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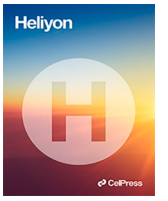

Prognostic value of red blood cell distribution width combined with chloride in predicting short- and long-term mortality in critically ill patients with congestive heart failure: Findings from the MIMIC-IV database

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ABSTRACT

Background: Hypochloremia and red blood cell distribution width (RDW) play important roles in congestive heart failure (CHF) pathophysiology, and they were associated with the prognosis of CHF. However, the prognostic value of chloride combined with RDW in patients with CHF remains unknown.

Methods: We retrospectively analyzed critically ill patients with CHF. The database was derived from the Medical Information Mart for Intensive Care IV v2.0 (MIMIC-IV-v2.0) database.

Results: In the final analysis, 5376 critically ill patients with CHF were included, and 2428 patients (45.2 %) experienced 5-year mortality. The restricted cubic spline model revealed a positive correlation between RDW and 5-year mortality, whereas chloride showed a U-shaped correlation with 5-year mortality. The median values of RDW and chloride were used to classify patients into four groups: high chloride/low RDW, low chloride/low RDW, high chloride/high RDW, and low chloride/high RDW. We observed the prognostic value of RDW combined with chloride in the Cox proportional hazard model, in predicting 5-year mortality, in-hospital mortality and 1-year mortality. Furthermore, we discovered that patients with chronic kidney disease (CKD) had a higher 5-year mortality risk than patients without CKD.

Conclusion: We found the translational potential role of chloride combined with RDW in prioritizing patients at high risk for short- and long-term mortality in a cohort of critically ill patients with CHF. Prospective multicenter investigations are warranted to validate our results.

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1. Introduction

Congestive heart failure (CHF) has a higher risk of morbidity and mortality worldwide, with a 5-year mortality rate of ~50 % after diagnosis, putting a significant strain on the global health care system [1]. Electrolyte imbalances have been demonstrated to play an important role in fluid homeostasis and influencing the progression of CHF [2]. However, in recent decades, practice guidelines have primarily focused on sodium, whereas chloride has recently been shown to be associated with neurohormonal system activity in CHF and to be superior to sodium as an independent risk factor for the prognosis of CHF in patients [1,3,4]. Furthermore, chronic kidney disease (CKD) is prevalent in patients with hypochloremia, which interferes with the kidneys' role in regulating electrolyte balances and diuresis, but there is limited evidence that chloride has a predictive value in patients with CHF and CKD.

In addition, a higher level of red blood cell distribution width (RDW) is associated with a higher risk of mortality in patients with CHF [5,6]. Previous research revealed that inflammation, neurohormonal system activity, and endothelial dysfunction (ED) may cause red blood cell (RBC) maturation by disrupting the RBC membrane, resulting in a higher level of RDW [5,7,8]. RDW has also recently been linked to an increased risk of mortality and accelerated CKD deterioration in patients with CKD [9]. RDW has been linked to functional iron availability, erythropoietic activity, and interleukin-6 in patients with CHF and CKD in previous studies [10,11]. Therefore, RDW has predictive value in the prognosis of cardiorenal patients.

Considering hypochloremia is a major determinant of changes in renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system, and plasma volume, and that neurohormonal system activation increase the RDW level, we hypothesized that chloride combined with RDW could be useful in the risk stratification of critically ill patients with CHF. Furthermore, we investigated whether chloride combined with RDW showed a prognostic impact in critically ill patients with CHF and CKD, and whether the role of RDW combined with chloride in predicting mortality is consistent across different cardiac function states.

2. Methods

2.1. Study population

This is an observational study. Data were extracted from the Medical Information Mart for Intensive Care IV v2.0 (MIMIC-IV-v2.0) database, which is a single database maintained by the Massachusetts Institute of Technology (MIT) that contains medical data from Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) between 2008 and 2019. Chong Zhang, one of the scholars, is authorized to use the database (Record ID 51185766). Moreover, the extract data were validated and checked by Drs Chong Zhang，Tian-hua Hou, and Wei-ru Liang to ensure accuracy of data. The database is publicly available with a waiver for ethical approval statement and informed consent.

We included 5433 patients who were diagnosed with CHF and first admitted to the intensive care unit (ICU), from the MIMIC-IV database. Patients who were discharged or died within 24 h of being admitted to the hospital were excluded. Finally, we analyzed data from 5376 patients with CHF. Fig. 1 depicts the study design.

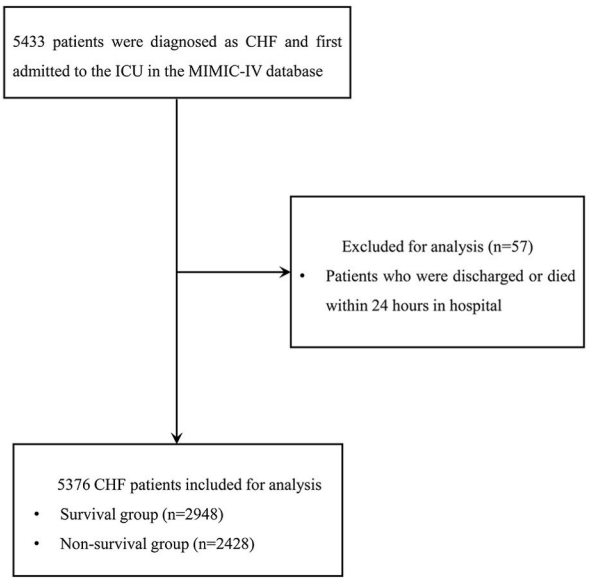


Fig. 1. Flow chart of the study.

Table 1
The baseline characteristics of critically ill patients with CHF.

Categories	Survival group (n = 2948)	Non-survival group (n = 2428)	*P* value
Demographic			
Age, year	68.5 ± 13.4	74.0 ± 12.3	<0.001
Sex, male, n (%)	1729 (58.6)	1376 (56.7)	0.14
Body mass index, kg/m^2	28.5 ± 5.3	27.1 ± 5.6	<0.001
Comorbidities, n (%)			
CKD	799 (27.1)	1065 (43.9)	<0.001
COPD	56 (1.9)	69 (2.8)	0.023
Hypertension	768 (26.1)	473 (19.5)	<0.001
Diabetes	1114 (37.8)	1048 (43.2)	<0.001
Laboratory tests			
eGFR, mL/min/1.73m^2	67.1 (43.7, 89.5)	41.1 (22.7, 65.5)	<0.001
Glucose, mg/dL	124.0 (105.0, 155.0)	131.0 (106.0, 178.0)	<0.001
HbA1c, %	5.9 (5.5, 6.8)	5.8 (5.3, 6.6)	<0.001
NT-proBNP, pg/mL	7139.2 (1856.5, 18231.0)	11174.8 (3955.0, 23004.6)	<0.001
PH	7.4 (7.3, 7.4)	7.4 (7.3, 7.4)	<0.001
Sodium, mmol/L	139.0 (136.0, 141.0)	139.0 (135.0, 141.0)	0.77
Potassium, mmol/L	4.3 (4.0, 4.6)	4.3 (3.9, 4.8)	0.01
Bicarbonate, mmol/L	24.0 (22.0, 26.0)	23.0 (20.0, 27.0)	0.001
Chloride, mmol/L	105.0 (101.0, 108.0)	103.0 (98.0, 107.0)	<0.001
PLT, 10^9/L	199.0 (153.0, 258.0)	208.0 (150.0, 286.0)	0.026
WBC, 10^9/L	13.3 (9.7, 18.1)	12.8 (8.8, 17.9)	<0.001
HGB, mg/dL	11.0 (9.9, 12.5)	10.5 (9.2, 12.0)	<0.001
RDW, %	14.8 (13.7, 16.3)	16.1 (14.8, 17.9)	<0.001
ICU admission			
LODS score	5.0 (3.0, 7.0)	6.0 (4.0, 9.0)	<0.001
APSIII score	36.0 (29.0, 44.0)	43.0 (35.0, 52.0)	<0.001
SIRS score	3.0 (2.0, 3.0)	3.0 (2.0, 3.0)	<0.001
SOFA score	3.0 (2.0, 6.0)	4.0 (2.0, 7.0)	<0.001
MELD score	12.9 (9.0, 18.3)	18.7 (12.0, 25.0)	<0.001
ICU types, n (%)			<0.001
CVICU	1328 (45.0)	347 (14.3)	
CCU	745 (25.3)	676 (27.8)	
MICU/SICU	707 (24.0)	1204 (49.6)	
NSICU	44 (1.5)	58 (2.4)	
TSICU	124 (4.2)	143 (5.9)	
Vital signs			
Heart rate, bpm	82 (74, 92)	84 (73, 96)	<0.001
SBP, mmHg	113.0 (106.0, 122.0)	111.0 (102.0, 123.0)	<0.001
DBP, mmHg	59 (53, 66)	58 (52, 66)	0.001
Medication, n (%)			
ACEI/ARB	1563 (53.0)	799 (32.9)	<0.001
β-blocker	2413 (81.9)	1711 (70.5)	<0.001
MRAs	26 (0.9)	11 (0.5)	0.058
Diuretics	2579 (87.5)	1966 (81.0)	<0.001

Abbreviations: ACEIs/ARBs = angiotensin converting enzyme inhibitors/angiotensin receptor blockers; APS III = acute physiology score III; CCU = coronary care unit; CHF = congestive heart failure; CKD = chronic kidney diseases; COPD = chronic obstructive pulmonary disease; CVICU = cardiovascular intensive care unit; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HGB = hemoglobin; ICU = intensive care unit; LODS = logistic organ dysfunction system; MELD = model for end-stage liver disease; MICU/SICU = medical intensive care unit/surgical intensive care unit; MRAs = mineralocorticoid receptor antagonists; NSICU = neurosurgical intensive care unit; PLT = platelet; RDW = red blood cell distribution width; SBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome; SOFA = sequential organ failure assessment; TSICU = trauma/surgical intensive care unit; WBC = white blood cell.

2.2. Study variables

The data were extracted from the MIIMIC-IV database using PostgreSQL (version 14.5) and Navicat Premium (version 15.0). Demographic characteristics included age, gender, and body mass index (BMI); laboratory tests performed within 24 h of hospitalization included: hemoglobin (HGB), platelet (PLT), white blood cell (WBC), RDW, PH, sodium, potassium, chloride, bicarbonate, estimated glomerular filtration rate (eGFR), glucose (Glu), and N-terminal probrain natriuretic peptide (NT-proBNP); the following vital indicators were recorded: systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate. The ICU admission were as follows: sequential organ failure assessment (SOFA) score, systemic inflammatory response syndrome (SIRS) score, logistic organ dysfunction system (LODS) score, acute physiology score III (APS III), model for end-stage liver disease (MELD), and ICU types; comorbidities were as follows: hypertension (HTN), chronic kidney disease (CKD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD); medications during hospitalization included: diuretics, angiotensin converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), β-blocker, mineralocorticoid receptor antagonists (MRAs). Discharge diagnosis was used to determine

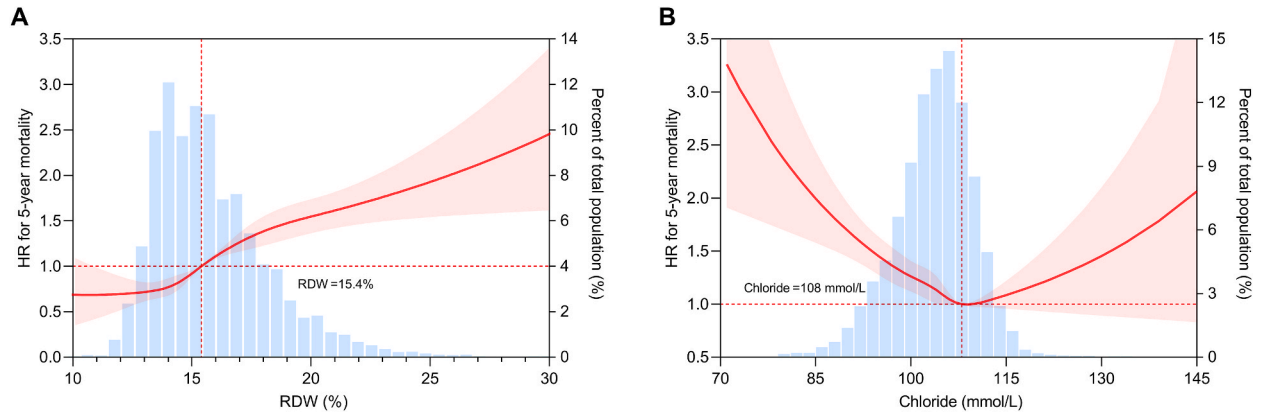


Fig. 2. Restricted cubic spline analysis of RDW and chloride with 5-year mortality. Heavy central lines represent the hazard ratio, with shaded ribbons denoting the 95 % confidence interval. **A:** Association between RDW and 5-year mortality. The reference is the median value of RDW. **B:** Association between chloride and 5-year mortality.

comorbidities using International Classification of Diseases, version 9 (ICD-9) codes and International Classification of Diseases, version 10 (ICD-10) codes.

2.3. Adverse clinical events

The investigation began at the time that patients were admitted to the hospital. The primary outcome was 5-year mortality. The secondary outcomes included in-hospital mortality and 1-year mortality.

2.4. Statistical analysis

Patients with CHF were divided into a survival group and a non-survival group. Continuous variables with a normal distribution are expressed as the mean ± standard deviation (SD), whereas nonparametric continuous variables are expressed as the medians and interquartile ranges (25th-75th percentiles). Categorical variables are expressed as frequencies and percentages. Furthermore, the unpaired *t*-test and the Mann-Whitney *U* test were used to test for differences between groups for continuous variables, while the chi-squared test was used for categorical variables.

We analyzed the relationship between RDW and chloride using Spearman's correlation after logarithmic transformation. The Kaplan-Meier survival analysis and the Cox proportional hazard model were used to estimate the risk of 5-year mortality, 1-year mortality, and in-hospital mortality based on the RDW stratified by chloride—high chloride/low RDW, low chloride/low RDW, high chloride/high RDW, and low chloride/high RDW, according to the median values of RDW and chloride. A restricted cubic spline (RCS) model with five knots was used to assess the association between RDW, chloride, and 5-year mortality. Multivariate imputation (MI) was used to deal with missing values below 30 %. Age, BMI, HGB, PLT, WBC, potassium, bicarbonate, PH, eGFR, Glu, NT-proBNP, SBP, DBP, heart rate, SIRS score, SOFA score, MELD score, LODS score, APS III score, HTN, CKD, DM, COPD, diuretics, ACEI/ARB, and β-blockers were included as covariates in the adjusted model. The covariates were statistically different between patients with CHF in the survival group and the non-survival group. We used Stata 17.0 (StataCorp., College Station, TX) for all analyses. A two-tailed *P* value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

We included 5376 critically ill patients with CHF in the analysis, and 2428 patients (45.2 %) experienced 5-year mortality. Compared to the non-survival group, the survival group had more elderly people, a higher RDW, a lower chloride level, higher disease severity scores, a high proportion of patients with comorbidities, and a lower use of medications during hospitalization (Table 1).

3.2. Association between RDW, chloride and 5-year mortality during follow-up

Spearman's correlation analysis revealed an inverse relationship between RDW and chloride, with a correlation coefficient of −0.1 ($P < 0.001$). Furthermore, we used Spearman's correlation analysis to estimate the relationship between RDW, chloride, and WBC, and the correlation coefficients were −0.04 ($P = 0.004$) and 0.11 ($P < 0.001$) respectively. The RCS model showed a positive relationship between RDW and 5-year mortality (Fig. 2A); additionally, chloride showed a U-shaped correlation with 5-year mortality, with a lower

chloride level associated with a higher risk of 5-year mortality, while the risk of mortality for high chloride showed no statistical significance (Fig. 2B).

3.3. Association between RDW stratified by chloride and short- and long-term mortality during follow-up

Patients were categorized into four groups based on the median values of RDW (15.4 %) and chloride (104 mmol/L)—high chloride/low RDW, low chloride/low RDW, high chloride/high RDW, and low chloride/high RDW. The incidence rate of in-hospital mortality, 1-year mortality, and 5-year mortality were highest in the low chloride/high RDW group compared with the high chloride/low RDW group (Table 2). The Kaplan-Meier survival analysis (Fig. 3A) revealed that the low chloride/high RDW group showed the highest risk of 5-year mortality among the four groups. We observed the predictive efficacy of RDW combined with chloride in predicting in-hospital mortality, 1-year mortality, and 5-year mortality in the Cox proportional hazard model (Table 3). Moreover, the relationship between other risk factors and mortality were shown in (Supplementary Tables S1–S3).

3.4. Sensitivity analysis

We discovered the predictive efficacy of RDW combined with chloride in predicting 5-year mortality among patients with and without CKD using the Cox proportional hazard model. Furthermore, we found that patients with CKD showed a higher risk of 5-year mortality (hazard ratio [HR] 2.00, 95 % confidence interval [CI] 1.62 to 2.47, $P < 0.001$) than patients with no CKD (HR 1.70, 95 % CI 1.44 to 2.01, $P < 0.001$) (Table 4). In addition, the predictive value remains significant among patients in different cardiac function states classified by tertiles of baseline NT-proBNP levels (Table 4).

3.5. Subgroup analyses

We estimated the relationship between chloride and 5-year mortality based on various risk factors, including age, gender, BMI, HTN, and DM. We found that there was no interaction between these risk factors, demonstrating the prognostic value of RDW combined with chloride in distinct populations (Fig. 3B).

4. Discussion

In this study, we discovered that critically ill patients with CHF had a higher 5-year mortality rate of 45.2 %. RDW had an inverse relationship with chloride and a positive relationship with 5-year mortality, whereas chloride had a U-shaped correlation with 5-year mortality, and a lower chloride level was related to a higher risk of 5-year mortality compared to a higher chloride level. Furthermore, RDW combined with chloride may be useful for risk stratification in critically ill patients with CHF as well as patients with CKD and different cardiac function states. Since RDW and chloride are rapid, inexpensive, and readily available parameters in clinical practice, we believe that RDW combined with chloride can help prioritize patients at high risk of short- and long-term mortality in critically ill patients with CHF.

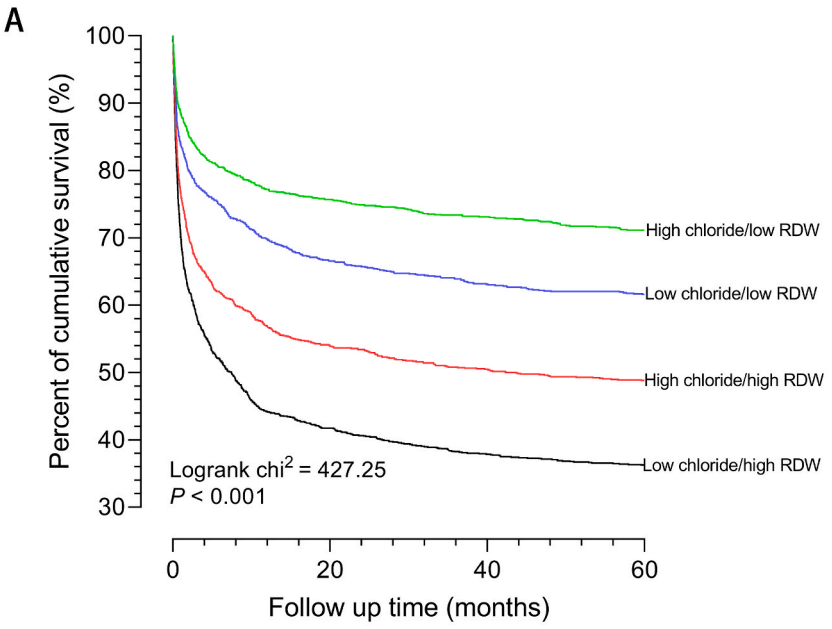
Considering chloride is important in CHF pathophysiology and there is no consensus on the normal ranges of chloride levels, we chose the median value of chloride to define hypochloremia and hyperchloremia. Hypochloremia can cause arrhythmias [12], RAAS activation [1], sympathetic nervous system activation [1], and diuretic resistance [3], all of which worsen congestion in patients with CHF. Previous research has linked hypochloremia to major adverse cardiovascular events (MACEs) [13–16], but other research has revealed hypochloremia and hyperchloremia to be independent risk factors for MACEs [17–20]. In this study, we found that chloride showed a U-shaped correlation to 5-year mortality, and only hypochloremia was statistically significant. Hypochloremia stimulates neurohormonal system activity, which leads to increased levels of RDW by promoting RBC maturation that disturbs the red cell membrane. Furthermore, chloride channel subtype 3 (CIC-3) has recently been linked to the inflammatory response, oxidative stress, and regulatory volume decrease (RVD) in patients with CHF who have hypochloremia [21], implying that higher RDW levels are induced. In this study, we discovered hypochloremia and higher RDW levels were associated with higher WBC levels, which reflected the state of the inflammatory response, and that the low chloride/high RDW group had the highest risk of short-term and long-term mortality among the four groups, which is consistent with the findings of previous studies.

We also found that RDW combined with chloride showed a higher risk of 5-year mortality in patients with CKD compared to

Table 2
The incidence of mortality of critically ill patients categorized by chloride with RDW.

	High chloride/low RDW (n = 1525)	Low chloride/low RDW (n = 1219)	High chloride/high RDW (n = 1264)	Low chloride/high RDW (n = 1368)	*P* value
In-hospital mortality, n (%)	144 (9.4)	156 (12.8)	255 (20.2)	354 (25.9)	<0.001
1-year mortality, n (%)	348 (22.8)	368 (30.2)	545 (43.1)	763 (55.8)	<0.001
5-year mortality, n (%)	440 (28.9)	468 (38.4)	647 (51.2)	873 (63.8)	<0.001

Abbreviations: RDW = red blood cell distribution width.



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	Total (n=5376)	High chloride (n=2789)	Low chloride (n=2587)	Hazard Ratios (95% Confidence Interval)
Age			Favor low chloride ← → Favor high chloride	P_{int}=0.980
<65	1555 (28.9)	771 (49.6)	784 (50.4)	1.19 (0.97 to 1.46)
>=65	3821 (71.1)	2018 (52.8)	1803 (47.2)	1.22 (1.10 to 1.35)
Gender				P_{int}=0.831
Female	2271 (42.2)	1145 (50.4)	1126 (49.6)	1.18 (1.03 to 1.35)
Male	3105 (57.8)	1644 (52.9)	1461 (47.1)	1.23 (1.09 to 1.38)
BMI				P_{int}=0.988
Low BMI	3681 (68.5)	1932 (52.5)	1749 (47.5)	1.24 (1.11 to 1.37)
High BMI	1695 (31.5)	857 (50.6)	838 (49.4)	1.12 (0.94 to 1.35)
Hypertension				P_{int}=0.397
No	4135 (76.9)	2060 (49.8)	2075 (50.2)	1.19 (1.07 to 1.31)
Yes	1241 (23.1)	729 (58.7)	512 (41.3)	1.33 (1.09 to 1.63)
Diabetes				P_{int}=0.807
No	3214 (59.8)	1769 (55.0)	1445 (45.0)	1.23 (1.09 to 1.38)
Yes	2162 (40.2)	1020 (47.2)	1142 (52.8)	1.20 (1.04 to 1.38)

Fig. 3. **A:** Kaplan-Meier survival analysis curves for 5-year mortality based on the RDW stratified by chloride. **B:** Forest plots of the hazard ratio for 5-year mortality.

patients with no CKD. Critically ill patients with CHF and CKD have a poor prognosis. Patients with CHF usually have compromised renal perfusion due to lower cardiac output and venous system congestion. Chloride regulates tubuloglomerular feedback to maintain electrolyte balances. The low chloride/high RDW group has the worst symptoms of congestion, sympathetic nervous system activation, and inflammatory response activation, all of which contribute to a poor prognosis for patients with CHF. Furthermore, RDW combined with NT-proBNP improves the prognostic value of CHF [6], but it is unclear whether NT-proBNP regulates the prognostic value of chloride. Cuthbert et al. discovered that hypochloremia was associated with mortality, regardless of NT-proBNP [17]. However, Armstrong et al. found that a higher chloride level was associated with a decreased risk of MACEs after adjustment using covariates including NT-proBNP [22]. In this study, we evaluated the association between NT-proBNP and RDW combined with chloride, and we found that the low chloride/high RDW group showed the highest risk of 5-year mortality among different NT-proBNP levels, indicating that RDW and chloride had a prognostic value independent of NT-proBNP.

Nevertheless, this study has several limitations: (1) This was a single-center retrospective cohort study, and prospective multicenter studies are required to validate our findings; (2) because the MIMIC-IV-ECHO module was under embargo until: Jan. 17, 2024 (URL: https://www.physionet.org/content/mimic-iv-echo/0.1/). Therefore, we had no access to acquire records in MIMIC-IV-ECHO as well as left ventricular ejection fraction (LVEF), and we were unable to investigate the role of RDW combined with chloride in clinical subtypes of heart failure, such as heart failure with preserved ejection fraction (HFpEF), heart failure with mildly reduced EF

Table 3
Cox proportional hazard models for chloride combined with RDW and mortality during follow-up.

Categories	Crude model		Adjusted model	
	HR and 95%CI	*P* value	HR and 95%CI	*P* value
In-hospital mortality				
High chloride/low RDW	Ref.		Ref.	
Low chloride/low RDW	1.39 (1.11–1.74)	0.005	1.39 (1.10–1.76)	0.006
High chloride/high RDW	2.27 (1.85–2.79)	<0.001	1.48 (1.20–1.83)	<0.001
Low chloride/high RDW	3.01 (2.48–3.65)	<0.001	1.89 (1.52–2.34)	<0.001
1-year mortality				
High chloride/low RDW	Ref.		Ref.	
Low chloride/low RDW	1.39 (1.20–1.61)	<0.001	1.24 (1.07–1.45)	0.005
High chloride/high RDW	2.18 (1.91–2.50)	<0.001	1.58 (1.38–1.81)	<0.001
Low chloride/high RDW	3.08 (2.71–3.49)	<0.001	1.93 (1.67–2.22)	<0.001
5-year mortality				
High chloride/low RDW	Ref.		Ref.	
Low chloride/low RDW	1.42 (1.24–1.62)	<0.001	1.25 (1.09–1.43)	0.002
High chloride/high RDW	2.13 (1.88–2.40)	<0.001	1.57 (1.39–1.78)	<0.001
Low chloride/high RDW	2.97 (2.65–3.33)	<0.001	1.86 (1.63–2.11)	<0.001

Note: Covariates for the adjusted model included age, BMI, HGB, PLT, WBC, potassium, bicarbonate, PH, eGFR, Glu, NT-proBNP, SBP, DBP, heart rate, SIRS, SOFA, MELD, LODS, APS III, hypertension, CKD, diabetes, COPD, diuretics, ACEI/ARB, β-blocker.
Abbreviations: ACEI/ARB = angiotensin converting enzyme inhibitors/angiotensin receptor blockers; APS III = acute physiology score III; BMI = body mass index; CKD = chronic kidney diseases; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; Glu = glucose; HGB = hemoglobin; LODS = logistic organ dysfunction system; MELD = model for end-stage liver disease; NT-proBNP=N-terminal probrain natriuretic peptide; PLT = platelet; RDW = red blood cell distribution width; SBP = systolic blood pressure; SIRS = systemic inflammatory response syndrome; SOFA = sequential organ failure assessment; WBC = white blood cell.

Table 4
Sensitivity analysis for association between chloride combined with RDW and 5-year mortality.

Categories	Crude model		Adjusted model	
	HR and 95%CI	*P* value	HR and 95%CI	*P* value
CKD patients				
High chloride/low RDW	Ref.		Ref.	
Low chloride/low RDW	1.32 (1.06–1.64)	0.013	1.17 (0.93–1.48)	0.139
High chloride/high RDW	2.05 (1.68–2.51)	<0.001	1.68 (1.37–2.06)	<0.001
Low chloride/high RDW	2.59 (2.15–3.13)	<0.001	2.00 (1.62–2.47)	<0.001
Non-CKD patients				
High chloride/low RDW	Ref.		Ref.	
Low chloride/low RDW	1.41 (1.20–1.65)	<0.001	1.28 (1.08–1.52)	0.004
High chloride/high RDW	2.00 (1.72–2.34)	<0.001	1.48 (1.26–1.73)	<0.001
Low chloride/high RDW	2.85 (2.46–3.31)	<0.001	1.70 (1.44–2.01)	<0.001
NT-proBNP (T1)				
High chloride/low RDW	Ref.		Ref.	
Low chloride/low RDW	1.49 (1.17–1.90)	0.001	1.31 (1.02–1.70)	0.036
High chloride/high RDW	2.06 (1.63–2.60)	<0.001	1.73 (1.37–2.20)	<0.001
Low chloride/high RDW	3.23 (2.59–4.03)	<0.001	2.31 (1.80–2.96)	<0.001
NT-proBNP (T2)				
High chloride/low RDW	Ref.		Ref.	
Low chloride/low RDW	1.23 (1.00–1.53)	0.054	1.26 (1.01–1.58)	0.042
High chloride/high RDW	1.78 (1.45–2.18)	<0.001	1.50 (1.22–1.85)	<0.001
Low chloride/high RDW	2.42 (2.00–2.93)	<0.001	1.70 (1.37–2.11)	<0.001
NT-proBNP (T3)				
High chloride/low RDW	Ref.		Ref.	
Low chloride/low RDW	1.57 (1.26–1.97)	<0.001	1.18 (0.93–1.49)	0.182
High chloride/high RDW	2.49 (2.04–3.04)	<0.001	1.55 (1.26–1.91)	<0.001
Low chloride/high RDW	3.14 (2.60–3.80)	<0.001	1.79 (1.44–2.22)	<0.001

Note: Different cardiac function states that were categorized according to the tertiles of baseline NT-proBNP levels including T1, T2 and T3. Covariates for the adjusted model included age, BMI, HGB, PLT, WBC, potassium, bicarbonate, PH, eGFR, Glu, NT-proBNP, SBP, DBP, heart rate, SIRS, SOFA, MELD, LODS, APS III, hypertension, CKD, diabetes, COPD, diuretics, ACEI/ARB, β-blocker.
Abbreviations: ACEI/ARB = angiotensin converting enzyme inhibitors/angiotensin receptor blockers; APS III = acute physiology score III; BMI = body mass index; CKD = chronic kidney diseases; COPD = chronic obstructive pulmonary disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HGB = hemoglobin; LODS = logistic organ dysfunction system; MELD = model for end-stage liver disease; NT-proBNP=N-terminal probrain natriuretic peptide; PLT = platelet; RDW = red blood cell distribution width; Glu = glucose; SBP = systolic blood pressure; SOFA = sequential organ failure assessment; SIRS = systemic inflammatory response syndrome; WBC = white blood cell.

(HFmrEF), and heart failure with reduced EF (HFrEF). Admittedly, we have no information concerning LVEF. However, NT-proBNP that was measured first 24 h of hospitalization would be an important measurement for left ventricular function, which has nearly the same function as LVEF. Moreover, incorporating LVEF into the Cox proportional hazard model would introduce the potential issue of collinearity with NT-proBNP; (3) due to the design of MIMIC-IV-v2.0 database didn't involve paraclinical parameters data during post-discharge follow-up, we therefore couldn't obtain the levels of chloride and RDW during the 5 years.

5. Conclusion

In conclusion, we found a translational role of chloride combined with RDW in prioritizing patients at high risk for short-term and long-term mortality in a cohort of critically ill patients with CHF. Prospective multicenter studies are warranted to validate our findings.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability

Date will be made available on request.

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CRediT authorship contribution statement

Chong Zhang: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Tian-hua Hou:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Wei-ru Liang:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Cui-jun Hao:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Fei Wang:** Writing – review & editing, Writing – original draft. **Jia-yan Xin:** Writing – original draft, Formal analysis. **Bin Su:** Writing – original draft, Formal analysis. **Meng Ning:** Investigation, Formal analysis. **Ying-wu Liu:** Writing – review & editing, Conceptualization.

Abbreviations

CHF	congestive heart failure
ED	endothelial dysfunction
HR	hazard ratio
MIMIC-IV	Medical Information Mart for Intensive Care IV
RAAS	renin-angiotensin-aldosterone system
RDW	red blood cell distribution width
ICU	intensive care unit
BMI	body mass index

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e23353.

References

[1] A.J.L. Zandijk, M.R. van Norel, F.E.C. Julius, N. Sepehrvand, N. Pannu, F.A. McAlister, et al., Chloride in heart failure: the neglected electrolyte, JACC. Heart. Fail. 9 (2021) 904–915, https://doi.org/10.1016/j.jchf.2021.07.006.

[2] A.A. Kammerlander, With a grain of salt: sodium levels in heart failure, Int. J. Cardiol. 290 (2019) 125–126, https://doi.org/10.1016/j.ijcard.2019.05.027.

[3] J.S. Hanberg, V. Rao, J.M. Ter Maaten, O. Laur, M.A. Brisco, F. Perry Wilson, et al., Hypochloremia and diuretic resistance in heart failure: mechanistic insights, Circ. Heart. Fail. 9 (2016), https://doi.org/10.1161/circheartfailure.116.003180.

[4] A. Kazory, Chloride and cardiorenal interactions in heart failure, Nephron 147 (2023) 6–8, https://doi.org/10.1159/000524987.

[5] A. Xanthopoulos, G. Giamouzis, A. Dimos, E. Skoularigki, R.C. Starling, J. Skoularigis, et al., Red blood cell distribution width in heart failure: pathophysiology, prognostic role, controversies and dilemmas, J. Clin. Med. 11 (2022), https://doi.org/10.3390/jcm11071951.

[6] L. Liang, L. Huang, X. Zhao, L. Zhao, P. Tian, B. Huang, et al., Prognostic value of RDW alone and in combination with NT-proBNP in patients with heart failure, Clin. Cardiol. 45 (2022) 802–813, https://doi.org/10.1002/clc.23850.

[7] T. Mohaissen, B. Proniewski, M. Targosz-Korecka, A. Bar, A. Kij, K. Bulat, et al., Temporal relationship between systemic endothelial dysfunction and alterations in erythrocyte function in a murine model of chronic heart failure, Cardiovasc. Res. 118 (2022) 2610–2624, https://doi.org/10.1093/cvr/cvab306.

[8] R. Hullin, N. Barras, T. Abdurashidova, P. Monney, J. Regamey, Red cell distribution width and prognosis in acute heart failure: ready for prime time, Intern. Emerg. Med. 14 (2019) 195–197, https://doi.org/10.1007/s11739-018-1995-7.

[9] X. Deng, B. Gao, F. Wang, M.H. Zhao, J. Wang, L. Zhang, Red blood cell distribution width is associated with adverse kidney outcomes in patients with chronic kidney disease, Front. Med. 9 (2022), 877220, https://doi.org/10.3389/fmed.2022.877220.

[10] M.E. Emans, K. van der Putten, K.L. van Rooijen, R.J. Kraaijenhagen, D. Swinkels, W.W. van Solinge, et al., Determinants of red cell distribution width (RDW) in cardiorenal patients: RDW is not related to erythropoietin resistance, J. Card. Fail. 17 (2011) 626–633, https://doi.org/10.1016/j.cardfail.2011.04.009.

[11] B. Afsar, M. Saglam, C. Yuceturk, E. Agca, The relationship between red cell distribution width with erythropoietin resistance in iron replete hemodialysis patients, Eur. J. Intern. Med. 24 (2013) e25–e29, https://doi.org/10.1016/j.ejim.2012.11.017.

[12] G.B. Adkins, M.J. Curtis, Potential role of cardiac chloride channels and transporters as novel therapeutic targets, Pharmacol. Ther. 145 (2015) 67–75, https://doi.org/10.1016/j.pharmthera.2014.08.002.

[13] J.L. Grodin, J.L. Sun, K.J. Anstrom, H.H. Chen, R.C. Starling, J.M. Testani, et al., Implications of serum chloride homeostasis in acute heart failure (from ROSE-AHF), Am. J. Cardiol. 119 (2017) 78–83, https://doi.org/10.1016/j.amjcard.2016.09.014.

[14] J.L. Grodin, F.H. Verbrugge, S.G. Ellis, W. Mullens, J.M. Testani, W.H. Tang, Importance of abnormal chloride homeostasis in stable chronic heart failure, Circ. Heart. Fail. 9 (2016), e002453, https://doi.org/10.1161/circheartfailure.115.002453.

[15] J.L. Grodin, W. Mullens, M. Dupont, D.O. Taylor, P.M. McKie, R.C. Starling, et al., Hemodynamic factors associated with serum chloride in ambulatory patients with advanced heart failure, Int. J. Cardiol. 252 (2018) 112–116, https://doi.org/10.1016/j.ijcard.2017.11.024.

[16] J.L. Grodin, J. Simon, R. Hachamovitch, Y. Wu, G. Jackson, M. Halkar, et al., Prognostic role of serum chloride levels in acute decompensated heart failure, J. Am. Coll. Cardiol. 66 (2015) 659–666, https://doi.org/10.1016/j.jacc.2015.06.007.

[17] J.J. Cuthbert, P. Pellicori, A. Rigby, D. Pan, S. Kazmi, P. Shah, et al., Low serum chloride in patients with chronic heart failure: clinical associations and prognostic significance, Eur. J. Heart Fail. 20 (2018) 1426–1435, https://doi.org/10.1002/ejhf.1247.

[18] J.P. Ferreira, N. Girerd, K. Duarte, S. Coiro, J.J. McMurray, H.J. Dargie, et al., Serum chloride and sodium interplay in patients with acute myocardial infarction and heart failure with reduced ejection fraction: an analysis from the high-risk myocardial infarction database initiative, Circ. Heart. Fail. 10 (2017), https://doi.org/10.1161/circheartfailure.116.003500.

[19] J.L. Grodin, J.M. Testani, A. Pandey, K. Sambandam, M.H. Drazner, J.C. Fang, et al., Perturbations in serum chloride homeostasis in heart failure with preserved ejection fraction: insights from TOPCAT, Eur. J. Heart Fail. 20 (2018) 1436–1443, https://doi.org/10.1002/ejhf.1229.

[20] J.M. Testani, J.S. Hanberg, J.P. Arroyo, M.A. Brisco, J.M. Ter Maaten, F.P. Wilson, et al., Hypochloraemia is strongly and independently associated with mortality in patients with chronic heart failure, Eur. J. Heart Fail. 18 (2016) 660–668, https://doi.org/10.1002/ejhf.477.

[21] N.M. Kouyoumdzian, G. Kim, M.J. Rudi, N.L. Rukavina Mikusic, B.E. Fernández, M.R. Choi, Clues and new evidences in arterial hypertension: unmasking the role of the chloride anion, Pflugers. Arch. 474 (2022) 155–176, https://doi.org/10.1007/s00424-021-02649-5.

[22] P.W. Armstrong, B. Pieske, K.J. Anstrom, J. Ezekowitz, A.F. Hernandez, J. Butler, et al., Vericiguat in patients with heart failure and reduced ejection fraction, N. Engl. J. Med. 382 (2020) 1883–1893, https://doi.org/10.1056/NEJMoa1915928.