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ORIGINAL RESEARCH

Unveiling the Prognostic Power of HRR in ICU-Admitted COPD Patients: A MIMIC-IV Database Study

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Objective: This study sought to examine the potential relationship between Hemoglobin/Red Cell Distribution Width Ratio (HRR) and the all-cause mortality risk in critically ill patients with chronic obstructive pulmonary disease (COPD).

Patients and Methods: In a retrospective analysis of the MIMIC-IV database, patients were divided into two groups based on a specific HRR threshold. Propensity score matching (PSM) was employed to address covariate imbalances. Logistic regression models was used to examine the association between HRR and mortality. A restricted cubic spline (RCS) model was employed to visualize the association between HRR and mortality. Receiver Operating Characteristic (ROC) curves were utilized to assess the predictive capability of HRR, and Decision Curve Analysis (DCA) was conducted for clinical evaluation. Furthermore, subgroup analyses were performed to explore potential variations within specific cohorts.

Results: A comprehensive analysis identified a total of 1,061 patients. The threshold value established for HRR is 5.395 g/L/%. Following the application of PSM, the matched cohort comprised 544 patients. Both the original and matched cohorts exhibited higher rates of all-cause mortality and extended hospital stays among individuals with low HRRs. Logistic regression analyses demonstrated that HRR is an independent risk factor of mortality. The RCS analysis demonstrated a significant linear relationship between HRR and mortality. The ROC curves yielded values of 0.58 for the original cohort and 0.60 for the matched cohort. DCA analysis indicated that HRR is clinically valuable. Subgroup analyses further validated the robustness of these core findings.

Conclusion: A lower HRR is positively associated with all-cause mortality in critically ill patients with COPD.

Keywords: COPD, red blood cell distribution width, hemoglobin, all-cause hospital mortality, MIMIC-IV

Background

The chronic obstructive pulmonary disease (COPD) occurs in more than 300 million people worldwide.[1] It is characterized by airflow obstruction, respiratory symptoms, and daily breathing difficulties.[2] In fact, it is one of the leading causes of morbidity, with a high disease burden and significant healthcare costs.[3] Patients with COPD are at an increased risk of exacerbations, hospitalizations, and mortality, with the mortality rate of COPD patients with ICU admissions being higher than those admitted to general wards.[4] The identification of reliable prognostic markers for ICU admission in COPD patients is crucial to guide appropriate clinical management and improve outcomes.

Hemoglobin/Red Cell Distribution Width Ratio (HRR) is a novel biomarker that reflects the balance between oxygen-carrying capacity and red blood cell volume.[5] It has been shown to be associated with various clinical outcomes and has gained increasing attention in recent years. HRR has been found to be related to the diagnosis, severity, and prognosis of several common diseases, including malignant tumors, cardiovascular diseases, diabetes, and sepsis.[6–9] These studies have demonstrated the potential of HRR as a prognostic marker and highlighted its clinical significance in various medical conditions. However, there is limited research on the relationship between HRR and COPD. HRR remains

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unclear in relation to the prognosis of COPD, particularly in ICU patients. Our study aims to investigate the association between HRR and outcomes in critically ill COPD patients. Understanding the prognostic significance of HRR in this patient population could provide valuable insights for clinical decision-making and improve risk stratification in the management of severe COPD exacerbations.

Materials and Methods

Data Sources

An analysis of MIMIC-IV (version 2.2) database data was conducted in this study.[10] There are over 280,000 admissions to Beth Israel Deaconess Medical Center in Boston, Massachusetts, represented in the MIMIC-IV Database, which is publicly available. It includes information such as demographics, vital signs, laboratory measurements, medications, and more, making it a valuable resource for conducting clinical research.[11] The use of the MIMIC-IV Database allows for the exploration of associations and patterns in a large and diverse patient population, which may not be feasible in single-center studies. Access to the MIMIC-IV Database was obtained after completion of the National Institutes of Health's online training course on protecting human research participants, and approval from their institutional review board.[12] The Institutional Review Boards of Beth Israel Deaconess Medical Center exempted the requirement for individual patient consent, as the project posed no significant impact on clinical care and all protected health information was de-identified.[13] Since the patient data did not originate from the Second People's Hospital of Meishan City, Yunchang Hospital, or Chengdu Sixth People's Hospital, the Institutional Review Boards of these institutions also waived the need for ethical approval. Furthermore, because the study was retrospective, the Institutional Review Boards of the Second People's Hospital of Meishan City, Yunchang Hospital, and Chengdu Sixth People's Hospital granted a waiver for written informed consent.

Selection of Study Population

The study cohort will comprise individuals with COPD who have been diagnosed with the ICD-10 code J449, are aged 18 years or older, have been admitted to the ICU for the initial time, and have had an ICU stay exceeding 24 hours. Exclusion criteria will encompass patients with inadequate laboratory data, absence of ICU admission, recurrent ICU admissions, or ICU stays lasting less than 24 hours.

Variable Extraction

A data management platform was created using Navicat Premium 15 (version 15.0.12). In this study, R and STATA were used for the analysis of research data. The research addressed a variety of key variables essential for analyzing the participating subjects. Among these were demographic factors such as age and gender. Furthermore, the study placed significant emphasis on vital signs, particularly the respiratory rate (RR), heart rate (HR), and mean non-invasive blood pressure (NBPm). The initial laboratory data collected were extensive, incorporating white blood cell (WBC) counts, neutrophil counts, lymphocyte counts, platelet counts, hemoglobin concentrations, red blood cell distribution width (RDW), as well as creatinine and lactate levels. Additionally, the investigation gathered pivotal information related to treatment strategies, including data on the administration of antibiotics, glucocorticoids, and ventilation methods. Besides these variables, scores from various acute illness severity assessment tools were also obtained to enrich the study's analytical framework. Specifically, the Acute Physiological Score III (APS III), the Oxford Acute Severity of Illness Score (OASIS), and the Sequential Organ Failure Assessment (SOFA) scores were considered. The HRR (g/l/%) was calculated by dividing hemoglobin by the RDW (%). Hypertension, type 2 diabetes, heart failure, and malignant cancer were used to identify comorbidities.

This study's primary outcome was all-cause hospital mortality, with length of stay as its secondary outcome.

Statistical Analysis

The optimal HRR cutoff was determined by maximizing Receiver Operating Characteristic Curve (ROC) in terms of specificity and sensitivity, resulting in a high and low HRR group. Statistical analyses included a *t*-test for assessing differences in continuous variables with normal distributions and homogeneity, the Wilcoxon rank-sum test for analyzing

differences in continuous variables with non-normal distributions or lack of homogeneity, and a chi-square test for comparing differences between groups based on categorical variables.

A 1:1 PSM technique was employed to address any potential imbalances in covariates between the two study groups, ensuring the reliability of the findings. Analyses using univariate and multivariate logistic regression were performed on the original cohort and matched cohort odds ratios (ORs). Model 1 included adjustments for age and gender, while Model 2 incorporated variables from Model 1 as well as comorbidities (hypertension, type 2 diabetes, heart failure, and malignant cancer). In Model 3, scoring systems (APS III, OASIS, and SOFA) and comorbidity indices were introduced, and in Model 4, vital signs (RR, HR, NBPm) and laboratory data (white blood cell counts, neutrophil counts, lymphocyte counts, platelet counts, hemoglobin concentrations, red blood cell distribution width creatinine and lactate levels) were adjusted to account for the variables introduced in Model 3. Restricted cubic splines (RCS) were utilized to investigate possible non-linear associations between HRR and all-cause mortality in individuals with COPD. Various knot placements ranging from 3 to 7 were tested, and the model with the lowest Akaike Information Criterion (AIC) value was selected for Restricted Cubic Splines (RCS), ultimately employing 3 knots. Subgroup analyses were performed considering variables such as age (<70 and≥70 years old), sex (Male/Female), hypertension (Yes/No), diabetes (Yes/No), heart failure (Yes/No) and malignant cancer (Yes/No). The ROC curve was utilized to compare the predictive performance of HRR in predicting hospital mortality. A comprehensive assessment of the clinical utility of HRR was performed using decision curve analysis (DCA). All statistical analyses were carried out using R software version 4.0.1.2, with statistical significance set at $p<0.05$.

Results

Patient Characteristics

In the MMIC-IV database (version 2.0) and based on the criteria outlined above, 1061 COPD patients admitted to ICUs were identified Figure 1. Detailed information on the baseline clinical characteristics of patients in the original cohort prior to PSMcan be found in Table 1. In the initial cohort, a cutoff value of 5.395 for HRR was chosen by maximizing the total of ROC curve specificity and sensitivity before performing PSM. Subsequently, The patients enrolled in the study

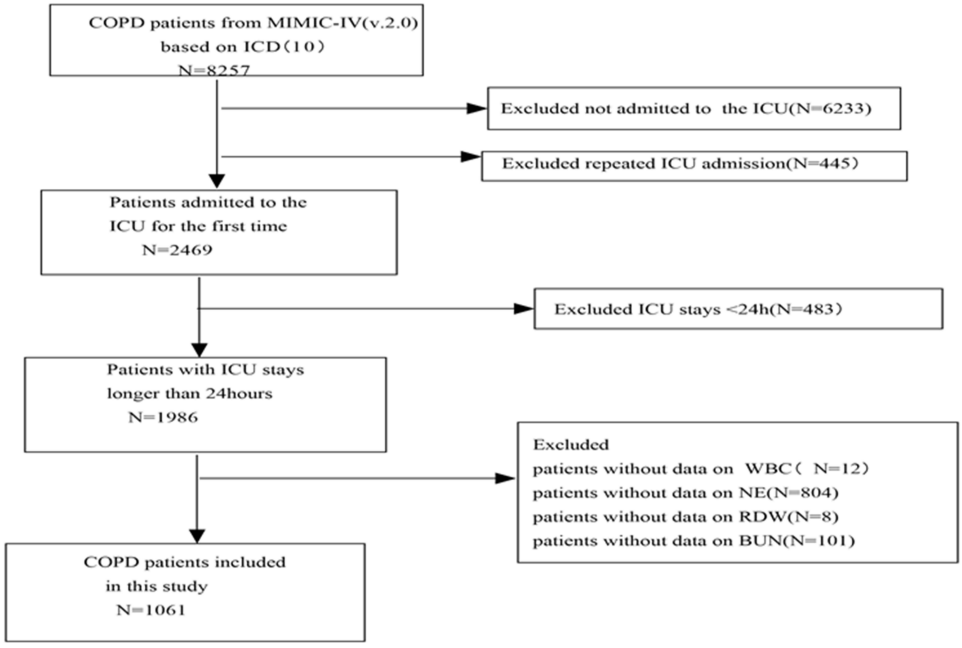

Figure 1 Flowchart for the inclusion of patients.
Note: This study included 1061 COPD patients admitted to the intensive care unit.
Abbreviations: ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care version IV; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; RDW, red blood cell distribution width; Cr, Creatinine.

Table 1 The Characteristics of the Original Cohort of COPD Patients Admitted to the ICU

Variables	Overall (N = 1061)	Low HRR (n = 277)	High HRR (n = 784)	*P*
Demographics				
Age, Year	72.00 (65.00, 79.00)	72.00 (65.00, 81.00)	72.00 (64.00, 79.00)	0.211
Male, n (%)	583 (54.95)	138 (49.82)	445 (56.76)	0.046
Vital signs				
HR, beat/min	87.00 (77.00, 102.00)	88.00 (77.00, 105.00)	86.00 (76.75, 101.00)	0.295
NBPm, mmHg	78.00 (68.00, 90.00)	75.00 (66.00, 89.00)	79.00 (69.00, 91.00)	0.005
RR, beat/min	19.00 (15.00, 24.00)	20.00 (16.00, 24.00)	19.00 (15.00, 24.00)	0.615
Scoring system				
SOFA score	6.00 (4.00, 8.00)	7.00 (4.00, 10.00)	5.00 (3.00, 8.00)	<0.001
APS III score	46.00 (35.00, 59.00)	52.00 (41.00, 64.00)	44.00 (33.00, 57.00)	<0.001
OASIS score	34.00 (28.00, 39.00)	34.00 (29.00, 40.00)	33.00 (28.00, 39.00)	0.047
Laboratory parameters				
WBC, 10^9cells/L	12.20 (8.80, 16.70)	11.50 (8.20, 16.70)	12.40 (9.10, 16.72)	0.055
Neutrophil count,10^9cells/L	9.69 (6.46, 13.96)	9.38 (5.95, 13.98)	9.79 (6.80, 13.96)	0.101
Lymphocytes,10^9 cells/L	1.12 (0.61, 1.81)	0.93 (0.48, 1.52)	1.21 (0.66, 1.90)	<0.001
Platelet,10^9cells/L	172.00 (126.00, 238.00)	163.00 (112.00, 252.00)	174.00 (130.00, 234.00)	0.122
Hemoglobin, g/L	99.00 (84.00, 115.00)	79.00 (72.00, 85.00)	107.00 (93.00, 120.00)	<0.001
RDW, %	14.80 (13.70, 16.70)	17.70 (16.00, 19.70)	14.40 (13.30, 15.40)	<0.001
Lactate, mmol/l	1.70 (1.20, 2.50)	1.50 (1.20, 2.30)	1.80 (1.20, 2.60)	0.003
Creatinine, mg/dl	1.10 (0.80, 1.70)	1.30 (0.90, 2.40)	1.00 (0.70, 1.50)	<0.001
Treatments				
Antibiotic, n(%)	991 (93.40)	259 (93.50)	732 (93.37)	0.938
Glucocorticoids, n(%)	168 (15.83)	51 (18.41)	117 (14.92)	0.172
Ventilation, n(%)	993 (93.59)	254 (91.70)	739 (94.26)	0.134
Comorbidities				
Hypertension, n (%)	365 (34.40)	93 (33.57)	272 (34.69)	0.736
Type 2 diabetes, n(%)	387 (36.48)	101 (36.46)	286 (36.48)	0.996
Heart failure, n (%)	502 (47.31)	135 (48.74)	367 (46.81)	0.581
Malignant cancer, n (%)	215 (20.26)	54 (19.49)	161 (20.54)	0.711

Notes: Continuous variables are represented as median [IQR]; Categorical variables are represented as n (%).
Abbreviations: HRR, Hemoglobin/Red Cell Distribution Width Ratio; RR, respiratory rate; HR, heart rate; NBPm, mean non-invasive blood pressure; RDW, red blood cell distribution width; SOFA, sequential organ failure assessment; OASIS, oxford acute severity of illness score; APS III, acute physiological score III; WBC, white blood cell.

were divided into two distinct groups based on their HRR levels: those in the low HRR group (<5.395) and those in the high HRR group (≥5.39). The enrolled patients were divided into two groups based on their HRR: low and high (≥5.395). There were no significant differences between the two groups in terms of age, HR, RR, white blood cell count, neutrophil count, platelet count, antibiotic use, glucocorticoid use, ventilation status, hypertension, Type 2 diabetes, heart failure, or malignant cancer. However, the groups did differ significantly in terms of gender (P<0.05), NBPm (P<0.001), SOFA score (P<0.001), APS III score (P<0.001), OASIS score (P<0.005), lymphocyte count (P<0.001), hemoglobin level (P<0.001), Red Cell Distribution Width (RDW) (P<0.001), lactate level (P<0.001), and creatinine level (P<0.001).

In a matched cohort, a total of 554 individuals with COPD were categorized into groups based on their HRR levels, taking into account factors such as age, gender, vital signs, comorbidities, and treatment (Table 2). A comparison between the group with low HRR and the group with high HRR revealed significant differences in various parameters. Specifically, the low HRR group exhibited lower Neutrophil count (9.38×10^9/L compared to 10.07×10^9/L, P=0.046), Lactate levels (1.5 mmol/L compared to 1.8 mmol/L, P=0.017), hemoglobin levels (79 g/L compared to 124 g/L, P<0.001), and Lymphocytes count (0.93×10^9/L compared to 1.22×10^9/L, P=0.001). On the other hand, the low HRR group showed significantly higher WBC count (12.60×10^9/L compared to 11.5×10^9/L, P=0.045), RDW (17.7%

Table 2 Baseline Characteristics for the Matched Cohort of Patients with COPD Admitted to the ICU

Variables	Overall (N = 554)	Low HRR (n = 277)	High HRR (n = 277)	*P*
Demographics				
Age, Year	72.00 (64.25, 79.00)	72.00 (65.00, 81.00)	71.00 (64.00, 77.00)	0.083
Male, n (%)	319 (57.58)	138 (49.82)	181 (65.34)	<0.001
Vital signs				
HR, beat/min	87.50 (77.00, 104.00)	88.00 (77.00, 105.00)	86.00 (78.00, 102.00)	0.683
NBPm, mmHg	79.00 (68.00, 91.00)	75.00 (66.00, 89.00)	82.00 (70.00, 93.00)	<0.001
RR, beat/min	19.00 (16.00, 24.00)	20.00 (16.00, 24.00)	19.00 (16.00, 24.00)	0.501
Scoring system				
SOFA score	6.00 (4.00, 9.00)	7.00 (4.00, 10.00)	5.00 (3.00, 8.00)	<0.001
APS III score	47.00 (36.00, 60.00)	52.00 (41.00, 64.00)	43.00 (32.00, 55.00)	<0.001
OASIS score	34.00 (28.00, 39.00)	34.00 (29.00, 40.00)	33.00 (28.00, 39.00)	0.071
Laboratory parameters				
WBC, 10^9cells/L	12.00 (8.60, 17.08)	12.60 (9.10, 17.40)	11.50 (8.20, 16.70)	0.045
Neutrophil count,10^9cells/L	9.75 (6.43, 14.00)	9.38 (5.95, 13.98)	10.07 (7.34, 14.11)	0.046
Lymphocytes,10^9 cells/L	1.06 (0.54, 1.71)	0.93 (0.48, 1.52)	1.22 (0.63, 1.90)	0.001
Platelet,10^9cells/L	174.00 (125.25, 238.00)	163.00 (112.00, 252.00)	179.00 (139.00, 228.00)	0.064
Hemoglobin, g/L	100.00 (78.25, 123.75)	79.00 (72.00, 85.00)	124.00 (114.00, 136.00)	<0.001
RDW, %	15.15 (13.70, 17.80)	17.70 (16.00, 19.70)	13.70 (13.00, 14.60)	<0.001
Lactate, mmol/l	1.70 (1.20, 2.40)	1.50 (1.20, 2.30)	1.80 (1.20, 2.60)	0.017
Creatinine, mg/dl	1.10 (0.80, 1.78)	1.30 (0.90, 2.40)	1.00 (0.80, 1.40)	<0.001
Treatments				
Antibiotic, n(%)	521 (94.04)	259 (93.50)	262 (94.58)	0.590
Glucocorticoids, n(%)	102 (18.41)	51 (18.41)	51 (18.41)	1.000
Ventilation, n(%)	513 (92.60)	254 (91.70)	259 (93.50)	0.417
Comorbidities				
Hypertension, n (%)	186 (33.57)	93 (33.57)	93 (33.57)	1.000
Type 2 diabetes, n(%)	202 (36.46)	101 (36.46)	101 (36.46)	1.000
Heart failure, n (%)	268 (48.38)	135 (48.74)	133 (48.01)	0.865
Malignant cancer, n (%)	107 (19.31)	54 (19.49)	53 (19.13)	0.914

Notes: Continuous variables are represented as median [IQR]; Categorical variables are represented as n (%).
Abbreviations: HRR, Hemoglobin/Red Cell Distribution Width Ratio; RR, respiratory rate; HR, heart rate; NBPm, mean non-invasive blood pressure; RDW, red blood cell distribution width; SOFA, sequential organ failure assessment; OASIS, oxford acute severity of illness score; APS III, acute physiological score III; WBC, white blood cell.

compared to 13.7%, P<0.001), SOFA score (7 compared to 5, P<0.001), APS III score (53 compared to 43, P<0.001), and Creatinine levels (1.30 mg/dL compared to 1.00 mg/dL, P<0.001).

Clinical Outcomes

The clinical outcomes of patients with COPD are presented in Table 3. In the original cohort, in-hospital mortality was significantly higher in the low HRR group, with 68 patients (24.55%) compared to 105 patients (13.39%) in

Table 3 Clinical Outcomes of COPD Patients Admitted to the ICU in the Original and Matched Cohorts

		Overall	Low HRR	High HRR	P
Original cohort	Hospital stays, day	9(7, 17)	12 (8,23)	7 (6, 15)	<0.001
	Hospital mortality	173 (16.31)	68 (24.55)	105 (13.39)	<0.001
Matched cohort	Hospital stays, day	11 (8, 19)	12 (10,23)	9(7, 17)	0.005
	Hospital mortality	102 (18.41)	68 (24.55)	34 (12.27)	<0.001

Abbreviations: HRR, Hemoglobin/Red Cell Distribution Width Ratio; ICU, intensive care unit; COPD, chronic obstructive pulmonary disease.

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the higher HRR group (P<0.001). Similar findings were observed in the matched cohort, where the low HRR group had 68 patients (24.55%) versus 34 patients (12.27%) in the higher HRR group (P<0.001). Additionally, the length of stay for patients in the low HRR group was longer in both the original cohort (12 days vs.7 days, P<0.001) and the matched cohort (12 days vs.9 days, P=0.005).

Association Between HRR and Hospital Mortality

A logistic regression analysis was performed on HRR to predict hospital mortality in COPD patients, as outlined in Table 4. The initial model, prior to adjusting for variables, indicated that HRR is linked to hospital mortality (Original cohort: OR 2.10, 95% CI 1.49–2.96, P<0.01; Matched cohort: OR 2.33, 95% CI 1.48–3.65, P<0.01). Following this, covariates were taken into consideration when adjusting the ORs of Model 1, Model 2, Model 3, and Model 4. Among the original cohort, the adjusted ORs for Model 1, Model 2, Model 3, and Model 4 were 2.03 (95% CI 1.44–2.87, P<0.01), 2.02 (95% CI 1.43–2.86, P<0.01), 1.65 (95% CI 1.14–2.39, P<0.01), and 2.10 (95% CI 1.49–2.96, P<0.01), respectively. Similar adjusted ORs were observed in the matched cohort, with values of 2.14 (95% CI 1.35–3.38, P<0.01), 2.17 (95% CI 1.36–3.45, P<0.01), 1.72 (95% CI 1.05–2.82, P<0.01), and 2.33 (95% CI 1.48–3.65, P<0.01), respectively. Hospital mortality among COPD patients admitted to the ICU was independently associated with low HRR levels. Subgroup analysis explored the relationship between HRR and all-cause mortality, based on age, sex, hypertension, diabetes, heart failure and malignant cancer. Core results remained consistent, and there was no significant interaction between these characteristics and HRR (P for interaction>0.05) (Table 5).

RCS analysis revealed a positive linear association between HRR and all-cause mortality (*P* for nonlinear =0.076) (Figure 2).

Clinical Value of HRR

HRR is an effective predictor of hospital mortality according to a ROC curve (Figure 3). The AUC for the original cohort (Figure 3A) was 0.580, with an HRR cutoff of 5.395, resulted in an sensitivity of 0.693 and a specificity of 0.765. This cohort's HRR cut-off was 4.478, which achieved 0.622 and 0.888 sensitivity and specificity, respectively, in the matched cohort (Figure 3B).

Table 4 Hospital Mortality Prediction in COPD Patients Admitted to the ICU Based on Logistic Regression Analysis

	Original Cohort		Matched Cohort	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Unadjusted	2.10 (1.49–2.96)	<0.001	2.33 (1.48–3.65)	<0.001
Model 1	2.03 (1.44–2.87)	<0.001	2.14 (1.35–3.38)	<0.001
Model 2	2.02 (1.43–2.86)	<0.001	2.17 (1.36–3.45)	<0.001
Model 3	1.65 (1.14–2.39)	<0.001	1.72 (1.05–2.82)	<0.001
Model 4	2.10 (1.49–2.96)	<0.001	2.33 (1.48–3.65)	<0.001

Notes: Model 1 adjusted for age and gender; Model 2 adjusted for Model 1 plus comorbidities (hypertension, type 2 diabetes, heart failure, and malignant cancer); Model 3, adjusted for Model 2 plus scoring systems (APS III, OASIS, and SOFA); Model 4 adjusted for model 3 plus vital signs (RR, HR, NBPm) and laboratory parameters (white blood cell counts, neutrophil counts, lymphocyte counts, platelet counts, hemoglobin concentrations, red blood cell distribution width creatinine and lactate levels).

Abbreviations: OR, odds ratio; 95% CI, 95% confidence index; RR, respiratory rate; HR, heart rate; NBPm, mean non-invasive blood pressure; SOFA, sequential organ failure assessment; OASIS, oxford acute severity of illness score; APS III, acute physiological score III.

Table 5 Subgroup Analysis for the Associations of HRR with All-Cause Mortality in Patients with COPD

Subgroup	High HRR Group	Low HRR Group	OR (95% CI)	P value	P for Interaction
Overall	105/784 (13.4)	68/277 (24.5)	2.10 (1.49–2.96)	<0.001	
Hypertension					0.082
NO	73/512 (14.3)	41/184 (22.3)	1.72 (1.12–2.63)	0.012	
YES	32/272 (11.8)	27/93 (29.0)	3.07 (1.71–5.48)	<0.001	
Type 2 diabetes					0.708
NO	64/498 (12.9)	40/176 (22.7)	1.99 (1.26–3.09)	0.002	
YES	41/286 (14.3)	28/101 (27.7)	2.29 (1.32–3.95)	0.003	
Heart failure					0.218
NO	49/417 (11.8)	36/142 (25.4)	2.55 (1.57–4.12)	<0.001	
YES	56/367 (15.3)	32/135 (23.7)	1.73 (1.05–2.80)	0.029	
Malignant cancer					0.638
NO	90/623 (14.4)	60/223 (26.9)	2.18 (1.50–3.15)	<0.001	
YES	15/161 (9.3)	8/54 (14.8)	1.69 (0657–4.16)	0.262	
Gender					0.104
F	46/339 (13.6)	42/139 (30.2)	2.76 (1.71–4.45)	<0.001	
M	59/445 (13.3)	26/138 (18.8)	1.52 (0.90–2.50)	0.106	
Age					0.752
<70	36/350 (10.3)	21/116 (18.1)	1.93 (1.06–3.44)	0.028	
≧70	69/434 (15.9)	47/161 (29.2)	2.18 (1.42–3.33)	<0.001	

Abbreviations: COPD, chronic obstructive pulmonary disease; HRR, Hemoglobin/Red Cell Distribution Width Ratio; OR, odds ratio; 95% CI, 95% confidence index.

We used decision curve analysis (DCA) to evaluate HRR's ability to predict hospital mortality. Figures 4A and 4B indicate that HRR provided greater net benefit compared to the "all treatment" or "no treatment" strategies within a risk threshold probability range of 0–100%. These results suggest that HRR may demonstrate good performance in terms of clinical utility.

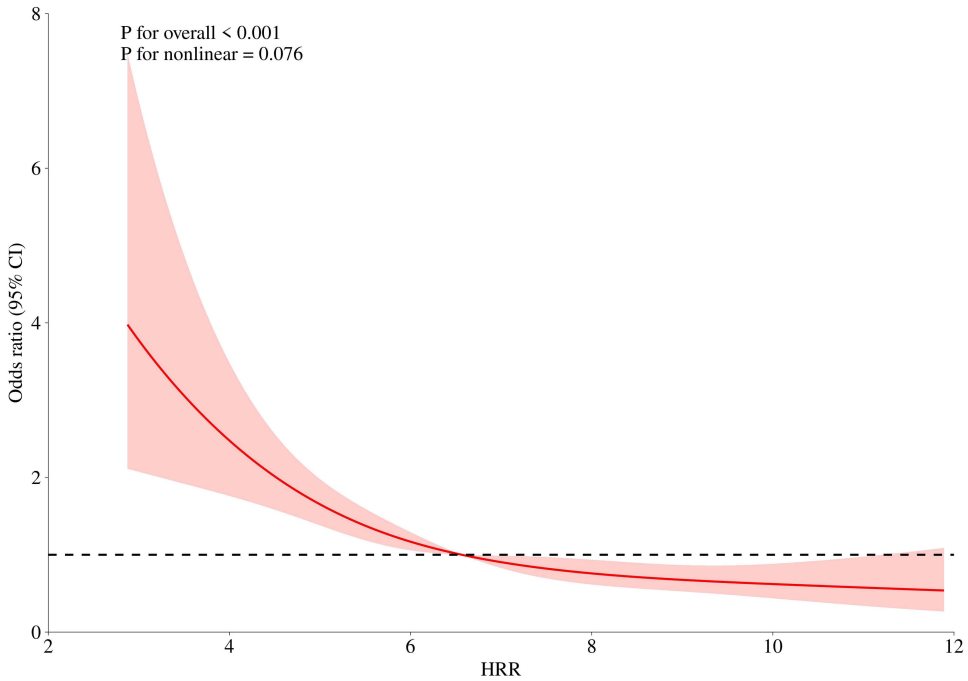

Figure 2 The adjusted restricted cubic splines depicting the relationships between HRR levels and mortality.
Abbreviation: HRR, Hemoglobin/Red Cell Distribution Width Ratio.

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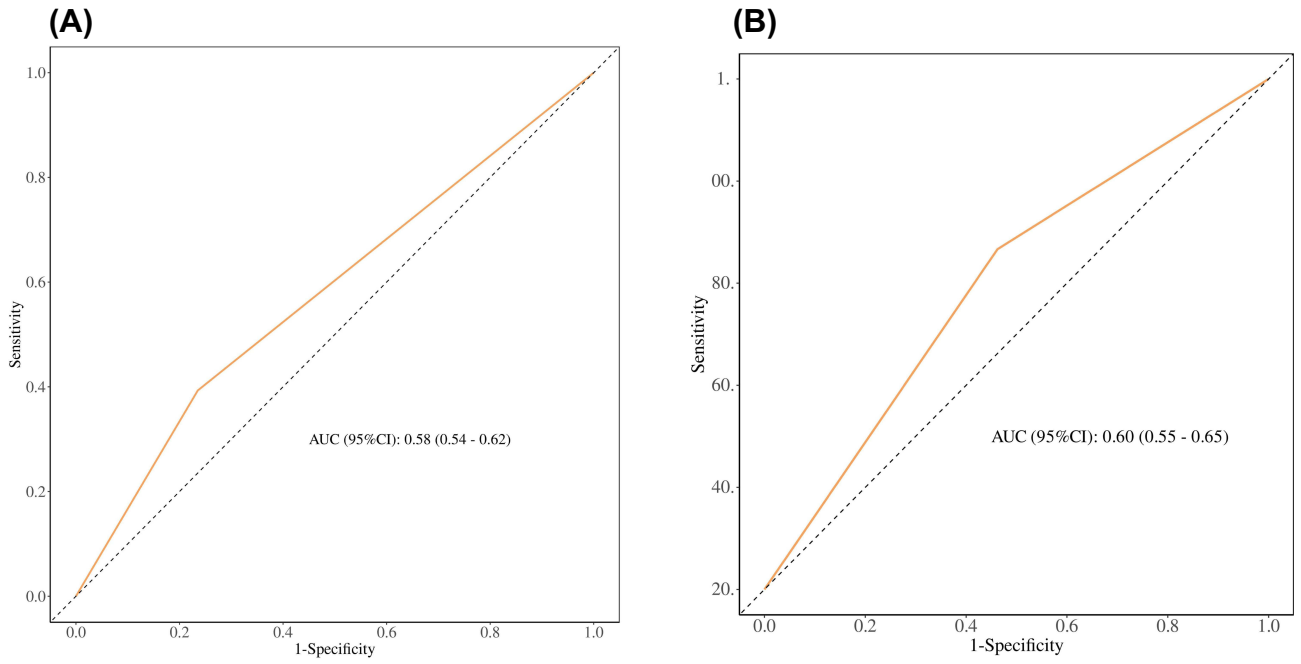

Figure 3 HRR's ROC curves for predicting hospital mortality in the original and matched COPD patients in the ICU (**A** and **B**).
Notes: For HRR to predict hospital mortality in the original cohort, the areas under the ROC curve (AUC) was 0.580. In the matched cohort, the AUCs for HRR to predict hospital mortality were 0.60.
Abbreviations: HRR, Hemoglobin/Red Cell Distribution Width Ratio; AUC, the areas under the receiver operating characteristic curve.

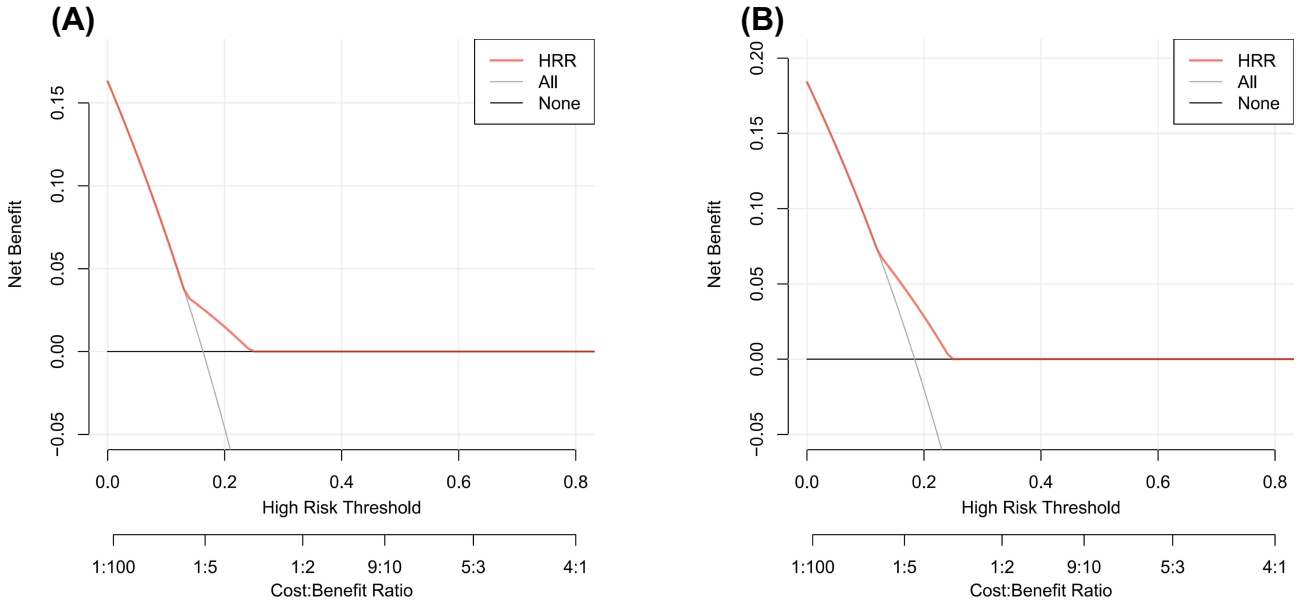

Figure 4 DCA was used to evaluate HRR effectiveness in COPD patients admitted to ICUs in the original cohort (**A**) and the matched cohort (**B**).
Notes: HRR added a higher net benefit than the "all treatment" or "none treatment" approach in the original cohort and the matched cohort when the risk threshold probability was in the range of 0–100%.
Abbreviations: HRR, Hemoglobin/Red Cell Distribution Width Ratio; DCA, Decision curve analysis; COPD, chronic obstructive pulmonary disease.

Discussion

As part of a first-of-its-kind study, this study analyzed the association between HRR and the risk of hospital mortality in ICU patients with COPD in the MIMIC-IV database. There is evidence that HRR can be used to predict the outcome of severe COPD patients. There is a significant correlation between lower HRR levels and higher hospital mortality. This association was still significant after PSM analysis and subgroup analysis had taken place.

RDW elevation was recently identified as a predictive marker for a variety of illnesses including cardiovascular diseases, malignancies, and inflammatory disorders.[14–16]Morever, the relationship between RDW and COPD has been a topic of interest in recent clinical research. COPD is a chronic inflammatory lung disease characterized by airflow limitation, and RDW is a measure of variability in red blood cell size.[17] Several studies have suggested a potential association between RDW and COPD, indicating its potential role as a biomarker for the disease.[18] RDW may be involved in COPD through various possible mechanisms. Chronic inflammation in COPD can lead to changes in bone marrow function and subsequently affect RDW.[19] Additionally, hypoxia, a common feature of COPD, can also impact RDW by influencing the production and maturation of red blood cells.[20] These potential mechanisms suggest that RDW may be linked to the pathophysiology of COPD.

Numerous studies have investigated the relationship between RDW and COPD diagnosis, disease severity, and prognosis. For example, a study by Epstein D et al involving a sample of 500 COPD patients found that higher RDW levels were associated with increased COPD exacerbations and hospitalizations, indicating a potential prognostic value of RDW in COPD.[21] Another study by Huang Y et al with a sample of 300 COPD patients demonstrated that elevated RDW was correlated with more severe airflow limitation and poorer lung function, suggesting a potential link between RDW and disease severity in COPD.[22] Other research by Karampitsakos T et al also supported the association between RDW and COPD, highlighting its potential diagnostic and prognostic significance. These observations led us to speculate that chronic inflammation in COPD may contribute to high mortality rates in COPD patients with high RDW.[23]

The hemoglobin within red blood cells plays a vital role in the oxygen transport process. In the context of COPD, reduced hemoglobin levels may exacerbate tissue hypoxia, leading to increased pulmonary vasoconstriction and pulmonary hypertension.[24] Additionally, chronic inflammation in COPD can contribute to the development of anemia, further affecting hemoglobin levels.[25] Moreover, low hemoglobin levels have been associated with reduced exercise capacity and increased dyspnea in COPD patients.[26]

Several studies have examined how hemoglobin levels contribute to COPD severity and prognosis. A study by Park SC et al involving a sample of 500 COPD patients found that significantly lower hemoglobin levels were associated with more severe COPD, as measured by lung function parameters and symptom scores.[27] In another study by Toft-Petersen AP et al with a sample size of 600 COPD patients, it was observed that lower hemoglobin levels were independently associated with increased risk of COPD exacerbations and hospitalizations.[28] Similarly, a study by Xiong W et al with a cohort of 800 COPD patients reported that low hemoglobin levels were predictive of poorer prognosis in terms of mortality and disease progression.[29] These findings suggest that blood hemoglobin levels are closely linked to the severity and prognosis of COPD, emphasizing the clinical relevance of monitoring hemoglobin in COPD management.

Recently, The risk of dying from acute respiratory distress syndrome, stroke, and cancer has gradually been linked to HRR.[15,30,31] There is however a lack of studies that link HRR with COPD mortality. In our study, HRR predicted hospital mortality in patients with COPD admitted to ICUs. A significant increase in peripheral blood leukocytes was found in the low HRR group following PSM, suggesting HRR may be affected by inflammation. In light of the possible mechanisms associated with RDW and hemoglobin, the role of hypoxia and inflammation may explain how HRR predicts hospital mortality. But, the AUC of the ROC is comparatively low, and DCA) curves exhibit substantial overlap with both the "ALL" and "NONE" curves, indicating a narrow threshold range. One possible reason is the heterogeneous nature of COPD, which encompasses a range of different phenotypes and underlying pathophysiological mechanisms. As a result, a single biomarker may not be able to accurately capture the complexity of the disease. Additionally, the HRR in diagnosing COPD may be influenced by various confounding factors, such as comorbidities, smoking status, and medication use. These factors could contribute to a decrease in the discriminatory power of the biomarker, leading to a lower AUC value and a narrow threshold range. Despite the AUC values and DCA results presented in this study being suboptimal, our findings suggest that the HRR is a promising and readily accessible peripheral blood marker for evaluating mortality risk in patients with COPD.

Conclusion

This study used MIMIC-IV (version 2.2), and 1061 patients were included, indicating a substantial sample size and yielding compelling findings. There is no doubt that confounding factors affect results in retrospective studies, but PSM

analysis allowed us to adjust for this imbalance, and after PSM analysis. Both before and after PSM, there was a stronger correlation between HRR and hospital mortality in critically ill patients with COPD. Further, neither age nor coexisting diseases affected the results of this study. Despite this, there were some limitations to the study. Firstly, public databases were consulted for the data, and some indicators were not included due to a large number of missing values. The study was conducted in one center, which may have contributed to selection bias, and its results need to be validated. Moreover, The RDW and hemoglobin values were only analyzed at admission, leaving out the dynamic effects of HRR on their evolution. There were no mechanistic studies conducted in this study, so future studies will have to focus on these mechanisms in more depth.

Data Sharing Statement

The data incorporated in this study were obtained from the Medical Information Mart for Intensive Care IV (MIMICIV) Database (version 2.0), which was an open-access database and could be visited on the website after application: https://physionet.org/content/mimiciv/2.0/.

Ethics Approval and Consent to Participate

The MIMIC-IV database has received ethical approval from the institutional review boards (IRBs) at Beth Israel Deaconess Medical Center and Massachusetts Institute of Technology. Because the database does not contain protected health information, a waiver of the requirement for informed consent was included in the IRB approval.

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Author Contributions

The first author and corresponding author of this article are both Yuan Wang. 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.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

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