BMC Cardiovascular Disorders

RESEARCH

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Association of hemoglobin-to-red blood cell distribution width ratio with mortality in critically Ill patients with heart failure and acute kidney injury: insights from the MIMIC-IV database

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Abstract

Background The association between the hemoglobin-to-red cell distribution width ratio (HRR) and mortality in critically ill patients with heart failure (HF) and acute kidney injury (AKI) remains uncertain. This research focuses on exploring the association between HRR and both short-term and long-term all-cause mortality in these patients.

Methods Participants were selected from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database and categorized into tertiles based on HRR values. The primary endpoint was 28-days ICU all-cause mortality. Secondary endpoints included 28-days hospital and 90-days hospital all-cause mortality. Cox proportional hazards models and restricted cubic splines were used to analyze the association between HRR and mortality in patients with HF and AKI. Kaplan-Meier survival analysis estimated endpoint differences across tertiles.

Results A total of 7561 patients were included, with 55.5% being male (n=4199). Cox proportional hazards analysis showed a significant link between HRR and both short-term and long-term mortality in critically ill patients with HF and AKI. This association remained significant after adjusting for confounders. The restricted cubic splines model demonstrated a linear relationship between a higher HRR index and a reduced mortality risk. Kaplan-Meier survival analysis revealed significant differences in short-term and long-term mortality among the tertile groups.

Conclusion The study results show a strong association between lower HRR and increased short-term and long-term mortality in critically ill patients with heart failure and AKI. HRR proves to be a valuable and cost-effective marker for identifying high-risk patients.

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Keywords Hemoglobin-to-red cell distribution width ratio, Heart failure, Acute kidney injury, MIMIC-IV database, Mortality

Background

Heart failure (HF) is a major public health concern, affecting millions globally and leading to significant hospitalizations [1, 2]. Its burden is expected to grow due to an aging population and improved treatments [3]. A serious complication of HF is acute kidney injury (AKI), which worsens patient outcomes, including prolonged hospital stays, higher readmission rates, and increased mortality [4–7]. Definitions of AKI have evolved, from the RIFLE criteria to the AKIN criteria, and most recently, the KDIGO guidelines, which provide a comprehensive diagnostic framework [8–11]. The interaction between HF and AKI is complex, involving decreased renal perfusion, increased venous pressure, systemic inflammation, and the use of nephrotoxic drugs [12, 13]. Identifying high-risk factors such as advanced age, pre-existing chronic kidney disease, diabetes, hypertension, and elevated baseline serum creatinine is crucial [14]. Continued research is essential to further elucidate the pathophysiology and interplay between HF and AKI. This understanding will aid in the development of effective strategies for early detection and intervention, ultimately improving patient outcomes and reducing the healthcare burden associated with these conditions [15]. Addressing these high-risk factors not only enhances patient care but also reduces the long-term economic impact on the healthcare system.

The hemoglobin-to-red cell distribution width ratio (HRR) is an innovative clinical marker calculated as the ratio of hemoglobin concentration (g/L) to red cell distribution width (RDW) [16]. This metric integrates the prognostic implications of both hemoglobin levels and RDW, offering a comprehensive indicator of systemic inflammation and overall patient health [17]. HRR has shown significant prognostic value across various diseases. In cardiovascular diseases, low HRR levels are associated with increased mortality and hospitalizations in heart failure patients, highlighting its utility in predicting long-term outcomes [18]. In cancer patients, including those with gastric [19], esophageal [16], and lung cancers [20], HRR reflects tumor-related inflammation and nutritional status, correlating with survival outcomes. Additionally, HRR serves as a prognostic marker in inflammatory conditions such as sepsis [21], where lower HRR indicates higher mortality risk, and in atrial fibrillation [22], predicting adverse outcomes. Despite these insights, the prognostic significance of HRR in heart failure patients complicated by AKI remains unclear. Further research is needed to determine HRR's role in predicting outcomes in this high-risk population, potentially improving clinical decision-making and patient care through early identification of those at greatest risk for adverse events.

This study aimed to explore the association between HRR and both short-term and long-term mortality in critically ill heart failure patients with AKI. The goal was to establish an effective and convenient predictor to identify critically ill patients at high risk.

Methods

Data source

The Medical Information Mart for Intensive Care IV (MIMIC-IV) database is a publicly accessible resource containing detailed and de-identified health data from patients admitted to the intensive care units at Beth Israel Deaconess Medical Center in Boston, MA, from 2008 to 2022 (https://physionet.org/content/mimiciv/3.0/) [23–25]. This extensive database includes information on patient demographics, clinical notes, ICD-9 and ICD-10 diagnoses, laboratory test results, medication records, procedures, fluid balance data, discharge summaries, bedside vital signs, caregiver notes, radiology reports, and survival outcomes. Researchers can access MIMIC-IV after completing the Collaborative Institutional Training Initiative (CITI) program to ensure compliance with ethical standards. One of the authors, Yangang Zhu, has successfully completed the CITI program (certification number: 64180628) and has obtained the necessary permissions to utilize this database for research purposes. The database facilitates a wide range of critical care research by providing comprehensive patient data without compromising patient privacy.

Study participants and data selection

Data extraction was conducted using PgAdmin PostgreSQL (version 16.0) and Navicat Premium (version 17.0.4). The criteria for including patients in this study were: (1) age over 18 years, (2) first-time admission to the intensive care unit (ICU) and first hospitalization, (3) ICU stay longer than one day, and (4) a diagnosis of both heart failure and acute kidney injury (AKI). The criteria for AKI diagnosis included a 1.5-fold increase in serum creatinine within the past seven days, an increase of $\geq$0.3 mg/dL within 48 hours, or a urine output of <0.5 mL/kg/h for at least six hours. The patient selection methodology is shown in Figure 1. Diagnostic details were obtained

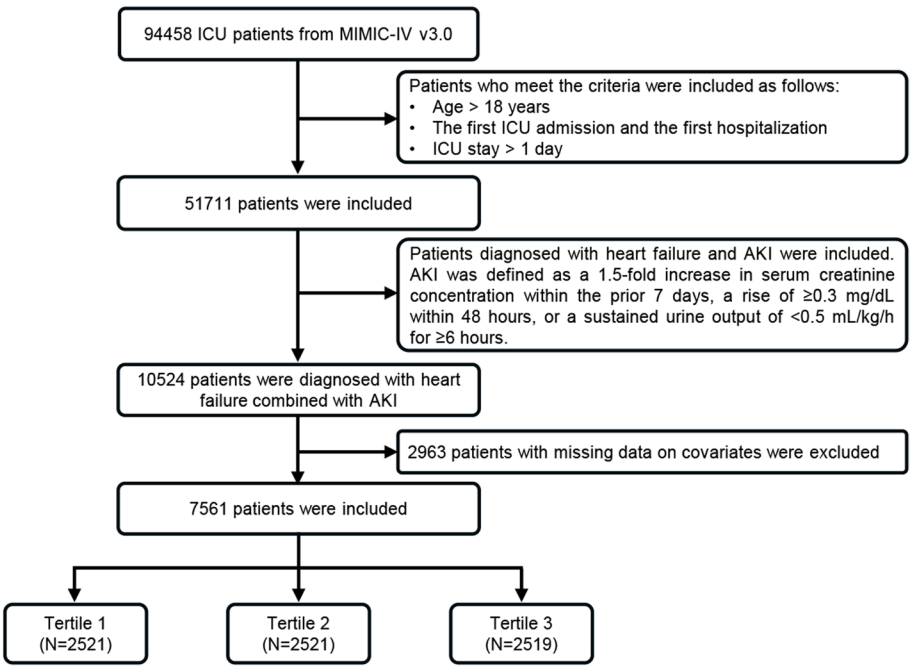

Fig 1 Procedure for participant selection

from the 'diagnoses_icd' and 'd_icd_diagnoses' tables in the database. Table S1 in the Supporting Information lists the International Classification of Diseases (ICD) codes for heart failure and other related conditions.

The extracted data included: (1) demographic information such as age (in years), gender (male or female), race (categorized as White, Black, or Others), and marital status (single, married, divorced, widowed); (2) laboratory values detected within 24 hours of ICU admission, including white blood cell count (WBC, K/μL), red blood cell count (RBC, M/μL), platelet count (PLC, K/μL), hemoglobin (g/dL), red cell distribution width (RDW, %), sodium (mEq/L), potassium (mEq/L), chloride (mEq/L), glucose (mmol/L), blood urea nitrogen (BUN, mg/dL), creatinine (mg/dL), heart rate (bpm), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiration rate (insp/min), oxygen saturation (SpO2, %), and body temperature (°C); and (3) comorbid conditions including hypertension, diabetes mellitus, chronic obstructive pulmonary disease, myocardial infarction, malignant tumors, and stroke. Patients with missing covariate data were excluded. Finally, 7561 patients met the inclusion criteria and were included in the analysis. For all laboratory data and vital signs (blood pressure, heart rate, temperature, SpO2 et al.), we used the first measured values within 24 hours of ICU admission.

HRR is defined as the ratio of hemoglobin (g/L) to red blood cell distribution width (%): HRR = hemoglobin (g/L) / red blood cell distribution width (%)

Patients were categorized into three groups based on tertiles of HRR.

Endpoints of interest

The primary endpoint was all-cause mortality within 28 days in the ICU. Secondary endpoints included all-cause mortality within 28 days in the hospital and all-cause mortality within 90 days in the hospital.

Statistical analysis

Continuous variables were expressed as means with standard deviations, whereas categorical variables were shown as frequencies and percentages. To analyze continuous variables, methods such as Student's t-test, one-way ANOVA, or Kruskal-Wallis test were utilized. For categorical variables, chi-square tests or Fisher's exact tests were employed.

A series of Cox proportional hazards models were utilized to examine the relationships between HRR and three endpoints: 28-day all-cause mortality in the ICU, 28-day all-cause mortality in the hospital, and 90-day all-cause mortality in the hospital. The outcomes were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Trend p-values were calculated based on tertile levels of HRR.

- Model 1 was unadjusted.

- Model 2 included adjustments for demographic and lifestyle variables, such as age, gender, race, and marital status.
- Model 3 additionally accounted for laboratory parameters, including WBC, RBC, PLC, sodium, potassium, chloride, glucose, BUN, creatinine, heart rate, systolic blood pressure, diastolic blood pressure, respiration rate, SpO2, and temperature.
- Model 4 incorporated all adjustments from Model 3 and further included comorbid conditions such as hypertension, diabetes, myocardial infarction, malignant tumor, stroke, and COPD.

Kaplan-Meier survival curves were plotted to visualize survival over time, and the log-rank test was employed to compare differences among the survival curves. Moreover, a restricted cubic splines model was utilized to examine the potential dose-response relationship between HRR and all-cause mortality in a fully adjusted model.

To evaluate the consistency of HRR's prognostic value across different subgroups, additional analyses were conducted. These subgroups were defined by gender, race, marital status, hypertension, diabetes, myocardial infarction, malignant tumor, stroke, and COPD. The interactions between HRR and these stratification variables were assessed using likelihood ratio tests. We also utilized the survivalROC package in R to construct time-dependent Receiver Operating Characteristic (ROC) curves for evaluating the prognostic performance of three biomarkers: HRR, RDW, and Hemoglobin. We analyzed the predictive ability for mortality at different time points, including 28-days ICU mortality, 28-days hospital mortality, and 90-days hospital mortality. ROC curves were plotted with false positive rates on the x-axis and true positive rates on the y-axis, with the Area Under the Curve (AUC) calculated using the Kaplan-Meier method to assess each biomarker's discriminative ability. Statistical significance was determined with a two-sided p-value threshold of less than 0.05. All statistical analyses were performed using R software (version 4.4.0, https://cran.r-project.org/). A p-value of less than 0.05 was considered indicative of statistical significance.

Results

Patient characteristics

As shown in Table 1, a total of 7561 patients were included in this study, with a median age of 76 years (range 18–100), and 55.5% were male (n=4199). The median HRR value was 6.81 (range 1.86–14.4). The 28-day all-cause mortality rates were 9.8% (n=742) in the ICU, 14.6% (n=1105) in the hospital, and the 90-day all-cause mortality rate in the hospital was 15.8% (n=1198). Table 1 details the baseline characteristics of patients stratified into HRR tertiles (T1: 1.86–5.95; T2: 5.95–7.72; T3: 7.72–14.4). In the T3 group, increased RBC counts, higher blood pressure, a greater prevalence of hypertension, and a lower prevalence of diabetes mellitus, malignant tumors, and COPD were observed. Mortality rates decreased progressively with higher HRR tertiles: 28-days ICU mortality (13.2% vs. 10.0% vs. 6.3%, p<0.001), 28-days hospital mortality (20.2% vs. 14.2% vs. 9.5%, p<0.001), and 90-days hospital mortality (22.5% vs. 15.1% vs. 10.0%, p<0.001).

Association between HRR and both short-term and long-term all-cause mortality

Kaplan-Meier survival analyses were conducted to assess the impact of HRR across different tertiles on three endpoints. Figure 2 indicated that patients in the lower HRR tertiles exhibited significantly higher mortality rates for 28-day ICU mortality, 28-day hospital mortality, and 90-day hospital mortality (log-rank $p < 0.0001$).

The findings from the Cox regression models are detailed in Table 2. In the unadjusted model, the hazard ratios (HRs) for continuous HRR were 0.840 (95% CI 0.806–0.875) for 28-days ICU mortality, 0.886 (95% CI 0.857–0.916) for 28-days hospital mortality, and 0.883 (95% CI 0.855–0.912) for 90-days hospital mortality. For HRR tertiles, the HRs for 28-days ICU mortality were 0.823 (95% CI 0.699–0.970) for T2 and 0.494 (95% CI 0.409–0.597) for T3, for 28-days hospital mortality were 0.843 (95% CI 0.736–0.965) for T2 and 0.598 (95% CI 0.512–0.697) for T3, and for 90-days hospital mortality were 0.833 (95% CI 0.731–0.949) for T2 and 0.591 (95% CI 0.509–0.686) for T3 (Table 2, Model 1). After adjusting for demographic variables such as age, gender, race, and marital status, the HRs for continuous HRR and tertiles of HRR remained significant across all endpoints (Table 2, Model 2). Further adjustment for laboratory parameters, including WBC, RBC, sodium, potassium, chloride, glucose, urea nitrogen, creatinine, HR, BPS, BPD, RR, SpO2, and temperature, also showed significant HRs for continuous HRR and tertiles of HRR for the different endpoints (Table 2, Model 3). Finally, after further adjusting for comorbidities such as hypertension, diabetes mellitus, myocardial infarction, malignant tumor, stroke, and COPD, the association between HRR and all-cause mortality persisted. The adjusted HRs for continuous HRR were 0.865 (95% CI 0.814–0.920) for 28-days ICU mortality, 0.885 (95% CI 0.843–0.929) for 28-days hospital mortality, and 0.884 (95% CI 0.843–0.926) for 90-days hospital mortality. For HRR tertiles, the adjusted HRs for 28-days ICU mortality were 0.852 (95% CI 0.709–1.024) for T2 and 0.635 (95% CI 0.492–0.820) for T3, for 28-days hospital mortality were 0.820 (95% CI 0.705–0.953) for T2 and 0.630 (95% CI 0.513–0.773) for

Table 1 Baseline characteristics of patients

Characteristics	Tertiles			Overall (*N*=7561)	*p*
	T1 (*N*=2521)	T2 (*N*=2521)	T3 (*N*=2519)		
Age, years	74.5 (12.5)	75.5 (12.4)	72.5 (14.2)	74.1 (13.1)	< 0.001
Gender, n (%)					
Male	1319 (52.3%)	1289 (51.1%)	1591 (63.2%)	4199 (55.5%)	< 0.001
Female	1202 (47.7%)	1232 (48.9%)	928 (36.8%)	3362 (44.5%)	
Race, n (%)					
White	1806 (71.6%)	1858 (73.7%)	1833 (72.8%)	5497 (72.7%)	0.001
Black	326 (12.9%)	269 (10.7%)	234 (9.3%)	829 (11.0%)	
Other	389 (15.4%)	394 (15.6%)	452 (17.9%)	1235 (16.3%)	
Marital status, n (%)					
Single	578 (22.9%)	593 (23.5%)	613 (24.3%)	1784 (23.6%)	< 0.001
Married	1162 (46.1%)	1126 (44.7%)	1254 (49.8%)	3542 (46.8%)	
Divorced	204 (8.1%)	187 (7.4%)	188 (7.5%)	579 (7.7%)	
Windowed	577 (22.9%)	615 (24.4%)	464 (18.4%)	1656 (21.9%)	
WBC, k/μL	12.1 (8.84)	12.5 (9.19)	12.1 (5.35)	12.2 (7.99)	< 0.001
RBC, m/μL	3.02 (0.567)	3.52 (0.544)	4.18 (0.565)	3.57 (0.732)	< 0.001
PLC, k/μL	207 (114)	212 (98.6)	206 (84.2)	208 (99.5)	0.022
Hb, g/dL	8.57 (1.08)	10.4 (1.10)	12.7 (1.47)	10.5 (2.08)	< 0.001
RDW, %	17.6 (2.53)	15.2 (1.44)	14.0 (1.10)	15.6 (2.35)	< 0.001
Sodium, mEq/L	138 (5.24)	138 (5.12)	138 (4.87)	138 (5.08)	< 0.001
Potassium, mEq/L	4.36 (0.654)	4.29 (0.599)	4.23 (0.550)	4.29 (0.605)	< 0.001
Chloride, mEq/L	102 (6.73)	102 (6.65)	102 (5.74)	102 (6.39)	0.066
Glucose, mmol/L	7.91 (2.95)	8.25 (3.30)	8.34 (3.20)	8.17 (3.16)	< 0.001
Ureanitrogen, mg/dL	44.9 (29.4)	36.3 (24.4)	28.0 (18.2)	36.4 (25.4)	< 0.001
Creatinine, mg/dL	2.33 (2.02)	1.90 (1.82)	1.41 (1.11)	1.88 (1.74)	< 0.001
HR, bpm	84.9 (16.9)	84.7 (16.4)	86.1 (18.1)	85.2 (17.1)	0.160
BPS, mmHg	114 (17.6)	115 (17.8)	117 (17.8)	115 (17.8)	< 0.001
BPD, mmHg	60.3 (11.7)	61.5 (11.7)	66.7 (12.0)	62.8 (12.1)	< 0.001
RR, insp/min	20.0 (4.44)	20.1 (3.88)	20.4 (3.74)	20.2 (4.04)	< 0.001
SpO2, %	96.8 (1.98)	96.4 (2.20)	96.0 (2.04)	96.4 (2.10)	< 0.001
Temperature, °C	36.7 (0.468)	36.8 (0.459)	36.8 (0.455)	36.8 (0.462)	< 0.001
Hypertension, n (%)	439 (17.4%)	714 (28.3%)	805 (32.0%)	1958 (25.9%)	< 0.001
Diabetes mellitus, n (%)	1178 (46.7%)	1109 (44.0%)	882 (35.0%)	3169 (41.9%)	< 0.001
Myocardial infarction, n (%)	363 (14.4%)	341 (13.5%)	462 (18.3%)	1166 (15.4%)	< 0.001
Malignant tumor, n (%)	530 (21.0%)	477 (18.9%)	355 (14.1%)	1362 (18.0%)	< 0.001
Stroke, n (%)	253 (10.0%)	287 (11.4%)	266 (10.6%)	806 (10.7%)	0.485
COPD, n (%)	386 (15.3%)	369 (14.6%)	294 (11.7%)	1049 (13.9%)	0.001
HRR	4.92 (0.726)	6.82 (0.509)	9.06 (1.08)	6.94 (1.87)	< 0.001
ICU length of stay, days	4.82 (5.29)	4.57 (5.22)	4.72 (5.36)	4.70 (5.29)	0.173
Hospital length of stay, days	14.9 (14.1)	12.1 (10.7)	11.4 (10.2)	12.8 (11.9)	< 0.001
28-days ICU mortality, n (%)	332 (13.2%)	251 (10.0%)	159 (6.3%)	742 (9.8%)	< 0.001
28-days hospital mortality, n (%)	508 (20.2%)	358 (14.2%)	239 (9.5%)	1105 (14.6%)	< 0.001
90-days hospital mortality, n (%)	566 (22.5%)	380 (15.1%)	252 (10.0%)	1198 (15.8%)	< 0.001

Abbreviations: *BPD* diastolic blood pressure, *BPS* systolic blood pressure, *COPD* chronic obstructive pulmonary disease, *Hb* hemoglobin, *HR* heart rate, *HRR* hemoglobin-to-red cell distribution width ratio, *PLC* platelet count, *RBC* red blood cell, *RDW* red cell distribution width, *RR* respiration rate, *SpO2* oxygen saturation, *WBC* white blood cell.

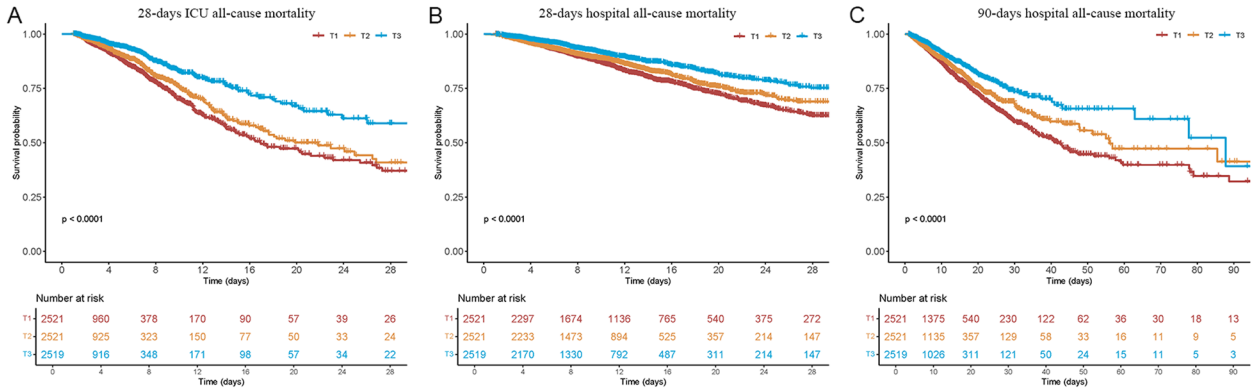

Fig 2 Kaplan–Meier survival curves for mortality. **A** 28-days ICU all-cause mortality; **B**. 28-days hospital all-cause mortality; **C**. 90-days hospital all-cause mortality

T3, and for 90-days hospital mortality were 0.813 (95% CI 0.703–0.940) for T2 and 0.633 (95% CI 0.519–0.772) for T3 (Table 2, Model 4).

Figure 3 illustrates the restricted cubic splines regression model, demonstrating the dose-response relationship between HRR and all-cause mortality in fully adjusted models. The analysis indicates that higher HRR values are associated with lower hazard ratios for 28-days ICU mortality, 28-days hospital mortality, and 90-days hospital mortality. The P-values for non-linearity were 0.869 for 28-days ICU mortality, 0.819 for 28-days hospital mortality, and 0.572 for 90-days hospital mortality, suggesting a linear relationship between HRR and mortality risk across all endpoints.

Subgroup analysis

The prognostic value of HRR for both short-term and long-term all-cause mortality was further evaluated across various subgroups, including gender, race, marital status, hypertension, diabetes, myocardial infarction, malignant tumor, stroke, and COPD (Figure 4, S1, S2). The analysis revealed that a higher HRR (T3) was significantly associated with reduced 28-days ICU mortality in multiple subgroups. Specifically, significant associations were observed in males [HR (95% CI) 0.670 (0.467–0.960)], females [HR (95% CI) 0.688 (0.478–0.991)], white individuals [HR (95% CI) 0.674 (0.497–0.914)], individuals of other races [HR (95% CI) 0.529 (0.296–0.947)], married individuals [HR (95% CI) 0.652 (0.448–0.949)], those without hypertension [HR (95% CI) 0.630 (0.470–0.844)], those without diabetes [HR (95% CI) 0.607 (0.435–0.846)], those without myocardial infarction [HR (95% CI) 0.641 (0.485–0.848)], those with malignant tumors [HR (95% CI) 0.538 (0.296–0.978)], those without malignant tumors [HR (95% CI) 0.658 (0.495–0.874)], those with stroke [HR (95% CI) 0.538 (0.296–0.978)], those without stroke [HR (95% CI) 0.609 (0.465–0.799)], and those without COPD [HR (95% CI) 0.644 (0.488–0.850)] (Figure 4).

The HRR also showed a significant association with both 28-days and 90-days hospital mortality for T3 across various subgroups, including males, females, white individuals, individuals of other races, married individuals, those with and without hypertension, diabetes, malignant tumors, and those without myocardial infarction or stroke (Figure S1 and S2). Additionally, significant relationships between marital status and HRR were observed in subgroup analyses (28-days ICU mortality: p=0.028, 28-days hospital mortality: p=0.023, 90-days hospital mortality: p=0.018).

To evaluate the prognostic value of HRR and its components, we performed ROC curve analyses comparing HRR with hemoglobin (HB) and RDW (Figure S3). For 28-day ICU mortality prediction, HRR exhibited superior discriminative ability (AUC=0.611) compared to both RDW (AUC=0.567) and HB (AUC=0.604). In predicting 28-day hospital mortality, HRR (AUC=0.563) showed better performance than HB (AUC=0.547), though comparable to RDW (AUC=0.568). For 90-day hospital mortality, HRR (AUC=0.539) demonstrated slightly better predictive capability than RDW (AUC=0.522), while HB showed similar performance (AUC=0.549). These findings suggest that HRR, as a composite marker, provides enhanced prognostic value particularly in predicting short-term ICU mortality in critically ill patients.

Discussion

In this large-scale study, we employed various methods to investigate the relationship between HRR and both short-term and long-term all-cause mortality in ICU patients with heart failure combined with AKI. Our findings revealed a strong association between HRR and the

Table 2 Cox proportional hazard ratios for short-term and long-term all-cause mortality

	Model 1			Model 2			Model 3			Model 4		
	HR (95% CI)	p-value	p for trend	HR (95% CI)	p-value	p for trend	HR (95% CI)	p-value	p for trend	HR (95% CI)	p-value	p for trend
28-days ICU mortality												
Continuous HRR	0.840 (0.806, 0.875)	<0.001		0.846 (0.811, 0.882)	<0.001		0.871 (0.820, 0.925)	<0.001		0.865 (0.814, 0.920)	<0.001	
T1 (*N*=2521)	Ref		<0.001	Ref		<0.001	Ref		<0.001	Ref		<0.001
T2 (*N*=2521)	0.823 (0.699, 0.970)	0.020		0.780 (0.662, 0.919)	0.003		0.860 (0.716, 1.033)	0.107		0.852 (0.709, 1.024)	0.088	
T3 (*N*=2519)	0.494 (0.409, 0.597)	<0.001		0.518 (0.429, 0.627)	<0.001		0.649 (0.504, 0.836)	<0.001		0.635 (0.492, 0.820)	<0.001	
28-days hospital mortality												
Continuous HRR	0.886 (0.857, 0.916)	<0.001		0.890 (0.860, 0.921)	<0.001		0.890 (0.848, 0.934)	<0.001		0.885 (0.843, 0.929)	<0.001	
T1 (*N*=2521)	Ref		<0.001	Ref		<0.001	Ref		<0.001	Ref		<0.001
T2 (*N*=2521)	0.843 (0.736, 0.965)	0.014		0.806 (0.703, 0.923)	0.002		0.824 (0.709, 0.957)	0.011		0.820 (0.705, 0.953)	0.01	
T3 (*N*=2519)	0.598 (0.512, 0.697)	<0.001		0.615 (0.527, 0.718)	<0.001		0.643 (0.524, 0.788)	<0.001		0.630 (0.513, 0.773)	<0.001	
90-days hospital mortality												
Continuous HRR	0.883 (0.855, 0.912)	<0.001		0.886 (0.857, 0.916)	<0.001		0.889 (0.849, 0.932)	<0.001		0.884 (0.843, 0.926)	<0.001	
T1 (*N*=2521)	Ref		<0.001	Ref		<0.001	Ref		<0.001	Ref		<0.001
T2 (*N*=2521)	0.833 (0.731, 0.949)	0.006		0.792 (0.695, 0.903)	<0.001		0.820 (0.709, 0.948)	0.007		0.813 (0.703, 0.940)	0.005	
T3 (*N*=2519)	0.591 (0.509, 0.686)	<0.001		0.608 (0.524, 0.707)	<0.001		0.647 (0.532, 0.788)	<0.001		0.633 (0.519, 0.772)	<0.001	

Model 1: unadjusted

Model 2: adjusted for age, gender, race, marital status

Model 3: Model 2 plus WBC, RBC, sodium, potassium, chloride, glucose, ureanitrogen, creatinine, HR, BPS, BPD, RR, SpO2, temperature

Model 4: Model 3 plus hypertension, diabetes mellitus, myocardial infarction, malignant tumor, stroke, COPD

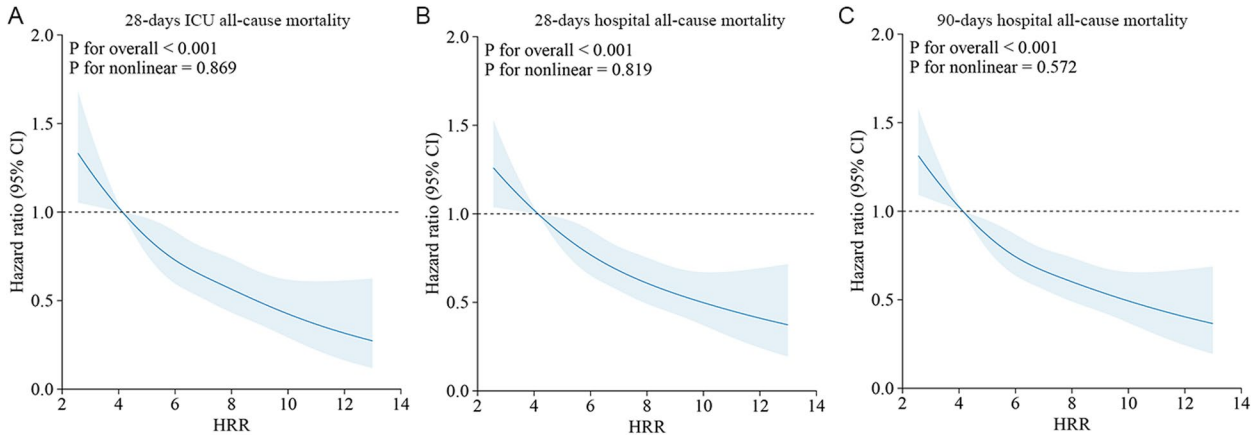

Fig 3 Restricted cubic spline for mortality. **A** 28-days ICU all-cause mortality; **B**. 28-days hospital all-cause mortality; **C**. 90-days hospital all-cause mortality

risk of mortality, which remained significant even after adjusting for potential confounders. Kaplan-Meier survival analysis demonstrated that patients in the lower HRR tertiles experienced significantly poorer outcomes in terms of both short-term and long-term mortality. Additionally, the restricted cubic splines model indicated a linear relationship between HRR and mortality risk across these endpoints. Thus, HRR emerged as a significant predictor of prognosis for heart failure patients with AKI in a critical care setting.

Despite advancements in treatment strategies and interventions guided by clinical practice guidelines, HF remains a prevalent and severe condition associated with significant morbidity and mortality, imposing a growing public health burden globally [2, 13, 26–28]. AKI occurs in approximately 47% of HF patients, particularly those critically ill in the ICU, and is often linked to higher short-term and long-term mortality rates [26]. The interaction between cardiac and renal dysfunction is complex and bidirectional, with each condition exacerbating the other [12]. Mechanistically, HF and AKI share common pathogenesis, including sympathetic nervous system activation, persistent renin-angiotensin-aldosterone system activation, and inflammation-induced tissue damage [6, 29, 30]. These non-hemodynamic pathways contribute to the worsening of both cardiac and renal injuries. In HF, decreased cardiac output leads to reduced renal perfusion, tubular hypoxia, and acute tubular necrosis, further aggravating renal dysfunction [31]. The subsequent activation of the renin-angiotensin-aldosterone system due to long-term renal hypoperfusion exacerbates renal injury and affects glomerular and tubular function [32, 33]. Additionally, diuretic use in HF management, aimed at controlling fluid retention, can increase renal excretion of sodium and activate the renin-angiotensin-aldosterone system, leading to further renal impairment [34]. The interplay between HF and renal dysfunction forms a vicious cycle, where the progression of one condition accelerates the decline of the other, resulting in poor clinical outcomes. Given this intricate relationship, there is an urgent need to identify novel biomarkers and high-risk factors to improve the prognosis of HF patients with AKI in the ICU. Up to now, this is the first research to report the relationship between HRR and short-term and long-term all-cause mortality in critically ill patients with heart failure and AKI.

HRR has recently emerged as a prognostic biomarker for critically ill patients, particularly those suffering from HF or AKI in intensive care units [35, 36]. Notably, no existing studies have explored the relationship between HRR and patients who have both HF and AKI. RDW, which quantifies the variation in erythrocyte size, is readily obtained from routine blood tests and has been used to diagnose anemia [37]. RDW was first identified as a powerful prognostic marker in heart failure through the landmark CHARM study [38], which demonstrated that elevated RDW was among the most powerful independent predictors of morbidity and mortality in heart failure patients, with prognostic value comparable to NYHA class and ejection fraction. Subsequently, evidence has emerged linking elevated RDW to various cardiovascular conditions through multiple pathophysiological mechanisms. As demonstrated in both experimental and clinical studies, RDW elevation appears to be closely associated with inflammatory stress, oxidative stress, nutritional deficiencies, and impaired iron metabolism - factors known to affect both erythropoiesis and cardiovascular function [39]. Recent research has also shown that RDW may serve as an integrative marker reflecting multiple pathological processes in cardiovascular disease,

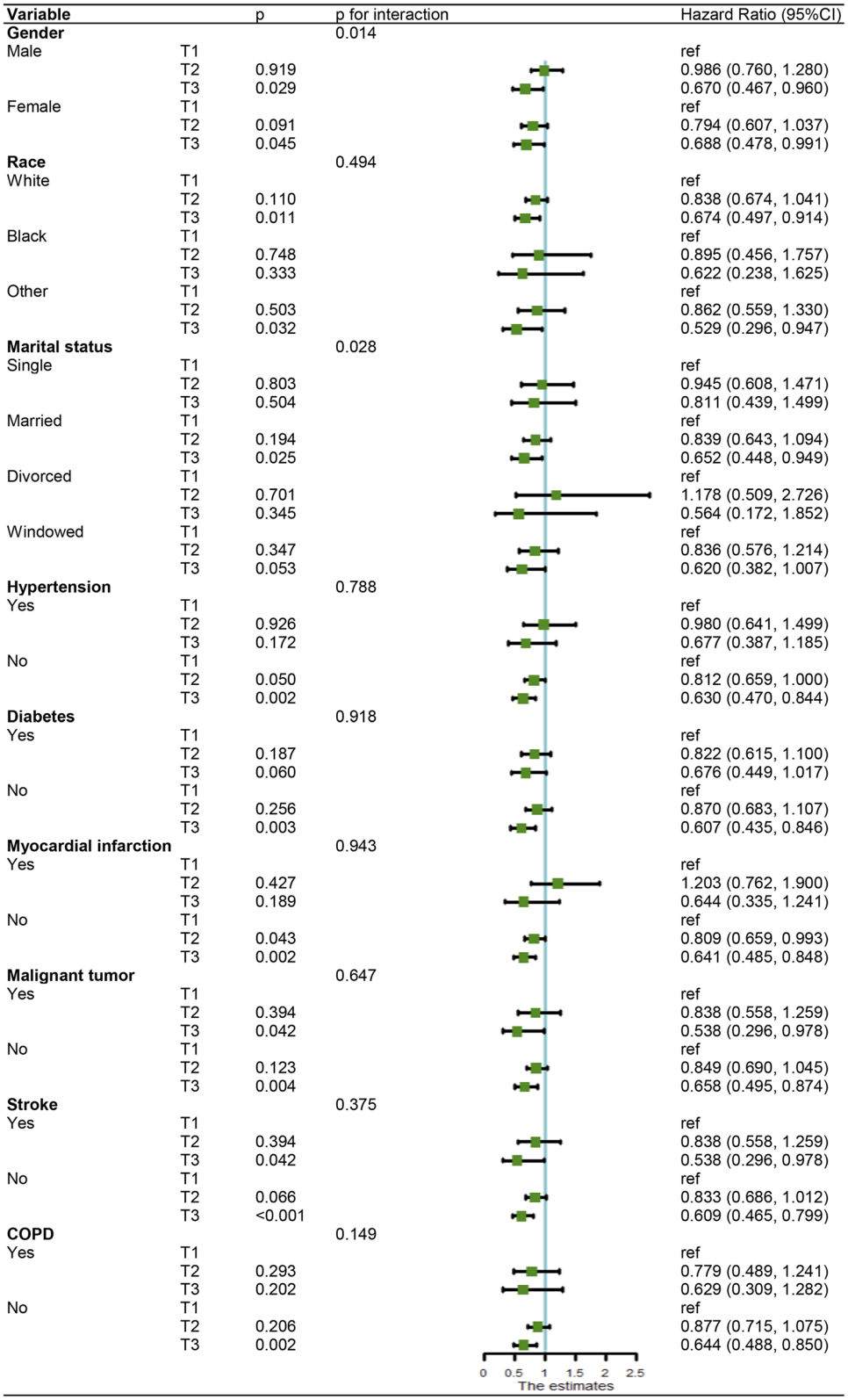

Fig 4 Subgroup analysis of the associations between HRR and 28-days ICU all-cause mortality

including endothelial dysfunction, atherosclerosis, and myocardial injury [40]. Furthermore, RDW has been recognized as a marker of systemic inflammation, closely linked with inflammatory biomarkers such as C-reactive protein (CRP) [41]. Elevated RDW levels indicate increased inflammation and oxidative stress [37], both of which are critical in the pathogenesis of HF and AKI. Additionally, RDW has been associated with various disease states, including liver disease [42], malnutrition [43], and cancer [44], all of which can aggravate HF and AKI. Malnutrition, prevalent among critically ill patients, adversely affects clinical outcomes and is strongly correlated with elevated RDW levels [45]. Research has demonstrated that low cholesterol levels, indicative of malnutrition, are closely associated with higher RDW levels and poor outcomes [27, 46, 47]. Hemoglobin, crucial for oxygen transport, when combined with RDW in the HRR, provides a comprehensive indicator of a patient's inflammatory and oxidative status. Low HRR reflects both anemia and increased RDW, encapsulating the combined impact of these conditions on patient outcomes [48]. Studies have shown that anemia significantly increases the risk of AKI and that low hemoglobin levels are associated with higher mortality rates in critically ill patients [49]. Thus, by incorporating both hemoglobin and RDW, HRR effectively identifies patients at elevated risk of adverse outcomes.

Therefore, the identification of HRR as a prognostic marker is critical for enabling timely interventions and personalized treatment strategies to reduce adverse outcomes. The results of this study highlight the significant prognostic value of HRR, indicating that regular monitoring of HRR could identify high-risk patients and optimize their clinical management. Further studies are essential to confirm the clinical applicability of HRR and to elucidate the mechanisms underlying its prognostic significance.

This study has several limitations. First, the findings are based on a single-center retrospective cohort from the MIMIC-IV 3.0 database, which may limit generalizability to other regions or countries. Additional research is needed to validate these findings across diverse clinical settings. Second, HRR was calculated from initial hemoglobin and RDW measurements, potentially not reflecting the patients' overall condition. Future research should include multiple HRR measurements over time to better evaluate its predictive value for AKI risk. Third, important biomarkers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were excluded due to missing data. Incorporating these biomarkers in future studies will provide a more comprehensive analysis. Finally, while we used Cox regression analysis for all outcomes, logistic regression might have been an alternative statistical approach for analyzing the different end point outcomes. However, we chose Cox regression to maintain consistency across all analyses and to account for the time-varying nature of events. Future studies might consider employing both methods to validate the findings.

Conclusion

In conclusion, our study found a strong link between lower HRR and higher short-term and long-term all-cause mortality in critically ill patients with heart failure and AKI. Based on these findings, we suggested that patients with lower HRR values may benefit from more intensive monitoring and early intervention strategies. Potential approaches could include more frequent assessment of cardiac and renal function, optimization of fluid status, early adjustment of medications affecting kidney function, and closer attention to anemia management. However, further prospective studies are needed to evaluate whether HRR-guided treatment modifications can improve patient outcomes.

Abbreviations

BPD	diastolic blood pressure
BPS	systolic blood pressure
BUN	blood urea nitrogen
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
Hb	hemoglobin
HF	heart failure
HR	heart rate
HRR	hemoglobin-to-red cell distribution width ratio
ICU	intensive care unit
MIMIC-IV	Medical Information Mart for Intensive Care IV
PLC	platelet count
RBC	red blood cell
RDW	red cell distribution width
RR	respiration rate
SpO2	oxygen saturation
WBC	white blood cell

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04632-9.

Additional file 1. Figure S1 Subgroup analysis of the associations between HRR and 28-days hospital all-cause mortality

Additional file 2. Figure S2 Subgroup analysis of the associations between HRR and 90-days hospital all-cause mortality

Additional file 3. Figure S3 ROC curves of HRR, RDW and HB for predicting 28-days ICU mortality, 28-days and 90-days hospital mortality

Additional file 4. Table S1 ICD codes or SQL queries for obtaining ICD codes

Acknowledgements

We appreciate the researchers at the MIT Laboratory for Computational Physiology for public sharing of the MIMIC-IV clinical database.

Authors' contributions

The project was designed by J.S and Y.X. Material preparation, data collection, and analysis were performed by R.Y, X.X, and Y.Z. The first draft of the manuscript was written by R.Y, Y.Y and X.X, and critically revised by J.S and Y.X.

X.X and Y.Y revised the manuscript. Xinping Xu, Rong Yang, and Yujie Yin are co-first authors. Jianhong Si is the co-corresponding author. Ya Xu is the primary corresponding author. All authors reviewed and approved the final manuscript.

Funding
None

Data availability
The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 29 October 2024 Accepted: 6 March 2025
Published online: 25 March 2025

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