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Independent effects of the hemoglobin-to-red blood cell distribution width ratio on 180-day mortality in critically ill patients with Gastrointestinal bleeding: analysis from the MIMIC-IV database

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Abstract

Background Gastrointestinal bleeding (GIB) is associated with high mortality rates among critically ill patients. The hemoglobin-to-red blood cell distribution width ratio (HRR) has recently emerged as a potential prognostic marker in various clinical settings. However, the association between HRR and prognosis in critically ill patients with GIB is unclear.

Methods We conducted a retrospective cohort study using the MIMIC-IV database (version 2.2). Patients diagnosed with GIB were included based on predefined criteria. The HRR was calculated as the ratio of hemoglobin to red blood cell distribution width. Kaplan-Meier curves and multivariate Cox regression models assessed the association between HRR and 180-day mortality. Restricted cubic spline curves were employed to evaluate the nonlinear relationship between HRR and mortality. Additionally, a segmented regression model was constructed to determine the threshold effect in nonlinearity. Subgroup analyses were performed to assess the consistency of the relationship between HRR and 180-day mortality across different patient populations.

Results A total of 2,346 patients met the inclusion criteria. Higher HRR was independently associated with reduced 180-day all-cause mortality (adjusted HR, 0.15; 95% CI, 0.07–0.31; $P < 0.001$). Non-linear associations were observed using restricted cubic splines (P for overall < 0.001, P for non-linearity = 0.002). When HRR was less than 0.81, each unit increase in HRR was associated with a 90% reduction in 180-day mortality among patients with GIB (HR, 0.10; 95% CI, 0.04–0.24; $P < 0.001$). Subgroup analyses demonstrated that the association between HRR and 180-day mortality was consistent across all subgroups.

Conclusion HRR exhibits a significant nonlinear negative association with 180-day mortality in critically ill patients with GIB. This association was consistent across multiple subgroups, suggesting that HRR may serve as a simple and effective prognostic biomarker in patients with GIB.

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Keywords HRR, Gastrointestinal bleeding, All-cause mortality, Intensive care unit

Introduction

Gastrointestinal bleeding (GIB) is a critical medical emergency associated with significant morbidity and mortality, posing a substantial challenge to public health [1, 2]. Clinically, GIB manifests as hematemesis (vomiting of blood), melena (black stools), or occult blood in the stool. Internally, it results in blood loss, which may lead to hemodynamic instability or symptomatic anemia, both of which can be life-threatening [3]. Effective management of GIB relies on rapid diagnosis and accurate risk stratification to optimize patient outcomes [1, 4]. Studies have shown that the emergency mortality rate for GIB can be as high as 10% [5]. Given this high mortality rate, it is essential to pay closer attention to the prevention and management of GIB in patients admitted to the intensive care unit (ICU) [6].

The primary etiologies of gastrointestinal bleeding (GIB) include inflammation, esophagitis, esophagogastric varices, erosive gastritis, peptic ulcer disease, and colitis [4]. Additionally, previous studies have demonstrated significant associations between inflammatory markers and the development and prognosis of GIB. These markers include interleukin levels, C-reactive protein (CRP), and the neutrophil-to-lymphocyte ratio (NLR) [7–11].

The hemoglobin-to-red cell distribution width ratio (HRR) is an emerging biomarker of chronic inflammation, calculated by dividing the level of hemoglobin (Hb) by the red cell distribution width (RDW), this ratio reflects erythrocyte heterogeneity and may predict underlying inflammatory processes [12]. Previous studies have shown that HRR is associated with poor prognosis in a range of diseases, including cardiovascular disease, certain types of cancer, kidney injury, and depression [13–16]. However, the relationship between HRR and prognosis in critically ill patients with GIB remains understudied.

This study aims to investigate the association between the HRR and the 180-day mortality rate in critically ill patients with GIB. Our research has the potential to transform clinical practice by offering a simple blood test to predict long-term outcomes in patients with GIB.

Method

Data source

This study employed a retrospective cohort analysis utilizing the MIMIC-IV database (version 2.2), which encompasses clinical data of patients admitted to the ICU at Beth Israel Deaconess Medical Center (BIDMC) from 2008 to 2019. The database has been duly approved by the Institutional Review Boards of both the Massachusetts Institute of Technology and BIDMC. One of the authors, Yanling Xiao, has completed the requisite training examination (Certification Number: 13454932) and was responsible for the extraction of the data utilized in this research.

In the present study, the selection of research subjects was based on the following inclusion and exclusion criteria. The inclusion criteria were as follows: (1) Patients diagnosed with GIB, patients were included if they had an admission diagnosis containing the terms "gastro", "bleed", "melena", and "hematochezia" [17], International Classification of Diseases (ICD) 9/10 codes for GIB patients are in Supplementary Table 1; (2) Patients aged over 18 years. The exclusion criteria included: (1) Patients admitted to the ICU for less than one day; (2) Patients lacking HRR information; (3) Patients who were not first-time ICU admissions. Based on these criteria, our study considered 2,346 patients diagnosed with GIB. The detailed screening process is depicted in Fig. 1.

Data extraction

Based on previously published literature and our clinical experience, we selected a range of variables encompassing demographic characteristics, vital signs, laboratory tests, and medical history [18, 19]. Demographic information included age, gender, and body weight. Laboratory tests comprised white blood cell (WBC), red blood cell (RBC), platelet, HB, RDW, anion gap (AG), calcium, potassium, sodium, chloride, glucose, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), creatinine, and blood urea nitrogen (BUN). Disease severity scores such as the Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score (APS) III, Simplified Acute Physiology Score (SAPS) II, Oxford Acute Severity of Illness Score (OASIS), Glasgow Coma Scale (GCS) were also included. Vital sign data included heart rate, oxygen saturation (SpO_2), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), respiratory rate, and temperature. The presence of hypertension, type 2 diabetes mellitus (T2DM), heart failure, myocardial infarction, chronic kidney disease (CKD), hyperlipidemia, and whether enteral nutritional support was provided was also accounted for. We removed variables with missing values above 20% and applied the random forest method to interpolate variables with missing values below 20%.

Exposure variable and outcome event

HRR, which served as the primary variable in this study, was calculated using the following formula [12]:

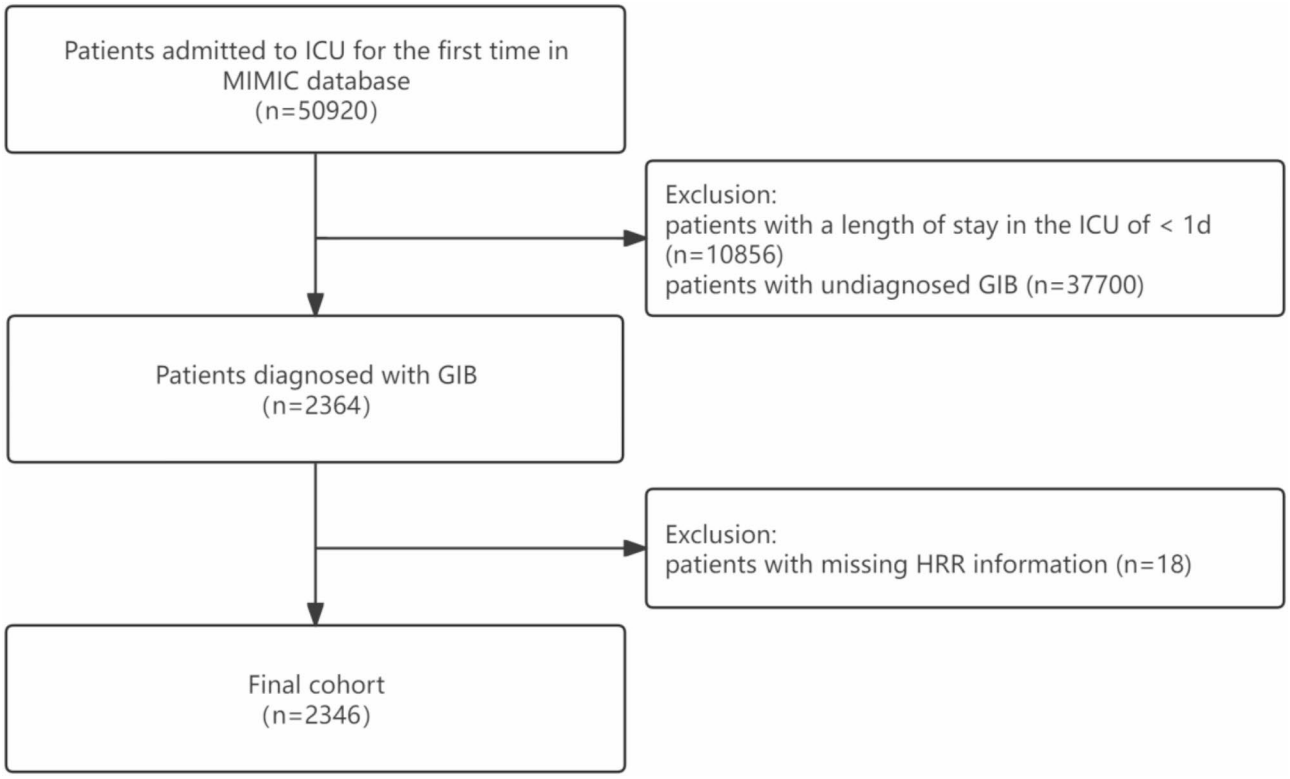

Fig. 1 Flowchart of participant screening in this study

$$\mathrm{HRR} = \frac{\mathrm{HB\ (g/L)}}{\mathrm{RDW}\ \left(10^9\right)}$$

The primary outcome was all-cause mortality at 180 days. 180 days is a reasonable observation window to cover the complete course of acute GIB patients from admission to long-term prognosis, and this time point is also a commonly used endpoint in the MIMIC-IV database [20, 21].

To ensure that the patients included met the criteria for critical illness, we restricted our cohort to patients admitted to the ICU. Additionally, we recorded disease severity scores for each patient to further assess the severity of their illness.

Statistical analysis

Continuous variables are presented as mean ± standard deviation. Categorical variables are expressed as frequencies and percentages. Continuous variables were assessed for differences across HRR quartiles using one-way analysis of variance (ANOVA), and the independent samples t-test was utilized to detect differences between participants who did and did not die within 180 days. Categorical variables were analyzed using the chi-square test.

The study population was stratified into four groups based on HRR quartiles ($Q1 \le 0.49$, $0.49 < Q2 \le 0.58$, $0.58 < Q3 \le 0.70$, and $Q4 > 0.70$), and the association between different levels of HRR and 180-day mortality in critically ill patients with GIB was compared using Kaplan-Meier curves. Additionally, multivariate Cox proportional hazards regression models were constructed in three different models: Model 1 (unadjusted), Model 2 (adjusted only for age, gender, weight, WBC, RBC, and platelet), and Model 3 (adjusted for age, gender, weight, WBC, RBC, platelet, sodium, potassium, chloride, calcium, glucose, PTT, INR, BUN, creatinine, hypertension, T2DM, heart failure, CKD, hyperlipidemia, myocardial infarction, OASIS, GCS, heart rate, DBP, MBP, respiratory rate, temperature, $SpO_{2,}$ and enteral nutrition) to explore the relationship between HRR and 180-day mortality in GIB patients. In addition, we used restricted cubic spline (RCS) to visualize the potentially non-linear relationship between HRR and 180-day mortality, we set up 4 nodes placed at the 10th percentile, 30th percentile, 70th percentile, and 90th percentile of the data. Subsequently, a threshold effects model was developed to analyze the inflection point of HRR. Finally, subgroup analysis and interaction tests were conducted among populations with different clinical characteristics.

All statistical analyses in this study were computed using R software (version 4.2.2), and a two-tailed P-value of less than 0.05 was considered statistically significant.

Results

Participant baseline characteristics

Table 1 presents the characteristics and outcomes of the 2,346 critically ill GIB participants categorized by HRR quartiles. The study found significant differences in age, weight, RBC, platelet, hemoglobin, RDW, sodium, potassium, calcium, chloride, AG, PT, PTT, INR, BUN, creatinine, some disease severity scores, DBP, MBP, SpO_2, some comorbidities, and mortality between HRR quartiles.

Supplementary Table 2 lists the baseline characteristics of survivors and non-survivors within the 2,346 GIB patient cohort at 180 days. The study revealed significant differences in various parameters between these two groups. Non-survivors were older, and had higher WBC, RDW, lower levels of RBC, platelets, hemoglobin, HRR, sodium, potassium, calcium, and chloride, compared to survivors. Non-survivors also had higher blood glucose, AG, PT, PTT, INR, BUN, creatinine, SOFA, APS III, SAPS II, OASIS, and GCS levels. In addition, non-survivors had higher heart and respiratory rates, lower MBP, body temperature, and SpO_2. Non-survivors were more likely to have heart failure, myocardial infarction, and receive enteral nutrition.

Association between HRR and 180-day mortality in GIB patients

We conducted a Kaplan-Meier curve analysis to investigate the association between HRR quartiles and all-cause mortality at 180 days (Fig. 2). The results demonstrated significant differences in survival curves among groups with different HRR quartiles, with patients in the lower HRR quartiles exhibiting a higher risk of death compared to those in the higher HRR quartiles (log-rank $P < 0.05$).

Table 2 presents the results of a multivariate Cox regression analysis examining the relationship between HRR and all-cause mortality at 180 days in critically ill patients with GIB. Model 1 showed that HRR was significantly associated with a reduced risk of death (HR = 0.19, 95% CI: 0.12–0.30). In Model 3, a higher HRR was independently associated with a reduced risk of death in GIB critically ill patients, even after accounting for various confounding factors (HR = 0.15, 95% CI: 0.07–0.31). In addition, when HRR was divided into quartiles, participants' HRR remained independently negatively correlated with 180-day mortality in Q4 compared to Q1 (adjusted HR = 0.50, 95% CI: 0.37–0.67).

Dose-response

The association between HRR and all-cause mortality at 180 days was characterized using RCS analysis (Fig. 3). The results revealed a significant non-linear relationship between the two, with an overall P-value of less than 0.001 (P for non-linear = 0.002). Given the reliability of this nonlinear relationship, we performed a threshold effect analysis, and the results are shown in Table 3. The 180-day mortality risk thresholds were 0.81. below the altered threshold, the risk of death decreased significantly with increasing HRR.

Subgroup analysis

In the subgroup analysis examining the relationship between HRR and all-cause mortality at 180 days, we investigated the impact of various characteristics, including age, gender, hypertension, T2DM, heart failure, myocardial infarction, and enteral nutrition (Fig. 4). The results suggest that the association between HRR and 180-day mortality remains meaningful in most subgroups.

Discussion

This is the first study to examine the relationship between HRR and mortality in critically ill patients with GIB. Our findings indicate that a higher HRR is independently associated with lower 180-day mortality. Further analysis using RCS revealed a significant non-linear association between HRR and 180-day mortality. Additionally, we explored the HRR inflection point using threshold analysis of continuous variables.

The HRR has increasingly been recognized as a valuable prognostic indicator across various severe diseases, offering a deeper understanding of inflammation and disease severity [22]. For instance, in a study by Yildiz et al., HRR was examined in the context of hemodynamically significant patent ductus arteriosus (hsPDA) among preterm infants. The study demonstrated that a lower HRR was significantly associated with hsPDA, exhibiting high sensitivity and specificity for this condition [23]. Similarly, a cross-sectional study by Xi et al. explored the relationship between HRR and depression in the elderly. The results indicated that HRR is a superior predictor of depression compared to hemoglobin or RDW alone, with lower HRR values correlating with a higher prevalence of depression [14]. Additionally, Zhu et al. showed in a study of community-dwelling elderly individuals that lower HRR was independently associated with frailty [24]. Within the digestive system, Yu et al. assessed the association between HRR and 30-day mortality in 177 patients with hepatitis B virus (HBV)-related decompensated cirrhosis. They found that a lower HRR may serve as an effective predictor of poor prognosis in this population [25]. These findings are consistent with our results, which link lower HRR to increased all-cause mortality at 180 days in critically ill patients with GIB.

Although our study did not further explore the potential mechanisms underlying the association between HRR and mortality in critically ill patients with GIB, previous literature suggests several plausible explanations. First, HRR is considered a marker of inflammation, which is a

Table 1 Characteristics and outcomes of participants categorized by HRR quartiles

Characteristics	Total (*n* = 2,346)	Q1 (*n* = 587)	Q2 (*n* = 586)	Q3 (*n* = 586)	Q4 (*n* = 587)	*P*
Age, years	67.29 ± 16.00	66.48 ± 15.02	68.38 ± 15.60	68.49 ± 15.33	65.83 ± 17.78	0.006
Gender, n (%)						0.056
female	1442 (61.47)	376 (64.05)	333 (56.83)	364 (62.12)	369 (62.86)	
male	904 (38.53)	211 (35.95)	253 (43.17)	222 (37.88)	218 (37.14)	
Weight, Kg	80.82 ± 21.93	82.61 ± 22.28	79.10 ± 21.66	81.29 ± 23.44	80.28 ± 20.12	0.043
WBC, K/μL	11.94 ± 10.07	11.70 ± 8.61	11.97 ± 10.44	12.40 ± 13.76	11.69 ± 5.80	0.594
RBC, m/μL	3.19 ± 0.62	2.67 ± 0.42	2.97 ± 0.43	3.25 ± 0.36	3.86 ± 0.55	< 0.001
Platelet, K/μL	180.40 ± 107.59	163.72 ± 113.50	178.84 ± 109.84	188.00 ± 114.69	191.04 ± 88.37	< 0.001
Hemoglobin, g/dL	9.62 ± 1.81	7.91 ± 0.89	8.86 ± 0.92	9.83 ± 0.88	11.85 ± 1.49	< 0.001
RDW, %	16.35 ± 2.52	19.10 ± 2.52	16.67 ± 1.72	15.41 ± 1.24	14.24 ± 1.21	< 0.001
Sodium, mmol/L	139.00 ± 4.83	138.40 ± 5.57	138.88 ± 4.81	139.38 ± 4.64	139.33 ± 4.14	0.001
Potassium, mmol/L	4.20 ± 0.59	4.29 ± 0.67	4.21 ± 0.58	4.18 ± 0.56	4.13 ± 0.54	< 0.001
Calcium, mg/dL	8.14 ± 0.71	8.25 ± 0.74	8.08 ± 0.71	8.07 ± 0.66	8.17 ± 0.73	< 0.001
Chloride, mmol/L	105.22 ± 6.24	103.90 ± 7.09	105.37 ± 6.06	106.33 ± 5.91	105.30 ± 5.56	< 0.001
Glucose, mg/dL	138.41 ± 51.60	136.80 ± 49.77	137.63 ± 49.12	137.30 ± 52.61	141.89 ± 54.68	0.302
AG, mmol/L	14.67 ± 4.47	15.45 ± 5.03	14.51 ± 4.39	13.97 ± 4.02	14.75 ± 4.25	< 0.001
PT, sec	16.81 ± 6.52	18.99 ± 7.27	17.08 ± 7.29	16.32 ± 6.01	14.85 ± 4.41	< 0.001
PTT, sec	37.09 ± 16.34	39.43 ± 16.04	35.89 ± 14.10	36.27 ± 16.24	36.79 ± 18.49	< 0.001
INR	1.54 ± 0.62	1.76 ± 0.69	1.56 ± 0.69	1.48 ± 0.56	1.35 ± 0.43	< 0.001
BUN, mg/dL	36.00 ± 27.16	43.98 ± 29.71	38.12 ± 26.22	34.30 ± 27.16	27.60 ± 22.47	< 0.001
Creatinine, mg/dL	1.59 ± 1.49	1.89 ± 1.59	1.66 ± 1.61	1.45 ± 1.30	1.36 ± 1.37	< 0.001
SOFA	5.71 ± 4.17	6.97 ± 4.43	5.87 ± 4.20	5.15 ± 3.72	4.86 ± 3.99	< 0.001
APSIII	49.97 ± 21.30	55.85 ± 22.73	51.13 ± 20.34	48.12 ± 19.90	44.75 ± 20.59	< 0.001
SAPS II	38.83 ± 14.34	41.61 ± 14.71	39.43 ± 13.42	38.40 ± 14.18	35.87 ± 14.46	< 0.001
OASIS	32.24 ± 8.74	32.75 ± 8.80	32.40 ± 8.60	32.18 ± 8.48	31.63 ± 9.06	0.163
GCS	13.86 ± 2.46	13.74 ± 2.52	13.97 ± 2.19	13.94 ± 2.46	13.79 ± 2.64	0.294
Heart rate, minute	86.33 ± 15.55	86.57 ± 15.45	87.24 ± 14.86	86.27 ± 15.43	85.25 ± 16.37	0.171
SBP, mmHg	119.34 ± 112.88	113.53 ± 15.47	125.48 ± 224.09	117.53 ± 15.65	120.82 ± 17.15	0.316
DBP, mmHg	64.80 ± 78.60	60.50 ± 12.36	61.42 ± 10.40	63.25 ± 10.52	74.04 ± 155.67	0.011
MBP, mmHg	76.21 ± 10.81	73.59 ± 10.13	74.85 ± 10.37	76.32 ± 9.89	80.07 ± 11.67	< 0.001
Respiratory rate, minute	19.06 ± 3.89	18.99 ± 3.75	19.11 ± 3.58	18.76 ± 3.40	19.37 ± 4.69	0.061
Temperature, ℃	36.70 ± 1.71	36.75 ± 0.66	36.64 ± 2.40	36.68 ± 1.71	36.72 ± 1.61	0.762
SpO_2, %	97.29 ± 1.93	97.38 ± 1.61	97.50 ± 1.86	97.37 ± 1.85	96.90 ± 2.27	< 0.001
Hypertension, n (%)						< 0.001
no	1434 (61.13)	406 (69.17)	371 (63.31)	353 (60.24)	304 (51.79)	
yes	912 (38.87)	181 (30.83)	215 (36.69)	233 (39.76)	283 (48.21)	
T2DM, n (%)						< 0.001
no	1652 (70.42)	402 (68.48)	398 (67.92)	398 (67.92)	454 (77.34)	
yes	694 (29.58)	185 (31.52)	188 (32.08)	188 (32.08)	133 (22.66)	
Heart failure, n (%)						0.002
no	1717 (73.19)	402 (68.48)	421 (71.84)	436 (74.40)	458 (78.02)	
yes	629 (26.81)	185 (31.52)	165 (28.16)	150 (25.60)	129 (21.98)	
Myocardial infarction, n (%)						0.547
no	2174 (92.67)	538 (91.65)	547 (93.34)	548 (93.52)	541 (92.16)	
yes	172 (7.33)	49 (8.35)	39 (6.66)	38 (6.48)	46 (7.84)	
CKD, n (%)						< 0.001
no	1830 (78.01)	427 (72.74)	433 (73.89)	473 (80.72)	497 (84.67)	
yes	516 (21.99)	160 (27.26)	153 (26.11)	113 (19.28)	90 (15.33)	
Hyperlipidemia, n (%)						0.001
no	1628 (69.39)	442 (75.30)	410 (69.97)	394 (67.24)	382 (65.08)	
yes	718 (30.61)	145 (24.70)	176 (30.03)	192 (32.76)	205 (34.92)	
Enteral nutrition, n (%)						0.234
no	2282 (97.27)	572 (97.44)	565 (96.42)	568 (96.93)	577 (98.30)	

Table 1 (continued)

Characteristics	Total (*n* = 2,346)	Q1 (*n* = 587)	Q2 (*n* = 586)	Q3 (*n* = 586)	Q4 (*n* = 587)	*P*
yes	64 (2.73)	15 (2.56)	21 (3.58)	18 (3.07)	10 (1.70)	
Hospital-mortality, n (%)						< 0.001
no	1996 (85.08)	461 (78.53)	505 (86.18)	518 (88.40)	512 (87.22)	
yes	350 (14.92)	126 (21.47)	81 (13.82)	68 (11.60)	75 (12.78)	
ICU-mortality, n (%)						0.003
no	2114 (90.11)	507 (86.37)	540 (92.15)	539 (91.98)	528 (89.95)	
yes	232 (9.89)	80 (13.63)	46 (7.85)	47 (8.02)	59 (10.05)	
180-day mortality, n (%)						< 0.001
no	1591 (67.82)	335 (57.07)	384 (65.53)	425 (72.53)	447 (76.15)	
yes	755 (32.18)	252 (42.93)	202 (34.47)	161 (27.47)	140 (23.85)	

HRR quartiles: Q1 ≤ 0.49, 0.49 < Q2 ≤ 0.58, 0.58 < Q3 ≤ 0.70, and Q4 > 0.70

Abbreviation: HRR, hemoglobin-to-red blood cell distribution width ratio; WBC, white blood cell; RBC, red blood cell; RDW, red blood cell distribution width; AG, anion gap; PT, prothrombin time; PTT, partial thromboplastin time; INR, international normalized ratio; BUN, blood urea nitrogen; SOFA, sequential organ failure assessment; APS III, acute physiology scores III; SAPS II, simplified acute physiology; OASIS, oxford acute severity of illness score; GCS, glasgow coma scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO_2, percutaneous arterial oxygen saturation; ICU, intensive care unit; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus

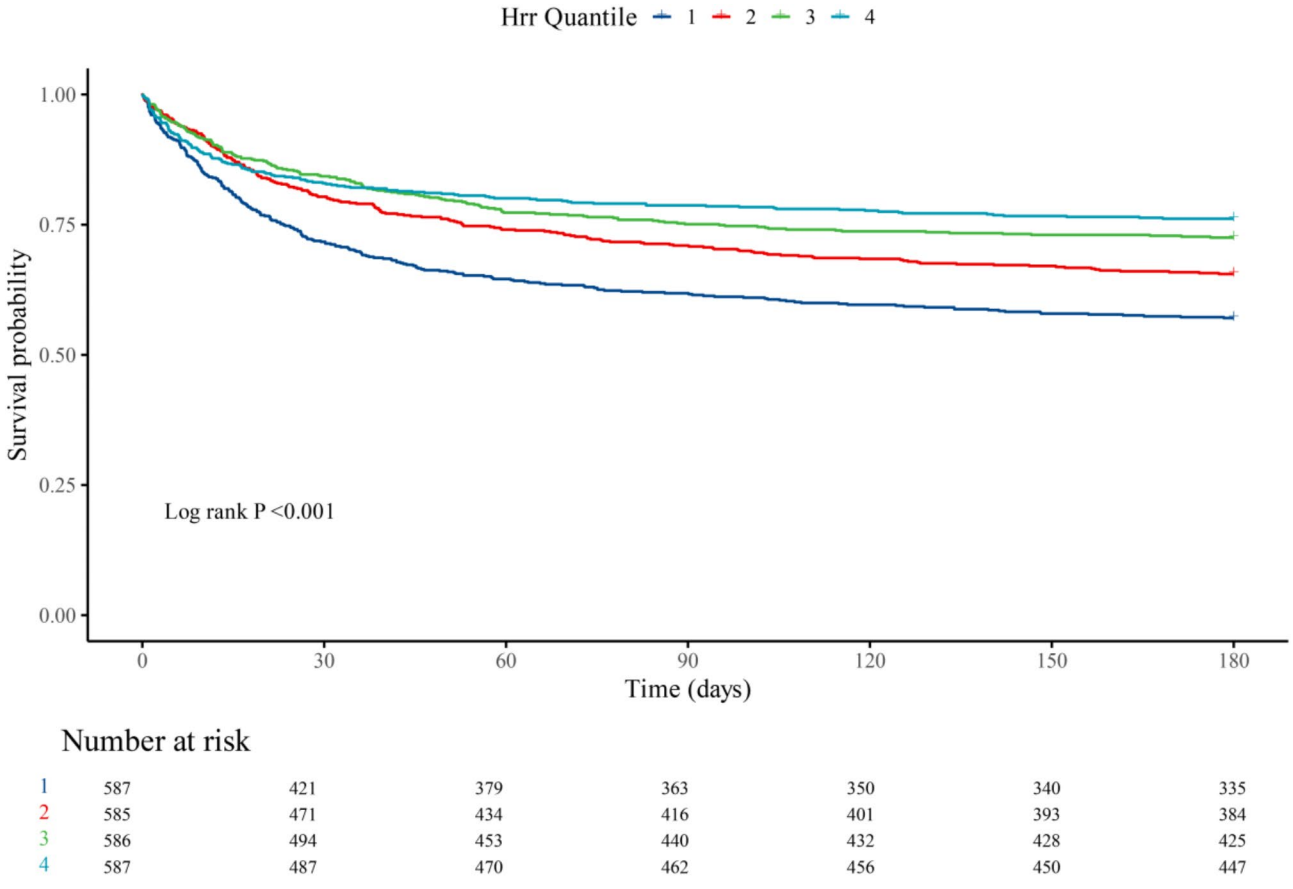

Fig. 2 Kaplan-Meier analysis for 180-day mortality. HRR, hemoglobin-to-red blood cell distribution width ratio

key factor in the development and progression of many chronic diseases [26]. Inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) may affect HRR values by inhibiting RBC production and promoting the release of immature RBCs, thereby increasing RDW [27, 28]. Second, HRR is closely related to the production and function of red blood cells. Anemia, particularly inflammatory anemia caused by chronic diseases, is characterized by low hemoglobin levels, which can lead to tissue hypoxia and subsequently impair the function of vital organs and overall health [29, 30]. Lastly, HRR is associated with the risk of cardiovascular diseases, which are among the main causes of all-cause mortality. Abnormalities in HRR may reflect the

Table 2 Association between HRR and 180-day all-cause mortality of critically ill patients with GIB

	Model 1		Model 2		Model 3	
	HR (95% CI)	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
HRR	0.19 (0.12–0.30)	< 0.001	0.10(0.05–0.19)	< 0.001	0.15 (0.07–0.31)	< 0.001
HRR quartiles						
Q1	1.00		1.00		1.00	
Q2	0.74 (0.61–0.89)	0.001	0.69 (0.57–0.84)	< 0.001	0.79 (0.65–0.97)	0.022
Q3	0.57 (0.47–0.70)	< 0.001	0.50 (0.40–0.62)	< 0.001	0.63 (0.50–0.79)	< 0.001
Q4	0.50 (0.40–0.61)	< 0.001	0.43 (0.32–0.56)	< 0.001	0.50 (0.37–0.67)	< 0.001

Model 1: no adjusted;

Model 2: adjusted for age, gender, weight, WBC, RBC, and platelet;

Model 3: adjusted for age, gender, weight, WBC, RBC, platelet, sodium, potassium, chloride, calcium, glucose, PTT, INR, BUN, creatinine, hypertension, T2DM, heart failure, CKD, hyperlipidemia, myocardial infarction, OASIS, GCS, heart rate, DBP, MBP, respiratory rate, temperature, SpO_2, and enteral nutrition

Abbreviation: WBC, white blood cell; RBC, red blood cell; RDW, red blood cell distribution width; AG, anion gap; PTT, partial thromboplastin time; INR, international normalized ratio; OASIS, oxford acute severity of illness score; GCS, glasgow coma scale; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO_2, percutaneous arterial oxygen saturation; CKD, chronic kidney disease; T2DM, type 2 diabetes mellitus; HR, hazard ratio; CI, confidence interval

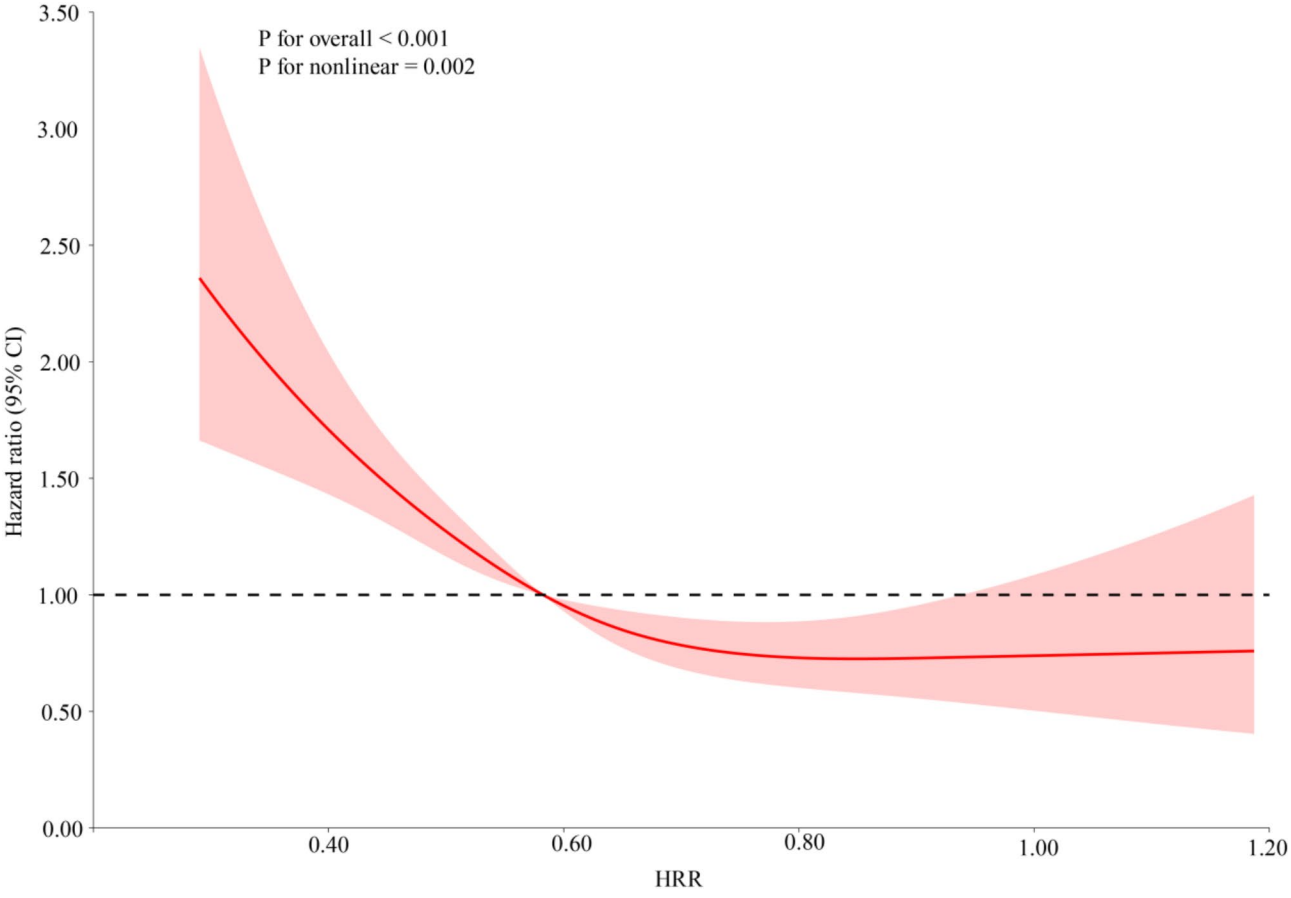

Fig. 3 RCS plot for 180-day mortality. HRR, hemoglobin-to-red blood cell distribution width ratio

progression of endothelial dysfunction and atherosclerosis, both of which are key factors in the development of cardiovascular diseases [31, 32].

In the present study, although we explored the relationship between HRR and all-cause mortality in patients with GIB. However, due to the limitations of the MIMIC-IV database, we were unable to distinguish the specific cause of death (e.g., whether the death was a direct result of GIB or other causes). This limitation may have important implications for the interpretation of the

Table 3 Two-piecewise Cox proportional hazards model

	HR (95% CI)	*P*
Model 1 Fitting model by standard linear regression	0.15 (0.07–0.31)	< 0.001
Model 2 Fitting model by two-piecewise linear regression		
Inflection point (0.81)		
< 0.81	0.10 (0.04–0.24)	< 0.001
≥ 0.81	0.08 (0.00-1.79)	0.113
P for likelihood test		< 0.001

study results, as other causes of death (e.g., cardiovascular disease, infection, or multiple organ failure) may be independently associated with HRR. Therefore, we have to recognize that the results of this study may be influenced by confounding effects. For example, cardiovascular disease is a common cause of death among ICU patients, and HRR may be associated with an increased risk of cardiovascular disease [33–35]. Thus, the association between HRR and 180-day mortality may be partially attributable to cardiovascular disease or other non-GIB-related causes of death. To better understand the prognostic value of HRR in patients with GIB, future studies could further validate the role of HRR through a prospective design and a more detailed categorization of the causes of death (e.g., distinguishing between deaths directly attributable to GIB and deaths from other causes). This would help to more accurately assess the

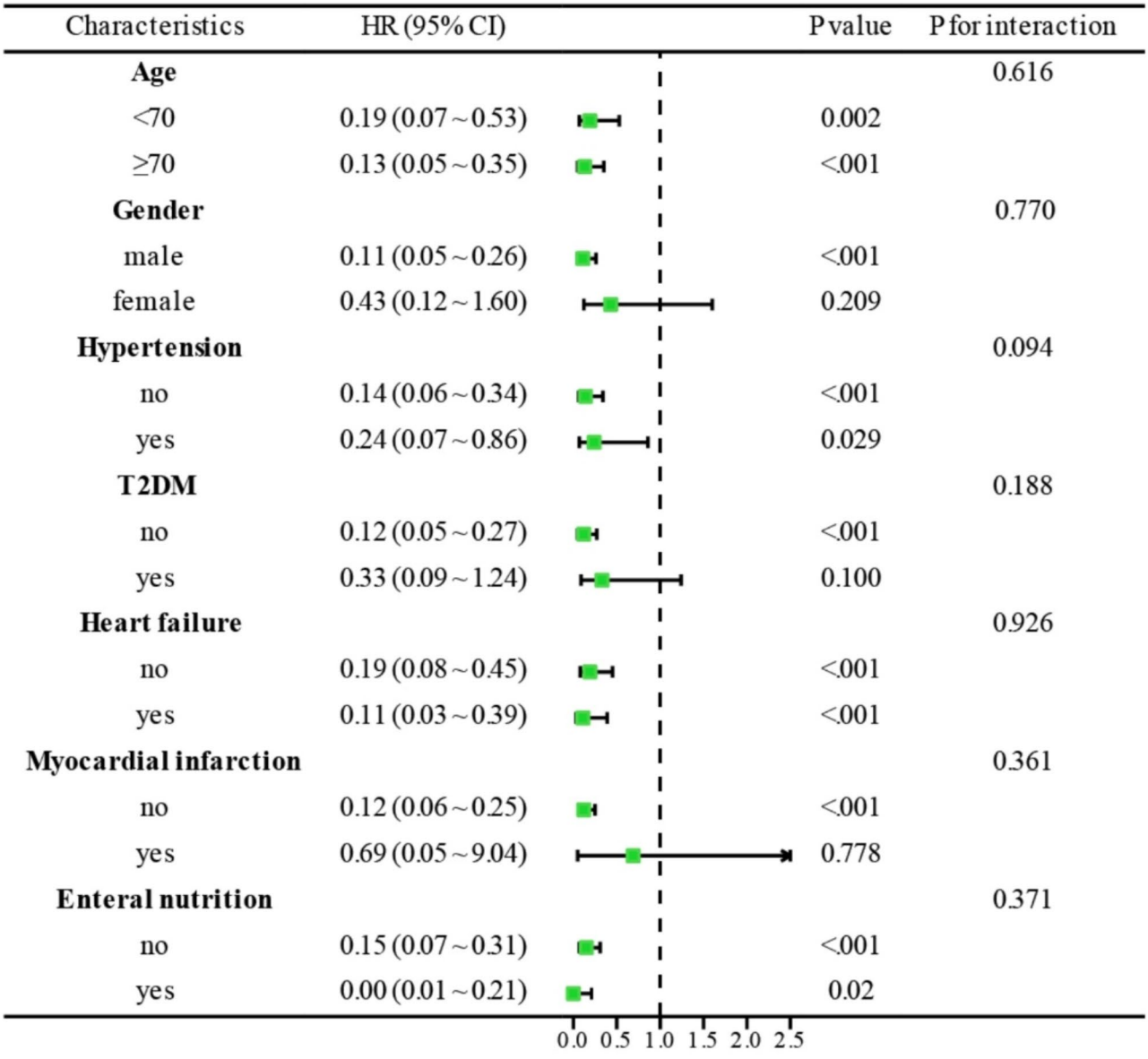

Fig. 4 Subgroup analysis for 180-day mortality

independent prognostic value of HRR in patients with GIB.

Despite leveraging a substantial number of subjects from the MIMIC database, our study is not without limitations. First, the retrospective nature of the study design introduces potential biases, including selection bias and information bias. For example, our inclusion criteria required complete HRR data, which may introduce selection bias and affect the interpretation of results. Sources of information bias include the possibility of incomplete recording of clinical data (e.g., laboratory test results, vital signs, etc.) and the fact that the diagnosis of GIB relies on clinician judgment and ICD code recording, which can be subjective. Second, our analysis is based on a single-center dataset from the Beth Israel Deaconess Medical Center. This limitation may restrict the generalizability of our findings to other populations or healthcare settings. Third, although we adjusted for multiple potential confounders in our analysis, the possibility of unmeasured or residual confounders remains. For example, we were unable to account for C-reactive protein (CRP) levels, which may influence the relationship between HRR and mortality. Future research should consider a prospective, multicenter design to enhance the robustness and generalizability of the findings. Additionally, further investigation into the potential mechanisms linking HRR and mortality is warranted.

Conclusion

This study demonstrates that the HRR is an effective indicator for predicting short-term mortality in critically ill patients with GIB. After adjusting for significant confounding factors, the relationship between HRR and 180-day all-cause mortality was found to be non-linear.

Abbreviations

HRR	Hemoglobin-to-Red Blood Cell Distribution Width Ratio
GIB	Gastrointestinal Bleeding
ICU	Intensive Care Unit
MIMIC-IV	Medical Information Mart for Intensive Care IV
RDW	Red Blood Cell Distribution Width
Hb	Hemoglobin
CI	Confidence Interval
P	Probability or P-value
SOFA	Sequential Organ Failure Assessment
APS III	Acute Physiology Score III
SAPS II	Simplified Acute Physiology Score II
OASIS	Oxford Acute Severity of Illness Score
WBC	White Blood Cell
RBC	Red Blood Cell
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
INR	International Normalized Ratio
BUN	Blood Urea Nitrogen
AG	Anion Gap
SpO_2	Oxygen Saturation
T2DM	Type 2 Diabetes Mellitus
CKD	Chronic Kidney Disease
IL-6	Interleukin-6
TNF-α	Tumor Necrosis Factor-alpha
hsPDA	Hemodynamically Significant Patent Ductus Arteriosus
HBV	Hepatitis B Virus

Supplementary Information

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Supplementary Material 1

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Author contributions

Y.L.X. designed the study and drafted the manuscript. L.X. L. conducted the data analysis and contributed to interpreting the results. Y.L.X. and X.Y. P. were responsible for data collection and management. Y. W. provided critical revisions of the manuscript for important intellectual content. Z.W. X. contributed to the conception of the study and participated in its design and coordination. All authors read and approved the final manuscript.

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Data availability

The data for the results of this study are available from the publicly accessible MIMIC-IV database. Link: MIMIC-IV v2.0 (physionet.org).

Declarations

Ethical approval

The data used in this study were obtained from the MIMIC-IV Database, which is a publicly available, de-identified critical care database. The use of this database for research purposes has been approved by the Partners Human Research Committee.

Consent to publish

Not applicable.

Competing interests

The authors declare no competing interests.

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