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Relationship Between the Hemoglobin-to-Red Cell Distribution Width Ratio and in-Hospital Mortality in Patients with Chronic Heart Failure

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Purpose: Hemoglobin (Hb) levels and red cell distribution width (RDW) are standard and widely used parameters that predict clinical outcomes in patients with chronic heart failure (CHF). The Hb to RDW ratio (HRR) provides an incremental clinical prediction, as it reflects the various clinical characteristics of patients. No published data exists in the Medical Information Mart for Intensive Care (MIMIC-IV) and eICU Collaborative Research Database (eICU-CRD) databases on HRR and its association with in-hospital mortality among patients with CHF. The aim of this study was to evaluate the relationship between the HRR and in-hospital mortality in two large real-world cohorts of patients with chronic CHF.

Patients and Methods: Data from the MIMIC-IV and eICU-CRD databases were used to explore the association between HRR and in-hospital mortality. Multivariate logistic regression, stratified analysis with interaction, and restricted cubic splines were used to investigate the association between HRR and in-hospital mortality.

Results: A total of 30,411 patients with CHF were enrolled based on the MIMIC-IV and multicenter eICU-CRD databases (15,983 and 14,428, respectively), including 16,295 men and 14,116 women with a median age of 73 years. The mean HRR was 0.69 ± 0.20. The overall in-hospital mortality rate was 12.63%. Increasing quantiles of HRR were associated with reduced in-hospital mortality rates. After adjusting for significant predictors, multivariate logistic regression analysis demonstrated that a low HRR was a significant predictor of in-hospital mortality, with a graded reduction in risk as HRR increased. Sensitivity analysis using restricted cubic splines demonstrated a continuous increase in in-hospital mortality risk with decreasing HRR (P = 0.262 for the non-linear model).

Conclusion: A linear relationship was observed between baseline HRR levels and in-hospital mortality. Lower HRR levels were associated with higher in-hospital mortality in patients with CHF. HRR could be a reliable clinical metric for assessing in-hospital mortality risk.

Keywords: MIMIC-IV, eICU collaborative research database, clinical outcomes, statistical analyses, mortality rate

Introduction

Heart failure (HF) is an advanced stage of various heart-related diseases characterized by high long-term mortality and frequent readmissions. In 2015, approximately 40 million people worldwide were affected by HF, with around 2% of adults experiencing HF, which increases to 6–10% among adults aged ≥ 65 years.[1] Data from an HF study in China indicate an in-hospital mortality rate of 4.1% for patients with HF.[2] Despite advancements in medical technology that have improved outcomes for some cardiovascular diseases, the damage inflicted by HF remains largely irreversible, making HF an end-stage manifestation that ultimately leads to patient mortality.[3] Thus, improving HF diagnosis and treatment remains a challenge for cardiovascular specialists worldwide.[4]

Hemoglobin (Hb) is an essential and readily obtainable blood marker, which is a standardized parameter that markedly influences the prognosis of patients with HF.[5,6] Another vital hematological parameter is the red blood cell

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distribution width (RDW), which quantifies red blood cell heterogeneity. Imbalances in red blood cell homeostasis and turnover can negatively impact the outcomes of patients with HF.[7,8] The Hb to RDW ratio (HRR) is a powerful predictor of clinical outcomes for patients with HF.[9–11] HRR is a simple and easily accessible predictive tool, with a decrease in Hb levels and an increase in RDW indicating the severity of CHF in patients. The HRR can help clinicians stratify the risk of heart failure in patients. Many patients in the intensive care unit (ICU) have chronic heart failure (CHF) as a comorbidity, which markedly increases their mortality risk. Therefore, identifying simple and reliable biomarkers to assess in-hospital mortality risk for patients with CHF is essential. However, no existing data in the Medical Information Mart for Intensive Care (MIMIC-IV) or the eICU Collaborative Research Database (eICU-CRD) exist, and the relationship between HRR and in-hospital mortality in patients with CHF remains unclear. Therefore, the aim of this study was to investigate HRR as a potentially valuable predictor for in-hospital mortality among patients with CHF.

Material and Methods

Data Sources

This study had a retrospective observational design, and the study data were downloaded from a large publicly accessible database called the Dryad Digital Repository. The data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi: 10.5061/dryad.tx95x6b18.[12] All patients were recruited from the MIMIC-IV and eICU-CRD databases, which are single-center, free-access databases that contain data from over 40,000 patients in the ICU from 2008 to 2019 (Bulgarelli L, Pollard T, Johnson A. MIMIC-IV version 0.4. PhysioNet, 2020.[13]). eICU-CRD is a database of multiple longitudinal multicenter retrospective cohort studies on 335 patients in the USA from 2014 to 2015.[14] It includes demographic records, physiological indicators for bedside monitoring, diagnoses based on the International Classification of Disease-9 (ICD-9) codes, and other laboratory data. All data were anonymized to protect patient privacy, and the need for informed consent was waived. The data are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Reporting Guidelines.

Study Population

A total of 30,474 patients with CHF and first ICU admission were selected based on the ICD-9 code 4280 records (MIMIC-IV database N = 16,012; eICU database N = 14,462). The exclusion criteria were as follows: (1) age < 18 years, (2) participants who had missing Hb or RDW data, and (3) missing outcome data. Finally, 30,411 patients were included in the study (MIMIC-IV database N = 15,983; eICU database N = 14,428) (Figure 1).

Data Extraction and Endpoints

Full details of the data extraction process have been reported previously.[15] Variables included demographics, vital signs, comorbidities, laboratory variables, severity scoring systems, and drug use. The collected patient characteristics were as follows: (1) demographics: age, ethnicity, sex; (2) the first value of vital signs within 24 h of ICU admission: systolic blood pressure (SBP), mean blood pressure (MBP), respiratory rate (RR), heart rate (HR) and temperature; (3) comorbidities: chronic obstructive pulmonary disease (COPD), diabetes, hepatic failure (HepF), and acute myocardial infarction (AMI); (4) the first value of laboratory data within 24 h of ICU admission: anion gap (AG), chloride, blood urea nitrogen (BUN), calcium, creatinine, potassium, sodium, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), platelet, Hb, RDW, red blood cell (RBC), and white cell count. (5) Severity scoring system: sequential organ failure assessment (SOFA) score and Acute Physiology Score III (APS III); (6) drug use: norepinephrine, dopamine, epinephrine, phenylephrine, and vasopressin; (7) respiratory therapy information: mechanical ventilation and intubation; and (8) HRR calculation: HRR = Hb (g/L)/RDW (%), Six categories were created based on HRR hexiles.[10] The primary outcome was in-hospital mortality, which was described as the patient's survival status at the time of hospital discharge.[16]

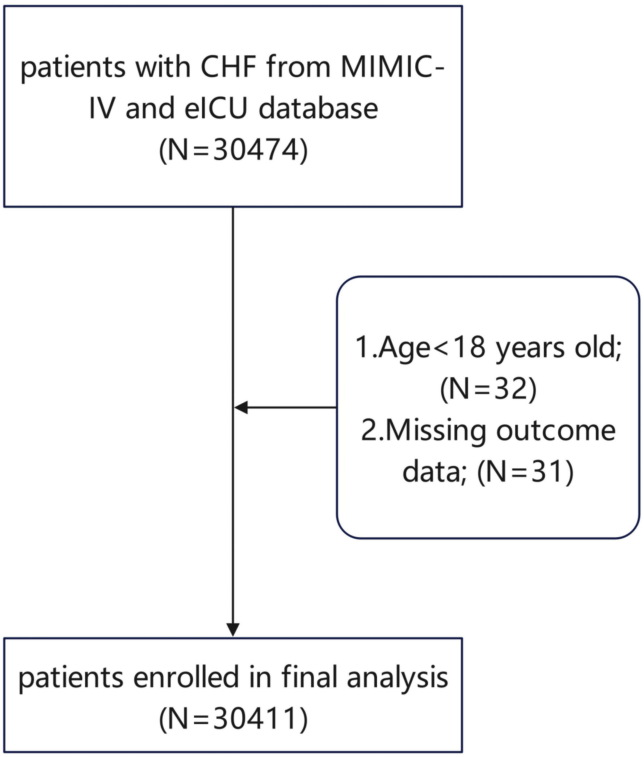

Figure 1 Flow chart of the study population.

Statistical Analyses

Descriptive analysis was performed for categorical variables according to HRR hexiles (≤ 0.48; 0.49–0.57; 0.58–0.66; 0.67–0.75; 0.76–0.87; ≥ 0.88) using the Kruskal–Wallis test or one-way analysis of variance. For categorical variables, baseline characteristic data are presented as proportions (%) and compared using the chi-square test. Normally distributed continuous data were presented as the mean ± standard deviation and compared using Student's *t*-test between groups, whereas skewed distribution median data were presented as interquartile range and compared using the Wilcoxon rank-sum test.

Univariate and multivariate regression analyses were performed to reduce the influence of potential confounding factors on in-hospital mortality rates. The screening of confounders was based on the following criteria: (1) the basis of their associations with the outcomes of interest or a change-in-effect estimate of > 10%. (2) Certain factors may have a significant impact on the outcome variable based on previous experience. (3) The covariates ($P < 0.01$) were modified for the univariate analysis. Four multivariate logistic regression models were constructed to assess the independent association between HRR and in-hospital mortality: Model 1 was adjusted for age, sex, and ethnicity; Model 2 was additionally adjusted for COPD, diabetes, HepF, SOFA score, temperature, RR, HR and SBP; Model 3 was additionally adjusted for AG, BUN, calcium, creatinine, MCH, MCHC, MCV, platelet, potassium, RBC, sodium and WBC; and Model 4 was additionally adjusted for ventilator use, intubation, and dopamine, epinephrine, phenylephrine, and vasopressin usage. Stratified HRR hexiles were used to observe the relationship with in-hospital mortality to ensure the robustness of the data analysis. To validate the stability of the possibility of a linear relationship between HRR and in-hospital mortality, a test for linear trends was conducted using hexiles of the exposure variable as a continuous variable by assigning the median values of the hexiles to the variable. HRR was transformed into a continuous variable, and a curve fitting and restricted cubic spline regression analysis was performed, which was adjusted for parameters included in the four models in the multivariate logistic regression analysis.

The subgroup and interaction analyses were applied according to sex (male or female), age (< 65 or ≥ 65 years), race (White, Black, and others), SBP (< 90 or ≥ 90 mmHg), temperature (< 36.0 or ≥ 36.0 °C), ventilator use (yes or no), AMI (yes or no), diabetes (yes or no), and HepF (yes or no) using stratified logistic regressions and presented in forest plots. Each stratification was adjusted for age, sex, race, norepinephrine, dopamine, epinephrine, phenylephrine, and

vasopressin use, intubation, SOFA score, RR, HR, AG, BUN, calcium, chloride, creatinine, MCH, MCHC, MCV, platelets, potassium, RBC, sodium, WBC, ventilation, AMI, diabetes, and HepF, except for the stratification factor itself.

The statistic program packages R 4.2.2 (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.9 (Beijing, China) were used to complete all analyses. A two-tailed test was performed, and statistical significance was denoted by P <0.05.

Results

Baseline Characteristics

The data of 30,411 patients (15983 (52.6%) from MIMIC-IV and 14428 (47.4%) from eICU) with CHF were analyzed. The baseline characteristics of the study participants are shown in Table 1. The average age of the study population was 71.67 ± 13.69 years, average HRR was 6.85 ± 1.96, and overall in-hospital mortality was 12.63%. Participants with a higher HRR generally had no mechanical ventilation and intubation, were White, had no vasoreactive drug use, no comorbidities, had lower age, SOFA score, APS III, BUN, chloride, creatinine, and potassium levels, and had higher HR, RR, SBP, calcium, MCH, platelet, RBC, and WBC counts. Women showed a lower HRR value than men.

Univariate Analyses

Univariate analyses of the association between the HRR and in-hospital mortality are shown in Table 2. Norepinephrine, dopamine, phenylephrine, epinephrine and vasopressin use, ventilation, intubation, RDW, COPD, AMI, HepF, age, SOFA score, APS III, RR, HR, AG, BUN, creatinine, MCV, potassium, and WBC count were positively associated with the risk of in-hospital mortality. Hb, diabetes, temperature, SBP, MBP, calcium, chloride, MCHC, platelet count, RBC count, and HRR were negatively associated with the risk of in-hospital mortality.

Relationship Between HRR and in-Hospital Mortality

Table 3 shows the results of the multivariate logistic regression analysis for in-hospital mortality according to HRR. Log HRR demonstrated a strongly negative association with in-hospital mortality (odds ratio [OR], 0.11; 95% confidence interval [CI], 0.08–0.14) in the crude model. In Model 1, the association with in-hospital mortality was the same as that of the crude model. The risk of in-hospital mortality was weak in Model 2 (OR, 0.13; 95% CI, 0.1–0.17) and weaker in Model 3 *than in* crude model (OR, 0.24; 95% CI, 0.18–0.32). A weak correlation was also observed in Model 4 (OR, 0.25; 95% CI, 0.19–0.35). HRR was treated as a category variable (hexiles) for sensitivity analysis to ensure that the association between HRR and in-hospital mortality was robust. HRR was negatively correlated with in-hospital mortality. Compared with the lowest hexiles (H1), the highest hexiles (H6) were associated with a decreased OR estimate of in-hospital mortality (HR: 0.61, 95% CI: 0.53–0.7). The curve fitting was individually constructed with the MIMIC and eICU databases, using restricted cubic splines, to identify whether a non-linear relationship existed between HRR and in-hospital mortality (Figure 2). The P-value for non−linearity was 0.262 after adjusting for parameters included in the multivariate analysis.

Subgroup Analyses

The subgroup and interaction analyses indicated age interactions (P = 0.002 for the interaction test) between HRR and the ratio of in-hospital mortality. Stronger correlations were observed in participants aged < 65 years than in those aged > 65, and in-hospital mortality in the younger subgroup significantly decreased as HRR increased (OR: 0.05; 95% CI: 0.02–0.1) (Figure 3).

Discussion

Using data from the MIMIC-IV and eICU-CRD bases, the current study identified a significant inverse correlation between HRR and in-hospital mortality, highlighting the potential of HRR as a robust prognostic indicator. A negative correlation was observed between HRR and in-hospital mortality. Norepinephrine, dopamine, phenylephrine, epinephrine and vasopressin use, ventilation, intubation, RDW, COPD, AMI, HepF, age, SOFA, APS III, RR, HR, AG, BUN,

Table 1 Demographics and Clinical Characteristics of Patients with Heart Failure According to HRR Hexiles

Variables	Total (n = 30411)	Q1 (n = 4771)	Q2 (n = 4985)	Q3 (n = 5366)	Q4 (n = 4905)	Q5 (n = 5095)	Q6 (n = 5289)	p
Database (%)								< 0.001
eICU	14428 (47.4)	1985 (41.6)	2165 (43.4)	2437 (45.4)	2324 (47.4)	2523 (49.5)	2994 (56.6)	
MIMIC	15983 (52.6)	2786 (58.4)	2820 (56.6)	2929 (54.6)	2581 (52.6)	2572 (50.5)	2295 (43.4)	
Age, years	73.0 (63.0, 82.0)	73.0 (63.0, 81.0)	74.0 (64.0, 83.0)	74.0 (65.0, 83.0)	75.0 (64.0, 84.0)	74.0 (63.0, 83.0)	69.0 (59.0, 81.0)	< 0.001
Gender (%)								< 0.001
Male	16295 (53.6)	2498 (52.4)	2425 (48.6)	2669 (49.7)	2530 (51.6)	2706 (53.1)	3467 (65.6)	
Female	14116 (46.4)	2273 (47.6)	2560 (51.4)	2697 (50.3)	2375 (48.4)	2389 (46.9)	1822 (34.4)	
Race (%)								< 0.001
White	21862 (71.9)	3320 (69.6)	3561 (71.4)	3893 (72.5)	3494 (71.2)	3701 (72.6)	3893 (73.6)	
Black	4909 (16.1)	874 (18.3)	852 (17.1)	867 (16.2)	805 (16.4)	808 (15.9)	703 (13.3)	
Other	3640 (12.0)	577 (12.1)	572 (11.5)	606 (11.3)	606 (12.4)	586 (11.5)	693 (13.1)	
Norepinephrine (%)								< 0.001
No	25819 (84.9)	3816 (80)	4133 (82.9)	4557 (84.9)	4212 (85.9)	4442 (87.2)	4659 (88.1)	
Yes	4592 (15.1)	955 (20)	852 (17.1)	809 (15.1)	693 (14.1)	653 (12.8)	630 (11.9)	
Dopamine (%)								0.537
No	29859 (98.2)	4678 (98.1)	4899 (98.3)	5278 (98.4)	4804 (97.9)	4999 (98.1)	5201 (98.3)	
Yes	552 (1.8)	93 (1.9)	86 (1.7)	88 (1.6)	101 (2.1)	96 (1.9)	88 (1.7)	
Epinephrine (%)								0.005
No	29589 (97.3)	4608 (96.6)	4834 (97)	5226 (97.4)	4791 (97.7)	4974 (97.6)	5156 (97.5)	
Yes	822 (2.7)	163 (3.4)	151 (3)	140 (2.6)	114 (2.3)	121 (2.4)	133 (2.5)	
Phenylephrine (%)								0.002
No	28928 (95.1)	4505 (94.4)	4719 (94.7)	5087 (94.8)	4667 (95.1)	4880 (95.8)	5070 (95.9)	
Yes	1483 (4.9)	266 (5.6)	266 (5.3)	279 (5.2)	238 (4.9)	215 (4.2)	219 (4.1)	
Vasopressin (%)								< 0.001
No	29210 (96.1)	4502 (94.4)	4750 (95.3)	5162 (96.2)	4723 (96.3)	4936 (96.9)	5137 (97.1)	
Yes	1201 (3.9)	269 (5.6)	235 (4.7)	204 (3.8)	182 (3.7)	159 (3.1)	152 (2.9)	
Vent (%)								< 0.001
No	8307 (27.3)	1257 (26.3)	1239 (24.9)	1326 (24.7)	1300 (26.5)	1449 (28.4)	1736 (32.8)	
Yes	22104 (72.7)	3514 (73.7)	3746 (75.1)	4040 (75.3)	3605 (73.5)	3646 (71.6)	3553 (67.2)	
Intubated (%)								< 0.001
No	23625 (77.7)	3605 (75.6)	3811 (76.4)	4141 (77.2)	3801 (77.5)	4017 (78.8)	4250 (80.4)	
Yes	6786 (22.3)	1166 (24.4)	1174 (23.6)	1225 (22.8)	1104 (22.5)	1078 (21.2)	1039 (19.6)	
COPD (%)								< 0.001
No	21090 (69.3)	3326 (69.7)	3389 (68)	3637 (67.8)	3341 (68.1)	3556 (69.8)	3841 (72.6)	
Yes	9321 (30.7)	1445 (30.3)	1596 (32)	1729 (32.2)	1564 (31.9)	1539 (30.2)	1448 (27.4)	
AMI (%)								0.037
No	25104 (82.5)	3899 (81.7)	4072 (81.7)	4404 (82.1)	4067 (82.9)	4240 (83.2)	4422 (83.6)	
Yes	5307 (17.5)	872 (18.3)	913 (18.3)	962 (17.9)	838 (17.1)	855 (16.8)	867 (16.4)	

(*Continued*)

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Table 1 (Continued).

Variables	Total (n = 30411)	Q1 (n = 4771)	Q2 (n = 4985)	Q3 (n = 5366)	Q4 (n = 4905)	Q5 (n = 5095)	Q6 (n = 5289)	p
MC (%)								< 0.001
No	28645 (94.2)	4324 (90.6)	4584 (92)	5022 (93.6)	4672 (95.2)	4898 (96.1)	5145 (97.3)	
Yes	1766 (5.8)	447 (9.4)	401 (8)	344 (6.4)	233 (4.8)	197 (3.9)	144 (2.7)	
Diabetes (%)								< 0.001
No	18816 (61.9)	2714 (56.9)	2886 (57.9)	3142 (58.6)	2985 (60.9)	3336 (65.5)	3753 (71)	
Yes	11595 (38.1)	2057 (43.1)	2099 (42.1)	2224 (41.4)	1920 (39.1)	1759 (34.5)	1536 (29)	
HepF (%)								< 0.001
No	29831 (98.1)	4548 (95.3)	4871 (97.7)	5265 (98.1)	4844 (98.8)	5053 (99.2)	5250 (99.3)	
Yes	580 (1.9)	223 (4.7)	114 (2.3)	101 (1.9)	61 (1.2)	42 (0.8)	39 (0.7)	
In-hospital Mortality (%)								< 0.001
No	26571 (87.4)	3903 (81.8)	4225 (84.8)	4683 (87.3)	4309 (87.8)	4603 (90.3)	4848 (91.7)	
Yes	3840 (12.6)	868 (18.2)	760 (15.2)	683 (12.7)	596 (12.2)	492 (9.7)	441 (8.3)	
SOFA	4.0 (2.0, 6.0)	5.0 (3.0, 7.0)	4.0 (2.0, 7.0)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	4.0 (2.0, 6.0)	3.0 (1.0, 6.0)	< 0.001
APSIII	46.0 (35.0, 62.0)	52.0 (40.0, 69.0)	50.0 (39.0, 67.0)	47.0 (36.0, 63.0)	45.0 (35.0, 61.0)	43.0 (32.0, 58.0)	39.0 (29.0, 54.0)	< 0.001
Temperature, °C	36.6 (36.3, 36.9)	36.6 (36.3, 36.9)	36.6 (36.3, 36.9)	36.6 (36.3, 36.9)	36.6 (36.3, 36.9)	36.6 (36.3, 36.9)	36.6 (36.3, 36.9)	0.125
Respiratory Rate, (breaths per minute)	21.0 (17.0, 29.0)	21.0 (17.0, 28.0)	21.0 (17.0, 28.0)	21.0 (17.0, 29.0)	21.0 (17.0, 29.0)	22.0 (17.0, 29.0)	22.0 (17.0, 31.0)	< 0.001
HeartRate, (beats per minute)	90.0 (74.0, 107.0)	89.0 (74.0, 105.0)	89.0 (74.0, 106.0)	89.0 (74.0,106.0)	89.0 (72.0, 106.0)	91.0 (73.0, 108.0)	95.0 (76.0, 113.0)	< 0.001
SBP, mmHg	115.0 (103.0, 132.0)	113.0 (101.0, 127.0)	114.0 (103.0, 130.0)	116.0 (104.0, 131.0)	117.0 (105.0, 133.0)	116.0 (104.0, 132.0)	117.0 (104.0, 133.0)	< 0.001
AG	13.0 (10.0, 16.0)	13.0 (10.0, 17.0)	13.0 (10.0, 16.0)	13.0 (10.0, 16.0)	13.0 (10.0, 16.0)	13.0 (10.0, 16.0)	13.0 (10.0, 16.0)	< 0.001
BUN, mg/dL	29.0 (19.0, 46.0)	38.0 (23.0, 62.0)	35.0 (22.0, 54.0)	32.0 (20.0, 51.0)	29.0 (19.0, 45.0)	25.0 (18.0, 39.0)	22.0 (16.0, 32.0)	< 0.001
Calcium, mg/dL	8.6 (8.1, 9.0)	8.4 (7.9, 8.8)	8.4 (8.0, 8.9)	8.5 (8.0, 9.0)	8.6 (8.1, 9.0)	8.6 (8.2, 9.1)	8.8 (8.3, 9.2)	< 0.001
Chloride, mmol/L	102.0 (98.0, 106.0)	102.0 (97.0, 107.0)	102.0 (98.0, 107.0)	102.0 (97.0, 106.0)	102.0 (98.0, 106.0)	102.0 (98.0, 106.0)	102.0 (98.0, 105.0)	< 0.001
Sodium, mmol/L	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	138.0 (135.0, 141.0)	138.0 (136.0, 141.0)	0.092
Potassium, mmol/L	4.2 (3.8, 4.7)	4.2 (3.8, 4.8)	4.2 (3.8, 4.8)	4.2 (3.8, 4.7)	4.2 (3.8, 4.6)	4.1 (3.8, 4.6)	4.1 (3.8, 4.5)	< 0.001
Creatinine, mg/dL	1.3 (0.9, 2.2)	1.7 (1.1, 2.9)	1.6 (1.0, 2.7)	1.5 (1.0, 2.5)	1.3 (0.9, 2.1)	1.2 (0.9, 1.7)	1.1 (0.9, 1.5)	< 0.001
MCH, pg	29.7 (27.9, 31.1)	28.4 (25.9, 30.5)	29.0 (27.0, 30.7)	29.4 (27.6, 30.9)	29.7 (28.1, 31.1)	30.0 (28.6, 31.4)	30.6 (29.4, 31.9)	< 0.001
MCHC, g/L	32.4 (31.3, 33.4)	31.4 (30.2, 32.5)	31.9 (30.8, 33.0)	32.2 (31.2, 33.1)	32.5 (31.5, 33.3)	32.8 (31.9, 33.7)	33.2 (32.4, 34.0)	< 0.001
MCV, fL	91.0 (87.0, 96.0)	90.0 (84.0, 96.0)	90.0 (85.2, 95.0)	91.0 (86.0, 95.8)	91.0 (87.0, 95.7)	91.5 (87.8, 96.0)	92.0 (88.6, 96.0)	< 0.001
Platelet, ×109/L	196.0 (146.0, 258.0)	185.0 (126.0, 263.0)	198.0 (141.0, 267.0)	196.0 (144.0, 263.0)	197.0 (149.0, 258.0)	199.0 (152.0, 252.0)	198.0 (158.0, 249.0)	< 0.001
RBC, ×109/L	3.6 (3.1, 4.2)	2.8 (2.5, 3.3)	3.1 (2.8, 3.5)	3.4 (3.0, 3.8)	3.6 (3.3, 4.0)	3.9 (3.6, 4.3)	4.5 (4.1, 4.9)	< 0.001
WBC, ×109/L	10.1 (7.3, 13.9)	9.7 (6.7, 14.0)	9.8 (7.0, 13.7)	9.9 (7.2, 13.8)	10.0 (7.4, 13.8)	10.2 (7.6, 13.8)	10.6 (8.0, 14.1)	< 0.001

Notes: Diabetes mellitus defined as fasting plasma glucose ≥ 126 mg/dL or glucose lowering treatment.

Abbreviations: AG, anion gap; AMI, acute myocardial infarction; APSIII, Acute Physiology Score III; BUN, blood urea nitrogen; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eICU-CRD, eICU Collaborative Research Database; HepF, hepatic failure; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; MIMIC-IV, Medical Information Mart for Intensive Care; RBC, red blood cell; RDW, red blood cell distribution width; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; WCC, white cell count;

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Table 2 Association Between HRR and in-Hospital Mortality in Univariate Analysis

Variable	OR_95CI	P_value
Age, years	1.03 (1.02~1.03)	<0.001
Gender (%)		
Male	Ref	
Female	0.99 (0.93~1.06)	0.797
Race (%)		
White	Ref	
Black	0.77 (0.7~0.85)	<0.001
Other	1.16 (1.05~1.28)	0.005
Norepinephrine (%)		
No	Ref	
Yes	4.29 (3.98~4.63)	<0.001
Dopamine (%)		
No	Ref	
Yes	6.69 (5.64~7.93)	<0.001
Epinephrine (%)		
No	Ref	
Yes	3.98 (3.43~4.61)	<0.001
Phenylephrine (%)		
No	Ref	
Yes	5.07 (4.54~5.67)	<0.001
Vasopressin (%)		
No	Ref	
Yes	8.97 (7.96~10.1)	<0.001
Ventilation use (%)		
No	Ref	
Yes	1.97 (1.81~2.16)	<0.001
Intubated (%)		
No	Ref	
Yes	2.35 (2.18~2.52)	<0.001
Hb (%)		
No	Ref	
Yes	0.95 (0.93~0.96)	<0.001
RDW (%)		
No	Ref	
Yes	1.15 (1.14~1.17)	<0.001
COPD (%)		
No	Ref	
Yes	0.97 (0.9~1.04)	0.37
AMI (%)		
No	Ref	
Yes	1.17 (1.07~1.27)	<0.001
MC (%)		
No	Ref	
Yes	1.71 (1.51~1.94)	<0.001
Diabetes (%)		
No	Ref	
Yes	0.89 (0.83~0.96)	0.002
HepF (%)		
No	Ref	
Yes	2.1 (1.72~2.55)	<0.001

(*Continued*)

Table 2 (Continued).

Variable	OR_95CI	P_value
SOFA (%)		
No	Ref	
Yes	1.27 (1.26~1.28)	<0.001
APSIII	1.03 (1.03~1.04)	<0.001
Temperature, °C	0.74 (0.71~0.77)	<0.001
Respiratory Rate, breaths per minute	1.02 (1.02~1.02)	<0.001
Heart Rate, beats per minute	1.01 (1.01~1.01)	<0.001
SBP, mmHg	0.98 (0.98~0.98)	<0.001
MBP, mmHg	0.99 (0.99~1)	<0.001
AG	1.08 (1.07~1.09)	<0.001
BUN, mg/dL	1.02 (1.01~1.02)	<0.001
Calcium, mg/dL	0.78 (0.74~0.81)	<0.001
Chloride, mmol/L	0.99 (0.99~1)	0.001
Creatinine, mg/dL	1.07 (1.06~1.09)	<0.001
MCH, pg	1.01 (1~1.02)	0.095
MCHC, g/L	0.86 (0.84~0.87)	<0.001
MCV, fL	1.03 (1.02~1.03)	<0.001
Platelet, ×109/L	1 (1~1)	<0.001
Potassium, mmol/L	1.31 (1.25~1.36)	<0.001
RBC, ×109/L	0.86 (0.82~0.9)	<0.001
Sodium, mmol/L	1 (0.99~1)	0.293
WBC, ×109/L	1.04 (1.03~1.04)	<0.001

Notes: Diabetes mellitus defined as fasting plasma glucose ≥ 126 mg/dL or glucose lowering treatment.

Abbreviations: AG, anion gap; AMI, acute myocardial infarction; APSIII, Acute Physiology Score III; BUN, blood urea nitrogen; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; eICU-CRD, HepF, hepatic failure; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell; RDW, red blood cell distribution width; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; WCC, white cell count;

creatinine, MCV, potassium, and WBC were positively related to in-hospital mortality. However, Hb level, diabetes, body temperature, SBP, MBP, calcium level, chloride level, MCHC, and platelet count were negatively correlated with in-hospital mortality. Furthermore, an age interaction was observed between HRR and in-hospital mortality in patients with CHF; a stronger correlation was observed among participants aged < 65 years, with a significant decrease in in-hospital mortality in the younger subgroup as HRR increased. These findings extend the predictive use of Hb and RDW beyond their independent roles and suggest that HRR may be a sensitive and integrated marker of mortality risk in critically ill patients with CHF. The same results were obtained from MIMIC-IV and eICU-CRD, providing the first evidence that the risk of in-hospital mortality in patients with CHF and a reduced HRR is increasing.

HF is caused by structural and functional abnormalities in the heart that lead to increased intracardiac pressure or insufficient cardiac output at rest or during exercise.[17] HF is classified into acute heart failure (AHF) and CHF. CHF is characterized by the gradual appearance of HF symptoms based on existing chronic heart disease. Objective evidence of symptoms and signs of HF and cardiac dysfunction, including breathing difficulties, abdominal distension, and lower limb edema, are required to diagnose CHF. When patients with CHF experience worsening conditions, they face a high risk of fatal outcomes. Recent European data show that the all-cause mortality rate within 1 year was 16.9% for hospitalized patients with CHF.[18] Cardiovascular diseases have been the leading cause of death in the United States for decades, followed by cancer.[19] China is the largest developing country worldwide and is about to become an aging society, with approximately 4 million people dying from cardiovascular diseases annually, accounting for 40% of the total number of deaths.[20] This surge highlights the urgent clinical need to manage CHF effectively. Identifying and

Table 3 Association Between HRR and in-Hospital Mortality in Multiple Regression Model

Variable	N.total	N.event_%	Crude		Mode 1		Mode 2		Mode 3		Model 4	
			Crude.OR_95CI	Crude.P_value	Adj.OR_95CI	Adj.P_value	Adj.OR_95CI	Adj.P_value	Adj.OR_95CI	Adj.P_value	Adj.OR_95CI	Adj.P_value
HRR INDEX	30411	3840 (12.6)	0.86 (0.84~0.87)	<0.001	0.86 (0.84~0.87)	<0.001	0.83 (0.8~0.86)	<0.001	0.91 (0.9~0.93)	<0.001	0.92 (0.9~0.94)	<0.001
log HRR	30411	3840 (12.6)	0.11 (0.08~0.14)	<0.001	0.11 (0.08~0.14)	<0.001	0.13 (0.1~0.17)	<0.001	0.24 (0.18~0.32)	<0.001	0.25 (0.19~0.35)	<0.001
HRR HEXILES												
H1	4771	868 (18.2)	1(Ref)		1(Ref)		1(Ref)		1(Ref)		1(Ref)	
H2	4985	760 (15.2)	0.81 (0.73~0.9)	<0.001	0.79 (0.71~0.88)	<0.001	0.89 (0.79~1)	0.047	0.93 (0.83~1.05)	0.248	0.93 (0.82~1.05)	0.215
H3	5366	683 (12.7)	0.66 (0.59~0.73)	<0.001	0.63 (0.57~0.71)	<0.001	0.74 (0.66~0.84)	<0.001	0.81 (0.71~0.91)	0.001	0.8 (0.7~0.9)	<0.001
H4	4905	596 (12.2)	0.62 (0.56~0.7)	<0.001	0.59 (0.53~0.67)	<0.001	0.76 (0.67~0.86)	<0.001	0.83 (0.73~0.94)	0.004	0.82 (0.72~0.93)	0.002
H5	5095	492 (9.7)	0.48 (0.43~0.54)	<0.001	0.47 (0.41~0.53)	<0.001	0.61 (0.54~0.7)	<0.001	0.66 (0.58~0.75)	<0.001	0.65 (0.57~0.75)	<0.001
H6	5289	441 (8.3)	0.41 (0.36~0.46)	<0.001	0.42 (0.37~0.47)	<0.001	0.58 (0.5~0.66)	<0.001	0.6 (0.53~0.69)	<0.001	0.61 (0.53~0.7)	<0.001
Trend.test	30411	3840 (12.6)	0.84 (0.82~0.86)	<0.001	0.84 (0.82~0.86)	<0.001	0.9 (0.88~0.92)	<0.001	0.91 (0.88~0.93)	<0.001	0.91 (0.88~0.93)	<0.001

Notes: Crude model: adjusted for none; Model 1 was adjusted only for age, sex and ethnicity; Model 2 was additionally adjusted for COPD, diabetes, HepF, SOFA score, temperature, Respiratory Rate, Heart Rate and SBP; Model 3 was additionally adjusted for AG, BUN, Calcium, Creatinine, MCH, MCHC, MCV, Platelet, Potassium, RBC, Sodium and WBC; Model 4 was additionally adjusted for ventilator use, intubated, dopamine, epinephrine, phenylephrine, and vasopressin usage.

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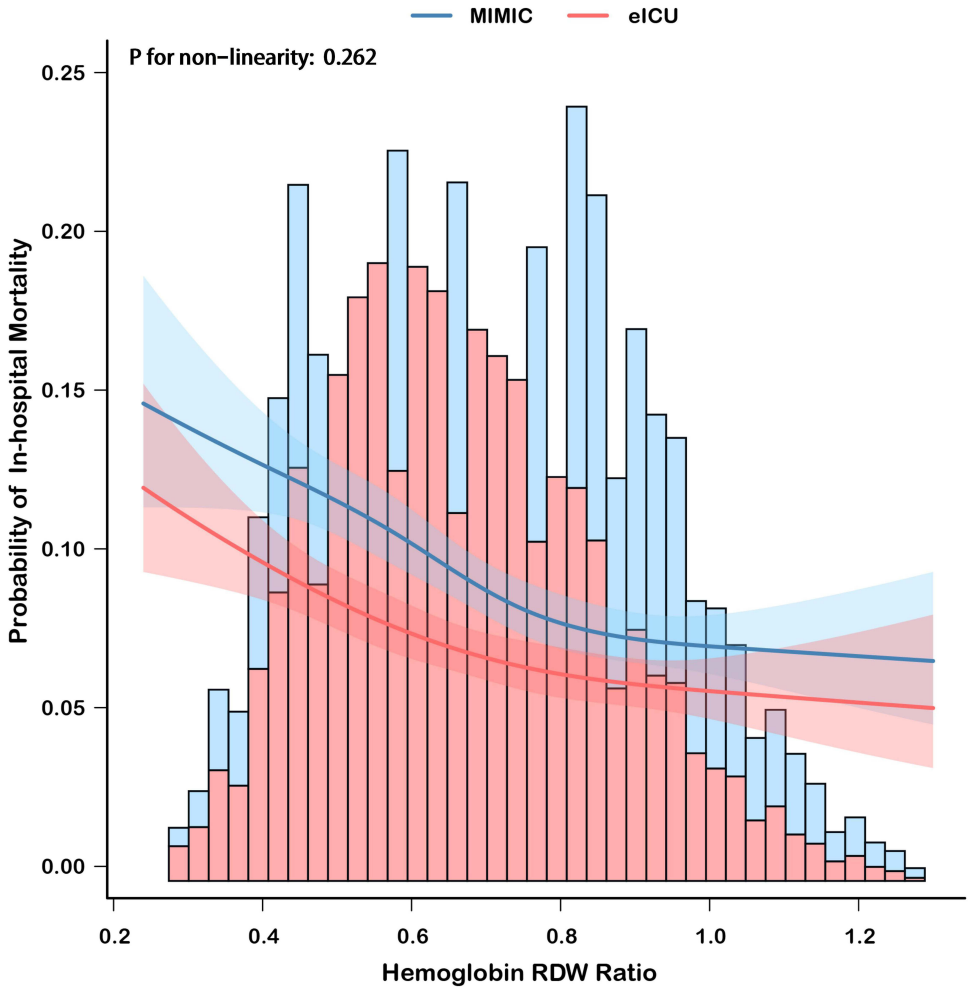

Figure 2 Smooth curve fitting of relationship between the Hemoglobin-to-Red Cell Distribution Width Ratio and in-hospital mortality in Patients with CHF. The solid line and dashed line represent the estimated values and their corresponding 95% confidence intervals. Adjusted for parameters that were included in the multiple regression model 4 of Logistic regression analysis.

addressing in-hospital mortality and readmission risk factors for discharged CHF patients is a primary goal for cardiovascular specialists.

Patients with CHF frequently present with anemia and low Hb levels, a marker of HF severity that impacts risk factors like chronic inflammation, malnutrition, iron deficiency, bleeding, and chronic kidney disease.[21] Acute Hb decline increases the risk of death in patients with HF after acute attacks.[3] The RDW reflects the heterogeneity of peripheral RBC volume and is an inherent parameter in routine blood examinations. One meta-analysis showed that an increase in RDW was associated with an increased risk of all-cause mortality in patients with cardiovascular disease.[22] In contrast, another meta-analysis showed that a 1% increase in RDW was associated with a 9.1% increase in the hospitalization risk for HF combined with adverse events.[23] Previous studies have investigated the relationship between Hb, RDW, and clinical outcomes in patients with various cardiovascular diseases, demonstrating that elevated Hb and RDW levels individually correlate with an increased risk of adverse outcomes in patients with HF. The present study expands on this knowledge by demonstrating that a lower HRR is a strong predictor of in-hospital mortality for patients with CHF. Research on the relationship between HRR and patients with tumors has increased recently.[24–26] Studies have reported the relationship between HRR and the prognosis of patients with AHF, as well as the use of HRR as a predictive indicator and clinical outcome of patients with HF.[11] However, the current study differs from previous studies as it is the first to report the relationship between HRR and in-hospital mortality in patients with CHF. Elevated RDW in patients with HF is also potentially closely related to inflammation.[27,28] Patients with end-stage HF often have weakened immunity. Clinically,

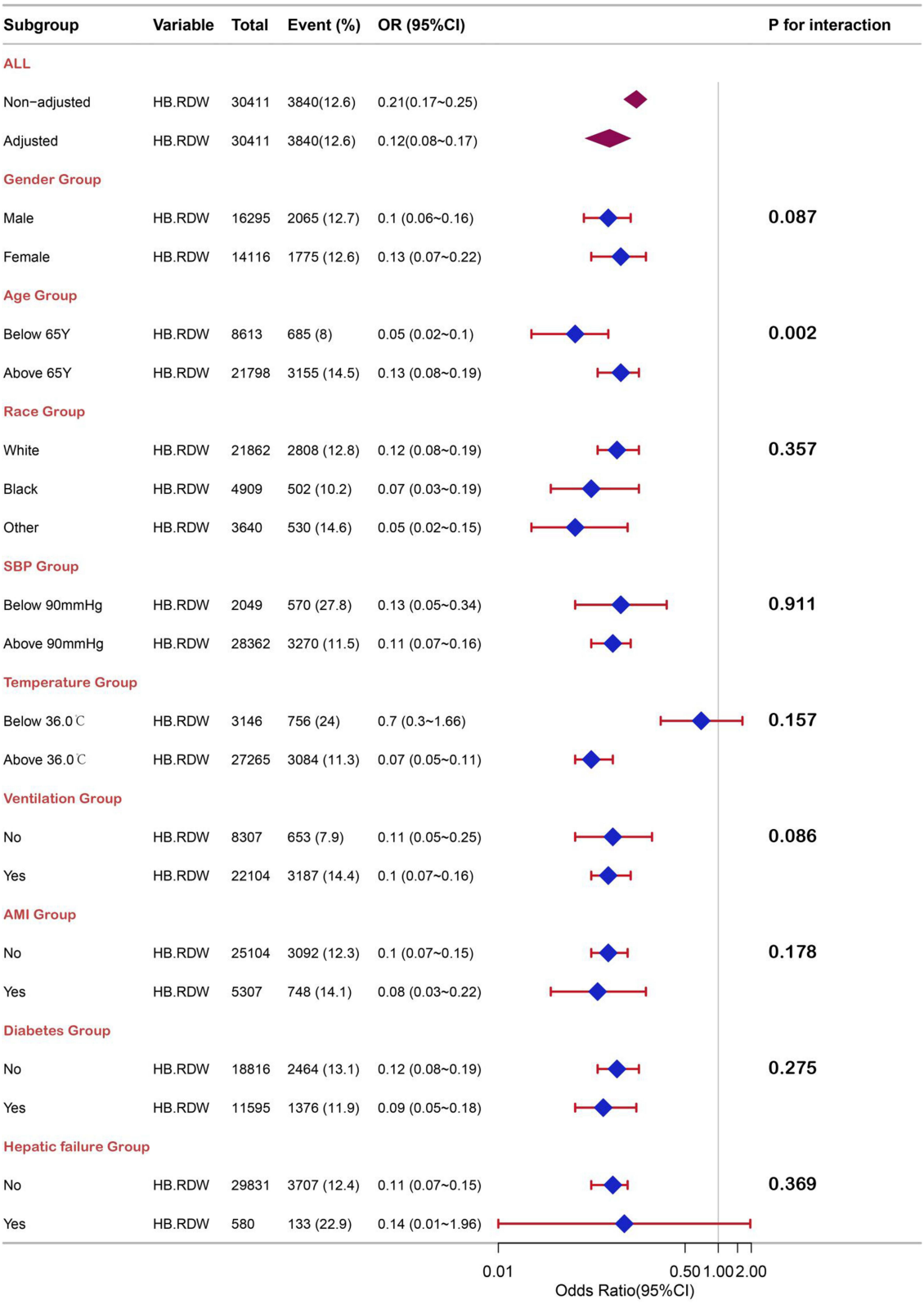

Figure 3 Association between the Hemoglobin-to-Red Cell Distribution Width Ratio and in-hospital mortality in Patients with CHF. Each stratification was adjusted for age, sex, race and Norepinephrine, Dopamine, Epinephrine, Phenylephrine, Vasopressin, Intubated, SOFA, Respiratory Rate, Heart Rate, AG, BUN, Calcium, Chloride, Creatinine, MCH, MCHC, MCV, Platelet, Potassium, RBC, Sodium, WBC, Vent, AMI, Diabetes, HepF except the stratification factor itself. Squares indicate odds ratios (OR), with horizontal lines indicating 95% CI.

lung infections or infections in other areas are vital triggering factors for CHF exacerbation.[29] Therefore, an increase in RDW often indicates that concurrent infections in patients with CHF are clinically significant.

However, this study has several limitations. First, using the public database, while advantageous for its accessibility and large sample size, presents inherent limitations. Second, only the first HRR record collected during ICU admission was analyzed; therefore, the results are limited to a confined period during which HRR was measured. Third, the study design is observational; thus, causality between HRR and in-hospital mortality could not be established.

Conclusion

A linear relationship was observed between baseline HRR levels and in-hospital mortality. Lower HRR levels were associated with higher in-hospital mortality in patients with CHF. HRR could be a reliable clinical metric for assessing in-hospital mortality risk. Future research could focus on conducting prospective cohort studies or randomized controlled trials to strengthen causal inferences and validate HRR as a potential therapeutic target.

Data Sharing Statement

Publicly available datasets were analyzed in this study. This data can be found here: https://doi.org/10.5061/dryad.tx95x6b18 and https://doi.org/10.1136/bmjopen-2021-059761.

Ethics Approval

The study was approved by the Ethic Committee of the First People's Hospital of Changde City (No. YX-2024-031-01). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author Contributions

Ying li is he first author. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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