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Lower Hemoglobin-to-Red Blood Cell Distribution Width Ratio Is Independently Associated With Frailty in Community-dwelling Older Adults: a cross-sectional study

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Lower Hemoglobin-to-Red Blood Cell Distribution Width Ratio Is Independently Associated With Frailty in Community-dwelling Older Adults: a cross-sectional study

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Abstract

Objectives: Frailty becomes an emerging global public health burden, with the rapid growth of the global elderly population. We investigated the association between hemoglobin-to-red blood cell distribution width ratio (HRR) and frailty in older adults.

Design: Cross-sectional analysis of associations of HRR and frailty in older people.

Setting: Enrolled community-dwelling older adults older than 65 years old in Wuhan during September 2021 and December 2021.

Participants: A total of 1296 community-dwelling older adults (age ⩾ 65 years) in Wuhan were included in the study.

Main outcome measures: The main outcome measure was frailty, and the Fried Frailty Phenotype Scale was used to evaluate the frailty status of the participants.

Results: A total of 1296 (564 man) older adults were included in this cross-sectional study. Their mean age was 70.89 ± 4.85 years. ROC analysis showed that HRR is a good predictor of frailty in older people, the area under the curve (AUC) was 0.802 (95% CI: 0.755 to 0.849), and the highest sensitivity was 84.5% and the specificity was 61.9% with the optimal critical values 9.97 (P<0.001). Multiple logistic regression analysis indicated that lower HRR (<9.97) (OR:3.419, 1.679-6.964, P=0.001) is independently associated with frailty in older people, even after adjusting confounding factors.

Conclusion: Lower HRR is closely associated with an increased risk of frailty in the older people. Lower HRR may be an independent risk factor for frailty in community-dwelling older adults.

Keywords: Older people, Frailty, Healthy aging, Risk factor, HRR

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Strengths and limitations of this study

This is the first study reporting an association of HRR with the frailty in community-dwelling older adults.

HRR may help clinicians to identify people at high risk of frailty and take effective measures to reduce the occurrence and development of frailty, reduce the rate of disability and mortality related to frailty in the elderly.

Our findings should facilitate further research to investigate any causal association of HRR and frailty in older people.

This was a cross-sectional study that cannot assess the cause-effect relationship.

Introduction

As life expectancy increases, human societies are aging globally, in both developed and developing countries.[1] By 2050, the proportion of people aged over 60 years is projected to increase from 11% to 22%, and the number of aged over 60 years will increase from 605 million to 2.1 billion, including 425 million people aged over 80 in the world.[2] Frailty becomes an emerging global public health burden, with the rapid growth of the global aging population. Frailty is considered to be a complex age-related clinical condition characterized by a decline in the physiological function of multiple organs, with a resultant increased vulnerability to stressors.[3] It is related to adverse health-related events, including increased mortality, hospitalization, falls and fractures, cognitive decline, disability, and admission to long-term care.[4] Therefore, early identifying modifiable risk factors of frailty is becoming increasing

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crucial for delaying and reversing frailty and its associated adverse events in older persons.[5]

As an important part of CBC, hemoglobin (Hb) is usually used as an indicator of the degree of anemia. However, previous studies showed that low Hb reflect to a decline in the physiological function including the decreased immune response, malnutrition, and the low resistance to external invasion.[6] Meanwhile, there are several studies indicated that Hb is related to frailty in older persons.[7-10] As an indicator of heterogeneity of the erythrocyte volume, red blood cell distribution width (RDW) is thought to be related to the prognosis of many diseases. Hou et al. indicated that RDW is significantly associated with the risk of frailty in older patients with coronary heart disease (CHD).[11] In addition, studies showed that RDW is associated with frailty both in older inpatients and community-dwelling older people.[12,13]

RDW can be affected by complex conditions, the effect of RDW on frailty is not only related to inflammatory response, but also association with a decline in the physiological function and oxygen.[14] RDW alone may not provide definitive predictive information.[14,15] The hemoglobin-to-RDW ratio (HRR) is a cheap, rapid and readily available novel prognostic, which combines the prognostic information of Hb and RDW and reflects a more comprehensive health status.[14,16] Recently, Qu et al. found that lower HRR is independent related to the risk of frailty in older patients with CHD.[14] They verified that HRR maybe a more useful biomarker comparing with RDW or Hb alone.[14]

Studies have showed a significant association of HRR with frailty in specific populations (patients with coronary heart disease).[14] However, research on HRR and frailty in the general older persons is still limited, and the significance of evaluating frailty is not yet clear. In the present study, we investigated the relationship between HRR and frailty in

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community-dwelling older adults.

Material & Methods

Ethical Approval

The research protocol was approved by the Medical Ethics Committee of Liyuan Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRB ID: [2020] IEC (A016)). All the participants gave written informed consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

Sampling size and sampling procedure

A sample size of 1,296 was calculated using 2% error, 95% confidence interval using the formula below :

$$n = \frac{z^2 \times p(1-p)}{e^2}$$

n = minimum sample size.

z = confidence interval at 95%, 1.96.

p = estimated proportion of frailty, 10%.[17]

e = margin of error at 2%.

Then we kept the design effect at 1.5. n = 864 X 1.5 = 1,296

Totally, 1,296 participants were examined.

Since, it was a cluster sampling we kept the design effect at 1.5. n = 864 X 1.5 = 1296

Patient and public involvement

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The source population was the community-dwelling adults older than 65 living in communities in Wuhan. The study population consisted of a random sample of older people from each community.

Participants and Sociodemographic Characteristics

In this present study, we recruited 1,296 community-dwelling adults older than 65 living in communities in Wuhan between September 2021 and December 2021. Sociodemographic characteristics, including age, gender, education years, marital status, smoking history, alcohol consumption, comorbidities, including hypertension, diabetes, CHD, hyperlipidemia, and cerebrovascular disease were recorded. Then body mass index (BMI), waistline , blood pressure and pulse rate were measured by two professional clinicians.

Peripheral Blood Parameters

Blood samples were collected, and full blood count was measured by automated hematology analyzer (Mindray, BC7500, China). Other related biochemical indicators were detected by automatic biochemical analyzer (Beckman, AU680, American). HRR = Hb (g/L)/RDW (%).

Fried's frailty phenotype

According to the Fried's frailty phenotype, we evaluated frailty in five criteria, as follows (1) Weight loss: unintentional weight loss >5% or a loss of more than 4.5 kg in the past 1 year. (2) Physical weakness: dynamometer was used for participants for three trials, the maximum value was recorded. Low grip strength was defined according to the standards proposed by Fried et al.[18] (3) Slowness: slowness was defined as when the time required to walk 4.6 meters was more than 7 seconds for males (height ≤ 173 cm) and females (height ≤ 159 cm) or more than 6 seconds for males (height >173 cm) and females (height >159 cm). (4) Physical activity:

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low physical activity was defined as less than 383 kcal/week for males and less than 270 kcal/week for females. (5) Exhaustion: exhaustion was assessed by the following two questions from the CES-D. “In the last week, I felt that everything I did was an effort” and “Could not get going in the last week.” If the participant responded “yes” to either of these questions, the participant was considered exhausted. Participants with >3 indicators were defined as frail, 1-2 as prefrail and none as robust.

Statistical analysis

Continuous and categorical variables were expressed as the mean ± standard deviation and numbers with percentages, respectively. The baseline characteristics of the groups were compared using one-way analysis of variance and chi-squared test. The predictive value of HRR for frailty was assessed by receiver operating curve (ROC) analysis. The prognostic value of lower HRR on frailty was assessed using logistic regression model. Variables were selected as candidates for the multivariate analysis when $p<0.1$ in the univariate analysis. After adjustment for confounding factors including age, gender, marital status, education years, alone living, BMI, diabetes, RBC, albumin, triglyceride, HDL-C and LDL-C, assessing the independent risk factors for frailty in older adults. Kendall's tau-b correlation analysis was used to assessing the correlation between lower Hb, lower RDW, lower HRR, and frailty in older adults. The p-values <0.05 was considered statistically significant. All statistical analysis were conducted using SPSS (ver. 26.0, IBM Corporation, Armonk, NY, USA).

Result

Characteristics of the study population

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A total of 1296 (564 man) older adults were included in our study. Their mean age was 70.89 ± 4.85 years. Of the 1296 participants, 582 (44.9%) has hypertension, 183 (14.1%) were diabetes patients, 98 (7.6%) had cardiac diseases, and 43 (3.3%) had cranial vascular disease. The proportions of individuals with a habit of smoking and drinking were 11.1% and 11.7%, respectively. And 149 (11.5%) older adults were living alone. According to Fried's frailty phenotype, there were 55.09% (714) in robust group, 36.81% (477) in pre-frail group, and 8.10% (105) in frail group. Baseline characteristics of three group were shown in Table 1.

Table1. Baseline characteristics of the study population stratified by frailty

Characteristics	Robust (n=714)	Pre-frail (n=477)	Frailty (n=105)	p-value
Age, years (SD)	69.81 ± 3.89	71.71 ± 5.34	70.89 ± 4.85	<0.001
Male gender, n (%)	347 (48.60%)	184 (38.57%)	33 (31.43%)	<0.001
Marital status Married, n (%)	622 (87.11%)	408 (85.53)	77 (73.33%)	0.001
Other*, n (%)	92 (12.89%)	69 (14.47%)	28 (26.67%)	
Education years 0-12, n (%)	466(65.27%)	337(70.65%)	85(80.95%)	0.002
>12, n (%)	248(24.73%)	140(29.35%)	20(19.05%)	
Alone living, n (%)	74 (10.36%)	53 (11.11%)	22 (20.95%)	0.006
Smoking, n (%)	90(12.61%)	44(9.22%)	10(9.52%)	0.165
Drinking, n (%)	92(12.89%)	50(10.48%)	10(9.52%)	0.345
Hypertension, n (%)	314(43.98%)	212(44.44%)	56(53.33%)	0.192
Diabetes mellitus, n (%)	81(11.34%)	82(17.19%)	20(19.05%)	0.006
Cardiac diseases, n (%)	46(6.44%)	41(8.60%)	11(10.48%)	0.194
Cranial vascular disease, n (%)	24(2.94%)	15(3.14%)	4(3.80%)	0.938
BMI, kg/m^2 (SD)	24.69 ± 3.05	24.32 ± 3.14	23.83 ± 3.51	0.011
Waist circumference, cm (SD)	86.99 ± 8.66	86.32 ± 8.57	85.42 ± 9.46	0.143
SBP, mmHg (SD)	141.61 ± 18.53	142.73 ± 17.74	143.01 ± 19.37	0.516
DBP, mmHg (SD)	83.77 ± 10.44	82.87 ± 9.75	80.44 ± 10.91	0.006
Heart rate, beats/min (SD)	79.9 ± 13.4	79.8 ± 13.2	81.1 ± 13.0	0.659
WBC, 10^9/L (SD)	6.39 ± 1.51	6.36 ± 1.56	6.29 ± 1.69	0.781
Neutrophils, 10^9/L (SD)	3.89 ± 1.22	3.86 ± 1.26	3.96 ± 1.29	0.699
Lymphocytes, 10^9/L (SD)	1.95 ± 0.58	1.96 ± 0.64	1.76 ± 0.59	0.007
Eosinophils, 10^9/L (SD)	0.14 ± 0.12	0.14 ± 0.12	0.15 ± 0.18	0.628
PLT, 10^9/L (SD)	212.4 ± 52.2	216.3 ± 52.0	207.9 ± 66.1	0.251
RBC, 10^9/L (SD)	4.73 ± 0.41	4.51 ± 0.42	4.41 ± 0.65	<0.001
Hemoglobin, g/L (SD)	145.51 ± 12.15	137.29 ± 11.79	129.55 ± 13.73	<0.001

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Anemia, n (%)	6 (0.84%)	17 (3.56%)	21 (20%)	<0.001
RDW, % (SD)	12.89 ± 0.55	13.15 ± 0.69	13.88 ± 1.39	<0.001
HRR	11.31 ± 1.02	10.47 ± 1.05	9.43 ± 1.41	<0.001
FBG, mmol/L (SD)	6.28 ± 1.59	6.37 ± 1.90	6.56 ± 2.13	0.278
Albumin, g/dL (SD)	46.23 ± 2.19	45.86 ± 2.47	45.13 ± 2.90	<0.001
Globulin, g/dL (SD)	30.26 ± 3.44	30.64 ± 3.65	30.55 ± 5.25	0.194
Triglyceride, mmol/L (SD)	1.49 ± 0.85	1.46 ± 0.90	1.44 ± 0.85	0.883
Total Cholesterol, mmol/L (SD)	5.17 ± 1.04	5.19 ± 1.15	4.96 ± 1.05	0.122
HDL-C, mmol/L (SD)	1.50 ± 0.39	1.54 ± 0.42	1.54 ± 0.38	0.333
LDL-C, mmol/L (SD)	3.03 ± 0.82	3.02 ± 0.90	2.82 ± 0.88	0.060

SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, FBG=fasting blood-glucose, WBC=white blood cell, PLT=platelets count, RBC=red blood cell, RDW=red blood cell distribution width, HRR=hemoglobin-to-RDW ratio.

Other* including separated, divorced, never married or widowed

ROC curve analysis

The predictive value of HRR for frailty in older adults was assessed by ROC analysis. The AUC for HRR in the frailty older adults was 0.802 (95% CI: 0.755 to 0.849), and the highest sensitivity was 84.5% and the specificity was 61.9% with the optimal critical values 9.97 (Figure 1). The AUC for Hb was 0.742 (95% CI: 0.691 to 0.793), the highest sensitivity was 81% and the specificity was 57.1% with the optimal critical values 131.5 (Figure 1). The AUC for RDW was 0.712 (95% CI: 0.651 to 0.772), the highest sensitivity was 56.2% and the specificity was 81.1% with the optimal critical values 13.45 (Figure 1). Compared with Hb and RDW alone, HRR was a more strong prognostic biomarker for frailty.

Differences in clinical characteristics of the study population stratified by HRR

According to ROC analysis, the optimal critical values of HRR was 9.97. Participants were grouped according to the optimal critical values of HRR, as follows: 1046 (80.71%) in the normal HRR group and 250(19.29%) in the lower HRR group (Table 2). Compared with the

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normal HRR group, the lower HRR group had a higher lymphocytes count (P=0.002), and RDW (P<0.001), but a lower hemoglobin (P<0.001), RBC (P<0.001) and albumin (P<0.001). Compared with normal HRR group, the lower HRR group were more likely to have frailty (P<0.001).

Table2. Baseline characteristics of the study population stratified by HRR

Characteristics	Normal HRR (n=1046)	Lower HRR (n=250)	P-value
Age, years (SD)	70.50 ± 4.64	72.50 ± 5.40	<0.001
Male gender, n (%)	501 (47.9%)	63 (25.2%)	<0.001
Marital status Married, n (%)	901 (86.14%)	206 (82.4%)	0.133
Other*, n (%)	145 (13.86%)	44 (17.6%)	
Education years 0-12, n (%)	691 (66.06%)	197 (78.8%)	<0.001
>12, n (%)	355 (33.94%)	53 (21.2%)	
Alone living, n (%)	114 (10.90%)	35 (14.0%)	0.167
Smoking, n (%)	129 (12.33%)	15 (6.0%)	0.004
Drinking, n (%)	136 (13.0%)	16 (6.4%)	0.004
Hypertension, n (%)	456 (43.59%)	126 (50.4%)	0.052
Diabetes mellitus, n (%)	140 (13.38%)	43 (17.2%)	0.120
Cardiac diseases, n (%)	82 (7.84%)	16 (6.4%)	0.439
Cranial vascular disease, n (%)	32 (3.06%)	11 (4.4%)	0.288
BMI, kg/m^2 (SD)	24.56 ± 3.07	24.15 ± 3.36	0.026
Waist circumference, cm (SD)	86.90 ± 8.51	85.45 ± 9.37	0.143
SBP, mmHg (SD)	142.3 ± 18.3	141.3 ± 18.5	0.611
DBP, mmHg (SD)	83.7 ± 10.2	80.9 ± 10.1	0.004
Heart rate, beats/min (SD)	80.2 ± 13.4	79.0 ± 12.7	0.362
WBC, 10^9/L (SD)	6.39 ± 1.49	6.28 ± 1.75	0.556
Neutrophils, 10^9/L (SD)	3.89 ± 1.19	3.86 ± 1.43	0.441
Lymphocytes, 10^9/L (SD)	1.96 ± 0.59	1.86 ± 0.69	0.002
Eosinophils, 10^9/L (SD)	0.14 ± 0.11	0.15 ± 0.17	0.621
PLT, 10^9/L (SD)	212.3 ± 50.8	218.3 ± 62.8	0.264
RBC, 10^9/L (SD)	4.71 ± 0.38	4.27 ± 0.56	<0.001
Hemoglobin, g/L (SD)	145.08 ± 10.98	124.90 ± 8.46	<0.001
RDW, % (IQR)	12.89 ± 0.51	13.79 ± 1.09	<0.001
FBG, mmol/L (SD)	6.36 ± 1.77	6.24 ± 1.70	0.166
Albumin, g/dL (SD)	46.18 ± 2.27	45.30 ± 2.69	<0.001
Globulin, g/dL (SD)	30.35 ± 3.45	30.72 ± 4.58	0.708
Triglyceride, mmol/L (SD)	1.48 ± 0.87	1.42 ± 0.83	0.755
Total Cholesterol, mmol/L (SD)	5.17 ± 1.07	5.10 ± 1.27	0.041
HDL-C, mmol/L (SD)	1.50 ± 0.39	1.58 ± 0.42	0.539
LDL-C, mmol/L (SD)	3.03 ± 0.85	2.91 ± 0.87	0.019
Frailty status Robust, n (%)	669 (63.96%)	45 (18.0%)	<0.001

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Pre-frail, n (%)	337 (32.22%)	140 (56.0%)
Frailty, n (%)	40 (3.82%)	65 (26.0%)

SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, FBG=fasting blood-glucose, WBC=white blood cell, PLT=platelets count, RBC=red blood cell, RDW=red blood cell distribution width, HRR=hemoglobin-to-RDW ratio.

Normal HRR=HRR above 9.97, Lower HRR: HRR below 9.97 (Optimal cut-off value of the ROC curve)

Other* including separated, divorced, never married or widowed

Logistic regression analysis

Among 1296 older adults, 105 (8.10%) were considered frail. Multiple logistic regression analysis was conducted to assessing the associations of the lower HRR with frailty. Unadjusted model1 showed that lower Hb (OR:2.129,1.133-4.001, p=0.019) and lower HRR (OR:3.285,1.676-6.440, p=0.001) were risk factors related to frailty, whereas lower RDW (OR:0.310, 0.193-0.497, p<0.001) was a protective factor. After adjustment for confounding factors (including age, gender, marital status, education years, living alone, BMI, diabetes, RBC, albumin, triglyceride, HDL-C and LDL-C), there was significant association of lower HRR (OR:3.419, 1.679-6.964, p=0.001) and lower RDW (OR:0.285, 0.170-0.477, p< 0.001) with frailty (Table 3). Lower HRR was independently related to frailty in older adults.

Table3. Multiple logistic regression analysis of blood parameters and frailty in older adults

	Model1		Model2	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Categorical variable				
Lower Hb	2.129 (1.133-4.001)	0.019	1.163 (0.562-2.409)	0.684
Lower RDW	0.310(0.193-0.497)	<0.001	0.285 (0.170-0.477)	<0.001
Lower HRR	3.285 (1.676-6.440)	0.001	3.419 (1.679-6.964)	0.001

Hb=hemoglobin, RDW=red blood cell distribution width, HRR=hemoglobin-to-RDW ratio.

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Lower Hb: <131.5g/L, Lower RDW: <13.45%, Lower HRR: <9.97. (Optimal cut-off value of the ROC curve)

OR: odds ratio, CI: confidence interval, Model 1, unadjusted; Model 2, adjusted for age, gender, marital status, education years, alone living, BMI, diabetes, RBC, albumin, triglyceride, HDL-C and LDL-C.

Correlation Analysis

Correlation analysis indicated that there was an obvious positive correlation between RDW (Kendall's tau-b=0.173, P<0.001) and frailty. Nevertheless, HRR (Kendall's tau-b=-0.239, P<0.001) and Hb (Kendall's tau-b=-0.194, P<0.001) were a negative correlation with frailty (Table 4).

Table4. Correlation analysis of Hb, RDW, HRR, and frailty in older adults

	Kendall's tau-b	p
Hb	-0.194	<0.001
RDW	0.173	<0.001
HRR	-0.239	<0.001

**. Correlation is significant at the 0.01 level (2-tailed).

Discussion

Frailty, as a geriatric syndrome, has attracted more and more scientific attention in the background of continuously increase global population ageing.[19] In this cross-sectional study including 1,296 community-dwelling older adults, we found that lower HRR is independently related to frailty in older people, even after adjusting confounding factors. Multiple logistic regression analysis showed that lower HRR is associated with to a 3-fold more likelihood or

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odds of frailty. ROC analysis showed that AUC and highest sensitivity of HRR are higher than RDW. Thus, HRR may be a more powerful marker for frailty than RDW.

HRR is cost-effective, common, and accessible laboratory parameter for clinicians. As a novel inflammatory factor, Qu et.al found that HRR is a significant associated with frailty in older patients with CHD.[14] In there study the AUC for HRR in the frailty patients was exceed Hb and RDW, and after adjusting confounding factors lower HRR was a risk factor for frailty in older patients with CHD. These findings are consistent with our results. Now the pathophysiological mechanism has not been fully understood. We try to provide a possible explanation for the association between HRR and frailty in older adults.

A decreased in HRR may be due to low Hb, high RDW, or both. As we all know, low Hb indicates a condition of anemia, which is one of the acknowledged risk factors for hospitalization, morbidity, and mortality in older people.[20] Anemia decreases the oxygen-carrying capacity, leading to tissue hypoxia and even organ failure, especially in older patients, increasing the risk of frailty.[21] Besides, anemia can cut down submaximal and maximal aerobic capacity, leading to several adverse outcomes including loss of muscle strength, cognitive decline and development of frailty.[10] In addition, chronic conditions and comorbidities leading to a low grade of inflammation reducing hemoglobin level,[22] also known as chronic diseases anemia, which is the most common type of anemia in older adults.[21] And a state of chronic inflammation has been suggested as contributors to frailty.[23] Furthermore, anemia caused by malnutrition is also a significance health-affecting factor among older adults.[21]

Anemia reaching a prevalence of 17% in older people, is a threat to healthy aging.[24]

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Corona et.al found that lower hemoglobin and anemia were related to frailty in Brazilian older adults.[8] In their study, anemia was related to low physical activity, weakness(weaker) and walked more slowly. Another study from Spain indicated that anemia is independently associated with frailty in older people.[25] Moreover, Xu et.al found that Hb is closely associated with frailty in elder patients in hospital.[9] A systematic review and meta-analysis including 19 studies indicated that older adults with anemia have more than a two-fold increased odds of frailty.[26] Silva et.al suggested that lower Hb level should be considered a significant component of frailty in older persons.[27] Similarly, another meta-analysis including 32,934 robust participants and 6864 frail participants found that Hb is a useful biomarker of frailty.[7] However, there were no significant association of lower Hb and frailty after adjusting confounding factors in our study. The discrepancy of results may be due to the definition of lower Hb is determined by the optimal cut-off value of the ROC curve in this research. Therefore, further studies are needed to confirm the relationship between Hb and frailty in older people.

A increasing RDW also can lead to low HRR. Studies have proved that increased RDW is related to inflammation. Inflammatory cytokines reduce erythropoietin gene expression and erythropoietin receptor expression, which lead to the release of immature erythrocytes and heterogeneity of the erythrocyte volume increasing.[28,29] In addition, metabolic abnormalities including shortened telomere length, oxidative stress, and malnutrition may also contribute to increased RDW.[30,31] What's more, others have suggested that RDW may be a potential biomarker for biological aging.[29] Study has indicated that a high RDW was related to a high sarcopenia risks.[32] Sarcopenia, which plays a key role in frailty, is a progressive loss of

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skeletal muscle mass and strength.[27]

RDW is a biomarker of inflammation, oxidative stress, poor nutritional status, aging, and sarcopenia, and all of these could be underlying reasons of development of frailty. A study enrolled 3,635 community-dwelling older men indicated that participants with a high RDW are more likely to have functional limitations and frailty.[29] Li et.al indicated that increased RDW may be closely related to frailty through inflammation.[13] Hou et.al proved that frailty is closely associated with RDW in elder patients with CHD.[11] Another study including 2,932 community-dwelling older adults found RDW is independently associated with high frailty risk even after adjusting for potential confounding factors.[12]

To sum up, a large number of researches have verified the association between frailty and a low Hb and a high RDW among older persons. However, both RDW and Hb are susceptible to many other diseases conditions and sub-health states, HRR may provide a more powerful parameter than a single parameter alone. Moreover, ROC analysis showed that the AUC and highest sensitivity of HRR are higher than RDW and Hb. It may be a more reliable and effective marker than Hb and RDW alone.

There were also some limitations of our present study. Firstly, this was a cross-sectional study that cannot assess the cause-effect relationship. Secondly, our participants are limited to local participants, these findings need to be validated in different populations around the world. Finally, we did not assess iron, folic, and vitamin B12, which may affect RDW and Hb level.

Conclusion

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In conclusion, a low HRR is independent associated with higher frailty risk in community-dwelling older adults. This inexpensive and common laboratory parameter may provide useful information to identify the risk of frailty in older adults. Furthermore, use of the HRR may help clinicians to identify people at high risk of frailty and take effective measures to reduce the occurrence and development of frailty, reduce the rate of disability and mortality related to frailty in the elderly, and reduce the waste of medical resources, and promote healthy ageing. Evidence is needed from cohort studies to verify this conclusions in the future.

Author contributions

Conceptualization: Zhifan Xiong, Mengpei Zhu

Data curation: Mengpei Zhu, Chao Wei, Yushuang Xu

Formal analysis: Mengpei Zhu, Chao Wei

Visualization: Xiongjun Yang, Yumei Huang

Writing – original draft: Mengpei Zhu

Writing – review and editing: Zhifan Xiong, Mengpei Zhu, Chao Wei, Xiongjun Yang, Yumei Huang, Yushuang Xu. All authors read and approved the final manuscript.

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Data availability

Data for this study are available from the corresponding author.

Declaration

The authors report no conflicts of interest in this work.

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Figure legends

Figure1 ROC curve for HRR (A), Hb (B) and RDW (C)

Notes:

A. ROC curve indicated that the best intercept value for HRR was 9.97 (sensitivity 84.5%, specificity 61.9%, AUC = 0.802, P<0.001)

B. ROC curve indicated that the best intercept value for Hb was 131.5 (sensitivity 81% , specificity 57.1%, AUC = 0.742, P<0.001)

C. ROC curve indicated that the best intercept value for RDW was 13.45 (sensitivity 56.2% ,

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423 specificity 81.1%, AUC = 0.712, P<0.001)

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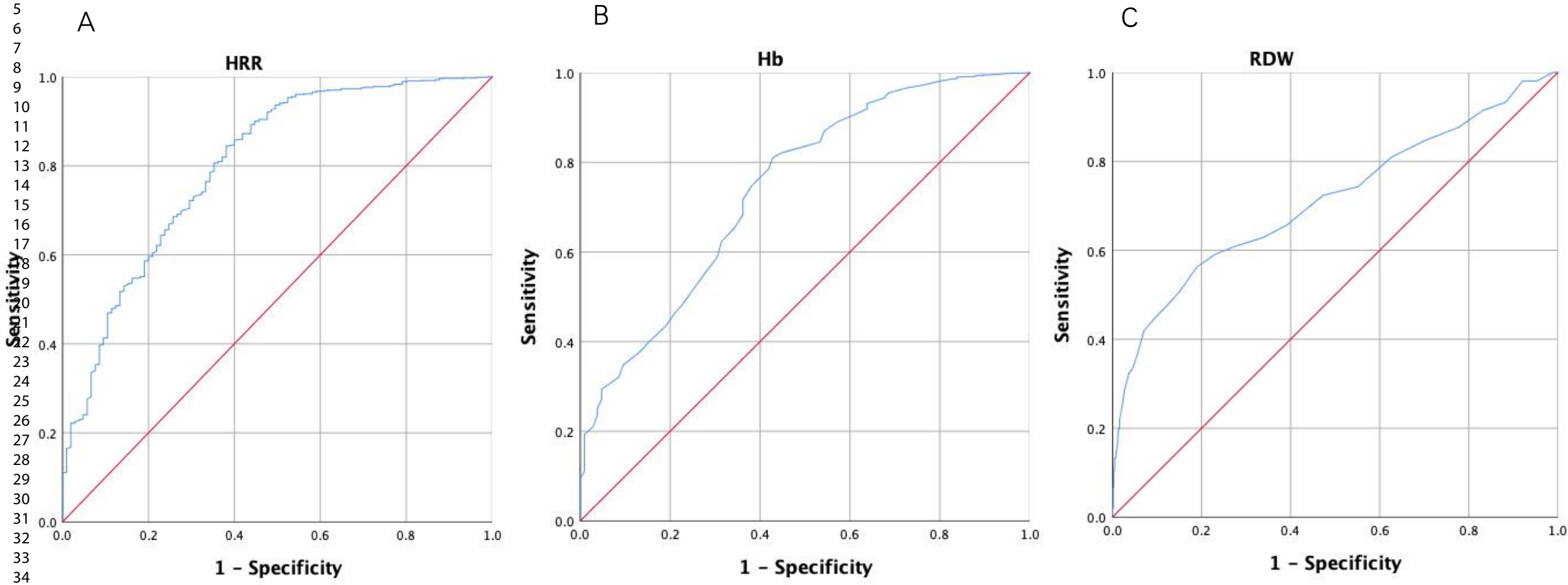
Figure1.


A
HRR
Sensitivity
1 – Specificity
0.0
0.2
0.4
0.6
0.8
1.0
B
Hb
Sensitivity
1 – Specificity
C
RDW
Sensitivity
1 – Specificity

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5*

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Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11

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		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Lower Hemoglobin-to-Red Blood Cell Distribution Width Ratio Is Independently Associated With Frailty in Community-dwelling Older Adults: a cross-sectional study

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Secondary Subject Heading:	Global health
Keywords:	GERIATRIC MEDICINE, EPIDEMIOLOGY, GENERAL MEDICINE (see Internal Medicine)

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Lower Hemoglobin-to-Red Blood Cell Distribution Width Ratio Is Independently Associated With Frailty in Community-dwelling Older Adults: a cross-sectional study

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Abstract

Objectives: The importance of blood cell markers in frailty has been studied. However, research on hemoglobin-to-red blood cell distribution width ratio (HRR) and frailty in older persons is still limited. We investigated the association between HRR and frailty in older adults.

Design: Cross-sectional population-based study.

Setting: Community-dwelling older adults older than 65 years old were recruited from September 2021 to December 2021.

Participants: A total of 1296 community-dwelling older adults (age ⩾ 65 years) in Wuhan were included in the study.

Main outcome measures: The main outcome was the presence of frailty. The Fried Frailty Phenotype Scale was used to evaluate the frailty status of the participants. Multivariable logistic regression analysis was performed to determine the relationship between HRR and frailty.

Results: A total of 1296 (564 man) older adults were included in this cross-sectional study. Their mean age was 70.89 ± 4.85 years. ROC analysis showed that HRR is a good predictor of frailty in older people, the area under the curve (AUC) was 0.802 (95% CI: 0.755 to 0.849), and the highest sensitivity was 84.5% and the specificity was 61.9% with the optimal critical values 9.97 (P<0.001). Multiple logistic regression analysis indicated that lower HRR (<9.97) (OR:3.419, 1.679-6.964, P=0.001) is independently associated with frailty in older people, even after adjusting confounding factors.

Conclusion: Lower HRR is closely associated with an increased risk of frailty in the older people. Lower HRR may be an independent risk factor for frailty in community-dwelling older

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adults.

Keywords: Older people, Frailty, Healthy aging, Risk factor, HRR

Strengths and limitations of this study

Frailty was diagnosed in accordance with the Fried's frailty phenotype.

This cross-sectional analysis was performed in a medium volume population.

Some variables were self-reported, but best available measures were used.

The study reflects the situation of older adults in Wuhan, China, and the generalizability needs to be further verified.

This was a cross-sectional study that cannot assess the cause-effect relationship.

Introduction

As life expectancy increases, human societies are aging globally, in both developed and developing countries.[1] By 2050, the proportion of people aged over 60 years is projected to increase from 11% to 22%, and the number of aged over 60 years will increase from 605 million to 2.1 billion, including 425 million people aged over 80 in the world.[2] Frailty becomes an emerging global public health burden, with the rapid growth of the global aging population. Frailty is considered to be a complex age-related clinical condition characterized by a decline in the physiological function of multiple organs, with a resultant increased vulnerability to stressors.[3] It is related to adverse health-related events, including increased mortality, hospitalization, falls and fractures, cognitive decline, disability, and admission to long-term care.[4] Therefore, early identifying modifiable risk factors of frailty is becoming increasing

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crucial for delaying and reversing frailty and its associated adverse events in older persons.[5]

As an important part of CBC, hemoglobin (Hb) is usually used as an indicator of the degree of anemia. However, previous studies showed that low Hb reflect to a decline in the physiological function including the decreased immune response, malnutrition, and the low resistance to external invasion.[6] Meanwhile, there are several studies indicated that Hb is related to frailty in older persons.[7-10] As an indicator of heterogeneity of the erythrocyte volume, red blood cell distribution width (RDW) is thought to be related to the prognosis of many diseases. Hou et al. indicated that RDW is significantly associated with the risk of frailty in older patients with coronary heart disease (CHD).[11] In addition, studies showed that RDW is associated with frailty both in older inpatients and community-dwelling older people.[12,13]

RDW can be affected by complex conditions, the effect of RDW on frailty is not only related to inflammatory response, but also association with a decline in the physiological function and oxygen.[14] RDW alone may not provide definitive predictive information.[14,15] The hemoglobin-to-RDW ratio (HRR) is a cheap, rapid and readily available novel prognostic, which combines the prognostic information of Hb and RDW and reflects a more comprehensive health status.[14,16] Recently, Qu et al. found that lower HRR is independent related to the risk of frailty in older patients with CHD.[14] They verified that HRR maybe a more useful biomarker comparing with RDW or Hb alone.[14]

Studies have showed a significant association of HRR with frailty in specific populations (patients with coronary heart disease).[14] However, research on HRR and frailty in the general older persons is still limited, and the significance of evaluating frailty is not yet clear. In the present study, we investigated the relationship between HRR and frailty in

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community-dwelling older adults.

Material & Methods

Patient and public involvement

The source population was the community-dwelling adults older than 65 living in communities in Wuhan. The study population consisted of a random sample of older people from each community. Inclusion criteria were the community-dwelling adults older than 65 living in communities in Wuhan. Exclusion criteria were malignant disease or advanced organic diseases, hematologic diseases, acute stage of disease, and participants with missing the key parameters.

Participants and Sociodemographic Characteristics

In this present study, we recruited 1,296 community-dwelling adults older than 65 living in communities in Wuhan between September 2021 and December 2021. Sociodemographic characteristics, including age, gender, education years, marital status, smoking history, alcohol consumption, comorbidities, including hypertension, diabetes, CHD, hyperlipidemia, and cerebrovascular disease were recorded. Then body mass index (BMI), waistline , blood pressure and pulse rate were measured by two professional clinicians.

Peripheral Blood Parameters

Blood samples were collected, and full blood count was measured by automated hematology analyzer (Mindray, BC7500, China). Other related biochemical indicators were detected by automatic biochemical analyzer (Beckman, AU680, American). HRR = Hb (g/L)/RDW (%).

Fried's frailty phenotype

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According to the Fried's frailty phenotype, we evaluated frailty in five criteria, as follows (1) Weight loss: unintentional weight loss >5% or a loss of more than 4.5 kg in the past 1 year. (2) Physical weakness: dynamometer was used for participants for three trials, the maximum value was recorded. Low grip strength was defined according to the standards proposed by Fried et al.[17] (3) Slowness: slowness was defined as when the time required to walk 4.6 meters was more than 7 seconds for males (height ≤ 173 cm) and females (height ≤ 159 cm) or more than 6 seconds for males (height >173 cm) and females (height >159 cm). (4) Physical activity: low physical activity was defined as less than 383 kcal/week for males and less than 270 kcal/week for females. (5) Exhaustion: exhaustion was assessed by the following two questions from the CES-D. "In the last week, I felt that everything I did was an effort" and "Could not get going in the last week." If the participant responded "yes" to either of these questions, the participant was considered exhausted. Participants with >3 indicators were defined as frail, 1-2 as prefrail and none as robust.

Patient and public involvement statement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination of this research.

Statistical analysis

Continuous and categorical variables were expressed as the mean ± standard deviation and numbers with percentages, respectively. The baseline characteristics of the groups were compared using one-way analysis of variance and chi-squared test. The predictive value of HRR for frailty was assessed by receiver operating curve (ROC) analysis. The prognostic value of lower HRR on frailty was assessed using logistic regression model. Variables were

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selected as candidates for the multivariate analysis when p<0.1 in the univariate analysis. After adjustment for confounding factors including age, gender, marital status, education years, alone living, BMI, diabetes, RBC, albumin, triglyceride, HDL-C and LDL-C, assessing the independent risk factors for frailty in older adults. Kendall's tau-b correlation analysis was used to assessing the correlation between lower Hb, lower RDW, lower HRR, and frailty in older adults. The p-values <0.05 was considered statistically significant. All statistical analysis were conducted using SPSS (ver. 26.0, IBM Corporation, Armonk, NY, USA).

Result

Characteristics of the study population

A total of 1296 (564 man) older adults were included in our study. Their mean age was 70.89 ± 4.85 years. Of the 1296 participants, 582 (44.9%) has hypertension, 183 (14.1%) were diabetes patients, 98 (7.6%) had cardiac diseases, and 43 (3.3%) had cranial vascular disease. The proportions of individuals with a habit of smoking and drinking were 11.1% and 11.7%, respectively. And 149 (11.5%) older adults were living alone. According to Fried's frailty phenotype, there were 55.09% (714) in robust group, 36.81% (477) in pre-frail group, and 8.10% (105) in frail group. Baseline characteristics of three group were shown in Table 1.

Table1. Baseline characteristics of the study population stratified by frailty

Characteristics	Robust (n=714)	Pre-frail (n=477)	Frailty (n=105)	p-value
Age, years (SD)	69.81 ± 3.89	71.71 ± 5.34	70.89 ± 4.85	<0.001
Male gender, n (%)	347 (48.60%)	184 (38.57%)	33 (31.43%)	<0.001
Marital status Married, n (%)	622 (87.11%)	408 (85.53)	77 (73.33%)	0.001
Other*, n (%)	92 (12.89%)	69 (14.47%)	28 (26.67%)	
Education years 0-12, n (%)	466(65.27%)	337(70.65%)	85(80.95%)	0.002

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>12, n (%)	248(24.73%)	140(29.35%)	20(19.05%)	
Alone living, n (%)	74 (10.36%)	53 (11.11%)	22 (20.95%)	0.006
Smoking, n (%)	90(12.61%)	44(9.22%)	10(9.52%)	0.165
Drinking, n (%)	92(12.89%)	50(10.48%)	10(9.52%)	0.345
Hypertension, n (%)	314(43.98%)	212(44.44%)	56(53.33%)	0.192
Diabetes mellitus, n (%)	81(11.34%)	82(17.19%)	20(19.05%)	0.006
Cardiac diseases, n (%)	46(6.44%)	41(8.60%)	11(10.48%)	0.194
Cranial vascular disease, n (%)	24(2.94%)	15(3.14%)	4(3.80%)	0.938
BMI, kg/m^2 (SD)	24.69 ± 3.05	24.32 ± 3.14	23.83 ± 3.51	0.011
Waist circumference, cm (SD)	86.99 ± 8.66	86.32 ± 8.57	85.42 ± 9.46	0.143
SBP, mmHg (SD)	141.61 ± 18.53	142.73 ± 17.74	143.01 ± 19.37	0.516
DBP, mmHg (SD)	83.77 ± 10.44	82.87 ± 9.75	80.44 ± 10.91	0.006
Heart rate, beats/min (SD)	79.9 ± 13.4	79.8 ± 13.2	81.1 ± 13.0	0.659
WBC, 10^9/L (SD)	6.39 ± 1.51	6.36 ± 1.56	6.29 ± 1.69	0.781
Neutrophils, 10^9/L (SD)	3.89 ± 1.22	3.86 ± 1.26	3.96 ± 1.29	0.699
Lymphocytes, 10^9/L (SD)	1.95 ± 0.58	1.96 ± 0.64	1.76 ± 0.59	0.007
Eosinophils, 10^9/L (SD)	0.14 ± 0.12	0.14 ± 0.12	0.15 ± 0.18	0.628
PLT, 10^9/L (SD)	212.4 ± 52.2	216.3 ± 52.0	207.9 ± 66.1	0.251
RBC, 10^9/L (SD)	4.73 ± 0.41	4.51 ± 0.42	4.41 ± 0.65	<0.001
Hemoglobin, g/L (SD)	145.51 ± 12.15	137.29 ± 11.79	129.55 ± 13.73	<0.001
Anemia, n (%)	6 (0.84%)	17 (3.56%)	21 (20%)	<0.001
RDW, % (SD)	12.89 ± 0.55	13.15 ± 0.69	13.88 ± 1.39	<0.001
HRR	11.31 ± 1.02	10.47 ± 1.05	9.43 ± 1.41	<0.001
FBG, mmol/L (SD)	6.28 ± 1.59	6.37 ± 1.90	6.56 ± 2.13	0.278
Albumin, g/dL (SD)	46.23 ± 2.19	45.86 ± 2.47	45.13 ± 2.90	<0.001
Globulin, g/dL (SD)	30.26 ± 3.44	30.64 ± 3.65	30.55 ± 5.25	0.194
Triglyceride, mmol/L (SD)	1.49 ± 0.85	1.46 ± 0.90	1.44 ± 0.85	0.883
Total Cholesterol, mmol/L (SD)	5.17 ± 1.04	5.19 ± 1.15	4.96 ± 1.05	0.122
HDL-C, mmol/L (SD)	1.50 ± 0.39	1.54 ± 0.42	1.54 ± 0.38	0.333
LDL-C, mmol/L (SD)	3.03 ± 0.82	3.02 ± 0.90	2.82 ± 0.88	0.060

SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, FBG=fasting blood-glucose, WBC=white blood cell, PLT=platelets count, RBC=red blood cell, RDW=red blood cell distribution width, HRR=hemoglobin-to-RDW ratio.

Other* including separated, divorced, never married or widowed

ROC curve analysis

The predictive value of HRR for frailty in older adults was assessed by ROC analysis. The AUC for HRR in the frailty older adults was 0.802 (95% CI: 0.755 to 0.849), and the highest sensitivity was 84.5% and the specificity was 61.9% with the optimal critical values 9.97

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(Figure 1). The AUC for Hb was 0.742 (95% CI: 0.691 to 0.793), the highest sensitivity was 81% and the specificity was 57.1% with the optimal critical values 131.5 (Figure 1). The AUC for RDW was 0.712 (95% CI: 0.651 to 0.772), the highest sensitivity was 56.2% and the specificity was 81.1% with the optimal critical values 13.45 (Figure 1). Compared with Hb and RDW alone, HRR was a more strong prognostic biomarker for frailty.

Differences in clinical characteristics of the study population stratified by HRR

According to ROC analysis, the optimal critical values of HRR was 9.97. Participants were grouped according to the optimal critical values of HRR, as follows: 1046 (80.71%) in the normal HRR group and 250(19.29%) in the lower HRR group (Table 2). Compared with the normal HRR group, the lower HRR group had a higher lymphocytes count (P=0.002), and RDW (P<0.001), but a lower hemoglobin (P<0.001), RBC (P<0.001) and albumin (P<0.001). Compared with normal HRR group, the lower HRR group were more likely to have frailty (P<0.001).

Table2. Baseline characteristics of the study population stratified by HRR

Characteristics	Normal HRR (n=1046)	Lower HRR (n=250)	P-value
Age, years (SD)	70.50 ± 4.64	72.50 ± 5.40	<0.001
Male gender, n (%)	501 (47.9%)	63 (25.2%)	<0.001
Marital status Married, n (%)	901 (86.14%)	206 (82.4%)	0.133
Other*, n (%)	145 (13.86%)	44 (17.6%)	
Education years 0-12, n (%)	691 (66.06%)	197 (78.8%)	<0.001
>12, n (%)	355 (33.94%)	53 (21.2%)	
Alone living, n (%)	114 (10.90%)	35 (14.0%)	0.167
Smoking, n (%)	129 (12.33%)	15 (6.0%)	0.004
Drinking, n (%)	136 (13.0%)	16 (6.4%)	0.004
Hypertension, n (%)	456 (43.59%)	126 (50.4%)	0.052
Diabetes mellitus, n (%)	140 (13.38%)	43 (17.2%)	0.120
Cardiac diseases, n (%)	82 (7.84%)	16 (6.4%)	0.439
Cranial vascular disease, n (%)	32 (3.06%)	11 (4.4%)	0.288
BMI, kg/m^2 (SD)	24.56 ± 3.07	24.15 ± 3.36	0.026

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Waist circumference, cm (SD)		86.90 ± 8.51	85.45 ± 9.37	0.143
SBP, mmHg (SD)		142.3 ± 18.3	141.3 ± 18.5	0.611
DBP, mmHg (SD)		83.7 ± 10.2	80.9 ± 10.1	0.004
Heart rate, beats/min (SD)		80.2 ± 13.4	79.0 ± 12.7	0.362
WBC, 10^9/L (SD)		6.39 ± 1.49	6.28 ± 1.75	0.556
Neutrophils, 10^9/L (SD)		3.89 ± 1.19	3.86 ± 1.43	0.441
Lymphocytes, 10^9/L (SD)		1.96 ± 0.59	1.86 ± 0.69	0.002
Eosinophils, 10^9/L (SD)		0.14 ± 0.11	0.15 ± 0.17	0.621
PLT, 10^9/L (SD)		212.3 ± 50.8	218.3 ± 62.8	0.264
RBC, 10^9/L (SD)		4.71 ± 0.38	4.27 ± 0.56	<0.001
Hemoglobin, g/L (SD)		145.08 ± 10.98	124.90 ± 8.46	<0.001
RDW, % (IQR)		12.89 ± 0.51	13.79 ± 1.09	<0.001
FBG, mmol/L (SD)		6.36 ± 1.77	6.24 ± 1.70	0.166
Albumin, g/dL (SD)		46.18 ± 2.27	45.30 ± 2.69	<0.001
Globulin, g/dL (SD)		30.35 ± 3.45	30.72 ± 4.58	0.708
Triglyceride, mmol/L (SD)		1.48 ± 0.87	1.42 ± 0.83	0.755
Total Cholesterol, mmol/L (SD)		5.17 ± 1.07	5.10 ± 1.27	0.041
HDL-C, mmol/L (SD)		1.50 ± 0.39	1.58 ± 0.42	0.539
LDL-C, mmol/L (SD)		3.03 ± 0.85	2.91 ± 0.87	0.019
Frailty status	Robust, n (%)	669 (63.96%)	45 (18.0%)	<0.001
	Pre-frail, n (%)	337 (32.22%)	140 (56.0%)	
	Frailty, n (%)	40 (3.82%)	65 (26.0%)	

SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, FBG=fasting blood-glucose, WBC=white blood cell, PLT=platelets count, RBC=red blood cell, RDW=red blood cell distribution width, HRR=hemoglobin-to-RDW ratio.

Normal HRR=HRR above 9.97, Lower HRR: HRR below 9.97 (Optimal cut-off value of the ROC curve)

Other* including separated, divorced, never married or widowed

Logistic regression analysis

Among 1296 older adults, 105 (8.10%) were considered frail. Multiple logistic regression analysis was conducted to assessing the associations of the lower HRR with frailty. Unadjusted model1 showed that lower Hb (OR:2.129,1.133-4.001, p=0.019) and lower HRR (OR:3.285,1.676-6.440, p=0.001) were risk factors related to frailty, whereas lower RDW (OR:0.310, 0.193-0.497, p<0.001) was a protective factor. After adjustment for confounding factors (including age, gender, marital status, education years, living alone, BMI, diabetes, RBC, albumin, triglyceride, HDL-C and LDL-C), there was significant

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association of lower HRR (OR:3.419, 1.679-6.964, p=0.001) and lower RDW (OR:0.285, 0.170-0.477, p< 0.001) with frailty (Table 3). Lower HRR was independently related to frailty in older adults.

Table3. Multiple logistic regression analysis of blood parameters and frailty in older adults

	Model1		Model2	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Categorical variable				
Lower Hb	2.129 (1.133-4.001)	0.019	1.163 (0.562-2.409)	0.684
Lower RDW	0.310(0.193-0.497)	<0.001	0.285 (0.170-0.477)	<0.001
Lower HRR	3.285 (1.676-6.440)	0.001	3.419 (1.679-6.964)	0.001

Hb=hemoglobin, RDW=red blood cell distribution width, HRR=hemoglobin-to-RDW ratio.

Lower Hb: <131.5g/L, Lower RDW: <13.45%, Lower HRR: <9.97. (Optimal cut-off value of the ROC curve)

OR: odds ratio, CI: confidence interval, Model 1, unadjusted; Model 2, adjusted for age, gender, marital status, education years, alone living, BMI, diabetes, RBC, albumin, triglyceride, HDL-C and LDL-C.

Correlation Analysis

Correlation analysis indicated that there was an obvious positive correlation between RDW (Kendall's tau-b=0.173, P<0.001) and frailty. Nevertheless, HRR (Kendall's tau-b=-0.239, P<0.001) and Hb (Kendall's tau-b=-0.194, P<0.001) were a negative correlation with frailty (Table 4).

Table4. Correlation analysis of Hb, RDW, HRR, and frailty in older adults

	Kendall's tau-b	p

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Hb	-0.194	<0.001
RDW	0.173	<0.001
HRR	-0.239	<0.001

**. Correlation is significant at the 0.01 level (2-tailed).

Discussion

Frailty, as a geriatric syndrome, has attracted more and more scientific attention in the background of continuously increase global population aging.[18] In this cross-sectional study including 1,296 community-dwelling older adults, we found that lower HRR is independently related to frailty in older people, even after adjusting confounding factors (P=0.001). Multiple logistic regression analysis showed that lower HRR is associated with to a 3-fold more likelihood or odds of frailty (OR = 3.419, 95%CI 1.679-6.964). ROC analysis showed that the AUC for HRR in the frailty older adults was 0.802, and the highest sensitivity was 84.5% and the specificity was 61.9% with the optimal critical values 9.97. The results of the present study confirmed that HRR was also significantly associated with frailty in the general older people, not only in patients with coronary heart disease in previous studies.

HRR is cost-effective, common, and accessible laboratory parameter for clinicians. As a novel inflammatory factor, Qu et.al found that HRR is a significant associated with frailty in older patients with CHD.[14] In there study the AUC for HRR in the frailty patients was exceed Hb and RDW, and after adjusting confounding factors lower HRR was a risk factor for frailty in older patients with CHD. These findings are consistent with our results. Now the pathophysiological mechanism has not been fully understood. We try to provide a possible explanation for the association between HRR and frailty in older adults.

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A decreased in HRR may be due to low Hb, high RDW, or both. As we all know, low Hb indicates a condition of anemia, which is one of the acknowledged risk factors for hospitalization, morbidity, and mortality in older people.[19] Anemia decreases the oxygen-carrying capacity, leading to tissue hypoxia and even organ failure, especially in older patients, increasing the risk of frailty.[20] Besides, anemia can cut down submaximal and maximal aerobic capacity, leading to several adverse outcomes including loss of muscle strength, cognitive decline and development of frailty.[10] In addition, chronic conditions and comorbidities leading to a low grade of inflammation reducing hemoglobin level,[21] also known as chronic diseases anemia, which is the most common type of anemia in older adults.[20] And a state of chronic inflammation has been suggested as contributors to frailty.[22] Furthermore, anemia caused by malnutrition is also a significance health-affecting factor among older adults.[20]

Anemia reaching a prevalence of 17% in older people, is a threat to healthy aging.[23] Corona et.al found that lower hemoglobin and anemia were related to frailty in Brazilian older adults.[8] In their study, anemia was related to low physical activity, weakness(weaker) and walked more slowly. Another study from Spain indicated that anemia is independently associated with frailty in older people.[24] Moreover, Xu et.al found that Hb is closely associated with frailty in elder patients in hospital.[9] A systematic review and meta-analysis including 19 studies indicated that older adults with anemia have more than a two-fold increased odds of frailty.[25] Silva et.al suggested that lower Hb level should be considered a significant component of frailty in older persons.[26] Similarly, another meta-analysis including 32,934 robust participants and 6864 frail participants found that Hb is a useful biomarker of frailty.[7]

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However, there were no significant association of lower Hb and frailty after adjusting confounding factors in our study. The discrepancy of results may be due to the definition of lower Hb is determined by the optimal cut-off value of the ROC curve in this research. Therefore, further studies are needed to confirm the relationship between Hb and frailty in older people.

A increasing RDW also can lead to low HRR. Studies have proved that increased RDW is related to inflammation. Inflammatory cytokines reduce erythropoietin gene expression and erythropoietin receptor expression, which lead to the release of immature erythrocytes and heterogeneity of the erythrocyte volume increasing.[27,28] In addition, metabolic abnormalities including shortened telomere length, oxidative stress, and malnutrition may also contribute to increased RDW.[29,30] What's more, others have suggested that RDW may be a potential biomarker for biological aging.[28] Study has indicated that a high RDW was related to a high sarcopenia risks.[31] Sarcopenia, which plays a key role in frailty, is a progressive loss of skeletal muscle mass and strength.[26]

RDW is a biomarker of inflammation, oxidative stress, poor nutritional status, aging, and sarcopenia, and all of these could be underlying reasons of development of frailty. A study enrolled 3,635 community-dwelling older men indicated that participants with a high RDW are more likely to have functional limitations and frailty.[28] Li et.al indicated that increased RDW may be closely related to frailty through inflammation.[13] Hou et.al proved that frailty is closely associated with RDW in elder patients with CHD.[11] Another study including 2,932 community-dwelling older adults found RDW is independently associated with high frailty risk even after adjusting for potential confounding factors.[12]

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To sum up, a large number of researches have verified the association between frailty and a low Hb and a high RDW among older persons. However, both RDW and Hb are susceptible to many other diseases conditions and sub-health states, HRR may provide a more powerful parameter than a single parameter alone. Moreover, ROC analysis showed that the AUC and highest sensitivity of HRR are higher than RDW and Hb. It may be a more reliable and effective marker than Hb and RDW alone.

This inexpensive and common laboratory parameter may provide useful information to identify the risk of frailty in older adults. Furthermore, use of the HRR may help clinicians to identify people at high risk of frailty and take effective measures to reduce the occurrence and development of frailty, reduce the rate of disability and mortality related to frailty in the elderly, and reduce the waste of medical resources, and promote healthy ageing.

There were also some limitations of our present study. Firstly, because cross-sectional studies measure the outcome and the exposures in the study participants at the same time, it is difficult to assess the cause-effect relationship. Secondly, our participants are limited to local participants, these findings need to be validated in different populations around the world. What is more, we unable to investigate the temporal relation between outcomes and risk factors. In addition, despite the inevitable selection bias and information bias in cross-sectional studies, we improved this problem through more rational statistical methods and interviewer training. Finally, we did not assess iron, folic, and vitamin B12, which may affect RDW and Hb level.

Conclusion

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In conclusion, a low HRR is independent associated with higher frailty risk in community-dwelling older adults. And this relationship is not affected by confounding factors. However, the causal relationship and the specific mechanism between the HRR and frailty is unclear. Evidence is needed from prospective studies to verify this conclusions in the future.

Author contributions

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Writing – original draft: Mengpei Zhu

Writing – review and editing: Zhifan Xiong, Mengpei Zhu, Chao Wei, Xiongjun Yang, Yumei Huang, Yushuang Xu. All authors read and approved the final manuscript.

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Data availability

Data for this study are available from the corresponding author.

Declaration

The authors report no conflicts of interest in this work.

Ethics statements

Patient consent for publication

Not applicable.

Ethical approval

The research protocol was approved by the Medical Ethics Committee of Liyuan Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRB ID: [2020] IEC (A016)). All the participants gave written informed consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

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Figure legends

Figure1 ROC curve for HRR (A), Hb (B) and RDW (C)

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Notes:

A. ROC curve indicated that the best intercept value for HRR was 9.97 (sensitivity 84.5%, specificity 61.9%, AUC = 0.802, P<0.001)

B. ROC curve indicated that the best intercept value for Hb was 131.5 (sensitivity 81% , specificity 57.1%, AUC = 0.742, P<0.001)

C. ROC curve indicated that the best intercept value for RDW was 13.45 (sensitivity 56.2% , specificity 81.1%, AUC = 0.712, P<0.001)

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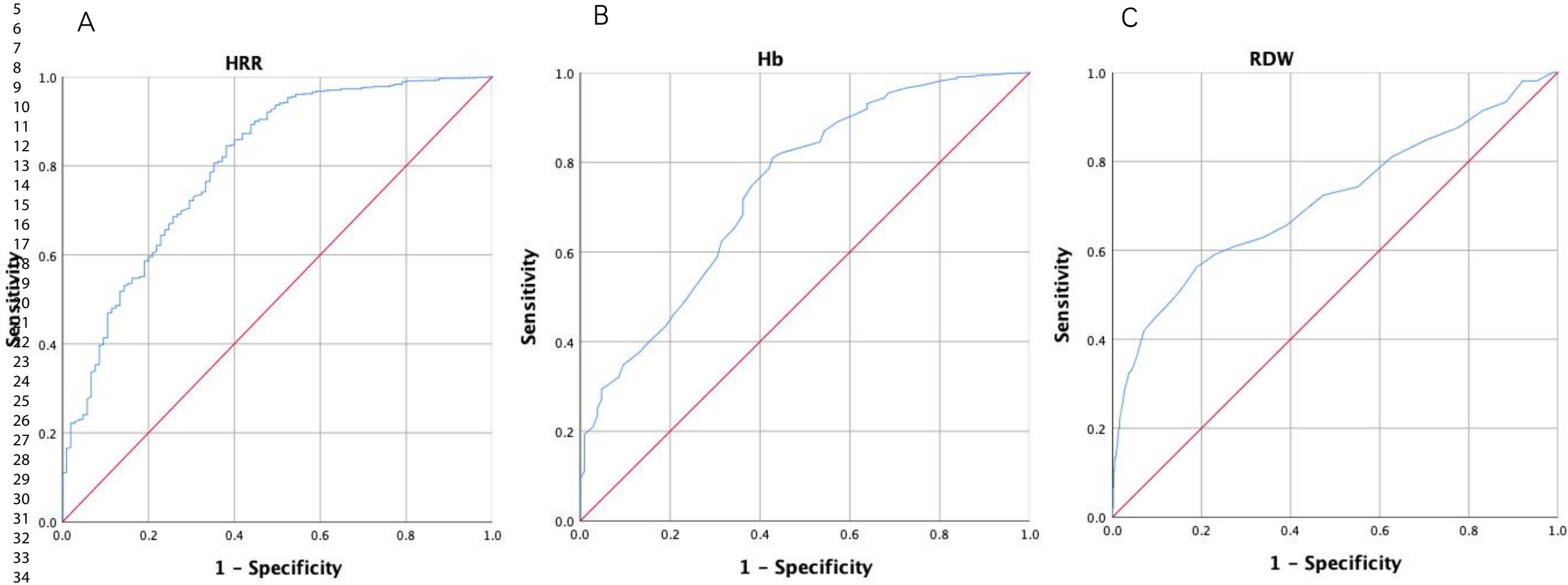
Figure1.


A
HRR
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B
Hb
Sensitivity
1 – Specificity
C
RDW
Sensitivity
1 – Specificity

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5*

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Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11

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		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Lower Hemoglobin-to-Red Blood Cell Distribution Width Ratio Is Independently Associated With Frailty in Community-dwelling Older Adults: a cross-sectional study

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Lower Hemoglobin-to-Red Blood Cell Distribution Width Ratio Is Independently Associated With Frailty in Community-dwelling Older Adults: a cross-sectional study

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Abstract

Objectives: The importance of blood cell markers in frailty has been studied. However, research on hemoglobin-to-red blood cell distribution width ratio (HRR) and frailty in older persons is still limited. We investigated the association between HRR and frailty in older adults.

Design: Cross-sectional population-based study.

Setting: Community-dwelling older adults older than 65 years old were recruited from September 2021 to December 2021.

Participants: A total of 1296 community-dwelling older adults (age ⩾ 65 years) in Wuhan were included in the study.

Main outcome measures: The main outcome was the presence of frailty. The Fried Frailty Phenotype Scale was used to evaluate the frailty status of the participants. Multivariable logistic regression analysis was performed to determine the relationship between HRR and frailty.

Results: A total of 1296 (564 men) older adults were included in this cross-sectional study. Their mean age was 70.89 ± 4.85 years. ROC analysis showed that HRR is a good predictor of frailty in older people, the area under the curve (AUC) was 0.802 (95% CI: 0.755 to 0.849), and the highest sensitivity was 84.5% and the specificity was 61.9% with the optimal critical values 9.97 (P<0.001). Multiple logistic regression analysis indicated that lower HRR (<9.97) (OR:3.419, 1.679-6.964, P=0.001) is independently associated with frailty in older people, even after adjusting confounding factors.

Conclusion: Lower HRR is closely associated with an increased risk of frailty in older people. Lower HRR may be an independent risk factor for frailty in community-dwelling older adults.

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Keywords: Older people, Frailty, Healthy aging, Risk factor, HRR

Strengths and limitations of this study

Frailty was diagnosed by following Fried's frailty phenotype.

This cross-sectional analysis was performed in a medium-volume population.

Some variables were self-reported, but the best available measures were used.

The study reflects the situation of older adults in Wuhan, China, and the generalizability needs to be further verified.

This was a cross-sectional study that cannot assess the cause-effect relationship.

Introduction

As life expectancy increases, human societies are aging globally, in both developed and developing countries.[1] By 2050, the proportion of people aged over 60 years is projected to increase from 11% to 22%, and the number of people aged over 60 years will increase from 605 million to 2.1 billion, including 425 million people aged over 80 in the world.[2] Frailty becomes an emerging global public health burden, with the rapid growth of the global aging population. Frailty is considered to be a complex age-related clinical condition characterized by a decline in the physiological function of multiple organs, with a resultant increased vulnerability to stressors.[3] It is related to adverse health-related events, including increased mortality, hospitalization, falls and fractures, cognitive decline, disability, and admission to long-term care.[4] Therefore, early identifying modifiable risk factors of frailty is becoming increasingly crucial for delaying and reversing frailty and its associated adverse events in older

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persons.[5]

As an important part of CBC, hemoglobin (Hb) is usually used as an indicator of the degree of anemia. However, previous studies showed that low Hb reflects to a decline in physiological function including decreased immune response, malnutrition, and low resistance to external invasion.[6] Meanwhile, there are several studies indicating that Hb is related to frailty in older persons.[7-10] Red blood cell distribution width (RDW) is a simple parameter of CBC, which reflects the degree of heterogeneity of the erythrocyte volume, and is traditionally used for the differential diagnosis of anemia.[11] However, with the deepening of the study, it was found to be related to the prognosis of many diseases. Increased RDW reflects dysregulation of erythrocyte homeostasis, which may be attributed to various underlying metabolic abnormalities such as shortened telomere length, oxidative stress, inflammation, malnutrition, dyslipidemia, hypertension, erythrocyte fragmentation, and altered erythropoietin function.[11]

Inflammation has been identified as a potential cause of frailty.[12] Inflammation in response to elevated RDW may be highly correlated with frailty. Hou et al. indicated that RDW is significantly associated with the risk of frailty in older patients with coronary heart disease (CHD).[13] In addition, studies showed that increased RDW is associated with frailty both in older inpatients and community-dwelling older people.[14,15] However, it is still controversial whether RDW alone can predict frailty.[16,17] The hemoglobin-to-RDW ratio (HRR) is a cheap, rapid, and readily available novel prognostic, which combines the prognostic information of Hb and RDW and reflects a more comprehensive health status.[16,18] Recently, Qu et al. found that lower HRR is independently related to the risk of frailty in older patients with CHD.[16] They

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verified that HRR may be a more useful biomarker compared with RDW or Hb alone.[16]

Studies have shown a significant association of HRR with frailty in specific populations (patients with coronary heart disease).[16] However, research on HRR and frailty in general older persons is still limited, and the significance of evaluating frailty is not yet clear. In the present study, we investigated the relationship between HRR and frailty in community-dwelling older adults.

Material & Methods

Patient and public involvement

The source population was the community-dwelling adults older than 65 living in communities in Wuhan. The study population consisted of a random sample of older people from each community. Inclusion criteria were the community-dwelling adults older than 65 living in communities in Wuhan. Exclusion criteria were malignant disease or advanced organic diseases, hematologic diseases, acute stage of disease, and participants with missing the key parameters.

Participants and Sociodemographic Characteristics

In this present study, we recruited 1,296 community-dwelling adults older than 65 living in communities in Wuhan between September 2021 and December 2021. Sociodemographic characteristics, including age, gender, education years, marital status, smoking history, alcohol consumption, and comorbidities, including hypertension, diabetes, CHD, hyperlipidemia, and cerebrovascular disease were recorded. The body mass index (BMI), waistline, blood pressure, and pulse rate were measured by two professional clinicians.

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Peripheral Blood Parameters

Blood samples were collected, and full blood count was measured by an automated hematology analyzer (Mindray, BC7500, China). Other related biochemical indicators were detected by an automatic biochemical analyzer (Beckman, AU680, American). HRR = Hb (g/L)/RDW (%).

Fried's frailty phenotype

According to Fried's frailty phenotype, we evaluated frailty in five criteria, as follows (1) Weight loss: unintentional weight loss >5% or a loss of more than 4.5 kg in the past 1 year. (2) Physical weakness: a dynamometer was used for participants for three trials, and the maximum value was recorded. Low grip strength was defined according to the standards proposed by Fried et al.[19] (3) Slowness: slowness was defined as when the time required to walk 4.6 meters was more than 7 seconds for males (height ≤ 173 cm) and females (height ≤ 159 cm) or more than 6 seconds for males (height >173 cm) and females (height >159 cm). (4) Physical activity: low physical activity was defined as less than 383 kcal/week for males and less than 270 kcal/week for females. (5) Exhaustion: exhaustion was assessed by the following two questions from the CES-D. "In the last week, I felt that everything I did was an effort" and "Could not get going in the last week." If the participant responded "yes" to either of these questions, the participant was considered exhausted. Participants with >3 indicators were defined as frail, 1-2 as prefrail, and none as robust.

Patient and public involvement statement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this research.

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Statistical analysis

Continuous and categorical variables were expressed as the mean standard deviation and numbers with percentages, respectively. The baseline characteristics of the groups were compared using a one-way analysis of variance and chi-squared test. The predictive value of HRR for frailty was assessed by receiver operating curve (ROC) analysis. The prognostic value of lower HRR on frailty was assessed using the logistic regression model. Variables were selected as candidates for the multivariate analysis when $p<0.1$ in the univariate analysis. After adjustment for confounding factors including age, gender, marital status, education years, alone living, BMI, diabetes, RBC, albumin, triglyceride, HDL-C, and LDL-C, assessing the independent risk factors for frailty in older adults. Kendall's tau-b correlation analysis was used to assessing the correlation between lower Hb, lower RDW, lower HRR, and frailty in older adults. The p-values <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (ver. 26.0, IBM Corporation, Armonk, NY, USA).

Result

Characteristics of the study population

A total of 1296 (564 men) older adults were included in our study. Their mean age was 70.89 ± 4.85 years. Of the 1296 participants, 582 (44.9%) has hypertension, 183 (14.1%) were diabetes patients, 98 (7.6%) had cardiac diseases, and 43 (3.3%) had cranial vascular disease. The proportions of individuals with a habit of smoking and drinking were 11.1% and 11.7%, respectively. And 149 (11.5%) older adults were living alone. According to Fried's

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frailty phenotype, there were 55.09% (714) in the robust group, 36.81% (477) in the pre-frail group, and 8.10% (105) in the frail group. The baseline characteristics of the three groups were shown in Table 1.

Table1. Baseline characteristics of the study population stratified by frailty

Characteristics	Robust (n=714)	Pre-frail (n=477)	Frailty (n=105)	p-value
Age, years (SD)	69.81 ± 3.89	71.71 ± 5.34	70.89 ± 4.85	<0.001
Male gender, n (%)	347 (48.60%)	184 (38.57%)	33 (31.43%)	<0.001
Marital status Married, n (%)	622 (87.11%)	408 (85.53)	77 (73.33%)	0.001
Other*, n (%)	92 (12.89%)	69 (14.47%)	28 (26.67%)	
Education years 0-12, n (%)	466(65.27%)	337(70.65%)	85(80.95%)	0.002
>12, n (%)	248(24.73%)	140(29.35%)	20(19.05%)	
Alone living, n (%)	74 (10.36%)	53 (11.11%)	22 (20.95%)	0.006
Smoking, n (%)	90(12.61%)	44(9.22%)	10(9.52%)	0.165
Drinking, n (%)	92(12.89%)	50(10.48%)	10(9.52%)	0.345
Hypertension, n (%)	314(43.98%)	212(44.44%)	56(53.33%)	0.192
Diabetes mellitus, n (%)	81(11.34%)	82(17.19%)	20(19.05%)	0.006
Cardiac diseases, n (%)	46(6.44%)	41(8.60%)	11(10.48%)	0.194
Cranial vascular disease, n (%)	24(2.94%)	15(3.14%)	4(3.80%)	0.938
BMI, kg/m^2 (SD)	24.69 ± 3.05	24.32 ± 3.14	23.83 ± 3.51	0.011
Waist circumference, cm (SD)	86.99 ± 8.66	86.32 ± 8.57	85.42 ± 9.46	0.143
SBP, mmHg (SD)	141.61 ± 18.53	142.73 ± 17.74	143.01 ± 19.37	0.516
DBP, mmHg (SD)	83.77 ± 10.44	82.87 ± 9.75	80.44 ± 10.91	0.006
Heart rate, beats/min (SD)	79.9 ± 13.4	79.8 ± 13.2	81.1 ± 13.0	0.659
WBC, 10^9/L (SD)	6.39 ± 1.51	6.36 ± 1.56	6.29 ± 1.69	0.781
Neutrophils, 10^9/L (SD)	3.89 ± 1.22	3.86 ± 1.26	3.96 ± 1.29	0.699
Lymphocytes, 10^9/L (SD)	1.95 ± 0.58	1.96 ± 0.64	1.76 ± 0.59	0.007
Eosinophils, 10^9/L (SD)	0.14 ± 0.12	0.14 ± 0.12	0.15 ± 0.18	0.628
PLT, 10^9/L (SD)	212.4 ± 52.2	216.3 ± 52.0	207.9 ± 66.1	0.251
RBC, 10^9/L (SD)	4.73 ± 0.41	4.51 ± 0.42	4.41 ± 0.65	<0.001
Hemoglobin, g/L (SD)	145.51 ± 12.15	137.29 ± 11.79	129.55 ± 13.73	<0.001
Anemia, n (%)	6 (0.84%)	17 (3.56%)	21 (20%)	<0.001
RDW, % (SD)	12.89 ± 0.55	13.15 ± 0.69	13.88 ± 1.39	<0.001
HRR	11.31 ± 1.02	10.47 ± 1.05	9.43 ± 1.41	<0.001
FBG, mmol/L (SD)	6.28 ± 1.59	6.37 ± 1.90	6.56 ± 2.13	0.278
Albumin, g/dL (SD)	46.23 ± 2.19	45.86 ± 2.47	45.13 ± 2.90	<0.001
Globulin, g/dL (SD)	30.26 ± 3.44	30.64 ± 3.65	30.55 ± 5.25	0.194
Triglyceride, mmol/L (SD)	1.49 ± 0.85	1.46 ± 0.90	1.44 ± 0.85	0.883
Total Cholesterol, mmol/L (SD)	5.17 ± 1.04	5.19 ± 1.15	4.96 ± 1.05	0.122
HDL-C, mmol/L (SD)	1.50 ± 0.39	1.54 ± 0.42	1.54 ± 0.38	0.333
LDL-C, mmol/L (SD)	3.03 ± 0.82	3.02 ± 0.90	2.82 ± 0.88	0.060

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SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, FBG=fasting blood-glucose, WBC=white blood cell, PLT=platelets count, RBC=red blood cell, RDW=red blood cell distribution width, HRR=hemoglobin-to-RDW ratio.

Other* including separated, divorced, never married or widowed

ROC curve analysis

The predictive value of HRR for frailty in older adults was assessed by ROC analysis. The AUC for HRR in the frailty older adults was 0.802 (95% CI: 0.755 to 0.849), the highest sensitivity was 84.5% and the specificity was 61.9% with the optimal critical value of 9.97 (Figure 1). The AUC for Hb was 0.742 (95% CI: 0.691 to 0.793), the highest sensitivity was 81% and the specificity was 57.1% with the optimal critical value of 131.5 (Figure 1). The AUC for RDW was 0.712 (95% CI: 0.651 to 0.772), the highest sensitivity was 56.2% and the specificity was 81.1% with the optimal critical values 13.45 (Figure 1). Compared with Hb and RDW alone, HRR was a more strong prognostic biomarker for frailty.

Differences in clinical characteristics of the study population stratified by HRR

According to ROC analysis, the optimal critical value of HRR was 9.97. Participants were grouped according to the optimal critical values of HRR, as follows: 1046 (80.71%) in the normal HRR group and 250(19.29%) in the lower HRR group (Table 2). Compared with the normal HRR group, the lower HRR group had a higher lymphocytes count (P=0.002), and RDW (P<0.001), but lower hemoglobin (P<0.001), RBC (P<0.001), and albumin (P<0.001). Compared with the normal HRR group, the lower HRR group was more likely to have frailty (P<0.001).

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Table2. Baseline characteristics of the study population stratified by HRR

Characteristics		Normal HRR (n=1046)	Lower HRR (n=250)	P-value
Age, years (SD)		70.50 ± 4.64	72.50 ± 5.40	<0.001
Male gender, n (%)		501 (47.9%)	63 (25.2%)	<0.001
Marital status	Married, n (%)	901 (86.14%)	206 (82.4%)	0.133
	Other*, n (%)	145 (13.86%)	44 (17.6%)	
Education years	0-12, n (%)	691 (66.06%)	197 (78.8%)	<0.001
	>12, n (%)	355 (33.94%)	53 (21.2%)	
Alone living, n (%)		114 (10.90%)	35 (14.0%)	0.167
Smoking, n (%)		129 (12.33%)	15 (6.0%)	0.004
Drinking, n (%)		136 (13.0%)	16 (6.4%)	0.004
Hypertension, n (%)		456 (43.59%)	126 (50.4%)	0.052
Diabetes mellitus, n (%)		140 (13.38%)	43 (17.2%)	0.120
Cardiac diseases, n (%)		82 (7.84%)	16 (6.4%)	0.439
Cranial vascular disease, n (%)		32 (3.06%)	11 (4.4%)	0.288
BMI, kg/m^2 (SD)		24.56 ± 3.07	24.15 ± 3.36	0.026
Waist circumference, cm (SD)		86.90 ± 8.51	85.45 ± 9.37	0.143
SBP, mmHg (SD)		142.3 ± 18.3	141.3 ± 18.5	0.611
DBP, mmHg (SD)		83.7 ± 10.2	80.9 ± 10.1	0.004
Heart rate, beats/min (SD)		80.2 ± 13.4	79.0 ± 12.7	0.362
WBC, 10^9/L (SD)		6.39 ± 1.49	6.28 ± 1.75	0.556
Neutrophils, 10^9/L (SD)		3.89 ± 1.19	3.86 ± 1.43	0.441
Lymphocytes, 10^9/L (SD)		1.96 ± 0.59	1.86 ± 0.69	0.002
Eosinophils, 10^9/L (SD)		0.14 ± 0.11	0.15 ± 0.17	0.621
PLT, 10^9/L (SD)		212.3 ± 50.8	218.3 ± 62.8	0.264
RBC, 10^9/L (SD)		4.71 ± 0.38	4.27 ± 0.56	<0.001
Hemoglobin, g/L (SD)		145.08 ± 10.98	124.90 ± 8.46	<0.001
RDW, % (IQR)		12.89 ± 0.51	13.79 ± 1.09	<0.001
FBG, mmol/L (SD)		6.36 ± 1.77	6.24 ± 1.70	0.166
Albumin, g/dL (SD)		46.18 ± 2.27	45.30 ± 2.69	<0.001
Globulin, g/dL (SD)		30.35 ± 3.45	30.72 ± 4.58	0.708
Triglyceride, mmol/L (SD)		1.48 ± 0.87	1.42 ± 0.83	0.755
Total Cholesterol, mmol/L (SD)		5.17 ± 1.07	5.10 ± 1.27	0.041
HDL-C, mmol/L (SD)		1.50 ± 0.39	1.58 ± 0.42	0.539
LDL-C, mmol/L (SD)		3.03 ± 0.85	2.91 ± 0.87	0.019
Frailty status	Robust, n (%)	669 (63.96%)	45 (18.0%)	<0.001
	Pre-frail, n (%)	337 (32.22%)	140 (56.0%)	
	Frailty, n (%)	40 (3.82%)	65 (26.0%)	

SBP=systolic blood pressure, DBP=diastolic blood pressure, BMI=body mass index, FBG=fasting blood-glucose, WBC=white blood cell, PLT=platelets count, RBC=red blood cell, RDW=red blood cell distribution width,

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HRR=hemoglobin-to-RDW ratio.

Normal HRR=HRR above 9.97, Lower HRR: HRR below 9.97 (Optimal cut-off value of the ROC curve)

Other* including separated, divorced, never married or widowed

Logistic regression analysis

Among 1296 older adults, 105 (8.10%) were considered frail. Multiple logistic regression analysis was conducted to assess the associations of the lower HRR with frailty. Unadjusted model1 showed that lower Hb (OR:2.129,1.133-4.001, p=0.019) and lower HRR (OR:3.285,1.676-6.440, p=0.001) were risk factors related to frailty, whereas lower RDW (OR:0.310, 0.193-0.497, p<0.001) was a protective factor. After adjustment for confounding factors (including age, gender, marital status, education years, living alone, BMI, diabetes, RBC, albumin, triglyceride, HDL-C, and LDL-C), there was a significant association of lower HRR (OR:3.419, 1.679-6.964, p=0.001) and lower RDW (OR:0.285, 0.170-0.477, p< 0.001) with frailty (Table 3). Lower HRR was independently related to frailty in older adults.

Table3. Multiple logistic regression analysis of blood parameters and frailty in older adults

	Model1		Model2	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Categorical variable				
Lower Hb	2.129 (1.133-4.001)	0.019	1.163 (0.562-2.409)	0.684
Lower RDW	0.310(0.193-0.497)	<0.001	0.285 (0.170-0.477)	<0.001
Lower HRR	3.285 (1.676-6.440)	0.001	3.419 (1.679-6.964)	0.001

Hb=hemoglobin, RDW=red blood cell distribution width, HRR=hemoglobin-to-RDW ratio.

Lower Hb: <131.5g/L, Lower RDW: <13.45%, Lower HRR: <9.97. (Optimal cut-off value of the ROC curve)

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OR: odds ratio, CI: confidence interval, Model 1, unadjusted; Model 2, adjusted for age, gender, marital status, education years, alone living, BMI, diabetes, RBC, albumin, triglyceride, HDL-C and LDL-C.

Correlation Analysis

Correlation analysis indicated that there was an obvious positive correlation between RDW (Kendall's tau-b=0.173, P<0.001) and frailty. Nevertheless, HRR (Kendall's tau-b=-0.239, P<0.001) and Hb (Kendall's tau-b=-0.194, P<0.001) were a negative correlation with frailty (Table 4).

Table4. Correlation analysis of Hb, RDW, HRR, and frailty in older adults

	Kendall's tau-b	p
Hb	-0.194	<0.001
RDW	0.173	<0.001
HRR	-0.239	<0.001

**. Correlation is significant at the 0.01 level (2-tailed).

Discussion

Frailty, as a geriatric syndrome, has attracted more and more scientific attention in the background of continuously increasing global population aging.[20] In this cross-sectional study including 1,296 community-dwelling older adults, we found that lower HRR is independently related to frailty in older people, even after adjusting confounding factors (P=0.001). Multiple logistic regression analysis showed that lower HRR is associated with a 3-fold more likelihood or odds of frailty (OR = 3.419, 95%CI 1.679-6.964). ROC analysis showed that the AUC for HRR in the frailty older adults was 0.802, the highest sensitivity was 84.5% and the specificity

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was 61.9% with the optimal critical value of 9.97. The results of the present study confirmed that HRR was also significantly associated with frailty in general older people, not only in patients with coronary heart disease in previous studies.

HRR is a cost-effective, common, and accessible laboratory parameter for clinicians. As a novel inflammatory factor, Qu et.al found that HRR is significant associated with frailty in older patients with CHD.[16] In their study the AUC for HRR in the frailty patients was exceed Hb and RDW, and after adjusting confounding factors lower HRR was a risk factor for frailty in older patients with CHD. These findings are consistent with our results. Now the pathophysiological mechanism has not been fully understood. We try to provide a possible explanation for the association between HRR and frailty in older adults.

A decrease in HRR may be due to low Hb, high RDW, or both. As we all know, low Hb indicates a condition of anemia, which is one of the acknowledged risk factors for hospitalization, morbidity, and mortality in older people.[21] Anemia decreases the oxygen-carrying capacity, leading to tissue hypoxia and even organ failure, especially in older patients, increasing the risk of frailty.[22] Besides, anemia can cut down submaximal and maximal aerobic capacity, leading to several adverse outcomes including loss of muscle strength, cognitive decline, and development of frailty.[10] In addition, chronic conditions and comorbidities leading to a low grade of inflammation-reducing hemoglobin level,[23] also known as chronic diseases anemia, which is the most common type of anemia in older adults.[22] And a state of chronic inflammation has been suggested as contributor to frailty.[24] Furthermore, anemia caused by malnutrition is also a significant health-affecting factor among older adults.[22]

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Anemia reaching a prevalence of 17% in older people, is a threat to healthy aging.[25] Corona et.al found that lower hemoglobin and anemia were related to frailty in Brazilian older adults.[8] In their study, anemia was related to low physical activity, weakness(weaker), and walking more slowly. Another study from Spain indicated that anemia is independently associated with frailty in older people.[26] Moreover, Xu et.al found that Hb is closely associated with frailty in elder patients in the hospital.[9] A systematic review and meta-analysis including 19 studies indicated that older adults with anemia have more than a two-fold increased odds of frailty.[27] Silva et.al suggested that lower Hb levels should be considered a significant component of frailty in older persons.[28] Similarly, another meta-analysis including 32,934 robust participants and 6864 frail participants found that Hb is a useful biomarker of frailty.[7] However, there were no significant association between lower Hb and frailty after adjusting confounding factors in our study. The discrepancy in results may be due to the definition of lower Hb being determined by the optimal cut-off value of the ROC curve in this research. Therefore, further studies are needed to confirm the relationship between Hb and frailty in older people.

An increasing RDW also can lead to low HRR. Studies have proved that increased RDW is related to inflammation. Inflammatory cytokines reduce erythropoietin gene expression and erythropoietin receptor expression, which leads to the release of immature erythrocytes and the heterogeneity of the erythrocyte volume increasing.[29,30] In addition, metabolic abnormalities including shortened telomere length, oxidative stress, and malnutrition may also contribute to increased RDW.[11,31] What's more, others have suggested that RDW may be a potential biomarker for biological aging.[30] Study has indicated that a high RDW was

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related to a high sarcopenia risk.[32] Sarcopenia, which plays a key role in frailty, is a progressive loss of skeletal muscle mass and strength.[28]

RDW is a biomarker of inflammation, oxidative stress, poor nutritional status, aging, and sarcopenia, and all of these could be underlying reasons for the development of frailty. A study that enrolled 3,635 community-dwelling older men indicated that participants with a high RDW are more likely to have functional limitations and frailty.[30] Li et.al indicated that increased RDW may be closely related to frailty through inflammation.[15] Hou et.al proved that frailty is closely associated with RDW in elder patients with CHD.[13] Another study including 2,932 community-dwelling older adults found RDW is independently associated with high frailty risk even after adjusting for potential confounding factors.[14]

Increased RDW combined with anemia is more likely to lead to decreased HRR. Elevated RDW suggests chronic inflammation, malnutrition, and aging.[11] Anemia is the cause of reduced tissue oxygenation and the consequent increase in fatigue, weakness, and functional impairment.[33] Also anemia may affect muscle mass and strength loss through inflammatory pathways.[33] Therefore, decreased HRR may be associated with sarcopenia, slowness, weakness, inflammation, malnutrition, and weight loss in frailty patients.

To sum up, a large number of researchers have verified the association between frailty and a low Hb and a high RDW among older persons. However, both RDW and Hb are susceptible to many other disease conditions and sub-health states, HRR may provide a more powerful parameter than a single parameter alone. Moreover, ROC analysis showed that the AUC and highest sensitivity of HRR are higher than RDW and Hb. It may be a more reliable and effective marker than Hb and RDW alone.

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This inexpensive and common laboratory parameter may provide useful information to identify the risk of frailty in older adults. Furthermore, the use of the HRR may help clinicians to identify people at high risk of frailty and take effective measures to reduce the occurrence and development of frailty, reduce the rate of disability and mortality related to frailty in the elderly, and reduce the waste of medical resources, and promote healthy aging.

There were also some limitations of our present study. Firstly, because cross-sectional studies measure the outcome and the exposures in the study participants at the same time, it is difficult to assess the cause-effect relationship. Secondly, our participants are limited to local participants, these findings need to be validated in different populations around the world. What is more, we are unable to investigate the temporal relation between outcomes and risk factors. In addition, despite the inevitable selection bias and information bias in cross-sectional studies, we improved this problem through more rational statistical methods and interviewer training. Finally, we did not assess iron, folic, and vitamin B12, which may affect RDW and Hb levels.

Conclusion

In conclusion, a low HRR is independently associated with higher frailty risk in community-dwelling older adults. And this relationship is not affected by confounding factors. However, the causal relationship and the specific mechanism between HRR and frailty are unclear. Evidence is needed from prospective studies to verify these conclusions in the future.

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Author contributions

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Writing – original draft: Mengpei Zhu

Writing – review and editing: Zhifan Xiong, Mengpei Zhu, Chao Wei, Xiongjun Yang, Yumei Huang, Yushuang Xu. All authors read and approved the final manuscript.

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Data availability

Data for this study are available from the corresponding author.

Declaration

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The authors report no conflicts of interest in this work.

Ethics statements

The research protocol was approved by the Medical Ethics Committee of Liyuan Hospital, Tongji Medical College, Huazhong University of Science and Technology (IRB ID: [2020] IEC (A016)). All the participants gave written informed consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

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Figure legends

Figure1 ROC curve for HRR (A), Hb (B) and RDW (C)

Notes:

A. ROC curve indicated that the best intercept value for HRR was 9.97 (sensitivity 84.5%, specificity 61.9%, AUC = 0.802, P<0.001)

B. ROC curve indicated that the best intercept value for Hb was 131.5 (sensitivity 81% , specificity 57.1%, AUC = 0.742, P<0.001)

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C. ROC curve indicated that the best intercept value for RDW was 13.45 (sensitivity 56.2% , specificity 81.1%, AUC = 0.712, P<0.001)

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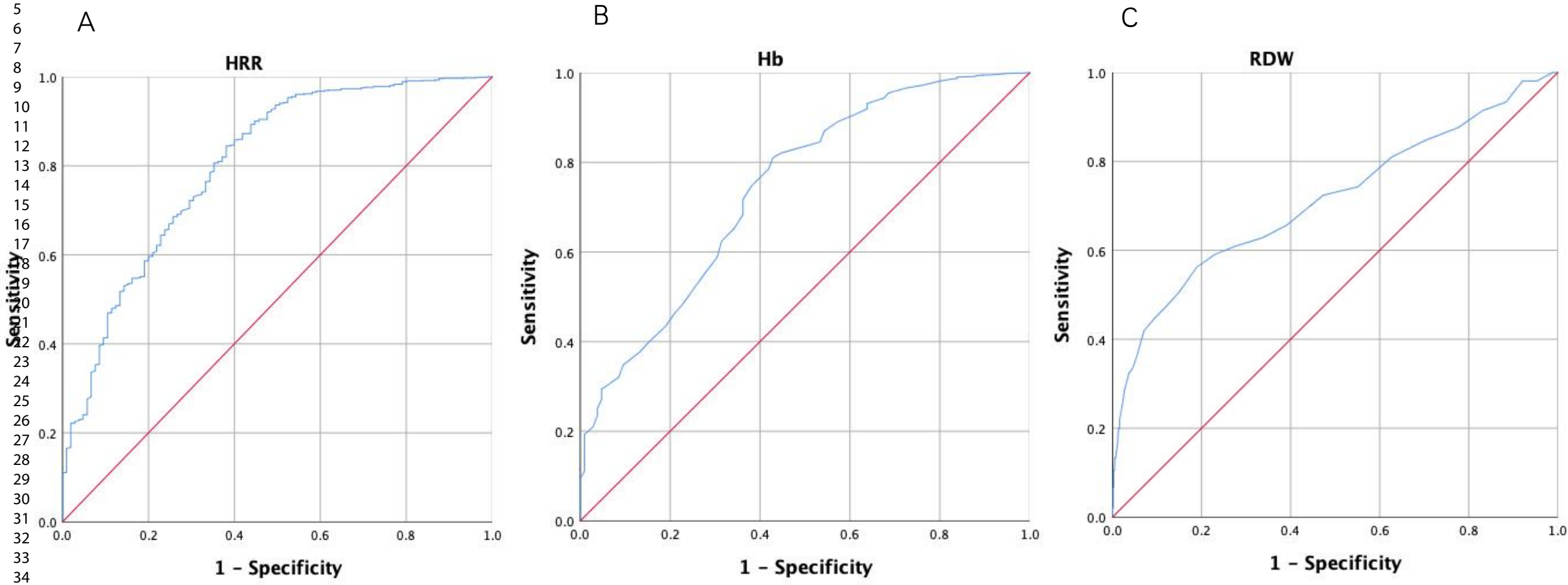
Figure1.


A
HRR
Sensitivity
1 – Specificity
0.0
0.2
0.4
0.6
0.8
1.0
B
Hb
Sensitivity
1 – Specificity
C
RDW
Sensitivity
1 – Specificity

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	4-5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	*5*
Study size	10	Explain how the study size was arrived at	
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	7
		(*e*) Describe any sensitivity analyses	7
Results			

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Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7-8
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-11
		(*b*) Report category boundaries when continuous variables were categorized	9-11
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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