	< 0.001		2.11 (1.74-2.55)	< 0.001	
Hospital mortality									
Continuous variable per 1 unit	1.21 (1.15-1.28)	< 0.001		1.23 (1.16-1.29)	< 0.001		1.17 (1.09-1.25)	< 0.001	
RAR, group			< 0.001			< 0.001			0.001
G1 (n = 793)	Ref.			Ref.			Ref.		
G2 (n = 793)	1.52 (1.11-2.08)	0.009		1.56 (1.14-2.14)	0.005		1.44 (1.03-2.01)	0.031	
G3 (n = 793)	2.23 (1.67-2.98)	< 0.001		2.35 (1.76-0.13)	< 0.001		1.73 (1.25-.38)	0.001	
ICU mortality									
Continuous variable per 1 unit	1.17 (1.09-1.26)	< 0.001		1.19 (1.11-1.28)	< 0.001		1.16 (1.06-1.28)	0.001	
RAR, group			< 0.001			< 0.001			0.003
G1 (n = 793)	Ref.			Ref.			Ref.		
G2 (n = 793)	1.35 (0.91-2.00)	0.142		1.4 (0.94-2.09)	0.096		1.47 (0.96-2.24)	0.073	
G3 (n = 793)	2.15 (1.5-3.08)	< 0.001		2.27 (1.59-3.26)	< 0.001		1.86 (1.23-2.79)	0.003	

RAR, red blood cell distribution width-albumin ratio; ICU, Intensive Care Unit; HR, hazard ratio; CI, confidence interval; Ref, reference.
Model 1: unadjusted; Model 2: adjusted for age, sex, and ethnicity; Model 3: adjusted for age, sex, ethnicity, weight, mean blood pressure, heart rate, respiratory rate, temperature, platelet level, neutrophils level, monocytes level, bicarbonate, anion gap, chloride, glucose, potassium levels, creatinine, blood urea nitrogen, SpO_2, myocardial infarct, acute kidney injury, metastatic solid tumor, congestive heart failure, dementia, malignant cancer, anemia, hematological tumor, Simplified Acute Physiology Score II, Sequential Organ Failure Assessment score, Charlson comorbidity index, renal replacement therapy, Extracorporeal Membrane Oxygenation, vasopressor use.

particularly at the one-year time point when it t outperforms the RDW and ALB models more prominently.

DISCUSSION

COPD is a prevalent and fatal disease characterized by complexity and heterogeneity, necessitating straightforward biomarkers for predicting its progression and prognosis. Using stratified analyses, this study identified a significant correlation between the RAR and one-year all-cause and in-hospital mortality in COPD patients. RAR demonstrated superior predictive capability for one-year mortality prediction in COPD patients compared with RDW and ALB levels individually. This result implies that RAR, as a novel composite index, may integrate information on inflammation, nutritional status, and other relevant physiopathological processes, offering a more comprehensive perspective for determining the survival risk of COPD patients.

RDW has grown in significance in the prognostic assessment of clinical diseases. In COPD patients admitted to the ICU, elevated RDW is associated with a higher risk of 28-day all-cause mortality.[17] Liu et al.[18] demonstrated that RDW was significantly associated with the 1-year readmission of COPD patients, especially those with hypertension, and that patients with a high RDW had a 3.3-fold higher chance of being readmitted than those with a low RDW. Kalemci et al.[19] revealed that RDW is independently associated with severe COPD [odds ratio, 3.67 (95% CI, 1.23-11.75), $p < 0.001$]. In addition, Saad E et al.[20] revealed a positive association between RDW and C-reactive protein levels. This result significantly reinforces the hypothesis that RDW can function as an indicator of inflammation. Many diseases with poor prognoses have elevated RDW, most likely because of its link to inflammation.[11,21,22] In COPD patients, the persistent inflammatory state interferes with the regulation of erythropoiesis, resulting in variably-sized newly formed erythrocytes and, ultimately, an elevated RDW.

ALB has conventionally been employed as a reliable biomarker to gauge the body's nutritional status. Numerous studies have demonstrated that serum ALB exhibits strong antioxidant capabilities. By effectively scavenging free radicals, it may minimize the detrimental effects of oxidative stress on cells. Additionally, ALB has been demonstrated to trigger the antiapoptotic signaling cascade, thereby inhibiting cell apoptosis and maintaining the integrity of the vascular endothelium.[12] Through these complex

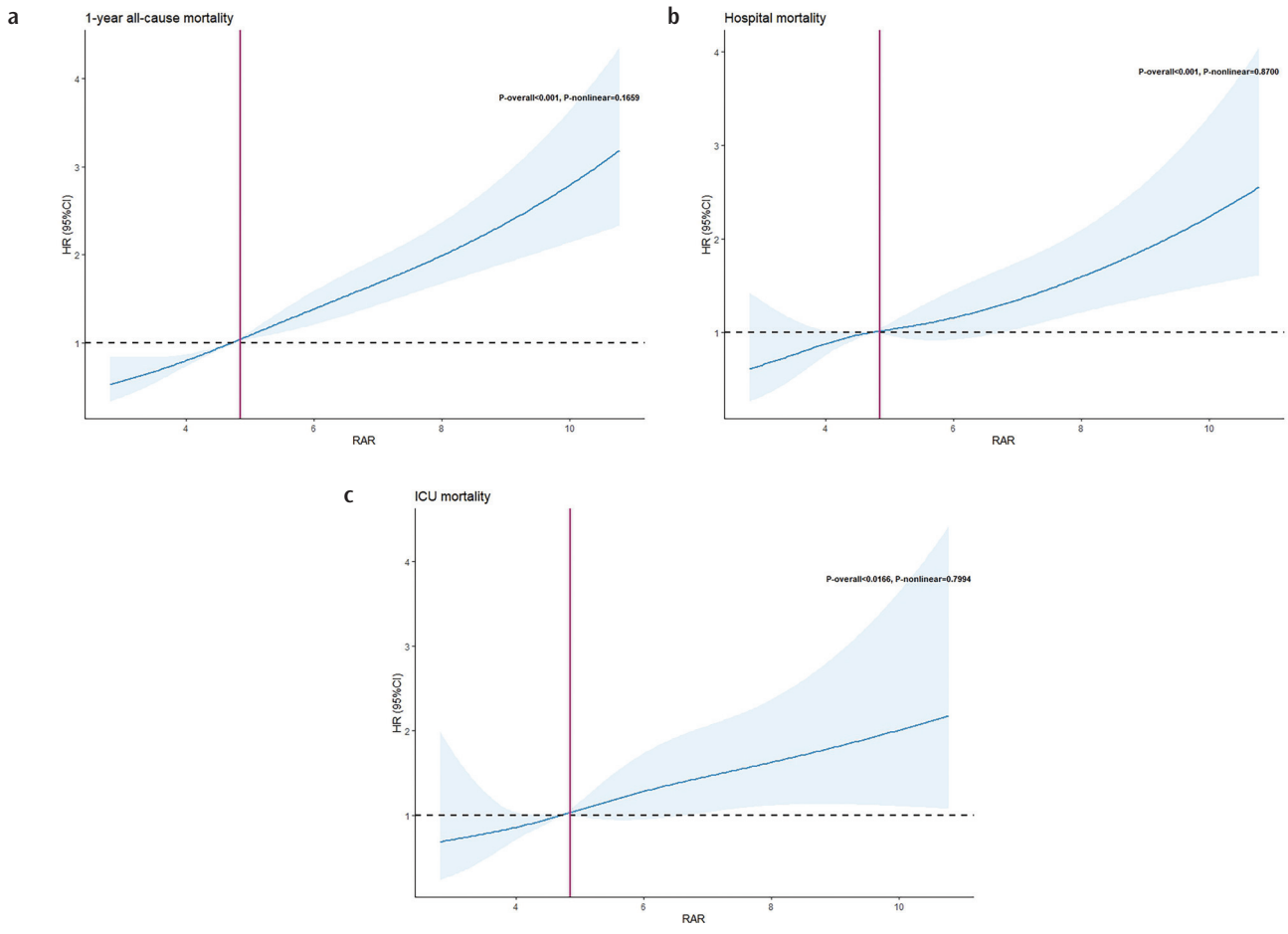

FIG. 3. Restricted cubic spline model for the relationship between RAR and mortality. 1-year mortality (a), hospital mortality (b), and ICU mortality (c). RAR, red blood cell distribution width-albumin ratio; ICU, intensive care unit.

mechanisms, ALB exerts a pronounced anti-inflammatory effect and is essential for safeguarding human health and well-being. Low ALB levels have been proven to significantly affect COPD patients. Upon Cox regression analysis, Gunen H et al.[23] found that long-term mortality was linked to lower ALB levels, with a relative risk of 0.41. Low ALB levels are a risk factor for long-term mortality in hospitalized COPD patients.[24] Conversely, it visually reflects the patient's malnutrition and is closely associated with reduced immunity and increased inflammatory response, which in turn are closely linked to poor prognosis in the patient.[25-27]

RAR is a composite measure of RDW and ALB that has been studied for its association with different inflammatory diseases, including diabetes[28], sepsis[29], and CKD.[30] A large-sample retrospective study involving 469,572 participants indicated that in the general population, a higher baseline RAR level was correlated with an increased risk of both all-cause mortality and mortality due to specific causes. The high RAR group had a threefold higher chance of death from respiratory-related diseases than the low RAR group. Currently, the body of research concerning the RAR within the domain of COPD remains conspicuously scarce. Eraslan BZ et al.[31] revealed that although RAR values were significantly correlated with several clinical outcome indicators such as disease severity, hospital stay duration, readmission rates, and mortality in COPD patients, RAR did not exhibit a significant difference in the short-term prognosis of 30 days, implying that RAR is more valuable in predicting disease progression in patients in the long-term (> 30 days) and adverse outcome. This is in complete agreement with our findings, which also demonstrated that higher RAR values tended to predict more severe disease and longer hospital stays. The comparatively superior efficacy of the RAR model for long-term prognosis is further supported by these AUC values from the time-ROC curves. Compared with the 30-day or half-year time points, the risk of all-cause mortality at 1 year showed a significant increase in terms of predicting the risk of death. RAR was found to be a risk factor for in-hospital mortality in all illness classes, with the exception of liver disease patients, according to Qiu et al.[32] In our study of COPD patients, no interaction effect was discovered between RAR and most of the subgroups, which is a strong indicator of the robustness of the findings. In particular, the subgroup analysis of various treatment modalities and illness characteristics yielded some significant results. In the subgroup analysis, patients undergoing ventilator therapy exhibited a significantly reduced mortality risk compared to those not receiving ventilation (without

ventilation HR, 2.00 (95% CI, 1.79-2.24) vs. with ventilation HR, 1.46 (95% CI, 1.29-1.64, p value = 0.001), although this group of patients tended to experience more severe disease. We hypothesize that this is probably related to the fact that prompt and effective respiratory support improves patients' oxygenation status[33], mitigates respiratory muscle fatigue[34], and stabilizes the body's internal environment.[35] Meanwhile, in the cancer-related subgroup analyses, the one-year mortality risk was greater in patients without cancer and metastases than in patients with cancer [without cancer HR, 1.82 (95% CI, 1.66-2.00) vs. cancer HR, 1.47 (95% CI, 1.23-1.75), p interaction = 0.025; without metastatic solid tumor HR, 1.82 (95% CI 1.67-1.99) vs. metastatic solid tumor HR, 1.22 (95% CI, 0.97-1.53, p interaction = 0.001). This phenomenon likely occurs because cancer alters the metabolic state of the organism and affects the RAR value. In addition, cancer therapy impacts the hematopoietic system and the hepatic synthetic function[36-38], causing changes in the width of

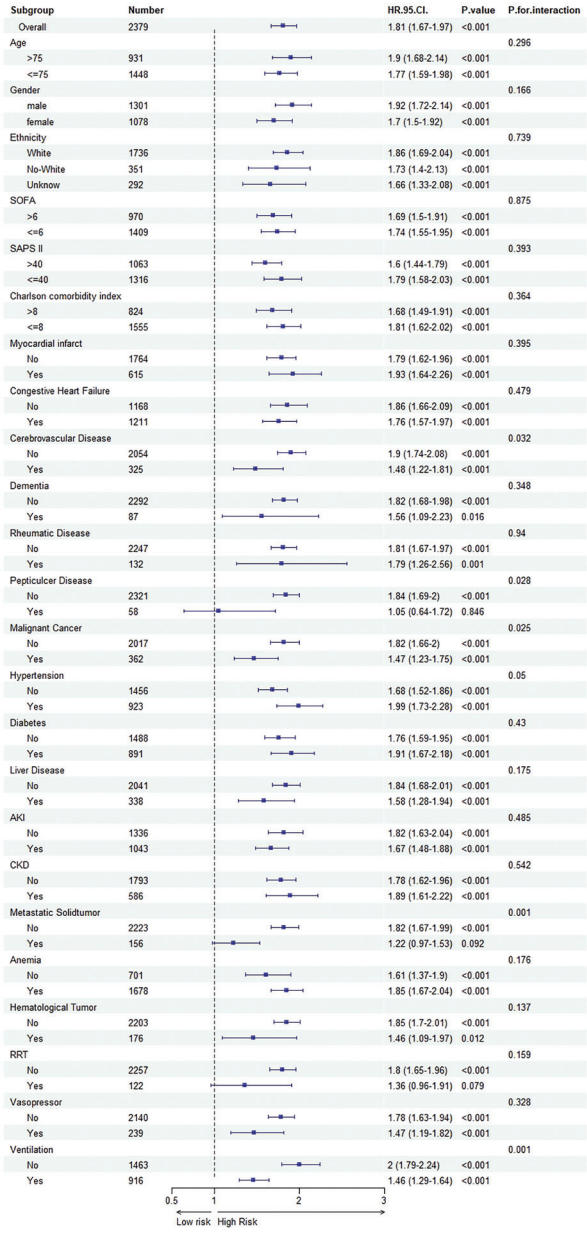

FIG. 4. Forest plot depicting the relationship between 1-year mortality and RAR for subgroup analysis. RAR, red blood cell distribution width-albumin ratio; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score; AKI, acute kidney injury; CKD, chronic kidney disease; RRT, renal replacement therapy; ECMO, Extracorporeal Membrane Oxygenation.

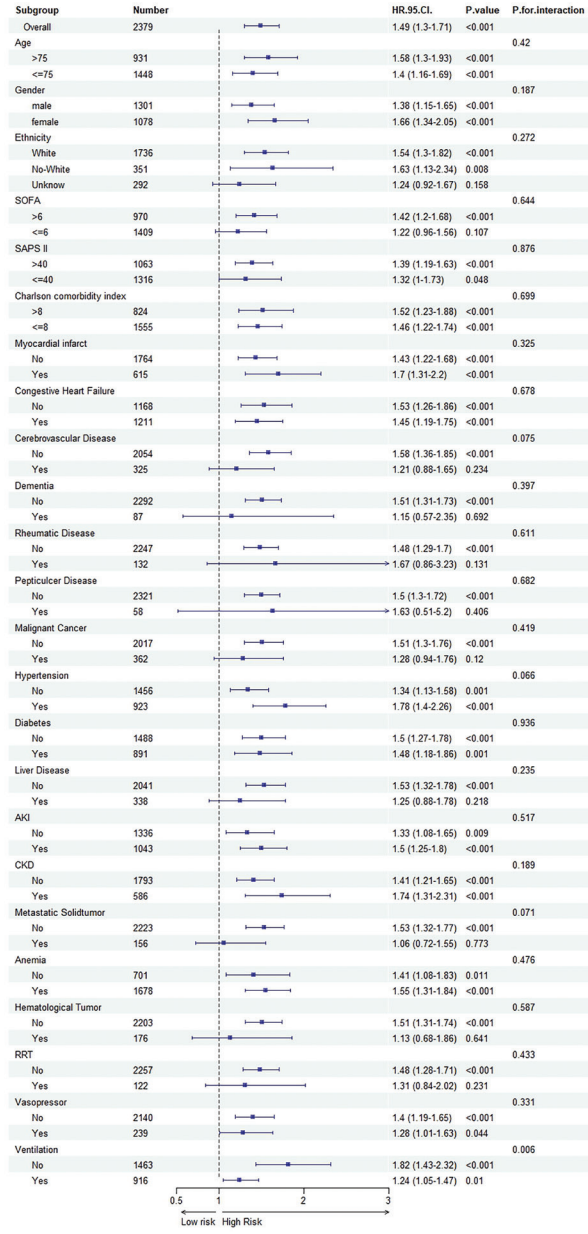

FIG. 5. Forest plot of the relationship between hospital mortality and RAR for subgroup analysis. RAR, red blood cell distribution width-albumin ratio; SOFA, Sequential Organ Failure Assessment; SAPS II, Simplified Acute Physiology Score; AKI, acute kidney injury; CKD, chronic kidney disease; RRT, renal replacement therapy; ECMO, Extracorporeal Membrane Oxygenation.

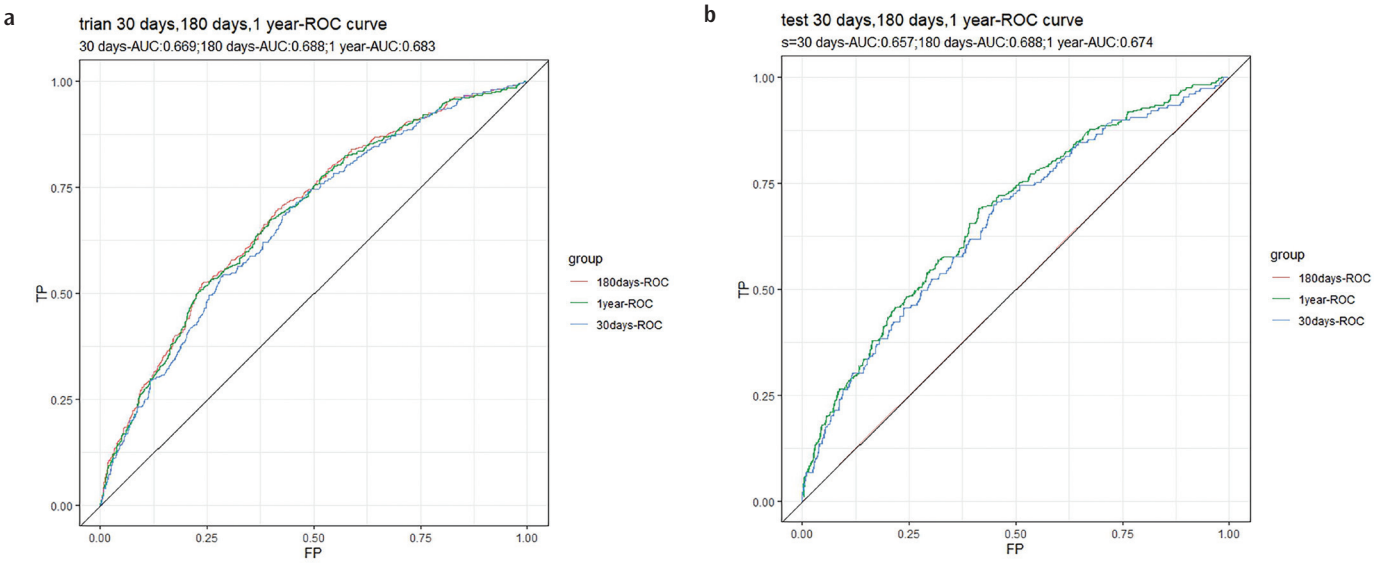

FIG. 6. Time-dependent ROC curves of RAR for predicting 30-day, 180-day, and 1-year mortality in patients with COPD. The train set (a). The testing set (b). ROC, receiver operating characteristics; RAR, red blood cell distribution width-albumin ratio; COPD, chronic obstructive pulmonary disease.

TABLE 3. Predicting Performance of RAR, RDW-Model, and ALB-Model.

	Training set (n = 1,666)	Testing set (n = 713)
Models	C-index (95% CI)	C-index (95% CI)
RDW-model	0.615 (0.593-0.637)	0.588 (0.555-0.621)
ALB-model	0.618 (0.596-0.640)	0.620 (0.589-0.651)
RAR-model	0.648 (0.626-0.670)	0.636 (0.605-0.667)

CI, confidence interval; RDW, red blood cell distribution width; ALB, albumin; RAR, red blood cell distribution width-albumin ratio.

erythrocyte distribution and fluctuations in ALB levels, interfering with the prediction of mortality risk by RAR in COPD.

Our study has several limitations. Initially, data were obtained from the MIMIC-IV database, a single-center retrospective study, limiting the generalizability of the findings. Second, due to the retrospective nature of this study, the RAR values were altered by diverse factors, including erythropoietin use and exogenous ALB use, which were difficult to differentiate. This interferes with the determination of the true role of the RAR and prevents a precise dissection of its role in the disease process. Additional studies need to incorporate outpatient electronic medical records to more accurately examine the mechanism of RAR. Third, while ICD codes provide practical utility for COPD detection in large databases, the absence of spirometric confirmation and GOLD staging data represents an inherent limitation. Future prospective studies incorporating pulmonary function tests and thorough phenotyping are warranted to corroborate our findings.

In conclusion, the current study identified a significant correlation between RAR and one-year mortality in COPD patients. This implies that as a simple yet easily accessible biomarker, RAR may be an effective tool for prognostic assessment in COPD patients.

Acknowledgments: This study was supported by the Major Project of the National Natural Science Foundation of China (Grant No. 72293582) and the ECCM Program of the Clinical Research Center of Shandong University (Grant No.2021SDUCRCB001).

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Data Sharing Statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- W.Z.; Design- Y.L.; Supervision- W.Z., Y.Q.; Fundings- Y.Q.; Materials- W.Z.; Data Collection or Processing- W.Z., C.H.; Analysis or Interpretation- W.Z., Y.L., C.H.; Writing- W.Z., Y.H.; Critical Review- Y.Q.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: The authors declared that this study received no financial support.

Supplementary: https://balkanmedicaljournal.org/img/files/supplementary-2025-1-141.pdf

REFERENCES

1. 2024 GOLD Report. Global initiative for chronic obstructive lung disease - *GOLD*. Accessed January 19, 2025. [CrossRef]
2. Salvagno GL, Sanchis-Gomar F, Picanza A, Lippi G. Red blood cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci*. 2015;52:86-105. [CrossRef]

3. Fukuta H, Ohte N, Mukai S, et al. Elevated plasma levels of B-type natriuretic peptide but not C-reactive protein are associated with higher red cell distribution width in patients with coronary artery disease. *Int Heart J*. 2009;50:301-312. [CrossRef]
4. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med*. 2005;352:1011-1023. [CrossRef]
5. Borné Y, Smith JG, Melander O, Engström G. Red cell distribution width in relation to incidence of coronary events and case fatality rates: a population-based cohort study. *Heart*. 2014;100:1119-1124. [CrossRef]
6. Zöller B, Melander O, Svensson P, Engström G. Red cell distribution width and risk for venous thromboembolism: a population-based cohort study. *Thromb Res*. 2014;133:334-339. [CrossRef]
7. Koma Y, Onishi A, Matsuoka H, et al. Increased red blood cell distribution width associates with cancer stage and prognosis in patients with lung cancer. *PLoS One*. 2013;8:e80240. [CrossRef]
8. Hu GP, Zhou YM, Wu ZL, et al. Red blood cell distribution width is an independent predictor of mortality for an acute exacerbation of COPD. *Int J Tuberc Lung Dis*. 2019;23:817-823. [CrossRef]
9. Guo L, Chen D, Cheng B, Gong Y, Wang B. Prognostic value of the red blood cell distribution width-to-albumin ratio in critically ill older patients with acute kidney injury: a retrospective database study. *Emerg Med Int*. 2023;2023:3591243. [CrossRef]
10. Chen S, Shi Y, Hu B, Huang J. A prediction model for in-hospital mortality of acute exacerbations of chronic obstructive pulmonary disease patients based on red cell distribution width-to-platelet ratio. *Int J Chron Obstruct Pulmon Dis*. 2023;18:2079-2091. [CrossRef]
11. Blood Features Associated with Viral Infection Severity: An Experience from COVID-19-Pandemic Patients Hospitalized in the Center of Iran, Yazd - PubMed. Accessed January 19, 2025. [CrossRef]
12. Fanali G, di Masi A, Trezza V, Marino M, Fasano M, Ascenzi P. Human serum albumin: from bench to bedside. *Mol Aspects Med*. 2012;33:209-290. [CrossRef]
13. Red cell distribution width to albumin ratio is associated with asthma risk: a population-based study - PubMed. Accessed January 19, 2025. [CrossRef]
14. Hong J, Hu X, Liu W, et al. Impact of red cell distribution width and red cell distribution width/albumin ratio on all-cause mortality in patients with type 2 diabetes and foot ulcers: a retrospective cohort study. *Cardiovasc Diabetol*. 2022;21:91. [CrossRef]
15. Hao M, Jiang S, Tang J, et al. Ratio of red blood cell distribution width to albumin level and risk of mortality. *JAMA Netw Open*. 2024;7:e2413213. [CrossRef]
16. Li H, Xu Y. Association between red blood cell distribution width-to-albumin ratio and prognosis of patients with acute myocardial infarction. *BMC Cardiovasc Disord*. 2023;23:66. [CrossRef]
17. Lan W, Liu E, Sun D, et al. Red cell distribution in critically ill patients with chronic obstructive pulmonary disease. *Pulmonology*. 2024;30:34-42. [CrossRef]
18. Liu Q, Wu K, Lin X, Xiang K, Wang J. Investigating the utility of red blood cell distribution width as a prognostic indicator for deterioration of patients with chronic obstructive pulmonary disease within one year. *Int J Gen Med*. 2024;17:3869-3877. [CrossRef]
19. Kalemci S, Akin F, Sarihan A, Sahin C, Zeybek A, Yilmaz N. The relationship between hematological parameters and the severity level of chronic obstructive lung disease. *Pol Arch Intern Med*. 2018;128:171-177. [CrossRef]
20. Saad E, Maamoun B, Nimer A. Increased red blood cell distribution predicts severity of chronic obstructive pulmonary disease exacerbation. *J Pers Med*. 2023;13:843. [CrossRef]
21. Hunziker S, Celi LA, Lee J, Howell MD. Red cell distribution width improves the simplified acute physiology score for risk prediction in unselected critically ill patients. *Crit Care*. 2012;16:R89. [CrossRef]
22. Red blood cell distribution width as a risk factor for inhospital mortality in obstetric patients admitted to an intensive care unit: a single centre retrospective cohort study - PubMed. Accessed January 19, 2025. [CrossRef]
23. Gunen H, Hacievliyagil SS, Kosar F, et al. Factors affecting survival of hospitalised patients with COPD. *Eur Respir J*. 2005;26:234-241. [CrossRef]
24. Pavliša G, Labor M, Puretić H, Hećimović A, Jakopović M, Samaržija M. Anemia, hypoalbuminemia, and elevated troponin levels as risk factors for respiratory failure in patients with severe exacerbations of chronic obstructive pulmonary disease requiring invasive mechanical ventilation. *Croat Med J*. 2017;58:395-405. [CrossRef]
25. Jin X, Li J, Sun L, et al. Prognostic value of serum albumin level in critically ill patients: observational data from large intensive care unit databases. *Front Nutr*. 2022;9:770674. [CrossRef]
26. Wiedermann CJ. Hypoalbuminemia as Surrogate and Culprit of Infections. *Int J Mol Sci*. 2021;22:4496. [CrossRef]
27. Tang Q, Li X, Sun CR. Predictive value of serum albumin levels on cancer survival: a prospective cohort study. *Front Oncol*. 2024;14:1323192. [CrossRef]
28. Chen S, Guan S, Yan Z, et al. Prognostic value of red blood cell distribution width-to-albumin ratio in ICU patients with coronary heart disease and diabetes mellitus. *Front Endocrinol (Lausanne)*. 2024;15:1359345. [CrossRef]
29. Shan X, Li Z, Jiang J, Li W, Zhan J, Dong L. Prognostic value of red blood cell distribution width to albumin ratio for predicting mortality in adult patients meeting sepsis-3 criteria in intensive care units. *BMC Anesthesiol*. 2024;24:208. [CrossRef]
30. Kimura H, Tanaka K, Saito H, et al. Impact of red blood cell distribution width-albumin ratio on prognosis of patients with CKD. *Sci Rep*. 2023;13:15774. [CrossRef]
31. Eraslan BZ, Cengiz SK, Sagmen SB, Yalçınkaya KZ, Kıral N, Cömert S. The importance of the erythrocyte distribution width/albumin ratio in patients with chronic obstructive pulmonary disease exacerbation. *Saudi Med J*. 2024;45:27-33. [CrossRef]
32. Qiu Y, Wang Y, Shen N, et al. Association between red blood cell distribution width-albumin ratio and hospital mortality in chronic obstructive pulmonary disease patients admitted to the intensive care unit: a retrospective study. *Int J Chron Obstruct Pulmon Dis*. 2022;17:1797-1809. [CrossRef]
33. Zhang K, Liang F, Wu Y, et al. Associations of arterial oxygen partial pressure with all-cause mortality in critically ill ischemic stroke patients: a retrospective cohort study from MIMIC IV 2.2. *BMC Anesthesiol*. 2024;24:355. [CrossRef]
34. Ferrer M, De Pascale G, Tanzarella ES, Antonelli M. Severe community-acquired pneumonia: noninvasive mechanical ventilation, intubation, and HFNT. *Semin Respir Crit Care Med*. 2024;45:169-186. [CrossRef]
35. Osadnik CR, Tee VS, Carson-Chahhoud KV, Picot J, Wedzicha JA, Smith BJ. Non-invasive ventilation for the management of acute hypercapnic respiratory failure due to exacerbation of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2017;7:CD004104. [CrossRef]
36. Deng H, Liu S, Li D, et al. Investigating the pharmacological mechanism of Zhengyuan jiaonang for treating colorectal cancer via network pharmacology analysis and experimental verification. *J Ethnopharmacol*. 2024;322:117607. [CrossRef]
37. Hammers HJ, Plimack ER, Infante JR, et al. Safety and efficacy of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma: the CheckMate 016 study. *J Clin Oncol*. 2017;35:3851-3858. [CrossRef]
38. Antonia S, Goldberg SB, Balmanoukian A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. *Lancet Oncol*. 2016;17:299-308. [CrossRef]