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Clinical significance of red cell distribution width-to-albumin ratio in patients with chronic obstructive pulmonary disease exacerbations

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Abstract:

BACKGROUND AND AIM: The role of the red cell distribution width-to-albumin ratio (RAR) in predicting adverse outcomes of chronic obstructive pulmonary disease exacerbation (ECOPD) is not completely understood. Our aim was to evaluate the clinical significance of RAR in predicting ECOPD outcomes.

METHODS: A hospital-based cross-sectional comparative study was conducted on 102 patients with ECOPD. The frequency of exacerbations, history of hospitalization for ECOPD in the previous year severity of the current exacerbation, length of hospital stay (LOS), occurrence of respiratory failure, need for mechanical ventilation (MV) support, short-term mortality, and long-term mortality risk were recorded.

RESULTS: The RAR was significantly increased in patients with frequent exacerbations, hospitalization in the last year, severe current exacerbation, respiratory failure, need for MV support, prolonged hospitalization, short-term mortality, and high-risk long-term mortality. RAR was negatively correlated with spirometric indices, PaO_2, and O_2 saturation (%), and positively correlated with hospital length of stay (LOS) and the BODE index (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity). The RAR was a significant predictive index for frequent exacerbations (ß=1.51), hospitalizations (ß=1.41), severe current exacerbation (ß=1.75), respiratory failure (ß=3.29), need for MV support (ß=1.85), prolonged hospitalizations (ß=5.99), short-term mortality (ß=0.814), and high-risk long-term mortality (ß=3.97).

CONCLUSIONS: The RAR is a significant predictive index of adverse exacerbation outcomes in chronic obstructive pulmonary disease (COPD), as it discriminates patients with frequent exacerbations, hospitalizations, severe exacerbation, respiratory failure, need for MV support, prolonged hospitalizations, short-term mortality, and higher-risk long-term mortality. Therefore, it can be used to identify, at an early stage, patients who are at increased risk of morbidity and mortality.

Keywords:

Acute exacerbation, chronic obstructive pulmonary disease, red cell distribution-albumin ratio, treatment outcome

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Introduction

Exacerbation of chronic obstructive pulmonary disease (ECOPD) is the most common cause of hospital admission and an important contributor to death in patients with chronic obstructive pulmonary disease (COPD).[1] Therefore, precise evaluation of outcomes is essential for the management of hospitalized COPD patients. The development of a specific, easily available indicator of in-hospital mortality is vital, as it can aid physicians in the early identification of patients at increased risk of in-hospital mortality and in adopting a more proactive management approach.[2]

The red cell distribution width (RDW), which reflects heterogeneity in the size of red blood cells, is a biomarker of systemic inflammation, oxidative stress, and malnutrition, all of which are common in COPD. Albumin, a negative acute-phase protein, is a well-documented index of both nutritional status and inflammatory processes. Combining these two indicators into a single measure, the red cell distribution width-to-albumin ratio (RAR), offers a comprehensive evaluation of inflammatory load and nutritional status.[3] Because RAR integrates both RDW and albumin, it may better indicate pathological states such as hematopoietic dysfunction and hypoproteinemia.[4]

In COPD patients, exacerbations are the leading cause of mortality.[5] ECOPDs that require hospital admission are independently linked to mortality, and the risk of mortality increases with exacerbation frequency.[6] Given that ECOPD increases mortality, evaluating long-term mortality risk in these patients is crucial. Numerous scoring systems are currently in use for this purpose, with the BODE index [Body mass index (BMI), Obstruction, Dyspnea, and Exercise] being the most frequently used one.[7]

The development of new, suitable indices with convenient predictive power that guide physicians to quickly identify ECOPD patients at a higher risk of adverse exacerbation outcomes remains an unmet need. Therefore, this research was conducted to evaluate the clinical significance of RAR in predicting COPD exacerbation outcomes. We hypothesized that a higher RAR is associated with more adverse ECOPD outcomes and a higher risk of mortality. To our knowledge, this research is among the few studies that investigate the relationship between RAR and ECOPD outcomes.

Materials and Methods

A total of 102 patients with ECOPD who were admitted to the chest diseases department were enrolled in this cross-sectional comparative study. The study was conducted during the period from September 2024 to February 2025 (6 months). The study subjects were 78 (76.5%) males and 24 (23.5%) females, with ages ranging from 45 to 80 years. Eighty-four (82.4%) of them were smokers, with a smoking index ranging from 23 to 120 pack-years, and only 18 (17.6%) were non-smokers. The BMI of patients ranged from 20.5 to 32 kg/m2. Thirty-two (31.4%) patients had moderate COPD, 44 (43.1%) patients had severe COPD, and 26 (25.5%) patients had very severe COPD. The exacerbation was due to bacterial infection in 47 (46.1%) patients (confirmed by sputum cultures), household air pollution exposure such as biomass use in 30 (29.4%) patients, and other causes such as smoking, cold weather, and non-adherence to COPD treatment in 25 (24.5%) patients.

The study was approved by the ethical committee of our institute, and it adhered to the Declaration of Helsinki. Written informed consent was obtained from each patient before participating in the study. Patients with comorbidities that could affect RDW and/or albumin levels were excluded from the study, e.g., advanced cardiovascular diseases, gastrointestinal bleeding, bleeding tendency, renal failure, nephrotic syndrome, liver cirrhosis, hematological disorders, and septic shock.

Data regarding age, smoking history, and history of hospitalization for an ECOPD attack in the last year were recorded. The diagnosis of ECOPD and the severity of the current exacerbation were assessed according to the criteria of Anthonisen et al.,[8] classifying cases into severe ECOPD and moderate ECOPD. The frequency of exacerbations was recorded, and patients were classified as having frequent exacerbations (≥2 exacerbations per year) or non-frequent exacerbations (<2 exacerbations per year).[9]

Spirometry was performed according to the American Thoracic Society (ATS) recommendations,[10] and the following measurements were recorded: forced expiratory volume in one second (FEV_1%), forced expiratory volume in one second/forced vital capacity (FEV_1\FVC) ratio, FVC%, and forced expiratory flow between 25% and 75% of vital capacity (FEF 25–75%). Inflammatory

parameters measured included white blood cells (WBC) count (103/cmm^3) and serum C-reactive protein (CRP). Patients were classified as having leukocytosis (WBC >10 cmm3) or no leukocytosis (WBC ≤10 cmm^3). Based on CRP levels, patients were classified as having high CRP (>6 mg/L) or normal CRP (0–6 mg/L). RDW and serum albumin were measured, and the RAR was calculated as "RDW % / albumin g/dL."[11] Oxygen saturation % (O_2 Sat %), arterial partial pressure of oxygen (PaO_2), and arterial partial pressure of carbon dioxide ($PaCO_2$) were recorded. All parameters were measured once at admission before initiation of ECOPD treatment.

Based on the indications for mechanical ventilation (MV) support (either non-invasive or invasive) cited by the Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2024),[9] patients were classified as needing MV support or not needing MV support. Hospitalization duration (in days) was recorded, and patients were divided into those with prolonged hospitalizations (length of stay [LOS] >10 days) and those with non-prolonged hospitalizations (LOS ≤10 days).[12]

The short-term mortality was assessed by following up the patients during hospitalization and up to 30 days, and mortality was recorded. Patients were classified into the short-term mortality group (those who died in hospital or within 30 days) and the no short-term mortality group. The long-term mortality risk was assessed using the BODE index scoring system, which is a composite measure including BMI, airflow obstruction measured by FEV_1%, dyspnea evaluated by the modified Medical Research Council scale (mMRC), and exercise capacity evaluated by the 6-minute walk distance (6MWD).[13] Based on the long-term mortality risk (BODE index), patients were classified into two groups: those at low risk of long-term mortality (BODE index <5, i.e. quartiles 1 and 2 combined) and those at high risk of long-term mortality (BODE score ≥5, i.e. quartiles 3 and 4 combined).[14]

Statistical analysis

The data were analyzed using SPSS version 17.0 (SPSS Inc., Chicago, USA). The normality of quantitative variables was tested using the Shapiro-Wilk test. As continuous variables were not normally distributed, they were presented as median and interquartile range (IQR), and differences between subgroups were evaluated using the Mann-Whitney U test. Qualitative data were presented as frequencies and percentages and analyzed using the Chi-square (X^2) test. Spearman's correlation coefficient (r) was used to evaluate the relationship between RAR and other quantitative variables. Univariate logistic regression analysis was employed to investigate the role of RAR in predicting adverse exacerbation outcomes such as frequent exacerbations, hospitalization, severe current exacerbation, development of respiratory failure, need for MV support, prolonged hospitalization, short-term mortality, and high risk of long-term mortality. Moreover, the receiver operating characteristic (ROC) curve analysis was used to identify the best significant cut-off value of RAR and to evaluate its predictive power for adverse exacerbation outcomes (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]). For all tests, a p-value <0.05 was considered statistically significant at a 95% confidence interval (CI).

Table 1: Characteristics of the studied patients

	ECOPD patients (n=102)
Age (years)	62 (58–70)
Males	78 (76.5%)
Females	24 (23.5%)
BMI	27.5 (24–31.1)
FEV_1/FVC ratio	60 (53–66)
FEV_1 (%)	43.5 (34–51)
FVC (%)	77 (74–81)
FEF (25–75%)	37.5 (27–51.5)
O_2 saturation (%)	94 (91–96)
PaO_2 mmHg	71.5 (51.8–76)
$PaCO_2$ mmHg	37 (34–40)
WBC (10^3/cmm)	8.4 (6.5–10.2)
CRP (mg/L)	12.3 (5.2–32.8)
RDW (%)	13.5 (12.8–14)
Albumin (g/dL)	4 (4–4.3)
RAR (% g/dL)	3.4 (3.1–4.5)
Hospitalization LOS (days)	7 (7–11.3)

ECOPD: Exacerbated chronic obstructive pulmonary disease; BMI: Body mass index; FEV_1%: Forced expiratory volume in the first second (% predicted); FVC%: Forced vital capacity (% predicted); FEF25-75%: Forced expiratory flow at 25-75% of vital capacity (% predicted); O_2 Sat %: Oxygen saturation %; PaO_2: Partial arterial pressure of oxygen; $PaCO_2$: Partial arterial pressure of carbon dioxide; WBC: White blood cells; CRP: C-reactive protein; RDW: Red cell distribution width; RAR: Red cell distribution width-to-albumin ratio

Results

Most of the studied patients were males (76.5%), with a median (IQR) age of 62 years (58–70), and a median (IQR) BMI of 27.5 (24–31.1). The spirometric indices, laboratory parameters, and hospitalization LOS are presented in Table 1.

Table 2: Subgroup analyses of red cell distribution width-to-albumin ratio (RAR) in patients with exacerbated chronic obstructive pulmonary disease (ECOPD)

Item	RAR (% g/dL)		p
	Median (IQR)	Range	
Frequent exacerbations			
No (n=53)	3.2 (2.9–3.4)	2.3–4.9	0.001*
Yes (n=49)	4.4 (3.4–4.8)	2.7–11.6	
Hospitalization in last year for ECOPD			
No (n=38)	3.2 (3–3.6)	2.3–4.9	0.001*
Yes (n=64)	4.4 (3.5–4.8)	2.7-–11.6	
Severe current exacerbation			
No (n=58)	3.2 (2.9–3.5)	2.3–4.8	0.001*
Yes (n=44)	4.4 (3.4–4.8)	2.8–11.6	
Leukocytosis			
No (n=74)	3.2 (2.9–3.5)	2.3–4.6	0.010*
Yes (n=28)	4.8 (4.5–5.4)	4–11.6	
High CRP level			
No (n=32)	2.9 (2.8–3.1)	2.6–4.5	0.002*
Yes (n=70)	4 (3.3–4.6)	2.3–11.6	
Respiratory failure			
No (n=55)	3.2 (3–3.7)	2.3–4.5	U=99
Yes (n=47)	4.8 (4.6–6.1)	3.4–11.6	
Need for MV support			
No (n=77)	3.2 (3–3.6)	2.3–4.9	0.001*
Yes (n=25)	4.5 (4–6.1)	3.4–11.6	
Prolonged hospitalization			
No (n=68)	3.2 (2.9–3.4)	2.34-–4.54	0.010*
Yes (n=34)	4.6 (4.4–4.9)	3.99–11.6	
Short-term mortality			
No (n=92)	3.3 (3–4.4)	2.3–4.5	0.010*
Yes (n=10)	4.7 (4.4–7.4)	3.6–11.6	
High-risk long-term mortality			
No (n=27)	2.9 (2.7–3.2)	2.6–4.5	0.010*
Yes (n=75)	3.8 (3.2–4.6)	2.3–11.6	

*: p<0.05 considered statistically significant. IQR: Interquartile range; CRP: C-reactive protein; MV: Mechanical ventilation

Table 3: Correlation of red cell distribution width-to-albumin ratio (RAR) with other studied parameters in patients with chronic obstructive pulmonary disease (COPD) exacerbation

Variable	RAR (% g/dL)	
	r	p
Age (years)	-0.016	0.870
BMI (kg/m^2)	-0.084	0.402
FEV_1/FVC ratio	-0.818	0.010*
FEV_1%	-0.595	0.001*
FVC %	-0.319	0.027*
FEF25–75%	-0.684	0.001*
O_2 sat %	-0.824	0.003*
PaO_2 mmHg	-0.700	0.001*
$PaCO_2$ mmHg	0.044	0.661
WBC (10^3/cmm)	0.850	0.001*
CRP (mg/L)	0.861	0.001*
Hospitalization LOS (days)	0.750	0.001*
BODE index	0.698	0.001*

*: p<0.05 considered statistically significant. r: Spearman's correlation coefficient. BMI: Body mass index; FEV_1%: Forced expiratory volume in the first-second (% predicted); FVC%: Forced vital capacity (% predicted); FEF25–75%: Forced expiratory flow between 25-75% of vital capacity (% predicted); O_2 Sat %: Oxygen saturation %; PaO_2: Partial arterial pressure of oxygen; $PaCO_2$: Partial arterial pressure of carbon dioxide; WBC: White blood cells; CRP: C-reactive protein; LOS: Length of stay; BODE: Body mass index, obstruction, dyspnea, exercise

The RAR was statistically significantly increased in the following patients: those with frequent exacerbations compared with those with infrequent exacerbations (p=0.001); patients with hospitalizations in the last year compared to those with no hospitalizations in the last year (p=0.001); patients with severe current exacerbation compared to those with moderate current exacerbation (p=0.001); patients with leukocytosis compared to those without leukocytosis (p=0.010); patients with high serum CRP levels compared to those with normal serum CRP levels (p=0.002); patients with respiratory failure compared to those without respiratory failure (p=0.003); patients who needed MV support compared to those who did not need MV support (p=0.001); patients with prolonged hospitalizations (LOS >10 days) compared to those with non-prolonged hospitalizations (LOS <10 days) (p=0.001); patients with short-term mortality compared to those with no short-term mortality (p=0.001); and patients at high risk of long-term mortality (BODE index ≥5) compared to those at low risk of long-term mortality (BODE index <5) (p=0.001) (Table 2).

The RAR was negatively correlated with FEV_1/FVC ratio (r=-0.818), FEV_1% (r=-0.595), FVC % (r=-0.319), FEF25–75% (r=-0.684), PaO_2 (r=-0.700), and O_2 sat % (r=-0.824). It was positively correlated with BODE index (r=0698), WBC count (r=0.850), CRP (r=0.861), and hospitalization LOS (days) (r=0.750) (Table 3) [Fig. 1].

The RAR was a significant predictive index for frequent exacerbations (ß=1.51), hospitalizations (ß=1.41), severe current exacerbation (ß=1.75), respiratory failure (ß=3.29), need for MV support (ß=1.85), prolonged hospitalizations (ß=5.99), short-term mortality (ß=0.814), and high risk of long-term mortality (BODE index ≥5) (ß=3.97) (Table 4).

The RAR at a cutoff >3.7% g/dL had 67.3% sensitivity, 86.8% specificity, 82.5% PPV, and 74.2% NPV for discriminating patients with frequent exacerbations from those

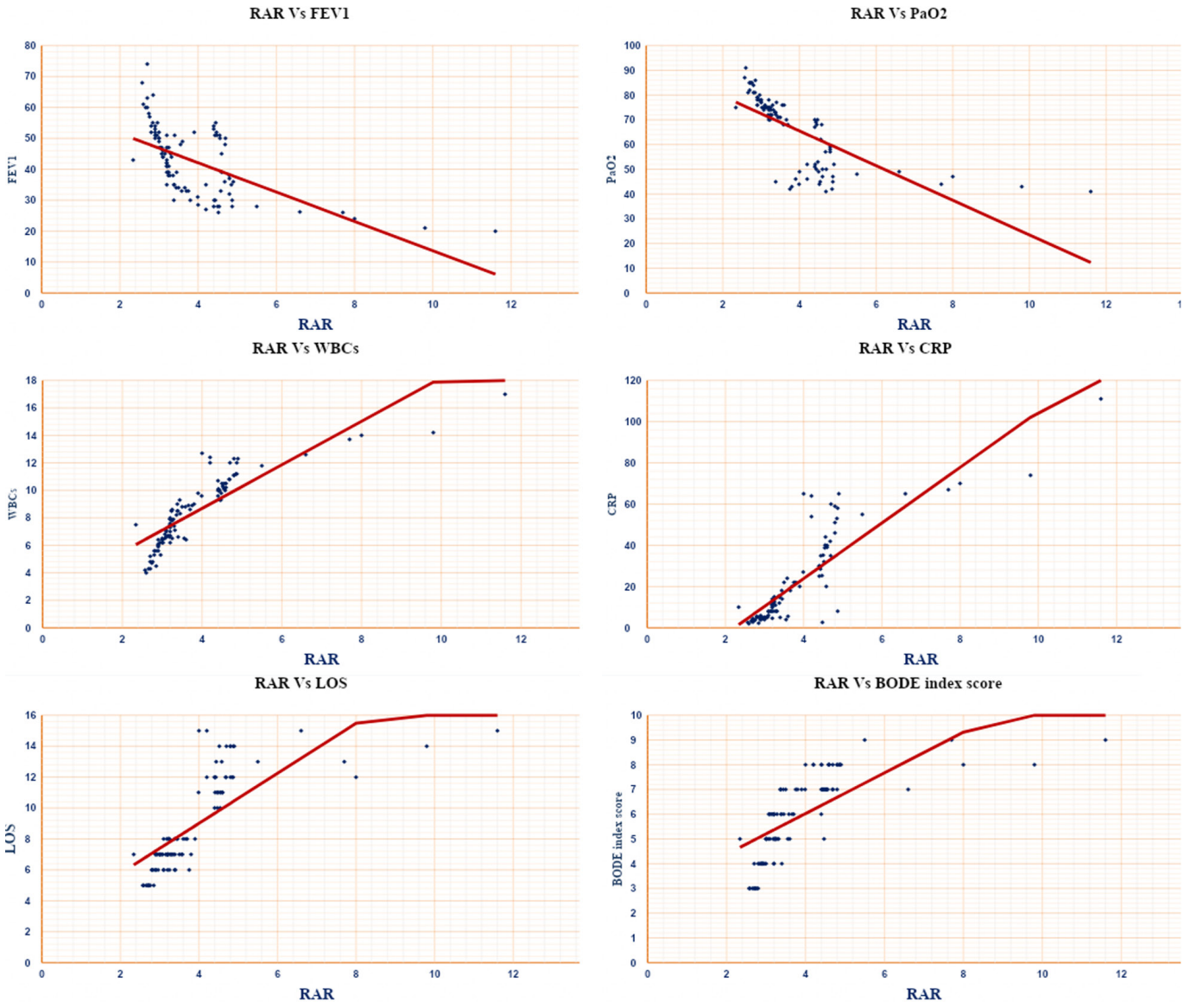

Figure 1: Correlation of red cell distribution width-to-albumin ratio (RAR) with other studied parameters in patients with chronic obstructive pulmonary disease (COPD) exacerbation

FEV_1%: Forced expiratory volume in the first second (% predicted), PaO_2: Partial arterial pressure of oxygen, WBC: White blood cells, CRP: C-reactive protein, LOS: Length of stay, BODE: Body mass index, obstruction, dyspnea, exercise

with non-frequent exacerbations (p=0.003). At a cutoff >3.75% g/dL, it had 73.7% sensitivity, 82.8% specificity, 71.8% PPV, and 84.1% NPP for discriminating patients with hospitalization from those without hospitalization (p=0.003). At a cutoff >3.75% g/dL, it had 72.7% sensitivity, 87.9% specificity, 82.1% PPV, and 81% NPP for discriminating patients with severe current exacerbation from those with moderate current exacerbation (p=0.002). The RAR at a cutoff >4.58% g/dL had 81% sensitivity, 97.5% specificity, 89.5% PPV, and 95.2% NPP for discriminating patients with respiratory failure from those without respiratory failure (p=0.001), while at cutoff >3.7% g/dL, it had 92% sensitivity, 77.9% specificity, 57.5% PPV, and 96.8% NPP for discriminating patients who needed MV support from those who did not need MV support (p=0.002). The RAR at a cutoff >3.9% g/dL had 100% sensitivity, 95.6% specificity, 91.9% PPV, and 96.8% NPP for discriminating patients with prolonged hospitalization from those with non-prolonged hospitalization (p=0.001). The RAR at a cutoff >3.55% g/dL had 100% sensitivity, 63% specificity, 22.7% PPV, and 100% NPP for discriminating patients with short-term mortality from those with no short-term mortality (p=0.003), while at a cutoff >2.96% g/dL, it had 98.7% sensitivity,

Table 4: Univariate logistic regression analysis of red cell distribution width-to-albumin ratio (RAR) in the prediction of adverse chronic obstructive pulmonary disease (COPD) exacerbation outcomes

Adverse ECOPD outcome	B	SE	p	OR	95% CI	
Frequent exacerbations	1.51	0.344	<0.001*	4.53	2.31	8.88
Hospitalization in last year for ECOPD	1.41	0.33	<0.001*	4.1	2.15	7.83
Severe current exacerbation	1.755	0.365	<0.001*	5.78	2.83	11.81
Respiratory failure	3.29	0.86	<0.001*	26.8	4.97	144.4
Need for MV support	1.85	0.427	<0.001*	6.34	2.74	14.64
Prolonged hospitalization	5.99	1.386	<0.001*	399.5	26.4	6044
Short-term mortality	0.814	0.262	0.002*	2.26	1.35	3.78
High-risk long-term mortality	3.97	1.046	<0.001*	53.02	6.82	412.2

*: p<0.05 considered statistically significant. B: Beta; SE: Standard error; OR: Odds ratio; CI: Confidence interval; MV: Mechanical ventilation

Table 5: Predictive performance of red cell distribution width-to-albumin ratio (RAR) in discriminating adverse exacerbation outcomes in patients with exacerbated chronic obstructive pulmonary disease (ECOPD)

Adverse ECOPD outcome	RAR cutoff	Predictive performance of RAR					
		AUC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	p
Frequent exacerbations	>3.7	0.795	67.3	86.8	82.5	74.2	0.003*
Hospitalization in last year for ECOPD	>3.75	0.793	73.7	82.8	71.8	84.1	0.003*
Severe current exacerbation	>3.75	0.808	72.7	87.9	82.1	81	0.002*
Respiratory failure	>4.58	0.942	81	97.5	89.5	95.2	0.001*
Need for MV support	>3.7	0.878	92	77.9	57.5	96.8	0.002*
Prolonged hospitalization (LOS > days)	>3.9	0.988	100	95.6	91.9	100	0.001*
Short-term mortality (in-hospital or within 30 days)	>3.55	0.865	100	63	22.7	100	0.003*
Long-term mortality (BODE index ≥5)	>2.96	0.912	98.7	70.4	90.2	95	0.001*

*: p<0.05 considered statistically significant. AUC: Area under the curve; PPV: Positive predictive value; NPV: Negative predictive value; MV: Mechanical ventilation; LOS: Length of stay; BODE: Body mass index, obstruction, dyspnea, exercise

70.4% specificity, 90.2% PPV, and 95% NPP for discriminating patients at high risk of long-term mortality from those at low risk of long-term mortality (BODE score <5) (p=0.001) (Table 5) [Fig. 2].

Discussion

As ECOPD is a common cause of hospital admission and an important contributor to death in COPD patients,[1] precise evaluation of attack severity with prediction of its outcome is important to guide management. Accordingly, we conducted the present study to evaluate the clinical significance of RAR in predicting COPD exacerbation outcomes.

The strong positive association of RAR with the studied inflammatory biomarkers (WBC and CRP) found in this study indicates that a higher RAR can be considered a relevant indicator of systemic inflammation in COPD exacerbation, as both components of RAR (RDW and albumin) have previously been documented to be related to systemic inflammation. Tan et al.[15] reported that diminished red blood cell production with reduced survival leads to an increase in RDW, which is associated with systemic inflammation. Additionally, Guo et al.[16] documented that the physiological functions of albumin include antioxidant activity, antiplatelet aggregation activity, anti-inflammatory effects, anticoagulant effects, and maintenance of colloid osmotic pressure. Therefore, RAR was considered a straightforward index for assessing underlying systemic inflammation in COPD exacerbation. This association between RAR and serum CRP was also documented in another study.[12]

This study revealed that the RAR was significantly increased in patients with frequent exacerbations and hospitalization for ECOPD in the previous year, and it was a significant predictive index for both frequent exacerbations and hospitalization. The RAR cutoff >3.75% g/dL had 73.7% sensitivity, 82.8% specificity,

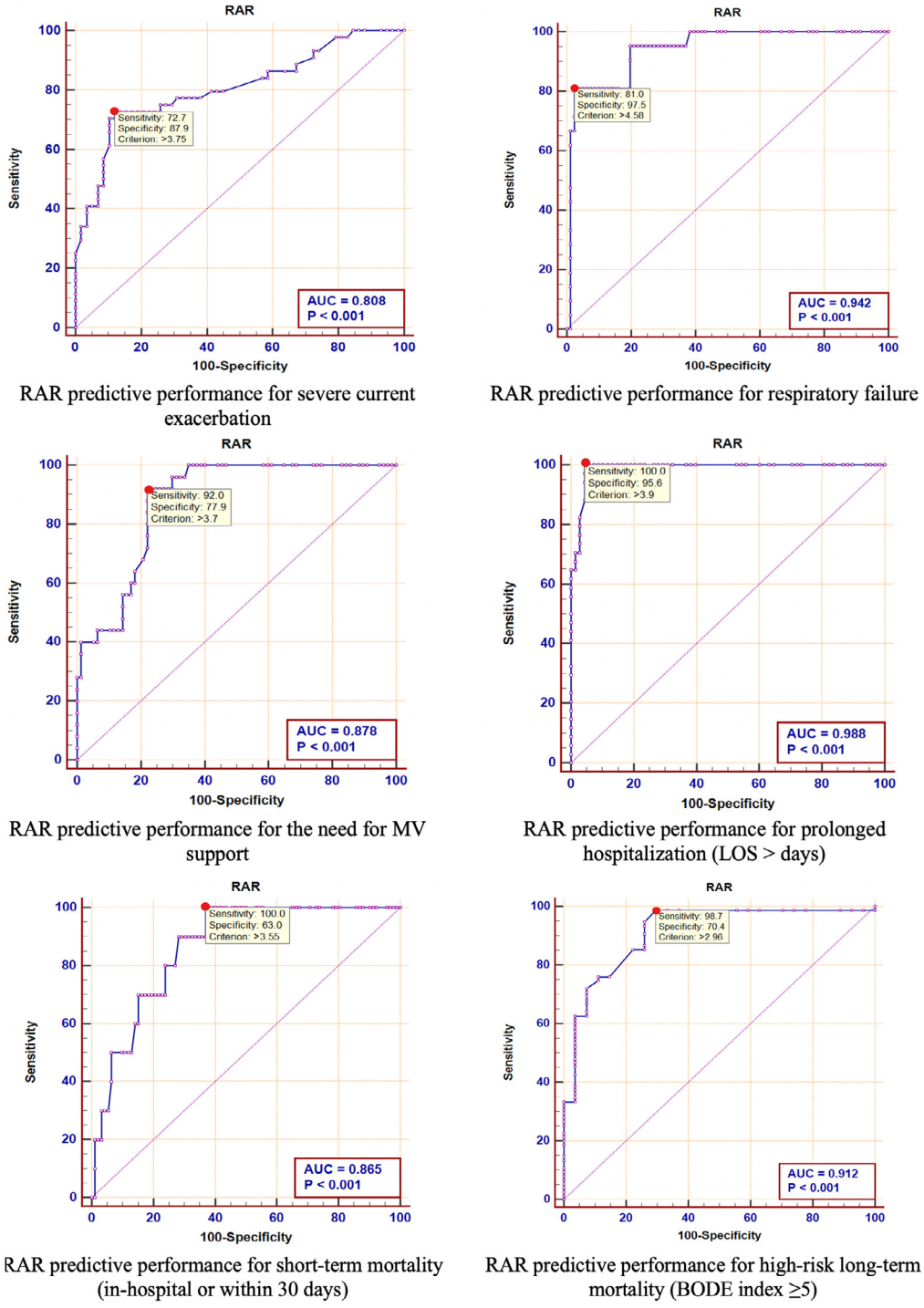

Figure 2: Receiver operating characteristic (ROC) curve of the predictive performance of red cell distribution width-to-albumin ratio (RAR) in discriminating adverse exacerbation outcomes in patients with exacerbated chronic obstructive pulmonary disease (ECOPD)

RAR: Red cell distribution width-to-albumin ratio, AUC: Area under the curve

71.8% PPV, and 84.1% NPV in predicting hospitalization, while for predicting frequent exacerbations, a cut-off >3.7% g/dL had 67.3% sensitivity, 86.8% specificity, 82.5% PPV, and 74.2% NPV. This significant association indicates that these patients have persistently higher systemic inflammation, which predisposes them to frequent exacerbations and hospitalizations. Similarly, Eraslan et al.[12] reported that RAR was higher in pa-

tients with a history of hospitalization for ECOPD in the last year. However, other studies reported a higher RAR cut-off (≥5.45) for predicting hospitalization, with 53.85% sensitivity, 84.38% specificity, 73.68% PPV, and 69.23% NPV. Additionally, patients with ≥3 COPD exacerbations had the greatest risk for mortality. Moreover, previous studies reported that higher RDW was associated with higher rates of readmission.[17,18]

During ECOPD, both systemic and airway inflammation increase.[12] This study demonstrated that the RAR was significantly higher in patients with severe current exacerbation and was a significant predictor for severe current exacerbation. Additionally, at a cutoff >3.75% g/dL, it had 72.7% sensitivity, 87.9% specificity, 82.1% PPV, and 81% NPV in predicting severe current exacerbations. These results could be explained by the fact that patients with severe exacerbations have greater airway and systemic inflammation, resulting in an increase in RAR. As severe COPD exacerbations have been shown to be associated with poor prognosis, RAR can be used for early identification of patients with severe exacerbations and to guide treatment strategies to improve disease outcomes.

One of the most common complications of ECOPD is acute respiratory failure, which often leads to mortality.[19] The current study revealed that the RAR was significantly increased in patients with respiratory failure and in those who needed MV support. It was negatively correlated with PaO_2 and O_2 saturation (%). The RAR was also found to be a significant predictive index for the need for MV support. At a cutoff >4.58, it predicted respiratory failure development with 81% sensitivity, 97.5% specificity, 89.5% PPV, and 95.2% NPV, while at a cutoff >3.7, it predicted the need for MV support with a sensitivity of 92%, specificity of 77.9%, PPV of 57.5%, and NPV of 96.8%. The exact mechanism for the association between RAR and respiratory failure in ECOPD is uncertain. A possible explanation may be that exacerbation-associated acute hypoxemia (decreased PaO_2) leads to substantially higher erythropoietin secretion from the renal cortex, thereby promoting the production of larger erythrocytes and resulting in increased RDW. Additionally, acute respiratory failure is often accompanied by inflammation; systemic inflammation and the release of cytokines can impair the hematopoietic function of erythrocytes, leading to an increase in RDW.[20] Furthermore, lower albumin levels in COPD patients, as part of malnutrition, reduce respiratory muscle strength and endurance, further aggravating respiratory failure.[21] Moreover, patients with respiratory failure, especially those receiving MV, need nutritional support,[19] which, if not provided, could further compromise the respiratory muscles and lead to progression of respiratory failure. Cytokines produced during inflammation shift amino acids away from albumin synthesis toward the synthesis of acute-phase proteins essential to the inflammatory process.[22] As early detection and treatment of respiratory failure can shorten hospitalization duration and improve outcomes, we recommend that during ECOPD, a higher RAR may be considered a reliable marker of tissue hypoxia. Previous studies have documented that RDW was significantly increased in patients requiring long-term oxygen therapy and non-invasive ventilation.[23] RDW was also inversely correlated with oxygen saturation.[24]

According to the present study results, we believe that RAR may predict prolonged hospitalization, as it was significantly increased in patients with prolonged hospitalization and positively correlated with hospitalization LOS. The RAR was a significant predictive index for prolonged hospitalization. Additionally, the RAR at a cutoff >3.9% g/dL can predict prolonged hospitalization with excellent predictive performance. This association between higher RAR and prolonged hospitalization may be explained by the fact that patients with higher RAR in our study had intense systemic inflammation (increased CRP and WBC), severe exacerbation, respiratory failure, and a higher need for MV support, all of which contribute to longer hospitalization. Our results are in agreement with Eraslan et al.,[12] who documented that RAR was positively correlated with hospitalization LOS, although they reported a significantly higher cutoff value of RAR (≥5.22) for predicting hospitalization duration (>10 days), with 68.42% sensitivity and 74.36% specificity. Similarly, Qiu et al.[2] reported that ECOPD patients with higher RAR had significantly longer hospitalization LOS in both the original (14 days vs. 9 days) and matched cohorts (13 days vs. 10 days).

The current study revealed that the RAR was significantly increased in patients with short-term mortality and that, at a cutoff >3.55% g/dL, it could predict short-term mortality with excellent sensitivity and NPV, fair specificity, and poor PPV. The mechanism by which higher RAR can predict short-term mortality was postulated by Zhu et al.,[17] who suggested that this may be explained by the synergistic effects of inflammation,

malnutrition, and hypoxia. Accordingly, we recommend that RAR, as an efficient and promising biomarker, can be used for early identification of patients at increased risk of hospital mortality and to guide treatment in order to improve ECOPD outcomes. The association between RAR and in-hospital mortality has been reported in previous studies in COPD without comorbidities[25] and in COPD with atrial fibrillation.[3] Qiu et al.[2] retrospectively investigated COPD patients admitted to the intensive care unit (ICU) for ECOPD and documented that a higher RAR was closely associated with in-hospital mortality (12.1%). However, they reported a higher RAR cutoff (>5.315% g/dL) for predicting in-hospital mortality in ECOPD patients, with 68.1% sensitivity and 65.8%. specificity. By contrast, another study including ECOPD patients hospitalized in the general ward found no association between RAR and mortality.[12] He et al.[19] documented that, in patients with acute respiratory failure, RAR had good predictive power for hospital stay (28 days) and 60-day mortality. Moreover, several studies have revealed that increased RDW is associated with an increased risk of death in both stable and exacerbated ECOPD patients,[24,26,27] that low albumin levels are a significant predictor of increased mortality in COPD.[28,29]

The five-year mortality rate in patients hospitalized with ECOPD is approximately 50%.[30] Regarding long-term mortality, the current study revealed that the RAR was significantly increased in patients at high risk of long-term mortality. The RAR was a significant predictive index for long-term mortality. At a cutoff >2.96% g/dL, RAR could predict patients at high risk of long-term mortality with excellent sensitivity, PPV, and 95% NPV, with fair specificity. Hu et al[18] found that RDW is independently associated with one-year mortality in COPD patients after adjusting for confounders such as age, BMI, heart failure, FEV_1 %, coronary heart disease, renal dysfunction, blood pH, PaO_2, and $PaCO_2$.

Our study has several strengths. First, it introduces the RAR as a novel, simple, and comprehensive indicator for early identification of adverse outcomes in ECOPD patients, helping physicians adjust the management plan to improve disease outcomes. RAR provides a comprehensive representation of the acute inflammatory response in ECOPD patients. When compared to individual markers such as RDW and albumin, RAR offers a more integrated assessment of disease progression and outcomes than RDW or albumin levels alone.[4]

However, this study had some limitations that should be mentioned. First, we excluded patients with other diseases that could alter RAR values from the analysis; therefore, these findings cannot be generalized to all ECOPD patients. Second, RAR levels were measured only once at the time of hospital admission, without investigating trends over time, which could have provided more thorough insights. Third, the cross-sectional design of this study precludes determining a causal association between RAR and COPD exacerbations; however, this limitation was addressed through subgroup analysis of the results.

Conclusion

This study revealed that a high RAR is a predictive risk factor for adverse outcomes in ECOPD patients. Therefore, it can be used for the early recognition of patients at high risk of morbidity and mortality and to guide their management strategies. The strong association of RAR with both short- and long-term mortality indicates that RAR is a promising biomarker for predicting mortality in ECOPD.

Ethics Committee Approval

The study was approved by the Al-Azhar University Ethics Committee (No: 01014995559, Date: 02/06/2024).

Informed Consent

A written informed consent was obtained from each patient before participating in the study.

Conflicts of Interest Statement

The authors have no conflicts of interest to declare.

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Use of AI for Writing Assistance

Artificial intelligence (AI) technology was not used in this study.

Author Contributions

Concept – A.S.E.F., M.R.H., S.F.Q.; Design – A.S.E.F., M.R.H., S.F.Q.; Supervision – A.S.E.F., M.R.H., S.F.Q.; Resource – A.S.E.F., S.F.Q.; Materials – A.S.E.F., M.R.H.; Data collection &/or processing – A.S.E.F., M.R.H.; Analysis and/or interpretation – A.S.E.F., S.F.Q.; Literature search – A.S.E.F.; Writing – A.S.E.F., M.R.H.; Critical review – A.S.E.F.

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