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Lower haemoglobin-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 haemoglobin-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 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. Receiver operating characteristic curve 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 to 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.

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 generalisability 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 ageing 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 years in the world.[2] Frailty becomes an emerging global public health burden, with the rapid growth of the global ageing population. Frailty is considered to be a complex age-related clinical condition characterised 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, hospitalisation, 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 persons.[5]

As an important part of complete blood count (CBC), haemoglobin (Hb) is usually used as an indicator of the degree of anaemia. 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 indicated 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 anaemia.[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, dyslipidaemia, 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*[13] indicated that RDW is significantly associated with the risk of frailty in older patients with coronary heart disease (CHD). In addition, studies showed that increased RDW is associated with frailty both in older inpatients and in community-dwelling older people.[14 15] However, it is still controversial whether RDW alone can predict frailty.[16 17] The Hb-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*[16] found that lower HRR is independently related to the risk of frailty in older patients with CHD. They 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 CHD).[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 AND METHODS

Patient and public involvement

The source population was the community-dwelling adults older than 65 years 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 years living in communities in Wuhan. Exclusion criteria were malignant disease or advanced organic diseases, haematologic diseases, acute stage of disease and participants missing the key parameters.

Participants and sociodemographic characteristics

In this study, we recruited 1296 community-dwelling adults older than 65 years 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, hyperlipidaemia and cerebrovascular disease, were recorded. The 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 an automated haematology analyzer (Mindray, BC-7500, 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 m was more than 7 s for men (height ≤173 cm) and women (height ≤159 cm) or more than 6 s for men (height >173 cm) and women (height >159 cm). (4) Physical activity: low physical activity was defined as <383 kcal/week for men and <270 kcal/week for women. (5) Exhaustion: exhaustion was assessed by the following two questions from the center for epidemiological-Depression Scale (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 SD and numbers with percentages, respectively. The baseline characteristics of the groups were compared using a one-way analysis of variance and χ^2 test. The predictive value of HRR for frailty was assessed by receiver operating characteristic 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, living alone, BMI, diabetes, RBC, albumin, triglyceride, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), the independent risk factors for frailty in older adults were assessed. 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 value<0.05 was considered statistically significant. All statistical analyses were conducted using SPSS (V.26.0, IBM Corporation).

Table 1 Baseline characteristics of the study population stratified by frailty

Characteristics	Robust (n=714)	Prefrail (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, mm Hg (SD)	141.61±18.53	142.73±17.74	143.01±19.37	0.516
DBP, mm Hg (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
Haemoglobin, g/L (SD)	145.51±12.15	137.29±11.79	129.55±13.73	<0.001
Anaemia, 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

*Including separated, divorced, never married or widowed.
BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HRR, haemoglobin-to-RDW ratio; LDL-C, low-density lipoprotein cholesterol; PLT, platelet count; RBC, red blood cell; RDW, red blood cell distribution width; SBP, systolic blood pressure; WBC, white blood cell.

RESULTS

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%) had hypertension, 183 (14.1%) were patients with diabetes, 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 the robust group, 36.81% (477) in the prefrail group and 8.10% (105) in the frail group. The baseline characteristics of the three groups were shown in table 1.

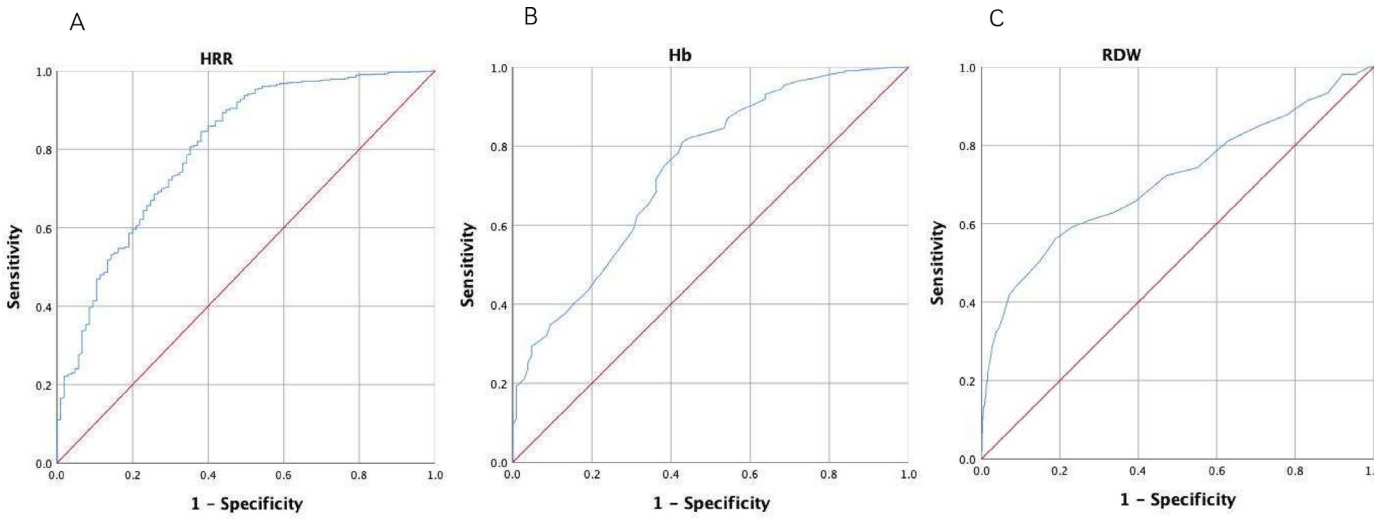

Figure 1 ROC curve for HRR (A), Hb (B) and RDW (C). (A) ROC curve indicated that the best intercept value for HRR was 9.97 (sensitivity 84.5%, specificity 61.9%, AUC=0.802, p<0.001). (B) ROC curve indicated that the best intercept value for Hb was 131.5 (sensitivity 81%, specificity 57.1%, AUC=0.742, 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). Hb, haemoglobin; HRR, Hb-to-RDW; RDW, red blood cell distribution width; ROC, receiver operating characteristic.

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 of 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 Hb (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).

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 model 1 showed that lower Hb (OR: 2.129, 1.133 to 4.001, p=0.019) and lower HRR (OR: 3.285, 1.676 to 6.440, p=0.001) were risk factors related to frailty, whereas lower RDW (OR: 0.310, 0.193 to 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 to 6.964, p=0.001) and lower RDW (OR: 0.285, 0.170 to 0.477, p<0.001) with frailty (table 3). Lower HRR was independently related to frailty in older adults.

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).

DISCUSSION

Frailty, as a geriatric syndrome, has attracted more and more scientific attention in the background of continuously increasing global population ageing.[20] In this cross-sectional study including 1296 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 threefold more likelihood or odds of frailty (OR=3.419, 95% CI 1.679 to 6.964). ROC analysis showed that the AUC of HRR was 0.802, the highest sensitivity was 84.5% and the specificity 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 CHD in previous studies.

HRR is a cost-effective, common and accessible laboratory parameter for clinicians. As a novel inflammatory

Table 2 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, mm Hg (SD)	142.3±18.3	141.3±18.5	0.611
DBP, mm Hg (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
Haemoglobin, 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
Prefrail, n (%)	337 (32.22)	140 (56.0)	
Frailty, n (%)	40 (3.82)	65 (26.0)	

Normal HRR=HRR above 9.97, Lower HRR: HRR below 9.97 (optimal cutoff value of the ROC curve).
*Including separated, divorced, never married or widowed.
BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HRR, haemoglobin-to-RDW ratio; LDL-C, low-density lipoprotein cholesterol; PLT, platelets count; RBC, red blood cell; RDW, red blood cell distribution width; ROC, receiver operating characteristic; SBP, systolic blood pressure; WBC, white blood cell.

Table 3 Multiple logistic regression analysis of blood parameters and frailty in older adults

	Model 1 OR (95% CI)	P value	Model 2 OR (95% CI)	P value
Categorical variable				
Lower Hb	2.129 (1.133 to 4.001)	0.019	1.163 (0.562 to 2.409)	0.684
Lower RDW	0.310 (0.193 to 0.497)	<0.001	0.285 (0.170 to 0.477)	<0.001
Lower HRR	3.285 (1.676 to 6.440)	0.001	3.419 (1.679 to 6.964)	0.001

Lower Hb: <131.5 g/L, lower RDW: <13.45%, lower HRR: <9.97 (optimal cutoff value of the ROC curve). 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.
BMI, body mass index; Hb, haemoglobin; HDL-C, high-density lipoprotein cholesterol; HRR, haemoglobin-to-RDW ratio; LDL-C, low-density lipoprotein cholesterol; RDW, red blood cell distribution width; ROC, receiver operating characteristic.

factor, Qu *et al*[16] found that HRR is significantly associated with frailty in older patients with CHD. In their study the AUC of HRR in the frailty patients was exceed Hb and RDW alone, 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 anaemia, which is one of the acknowledged risk factors for hospitalisation, morbidity and mortality in older people.[21] Anaemia decreases the oxygen-carrying capacity, leading to tissue hypoxia and even organ failure, especially in older patients, increasing the risk of frailty.[22] Besides, anaemia 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 lead to a low grade of inflammation-reducing Hb level,[23] also known as chronic disease anaemia, which is the most common type of anaemia in older adults.[22] And a state of chronic inflammation has been suggested as contributor to frailty.[24] Furthermore, anaemia caused by malnutrition is also a significant health-affecting factor among older adults.[22]

Anaemia, reaching a prevalence of 17% in older people, is a threat to healthy ageing.[25] Pires Corona *et al*[8] found that lower Hb and anaemia were related to frailty in Brazilian older adults. In their study, anaemia was related to low physical activity, weakness (weaker) and walking more slowly. Another study from Spain indicated that anaemia is independently associated with frailty in older people.[26] Moreover, Xu *et al*[9] found that Hb is closely associated with frailty in older patients in the hospital. A systematic review and meta-analysis including 19 studies indicated that older adults with anaemia have more than a twofold increased odds of frailty.[27] Silva *et al*[28] suggested that lower Hb levels should be considered a significant component of frailty in older persons. 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 cutoff value of the ROC curve in this research. Therefore, further studies are needed to confirm the relationship between Hb and frailty in older people.

Table 4 Correlation analysis of Hb, RDW, HRR and frailty in older adults

	Kendall's tau-b*	P values
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).
Hb, haemoglobin; HRR, haemoglobin-to-RDW ratio; RDW, red blood cell distribution width.

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 ageing.[30] Study has indicated that a high RDW was 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, ageing and sarcopenia, and all of these could be underlying reasons for the development of frailty. A study that enrolled 3635 community-dwelling older men indicated that participants with a high RDW are more likely to have functional limitations and frailty.[30] Li *et al*[15] indicated that increased RDW may be closely related to frailty through inflammation. Hou *et al*[13] proved that frailty is closely associated with RDW in older patients with CHD. Another study including 2932 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 anaemia is more likely to lead to decreased HRR. Elevated RDW suggests chronic inflammation, malnutrition and ageing.[11] Anaemia is the cause of reduced tissue oxygenation and the consequent increase in fatigue, weakness and functional impairment.[33] Also, anaemia 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.

This inexpensive and common laboratory parameter may provide useful information to identify the risk of frailty in older adults. Furthermore, the use of 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. First, 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. Second, 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 B_{12}, 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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Patient consent for publication Not applicable.

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REFERENCES

1 Kameda M, Teruya T, Yanagida M, *et al*. Frailty markers comprise blood metabolites involved in antioxidation, cognition, and mobility. *Proc Natl Acad Sci U S A* 2020;117:9483–9.
2 Travers J, Romero-Ortuno R, Bailey J, *et al*. Delaying and reversing frailty: a systematic review of primary care interventions. *Br J Gen Pract* 2019;69:e61–9.
3 Dent E, Martin FC, Bergman H, *et al*. Management of frailty: opportunities, challenges, and future directions. *Lancet* 2019;394:1376–86.
4 Coelho-Junior HJ, Marzetti E, Picca A, *et al*. Protein intake and frailty: a matter of quantity, quality, and timing. *Nutrients* 2020;12:2915.
5 Ward RE, Orkaby AR, Chen J, *et al*. Association between diet quality and frailty prevalence in the physicians' health study. *J Am Geriatr Soc* 2020;68:770–6.
6 Zhai Z, Gao J, Zhu Z, *et al*. The ratio of the hemoglobin to red cell distribution width combined with the ratio of platelets to lymphocytes can predict the survival of patients with gastric cancer liver metastasis. *Biomed Res Int* 2021;2021:8729869.
7 Mailliez A, Guilbaud A, Puisieux F, *et al*. Circulating biomarkers characterizing physical frailty: CRP, hemoglobin, albumin, 25OHD and free testosterone as best biomarkers. Results of a meta-analysis. *Exp Gerontol* 2020;139:111014.
8 Pires Corona L, Drumond Andrade FC, de Oliveira Duarte YA, *et al*. The relationship between anemia, hemoglobin concentration and frailty in Brazilian older adults. *J Nutr Health Aging* 2015;19:935–40.
9 Xu L, Zhang J, Shen S, *et al*. Clinical frailty scale and biomarkers for assessing frailty in elder inpatients in China. *J Nutr Health Aging* 2021;25:77–83.
10 Ruan Y, Guo Y, Kowal P, *et al*. Association between anemia and frailty in 13,175 community-dwelling adults aged 50 years and older in China. *BMC Geriatr* 2019;19:327.
11 Salvagno GL, Sanchis-Gomar F, Picanza A, *et al*. Red blood cell distribution width: a simple parameter with multiple clinical applications. *Crit Rev Clin Lab Sci* 2015;52:86–105.
12 Dent E, Lien C, Lim WS, *et al*. The Asia-Pacific clinical practice guidelines for the management of frailty. *J Am Med Dir Assoc* 2017;18:564–75.
13 Hou P, Xue H-P, Mao X-E, *et al*. Inflammation markers are associated with frailty in elderly patients with coronary heart disease. *Aging (Albany NY)* 2018;10:2636–45.
14 Li C-M, Chao C-T, Chen S-I, *et al*. Elevated red cell distribution width is independently associated with a higher frailty risk among 2,932 community-dwelling older adults. *Front Med (Lausanne)* 2020;7:470.
15 Li Q, Chen X, Han B. Red blood cell distribution width is associated with frailty in older Inpatients in China: sex differences in a cross-sectional study. *Exp Gerontol* 2021;150:111392.

16 Qu J, Zhou T, Xue M, *et al*. Correlation analysis of hemoglobin-to-red blood cell distribution width ratio and frailty in elderly patients with coronary heart disease. *Front Cardiovasc Med* 2021;8:728800.
17 Su Y-C, Wen S-C, Li C-C, *et al*. Low hemoglobin-to-red cell distribution width ratio is associated with disease progression and poor prognosis in upper tract urothelial carcinoma. *Biomedicines* 2021;9:672.
18 Sun P, Zhang F, Chen C, *et al*. The ratio of hemoglobin to red cell distribution width as a novel prognostic parameter in esophageal squamous cell carcinoma: a retrospective study from Southern China. *Oncotarget* 2016;7:42650–60.
19 Fried LP, Tangen CM, Walston J, *et al*. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–56.
20 Kojima G, Taniguchi Y, Iliffe S, *et al*. Transitions between frailty states among community-dwelling older people: a systematic review and meta-analysis. *Ageing Res Rev* 2019;50:81–8.
21 Lee CT, Chen MZ, Yip CYC, *et al*. Prevalence of anemia and its association with Frailty, physical function and cognition in community-dwelling older adults: findings from the HOPE study. *J Nutr Health Aging* 2021;25:679–87.
22 Röhrig G. Anemia in the frail, elderly patient. *Clin Interv Aging* 2016;11:319–26.
23 Steinmeyer Z, Delpierre C, Soriano G, *et al*. Hemoglobin concentration; a pathway to frailty. *BMC Geriatr* 2020;20:202.
24 Wilson D, Jackson T, Sapey E, *et al*. Frailty and sarcopenia: the potential role of an aged immune system. *Ageing Res Rev* 2017;36:1–10.
25 Stauder R, Valent P, Theurl I. Anemia at older age: etiologies, clinical implications, and management. *Blood* 2018;131:505–14.
26 Esquinas-Requena JL, García-Nogueras I, Hernández-Zegarra P, *et al*. Anemia and frailty in older adults from Spain. The FRADEA study. *Rev Esp Geriatr Gerontol* 2021;56:129–35.
27 Palmer K, Vetrano DL, Marengoni A, *et al*. The relationship between anaemia and frailty: a systematic review and meta-analysis of observational studies. *J Nutr Health Aging* 2018;22:965–74.
28 Silva JC, Moraes Z de, Silva C, *et al*. Understanding red blood cell parameters in the context of the frailty phenotype: interpretations of the FIBRA (frailty in Brazilian seniors) study. *Arch Gerontol Geriatr* 2014;59:636–41.
29 Pierce CN, Larson DF. Inflammatory cytokine inhibition of erythropoiesis in patients implanted with a mechanical circulatory assist device. *Perfusion* 2005;20:83–90.
30 Kim KM, Lui L-Y, Browner WS, *et al*. Association between variation in red cell size and multiple aging-related outcomes. *J Gerontol A Biol Sci Med Sci* 2021;76:1288–94.
31 Ghaffari S. Oxidative stress in the regulation of normal and neoplastic Hematopoiesis. *Antioxid Redox Signal* 2008;10:1923–40.
32 Kim J, Im J-S, Choi CH, *et al*. The association between red blood cell distribution width and sarcopenia in U.S. *Sci Rep* 2018;8.
33 Picca A, Coelho-Junior HJ, Calvani R, *et al*. Biomarkers shared by frailty and Sarcopenia in older adults: a systematic review and meta-analysis. *Ageing Res Rev* 2022;73:101530.