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ORIGINAL ARTICLE

Hemoglobin-to-Red Cell Distribution Width Ratio is Associated with All-Cause Mortality in Critically Ill Patients with Traumatic Brain Injury

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Abstract

BACKGROUND: Hemoglobin-to-red cell distribution width ratio (HRR) has shown good prognostic value in various cancers. However, the relationship between HRR and outcomes in critically ill patients with traumatic brain injury (TBI) remains unclear. This study aimed to investigate the association between HRR and mortality among critically ill patients with TBI.

METHODS: The Medical Information Mart for Intensive Care-IV (MIMIC-IV) database was utilized to conduct this retrospective cohort study. TBI patients were divided into four quartiles according to their HRR values. The primary outcome was 30-day mortality, whereas the secondary outcomes were 60-day and 120-day mortality. Univariable and multivariable Cox proportional risk models were performed to evaluate the hazard ratio (HR) and 95% confidence interval (CI) for the relationship between HRR and mortality. Receiver operating characteristic (ROC) curves were conducted to assess the prognostic value of HRR.

RESULTS: For 30-day mortality, after adjustment for all potential covariates, the relationship remained significant with HRR treated as a continuous variable (HR, 95% CI: 0.87 [0.81, 0.92]; $p < 0.001$). In the fully adjusted model, the HR with 95% CI for the second, third, and fourth quartile groups were 0.67 (0.5, 0.9), 0.65 (0.46, 0.94), and 0.5 (0.32, 0.79), respectively, compared to the first quartile group. A similar relationship was also observed for 60-day mortality and 120-day mortality. HRR had a better predictive value than hemoglobin and red cell distribution width (RDW).

CONCLUSIONS: A lower level of HRR is significantly associated with higher all-cause mortality among critically ill patients with TBI.

Abbreviations:

HRR	- Hemoglobin-to-red cell distribution width ratio
TBI	- traumatic brain injury
MIMIC-IV	- Medical Information Mart for Intensive Care-IV
HR	- hazard ratio
CI	- confidence interval
ROC	- receiver operating characteristic
RDW	- red cell distribution width
ICU	- intensive care unit
STROBE	- Strengthening the Reporting of Observational Studies in Epidemiology
GCS	- Glasgow coma scale
ICP	- intracranial pressure
BIDMC	- Beth Israel Deaconess Medical Center
CHF	- congestive heart failure
CCI	- Charlson comorbidity index
SOFA	- sequential organ failure assessment
SAPS II	- simplified acute physiology score II
WBC	- white blood cell
INR	- international normalized ratio
PT	- prothrombin time
PTT	- partial thromboplastin time
BUN	- blood urea nitrogen
MV	- mechanical ventilation
RRT	- renal replacement therapy
RBC	- red blood cell
SD	- standard deviation
IQR	- interquartile range
AUC	- area under the curves.

INTRODUCTION

Globally, traumatic brain injury (TBI) is a severe public health and socioeconomic issue (Roozenbeek *et al.* 2013). Each year, more than 50 million people suffer a TBI worldwide, with an estimated economic cost of $400 billion (Maas *et al.* 2017). Moreover, the prevalence of TBI is increasing globally, primarily due to accidents associated with the increased use of motor vehicles, especially in middle- and low-income nations (Roozenbeek *et al.* 2013). TBI has both short- and long-term poor clinical outcomes, including death and disability. In the United States, TBI is a major cause of mortality, accounting for almost one third of all injury-related deaths (Taylor *et al.* 2017). Even though clinical management has greatly improved over the past few decades, a number of clinical problems still need to be resolved.

Risk stratification is important for effective management of TBI patients in the intensive care unit (ICU). Early identification of disease severity not only contributes to improving treatment decisions for TBI patients but also helps family members prepare for possible situations. The Glasgow coma scale (GCS) is a traditional score used to assess the severity of TBI. However, GCS is not an objective indicator since it can be influenced by various factors, including mechanical ventilation, alcohol use, and pre-existing neurological disease (Murray *et al.* 2018). Intracranial pressure (ICP) monitoring is sometimes used in the management of severe TBI patients, but its invasiveness and the complexity of the resulting patterns limit its clinical use (Schweingruber *et al.* 2022; Yang *et al.* 2022). In recent years, various studies have focused on developing prognostic biomarkers for TBI patients (Czeiter *et al.* 2020; Frankel *et al.* 2019). However, many biomarkers are not widely used in clinical work for various reasons.

Recently, some studies have focused on the association between various parameters of routine blood tests taken upon admission and outcomes in TBI patients (Dolmans *et al.* 2020; Wang *et al.* 2020). Previous studies have shown that hemoglobin-to-red cell distribution width ratio (HRR) is correlated with outcomes in various cancers (Chi *et al.* 2022; Zhai *et al.* 2021). In addition, a few studies on the relationship between HRR and the outcomes of non-neoplastic diseases have been reported (Rahamim *et al.* 2022; Yu *et al.* 2022). However, to our knowledge, the relationship between HRR and outcomes in ICU patients with TBI remains unclear. Lower hemoglobin after admission has been shown to be associated with poor outcomes among patients with TBI (Litofsky *et al.* 2016). Another study found that red cell distribution width (RDW) on admission is independently associated with mortality in TBI patients (Lorente *et al.* 2021). HRR, a parameter that incorporates hemoglobin and RDW, may be independently associated with mortality in TBI patients. Thus, we conducted a cohort study with a relatively large sample size using the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database to explore the association between HRR and mortality in critically ill patients with TBI.

MATERIAL AND METHODS

Data Source

The data for this retrospective cohort study came from the MIMIC-IV database (version 2.0), a publicly accessible database containing the clinical information on more than 76,000 ICU stays at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019. This database has been approved by the Massachusetts Institute of Technology and the BIDMC Institutional Review Board, and any researcher who has finished the "Protection of Human Subjects" program can request access to the database (Johnson *et al.* 2018). Duo Yang, one of the authors, has obtained access to the database (certification number: 48247201). This study adhered to the Declaration of Helsinki and the guidelines for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).

Study Population

The inclusion criteria for our study were adult patients (age ≥ 18 years) diagnosed with traumatic brain injury based on the ninth or tenth revision of the International Classification of Diseases code (Taylor *et al.* 2017). Patients were excluded if they had no records of key data on the first day admitted to the ICU, including hemoglobin, RDW, and GCS. Moreover, for patients

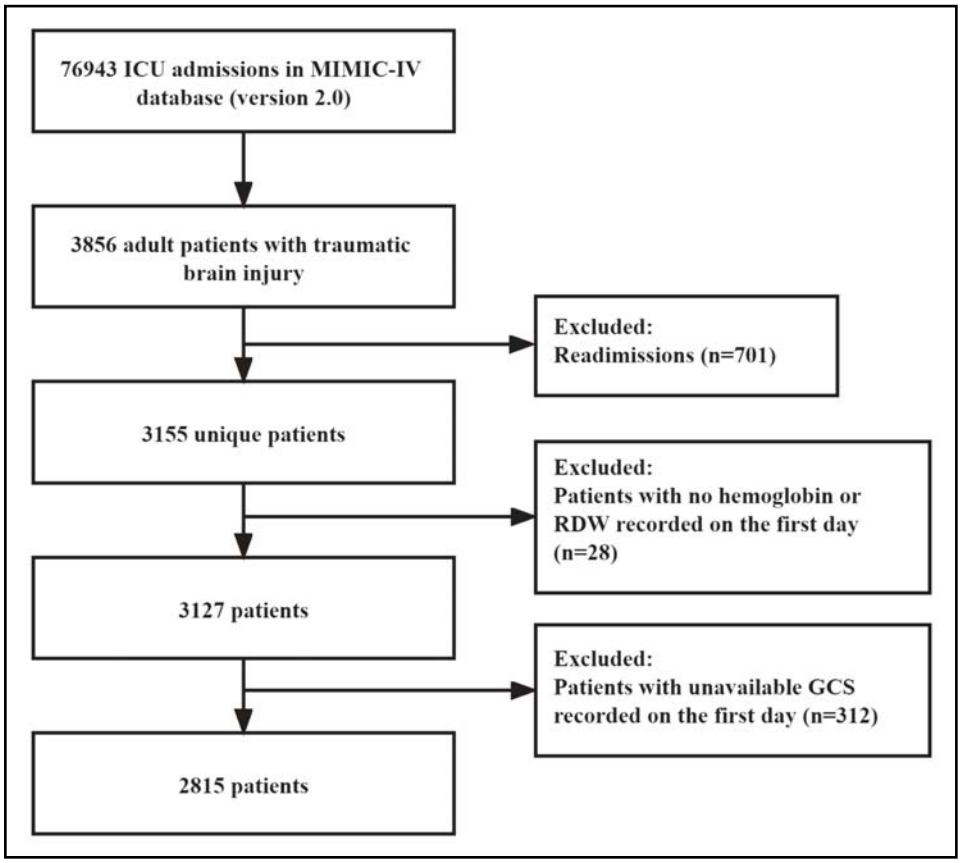

Fig. 1. Flowchart of the study cohort. Abbreviations: ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care-IV, RDW, red cell distribution width; GCS, Glasgow coma scale.

who had multiple ICU admissions, only the data of the first ICU admission were collected for the analysis.

Variable Extraction

Using the Navicat Premium 12 software and Structure Query Language, the following data were extracted from the MIMIC-IV database: (1) demographics: age, sex, race; (2) chronic comorbidity: hypertension, diabetes, congestive heart failure (CHF), cerebrovascular disease, chronic pulmonary disease, renal disease, liver disease, and malignancy; (3) severity scoring system: Charlson comorbidity index (CCI), sequential organ failure assessment (SOFA), simplified acute physiology score II (SAPS II), and GCS on the first day admitted to ICU; (4) the first value of laboratory data after ICU admission: hemoglobin, RDW, white blood cell (WBC), platelet, international normalized ratio (INR), prothrombin time (PT), partial thromboplastin time (PTT), anion gap, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine; (5) use of mechanical ventilation (MV), renal replacement therapy (RRT) and vasopressors during ICU hospitalization; (6) Neurosurgery and red blood cell (RBC) transfusion during hospitalization. Neurosurgery includes therapeutic craniotomy, ventriculostomy, and burr hole drainage. In addition, the mean hemoglobin and mean RDW on the first day admitted to the ICU were also extracted for sensitivity analysis. In this study, HRR was defined as hemoglobin (g/L) divided by RDW (%). Given the varied optimal HRR cutoff values in previous studies, the cutoff value was not specified in our study. Instead, the HRR values were divided into quartiles. The primary outcome was all-cause 30-day mortality, whereas the secondary outcomes were all-cause 60-day mortality and 120-day mortality after ICU admission.

Statistical Analysis

Patient characteristics were analyzed based on the HRR quartiles. Categorical variables were represented as numbers (percentages) and were compared using the chi-square test. Continuous variables were described as mean ± standard deviation (SD) for normal distributions or median and interquartile range (IQR) for skewed distributions. One-way analysis of variance or Kruskal–Wallis *H*-test was applied to evaluate the difference between continuous variables. Survival analysis was visualized using Kaplan–Meier curves and compared with a Log-rank test.

According to the principles of the STROBE statement, univariable and multivariable Cox proportional risk models were performed to evaluate the hazard ratio (HR) and 95% confidence interval (CI) for the relationship between HRR and mortality. For multivariable Cox analyses, covariates were chosen according to previous findings. We also adjusted for covariates that, when added to the model, changed the matched odds ratio by at least 10% (Jaddoe *et al.* 2014). In the multivariable model, we adjusted for age, sex, and race in model 1. In

Tab. 1. Baseline characteristics of the study population according to HRR

Characteristics	Total	HRR				*p*-Value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
		< 7.79	7.79 - 9.27	9.28 - 10.52	> 10.52	
N	2815	703	704	702	706	
Age (years)	62.2 ± 22.1	71.1 ± 17.8	68.1 ± 20.5	60.8 ± 21.8	48.8 ± 21.2	< 0.001
Sex (male)	1757 (62.4)	353 (50.2)	345 (49)	447 (63.7)	612 (86.7)	< 0.001
Race (White)	1822 (64.7)	487 (69.3)	461 (65.5)	472 (67.2)	402 (56.9)	< 0.001
Chronic comorbidity						
Hypertension	1174 (41.7)	310 (44.1)	340 (48.3)	309 (44)	215 (30.5)	< 0.001
Diabetes	501 (17.8)	192 (27.3)	152 (21.6)	92 (13.1)	65 (9.2)	< 0.001
CHF	297 (10.6)	156 (22.2)	88 (12.5)	39 (5.6)	14 (2)	< 0.001
Cerebrovascular disease	265 (9.4)	73 (10.4)	85 (12.1)	60 (8.5)	47 (6.7)	0.004
Chronic pulmonary disease	321 (11.4)	118 (16.8)	89 (12.6)	62 (8.8)	52 (7.4)	< 0.001
Renal disease	238 (8.5)	135 (19.2)	68 (9.7)	25 (3.6)	10 (1.4)	< 0.001
Liver disease	159 (5.6)	99 (14.1)	29 (4.1)	19 (2.7)	12 (1.7)	< 0.001
Malignancy	107 (3.8)	67 (9.5)	24 (3.4)	12 (1.7)	4 (0.6)	< 0.001
Disease severity score						
CCI	4.0 (1.0, 5.0)	5.0 (4.0, 7.0)	4.0 (3.0, 6.0)	3.0 (1.0, 5.0)	2.0 (0, 4.0)	< 0.001
SOFA	3.0 (2.0, 5.0)	4.0 (3.0, 6.0)	3.0 (2.0, 5.0)	3.0 (2.0, 4.0)	3.0 (1.0, 4.0)	< 0.001
SAPS II	31.0 ± 12.4	36.8 ± 12.3	33.5 ± 12.0	28.6 ± 11.3	24.9 ± 10.5	< 0.001
GCS	11.8 ± 3.5	11.3 ± 3.8	11.6 ± 3.5	12.2 ± 3.1	12.0 ± 3.3	< 0.001
Laboratory parameter						
Hemoglobin (g/L)	123.7 ± 21.8	96.6 ± 15.9	118.6 ± 9.0	131.7 ± 7.8	147.9 ± 9.9	< 0.001
RDW (%)	14.0 ± 1.8	15.9 ± 2.4	13.9 ± 1.0	13.3 ± 0.7	12.8 ± 0.6	< 0.001
WBC ($\times 10^9$/L)	10.8 (8.0, 14.7)	9.5 (6.7, 13.1)	10.9 (7.9, 14.6)	11.1 (8.3, 14.9)	12.1 (9.1, 16.3)	< 0.001

model 2, we further adjusted for CHF, cerebrovascular disease, renal disease, CCI, SOFA, SAPS II, GCS, WBC, PTT, BUN, creatinine, MV, RRT, vasopressors, neurosurgery, and RBC transfusion.

Curve-fitting was performed to evaluate the linear relationship between HRR and 30-day mortality of TBI patients. Subgroup analyses were conducted by age, sex, race, hypertension, diabetes, CHF, cerebrovascular disease, chronic pulmonary disease, MV, neurosurgery, and the first-day GCS (9-15, mild-moderate TBI; 3-8, severe TBI). The likelihood ratio tests were used to examine interactions between subgroups. To further assess the accuracy of the HRR in predicting mortality of TBI, receiver operating characteristic (ROC) curves were constructed. Moreover, DeLong tests were used to compare the area under the curves (AUC) between HRR and single parameters (hemoglobin and RDW).

Multiple imputation was used to account for missing data. In addition, the missing data for each variable is listed in Supplementary Table 1. Several sensitivity analyses were conducted to evaluate the robustness of our results. Multiple interpolation analyses were conducted to assess whether covariates with missing data introduced bias in our findings. Considering the possible impact of RBC transfusion on hemoglobin and RDW, we reanalyzed the association between HRR and mortality after excluding participants with RBC transfusion. In addition, the mean values of hemoglobin and RDW on the first day admitted to the ICU were also extracted to calculate HRR, and the relationship between HRR and mortality was reanalyzed.

Data analyses were conducted using the statistical software package R. version 3.4.3 (R Foundation, Vienna, Austria) and Free Statistics software version 1.7.1. Differences with a two-sided $p < 0.05$ were considered to be statistically significant.

RESULTS

Patient selection

Of 76,943 ICU admissions, 3,155 patients with TBI were identified. A flowchart of this study is presented

Characteristics	Total	HRR				*p*-Value
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
		< 7.79	7.79 - 9.27	9.28 - 10.52	> 10.52	
Platelet (×10^9/L)	220.1 ± 89.5	197.7 ± 109.3	216.6 ± 95.9	226.7 ± 73.6	239.4 ± 67.6	< 0.001
INR	1.1 (1.0, 1.2)	1.2 (1.1, 1.5)	1.1 (1.0, 1.3)	1.1 (1.0, 1.2)	1.1 (1.0, 1.1)	< 0.001
PT (s)	13.8 ± 6.6	15.6 ± 9.3	14.3 ± 7.6	13.1 ± 4.1	12.3 ± 2.7	< 0.001
PTT (s)	28.6 ± 8.9	30.2 ± 10.1	28.9 ± 11.1	27.8 ± 6.8	27.5 ± 6.3	< 0.001
Anion gap (mmol/L)	15.6 ± 3.7	15.4 ± 4.3	15.1 ± 3.5	15.6 ± 3.6	16.1 ± 3.5	< 0.001
Bicarbonate (mmol/L)	23.4 ± 3.7	23.3 ± 4.3	23.4 ± 3.7	23.6 ± 3.4	23.3 ± 3.3	0.37
Glucose (mg/dL)	137.2 ± 60.3	142.8 ± 81.1	139.6 ± 57.0	134.9 ± 49.9	131.4 ± 46.3	0.002
BUN (mg/dL)	16.0 (12.0, 22.0)	19.0 (13.0, 29.0)	17.0 (12.0, 24.0)	15.0 (11.0, 20.0)	14.0 (11.0, 18.0)	< 0.001
Creatinine (mg/dL)	0.9 (0.7, 1.1)	0.9 (0.7, 1.3)	0.9 (0.7, 1.1)	0.9 (0.7, 1.0)	0.9 (0.8, 1.1)	< 0.001
Organ support therapy						
MV	1003 (35.6)	258 (36.7)	258 (36.6)	211 (30.1)	276 (39.1)	0.003
RRT	42 (1.5)	35 (5)	3 (0.4)	3 (0.4)	1 (0.1)	< 0.001
Vasopressors	406 (14.4)	151 (21.5)	98 (13.9)	74 (10.5)	83 (11.8)	< 0.001
Neurosurgery	597 (21.2)	132 (18.8)	156 (22.2)	147 (20.9)	162 (22.9)	0.243
RBC transfusion	29 (1.0)	15 (2.1)	7 (1)	5 (0.7)	2 (0.3)	0.005
Outcomes						
30-day mortality	309 (11.0)	148 (21.1)	84 (11.9)	50 (7.1)	27 (3.8)	< 0.001
60-day mortality	367 (13.0)	179 (25.5)	100 (14.2)	56 (8)	32 (4.5)	< 0.001
120-day mortality	435 (15.5)	211 (30)	121 (17.2)	65 (9.3)	38 (5.4)	< 0.001

Note: Variables are presented as mean ± SD, median (IQR), or N (%).
Abbreviations: HRR, hemoglobin-to-red cell distribution width ratio; CHF, congestive heart failure; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; GCS, Glasgow coma scale; RDW, red cell distribution width; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; BUN, blood urea nitrogen; MV, mechanical ventilation; RRT, renal replacement therapy; RBC, red blood cell.

in Figure 1. The cohort for the final analysis included 2,815 participants.

Baseline characteristics of participants

The baseline characteristics of the participants stratified using HRR values are shown in Table 1. According to the HRR values, 703, 704, 702, and 706 patients belonged to the Quartile 1, Quartile 2, Quartile 3, and Quartile 4 groups, respectively. The mean age of all participants was 62.2 ± 22.1 years, with males accounting for 62.4%. GCS scores averaged 11.8 ± 3.5, mechanical ventilation treatment accounted for 35.6%, and neurosurgical operation accounted for 21.2%. The patients in the Quartile 1 group were older, had a higher CCI, SOFA, and SAPS II, and were more likely to use RRT and vasopressors. Patients with higher HRR had lower 30-day, 60-day, and 120-day all-cause mortality.

Association Between HRR and Mortality of TBI

The Kaplan–Meier curves for 30-day, 60-day, and 120-day survival are presented in Figure 2 (all p values for Log-rank tests < 0.0001). Both univariable and multivariable Cox proportional risk models were performed to investigate the relationship between the HRR and all-cause mortality in TBI patients. In Table 2, we show both the crude model and the adjusted models. In the crude model and model 1 (adjusted for age, sex, and race), HRR was negatively associated with 30-day mortality. Even after adjustment for all potential confounders (model 2), the association remained significant with HRR treated as a continuous variable (HR, 95% CI: 0.87 [0.81, 0.92]; p <0.001). A similar relationship was also observed for 60-day mortality and 120-day mortality. In model 2, higher HRR was independently associated with decreased 60-day (HR, 95% CI: 0.85 [0.8, 0.9]; p < 0.001) and 120-day (HR, 95% CI: 0.85 [0.8, 0.89]; p < 0.001) all-cause mortality. We also considered HRR as a categorical variable (the four quartiles) and used the first quartile as a reference group for comparison with other groups in the correlation analyses. For 30-day mortality, in the fully adjusted model (model 2), the HR with 95% CI for the second, third, and fourth

Tab. 2. Relationship between HRR and all-cause mortality among patients with TBI

	Crude model		Model 1		Model 2	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
30-day mortality						
HRR	0.75 (0.72, 0.79)	<0.001	0.8 (0.76, 0.85)	<0.001	0.87 (0.81, 0.92)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.54 (0.42, 0.71)	<0.001	0.57 (0.44, 0.75)	<0.001	0.67 (0.5, 0.9)	0.007
Quartile 3	0.32 (0.23, 0.44)	<0.001	0.42 (0.3, 0.58)	<0.001	0.65 (0.46, 0.94)	0.022
Quartile 4	0.17 (0.11, 0.25)	<0.001	0.32 (0.21, 0.49)	<0.001	0.5 (0.32, 0.79)	0.003
P for trend		<0.001		<0.001		0.001
60-day mortality						
HRR	0.74 (0.71, 0.77)	<0.001	0.79 (0.75, 0.83)	<0.001	0.85 (0.8, 0.9)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.53 (0.41, 0.68)	<0.001	0.56 (0.43, 0.71)	<0.001	0.64 (0.49, 0.83)	0.001
Quartile 3	0.29 (0.21, 0.39)	<0.001	0.38 (0.28, 0.51)	<0.001	0.58 (0.42, 0.82)	0.002
Quartile 4	0.16 (0.11, 0.23)	<0.001	0.3 (0.2, 0.45)	<0.001	0.47 (0.31, 0.71)	<0.001
P for trend		<0.001		<0.001		<0.001
120-day mortality						
HRR	0.74 (0.71, 0.77)	<0.001	0.79 (0.75, 0.82)	<0.001	0.85 (0.8, 0.89)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.53 (0.43, 0.67)	<0.001	0.56 (0.45, 0.7)	<0.001	0.63 (0.5, 0.81)	<0.001
Quartile 3	0.28 (0.21, 0.36)	<0.001	0.37 (0.28, 0.49)	<0.001	0.56 (0.41, 0.76)	<0.001
Quartile 4	0.16 (0.11, 0.22)	<0.001	0.31 (0.22, 0.44)	<0.001	0.47 (0.32, 0.69)	<0.001
P for trend		<0.001		<0.001		<0.001

Note: Crude model was adjusted for none; Model 1 was adjusted for age, sex and race; Model 2 was further adjusted (from Model 1) for CHF, cerebrovascular disease, renal disease, CCI, SOFA, SAPS II, GCS, WBC, PTT, BUN, creatinine, MV, RRT, vasopressors, neurosurgery, and RBC transfusion.

Abbreviations: HRR, hemoglobin-to-red cell distribution width ratio; TBI, traumatic brain injury; HR, hazard ratio; CI, confidence interval; Ref, reference; CHF, congestive heart failure; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology scoreII; GCS, Glasgow coma scale; WBC, white blood cell; PTT, partial thromboplastin time; BUN, blood urea nitrogen; MV, mechanical ventilation; RRT, renal replacement therapy; RBC, red blood cell.

quartile groups were 0.67 (0.5, 0.9), 0.65 (0.46, 0.94), and 0.5 (0.32, 0.79), respectively, compared to the first quartile group (p for trend = 0.001). A similar trend was also observed for 60-day mortality and 120-day mortality. Using curve-fitting, a linear relationship was found between HRR and 30-day mortality in patients with TBI (Supplementary Figure 1).

Subgroup analyses and ROC curves

Stratified and interaction analyses were performed to see whether the relationship between HRR and 30-day mortality was stable in different subgroups. The interaction tests were not statistically significant for age, sex, race, GCS, hypertension, diabetes, CHF, cerebrovascular disease, chronic pulmonary disease, MV, and neurosurgery (Figure 3). The ROC curves were utilized to assess the capacity of HRR to predict mortality in ICU patients with TBI. For 30-day mortality, the AUCs of HRR, hemoglobin, and RDW were 0.694, 0.671, and 0.663, respectively (Figure 4). Using DeLong tests to compare AUCs, we found that HRR had a better predictive value than hemoglobin (p = 0.002) and RDW (p = 0.017). For 60-day and 120-day mortality, the AUCs of HRR reached 0.707 and 0.713, respectively. In addition, similar results from DeLong tests were observed for 60-day and 120-day mortality.

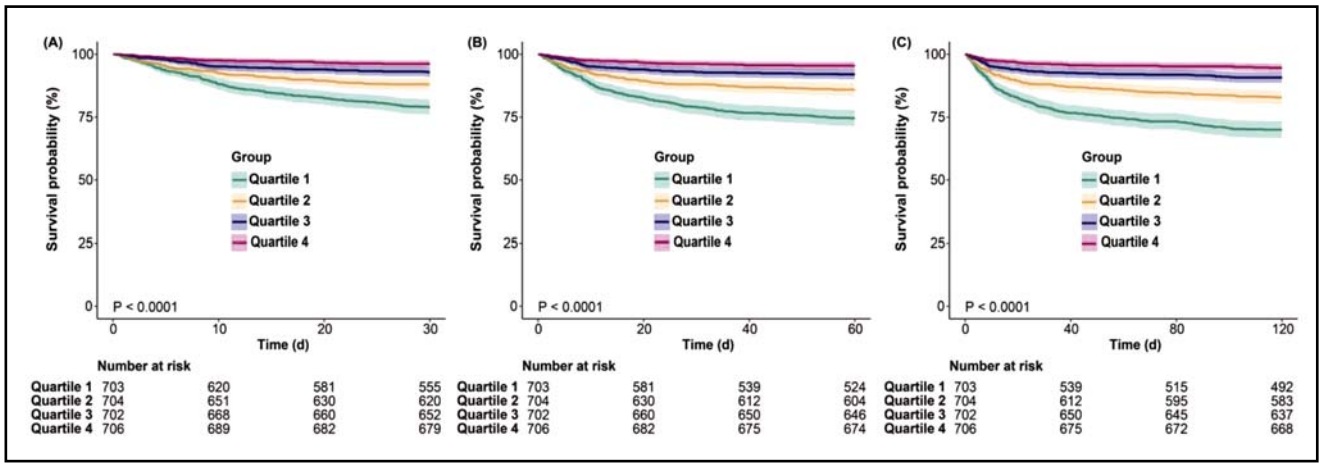

Fig. 2. Kaplan–Meier curves for 30-day (A), 60-day (B), and 120-day (C) survival of TBI patients according to the HRR levels. Abbreviations: HRR, hemoglobin-to-red cell distribution width ratio; TBI, traumatic brain injury.

Sensitivity analyses

In the sensitivity analyses, results remained robust using multiple interpolation (Supplementary Table 2). We reanalyzed the association between HRR and all-cause mortality after excluding the patients with RBC transfusion and found that the association between HRR and mortality remained reliable (Supplementary Table 3). In addition, the reanalysis of the relationship between HRR and mortality using the mean hemoglobin and mean RDW on the first day admitted to the ICU showed the robustness of our results (Supplementary Table 4).

DISCUSSION

The current study focused on the relationship between routine blood tests taken upon ICU admission and all-cause mortality among critically ill patients with TBI. We detected a negative correlation between HRR level and the risk of mortality in TBI patients, even after adjustments for essential confounders. Curve-fitting, stratified analyses, and sensitivity analyses suggested the robustness of our findings. In addition, we constructed ROC curves to evaluate the value of HRR as a stand-alone predictor and found that HRR has good predictive value for 60-day and 120-day mortality on its own. More importantly, HRR may be a better biomarker than hemoglobin and RDW for predicting mortality in patients with TBI. Our findings will contribute to an in-depth understanding of the relationship between HRR and mortality in ICU patients with TBI, thereby strengthening the physician's ability to risk-stratify patients and improving treatment decisions. Compared with some disease severity scores, such as CCI, SOFA, SAPS II, and GCS, HRR is more objective and accessible, which makes HRR directly applicable in the assessment of the prognosis of ICU patients with TBI.

Anemia is common following TBI, occurring in approximately 50% of TBI patients (Utter *et al.* 2011). Many studies have reported that hemoglobin levels may be closely associated with the prognosis of TBI patients, and lower hemoglobin could independently predict poor outcomes in TBI patients (Baltazar *et al.* 2015; Florez-Perdomo *et al.* 2021; Litofsky *et al.* 2016). The pathophysiological mechanisms underlying the association between worse prognoses and decreased hemoglobin levels are not exactly clear. A possible pathway by which anemia may cause secondary cerebral injury is by decreasing oxygen transport ability and brain tissue oxygen tension (Oddo *et al.* 2012). Anemia-induced tissue hypoxia is mechanistically demonstrated by the observations of increased expression of hypoxia-related molecules such as erythropoietin, endothelium-derived factors, and neuronal nitric oxide synthase (Hare, 2004). On the other hand, as anemia causes brain vasodilation mediated by nitric oxide, this may exacerbate cerebral oedema and elevate ICP (LeRoux, 2013). However, the association between anemia and adverse outcomes in TBI patients remains controversial due to inconsistencies in the definition of anemia and the timing of hemoglobin measurements in different studies. Some studies on anemia and TBI outcomes have not observed a consistent risk of harm (Dolmans *et al.* 2020; East *et al.* 2018). These studies suggest that a single indicator of hemoglobin may not accurately predict poor outcomes in patients with TBI.

RDW is an indicator of the size heterogeneity of erythrocytes, with higher values representing a larger disparity. It has recently received a lot of attention as a biomarker of inflammation and a promising prognostic indicator for various nonhematologic diseases (Anand *et al.* 2022; Salvagno *et al.* 2015). In another study, RDW was suggested to reflect the patient's nutritional status and tolerance ability (Yazici *et al.* 2017). In addition, it has also been reported that increased RDW is associated with inferior health status, which denotes a reduced capacity for systemic

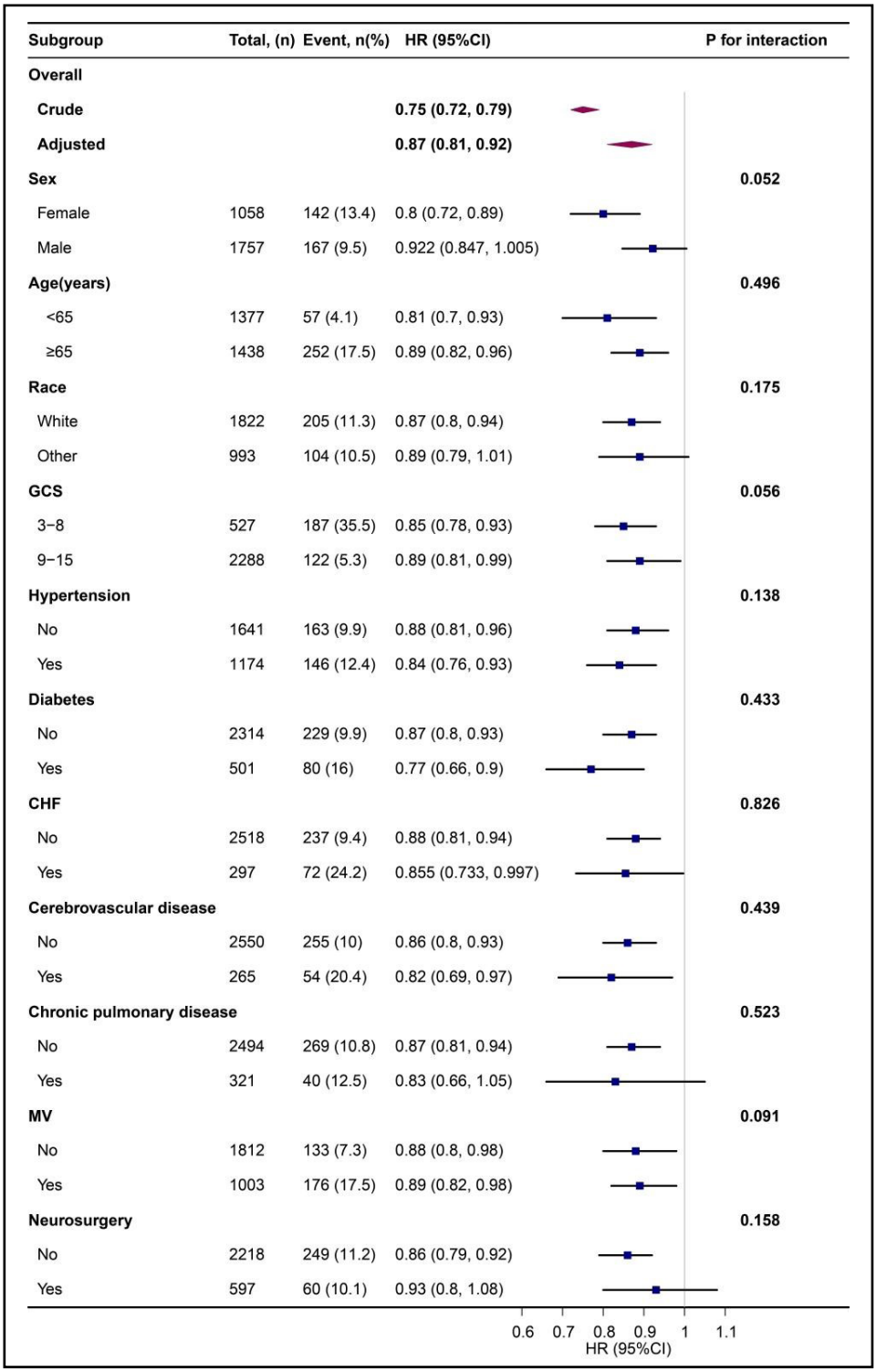

Fig. 3. Stratified analyses of the associations between HRR and 30-day mortality. HRs were adjusted for age, sex, race, CHF, cerebrovascular disease, renal disease, CCI, SOFA, SAPS II, GCS, WBC, PTT, BUN, creatinine, MV, RRT, vasopressors, neurosurgery, and RBC transfusion. Abbreviations: HRR, hemoglobin-to-red cell distribution width ratio; HR, hazard ratio; CHF, congestive heart failure; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; GCS, Glasgow coma scale; WBC, white blood cell; PTT, partial thromboplastin time; BUN, blood urea nitrogen; MV, mechanical ventilation; RRT, renal replacement therapy; RBC, red blood cell.

recovery and oxygenation (Sun *et al.* 2016). The study by Zhang *et al.* indicated that RDW is considered to be a predictor of mortality in TBI patients (Zhang & Zhao, 2015). Lorente *et al.* conducted a study focused on the relationship between RDW at admission and mortality in TBI patients and found that higher RDW can lead to an increased risk of mortality. In their research, inflammation and oxidative stress are considered to be the main mechanisms associated with RDW and mortality (Lorente *et al.* 2021). Based on the above considerations, the impact of RDW on the prognosis of TBI patients may be related to various factors.

When compared to hemoglobin and RDW, HRR has a better predictive value, as evidenced by the AUCs. The advantage of combining hemoglobin and RDW into a prognostic indicator was reported in previous studies, suggesting it as a potential

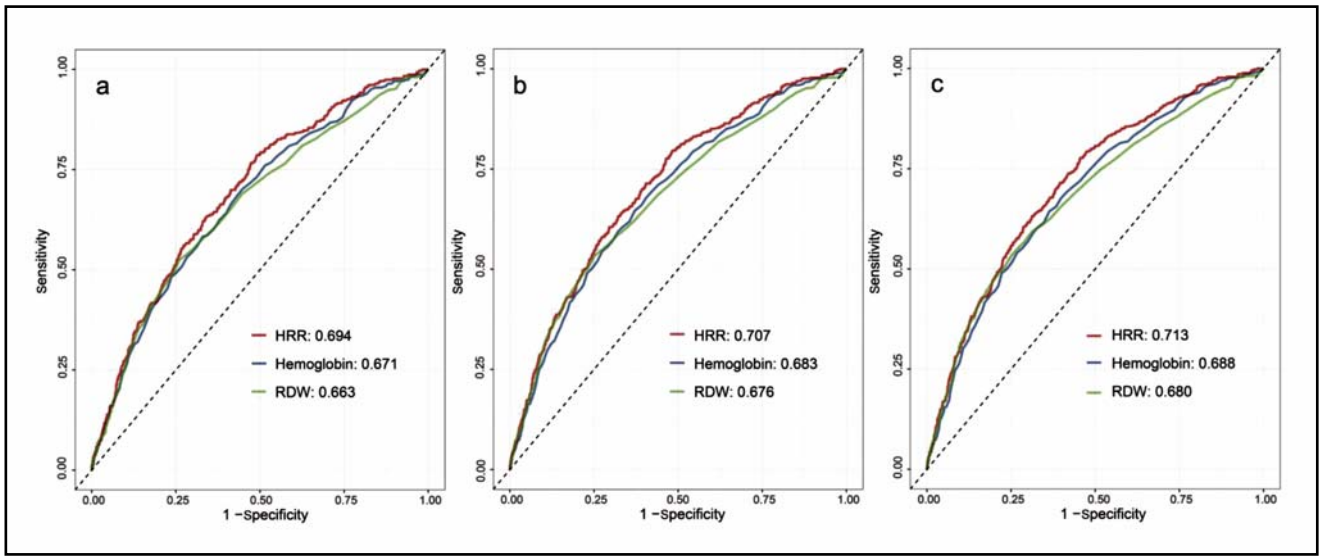

Fig. 4. ROC curve analyses for HRR, hemoglobin, and RDW based on 30-day (a), 60-day (b), and 120-day (c) mortality. Abbreviations: ROC, receiver operating characteristic; HRR, hemoglobin-to-red cell distribution width ratio; RDW, red cell distribution width.

prognostic biomarker in various cancers (Petrella *et al.* 2021; Yılmaz *et al.* 2020, 2021). Other studies have found that HRR is independently associated with prognosis in non-neoplastic diseases such as heart failure, decompensated cirrhosis, and ischemic stroke (Qin *et al.* 2022; Rahamim *et al.* 2022; Yu *et al.* 2022). In addition, the baseline HRR at admission has been demonstrated to be an independent predictor of poor prognosis following percutaneous coronary intervention (Xiu *et al.* 2022). In our study, a linear relationship was found between HRR and the primary outcome. However, the relationship between mortality and the HRR values was non-linear in two previous studies (Huang *et al.* 2022; Qin *et al.* 2022). In these two studies, the study populations were not exactly the same as ours. Therefore, the results do not represent the relationship between HRR and mortality in critically ill patients with TBI. Nevertheless, the results showed that lower HRR was associated with increased all-cause mortality in these two studies. The study by Yu *et al.* suggested that both hemoglobin and RDW are affected by various factors, including inflammation, malnutrition, and aging. Compared to hemoglobin or RDW alone, HRR may be a more stable and accurate prognostic biomarker since it is a ratio (Groarke & Young, 2019; Yu *et al.* 2022). Taken together, it is not unexpected that HRR is independently associated with mortality among patients with TBI.

One advantage of our study is the relatively large sample size from the MIMIC-IV database, which improves the statistical power and accuracy of data analyses. In addition, various robustness tests were performed to enhance the reliability of our findings. However, our study had certain shortcomings. Firstly, data from the MIMIC-IV database did not include long-term follow-up events or the Glasgow Outcome Scale. Secondly, we did not adjust for ICP in the multivariable Cox proportional risk models since it was only measured in a minority of participants. Thirdly, baseline values of hemoglobin and RDW were evaluated after ICU admission, and dynamic HRR values were not available in our study, so we could not assess the relationship between variation values of HRR and prognosis. Finally, as a single-center retrospective study, it might have been prone to selection bias. A prospective multicenter study is therefore required. Our findings should serve as a basis for future well-designed research to investigate the impact of HRR on prognosis and causality in TBI patients. Despite these shortcomings, this is the first study to explore the relationship between HRR and mortality among critically ill patients with TBI.

CONCLUSIONS

In conclusion, a lower level of HRR is significantly associated with higher all-cause mortality among critically ill patients with TBI. More studies are required to evaluate the prognostic value of HRR in critically ill patients with TBI.

ETHICS APPROVAL AND INFORMED CONSENT

The Massachusetts Institute of Technology and BIDMC approved the establishment of this database. The institutional review boards of the Massachusetts Institute of Technology and BIDMC both approved the use of the database for research. Informed consents were waived since the information of all patients in this database was anonymous. We also complied with all relevant ethical regulations regarding the use of the data in our study.

DATA AVAILABILITY

All the data used to support this study are available from the corresponding author upon request.

FUNDING

None received.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

DY wrote the manuscript; JL conducted data analyses; RX conducted data interpretation; KZ and SY conducted data curation and visualization; ZH edited tables and pictures; LZ reviewed the manuscript. All authors contributed to study design and interpretation. All authors have read and approved the final manuscript.

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Supplementary Table 1 (online only).

Description of missing data

Variables	Non-missing	Missing
Age	2815	0
Sex	2815	0
Race	2815	0
Hypertension	2815	0
Diabetes	2815	0
CHF	2815	0
Cerebrovascular disease	2815	0
Chronic pulmonary disease	2815	0
Renal disease	2815	0
Liver disease	2815	0
Malignancy	2815	0
CCI	2815	0
SOFA	2815	0
SAPS II	2815	0
GCS	2815	0
Hemoglobin	2815	0
RDW	2815	0
WBC	2815	0
Platelet	2815	0
INR	2699	116
PT	2699	116
PTT	2691	124
Anion gap	2787	28
Bicarbonate	2787	28
Glucose	2788	27
BUN	2809	6
Creatinine	2812	3
MV	2815	0
RRT	2815	0
Vasopressors	2815	0
Neurosurgery	2815	0
RBC transfusion	2815	0
30-day mortality	2815	0
60-day mortality	2815	0
120-day mortality	2815	0

Abbreviations: CHF, congestive heart failure; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; GCS, Glasgow coma scale; RDW, red cell distribution width; WBC, white blood cell; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; BUN, blood urea nitrogen; MV, mechanical ventilation; RRT, renal replacement therapy; RBC, red blood cell.

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Supplementary Table 2 (online only).

Relationship between HRR and all-cause mortality among patients with TBI after multiple imputation

	Crude model		Model 1		Model 2	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
30-day mortality						
HRR	0.75 (0.72, 0.79)	<0.001	0.8 (0.76, 0.85)	<0.001	0.87 (0.82, 0.93)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.54 (0.42, 0.71)	<0.001	0.57 (0.44, 0.75)	<0.001	0.71 (0.53, 0.94)	0.019
Quartile 3	0.32 (0.23, 0.44)	<0.001	0.42 (0.3, 0.58)	<0.001	0.74 (0.52, 1.05)	0.096
Quartile 4	0.17 (0.11, 0.25)	<0.001	0.32 (0.21, 0.49)	<0.001	0.53 (0.34, 0.83)	0.006
60-day mortality						
HRR	0.74 (0.71, 0.77)	<0.001	0.79 (0.75, 0.83)	<0.001	0.85 (0.8, 0.9)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.53 (0.41, 0.68)	<0.001	0.56 (0.43, 0.71)	<0.001	0.68 (0.52, 0.88)	0.003
Quartile 3	0.29 (0.21, 0.39)	<0.001	0.38 (0.28, 0.51)	<0.001	0.64 (0.46, 0.89)	0.008
Quartile 4	0.16 (0.11, 0.23)	<0.001	0.3 (0.2, 0.45)	<0.001	0.48 (0.32, 0.73)	0.001
120-day mortality						
HRR	0.74 (0.71, 0.77)	<0.001	0.79 (0.75, 0.82)	<0.001	0.85 (0.81, 0.9)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.53 (0.43, 0.67)	<0.001	0.56 (0.45, 0.7)	<0.001	0.67 (0.53, 0.85)	0.001
Quartile 3	0.28 (0.21, 0.36)	<0.001	0.37 (0.28, 0.49)	<0.001	0.6 (0.45, 0.81)	0.001
Quartile 4	0.16 (0.11, 0.22)	<0.001	0.31 (0.22, 0.44)	<0.001	0.48 (0.33, 0.71)	<0.001

Note: Crude model was adjusted for none; Model 1 was adjusted for age, sex and race; Model 2 was further adjusted (from Model 1) for CHF, cerebrovascular disease, renal disease, CCI, SOFA, SAPS II, GCS, WBC, PTT, BUN, creatinine, MV, RRT, vasopressors, neurosurgery, and RBC transfusion.

Abbreviations: HRR, hemoglobin-to-red cell distribution width ratio; TBI, traumatic brain injury; HR, hazard ratio; CI, confidence interval; CHF, congestive heart failure; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; GCS, Glasgow coma scale; WBC, white blood cell; PTT, partial thromboplastin time; BUN, blood urea nitrogen; MV, mechanical ventilation; RRT, renal replacement therapy; RBC, red blood cell.

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Supplementary Table 3 (online only).

Relationship between HRR and all-cause mortality among patients with TBI after excluding the patients with RBC transfusion

	Crude model		Model 1		Model 2	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
30-day mortality						
HRR	0.75 (0.72, 0.79)	<0.001	0.81 (0.76, 0.85)	<0.001	0.87 (0.81, 0.92)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.57 (0.44, 0.75)	<0.001	0.6 (0.46, 0.79)	<0.001	0.68 (0.51, 0.91)	0.01
Quartile 3	0.31 (0.22, 0.43)	<0.001	0.41 (0.3, 0.58)	<0.001	0.61 (0.42, 0.89)	0.01
Quartile 4	0.17 (0.11, 0.25)	<0.001	0.32 (0.21, 0.5)	<0.001	0.47 (0.3, 0.75)	0.001
60-day mortality						
HRR	0.74 (0.71, 0.78)	<0.001	0.79 (0.75, 0.83)	<0.001	0.85 (0.8, 0.9)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.54 (0.42, 0.69)	<0.001	0.57 (0.45, 0.73)	<0.001	0.63 (0.48, 0.82)	0.001
Quartile 3	0.28 (0.21, 0.38)	<0.001	0.37 (0.27, 0.51)	<0.001	0.55 (0.39, 0.77)	0.001
Quartile 4	0.16 (0.11, 0.23)	<0.001	0.3 (0.2, 0.45)	<0.001	0.44 (0.29, 0.67)	<0.001
120-day mortality						
HRR	0.74 (0.71, 0.77)	<0.001	0.79 (0.75, 0.83)	<0.001	0.85 (0.8, 0.9)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.54 (0.43, 0.68)	<0.001	0.57 (0.46, 0.72)	<0.001	0.62 (0.49, 0.8)	<0.001
Quartile 3	0.27 (0.2, 0.36)	<0.001	0.36 (0.27, 0.48)	<0.001	0.53 (0.39, 0.72)	<0.001
Quartile 4	0.16 (0.11, 0.22)	<0.001	0.31 (0.22, 0.45)	<0.001	0.45 (0.31, 0.66)	<0.001

Note: Crude model was adjusted for none; Model 1 was adjusted for age, sex and race; Model 2 was further adjusted (from Model 1) for CHF, cerebrovascular disease, renal disease, CCI, SOFA, SAPS II, GCS, WBC, PTT, BUN, creatinine, MV, RRT, vasopressors, and neurosurgery.
Abbreviations: HRR, hemoglobin-to-red cell distribution width ratio; TBI, traumatic brain injury; RBC, red blood cell; HR, hazard ratio; CI, confidence interval; CHF, congestive heart failure; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; GCS, Glasgow coma scale; WBC, white blood cell; PTT, partial thromboplastin time; BUN, blood urea nitrogen; MV, mechanical ventilation; RRT, renal replacement therapy.

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Supplementary Table 4 (online only).

Relationship between HRR (calculated from mean hemoglobin and mean RDW) and all-cause mortality among patients with TBI

	Crude model		Model 1		Model 2	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
30-day mortality						
HRR	0.72 (0.68, 0.76)	<0.001	0.78 (0.73, 0.82)	<0.001	0.86 (0.8, 0.92)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.5 (0.38, 0.66)	<0.001	0.54 (0.41, 0.71)	<0.001	0.63 (0.47, 0.84)	0.002
Quartile 3	0.32 (0.23, 0.44)	<0.001	0.4 (0.29, 0.54)	<0.001	0.59 (0.41, 0.85)	0.005
Quartile 4	0.16 (0.11, 0.24)	<0.001	0.28 (0.19, 0.43)	<0.001	0.51 (0.32, 0.8)	0.003
60-day mortality						
HRR	0.71 (0.68, 0.75)	<0.001	0.76 (0.72, 0.8)	<0.001	0.84 (0.78, 0.89)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.51 (0.4, 0.65)	<0.001	0.55 (0.43, 0.7)	<0.001	0.65 (0.5, 0.84)	0.001
Quartile 3	0.3 (0.23, 0.41)	<0.001	0.38 (0.28, 0.51)	<0.001	0.56 (0.4, 0.79)	0.001
Quartile 4	0.16 (0.11, 0.23)	<0.001	0.27 (0.18, 0.4)	<0.001	0.49 (0.32, 0.74)	0.001
120-day mortality						
HRR	0.71 (0.68, 0.74)	<0.001	0.76 (0.73, 0.8)	<0.001	0.84 (0.79, 0.89)	<0.001
HRR quartiles						
Quartile 1	1(Ref)		1(Ref)		1(Ref)	
Quartile 2	0.52 (0.42, 0.66)	<0.001	0.56 (0.45, 0.71)	<0.001	0.67 (0.53, 0.85)	0.001
Quartile 3	0.3 (0.23, 0.39)	<0.001	0.37 (0.28, 0.49)	<0.001	0.54 (0.4, 0.74)	<0.001
Quartile 4	0.15 (0.11, 0.21)	<0.001	0.27 (0.19, 0.39)	<0.001	0.47 (0.32, 0.68)	<0.001

Note: Crude model was adjusted for none; Model 1 was adjusted for age, sex and race; Model 2 was further adjusted (from Model 1) for CHF, cerebrovascular disease, renal disease, CCI, SOFA, SAPS II, GCS, WBC, PTT, BUN, creatinine, MV, RRT, vasopressors, neurosurgery, and RBC transfusion.

Abbreviations: HRR, hemoglobin-to-red cell distribution width ratio; RDW, red cell distribution width; TBI, traumatic brain injury; HR, hazard ratio; CI, confidence interval; CHF, congestive heart failure; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; GCS, Glasgow coma scale; WBC, white blood cell; PTT, partial thromboplastin time; BUN, blood urea nitrogen; MV, mechanical ventilation; RRT, renal replacement therapy; RBC, red blood cell.

Cite:
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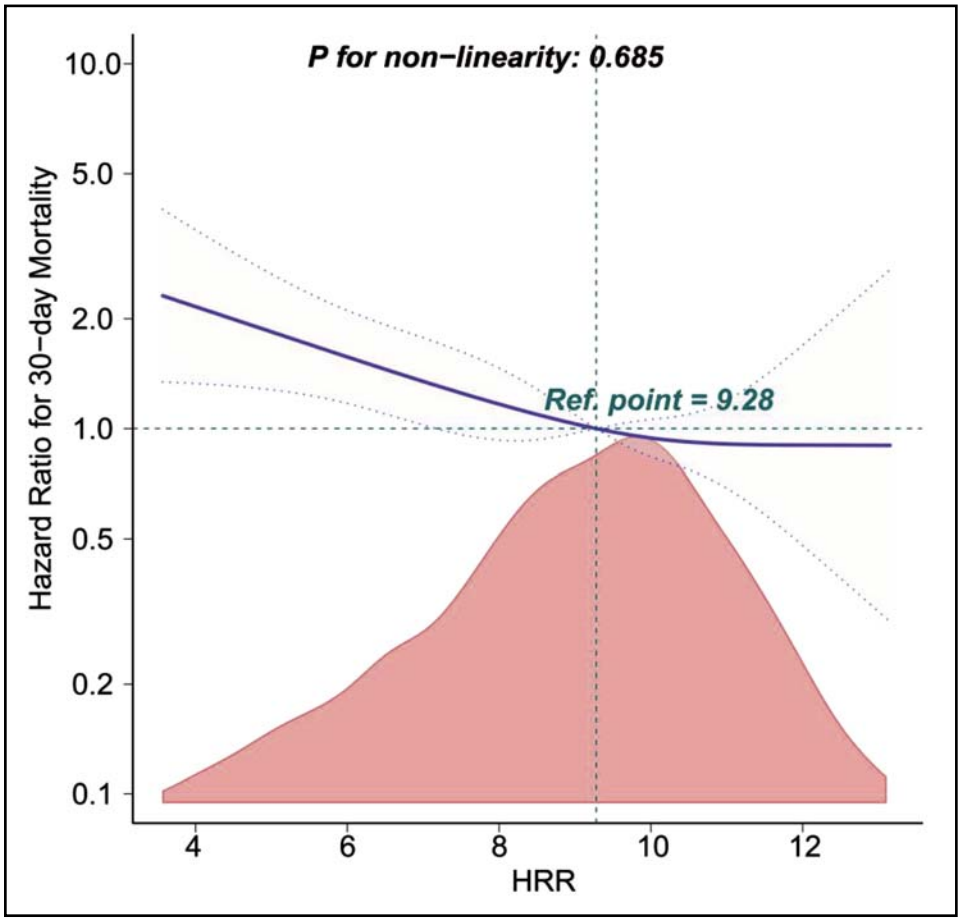

Supplementary Fig. 1 (online only). Association between HRR and 30-day mortality of TBI patients. Only 98% of the data is displayed. HRs were adjusted for age, sex, race, CHF, cerebrovascular disease, renal disease, CCI, SOFA, SAPS II, GCS, WBC, PTT, BUN, creatinine, MV, RRT, vasopressors, neurosurgery, and RBC transfusion. Abbreviations: HRR, hemoglobin-to-red cell distribution width ratio; TBI, traumatic brain injury; HR, hazard ratio; CHF, congestive heart failure; CCI, Charlson comorbidity index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; GCS, Glasgow coma scale; WBC, white blood cell; PTT, partial thromboplastin time; BUN, blood urea nitrogen; MV, mechanical ventilation; RRT, renal replacement therapy; RBC, red blood cell.

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