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ORIGINAL ARTICLE

In-hospital changes in the red blood cell distribution width and mortality in critically ill patients with heart failure

Qi Zhang[1], Bingyang Zhou[1], Ximing Li[1,2,3]* and Hongliang Cong[1,2,3]

[1]*Department of Cardiology, Tianjin Chest Hospital, Tianjin, China;* [2]*Tianjin Medical University, Tianjin, China; and* [3]*Tianjin University, Tianjin, China*

Abstract

Aims A high red blood cell distribution width (RDW) at admission or discharge is associated with a worse prognosis in hospitalized patients with heart failure (HF), and the prognostic value of the in-hospital change in RDW (ΔRDW) remains debatable.

Methods and results We included 5514 patients with critical illness and HF from the MIMIC-IV database. The ΔRDW was calculated by the RDW at discharge minus that at admission. Clinical outcomes included all-cause mortality at 90 day, 180 day, and 1 year after discharge. The median age of the patients was 73.91 years, and 46.37% were women. Kaplan–Meier curve and Cox regression analyses were used to examine the association between the ΔRDW and all-cause mortality at different time points. A multivariable Cox proportional hazard model showed that the ΔRDW (per 1% increase) was independently associated with all-cause mortality at 90 day, 180 day, and 1 year after adjusting for confounding factors (hazard ratio [HR] = 1.17, 95% confidence interval [CI] = 1.13–1.21, $P < 0.001$; HR = 1.17, 95% CI = 1.14–1.20, $P < 0.001$; and HR = 1.18, 95% CI = 1.15–1.20, $P < 0.001$, respectively). Restricted cubic splines showed a non-linear relationship between the ΔRDW and the risk of clinical outcomes. High ΔRDW was associated with a high risk of mortality at different time points. A subgroup analysis showed that this positive association remained consistent in pre-specified subgroups.

Conclusions Our study suggests that an increased RDW during hospitalization is independently associated with short- or long-term all-cause mortality in critical-ill patients with HF.

Keywords Critical care; Heart failure; Prognosis; Red blood cell

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**Correspondence to: Ximing Li, Department of Cardiology, Tianjin Chest Hospital, 261# Taierzhuangnan Road, Jinnan District, Tianjin, China. Email: ljsunlight@126.com*

Introduction

The red blood cell distribution width (RDW) reflects variation in the dimension of red blood cells and is widely used as a diagnostic tool for anaemia.[1] Several studies have shown that an increased RDW is related to an adverse outcome and is a novel risk factor for risk stratification in patients with cardiovascular diseases.[2–7]

Heart failure (HF) is one of the most prevalent cardiovascular diseases with an increasing mortality rate. In patients with HF, accurate risk stratification for a poor prognosis is crucial. Previous studies have shown that an increased RDW is associated with poor short- and long-term outcomes in acute or chronic HF.[8–20] An increased RDW indicates the deregulation of erythrocyte homeostasis and abnormal survival of red blood cells. This situation may lead to a variety of underlying pathophysiological disorders, such as oxidative stress, inflammation, and a poor nutritional status.[21] Baseline RDW has been incorporated in recent HF prognostic models and might be a promising treatsment target for patients with HF.

Although a high RDW at admission or discharge is associated with a worse prognosis in hospitalized patients with HF, the prognostic importance of an in-hospital change in RDW (ΔRDW) remains debatable.[22] Several studies have

shown that a persistent increase in the RDW during hospitalization is associated with adverse short-or long-term outcomes in patients with acute or chronic HF.[23–28] However, the RDW value may be different from that of general inpatients or outpatients with HF who are critically ill. A recent study showed that the baseline RDW was associated with in-hospital and short-term mortality in critically ill patients with HF.[9] However, the in-hospital ΔRDW and the mortality rate in the short or long term in critically ill patients with HF is unclear. Therefore, we aimed to perform a retrospective study to examine whether the in-hospital ΔRDW is independently associated with mortality at different time points in patients who are critically ill with HF.

Methods

Study design and data source

This study was a retrospective analysis using data from the open-accessed Medical Information Mart for Intensive Care database (MIMIC-IV), which is an updated version of MIMIC-III. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by an institutional review board approval. The Institutional Review Boards of the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center gave their approval for this project. The medical records, laboratory results, medical therapies, demographic information, and International Classification of Diseases (ICD) disease codes of patients who were admitted to the intensive care unit at Beth Israel Deaconess Medical Center between 2008 and 2019 are contained in the MIMIC-IV database. The patients' identity information was concealed to protect their privacy.

Inclusion and exclusion criteria

Patients with HF who were first admitted to the intensive care unit were identified on the basis of the ICD-9 and ICD-10 codes. HF may be not registered as the principal diagnosis. Therefore, we excluded records with HF in positions not in the first five diagnosis based on the ICD sequence. Patients with in-hospital death or no RDW records at admission or discharge were excluded. Additionally, patients with a length of hospitalization shorter than 3 days, those with malignant cancer or haematological disease, those with red blood cells transfusion during hospitalization, or with missing data (<10% of the total sample size) were also excluded (*Figure S1*).

Study variables

The RDW at admission was recorded as the first RDW measured within 24 h after admission. The RDW at discharge was recorded as the last measurement within 24 h before discharge. The in-hospital ΔRDW was calculated by the RDW at discharge minus the RDW at admission.

Other variables included demographic characteristics (age, sex, and race), body mass index (BMI), length of hospitalization, co-morbidities, physical examination results, laboratory test results, medication, and treatment. Co-morbidities included essential hypertension, type 2 diabetes mellitus, atrial fibrillation, myocardial infarction, cerebrovascular disease, peripheral vascular disease, pulmonary disease, liver disease, renal disease, and the Charlson co-morbidity index. A physical examination included heart rate, systolic and diastolic blood pressure, and mean arterial pressure. Laboratory tests included haemoglobin values, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, white blood cell count, platelet count, and concentrations of potassium, sodium, chloride, glucose, creatinine, blood urea nitrogen, and N terminal pro-brain natriuretic peptide (NT-proBNP). Medication and treatment included vasoactive agents (dobutamine, dopamine, epinephrine, milrinone, nesiritide, nitrate, nitroprusside sodium, norepinephrine, and vasopressin), angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists, beta-blockers, mineralocorticoid receptor antagonists, calcium channel blockers, diuretics, digoxin, ventilation, dialysis, an intra-aortic balloon pump, and extracorporeal membrane oxygenation. In addition, Sequential Organ Failure Assessment (SOFA) and the Simplified Acute Physiology Score II (SAPSII) were recorded.

The clinical outcome comprised all-cause 90 day (short term) mortality, 180 day (medium term) mortality, and 1 year (long term) mortality.

Statistical analysis

The baseline characteristics of our study population were compared after grouping by tertiles of the ΔRDW. All continuous variables are shown as the mean and standard deviation or median and interquartile range and were compared with one-way analysis of variance or Kruskal–Wallis one-way analysis of variance according to the distribution of data. Categorical variables, which are expressed as counts and percentages, were compared with the χ^2 test. *P* values for trend were calculated by the Mantel–Haenszel test. Kaplan–Meier curves for the outcomes were compared using the log-rank test according to ΔRDW tertiles.

A Cox regression analysis was conducted to evaluate the association between the ΔRDW tertiles and short-, me-

Table 1 Baseline characteristics and mortality of the study population according to ΔRDW tertiles

Items	Total	1st tertile	2nd tertile	3rd tertile	*P* for trend
ΔRDW		−11.7% to 0.19%	0.2% to 1.49%	1.5 to 16.3%	
N	5514	1835	1768	1911	
Age median (IQR), year	73.91 (63.67–83.20)	71.00 (60.59–81.37)	75.03 (64.39–83.53)	75.50 (65.72–84.29)	<0.001
Female, *n* (%)	2557 (46.37)	789 (43.00)	821 (46.44)	947 (49.56)	<0.001
Race, *n* (%)					<0.001
White	3652 (66.23)	1164 (63.43)	1183 (66.91)	1305 (68.29)	
Black	532 (9.65)	168 (9.16)	150 (8.48)	214 (11.20)	
Others	1330 (24.12)	503 (27.41)	435 (24.60)	392 (20.51)	
BMI, median (IQR), kg/m^2 (*n* = 3277)	29.93 (25.91–35.03)	30.34 (26.11–35.08)	29.97 (26.18–35.09)	29.53 (25.52–34.85)	0.464
Length of hospitalization, median (IQR), days	7.82 (5.29–12.11)	7.09 (4.98–10.85)	7.55 (5.21–11.78)	8.79 (5.91–13.85)	<0.001
Co-morbidities, *n* (%)					
Hypertension	2653 (48.11)	795 (43.32)	812 (45.93)	1046 (54.74)	<0.001
Type 2 diabetes mellitus	1532 (27.78)	468 (25.50)	440 (24.89)	624 (32.65)	<0.001
Atrial fibrillation	1795 (32.55)	549 (29.92)	498 (28.17)	748 (39.14)	<0.001
Myocardial Infarction	2002 (36.31)	612 (33.35)	623 (35.24)	767 (40.14)	<0.001
Cerebrovascular disease	324 (5.88)	85 (4.63)	94 (5.32)	145 (7.59)	<0.001
Peripheral vascular disease	855 (15.51)	235 (12.81)	247 (13.97)	373 (19.52)	<0.001
Pulmonary disease	944 (17.12)	285 (15.53)	257 (14.54)	402 (21.04)	<0.001
Liver disease	156 (2.83)	56 (3.05)	37 (2.09)	63 (3.30)	0.633
Renal disease	516 (9.36)	153 (8.34)	128 (7.24)	235 (12.30)	<0.001
Charlson co-morbidity index, mean ± SD	6.45 ± 2.30	6.16 ± 2.35	6.37 ± 2.31	6.79 ± 2.21	<0.001
Physical examination					
Heart rate, median (IQR), b.p.m.	83 (73–96)	84 (73–97)	83 (73–95)	82 (72–95)	0.015
Systolic blood pressure, mean ± SD, mmHg	123.39 ± 24.75	124.07 ± 24.34	123.41 ± 24.99	122.72 ± 24.91	0.095
Diastolic blood pressure, mean ± SD, mmHg	65.80 ± 17.27	67.12 ± 17.40	65.70 ± 17.46	64.64 ± 16.90	<0.001
Mean arterial pressure, mean ± SD, mmHg	82.03 ± 18.10	83.17 ± 18.26	81.77 ± 17.73	81.20 ± 18.25	<0.001
Laboratory test					
Haemoglobin, median (IQR), g/dL	12.5 (11.1–13.8)	12.4 (10.7–13.8)	12.6 (11.3–13.9)	12.5 (11.2–13.7)	0.081
Haematocrit, median (IQR), %	37.7 (33.7–41.3)	37.4 (33–41.3)	38.1 (34.1–41.5)	37.7 (34–41.1)	0.227
MCV median (IQR), fL	91 (87–95)	91 (86–95)	91 (87–95)	91 (87–95)	0.024
MCH median (IQR), pg	30.1 (28.6–31.5)	30 (28.4–31.5)	30.2 (28.8–31.5)	30.2 (28.6–31.6)	0.002
MCHC, median (IQR), g/dL	33.1 (32.1–34)	33 (31.9–34)	33.1 (32.2–34.1)	33.1 (32.1–34)	0.011
RDW at admission, mean±SD, %	14.53 ± 1.73	15.16 ± 2.06	14.17 ± 1.44	14.25 ± 1.43	<0.001
RDW at discharge, mean ± SD, %	15.70 ± 2.46	14.34 ± 1.63	14.89 ± 1.50	17.76 ± 2.50	<0.001
White blood cell, median (IQR), K/μL	8.2 (6.5–10.8)	8.3 (6.6–11)	8.3 (6.6–10.9)	8.1 (6.4–10.6)	0.004
Platelet, median (IQR), K/μL	226 (180–284)	224 (177–282)	225 (179–280)	230 (182–289)	0.019
Potassium, mean ± SD mmol/L	4.30 ± 0.69	4.30 ± 0.71	4.28 ± 0.67	4.32 ± 0.69	0.422
Sodium, median (IQR), mmol/L	139 (137–141)	139 (137–141)	139 (137–141)	139 (137–141)	0.514
Chloride, median (IQR), mmol/L	102 (99–104)	102 (98–105)	102 (99–104)	102 (99–104)	0.429
Glucose, median (IQR), mg/dL	118 (98–157)	118 (99–156)	119.5 (97–157)	117 (97–161)	0.100
Creatinine, median (IQR), mg/dL	1.1 (0.9–1.4)	1.1 (0.8–1.4)	1.1 (0.8–1.4)	1.1 (0.9–1.5)	0.329
Blood urea nitrogen, median (IQR), mg/dL	22 (16–31)	21 (15–32)	22 (16–30)	22 (16–32)	0.508
NT-proBNP, median (IQR), pg/mL (*n* = 3622)	2578.5 (933–6724)	2439 (848–6053)	2511 (864–6576)	2737.5 (1041.5–7428.5)	0.218
Medications, *n* (%)					
Vasoactive agents	2631 (47.71)	800 (43.60)	813 (45.98)	1018 (53.27)	<0.001
ACEI/ARB	3869 (70.17)	1257 (68.50)	1220 (69.00)	1392 (72.84)	0.004
Beta-blockers	4952 (89.81)	1605 (87.47)	1593 (90.10)	1754 (91.78)	<0.001
Mineralocorticoid receptor antagonist	1072 (19.44)	332 (18.09)	274 (15.50)	466 (24.39)	<0.001

(*Continues*)

Table 1 (continued)

Items	Total	1st tertile	2nd tertile	3rd tertile	*P* for trend
Calcium channel blockers	1947 (35.31)	582 (31.72)	604 (34.16)	761 (39.82)	<0.001
Diuretics	5165 (93.67)	1668 (90.90)	1653 (93.50)	1844 (96.49)	<0.001
Digoxin	844 (15.31)	259 (14.11)	239 (13.52)	346 (18.11)	<0.001
Treatment, *n* (%)					
Ventilation	4731 (85.80)	1552 (84.58)	1552 (87.78)	1627 (85.14)	0.647
Dialysis	367 (6.66)	105 (5.72)	95 (5.37)	167 (8.74)	<0.001
IABP	146 (2.65)	61 (3.32)	45 (2.55)	40 (2.09)	0.019
ECMO	14 (0.25)	3 (0.16)	3 (0.17)	8 (0.42)	0.119
SOFA, mean ± SD	3.50 ± 2.48	3.38 ± 2.51	3.49 ± 2.40	3.63 ± 2.51	0.002
SAPSII, median (IQR)	35 (29–42)	34 (27–41)	35 (29–42)	37 (30–44)	<0.001
Mortality, *n* (%)					
90 days	528 (9.58)	115 (6.27)	152 (8.60)	261 (13.66)	<0.001
180 days	739 (13.40)	156 (8.50)	209 (11.82)	374 (19.57)	<0.001
1 year	1069 (19.39)	234 (12.75)	301 (17.02)	534 (27.94)	<0.001

ACEI/ARB, angiotensin converting enzyme inhibitors/angiotensin receptor antagonists; BMI, body mass index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aotic balloon pump; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; NT-proBNP, N terminal pro-brain natriuretic peptide; RDW, red cell distribution width; SAPS, Simplified Acute Physiology Scores; SOFA, Sequential Organ Failure Assessment.

dium-, and long-term mortality. In each outcome, adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were computed with the ΔRDW as a continuous variable. Three multivariable models were constructed. Model 1 was adjusted for age, sex, race, BMI, and the length of hospitalization. Model 2 was adjusted for the same variables as those in Model 1 plus hypertension, type 2 diabetes mellitus, atrial fibrillation, myocardial infarction, the Charlson co-morbidity index, mean arterial pressure, heart rate, haemoglobin, white blood cells, platelets, and creatinine. Model 3 was adjusted for the same variables as those in Model 2 plus NT-proBNP, SOFA, SAPSII, and RDW at admission. Regarding the variables of BMI and NT-proBNP with missing values of >20% of the total sample size, dummy variables were used to indicate missing covariate values.

To further validate the predictive value of the ΔRDW for mortality, we calculated Harrell's C-index before and after adding ΔRDW to Model 3. We then performed the reclassification analysis to evaluate the improvement between the model containing the ΔRDW in addition to Model 3 and original Model 3. Continuous net reclassification improvement and integrated discrimination improvement were used in the reclassification analysis.

The relationship between the ΔRDW and the adjusted HR of each outcome is shown using four-knot restricted cubic splines. These splines were used to determine the reference point of the ΔRDW and investigate whether there was a non-linear relationship between the ΔRDW and mortality. A threshold analysis was further performed to examine if the association between the ΔRDW and mortality was non-linear. To further minimize the confounding bias, we also divided the study population into two groups according to the reference point of the ΔRDW and performed propensity matched score analysis (calliper was 0.05, ratio was 1:1) to balance the baseline characteristics.

Subgroup analyses for the association between the ΔRDW as a continuous variable (per 1%) and outcomes were performed in patients with different sexes, ages, baseline mean arterial pressure, haemoglobin concentrations, RDW at admission, and SOFA scores, and those with or without essential hypertension, type 2 diabetes mellitus, atrial fibrillation, or myocardial infarction. We further investigated the possibility of interactions by incorporating interaction terms into the adjusted models. A sensitivity analysis was performed by reanalysing when removing the missing data of BMI and NT-proBNP. Statistical software comprising Stata 17.0 (Stata Corporation, College Station, TX, USA), Free statistics software version 1.7.1 (Clinicalscientists Inc, Beijing, China), EmpowerStats version 4.1 (X&Y solutions Inc, Boston, USA), and package R 4.2.2 (Vienna, Austria) were used for all statistical analyses. Two-tailed *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics and outcome

We finally included 5514 patients according to the inclusion and exclusion criteria (*Figure S1*). The median age was 73.91 years, 46.37% of the patients were women, 48.11% had a history of hypertension, and 27.78% had a history of type 2 diabetes mellitus. *Table 1* shows the baseline characteristics and mortality rate of our study population according to the tertiles of the ΔRDW. Across the tertiles, the median age, proportions of female sex and White race, length of hospitalization, common co-morbidities (hypertension, type 2 diabetes mellitus, myocardial infarction, atrial fibrillation, cerebrovascular disease, peripheral vascular disease, pulmonary disease, and renal disease), the Charlson co-morbidity index, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, RDW at discharge, platelet count, use of vasoactive agents, angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists, beta-blockers, mineralocorticoid receptor antagonists, calcium channel blockers, diuretics, digoxin, the proportion of dialysis, the mean SOFA score, and the median SAPSII were progressively higher with increasing tertiles. The baseline heart rate, diastolic blood pressure, mean arterial pressure, white blood cell count, RDW at admission, and use of an intra-aortic balloon pump were progressively lower with increasing tertiles (all $P_{\text{for trend}} < 0.05$, *Table 1*). However, there were no significant differences in BMI, the proportion of liver disease, systolic blood pressure, concentrations of potassium, sodium, chloride, glucose, creatinine, blood urea nitrogen or NT-proBNP, the proportion of ventilation, or the proportion of extracorporeal membrane oxygenation across the ΔRDW tertiles (all $P_{\text{for trend}} > 0.05$, *Table 1*).

Among the 5514 patients, the 90 day, 180 day, and 1 year mortality rates were 9.58%, 13.40%, and 19.39%, respectively (*Table 1*). Across the ΔRDW tertiles, the 90 day, 180 day and 1 year mortality rates were progressively higher with increasing tertiles (all $P_{\text{for trend}} < 0.05$, *Table 1*).

Change in red blood cell distribution width and mortality

According to Kaplan–Meier curves (*Figure 1*), patients in the third tertile had a higher risk of 90 day, 180 day, and 1 year mortality than those in the first and second tertiles (log-rank $P < 0.001$, *Figure 1A–C*).

The univariable and multivariable Cox proportional hazard models and HRs for 90 day, 180 day, and 1 year mortality are shown in *Table 2*. After adjusting for the confounding factors of age, sex, race, BMI, length of hospitalization; hypertension, type 2 diabetes mellitus, atrial fibrillation, myocardial infarction, Charlson co-morbidity index, mean arterial pressure, heart rate, haemoglobin, white blood cell count, platelet count, creatinine, NT-proBNP, SOFA, SAPSII, and RDW at admission, patients in the third tertile of the ΔRDW still had an independent high risk of 90 day mortality (HR = 2.56, 95% CI = 2.02–3.24, $P < 0.001$), 180 day mortality (HR = 2.70, 95% CI = 2.21–3.30, $P < 0.001$), and 1 year mortality (HR = 2.67, 95% CI = 2.26–3.14, $P < 0.001$). The ΔRDW as a continuous variable (per 1% increase) was independently associated with a high risk of all-cause mortality (HR = 1.17, 95% CI = 1.13–1.21, $P < 0.001$ for 90 day mortality;

Figure 1 Kaplan–Meier curves for outcomes by ΔRDW tertiles. RDW, red cell distribution width.

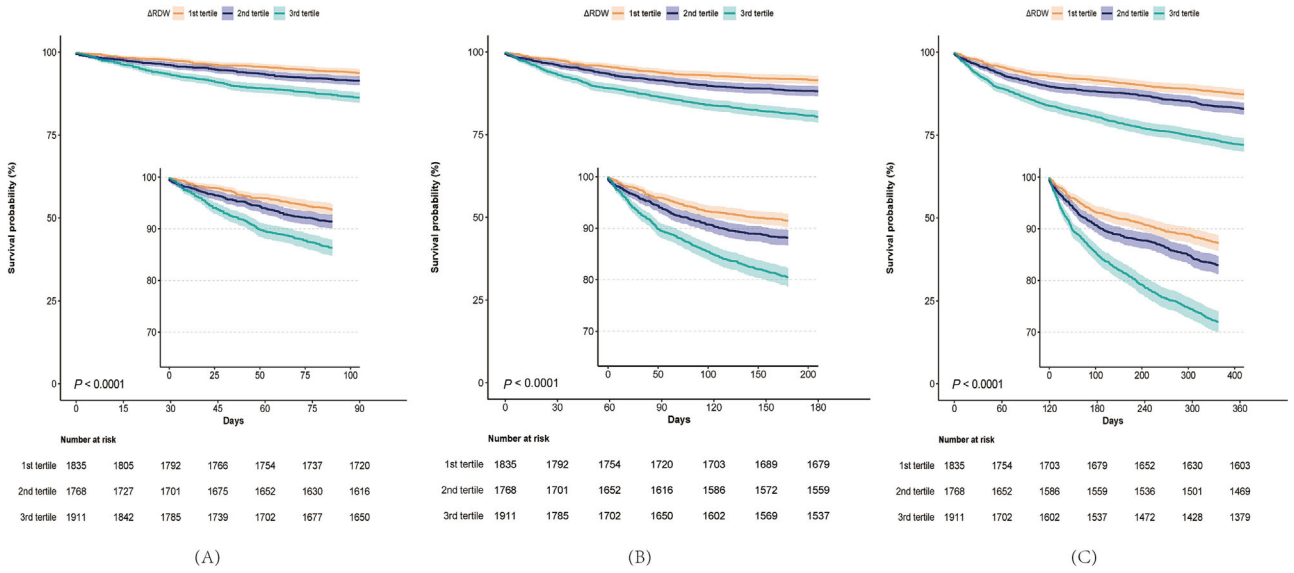


Table 2 Association between ΔRDW value and risk of mortality

Outcome	Univariable model HR (95% CI)	*P* for trend	Model 1 HR (95% CI)	*P* for trend	Model 2 HR (95% CI)	*P* for trend	Model 3 HR (95% CI)	*P* for trend
90 day mortality								
ΔRDW tertiles								
1st tertile	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
2nd tertile	1.34 (1.04–1.71)	0.022	1.18 (0.92–1.52)	0.187	1.20 (0.94–1.54)	0.150	1.47 (1.14–1.91)	0.003
3rd tertile	2.30 (1.85–2.88)	<0.001	1.89 (1.51–2.36)	<0.001	2.08 (1.66–2.61)	<0.001	2.56 (2.02–3.24)	<0.001
ΔRDW, %	1.13 (1.09–1.16)	<0.001	1.10 (1.07–1.14)	<0.001	1.14 (1.10–1.18)	<0.001	1.17 (1.13–1.21)	<0.001
180 day mortality								
ΔRDW tertiles								
1st tertile	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
2nd tertile	1.38 (1.12–1.70)	0.003	1.22 (0.99–1.51)	0.060	1.24 (1.01–1.54)	0.044	1.53 (1.23–1.91)	<0.001
3rd tertile	2.47 (2.05–2.98)	<0.001	2.05 (1.70–2.48)	<0.001	2.19 (1.81–2.66)	<0.001	2.70 (2.21–3.30)	<0.001
ΔRDW, %	1.14 (1.11–1.16)	<0.001	1.11 (1.08–1.14)	<0.001	1.14 (1.11–1.17)	<0.001	1.17 (1.14–1.20)	<0.001
1 year mortality								
ΔRDW tertiles								
1st tertile	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
2nd tertile	1.34 (1.13–1.60)	0.001	1.21 (1.01–1.43)	0.034	1.23 (1.03–1.46)	0.020	1.51 (1.26–1.81)	<0.001
3rd tertile	2.42 (2.07–2.82)	<0.001	2.06 (1.76–2.41)	<0.001	2.19 (1.87–2.56)	<0.001	2.67 (2.26–3.14)	<0.001
ΔRDW, %	1.14 (1.12–1.16)	<0.001	1.12 (1.10–1.15)	<0.001	1.15 (1.12–1.18)	<0.001	1.18 (1.15–1.20)	<0.001

Model 1 include age, gender, race, BMI, and length of hospitalization. Model 2 include model 1 plus hypertension, type 2 diabetes mellitus, atrial fibrillation, myocardial infarction, Charlson co-morbidity index, mean arterial pressure, heart rate, haemoglobin, white blood cell, platelet, and creatinine. Model 3 include model 2 plus NT-proBNP, SOFA, SAPSII, and RDW at admission.
BMI, body mass index; CI, confidential interval; HR, hazard ratio; NT-proBNP, N terminal pro-brain natriuretic peptide; RDW, red cell distribution width; SAPS, Simplified Acute Physiology Scores; SOFA, sequential organ failure assessment.

Table 3 Comparison between ΔRDW in addition to Model 3 and original Model 3 for predicting mortality

Outcomes		Model 3	ΔRDW+ Model 3	*P* value
90 day mortality				
	Harrell's C-index (95% CI)	0.741 (0.720–0.762)	0.761 (0.742–0.781)	<0.001
180 day mortality				
	Harrell's C-index (95% CI)	0.724 (0.706–0.741)	0.748 (0.731–0.765)	<0.001
1 year mortality				
	Harrell's C-index (95% CI)	0.711 (0.696–0.726)	0.739 (0.725–0.753)	<0.001

Model 3 adjusted for age, gender, race, BMI, length of hospitalization; hypertension, type 2 diabetes mellitus, atrial fibrillation, myocardial infarction, Charlson co-morbidity index, mean arterial pressure, heart rate, haemoglobin, white blood cell, platelet, creatinine, NT-proBNP, SOFA, SAPSII, and RDW at admission.
BMI, body mass index; CI, confidential interval; HR, hazard ratio; NT-proBNP, N terminal pro-brain natriuretic peptide; RDW, red cell distribution width; SAPS, Simplified Acute Physiology Scores; SOFA, Sequential Organ Failure Assessment.

HR = 1.17, 95% CI = 1.14–1.20, $P < 0.001$ for 180 day mortality; and HR = 1.18, 95% CI = 1.15–1.20, $P < 0.001$ for 1 year mortality).

Table 3 shows that a model containing the ΔRDW and all variables in Model 3 had a higher Harrell's C-index than that in the original Model 3 for predicting the mortality at different time points (*Table 3*). In the reclassification analysis, the addition of a ΔRDW to Model 3 showed a continuous net reclassification improvement of 20.2% (95% CI = 13.6–25.8, $P < 0.001$) and integrated discrimination improvement of 1.4% (95% CI = 0.7–2.4, $P < 0.001$) for 90 day mortality. The continuous net reclassification improvement and integrated discrimination improvement for the model remained positive for 180 day and 1 year mortality (*Table 4*). Our results suggested that including the ΔRDW in an established predictive model enhanced the prediction performance for all-cause mortality.

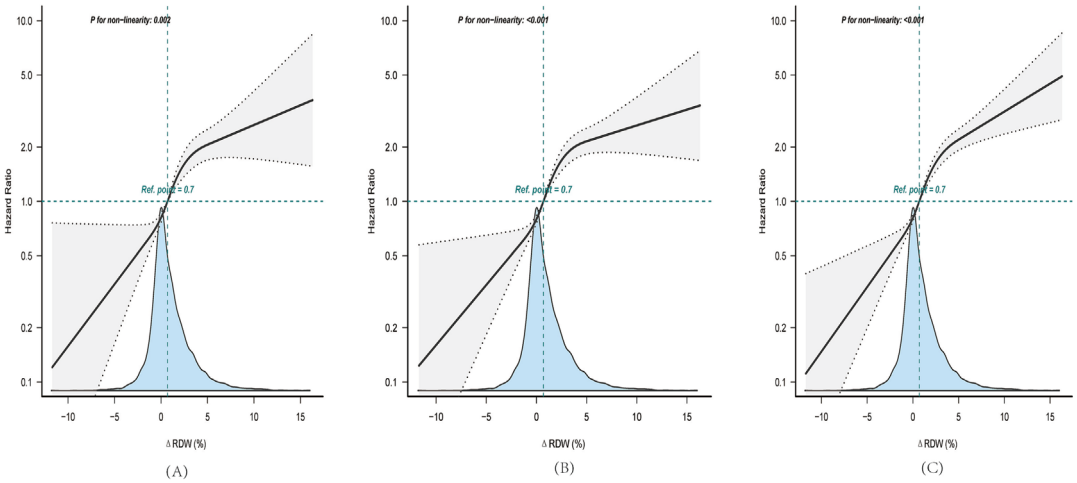
Restricted cubic splines (*Figure 2*) showed a non-linear relationship between the ΔRDW and the adjusted HRs for all outcomes (all $P_{\text{for non-linearity}} < 0.001$). A high ΔRDW was associated with a high risk of 90 day (*Figure 2A*), 180 day (*Figure 2B*), and 1 year mortality (*Figure 2C*). The splines showed that a ΔRDW = 0.7% was the reference point. When we used a model of two-piecewise linear regression, the corresponding thresholds for the ΔRDW at 6.65%, 6.19%, and 4.7% were identified for 90 day, 180 day, and 1 year mortality, respectively (*Table S1*). The ΔRDW in the majority of patients was below the threshold, and the all-cause mortality risk increased with a change in the ΔRDW (adjusted HR = 1.22, 95% CI = 1.16–1.28 for 90 day mortality; HR = 1.25, 95% CI = 1.20–1.30 for 180 day mortality; and HR = 1.27, 95% CI = 1.22–1.33 for 1 year mortality). However, in the minority of patients above the threshold, the mortality risk decreased with an increase in the ΔRDW for 90 day mortality (adjusted HR = 0.59, 95% CI = 0.41–0.86). Additionally, the association between the ΔRDW and the risk of 180 day and 1 year mortality was not significant above the threshold (both $P > 0.05$).

Table 4 Reclassification analysis for a model containing ΔRDW in addition to Model 3 and original Model 3 for predicting mortality

Outcomes	Continuous NRI (%, 95% CI)	*P* value	IDI (%, 95% CI)	*P* value
90 day mortality	20.2 (13.6–25.8)	<0.001	1.4 (0.7–2.4)	<0.001
180 day mortality	19.7 (15.1–24.6)	<0.001	1.6 (0.9–2.5)	<0.001
1 year mortality	23.4 (18.4–27.6)	<0.001	2.4 (1.6–3.4)	<0.001

Model 3 adjusted for age, gender, race BMI, length of hospitalization; hypertension, type 2 diabetes mellitus, atrial fibrillation, myocardial infarction, Charlson co-morbidity index, mean arterial pressure, heart rate, haemoglobin, white blood cell, platelet, creatinine, NT-proBNP, SOFA, SAPSII, and RDW at admission.
BMI, body mass index; CI, confidential interval; HR, hazard ratio; IDI, integrated discrimination improvement; NT-proBNP, N terminal pro-brain natriuretic peptide; NRI, net reclassification improvement; RDW, red cell distribution width; SAPS, Simplified Acute Physiology Scores; SOFA, Sequential Organ Failure Assessment.

Figure 2 Relationship between the ΔRDW and the risk of mortality shown by restricted cubic splines. RDW, red cell distribution width.



To further verify the association between the ΔRDW and mortality, we conducted a propensity-matched analysis according to the reference point of the ΔRDW (0.7%). Finally, 3818 patients were included after matching, and the baseline characteristics except the length of hospitalization were well balanced (*Table S2*). Kaplan–Meier curves for the matched data (*Figure S2*) showed that patients with a ΔRDW ≥0.7% had a higher risk of 90 day, 180 day, and 1 year mortality than patients with a ΔRDW <0.7% (all log-rank $P < 0.001$, *Figure S2A–C*). Patients with a ΔRDW ≥0.7% still had an independent high risk of 90 day (HR = 2.17, 95% CI = 1.72–2.74, $P < 0.001$), 180 day (HR = 2.13, 95% CI = 1.76–2.58, $P < 0.001$), and 1 year mortality (HR = 2.03, 95% CI = 1.74–2.38, $P < 0.001$) in the matched data after adjusting for confounding factors in line with the unmatched data. The ΔRDW as a continuous variable was an independent risk factor for each outcome (*Table S3*).

Subgroup analysis

Subgroup analyses (*Figure 3*) showed that the association between the ΔRDW as a continuous variable (per 1% increase) and mortality at 90 days, 180 days, and 1 year remained consistent among patients in subgroups with different sexes, ages, baseline mean arterial pressure, haemoglobin values, RDW at admission, and SOFA scores, and in patients with or without hypertension, diabetes mellitus, atrial fibrillation, or myocardial infarction. There was no interaction between the ΔRDW and the risk of mortality in these subgroups (all $P_{\text{for interaction}} > 0.05$, *Figure 3*).

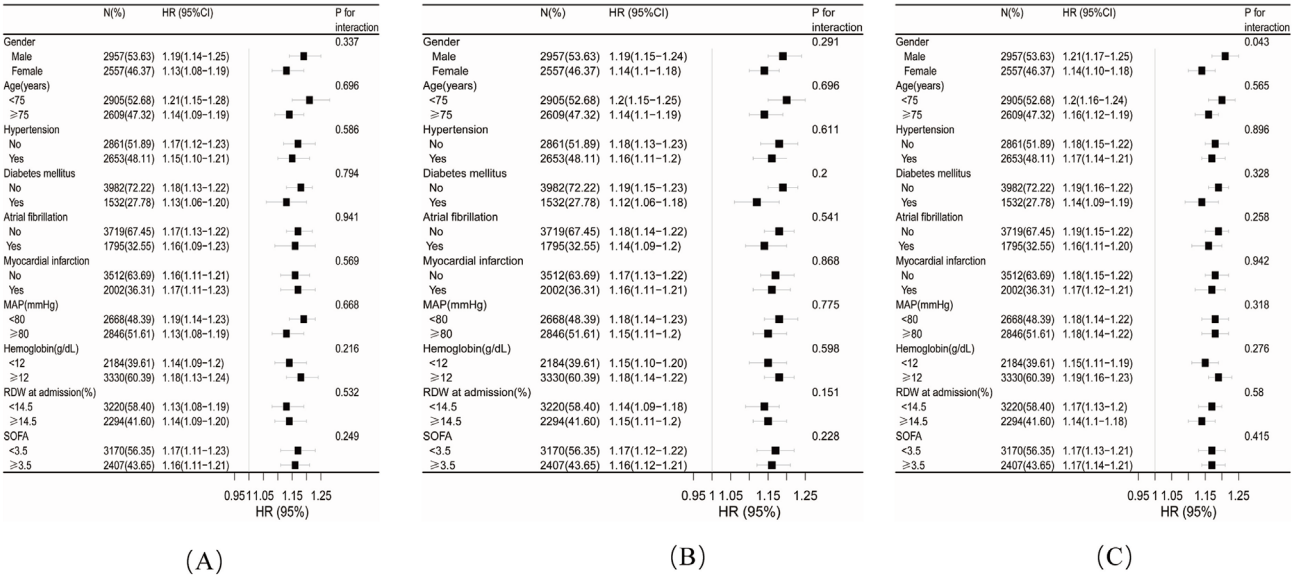
Sensitivity analysis

After excluding the patients with missing values for BMI or NT-proBNP (n = 3493), the results remained positive as in the original study population in the sensitivity analysis (*Table S4*). In 2021 patients without missing data, a high ΔRDW tertile or a ΔRDW as a continuous variable (per 1%) was independently associated with a higher risk of mortality at different time points (all $P < 0.05$).

Association between red blood cell distribution width at discharge and risk of mortality

To investigate the predictive value of RDW at discharge, we further include the RDW at discharge instead of ΔRDW as a

Figure 3 Risk of mortality for a 1% increase in the ΔRDW in pre-specified subgroups. CI, confidence interval; HR, hazard ratio; RDW, red cell distribution width.



continuous variable in the multivariable Cox proportional hazard model (Model 3). Our results also showed that RDW at discharge as a continuous variable was also positive associated with high risk of mortality at each time points (*Table S5*). Restricted cubic splines (*Figure S3*) also showed a non-linear relationship between the RDW at discharge and the adjusted HRs for all outcomes (all $P_{\text{for non-linearity}} < 0.001$). The splines showed that RDW = 15.2% was the reference point. A higher RDW at discharge was associated with higher risk of mortality at each time point.

To compare the predictive value of RDW at admission, at discharge, and ΔRDW on the all-cause mortality, we carried out the ROC curve analysis for all outcomes. Our results showed that RDW at discharge had a better predictive value for mortality at each time points than RDW at admission or ΔRDW (all $P < 0.001$, *Table S6* and *Figure S4*).

Independent factors associated with high change in red blood cell distribution width

A further analysis showed that patients with an older age, female sex, Black race, a prolonged length of hospitalization, hypertension, atrial fibrillation, peripheral vascular disease, pulmonary disease, renal disease, a higher Charlson comorbidity index, lower mean arterial pressure, mean corpuscular haemoglobin, RDW at admission, a higher platelet count, and a higher SAPSII were associated with a higher ΔRDW (*Table S7*).

Discussion

In this study, we found that a higher ΔRDW during hospitalization was associated with a higher risk of all-cause mortality at different time points and improved the risk stratification for mortality in critically ill patients with HF. Our results suggested that an in-hospital ΔRDW independently predicted a poor outcome in critically ill patients with HF. A dynamic ΔRDW during hospitalization could provide useful information to identify the risk of adverse events and guide the optimal treatment for patients with HF.

Several previous studies have shown that an elevated RDW during hospitalization is associated with adverse events in patients with acute HF.[23–25,27,28] However, recently, Xanthopoulos et al. reported that the in-hospital ΔRDW was not associated with a poor prognosis in patients with HF,[29] which indicates that the predictive value of a ΔRDW for mortality remains uncertain. Because of the small sample size or short-term follow-up in previous studies, we performed a retrospective cohort analysis from the MIMIC-IV database and finally included 5792 critically ill patients with HF. We investigated the association between the ΔRDW and mortality at different time points. The large sample, multiple regression, and propensity score matching analysis ensured a high credibility of our results, which are superior to those in the previous studies. We also showed the independent predictive value of the ΔRDW and all-cause mortality at different time points in critically ill patients with HF, which is consistent with previous studies.[23–25,27,28]

Recently, Zhang et al. showed that a higher RDW at baseline was an independent predictor for in-hospital and short-term all-cause mortality in critically ill patients with HF.[9] However, the dynamic ΔRDW in critically ill patients with HF is unknown. In our study, we focused on the in-hospital ΔRDW and short- and long-term mortality and showed the predictive value of a dynamic ΔRDW for adverse outcomes. Our finding emphasized that an in-hospital ΔRDW was associated with a poor prognosis and could improve the risk stratification in mortality in patients with HF. This conclusion is in accordance with a previous finding that a high RDW was a prognostic marker for mortality in patients with HF.[30] The potential mechanisms of how the RDW is related to adverse outcomes include abnormalities of inflammation and metabolism, iron deficiency,[16,31] anaemia, and malnutrition,[21] which are common and related to adverse events in HF. In addition, echocardiographic findings in acute HF have shown that a higher RDW is associated with a higher elevated left ventricular filling pressure and poorer left ventricular deformation.[32–34] In patients with chronic HF, studies have reported that a higher RDW is associated with an impaired exercise tolerance and poor stem cell mobilization.[35–37] These changes in patients with HF would also contribute to a poor prognosis.

Our subgroup analysis showed that the predictive value of a high ΔRDW for mortality was consistent in pre-specified subgroups. This finding indicated that an increased ΔRDW was associated with a high risk of all-cause mortality, regardless of the presence of anaemia, and common co-morbidities such as diabetes mellitus and coronary heart disease. This finding is in accordance with previous studies.[12,38–41] However, because HF is a complex syndrome caused by various heart diseases, the predictive value of the RDW for the prognosis could be different. Zhang et al. reported that the RDW was a prognostic indicator for patients with HF caused by coronary heart disease and dilated cardiomyopathy, but not valvular heart disease.[42] Moreover, several studies have shown that a high RDW is associated with an increased risk of mortality in patients with HF and a preserved ejection fraction, but not with a reduced ejection fraction.[43,44] Therefore, because of the complexity of HF syndrome, the predictive value of RDW for adverse events will be affected by the cause or co-morbidities of HF. Although there was no interaction between the ΔRDW and prespecified subgroups on mortality in our study, the ΔRDW value was associated with several factors such as co-morbidities of HF. Therefore, the prognostic value of the ΔRDW requires further investigation in HF with various heart diseases in future studies.

Our study also showed that the established model for mortality was improved after including the variable of ΔRDW, which suggested that the ΔRDW could improve the risk stratification in critically ill patients with HF. This finding is consistent with that in previous studies on baseline RDW.[9] Several studies showed that the RDW in combination with NT-proBNP improved the prognostic value in a traditional model in patients with acute or chronic HF.[12,15,45] In addition, many studies have shown that the baseline RDW is an independent predictive marker for all-cause mortality in patients with acute or chronic HF.[8,13,14,46] Moreover, a high RDW was also associated with increased all-cause mortality, even in patients with advanced HF who underwent cardiac resynchronization therapy,[47,48] implantation of a left ventricular assist device,[49,50] or heart transplantation.[51] In our study, the ΔRDW improved the risk stratification for short- and long-term mortality in the established model including baseline RDW and NT-proBNP. This finding suggested that a ΔRDW is a novel prognosticator in critically ill patients with HF.

To ensure the robustness of our results, we used a multivariable regression analysis to adjust for confounding factors and propensity score matching to balance the baseline variable, which could improve the credibility of our results. Restricted cubic splines showed that the relationship between the ΔRDW and the risk of all-cause mortality was non-linear. Additionally, the threshold effect analysis showed that a small part (<10%) of the study population did not show consistent results with the main results of our study. The reclassification analysis showed that the inclusion of the ΔRDW enhanced the predictive ability for mortality in the established model. In summary, our study showed the independent prognostic value of the ΔRDW during hospitalization for short- and long-term all-cause mortality. Physicians could regard an increased RDW during hospitalization as a novel marker to improve the risk stratification of adverse events in critically ill patients with HF.

Several studies showed that red blood cell transfusion would increase the RDW value in critically ill patients and affect the predictive value of RDW on mortality.[52,53] When considering this confounding factor, we excluded the patients who underwent red blood cell transfusion during hospitalization or patients with haematological diseases (leukaemia, aplastic anaemia, or polycythemia vera) in our analysis. Thus, the dynamic change of RDW may only influenced by the change of the condition in critically ill patients with HF during hospitalization.

In our study, we also examine the predictive value of RDW at discharge on the risk of mortality in different time points. Our results showed that RDW at discharge was also an independent predictor for the all-cause mortality, which was inconsistent with previous studies.[17,28] This finding suggested that the dynamic change of RDW could improve the risk stratification for mortality than baseline RDW. The potential mechanism might be the therapeutic effect during hospitalization on the change of RDW. Critically ill HF patients with high RDW at baseline would be improved during treatment while the RDW might be decreased. Thus, continuous elevated RDW would have better predictive value on mortality in HF patients. In addition, RDW at discharge would be better than ΔRDW during hospitalization on predicting the adverse

events, and this finding suggested that the updated RDW would be more accurate in the risk stratification than the dynamic change of RDW. The possible mechanism might be that the updated RDW value could reflect the improved condition of the patients at discharge better than the dynamic changes during hospitalization.

There are several limitations to our study. First, our study was a retrospective cohort analysis of the MIMIC database, and some bias of this study design is possible. Prospective cohort studies with a large sample should be carried out in the future to investigate the association between the ΔRDW and adverse events. Second, data on the left ventricular ejection fraction were not available in the database. Therefore, we failed to analyse the association between the ΔRDW and mortality in patients with HF and different phenotypes. Third, the variables of iron, ferritin, vitamin B12, and folic acid were not available in the database. A change in haematopoietic material during hospitalization should be taken into consideration in future studies. Fourth, although we used dummy variables in the multivariable analysis and removed missing data in the sensitivity analysis, the effect of the missing data for BMI and NT-proBNP cannot be neglected. Finally, our study focused on the in-hospital change and outcomes in HF. The longitudinal change of the RDW after discharge requires further study. Although several studies showed that serial increases in the RDW were associated with a poor long-term prognosis,[26,54] the longitudinal ΔRDW at a longer follow-up period and its relation to the risk of mortality in HF are unclear.

Conclusion

An increased RDW during hospitalization is independently associated with all-cause mortality in critically ill patients with HF. An in-hospital ΔRDW could be a novel marker for risk stratification for mortality in patients with HF.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Flow chart of the study population.
Figure S2. Kaplan–Meier curves for mortality in matched patients (A) 90-day mortality (B) 180-day mortality (C) 1-year mortality.
Figure S3. Relationship between RDW at discharge and risk of mortality presented by restricted cubic splines (A) 90-day mortality (B) 180-day mortality (C) 1-year mortality.
Figure S4. Comparison of the AUC of ROC curve of RDW at admission, ΔRDW and RDW at discharge for the prediction value of mortality (A) 90-day mortality (B) 180-day mortality (C) 1-year mortality.
Table S1. Threshold effect analysis of ΔRDW on mortality.
Table S2. Baseline characteristics of study population before and after matching according the reference point of ΔRDW (0.7%).
Table S3. Association between ΔRDW and risk of mortality before and after matching.
Table S4. Association between ΔRDW and mortality in patients without missing data (n = 2021).
Table S5. Association between RDW at discharge and risk of mortality.
Table S6. Comparison of the AUC of ROC curve of RDW at admission, ΔRDW and RDW at discharge for the prediction value of mortality.
Table S7. Associations between baseline characteristics and high ΔRDW(ΔRDW≥0.7).

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