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Impact of the hemoglobin-to-red cell distribution width ratio on 30-day readmission in patients with heart failure

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Abstract

Background Predicting all-cause readmission in patients with heart failure (HF) is crucial. This study investigated the independent risk factors for short-term readmission and assessed the potential mediators involved in this process.

Methods We evaluated data from 2,254 patients with HF admitted to our institution between January 2019 and December 2020. Logistic regression analysis was used to examine the association between sarcopenia index (SI), neutrophil-to-lymphocyte ratio (NLR), hemoglobin-to-red cell distribution width ratio (HRR), and all-cause 30-d readmission. A restricted cubic spline regression model with three knots assessed potential non-linear relationships between confounders and readmission risk. A mediation analysis was performed to evaluate the direct and indirect effects, as well as the proportion of mediation.

Results The mean age of the participants was 72 ± 12 years, with 1,324 males (58.7%). The all-cause 30-d readmission rate was 7.1%. HRR was independently associated with 30-d readmission among the evaluated biomarkers, whereas SI and NLR showed no significant correlation. A non-linear relationship was found between HRR and readmission risk, with an inflection point at 0.94. Patients with HRR < 0.94 exhibited a significantly higher risk of readmission, whereas no significant association was found for HRR ≥ 0.94. Mediation analysis revealed that N-terminal pro-B-type natriuretic peptide (NT-proBNP) partially mediated this relationship, which accounted for 13.6% of the effect.

Conclusions HRR is an independent predictor of all-cause 30-d readmission in patients with a non-linear relationship observed. An inverse association was found for HRR < 0.94, whereas no significant association was found for HRR ≥ 0.94. Additionally, NT-proBNP was identified as a partial mediator of this relationship.

Keywords Hemoglobin-to-red cell distribution width ratio, Heart failure, Hospital readmission, Non-linear relationship, Mediation analysis

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Background

Heart failure (HF) is an increasing concern in developed nations, with a high readmission rate [1]. Predicting readmission is crucial for patients with HF, with several clinical factors could be used for this purpose.

The sarcopenia index (SI) is a novel indicator for assessing muscle mass and is estimated based on the ratio of serum creatinine (Scr) to cystatin C (CysC). This innovative index provides clinicians with a simple, rapid, and cost-effective screening tool [2]. Research indicates that patients with liver cirrhosis who have a decreased SI tend to experience readmission within a 90-d period [3]. In the United States, there is a significant association between higher SI levels and a decreased likelihood of long-term cardiovascular and all-cause mortality. These results suggest that SI plays a crucial role in assessing cardiovascular risk [4].

The neutrophil-to-lymphocyte ratio (NLR) is a commonly used, simple, and convenient hematological indicator that assesses inflammation and immune status by calculating the ratio of neutrophils to lymphocytes in the blood [5]. A multicenter prospective study revealed that the blood NLR upon admission could help identify elderly patients with high mortality risk during hospitalization, regardless of their admission diagnosis, kidney function, or hemoglobin (Hb) levels [6]. Additionally, a systematic review and meta-analysis focusing on chronic obstructive pulmonary disease in Asia proposed that NLR should be recognized as a significant risk factor for readmission [7].

The Hb-to-red cell distribution width (RDW) ratio (HRR) is an emerging hematological indicator that calculates the ratio of Hb to RDW in the blood. The HRR is efficient in the prognostic assessment of various diseases, including infections, tumors, cardiovascular diseases, and autoimmune diseases. The HRR has been identified as a significant prognostic tool for predicting mortality and cardiovascular hospitalization in patients with HF [8]. Furthermore, a negative correlation has been observed between HRR levels and the likelihood of HF readmission within 3 months [9].

However, limited research has determined which of these three indicators should be classified as high-risk factors for all-cause 30-d readmission in patients with HF. Therefore, this study explored and determined the independent risk factors associated with short-term readmission in patients with HF and assessed the potential mediating factors.

Methods

Study design and participants

This retrospective study involved a real-world analysis of patients with HF who were admitted to the Affiliated Hospital of Guangdong Medical University. Data were extracted from 6,204 patients hospitalized between January 2019 and December 2020, including those admitted with acute or chronic decompensated HF and those hospitalized for other medical conditions. The inclusion criteria were: (1) age ≥ 18 years, (2) HF diagnosis according to the American College of Cardiology/American Heart Association Joint Committee clinical practice guidelines [10], and (3) HF treatment received during the hospitalization. We excluded patients (1) classified with New York Heart Association (NYHA) functional class I, (2) who died during the index admission, (3) with excessive missing baseline data, and (4) who lost to follow-up. Finally, 2,254 patients with HF were included in the analysis (Fig. 1). This study adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Review Committee of the Affiliated Hospital of Guangdong Medical University (Approval Number: PJKT2023-062).

Clinical data collection and definitions

Clinical data were obtained from the electronic medical records. Baseline clinical data included demographics, medical history, complete blood count (CBC), laboratory results, echocardiographic findings, and discharge medications.

Demographic information included age and sex, whereas medical history covered aspects, such as NYHA class, smoking, hypertension, diabetes, coronary heart disease (CHD), and atrial fibrillation (AF). Echocardiography was conducted according to the guidelines set by the American Society of Echocardiography and the European Association of Cardiovascular Imaging [11], and the echocardiographic findings mainly focused on the left ventricular ejection fraction (LVEF).

For CBC, parameters such as neutrophil count, lymphocyte count, Hb level, and RDW coefficient of variation (RDW-CV) were evaluated at admission. Laboratory parameters, including N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum uric acid (SUA), blood albumin (ALB), high-sensitivity cardiac troponin (hs-cTnT), Scr, serum CysC, serum sodium, serum potassium, and estimated glomerular filtration rate (eGFR), were also analyzed. These analyses were conducted using standard techniques on venous blood samples obtained after a fasting period of > 8 h.

The discharge medications included angiotensin-converting enzyme inhibitors/angiotensin (II) receptor blockers/angiotensin receptor-neprilysin inhibitors, diuretic or mineralocorticoid receptor antagonists (MRA), sodium-glucose cotransporter-2 inhibitors, digoxin, and β-receptor blockers.

LVEF was categorized into three groups: ≥ 50%, 40%–49%, and < 40%. Hyperkalemia was defined as a

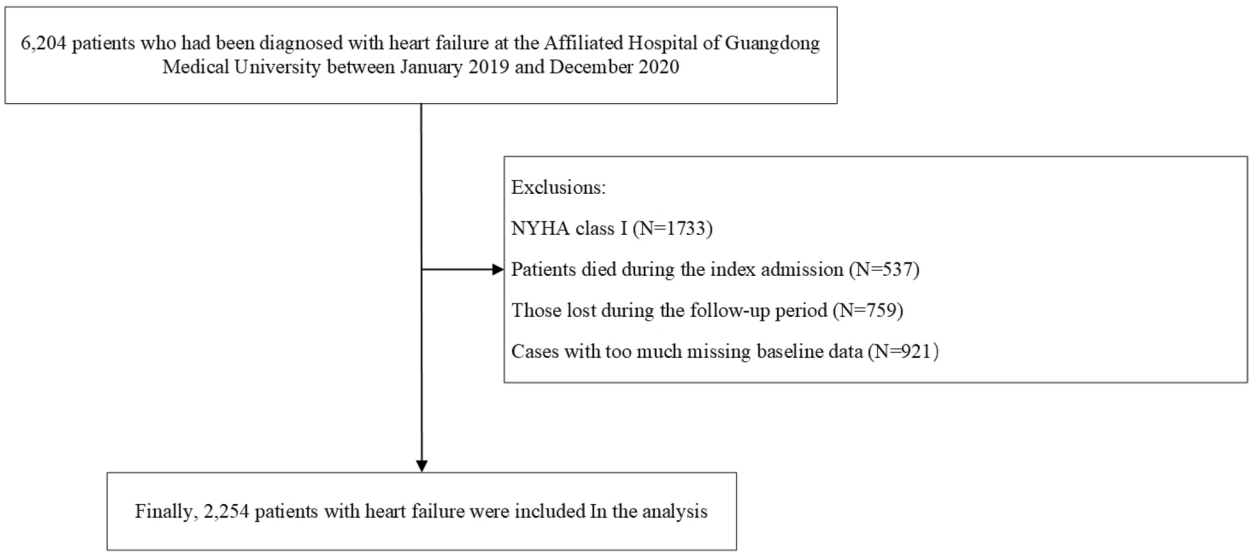

Fig. 1 The process of screening patients

serum potassium level > 5.0 mmol/L [12], while hyponatremia was defined as a serum sodium level of less than 135 mmol/L [13]. eGFR was divided into two groups: ≥ 60 mL/min/1.73 m^2 and < 60 mL/min/1.73 m^2 [14]. The diagnostic definition of hyperuricemia was: males with levels > 420 μmol/L and females with levels > 360 μmol/L [15]. Hypoalbuminemia was diagnosed when serum albumin level was < 35 g/L [16].

SI was calculated using the following formula: $\frac{\text{Scr [mg/dL]}}{\text{Cys C [mg/L]}} \times 100$ [17], NLR was determined by: $\frac{AbsoluteNeutrophilCount(ANC)}{AbsoluteLymphocyteCount(ALC)}$, and HRR was calculated as: $HRR = \frac{Hb(g/L)}{RDW-CV}$ (%) [18, 19].

Study endpoints

This study focused on the all-cause 30-d readmission rates within the cohort. Readmission occurring within 30 d of the initial discharge from the hospital was classified as a readmission event, and follow-up was conducted by phone or assessed through electronic medical records.

Statistical analysis

For missing data < 20%, the random forest model was used for imputation. Continuous variables were presented as means ± SDs or medians with interquartile ranges, depending on whether the distribution was normal or not. Categorical data were displayed as numbers and percentages. The Student's t- or Mann–Whitney U test was used to analyze group differences in continuous variables, whereas the Pearson chi-square or Fisher's exact test was used for categorical variables. Logistic regression analysis was conducted to determine the adjusted odds ratios and 95% confidence intervals for the relationship between the SI, NLR, and HRR and all-cause 30-d readmission.

To ensure a rigorous analysis of potential confounders influencing all-cause 30-d readmission rates, three progressively adjusted models were applied. Model 1 presented an unadjusted, crude association. Model 2 incorporated key demographic and clinical characteristics, including age, sex, NYHA functional class, smoking status, hypertension, diabetes, CHD, and AF at baseline, to account for their potential impact on the outcome. Model 3 built upon Model 2 and further adjusted for factors associated with HF prognosis, such as disease severity, laboratory parameters, and HF treatment at discharge. Additional variables included LVEF, hyperkalemia [12], hyponatremia [20], eGFR class [21], hypoalbuminemia [22], hyperuricemia [23], NT-proBNP, hs-cTnT [24], β-blocker, diuretic or MRA, SGLT2i, digoxin, and ACEI/ARB/ARNI. To evaluate any potential non-linear dose–response relationships between the confounding variables and all-cause 30-d readmission rates, a restricted cubic spline (RCS) regression model with three knots were used. Subgroup analysis was used to investigate the interactions among the variables. Subsequently, Pearson's correlation analysis was employed to assess the relationships among variables; a mediation analysis was conducted to evaluate the direct effects, indirect effects, and proportion of intermediary factors influencing the outcome. To evaluate collinearity, variance inflation factors (VIFs) and tolerances were computed. A VIF < 5 and a tolerance > 0.1 were deemed as indicators of insignificant collinearity.

All statistical analyses were performed using the R software (version 4.2.2; R Foundation of Statistical Computing, Vienna, Austria) and MSTATA software (https://www.mstata.com). Statistical significance was set at $p < 0.05$ (two-sided).

Results

Baseline characteristics

The baseline clinical data of all 2,254 individuals analyzed in this study are presented in Table 1. The median age of the participants was 72 ± 12 years, and 58.7% were male (1,324). The all-cause readmission rate within 30 d was 7.1%. Patients with HF were categorized into distinct groups based on their HRR quartiles. These subgroups were defined as Q1 (< 0.76), Q2 (≥ 0.76, < 0.889), Q3 (≥ 0.889, < 1.01), and Q4 (≥ 1.01). Compared with the other groups, the Q1 group (the lowest HRR) had elevated age and NT-proBNP levels; a higher percentage of female individuals; a prevalence of patients with NYHA class IV; and an increased occurrence of hyperkalemia, hyponatremia, eGFR (< 60 mL/min/1.73 m^2) impairment, hypoalbuminemia, and hyperuricemia.

Association between the SI, NLR, and HRR and all-cause 30-d readmission

Table 2 summarizes the logistic regression results assessing associations of SI, NLR, and HRR with all-cause 30-d readmission. Neither continuous nor quartile-grouped SI exhibited significant associations with readmission in unadjusted or fully adjusted models. While NLR quartiles showed a trend toward significance in the unadjusted model (p for trend < 0.05), no significant associations emerged when NLR was analyzed as a continuous variable in unadjusted or adjusted models. Similarly, NLR quartiles lacked significance in partially and fully adjusted analyses. Conversely, HRR demonstrated consistent and robust associations with readmission risk, whether analyzed as a continuous variable or in quartiles, across unadjusted (continuous: $p < 0.001$; quartiles: p for trend = 0.004), partially adjusted (continuous: p = 0.002; quartiles: p for trend = 0.007), and fully adjusted models (continuous: $p = 0.012$; quartiles: p for trend = 0.05).

From the analysis of the VIF values of the potential variables included in the model, all VIF values were significantly below the critical threshold of 5. Additionally, the tolerance level of each potential variable was well above 0.1 (Additional Files 1–3).

A non-linear relationship between the HRR and all-cause 30-d readmission

The findings from the multivariable-adjusted RCS regression analysis highlighted a significant non-linear correlation between the HRR and the likelihood of all-cause 30-d readmission (p for nonlinearity = 0.020; $p = 0.002$), as illustrated in Fig. 2. The inflection point of the HRR was 0.94. The HRR was split into two groups based on the inflection point, followed by a thorough segmented logistic regression analysis. Upon thorough adjustment for confounding variables, the findings demonstrated that regardless of whether the HRR values were standardized, an HRR level < 0.94 was significantly associated with an increased risk of all-cause 30-d readmission ($p = 0.001$). Conversely, HRR levels ≥ 0.94 exhibited no significant association with the readmission risk ($p = 0.10$; Fig. 3).

Subgroup analyses

The HRR was categorized into two groups based on the inflection point (HRR < 0.94 and HRR ≥ 0.94); age was divided into two groups with 65 years as the threshold (< 65 years and ≥ 65 years); and NT-proBNP was separated into two groups using the median value (< 1,640 pg/mL and ≥ 1,640 pg/mL). Additional variables, such as sex, LVEF, eGFR class, hyperkalemia, hyponatremia, hypoalbuminemia, and hyperuricemia, were also included in the model analysis. Subgroup analyses revealed no significant interactions between the HRR and other variables, including age, sex, LVEF, hyperkalemia, hyponatremia, hypoalbuminemia, hyperuricemia, eGFR class, and NT-proBNP level (all p-values for interaction > 0.05; Additional File 4).

Mediation analysis of the relationship between the HRR and all-cause 30-d readmission

Pearson's correlation analysis was used to assess the relationship between the HRR and variables such as age, SUA, NLR, ALB, eGFR, NT-proBNP, and hs-cTnT (Fig. 4). Significant negative correlations were observed between the HRR and age, SUA, and NT-proBNP ($r = -0.249$, $p < 0.0001$; $r = -0.047$, $p = 0.026$; $r = -0.230$, $p < 0.0001$, respectively), whereas significant positive correlations were observed between the HRR and ALB and eGFR ($r = 0.417$, $p < 0.0001$ and $r = 0.143$, $p < 0.0001$, respectively). Additionally, no significant correlation was observed between the HRR and the NLR or hs-cTnT levels ($p = 0.4333$ and $p = 0.0875$, respectively).

Table 3 presents the impact of mediators on the connection between the HRR and the all-cause 30-d readmission rate. The findings indicated that NT-proBNP played a significant mediating role in the relationship between the HRR and 30-d readmission (indirect effect, $p = 0.004$; direct effect, $p = 0.004$). Specifically, the mediating effect of the NT-proBNP level on the HRR-associated readmission risk was 13.6%. Conversely, the mediating effects of other variables, such as sex, age, SUA level, NLR, ALB level, eGFR, and hs-cTnT level, were found to be statistically insignificant.

Table 1 Patient baseline characteristics

Characteristic	Overall $N=2,254$[1]	HRR Q1 (< 0.76), $N=564$[1]	HRR Q2 (≥ 0.76, < 0.889), $N=563$[1]	HRR Q3 (≥ 0.889, < 1.01), $N=563$[1]	HRR Q4 (≥ 1.01), $N=564$[1]	*p*-value
HRR	0.88 ± 0.21	0.60 ± 0.13	0.83 ± 0.04	0.95 ± 0.04	1.12 ± 0.09	< 0.001[2]
Age, years	72 ± 12	75 ± 12	75 ± 11	71 ± 12	66 ± 13	< 0.001[2]
Sex, n(%)						< 0.001[3]
Female	930 (41.3%)	291 (51.6%)	273 (48.5%)	241 (42.8%)	125 (22.2%)	
Male	1,324 (58.7%)	273 (48.4%)	290 (51.5%)	322 (57.2%)	439 (77.8%)	
NYHA class, n(%)						< 0.001[3]
II	1,120 (49.7%)	206 (36.5%)	261 (46.4%)	303 (53.8%)	350 (62.1%)	
III	781 (34.6%)	225 (39.9%)	208 (36.9%)	188 (33.4%)	160 (28.4%)	
IV	353 (15.7%)	133 (23.6%)	94 (16.7%)	72 (12.8%)	54 (9.6%)	
Smoking, n(%)	269 (11.9%)	57 (10.1%)	61 (10.8%)	55 (9.8%)	96 (17.0%)	< 0.001[3]
Hypertension, n(%)	1,290 (57.2%)	329 (58.3%)	337 (59.9%)	328 (58.3%)	296 (52.5%)	0.063[3]
Diabetes, n(%)	826 (36.6%)	214 (37.9%)	190 (33.7%)	208 (36.9%)	214 (37.9%)	0.411[3]
CHD, n(%)	1,599 (70.9%)	385 (68.3%)	417 (74.1%)	403 (71.6%)	394 (69.9%)	0.167[3]
AF, n(%)	688 (30.5%)	178 (31.6%)	177 (31.4%)	157 (27.9%)	176 (31.2%)	0.479[3]
LVEF, n(%)						0.166[3]
≥ 50%	1,500 (66.5%)	385 (68.3%)	384 (68.2%)	373 (66.3%)	358 (63.5%)	
40% ~ 50%	394 (17.5%)	106 (18.8%)	93 (16.5%)	90 (16.0%)	105 (18.6%)	
< 40%	360 (16.0%)	73 (12.9%)	86 (15.3%)	100 (17.8%)	101 (17.9%)	
Potassium, mmol/L	3.98 ± 0.55	4.02 ± 0.65	3.97 ± 0.50	3.95 ± 0.55	3.97 ± 0.47	0.168[2]
Sodium, mmol/L	138.9 ± 4.7	138.0 ± 5.6	138.7 ± 4.8	139.4 ± 4.1	139.6 ± 4.0	< 0.001[2]
Scr, μmol/L	89 (72, 114)	97 (73, 135)	89 (72, 117)	85 (68, 107)	88 (74, 103)	< 0.001[4]
SUA, μmol/L	412 ± 139	426 ± 141	405 ± 145	409 ± 138	408 ± 130	0.045[2]
ALB, g/L	37.8 ± 4.5	35.1 ± 4.7	37.6 ± 4.4	38.8 ± 3.7	39.9 ± 3.7	< 0.001[2]
eGFR, ml/min/1·73 m^2	71 (53, 87)	60 (42, 82)	68 (50, 85)	73 (57, 88)	76 (63, 90)	< 0.001[4]
NLR	3.6 (2.4, 5.9)	4.2 (2.7, 6.9)	3.6 (2.4, 5.9)	3.6 (2.3, 5.8)	3.0 (2.1, 4.7)	< 0.001[4]
SI	109 ± 35	104 ± 40	106 ± 33	110 ± 33	117 ± 29	< 0.001[2]
Hyperkalemia, n(%)	87 (3.9%)	49 (8.7%)	14 (2.5%)	9 (1.6%)	15 (2.7%)	< 0.001[3]
Hyponatremia, n(%)	325 (14.4%)	112 (19.9%)	93 (16.5%)	68 (12.1%)	52 (9.2%)	< 0.001[3]
eGFR class, n(%)						< 0.001[3]
≥ 60 ml/min/1·73 m^2	1,469 (65.2%)	284 (50.4%)	344 (61.1%)	397 (70.5%)	444 (78.7%)	
< 60 ml/min/1·73 m^2	785 (34.8%)	280 (49.6%)	219 (38.9%)	166 (29.5%)	120 (21.3%)	
Hypoalbuminaemia, n(%)	539 (23.9%)	265 (47.0%)	141 (25.0%)	82 (14.6%)	51 (9.0%)	< 0.001[3]
Hyperuricemia, n(%)	1,152 (51.1%)	335 (59.4%)	282 (50.1%)	278 (49.4%)	257 (45.6%)	< 0.001[3]
NT-proBNP, pg/mL	1,645 (687, 4,453)	2,839 (1,192, 7,405)	1,951 (769, 5,148)	1,382 (617, 3,565)	1,032 (510, 2,574)	< 0.001[4]
hs-cTnT, ng/mL	0.03 (0.01, 0.05)	0.03 (0.02, 0.06)	0.03 (0.02, 0.05)	0.02 (0.01, 0.05)	0.02 (0.01, 0.05)	< 0.001[4]
β-blocker, n(%)	1,072 (47.6%)	238 (42.2%)	246 (43.7%)	298 (52.9%)	290 (51.4%)	< 0.001[3]
Diuretic or MRA, n(%)	1,025 (45.5%)	306 (54.3%)	261 (46.4%)	256 (45.5%)	202 (35.8%)	< 0.001[3]
SGLT2i, n(%)	207 (9.2%)	36 (6.4%)	48 (8.5%)	58 (10.3%)	65 (11.5%)	0.017[3]
Digoxin, n(%)	400 (17.7%)	105 (18.6%)	108 (19.2%)	96 (17.1%)	91 (16.1%)	0.517[3]
ACEI/ARB/ARNI, n(%)	1,004 (44.5%)	232 (41.1%)	228 (40.5%)	281 (49.9%)	263 (46.6%)	0.003[3]
30-day readmission, n(%)	160 (7.1%)	60 (10.6%)	34 (6.0%)	31 (5.5%)	35 (6.2%)	0.002[3]

HRR hemoglobin-to-red cell distribution width ratio, *NYHA* New York Heart Association, *CHD* coronary heart disease, *AF* atrial fibrillation, *LVEF* left ventricular ejection fraction, *SUA* serum uric acid, *ALB* blood albumin, *Scr* serum creatinine, *eGFR* estimated glomerular filtration rate, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *Hs-cTnT* high-sensitive cardiac troponin, *NLR* neutrophil-to-lymphocyte ratio, *SI* sarcopenia index, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin (II) receptor blockers, *ARNI* angiotensin receptor-neprilysin inhibitors, *β-blocker* β-receptor blocker, *MRA* mineralocorticoid receptor antagonist, *SGLT2i* sodium-glucose cotransporter-2 inhibitors

[1] Mean ± SD; n (%); Median (IQR); [2]One-way ANOVA; [3]Pearson's Chi-squared test; [4]Kruskal-Wallis rank sum test

Table 2 Association between SI, NLR, and HRR with all-cause 30-day readmission

Characteristic	Model 1				Model 2				Model 3			
	OR[1]	95% CI[1]	*p*-value	P for trend	OR[1]	95% CI[1]	*p*-value	P for trend	OR[1]	95% CI[1]	*p*-value	P for trend
SI (continuous)	1.00	1.00, 1.01	0.435		1.00	1.00, 1.01	0.718		1.00	0.99, 1.00	0.725	
SI				0.382				0.537				0.826
Q1(< 87.1)	Ref	Ref	—		Ref	Ref	—		Ref	Ref	—	
Q2 (< 105)	0.97	0.60, 1.58	0.915		0.95	0.58, 1.54	0.829		0.94	0.57, 1.56	0.819	
Q3 (< 125)	1.43	0.91, 2.23	0.118		1.44	0.90, 2.31	0.127		1.41	0.85, 2.35	0.181	
Q4 (≥ 125)	1.09	0.68, 1.74	0.720		1.03	0.61, 1.73	0.911		0.94	0.53, 1.67	0.825	
NLR (continuous)	1.00	1.00, 1.01	0.299		1.00	1.00, 1.01	0.330		1.00	0.99, 1.01	0.451	
NLR				**0.013**				0.085				0.261
Q1(< 2.36)	Ref	Ref	—		Ref	Ref	—		Ref	Ref	—	
Q2 (< 3.56)	0.97	0.59, 1.60	0.904		0.87	0.52, 1.45	0.592		0.85	0.51, 1.42	0.532	
Q3 (< 5.86)	1.33	0.83, 2.13	0.233		1.15	0.71, 1.86	0.563		1.12	0.69, 1.83	0.650	
Q4 (≥ 5.86)	1.63	1.04, 2.57	0.033		1.38	0.86, 2.22	0.177		1.22	0.74, 2.01	0.431	
HRR (continuous)	0.28	0.14, 0.59	**< 0.001**		0.28	0.13, 0.62	**0.002**		0.33	0.14, 0.78	**0.012**	
HRR				**0.004**				**0.007**				**0.050**
Q1(< 0.76)	Ref	Ref	—		Ref	Ref	—		Ref	Ref	—	
Q2 (< 0.889)	0.54	0.35, 0.84	0.006		0.55	0.35, 0.85	0.008		0.56	0.36, 0.89	0.014	
Q3 (< 1.01)	0.49	0.31, 0.77	0.002		0.51	0.32, 0.81	0.004		0.55	0.34, 0.90	0.017	
Q4 (≥ 1.01)	0.56	0.36, 0.86	0.008		0.55	0.34, 0.88	0.013		0.61	0.37, 1.03	0.062	

HRR hemoglobin-to-red cell distribution width ratio, *NYHA* New York Heart Association, *CHD* coronary heart disease, *AF* atrial fibrillation, *LVEF* left ventricular ejection fraction, *eGFR* estimated glomerular filtration rate, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *Hs-cTnT* high-sensitive cardiac troponin, *NLR* neutrophil-to-lymphocyte ratio, *SI* sarcopenia index, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin (II) receptor blockers, *ARNI* angiotensin receptor-neprilysin inhibitors, *β-blocker* β-receptor blocker, *MRA* mineralocorticoid receptor antagonist, *SGLT2i* sodium-glucose cotransporter-2 inhibitors

[1] *OR* Odds Ratio, *CI* Confidence Interval

Model 1: no covariates were adjusted

Model 2: adjusted for age, sex, NYHA class, smoking, hypertension, diabetes, CHD, and AF

Model 3: adjusted for age, sex, NYHA class, smoking, hypertension, diabetes, CHD, AF, LVEF, hyperkalemia, hyponatremia, eGFR class, hypoalbuminemia, hyperuricemia, NT-proBNP, hs-cTnT, β-blocker, diuretic or MRA, SGLT2i, digoxin, and ACEI/ARB/ARNI

Discussion

To the best of our knowledge, this study is the first to identify HRR as a significant predictor of all-cause 30-d readmission in patients with HF, whereas SI and NLR did not demonstrate a similar association. Notably, our findings highlight a non-linear relationship between HRR and all-cause readmission risk, with an inflection point at 0.94. Patients with HRR levels below this threshold exhibited a significantly higher likelihood of 30-day readmission, whereas those with HRR ≥ 0.94 showed no clear association with readmission risk. Additionally, our mediation analysis suggests that NT-proBNP partially mediates the relationship between HRR and all-cause 30-d readmission, accounting for 13.6% of the effect.

The SI is determined by dividing CysC levels by Scr levels, offering a convenient method for evaluating muscle mass [2]. Recent studies have established a strong association between SI and unfavorable outcomes as well as increased mortality rates, particularly in patients with conditions such as HF, cancer, and chronic obstructive pulmonary disease [25–29]. Nonetheless, this study concluded that SI was not significantly correlated with all-cause short-term readmission rates among patients with HF. This lack of association can be attributed to several factors. First, the SI, calculated as the ratio of creatinine to cystatin C, is influenced by renal function, which may limit its effectiveness as a proxy for muscle mass. Additionally, the SI does not capture other crucial aspects of sarcopenia, such as muscle strength and physical performance. This suggests that measures including handgrip strength, gait speed, skeletal muscle mass, or calf circumference may provide a more comprehensive assessment. [30]. Moreover, the 30-day observation period may be extremely brief to reveal the adverse effects of sarcopenia, which may become more evident over longer-term outcomes [31].

The NLR is recognized as a systemic inflammatory marker that is determined by the peripheral blood cell count. Studies have shown a notable link between NLR and mortality in patients with HF [32, 33]. Furthermore, some studies have suggested that the NLR may not be a reliable predictor of the 90-d or 60-d readmission rate

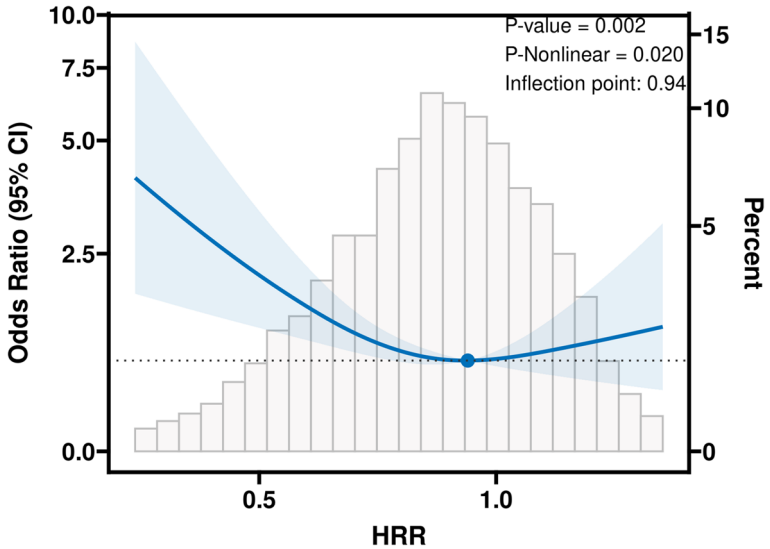

Fig. 2 Association between HRR and all-cause 30-day readmission with the RCS function. The model with 3 knots is located at 10th, 50th, and 90th percentiles. The Y-axis represents the OR to present 30-day readmission for any value of HRR compared to individuals with the reference value (50th percentile) of HRR. The logistic regression was adjusted for age, sex, NYHA class, smoking, hypertension, diabetes, CHD, AF, LVEF, hyperkalemia, hyponatremia, eGFR class, hypoalbuminemia, hyperuricemia, NT-proBNP, hs-cTnT, β-blocker, Diuretic or MRA, SGLT2i, Digoxin, and ACEI/ARB/ARNI. HRR, hemoglobin-to-red cell distribution width ratio; RCS, restricted cubic spline; NYHA, New York Heart Association; CHD, coronary heart disease; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Hs-cTnT, high-sensitive cardiac troponin; NLR, neutrophil-to-lymphocyte ratio; SI, sarcopenia index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin (II) receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; β-blocker, β-receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitors

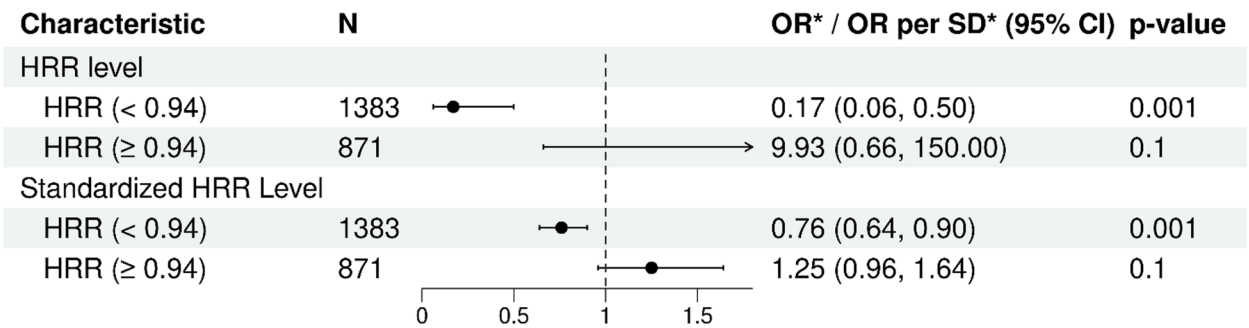

Fig. 3 HRR was split into two groups based on the inflection point, followed by a thorough segmented logistic regression analysis. OR, Odds Ratio; CI, Confidence Interval; HRR, hemoglobin-to-red cell distribution width ratio; RCS, restricted cubic spline; NYHA, New York Heart Association; CHD, coronary heart disease; AF, atrial fibrillation; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Hs-cTnT, high-sensitive cardiac troponin; NLR, neutrophil-to-lymphocyte ratio; SI, sarcopenia index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin (II) receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitors; β-blocker, β-receptor blocker; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter-2 inhibitors. * adjusted for age, sex, NYHA class, smoking, hypertension, diabetes, CHD, AF, LVEF, hyperkalemia, hyponatremia, eGFR class, hypoalbuminemia, hyperuricemia, NT-proBNP, hs-cTnT, β-blocker, diuretic or MRA, SGLT2i, digoxin, and ACEI/ARB/ARNI

among populations with gram-negative bacteremia or HF [34, 35]. The findings of this study support the notion that the NLR does not exhibit a significant correlation with all-cause short-term readmission rates, which is consistent with previous research in this area.

As the HRR is based on the Hb-to-RDW ratio, a decrease in Hb level or an increase in RDW can result in a reduction in HRR. The Hb level serves as a crucial marker for gauging the severity of HF and predicting its prognosis. Low Hb levels are frequently observed in patients with HF and are typically linked to a decline in the overall clinical condition and a negative prognosis [36]. Meanwhile, RDW may serve as a comprehensive indicator of various pathological mechanisms

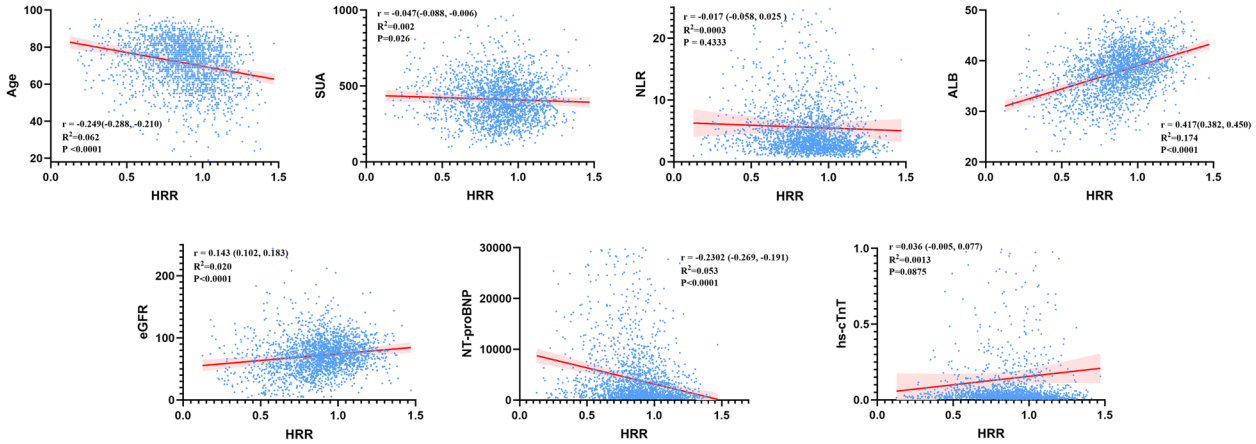

Fig. 4 Pearson correlation analysis was utilized to assess the relationship between HRR and variables such as age, SUA, NLR, ALB, eGFR, NT-proBNP, and hs-cTnT. HRR, hemoglobin-to-red cell distribution width ratio; eGFR, estimated glomerular filtration rate; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Hs-cTnT, high-sensitive cardiac troponin; NLR, neutrophil-to-lymphocyte ratio; SUA, serum uric acid; ALB, blood albumin

Table 3 Mediation analysis for the associations between HRR and 30-day readmission

Mediator	Indirect effect		Direct effect		Proportion mediated, % (95% CI)
	Coefficient (95% CI)	*P* value	Coefficient (95% CI)	*P* value	
Sex	0.01259 (−0.00017, 0.02822)	0.056	−0.12634 (−0.21555, −0.05071)	< 0.001	−10.9 (−36.1, 0.2)
Age	0.00185 (−0.01509, 0.01836)	0.808	−0.11705 (−0.21141, −0.04059)	0.004	−1.9 (−21.4, 14.5)
eGFR	−0.00473 (−0.01273, 0.00382)	0.236	−0.11031 (−0.20408, −0.03551)	0.004	4.1 (−3.0, 15.3)
Scr	−0.00145 (−0.01200, 0.00761)	0.780	−0.11365 (−0.20436, −0.03913)	0.004	1.1 (−8.4, 13.1)
SUA	−0.00052 (−0.00389, 0.00213)	0.732	−0.11381 (−0.20418, −0.03916)	0.004	0.3 (−2.3, 4.1)
ALB	−0.01083 (−0.03862, 0.02076)	0.460	−0.10391 (−0.20558, −0.02453)	0.008	10.2 (−19.8, 47.3)
NLR	−0.00016 (−0.00228, 0.00181)	0.880	−0.11474 (−0.20326, −0.03956)	< 0.001	0.1 (−1.5, 2.4)
NT-proBNP	−0.01524 (−0.02797, −0.00502)	**0.004**	−0.09841 (−0.18590, −0.02531)	**0.004**	**13.6 (4.2, 39.9)**
hs-cTnT	0.00027 (−0.00316, 0.00477)	0.868	−0.11479 (−0.20478, −0.03929)	< 0.001	−0.1 (−4.4, 3.6)

The mediation analyses were adjusted for LVEF, smoking, hypertension, diabetes, NYHA class, CHD, AF, β-blocker, diuretic or MRA, SGLT2i, digoxin, and ACEI/ARB/ARNI

HRR hemoglobin-to-red cell distribution width ratio, *NYHA* New York Heart Association, *CHD* coronary heart disease, *AF* atrial fibrillation, *LVEF* left ventricular ejection fraction, *SUA* serum uric acid, *ALB* blood albumin, *eGFR* estimated glomerular filtration rate, *NT-proBNP* N-terminal pro-B-type natriuretic peptide, *Hs-cTnT* high-sensitive cardiac troponin, *NLR* neutrophil-to-lymphocyte ratio, *ACEI* angiotensin-converting enzyme inhibitors, *ARB* angiotensin (II) receptor blockers, *ARNI* angiotensin receptor-neprilysin inhibitors, *β-blocker* β-receptor blocker, *MRA* mineralocorticoid receptor antagonist, *SGLT2i* sodium-glucose cotransporter-2 inhibitors

in HF, including nutritional deficiency, renal dysfunction, hepatic congestion, and inflammatory stress, all of which contribute to its association with patient outcomes [37]. Higher RDW in patients with acute HF is linked to worse long-term outcomes, regardless of Hb levels or anemia status [38]. Similarly, a lower HRR is associated with increased mortality risk in both acute decompensated HF and AF, highlighting its potential as a prognostic marker for adverse clinical outcomes [39, 40]. After adjusting for potential influencing variables in this study, it was determined that HRR is notably linked to the all-cause short-term readmission rate among patients with HF, which is roughly consistent with previous research findings.

Additionally, a retrospective cohort study detected a non-linear relationship between the HRR and HF 3-month readmission in elderly Chinese patients with two inflection points [9]. Xie et al. [41] reported a non-linear relationship in patients with acute ischemic stroke, where HRR below a certain threshold was associated with worse 3-month outcomes, whereas higher HRR values showed no significant correlation with prognosis. Our study identified a non-linear association between HRR and 30-d readmission in patients with HF, with an inflection point at 0.94. Specifically, HRR values < 0.94 were significantly associated with higher short-term readmission rates, while values above this threshold showed no further decrease in risk. These findings indicate that HRR

may serve as a practical, rapid, and effective marker for short-term prognosis in HF, which outperforms SI and NLR in this regard. Notably, the observed saturation effect suggests that improving HRR beyond 0.94 may not yield additional benefits for short-term readmission outcomes. While promising, these results warrant further investigation to confirm the clinical utility of HRR in managing HF prognosis.

This study represents an initial examination of the mediating factors of the HRR that affect all-cause short-term readmission rates. Our findings suggest that variables such as sex, age, SUA level, NLR, ALB level, eGFR, and hs-cTnT level did not play a role in this relationship. Only the baseline NT-proBNP level emerged as a significant mediating factor. However, its mediation only accounted for 13.6% of the overall effect. The potential mechanism underlying this association may involve elevated plasma volume, increased Endothelin-1, or neurohumoral and endocrine activation, which could influence NT-proBNP concentrations [42–44]. However, further studies are warranted to investigate this possibility.

Our study had several limitations. First, as a single-center retrospective study, it could not establish definitive causality and may be subject to selection bias. Second, although the initial dataset included 6,204 screened patients, a significant proportion were excluded owing to loss of follow-up or incomplete registries, which may limit the generalizability of the findings. Additionally, while the random forest model imputation was applied to input missing data for cases with up to 20% missing, residual bias is possible. Third, the low incidence of all-cause 30-d readmission, despite the relatively large sample size, may have resulted in an underpowered analysis. Fourth, the lack of repeated HRR measurements during hospitalization restricted our ability to assess its dynamic changes and their potential impact on outcomes. Fifth, several important clinical factors were not accounted for in this study, such as body mass index (BMI) or body weight (BW), which have introduced bias, particularly in the interpretation of the relationship between muscle mass and outcomes [45]. Future studies should consider standardizing SI by BW (SI/BW) or SI by BMI (SI/BMI) to further investigate their impact on the adverse prognosis of patients with HF. Fifth, the causative diseases of HF (e.g., valvular heart disease, dilated cardiomyopathy) were not stratified, which could affect the generalizability of our findings across different HF etiologies. Sixth, guideline-directed medical therapy (GDMT) usage in this cohort was relatively low, which may have influenced the prognosis and biomarker dynamics, including NT-proBNP levels. Seventh, post-discharge medication titration and adherence data were unavailable, which limited the evaluation of the impact of treatment optimization on short-term readmission. Eighth, this study focused exclusively on Chinese patients, thus necessitating further validation in diverse ethnic populations to confirm the broader applicability of these findings.

Conclusions

Our findings demonstrate that the HRR is significantly and independently associated with all-cause 30-d readmission in patients with HF, whereas the SI and NLR did not show a significant association. Notably, a threshold-driven relationship was observed, with HRR < 0.94 independently linked to an elevated all-cause readmission risk, while no significant association was found above this threshold. Additionally, our mediation analysis provided novel mechanistic insights, thus revealing that NT-proBNP partially mediated the HRR–readmission relationship. These findings highlight HRR as an accessible, clinically actionable biomarker for short-term readmission risk stratification in HF, highlighting the need for etiology-specific and longitudinal validation of its nonlinear prognostic utility.

Abbreviations

AF	Atrial fibrillation
ALB	Albumin
CBC	Complete blood count
CHD	Coronary heart disease
CysC	Cystatin C
eGFR	Estimated glomerular filtration rate
Hb	Hemoglobin
HF	Heart failure
HRR	Hemoglobin-to-red cell distribution width ratio
hs-cTnT	High-sensitivity cardiac troponin
LVEF	Left ventricular ejection fraction
NLR	Neutrophil-to-lymphocyte ratio
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
RCS	Restricted cubic spline
RDW	Red cell distribution width
RDW-CV	Red cell distribution width coefficient of variation
Scr	Serum creatinine
SI	Sarcopenia index
SUA	Serum uric acid
VIF	Variance inflation factor

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Authors' contributions

HZK: Formal analysis, Roles/Writing—original draft; ZCZ: Funding acquisition, Formal analysis, Supervision; CMH, CT, HF,and ZZL: Investigation, Data

Curation; HY: Methodology, Project administration; LM: Funding acquisition, Conceptualization, Writing—Review & Editing. All the authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Review Committee of the Affiliated Hospital of Guangdong Medical University (Approval Number: PJKT2023-062), and the requirement for written informed consent was waived due to the retrospective nature of this study design.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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