

Red Blood Cell Distribution Width/Hematocrit Ratio: A New Predictor of 28 Days All-Cause Mortality of AECOPD Patients in ICU

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Purpose: Elevated red blood cell distribution width (RDW) and decreased hematocrit (HCT) levels are associated with poor prognosis in chronic obstructive pulmonary disease (COPD) patients, but their significance in intensive care unit (ICU) patients with acute exacerbation of COPD (AECOPD) remains uncertain. The RDW/HCT ratio may offer a more comprehensive assessment compared to individual markers, potentially enhancing prognostic accuracy. Furthermore, the utility of RDW/HCT in improving traditional ICU scoring systems remains unexplored.

Patients and Methods: The optimal RDW/HCT ratio cutoff was identified via ROC curve analysis, guiding classification into high and low ratio groups. Univariate and multivariate logistic regression analyses, Kaplan-Meier survival curves, and propensity score matching (PSM) were performed to evaluate the association between RDW/HCT ratio and 28-day all-cause mortality. The predictive value of RDW/HCT ratio compared to traditional ICU scoring systems was assessed using the area under the curve (AUC). Additionally, the eICU database was utilized to validate the robustness of the association between RDW/HCT and mortality in patients with AECOPD.

Results: 624 patients were included, with 361 in the low RDW/HCT ratio group and 263 in the high ratio group. PSM yielded 145 matched pairs of patients with balanced baseline characteristics. Multivariate logistic regression analysis revealed that patients with RDW/HCT ratio ≥ 0.473 had significantly higher 28-day all-cause mortality compared to those with RDW/HCT ratio < 0.473 ($p < 0.001$). Combining RDW/HCT ratio with SOFA score improved the diagnostic accuracy significantly ($p=0.029$).

Conclusion: The RDW/HCT ratio is an independent predictor of 28-day all-cause mortality in AECOPD patients in the ICU. It can be used for a preliminary assessment before a systematic evaluation of the patient, indicating its potential value in early assessment of disease severity. In a comprehensive evaluation, combining the RDW/HCT ratio with the SOFA score can further enhance predictive accuracy.

Keywords: red blood cell distribution width, hematocrit, chronic obstructive pulmonary disease, intensive care unit, prognosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex condition characterized by persistent respiratory symptoms and progressive airflow limitation, primarily driven by lung inflammation.¹ Global estimates and literature findings indicate that COPD affects more than 300 million individuals and ranks as the third leading cause of mortality.² Moreover, with the aging population worldwide, COPD is anticipated to pose an even greater social and economic burden in the coming years.³ Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) denotes a sudden

worsening of symptoms in COPD patients, typically marked by heightened breathlessness and increased cough with sputum production, often triggered by pulmonary or systemic inflammatory processes.¹ AECOPD is frequently encountered in the intensive care unit (ICU), where it carries a substantial mortality risk ranging from 17.6% to 48.8% among admitted patients.⁴ Early stratification of patients by severity to implement individualized treatment and care strategies is key to reducing mortality, especially in severe cases of AECOPD.⁵ Furthermore, recent research indicates that designing specific medical strategies based on different risk stratifications can not only effectively reduce readmission rates post-discharge for AECOPD patients but also significantly improve their health outcomes after discharge.⁶ Thus, exploring relevant predictive biomarkers for early severity stratification and timely intervention is crucial for improving the prognosis of AECOPD patients in the ICU.

Red blood cell distribution width (RDW) serves as a marker reflecting the variability in the volume of red blood cells. Traditionally, RDW has been utilized to differentiate various types of anemia. Elevated RDW levels typically signify compromised red blood cell production and abnormal red blood cell survival, often linked to metabolic irregularities, oxidative stress, and inflammation.⁷ Recent investigations have highlighted the prognostic value of elevated RDW in conditions such as systemic lupus erythematosus, viral hepatitis, liver fibrosis, myelodysplastic syndrome, sepsis, and chronic kidney disease.^{8–12} Moreover, RDW has emerged as an independent predictor of mortality and readmission in AECOPD patients.^{13,14}

Hematocrit (HCT) denotes the volume percentage of blood cells in whole blood, primarily reflecting the total quantity of red blood cells due to the minimal presence of white blood cells and platelets. Studies have associated HCT with adverse outcomes in conditions such as gastric cancer, traumatic brain injury, and sepsis.^{15–17} Additionally, lower HCT levels have been identified as an independent risk factor for predicting mortality in severe COPD patients.¹⁸

However, previous investigations examining the relationship between RDW, HCT, and COPD prognosis may have overlooked critical confounding factors. For instance, patients with peripheral vascular diseases tend to exhibit higher levels of RDW and HCT. Moreover, COPD patients with concurrent peripheral vascular diseases typically experience worse prognoses compared to those without such comorbidities.^{19–21} Failure to account for these confounding variables may distort the true association between RDW, HCT, and COPD prognosis.

To comprehensively address these confounding factors, we employed propensity score matching (PSM) in our study. PSM is a statistical technique designed to mitigate bias arising from confounding variables by simulating randomization.²² By estimating the probability of each subject being assigned to the intervention group based on their characteristics, generating propensity scores, and then matching subjects between intervention and control groups, PSM effectively balances differences in confounding variables. This enhances comparability between groups, akin to a randomized controlled trial, thus improving research validity and efficiency.

Furthermore, limited research has focused on ICU patients with AECOPD concerning the relationship between RDW, HCT, and COPD prognosis. ICU-COPD patients present significant physiological distinctions compared to non-ICU-COPD patients. Yet, the precise association between RDW, HCT, and AECOPD patients in the ICU remains poorly understood.

Using either RDW or HCT in isolation may be influenced by a range of factors including nutritional status, fluid administration, red blood cell transfusions, and oxidative stress.^{7,23} However, employing the RDW/HCT ratio can mitigate the impact of individual variables and enhance stability. Moreover, compared to individual parameters, utilizing the RDW/HCT ratio offers insights into both red blood cell characteristics and quantity, rendering the metric more comprehensive and objective. Additionally, employing the ratio of red blood cell property parameters to quantity parameters has demonstrated efficacy in predicting outcomes in conditions such as sepsis, subarachnoid hemorrhage, and various malignancies.^{24–26} Thus, RDW/HCT holds promise as a predictive indicator.

The Sequential Organ Failure Assessment (SOFA) score, developed by the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine in 1996,²⁷ evaluates the severity and prognosis of patients by assessing the function of six systems: respiratory, cardiovascular, neurological, hepatic, coagulation, and renal. Widely adopted, the SOFA score has become the cornerstone of severity assessment in the ICU. Another commonly used scoring system is SAPS II (Simplified Acute Physiology Score II),²⁸ comprising 17 variables related to the patient's physiological status and clinical information. Despite their extensive use, variations in the performance of SOFA and SAPS II

persist across different disease populations.²⁹ Enhancing the accuracy of these scoring systems and exploring their applicability in diverse disease contexts remain areas of ongoing investigation.³⁰

This study endeavors to elucidate the relationship between RDW/HCT and the 28-day all-cause mortality rate among AECOPD patients in the ICU, aiming to furnish a straightforward and efficacious predictive marker for the early identification of critically ill AECOPD patients in the ICU. Furthermore, we sought to compare the efficacy of RDW/HCT with that of SOFA and SAPS II, as well as examine the potential benefits of their combined application.

Materials and Methods

Data Source

This study utilized data from two sources, the MIMIC-IV (v2.2) and eICU (v2.0) databases. Analysis and modeling were primarily conducted using the MIMIC-IV database, with the eICU database used for validation purposes. MIMIC-IV is a large, single-center medical database maintained by the Laboratory for Computational Physiology at the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center, which is affiliated with Harvard Medical School.³¹ The eICU database contains a large multicenter dataset with records from over 200,000 ICU admissions from 2014 to 2015.³² All information in the databases has been anonymized to ensure patient privacy, following protocols that included obtaining written informed consent from participants. Zhiwei Long, authorized to access both databases (name ID: 12635073, record ID: 58429392), has completed all necessary training. The retrospective design of this study and the thorough anonymization of all patient information led the Ethics Review Board at the First Affiliated Hospital of Guangzhou Medical University to waive the need for ethical review.

Inclusion and Exclusion Criteria

Inclusion criteria encompassed patients diagnosed with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) based on the International Classification of Disease, Tenth Revision. Exclusion criteria included patients not admitted to the ICU, ICU stays less than 24 hours, RDW/HCT measurements not taken within 24 hours of ICU admission, and instances of more than 15% missing data. Additionally, for patients with multiple ICU admissions, only the first hospitalization record was selected. After screening, the MIMIC-IV database included 624 patients, while the eICU database included 3125 patients. Details of the inclusion process can be seen in [Figure 1](#).

Data Extraction

Structured Query Language (SQL 16.0) was employed to extract information on patients admitted to the ICU within 24 hours, encompassing demographics (age, gender, height, weight, ethnicity), vital signs (heart rate, respiratory rate, blood pressure, oxygen saturation), laboratory indicators (RDW, HCT, WBC, PLT, electrolytes, renal function, blood gas analysis, liver function tests), comorbidities, prescriptions, mechanical ventilation status, and scoring systems (SOFA, SAPS II).

Primary and Secondary Research Objectives

The primary objective of this study is to evaluate the relationship between RHR and the 28-day mortality rate among patients with AECOPD in ICU. The secondary objectives are to compare the performance of RHR with classic scoring systems (SOFA and SAPS II) and to explore their combined application in the ICU setting.

Statistical Analysis

Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables are presented as median (interquartile range), while categorical variables are presented as percentages. Univariate analysis involved comparison of continuous variables using the *t*-test or Mann–Whitney test, and categorical variables using the chi-square or Fisher's exact test. Receiver operating characteristic (ROC) curves were generated, and the Youden index was calculated to determine the optimal cutoff value for the RDW/HCT ratio (RHR), dividing patients into high and low

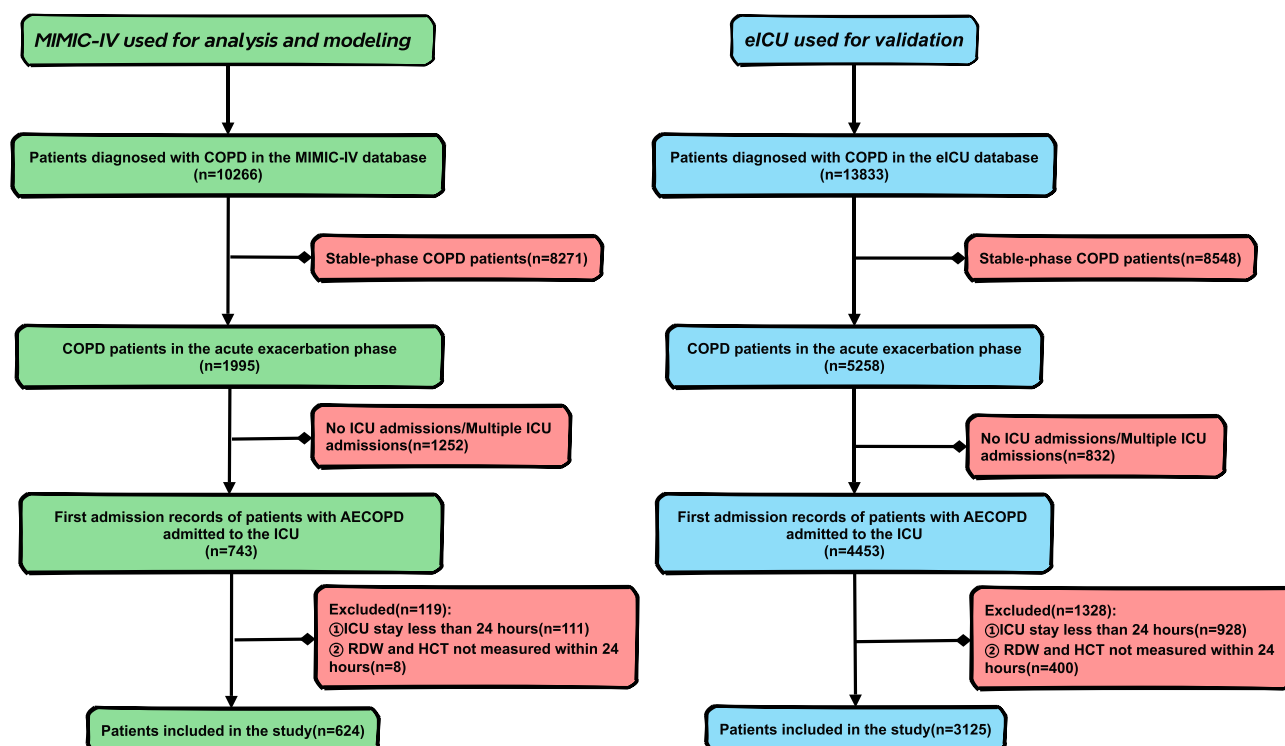


Figure 1 Inclusion process of study population.

RHR groups. The predictive abilities of RHR, SOFA score, and SAPS II score were evaluated by calculating the area under the curve (AUC).

Univariate and multivariate logistic regression analyses were conducted to assess the association between RHR and 28-day mortality. Variance inflation factor (VIF) was used to test for multicollinearity, with $VIF < 5$ indicating model stability. Confounding factors were selected based on specific criteria. Five models were constructed, progressively adjusting for relevant covariates.

To balance potential confounding factors between the high and low RHR groups, a 1:1 propensity score matching (PSM) was conducted. Logistic regression was used to calculate propensity scores for variables such as gender, age, ethnicity, and physiological parameters. Ultimately, 145 pairs of patients were successfully matched in the MIMIC-IV database. The reliability of PSM was assessed using standardized mean differences (SMD), density plots, and histograms based on propensity scores.

Kaplan-Meier (KM) survival curves were employed to compare 28-day mortality between the high and low RHR groups before and after PSM, with differences assessed using the Log rank test. Subgroup analysis was conducted based on relevant clinical variables. To ensure the reliability of the results, logistic regression was used to evaluate the performance of RHR in the eICU database.

Statistical analyses were performed using SPSS version 25.0, MedCalc statistical software version 20.022, Storm statistical platform, R version 4.3.0, and GraphPad Prism version 9.5.1. A two-tailed test was conducted, and $P < 0.05$ was considered statistically significant.

Results

Original Cohort

Figure 1 illustrates the inclusion process for the study population in the MIMIC-IV database, which encompasses a total of 624 patients. Table 1 provides a summary of the baseline characteristics of both survivors and non-survivors. Among the 624 patients, the median age was 72.2 years, with 48.7% being male and 51.3% female. The majority were of White

Table I Baseline Data of the Original Cohort

Variable	Total (n=624)	Survivors (n=499)	Non-Survivors (n=125)	P-value
Demographic				
Age	72.2 (65.6, 80.5)	71.2 (64.3, 78.3)	76.3 (68.7, 85.1)	<0.001
Male	304 (48.7)	249 (49.9)	55 (44.0)	0.238
Ethnicity				
White	422 (67.6)	338 (67.8)	84 (67.2)	0.670
Black	71 (11.4)	59 (11.8)	12 (9.6)	
Others	131 (21.0)	102 (20.4)	29 (23.2)	
Vital signs				
HR (beats/min)	107.0 (93.0, 122.0)	106.0 (92.0, 121.0)	112.0 (95.0, 130.0)	0.025
RR (beats/min)	30.0 (26.0, 34.0)	30.0 (26.0, 34.0)	31.0 (27.0, 35.0)	0.116
SBP (mmHg)	147.0 (132.0, 164.0)	147.0 (132.5, 165.0)	147.0 (132.0, 159.0)	0.497
DBP (mmHg)	93.0 (80.0, 107.0)	93.0 (80.0, 107.0)	92.0 (81.0, 104.6)	0.372
MAP (mmHg)	104.0 (93.0, 118.0)	104.0 (93.0, 119.0)	103.0 (92.0, 117.8)	0.293
SpO2 (%)	100.0 (99.0, 100.0)	100.00 (98.0, 100.0)	100.0 (99.0, 100.0)	0.181
Laboratory				
RDW (%)	15.3 (14.0, 17.0)	15.1 (13.9, 16.9)	15.8 (14.5, 17.5)	0.001
HCT (%)	34.5 (29.8, 39.7)	35.2 (30.2, 40.2)	32.1 (27.6, 36.7)	<0.001
RDW/HCT	0.45 (0.37, 0.56)	0.44 (0.36, 0.53)	0.49 (0.41, 0.60)	<0.001
WBC (K/uL)	11.9 (8.4, 16.1)	11.4 (8.3, 15.7)	13.0 (9.0, 17.5)	0.038
PLT (K/uL)	206.0 (153.0, 266.0)	209.0 (157.5, 268.0)	185.0 (137.0, 245.0)	0.010
Potassium (mEq/L)	4.5 (4.2, 5.0)	4.5 (4.1, 5.0)	4.5 (4.2, 5.1)	0.460
Sodium (mEq/L)	140.0 (137.0, 143.0)	140.0 (137.0, 143.0)	141.0 (138.0, 144.0)	0.162
Glucose (mg/dL)	158.50 (128.0, 205.0)	160.0 (129.0, 205.0)	153.0 (126.0, 201.0)	0.458
Cr (mg/dL)	1.1 (0.8, 1.6)	1.1 (0.8, 1.5)	1.3 (0.8, 2.1)	0.005
PH	7.39 (7.35, 7.44)	7.39 (7.35, 7.44)	7.39 (7.34, 7.43)	0.401
PaCO2 (mmHg)	55.0 (46.0, 69.1)	55.0 (46.0, 68.0)	57.0 (47.0, 72.0)	0.225
Anion gap (mEq/L)	15.0 (13.0, 18.0)	15.0 (13.0, 18.0)	16.0 (13.0, 19.0)	0.046
Bicarbonate (mEq/L)	27.0 (23.0, 31.0)	27.0 (23.0, 31.0)	26.0 (23.0, 30.0)	0.650
Comorbidities				
Hypertension	192 (30.8)	155 (31.1)	37 (29.6)	0.751
Diabetes	62 (9.9)	55 (11.0)	7 (5.6)	0.070
Asthma	30 (4.8)	27 (5.4)	3 (2.4)	0.159
Pulmonary embolism	24 (3.9)	13 (2.6)	11 (8.8)	0.003

(Continued)

Table I (Continued).

Variable	Total (n=624)	Survivors (n=499)	Non-Survivors (n=125)	P-value
Anemia	99 (15.9)	79 (15.8)	20 (16.0)	0.963
Hematological malignancies	18 (2.9)	12 (2.4)	6 (4.8)	0.258
Connective tissue diseases	23 (3.7)	20 (4.0)	3 (2.4)	0.557
Peripheral vascular diseases	45 (7.2)	37 (7.4)	8 (6.4)	0.695
Myocardial infarction	75 (12.0)	54 (10.8)	21 (16.8)	0.066
Liver disease	18 (2.9)	14 (2.8)	4 (3.2)	1.000
Chronic kidney disease	60 (9.6)	45 (9.0)	15 (12.0)	0.312
Malignant tumors	46 (7.4)	37 (7.4)	9 (7.2)	0.934
Sepsis	139 (22.3)	96 (19.2)	43 (34.4)	<0.001
Prescriptions*				
Corticosteroid	10 (1.6)	10 (2.0)	0 (0.0)	0.231
Bronchodilators	410 (65.7)	334 (66.9)	76 (60.8)	0.196
Vasopressors	20 (3.2)	13 (2.6)	7 (5.6)	0.157
Intravenous fluids	438 (70.2)	342 (68.5)	96 (76.8)	0.071
Blood transfusions	48 (7.7)	35 (7.0)	13 (10.4)	0.204
Mechanical ventilation				
Invasive	216 (34.6)	174 (34.9)	42 (33.6)	0.790
Non-invasive	147 (23.6)	108 (21.6)	39 (31.2)	0.024
Score				
SOFA	4.0 (2.0, 7.0)	4.0 (2.0, 7.0)	6.0 (3.0, 9.0)	<0.001
SAPSII	37.0 (29.0, 45.0)	35.0 (28.0, 43.0)	43.0 (37.0, 52.0)	<0.001
ICU stay (day)	3.0 (1.8, 6.0)	2.7 (1.7, 5.5)	4.1 (2.7, 8.6)	<0.001

Notes: *All prescriptions were issued within 24 hours of ICU admission for patients. A p-value less than 0.05 is considered statistically significant.

Abbreviations: HR, Heart Rate; RR, Respiratory Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; RDW, Red Blood Cell Distribution Width; HCT, Hematocrit; WBC, White Blood Cell; PLT, Platelet; Cr, Creatinine; SOFA, Sequential Organ Failure Assessment; SAPSII, Simplified Acute Physiology ScoreII.

ethnicity (67.6%), followed by Black (11.4%) and other ethnicities (21.0%). Of these, 499 were survivors, while 125 were non-survivors. Non-survivors tended to be older, had higher heart rates, wider red blood cell distribution width, lower hematocrit, significantly elevated white blood cell counts, reduced platelet counts, higher levels of creatinine and anion gap. Moreover, non-survivors presented with more cases of pulmonary embolism and sepsis, and received non-invasive ventilation more frequently. Furthermore, the non-survivor group had higher SOFA and SAPS II scores and longer ICU stays. All these differences were statistically significant with $p < 0.05$.

Before Propensity Score Matching

ROC curve analysis was conducted to assess the correlation between RHR and 28-day mortality, with detailed results provided in [Table S1](#) and [Figure S1](#). The calculated AUC area was 0.624 (95% CI, 0.585–0.662), with a maximum

Youden index of 0.213. Sensitivity was determined to be 62.12%, specificity was 59.20%, and the optimal cutoff value was identified as 0.473. Using this cutoff value, the study population was stratified into a low RHR group ($RHR < 0.473$) consisting of 361 individuals and a high RHR group ($RHR \geq 0.473$) consisting of 263 individuals. Their baseline characteristics are summarized in Table 2. The high RHR group exhibited a significantly higher proportion of males, lower diastolic and mean arterial pressures, and higher oxygen saturation. Laboratory tests revealed significantly elevated

Table 2 The Baseline Data for the High RHR Group and Low RHR Group Before PSM

Variable	RHR<0.473 (n=361)	RHR≥0.473(n=263)	P-value
Demographic			
Age	71.7 (65.5, 78.6)	73.8 (65.9, 82.1)	0.139
Male	304 (48.7)	191 (52.9)	0.014
Ethnicity			
White	237 (65.7)	185 (70.4)	0.416
Black	42 (11.6)	29 (11.0)	
Others	82 (22.7)	49 (18.6)	
Vital signs			
HR (beats/min)	107.0 (93.0, 123.0)	106.0 (90.0, 121.0)	0.343
RR (beats/min)	30.0 (27.0, 35.0)	30.0 (26.0, 33.0)	0.300
SBP (mmHg)	148.0 (134.0, 164.0)	145.0 (130.5, 161.5)	0.187
DBP (mmHg)	95.0 (81.0, 107.0)	89.0 (78.0, 104.6)	0.011
MAP (mmHg)	105.0 (95.0, 120.0)	102.0 (91.0, 117.8)	0.012
SpO2 (%)	99.0 (98.0, 100.0)	100.0 (99.0, 100.0)	<0.001
Laboratory			
WBC (K/uL)	12.1 (8.7, 16.4)	11.2 (7.9, 15.8)	0.93
PLT (K/uL)	208.0 (166.0, 262.0)	198.0 (131.5, 273.0)	0.101
Potassium (mEq/L)	4.6 (4.2, 5.0)	4.5 (4.1, 5.1)	0.359
Sodium (mEq/L)	140.0 (137.0, 143.0)	140.0 (137.0, 143.0)	0.584
Glucose (mg/dL)	159.0 (130.0, 209.0)	157.0 (125.5, 197.5)	0.262
Cr (mg/dL)	1.0 (0.7, 1.4)	1.3 (0.9, 2.2)	<0.001
PH	7.39 (7.35, 7.43)	7.40 (7.35, 7.45)	0.062
PaCO2 (mmHg)	56.0 (46.0, 71.0)	54.0 (45.5, 66.0)	0.036
Anion gap (mEq/L)	15.0 (13.0, 18.0)	16.0 (13.0, 18.0)	0.254
Bicarbonate (mEq/L)	27.0 (23.0, 31.0)	27.0 (23.0, 30.0)	0.740
Comorbidities			
Hypertension	132 (36.6)	60 (22.81)	<0.001
Diabetes	42 (11.6)	20 (7.60)	0.097

(Continued)

Table 2 (Continued).

Variable	RHR<0.473 (n=361)	RHR≥0.473(n=263)	P-value
Asthma	14 (3.9)	16 (6.08)	0.203
Pulmonary embolism	14 (3.9)	10 (3.80)	0.961
Anemia	59 (16.3)	40 (15.21)	0.702
Hematological malignancies	2 (0.6)	16 (6.1)	<0.001
Connective tissue diseases	13 (3.6)	10 (3.8)	0.895
Peripheral vascular diseases	17 (4.7)	28 (10.7)	0.005
Myocardial infarction	41 (11.4)	34 (12.9)	0.551
Liver disease	8 (2.2)	10 (3.8)	0.242
Chronic kidney disease	26 (7.2)	34 (12.9)	0.017
Malignant tumors	25 (6.9)	21 (8.0)	0.617
Sepsis	75 (20.8)	64 (24.3)	0.291
Prescriptions*			
Corticosteroid	4 (1.1)	6 (2.3)	0.249
Bronchodilators	246 (68.1)	164 (62.4)	0.133
Vasopressors	12 (3.3)	8 (3.0)	0.843
Intravenous fluids	244 (67.6)	194 (73.8)	0.096
Blood transfusions	5 (1.4)	43 (16.4)	<0.001
Mechanical ventilation			
Invasive	130 (36.0)	86 (32.7)	0.391
Non-invasive	92 (25.5)	55 (20.9)	0.184
Score			
SOFA	4.0 (2.0, 6.0)	5.0 (3.0, 8.0)	<0.001
SAPSII	36.0 (28.0, 43.0)	39.0 (31.0, 47.5)	0.001
ICU stay (day)	2.9 (1.7, 6.0)	3.2 (1.8, 6.1)	0.321
28-day mortality (%)	51 (14.1)	74 (28.1)	<0.001

Notes: *All prescriptions were issued within 24 hours of ICU admission for patients. A p-value less than 0.05 is considered statistically significant.

Abbreviations: HR, Heart Rate; RR, Respiratory Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; WBC, White Blood Cell; PLT, Platelet; Cr, Creatinine; SOFA, Sequential Organ Failure Assessment; SAPSII, Simplified Acute Physiology Score II.

creatinine levels and decreased PaCO₂ levels in the high RHR group. Additionally, the high RHR group showed significantly higher rates of hypertension, hematological malignancies, peripheral vascular diseases, and chronic kidney disease. Moreover, a higher proportion of patients in the high RHR group received red blood cell transfusions within 24 hours. Furthermore, the high RHR group demonstrated higher SOFA and SAPS II scores, as well as a greater 28-day mortality rate. All these differences were statistically significant with $p < 0.05$.

After Propensity Score Matching

To mitigate potential confounding factors, a 1:1 nearest neighbor propensity score matching (PSM) was conducted on the high and low RHR groups. Ultimately, 145 pairs of patients were obtained, and their characteristics are presented in Table 3. Following PSM, all baseline characteristics between the two groups were balanced ($P > 0.05$). Standardized

Table 3 The Baseline Data for the High RHR Group and Low RHR Group After PSM

Variable	RHR<0.473(n=145)	RHR≥0.473(n=145)	P-value
Demographic			
Age	72.1 (66.1, 80.6)	74.8 (63.8, 83.5)	0.513
Male	58 (40.0)	64 (44.1)	0.475
Ethnicity			
White	104 (71.7)	102 (70.3)	0.888
Black	19 (13.1)	18 (12.4)	
Others	22 (15.2)	25 (17.2)	
Vital signs			
HR (beats/min)	106.0 (93.0, 125.0)	108.0 (91.0, 121.0)	0.950
RR (beats/min)	30.0 (27.0, 35.0)	30.0 (26.0, 35.0)	0.576
SBP (mmHg)	148.0 (131.0, 163.0)	148.0 (133.0, 164.0)	0.861
DBP (mmHg)	94.0 (81.0, 107.0)	90.0 (79.0, 105.0)	0.224
MAP (mmHg)	103.0 (94.0, 122.0)	103.0 (92.0, 117.8)	0.249
SpO2 (%)	100.0 (99.0, 100.0)	100.0 (99.0, 100.0)	0.904
Laboratory			
WBC (K/uL)	11.9 (8.7, 15.3)	10.9 (7.9, 15.6)	0.500
PLT (K/uL)	219.0 (174.0, 264.0)	213.0 (151.0, 271.0)	0.302
Potassium (mEq/L)	4.5 (4.2, 5.1)	4.5 (4.1, 5.0)	0.236
Sodium (mEq/L)	141.0 (138.0, 143.0)	140.0 (137.0, 144.0)	0.571
Glucose (mg/dL)	150.0 (126.0, 197.0)	152.0 (122.0, 191.0)	0.688
Cr (mg/dL)	1.1 (0.8, 1.5)	1.1 (0.8, 1.8)	0.457
PH	7.40 (7.35, 7.45)	7.39 (7.35, 7.44)	0.453
PaCO2 (mmHg)	56.0 (46.0, 71.0)	56.0 (46.0, 68.0)	0.890
Anion gap (mEq/L)	15.0 (13.0, 18.0)	15.0 (13.0, 18.0)	0.561
Bicarbonate (mEq/L)	27.0 (23.0, 32.0)	27.0 (23.0, 30.0)	0.609
Comorbidities			
Hypertension	40 (27.6)	37 (25.5)	0.690
Diabetes	18 (12.4)	19 (13.1)	0.860

(Continued)

Table 3 (Continued).

Variable	RHR<0.473(n=145)	RHR≥0.473(n=145)	P-value
Asthma	8 (5.5)	8 (5.5)	1.000
Pulmonary embolism	6 (4.1)	4 (2.8)	0.520
Anemia	28 (19.3)	23 (15.9)	0.441
Hematological malignancies	1 (0.7)	3 (2.1)	0.615
Connective tissue diseases	5 (3.5)	5 (3.5)	1.000
Peripheral vascular diseases	11 (7.6)	9 (6.2)	0.643
Myocardial infarction	18 (12.4)	19 (13.1)	0.860
Liver disease	2 (1.4)	3 (2.1)	1.000
Chronic kidney disease	15 (10.3)	14 (9.7)	0.845
Malignant tumors	10 (6.9)	10 (6.9)	1.000
Sepsis	29 (20.0)	34 (23.5)	0.476
Prescriptions*			
Corticosteroid	3 (2.1)	4 (2.8)	1.000
Bronchodilators	90 (62.1)	98 (67.6)	0.325
Vasopressors	3 (2.1)	4 (2.8)	1.000
Intravenous fluids	97 (66.9)	103 (71.0)	0.446
Blood transfusions	5 (3.5)	4 (2.8)	1.000
Mechanical ventilation			
Invasive	42 (29.0)	46 (31.7)	0.609
Non-invasive	39 (26.9)	36 (24.8)	0.687
Score			
SOFA	4.0 (2.0, 6.0)	4.0 (3.0, 7.0)	0.321
SAPSII	36.0 (28.0, 44.0)	36.0 (28.0, 46.0)	0.643
ICU stay (day)	3.0 (1.7, 6.2)	3.2 (1.9, 6.0)	0.688
28-day mortality (%)	20 (13.8)	43 (29.7)	0.001

Notes: *All prescriptions were issued within 24 hours of ICU admission for patients. A p-value less than 0.05 is considered statistically significant.

Abbreviations: HR, Heart Rate; RR, Respiratory Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAP, Mean Arterial Pressure; WBC, White Blood Cell; PLT, Platelet; Cr, Creatinine; SOFA, Sequential Organ Failure Assessment; SAPSII, Simplified Acute Physiology ScoreII.

mean differences (SMD) before and after matching are provided in [Figure S2](#), indicating that most variables had an SMD < 0.1 between the high and low RHR groups after matching, signifying effective matching results. Propensity score probability density distribution plots and histograms before and after matching displayed similar shapes and heights for both groups, further confirming the quality of matching. These density plots and histograms are also provided in [Figure S3](#) and [S4](#).

Relationship Between RHR and 28-Days Mortality

The association between RHR and 28-day mortality was assessed through logistic regression, with the variance inflation factor (VIF) recorded in [Table S2](#). $VIF < 5$ was considered acceptable [Table 4](#) illustrates the relationship between RHR as a continuous variable and 28-day mortality before and after PSM. Results indicated a positive correlation between RHR and 28-day mortality both before and after PSM. Before PSM (Model 1: OR=12.603, 95% CI: 3.679–43.172, $p < 0.001$; Model 2: OR=15.648, 95% CI: 4.326–56.604, $p < 0.001$; Model 3: OR=9.934, 95% CI: 2.591–38.080, $p = 0.001$; Model 4: OR=17.830, 95% CI: 4.359–72.927, $p < 0.001$; Model 5: OR=11.152, 95% CI: 2.386–52.130, $p = 0.002$). After PSM (Model 1: OR=52.959, 95% CI: 6.690–419.222, $p < 0.001$; Model 2: OR=67.585, 95% CI: 7.646–597.413, $p < 0.001$; Model 3: OR=65.992, 95% CI: 6.427–677.622, $p < 0.001$; Model 4: OR=37.717, 95% CI: 3.584–369.107, $p = 0.002$; Model 5: OR=61.515, 95% CI: 5.034–751.686, $p = 0.001$). [Table 5](#) presents the results when RHR was treated as a categorical variable, revealing that the high RHR group ($RHR \geq 0.473$) exhibited significantly higher 28-day mortality rates compared to the low RHR group ($RHR < 0.473$) both before and after PSM. Before PSM (Model 1: OR=2.380, 95% CI: 1.595–3.550, $p < 0.001$; Model 2: OR=2.296, 95% CI: 1.524–3.461, $p < 0.001$; Model 3: OR=2.367, 95% CI: 1.544–3.629, $p < 0.001$; Model 4: OR=2.651, 95% CI: 1.699–4.136, $p < 0.001$; Model 5: OR=2.458, 95% CI: 1.531–3.945, $p < 0.001$). After PSM (Model 1: OR=2.635, 95% CI: 1.458–4.760, $p = 0.001$; Model 2: OR=2.608, 95% CI: 1.419–4.791, $p = 0.002$; Model 3: OR=2.813, 95% CI: 1.506–5.255, $p = 0.001$; Model 4: OR=2.697, 95% CI: 1.423–5.110, $p = 0.002$; Model 5: OR=2.652, 95% CI: 1.462–5.647, $p = 0.003$). [Figure 2](#) illustrates the Kaplan-Meier survival curves for the high and low RHR groups before and after PSM. Before PSM, it is visually apparent that the high RHR group exhibited a higher 28-day mortality rate, with the Log rank test yielding a p -value < 0.001 . After PSM, the high RHR group continued to display a higher 28-day mortality rate ($p = 0.001$). [Table S3](#) and [Figure S5](#) provide details on the ROC curves for RHR, RDW, and HCT. The findings indicated that the AUC area for RHR was higher compared to RDW (0.624 vs 0.593, $p = 0.098$) and HCT (0.624 vs 0.616, $p = 0.537$), albeit not significantly different. Additionally, the predictive capabilities of RHR, SOFA score, and SAPS II score for 28-day mortality were compared. As depicted in [Figure 3](#) and summarized in [Table 6](#), the AUC areas for SOFA score, SAPS II score, and RHR were 0.688, 0.640, and 0.624, respectively. No significant differences in AUC areas were observed between RHR and SOFA score or SAPS II score ($p > 0.05$). When RHR was combined with SOFA and SAPS II scores, the AUC areas were 0.670 and 0.701, respectively. Notably, the combination of RHR and SOFA score significantly enhanced the AUC area compared to SOFA score alone ($p = 0.029$).

Subgroup Analysis and Sensitivity Analysis

Subgroup analysis was conducted to explore the relationship between RHR and 28-day mortality in different populations, and the findings are presented in [Figure 4](#). The results indicated that there were no significant interactions between RHR and any of the subgroups ($P > 0.05$), demonstrating the stability of RHR. Sensitivity analysis was performed using logistic regression in the eICU database to further evaluate the robustness of RHR. Baseline information for AECOPD patients in the eICU database is documented in [Table S4](#). The logistic regression results are recorded in [Table S5](#), showing that high RHR is significantly positively associated with mortality in AECOPD patients, whether RHR is treated as a continuous or categorical variable.

Discussion

In this retrospective study, we analyzed data from 624 ICU patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) extracted from the MIMIC-IV database. Employing univariate logistic regression, multivariate logistic regression, and propensity score matching, we aimed to mitigate confounding factors. Our findings revealed a noteworthy correlation between elevated high RDW/HCT ratio (RHR) levels and increased 28-day all-cause mortality among ICU patients with AECOPD. Additionally, Kaplan-Meier curves illustrated a significantly lower 28-day survival rate among patients with $RHR \geq 0.473$ compared to those with $RHR < 0.473$, providing further support for our observations. Additionally, the robustness of RHR was validated using a multicenter cohort from the eICU database. Notably, this study marks the first instance where RHR has been identified as an independent predictor of adverse outcomes within 28 days among critically ill AECOPD patients.

Table 4 Multivariate Logistic Regression Analysis of the 28-Day All-Cause Mortality Rate in ICU Patients with AECOPD(RHR as a Continuous Variable)

	Model 1	OR	Model 2	OR	Model 3	OR	Model 4	OR	Model 5	OR
Before PSM	<0.001	12.603(3.679~43.172)	<0.001	15.648(4.326~56.604)	0.001	9.934(2.591~38.080)	<0.001	17.830(4.359~72.927)	0.002	11.152(2.386~52.130)
PSM	<0.001	52.959 (6.690~419.222)	<0.001	67.585 (7.646~597.413)	<0.001	65.992 (6.427~677.622)	0.002	37.717 (3.584~369.107)	0.001	61.515 (5.034~751.686)

Notes: Model 1 was not adjusted for any variables. Model 2 was adjusted for gender, age, and ethnicity. Model 3 was adjusted for hypertension, diabetes, asthma, pulmonary embolism, anemia, hematologic malignancy, connective tissue disease, myocardial infarction, peripheral vascular disease, liver disease, chronic kidney disease, malignancy, and sepsis. Model 4 was adjusted for heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, SpO2, white blood cell, platelet, potassium, sodium, glucose, creatinine, pH, PaCO2, anion gap, and bicarbonate. Model 5 was adjusted for age, gender, ethnicity, white blood cell, platelet, creatinine, hypertension, anemia, hematologic malignancy, connective tissue disease, peripheral vascular disease, myocardial infarction, liver disease, chronic kidney disease, sepsis, vasopressors, corticosteroids, intravenous fluids, red blood cell transfusions, SOFA, and SAPSII.

Table 5 Multivariate Logistic Regression Analysis of the 28-Day All-Cause Mortality Rate in ICU Patients with AECOPD(RHR as a Categorical Variable)

	Model 1	OR	Model 2	OR	Model 3	OR	Model 4	OR	Model 5	OR
Before PSM	<0.001	2.380(1.595~3.550)	<0.001	2.296(1.524~3.461)	<0.001	2.367(1.544~3.629)	<0.001	2.651(1.699~4.136)	<0.001	2.458(1.531~3.945)
PSM	0.001	2.635(1.458~4.760)	0.002	2.608(1.419~4.791)	0.001	2.813(1.506~5.255)	0.002	2.697(1.423~5.110)	0.003	2.652(1.462~5.647)

Notes: Model 1 was not adjusted for any variables. Model 2 was adjusted for gender, age, and ethnicity. Model 3 was adjusted for hypertension, diabetes, asthma, pulmonary embolism, anemia, hematologic malignancy, connective tissue disease, myocardial infarction, peripheral vascular disease, liver disease, chronic kidney disease, malignancy, and sepsis. Model 4 was adjusted for heart rate, respiratory rate, systolic blood pressure, diastolic blood pressure, SpO2, white blood cell, platelet, potassium, sodium, glucose, creatinine, pH, PaCO2, anion gap, and bicarbonate. Model 5 was adjusted for age, gender, ethnicity, white blood cell, platelet, creatinine, hypertension, anemia, hematologic malignancy, connective tissue disease, peripheral vascular disease, myocardial infarction, liver disease, chronic kidney disease, sepsis, vasopressors, corticosteroids, intravenous fluids, red blood cell transfusions, SOFA, and SAPSII.

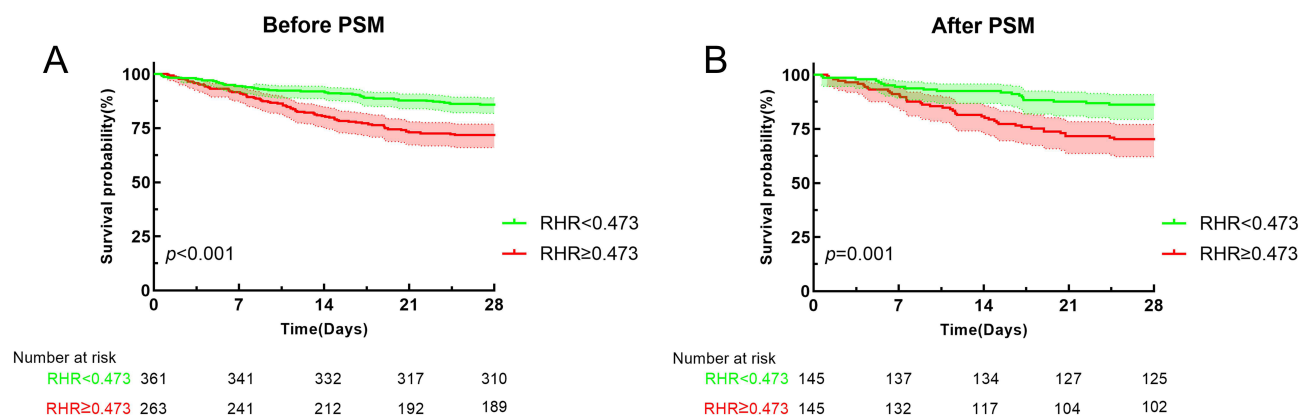


Figure 2 Kaplan-Meier curves for high and low RHR groups before and after propensity score matching (PSM). (A): Kaplan-Meier curves for high and low RHR groups before PSM. (B): Kaplan-Meier curves for high and low RHR groups after PSM.

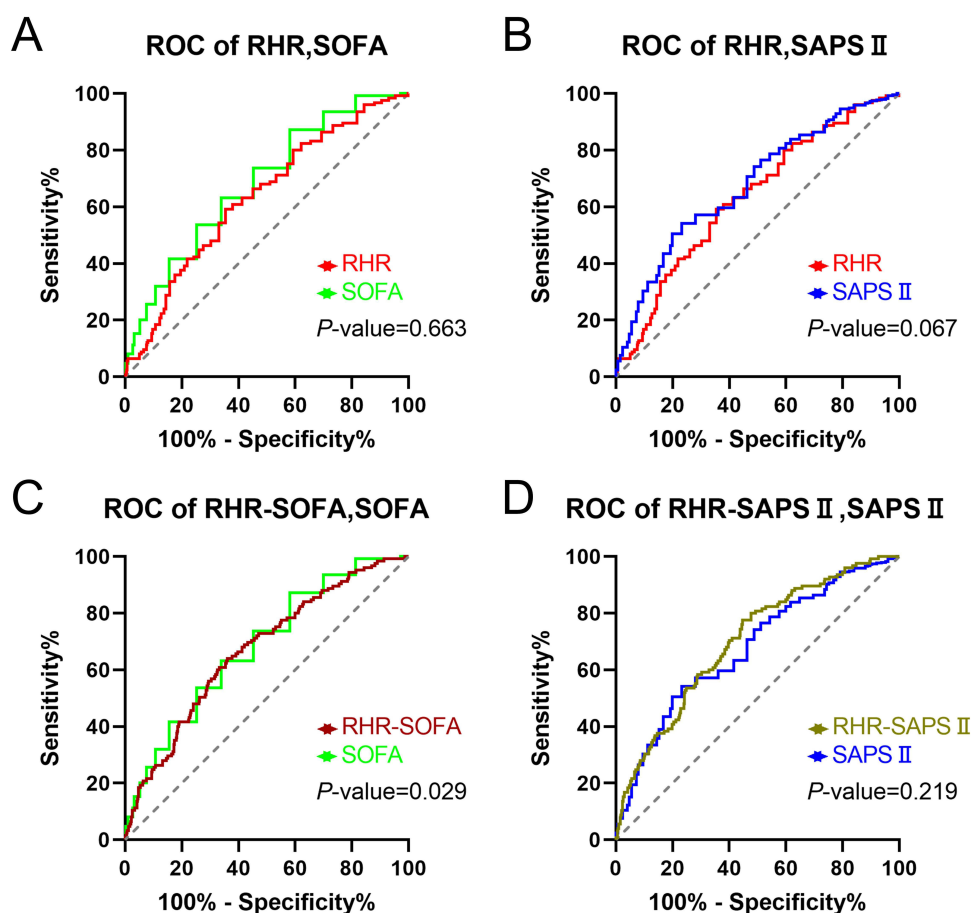


Figure 3 Receiver operating characteristic (ROC) curves for RHR, SOFA, SAPSII, RHR-SOFA and RHR-SAPSII in both the survival and non-survival groups, accompanied by the p-value indicating the difference between the ROC curves. (A): ROC curves for RHR and SOFA. (B): ROC curves for RHR and SAPS II. (C): ROC curves for combined RHR-SOFA and SOFA alone. (D): ROC curves for combined RHR-SAPSII and SAPSII alone.

Biomarkers are biochemical indicators that reflect the health of organs and tissues and are crucial for early disease detection. They are particularly useful in clinical settings because changes in biomarker levels can often be detected before symptoms and radiological findings become apparent. In COPD, biomarkers play a key role in diagnosis, prognostic evaluations, and treatment management. For example, a large-scale, multicenter, prospective study has

Table 6 Area Under the Curve (AUC), Cut-off Value, Sensitivity, Specificity for Predicting Death in AECOPD Patients by RHR, SOFA, SAPSII, RHR-SOFA, and RHR-SAPSII

Variables	AUC	95% CI	Cutoff	Sensitivity	Specificity
RHR	0.624	0.585–0.662	0.473	59.20%	62.12%
SOFA	0.640	0.601–0.677	5	53.60%	66.13%
SAPSII	0.688	0.650–0.724	36	76.60%	54.11%
RHR-SOFA	0.670	0.632–0.707	-	64.00%	63.93%
RHR-SAPSII	0.701	0.663–0.737	-	77.60%	55.31%

shown that early high levels of creatinine are associated with higher hospital mortality rates and increased ICU admissions among emergency department patients with AECOPD.³³ Additionally, elevated neutrophil and monocyte counts are early indicators of COPD, which help in timely diagnosis.³⁴ Eosinophil counts are also important for accurately classifying COPD types and guiding the administration of inhaled corticosteroids.³⁵ For the most critically ill COPD patients, especially those with AECOPD in the ICU, early prognostic evaluations and personalized management are vital for effective treatment. The use of biomarkers in this context holds great potential.

We observed that high RHR, calculated as the ratio of red cell distribution width (RDW) to hematocrit (HCT), exhibited comparable performance to the Sequential Organ Failure Assessment (SOFA) score in assessing severity within the ICU setting (area under the curve [AUC]: 0.624 vs 0.640, $p=0.663$). Although RHR demonstrated lower discriminatory ability compared to the Simplified Acute Physiology Score (SAPS) II, this difference was not statistically significant ($p=0.067$). Notably, RHR offers the advantage of being easily accessible through routine venous blood tests in clinical practice. Unlike the comprehensive data collection required for SOFA and SAPS II, the RDW/HCT ratio can provide an initial evaluation of AECOPD severity at an earlier stage due to its simplicity and accessibility.

Furthermore, our study highlighted the potential of combining RHR with the SOFA score to enhance prognostic accuracy. The joint application of RHR and SOFA score resulted in a significantly higher AUC area compared to using the SOFA score alone (0.640 vs 0.670, $p=0.029$). Since the SOFA score does not incorporate RDW or HCT-related indicators, integrating the RDW/HCT ratio with the SOFA score could augment the identification of critically ill AECOPD patients, thus facilitating more precise risk stratification and management decisions.

Kalemci and colleagues have previously noted a correlation between higher RDW levels and the severity of COPD, with RDW exceeding 14.45% associated with severe COPD.³⁶ Similarly, a prospective study by Hu et al identified RDW levels greater than 13.75% as an independent risk factor for in-hospital and one-year mortality in AECOPD patients.¹⁴ Consistent with these findings, our study revealed significantly elevated RDW levels in AECOPD patients who succumbed within 28 days in the ICU compared to survivors ($p=0.001$), with the optimal cutoff value determined as 14.6% based on the receiver operating characteristic (ROC) curve analysis.

Traditionally, it was believed that COPD patients would experience compensatory polycythemia due to hypoxemia resulting from diminished respiratory function, leading to an increase in hematocrit levels. However, recent evidence, including the observations of Quintana et al and Heinemann et al, challenges this notion, suggesting that lower hematocrit levels are associated with greater COPD severity and adverse outcomes.^{37,38} Consistent with these studies, our findings indicated significantly lower hematocrit levels in AECOPD patients who died within 28 days compared to survivors ($p<0.001$), with the optimal cutoff value determined as 35.5%.

While there is existing literature on the predictive value of RDW or hematocrit alone, our study investigated the combined ratio of RDW to hematocrit (RHR) as a potential prognostic indicator. Zhu et al reported the superiority of using a combination index of RDW and hemoglobin over individual parameters in identifying frail individuals in the community.³⁹ Additionally, the RDW to hemoglobin ratio has been validated in predicting prognosis in diseases such as sepsis and head and neck cancer.^{24,25} In line with these observations, our study demonstrated that RHR exhibited a larger

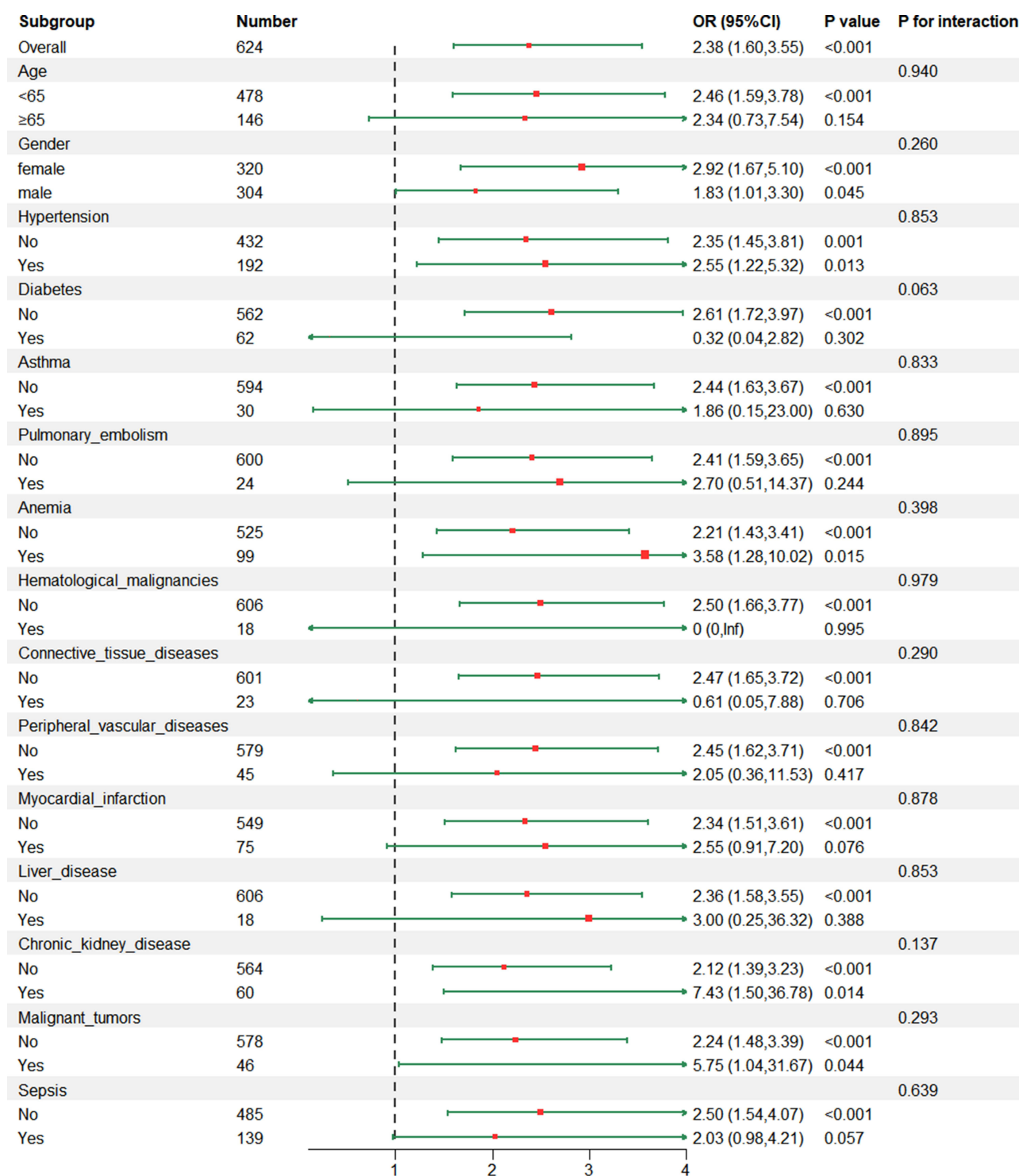


Figure 4 The relationship between RHR and 28-days mortality rates of ICU-admitted AECOPD patients in different subgroups.

AUC area compared to using RDW and HCT alone, albeit without a significant difference observed. Therefore, we elected to utilize RHR as a prognostic indicator for AECOPD patients, recognizing its potential in predicting adverse outcomes.

In our study, we established a cutoff value of 0.473 to classify patients into high and low RHR groups. The high RHR group showed significantly higher mortality compared to the low RHR group (28.1% vs 14.1%, $p < 0.001$). Moreover, even after adjusting for numerous confounding factors using multivariate logistic regression, high RHR levels remained significantly associated with 28-days all-cause mortality in ICU AECOPD patients, both before and after propensity score matching (PSM). Thus, RHR emerges as a stable parameter for assessing 28-days all-cause mortality in ICU AECOPD patients. Further research is warranted to explore the potential differences between RDW/hemoglobin and RDW/HCT and their implications in predicting outcomes in AECOPD patients.

The precise mechanism linking elevated RDW/HCT and increased mortality rates in AECOPD remains elusive. We hypothesize that elevated RDW/HCT, or the derived parameter RHR, may reflect heightened inflammation and oxidative stress levels. During AECOPD, renal cells sense decreased oxygen tension and release erythropoietin (EPO) into the bloodstream.⁴⁰ EPO stimulates bone marrow stem cell differentiation, erythropoiesis, and the release of immature red blood cells, influencing RDW levels. Although EPO may lead to increased hematocrit, intermittent hypoxemia in COPD patients, along with factors promoting red blood cell destruction, may counteract this effect.⁴¹

Inflammation and oxidative stress are key pathogenic mechanisms in COPD, particularly during AECOPD, manifesting as increased circulating inflammatory mediators such as IL-6, TNF- α , and CXCL8.^{42,43} These cytokines inhibit normal bone marrow red blood cell maturation, leading to the release of immature red blood cells into circulation, thereby increasing RDW.⁴⁴ Additionally, TNF and IL-1 can directly shorten red blood cell lifespan, lowering hematocrit.^{45,46} Systemic oxidative stress during AECOPD may disrupt the oxidative-antioxidant balance, activating neutrophils to release reactive oxygen species (ROS) into circulation.^{47,48} Increased ROS levels may elevate red blood cell lipid peroxidation, affecting cell volume and stiffness, and altering RDW.⁴⁹ Moreover, systemic oxidative stress may inhibit red blood cell generation, further decreasing hematocrit.⁵⁰

In summary, AECOPD patients experience a complex interplay of factors leading to red blood cell homeostatic imbalance and metabolic abnormalities, characterized by polychromatophilic erythropoiesis and decreased total red blood cell count.

Despite the insights gained, several limitations exist in this study. Firstly, being a retrospective cohort study, there might be residual confounding factors despite attempts to control known variables. Furthermore, RDW and HCT values were obtained within 24 hours of ICU admission. However, the study primarily focuses on conducting an initial prognosis assessment of ICU patients with AECOPD. In a clinical setting, continuous monitoring of the RDW/HCT ratio allows for a more precise real-time evaluation of patients. In a clinical setting, dynamic monitoring of the RDW/HCT ratio could provide a more accurate real-time assessment of patients. Future prospective multicenter studies are warranted to validate the prognostic utility of RHR in AECOPD patients.

Conclusion

The RDW/HCT ratio can serve as an independent predictor of 28-day all-cause mortality among AECOPD patients in the ICU and assists in the preliminary assessment of patient conditions prior to systematic evaluations. Additionally, the combined use of RHR and the SOFA score exhibits a higher potential for identifying critically ill patients compared to using the SOFA score alone.

Abbreviations

RDW, red blood cell distribution width; HCT, hematocrit; COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICU, intensive care unit; PSM, propensity score matching; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; RHR, RDW/HCT ratio.

Data Sharing Statement

The datasets generated and/or analysed during the current study are available in the MIMIC-IV database (<https://physionet.org/content/mimiciv/2.2/>) and eICU database (<https://physionet.org/content/eicu-crd/2.0/>).

Consent for Publication

All participants agreed to publish the article.

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 no financial or commercial conflict of interest in this work.

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