

# Effect Modification by Sex of the Hemoglobin Concentration on Frailty Risk in Hospitalized Older Patients

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**Background:** Hemoglobin concentration differs by sex, possibly affecting any association between hemoglobin and frailty. This study aimed to evaluate the potential interaction effect of hemoglobin and sex on frailty in Chinese older inpatients.

**Methods:** A cross-sectional study was conducted between February 2015 and November 2017 in a tertiary hospital. Frailty was defined by the Fried phenotype. Hemoglobin concentration was measured with a standard procedure. Covariates included demographics, clinical characteristics, and serum biomarkers. Logistic regression was applied to examine the association between hemoglobin concentration and frailty. The relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index (SI) were used to evaluate the additive interaction.

**Results:** A total of 619 older inpatients [mean age  $69.26 \pm 7.44$  years; 334 men, 285 women] were included. The mean hemoglobin concentration was significantly lower in the elderly who were frail (11.9 g/L in frail versus 13.1 g/L in non-frail;  $p < 0.001$ ). In the multivariable regression models, lower hemoglobin in patients was significantly associated with frailty (adjusted odds ratio (OR) = 2.51, 95% CI: 1.37, 4.60). The stratified analyses indicated that lower hemoglobin was associated with frailty among older inpatients with different characteristics. Female inpatients with lower hemoglobin had the highest risk of frailty (adjusted OR = 6.43, 95% CI: 2.38, 17.3); there were interactions between hemoglobin and sex on the development of frailty (RERI = 4.30, 95% CI = -1.41, 10.01; AP = 0.67, 95% CI = 0.37, 0.97; SI = 4.80, 95% CI = 1.22, 18.84).

**Conclusions and Implications:** Our study provided evidence that sex and lower hemoglobin have an interaction effect on frailty; it is suggested that clinicians may consider sex-specific strategies for the elderly to conform the concept of precision medicine.

**Keywords:** hemoglobin concentration, frailty phenotype, older inpatient, interaction effect

## Introduction

The aging population is a global challenge for governments. Older adults are more likely to be in functional decline and are prone to frailty. The prevalence of frailty is 7.4%~14.2% among Chinese community-dwelling adults age  $\geq 60$  years.<sup>1</sup> Studies have demonstrated that frailty could increase the prevalence of poor health outcomes, such as disability, falls, hospitalization, and even death.<sup>2-4</sup> Frailty is a reversible process, and knowing the factors of frailty could help with clinical decision-making and the development of targeted interventions to further delay the progress of frailty.<sup>5,6</sup> Lower hemoglobin level and frailty are conditions commonly

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encountered in older patients.<sup>7</sup> Palmer et al conducted a meta-analysis on 13 studies and the results indicated that the elderly with lower hemoglobin levels had more than twofold odds of developing frailty; nevertheless, the heterogeneity among these studies was as high as 91.3%.<sup>8</sup> Recent studies found the level of hemoglobin showed no significant correlation with frailty after adjusting for various covariates.<sup>9,10</sup> The evidence regarding the relationship between hemoglobin and frailty in hospitalized elderly patients is limited.

In addition, studies showed the distribution of hemoglobin concentration is not consistent across sexes, especially with increasing age.<sup>11</sup> Sex appears to be an important factor affecting the ageing trajectory, women tend to be more frail when compared with age-matched men.<sup>12</sup> Such sex differences may affect the relationships between hemoglobin concentration and frailty. One study indicated that lower hemoglobin was independently associated with frailty in females with adjusted odds ratio (OR) was 2.47 (95% confidence intervals 1.24, 4.90).<sup>13</sup> Another study showed the link between hemoglobin, anemia and frailty criterion could not be found in males.<sup>14</sup> These discrepancies may be attributed to the potentially important modulating role of sex in the relationship between those two variables, it is conceivable to hypothesize that sex may influence the association between hemoglobin concentration and frailty. However, this hypothetical explanation has not been examined. Most of previous studies only analyzed the risk factors for frailty, and rarely further explored the potential interactive effects.<sup>15–17</sup> It is imperative to identify modifiable protective factors for frailty to inform the nature of interventions required, which is in conformity with the concept of precision medicine.

Thus, this study aimed to elucidate the association between hemoglobin concentrations and frailty in hospitalized patients aged 60 years and older in mainland China, and determine the potential interaction effect of hemoglobin and sex on frailty.

## Materials and Methods

### Study Design and Participants

A cross-sectional design was employed between March 2015 and November 2017. Hospitalized participants aged 60 years or older were enrolled consecutively from a comprehensive tertiary hospital in Beijing, mainland China. The inclusion criteria were as follows: cooperated to complete the frailty assessment, and consented to participate. If they had a history

of stroke, Parkinson's disease, severe neurological disease, or taking antidepressants, because these disease or medications could cause symptoms that are potentially collinear with frailty,<sup>18</sup> or patients with unstable vital signs, they were excluded. If the participant's data were not complete, they were excluded. A total of 619 participants were finally enrolled in the study ([Supplementary Figure 1](#)).

### Hemoglobin Concentration Measurement

Blood hemoglobin concentration was determined in the laboratory at our hospital. Standardized enzyme-linked immunosorbent assay (ELISA) techniques were used to determine the values. According to the clinical diagnostics for Chinese, hemoglobin concentrations of less than 12 g/L for men and less than 11 g/L for women were defined as lower hemoglobin (anemic).<sup>19</sup>

### Frailty Assessment

Frailty was defined by Fried et al and Fried's phenotype, a widely used assessment tool, was applied in this study, which included five criteria.<sup>20,21</sup> Each criterion was evaluated by a trained nurse with a face-to-face interview and physical examination. Participants who met  $\geq 3$  frailty criteria were defined as frail, those who met 1 or 2 criteria were classified as pre-frail, and the others were robust. Pre-frail and robust were combined as non-frail.<sup>18,21</sup> The five criteria were operationalized as follows:

1. Unintentional weight loss:  $\geq 5\%$  of body weight loss in the past year not due to dieting.
2. Exhaustion: Questions 7 ("I felt that everything I did was an effort") and 20 ("I could not get going") on the Center for Epidemiological Studies – Depression Scale (CES-D) were queried. If the participant responded "occasionally," "a moderate amount of time," or "most or all of the time" for those questions, self-reported exhaustion was recorded.
3. Weakness: Grip strength was defined as lower than the minimum value after adjusting for sex and body mass index (BMI) quartile. Grip strength was measured using an electronic grip strength meter that has been used for national physique monitoring in China.
4. Slowness: Walking speed was assessed over a 15-foot distance. If the walking speed was lower than the minimum value according to sex and height, slowness was recorded.
5. Low physical activity: Low physical activity was defined as lower than the minimum value of the

International Physical Activity Questionnaire-Short Form, with  $\leq 600$  metabolic equivalent (MET)-mins/week classified as low physical activity.<sup>22</sup>

## Demographic Characteristics and Covariates

Participant information was recorded via face-to-face interviews and electronic medical records. Demographic characteristics included age, sex, current smoking and drinking history, BMI, and activities of daily living (ADL). BMI was calculated using height and weight. ADL was assessed using the tool of Barthel Index.<sup>23</sup> Clinical characteristics included the history of medical diagnosis (hypertension, diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, and malignant tumor), comorbidity status, and nutrition risk. Comorbidity status was assessed by the Charlson Comorbidity Index (CCI), with nutrition risk screened by the Nutritional Risk Screening 2002 (NRS 2002) system.<sup>24,25</sup>

## Blood Test

Serum biomarkers were obtained from a blood sample. All examinations were performed at our hospital. Albumin, prealbumin, and total cholesterol were determined using a Hitachi 7600 automatic biochemical analyzer (Hitachi, Tokyo, Japan). Red blood cell (RBC), white blood cell (WBC), and lymphocyte counts were determined using standard laboratory methods.

## Data Collection

Frailty status, demographic characteristics, and clinical characteristics of the participants were collected at the time of admission, and fasting blood was collected on the first day after admission to measure hemoglobin and serum biomarkers.

## Statistical Analysis

All statistical analyses were performed using the statistical software packages R (R Foundation for Statistical Computing; Vienna, Austria). Continuous variables were summarized as the mean $\pm$ standard deviation and categorical variables were summarized as percentages. An independent-sample *t*-test, Mann–Whitney *U*-test, chi-squared test, and Fisher's exact test were used to assess the between-group differences, as appropriate. The association of hemoglobin concentrations and frailty was assessed with the use of multivariable logistic regression models.

Unadjusted and adjusted OR with 95% CI were calculated. Interaction and stratified analyses were conducted according to baseline characteristics. We considered a *P* value  $< 0.05$  as significant. The estimates from logistic regression models were used to calculate the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S) using an Excel spreadsheet by Andersson et al.<sup>26</sup>

## Results

### Baseline Characteristics of Participants

Fifteen participants were excluded because of incomplete data. We compared the information between included and excluded samples and no significant difference was found for frailty status, demographic characteristics, and clinical characteristics (Supplementary Figure 1, Supplementary Table 1).

The characteristics of the enrolled participants stratified by anemia at baseline are presented in Table 1. Finally, 619 older inpatients [mean age  $69.26 \pm 7.44$  years; 334 men, 285 women] were analyzed in the current study. According to the Fried phenotype, the prevalence of frail and non-frail participants was 27.3% (169/619) and 72.7% (450/619), respectively. The prevalence of anemia was 20.4% (126/619). Frail patients were more likely to have a lower hemoglobin level ( $p < 0.001$ ). Current smoking and drinking were not associated with hemoglobin concentration ( $p > 0.05$ ). Hypertension, diabetes mellitus, and cardiovascular diseases based on medical diagnoses did not show a significant difference between different hemoglobin groups ( $p > 0.05$ ). Additional, the patients with higher CCI scores and nutrition risk had lower hemoglobin concentration compared to the others. The *p*-value was lower than 0.001, which means that the relationship between serum biomarkers and hemoglobin concentration were statistically significant.

### Hemoglobin Concentration and Frailty Status

As shown in Figure 1, the mean serum hemoglobin concentration in the frail group was significantly lower than that in the non-frail group ( $11.9 \pm 2.1$  g/L vs  $13.1 \pm 1.5$  g/L;  $p < 0.001$ ). We also analyzed the association between hemoglobin concentrations and the number of frailty criteria that were met. The analysis indicated as the number of frailty criteria increased, the levels of hemoglobin decreased (*p* for trend  $< 0.001$ ).

**Table 1** Baseline Characteristics of the Study Participants (n=619)

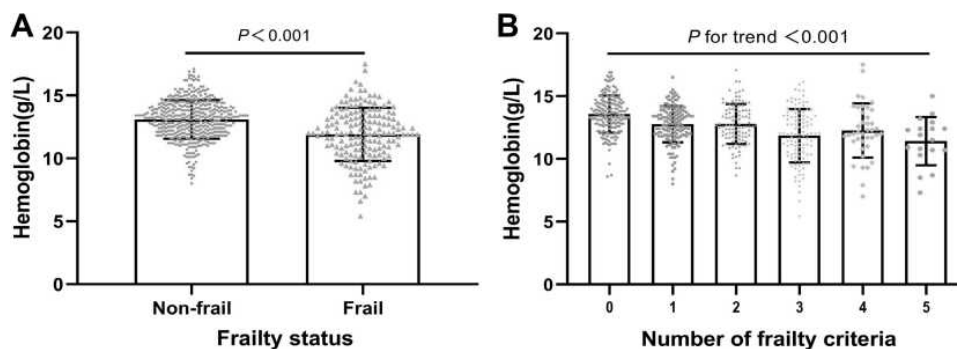
Characteristics	All Participants (N=619)	Patients with Anemia (N=126)	Patients without Anemia (N=493)	P-value
<b>Demographic</b>				
Age(years), mean±SD	69.3 ± 7.4	72.0±7.4	68.6 ± 7.3	<0.001
Male, no.(%)	334 (53.9)	85 (67.5)	249 (50.5)	0.001
BMI(kg/m <sup>2</sup> ), mean±SD	24.4 ± 3.5	23.3 ± 3.5	24.7 ± 3.4	<0.001
Current smoker, no.(%)	137 (22.1)	36 (28.6)	101 (20.5)	0.051
Current drinker, no.(%)	110 (17.8)	24 (19.1)	86 (17.4)	0.674
ADL<100, no.(%)	266 (42.9)	79 (62.7)	187 (37.9)	<0.001
<b>Clinical characteristics</b>				
Hypertension, no.(%)	267 (43.1)	57 (45.2)	210 (42.6)	0.593
Diabetes mellitus, no.(%)	134 (21.7)	32 (25.4)	102 (20.7)	0.252
Cardiovascular diseases, no.(%)	103 (16.6)	27 (21.4)	76 (15.4)	0.106
Cerebrovascular diseases, no.(%)	53 (8.6)	19 (15.1)	34 (6.9)	0.003
Malignant tumor, no.(%)	233 (37.6)	75 (59.5)	158 (32.1)	<0.001
CCI ≥3, no.(%)	211 (34.1)	61 (48.4)	150 (30.4)	<0.001
NRS 2002 ≥3, no.(%)	49 (7.9)	22 (17.5)	27 (5.5)	<0.001
<b>Serum biomarkers</b>				
Albumin(g/L), mean±SD	37.4 ± 4.7	33.1 ± 4.3	38.4 ± 4.1	<0.001
Prealbumin(g/L), mean±SD	201.3 ± 69.3	155.0 ± 57.3	213.1 ± 67.2	<0.001
Cholesterol(mmol/L), mean±SD	4.3 ± 1.2	3.8 ± 0.9	4.4 ± 1.2	<0.001
RBC(×10 <sup>12</sup> /L), mean±SD	4.3 ± 0.5	3.7 ± 0.4	4.4 ± 0.4	<0.001
WBC(×10 <sup>9</sup> /L), mean±SD	6.4 ± 2.5	6.4 ± 2.8	6.4 ± 2.4	<0.001
Lymphocytes(×10 <sup>9</sup> /L), mean±SD	1.7 ± 0.7	1.4 ± 0.6	1.8 ± 0.7	<0.001
<b>Frailty status</b>				
Frail, no.(%)	169 (27.3)	68 (53.8)	101 (20.5)	<0.001
<b>Hemoglobin(g/L), mean±SD</b>	<b>12.8 ± 1.8</b>	<b>10.3 ± 1.3</b>	<b>13.4 ± 1.3</b>	<b>&lt;0.001</b>

**Abbreviations:** BMI, body mass index; ADL, activities of daily living; CCI, Charlson Comorbidity Index; RBC, red blood cell count; WBC, white cell count; SD, standard deviation.

## The Association Between Hemoglobin Concentration and Frailty Status

The association between hemoglobin concentration, anemia, and frailty status for all participants are presented in Table 2.

In the univariate regression model, hemoglobin was significantly associated with frailty status (OR=0.68, 95% CI: 0.61, 0.76) and the presence of anemia showed a similar association (OR=4.55, 95% CI: 3.01, 6.88). Three multivariate



**Figure 1** Distribution of hemoglobin and frailty status in patients.

**Notes:** Values in the figure were expressed as mean (standard deviation). Hemoglobin concentration was compared according to the frailty status (A) and the number of frailty criteria (B). The mean serum hemoglobin concentration in the frail group was significantly lower than that in the non-frail group (11.9±2.1 g/L vs 13.1±1.5 g/L;  $p < 0.001$ ).

**Table 2** Association Between Hemoglobin Concentration and Frailty in Multiple Regression Model

Outcome	Non-Adjusted Model		Model I		Model II		Model III	
	OR(95% CI)	P-value	OR(95% CI)	P-value	OR(95% CI)	P-value	OR(95% CI)	P-value
Hemoglobin, Ig/L	0.68 (0.61, 0.76)	<0.001	0.72 (0.64, 0.81)	<0.001	0.80 (0.63, 0.99)	0.005	0.80 (0.64, 0.99)	0.048
Hemoglobin classification								
No anemia	Reference		Reference		Reference		Reference	
Anemia	4.55 (3.01, 6.88)	<0.001	4.14 (2.68, 6.41)	<0.001	2.47 (1.35, 4.53)	0.003	2.51 (1.37, 4.60)	0.003

**Notes:** Model I: Adjust for age and sex. Model II: Adjust for variables that, when added to this model, changed the matched odds ratio by at least 10%, including age, sex, diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, malignant tumor, CCI, ADL, albumin, prealbumin, cholesterol, RBC, and lymphocytes. Model III: Adjust for all of these variables, including age, sex, BMI, current smoker, current drinker, hypertension, diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, malignant tumor, CCI, ADL, nutrition risk, albumin, prealbumin, cholesterol, RBC, WBC and lymphocytes.

**Abbreviations:** OR, odds ratio; CI, confidence interval; BMI, body mass index; CCI, Charlson Comorbidity Index; ADL, activities of daily living; RBC, red blood cell count; WBC, white cell count.

regression models were created to clarify the association between hemoglobin and frailty. Patients with lower hemoglobin were significantly associated with frailty (adjusted OR = 2.51, 95% CI: 1.37, 4.60) after adjusting for all of the covariates. Each 1 g/L increase in hemoglobin concentration was associated with a 20% decrease in the prevalence of frailty (adjusted OR = 0.80, 95% CI: 0.64, 0.99).

## Stratified and Interaction Analysis of the Association Between Hemoglobin Concentration and Frailty Status

The results of the stratified and interaction analyses of the association between hemoglobin concentration and frailty are presented in Table 3. The stratified analyses indicated that there was a negative correlation between hemoglobin concentration and frailty in older inpatients with different characteristics. The result was consistent with that from the multivariable logistic regression analysis as well. Only the group of patients with BMI <18.5 showed no association between the hemoglobin concentration and frailty (OR = 1.03, 95% CI: 0.21, 5.15).

The interaction analysis revealed that sex played a role in the association between lower hemoglobin and frailty ( $P$  for interaction=0.029). Females with lower hemoglobin had larger ORs; the adjusted OR of frailty was 6.43 (95% CI: 2.38, 17.3; Table 4 and Figure 2). The relative excess risk of interaction (RERI) was 4.30 (95% CI: -1.41, 10.01); the attributable proportion due to interaction (AP) was 0.67 (95% CI: 0.37, 0.97); and the synergy index (S) was 4.80 (95% CI: 1.22, 18.84). The results indicated that there was an additive interaction effect of sex and lower hemoglobin on frailty.

## Discussion

This study provided evidence for an association between levels of hemoglobin concentration and frailty. After

adjusting for all covariates, as the levels of hemoglobin increased, the risk of frailty decreased, and patients with lower hemoglobin had a 2.51-fold higher risk of frailty than the other. Stratified analysis showed the negative association of hemoglobin with frailty was persistent. Moreover, further analysis revealed that there was an additive interaction effect of sex and lower hemoglobin on frailty; the adjusted OR of frailty was 6.43 (95% CI: 2.38, 17.34) for females with lower hemoglobin.

A great number of studies had proved that the hemoglobin was significantly lower in the frail group among community-dwelling older adults.<sup>27–30</sup> A study<sup>30</sup> included 1829 community-dwelling participants indicated that the hemoglobin and frailty was significantly related (adjusted OR=0.86, 95% CI 0.79, 0.94). In hospitalized patients, the hazard of geriatric syndromes is particularly high due to severe illness, decline of function, and disturbance of the internal environment.<sup>31</sup> Our study showed that it was more prone to frailty with the decrease of hemoglobin in the hospitalized elderly as well, and there was a dose-response effect between lower hemoglobin levels and the higher number of frailty criteria ( $P$  for trend <0.001), which was supported by the study performed by Pires et al.<sup>14</sup> The results from the multiple regression models were consistent in this study. After adjusting all of the covariates, each 1 g/L increase in hemoglobin was associated with a 20% decrease in the prevalence of frailty (adjusted OR = 0.80, 95% CI: 0.64, 0.99). Patients with lower hemoglobin had more than twofold odds of being frail (adjusted OR = 2.51, 95% CI: 1.37, 4.60). The study conducted by Perez-Ros et al also showed that low levels of hemoglobin increased, the occurrence of frailty decreased in older Spaniards (OR = 2.45, 95% CI: 1.19, 5.03).<sup>32</sup> In a study of 380 participants, the association



**Table 3** Stratified Analyses of the Association Between Anemia and Frailty Status According to Baseline Characteristics

Characteristics	Frail Anemia/Total (%)	Non-Frail Anemia/Total (%)	OR (95% CI)	P value for Interaction
Age				0.173
<70	23/65 (35.38)	28/303 (9.24)	5.38 (2.84, 10.20)	
≥70	45/104 (43.27)	30/147 (20.41)	2.97 (1.70, 5.20)	
Sex				0.029
Male	39/89 (43.82)	46/245 (18.78)	3.37 (1.99, 5.72)	
Female	29/80 (36.25)	12/205 (5.85)	9.15 (4.36, 19.17)	
BMI				0.150
<18.5	6/11 (54.55)	7/13 (53.85)	1.03 (0.21, 5.15)	
18.5–23.9	32/77 (41.56)	29/199 (14.57)	4.17 (2.29, 7.60)	
>23.9	30/81 (37.04)	22/238 (9.24)	5.78 (3.08, 10.83)	
Current smoker				0.736
No	51/134 (38.06)	39/348 (11.21)	4.87 (3.01, 7.89)	
Yes	17/35 (48.57)	19/102 (18.63)	4.13 (1.80, 9.46)	
Current drinker				0.120
No	54/144 (37.50)	48/365 (13.15)	3.96 (2.52, 6.24)	
Yes	14/25 (56.00)	10/85 (11.76)	9.55 (3.41, 26.71)	
CCI				0.889
<3	31/93 (33.33)	34/315 (10.79)	4.13 (2.36, 7.23)	
≥3	37/76 (48.68)	24/135 (17.78)	4.39 (2.34, 8.24)	
ADL				0.329
<100	56/123 (45.53)	23/143 (16.08)	4.36 (2.47, 7.71)	
100	12/56 (26.09)	35/307 (11.40)	2.74 (1.30, 5.79)	
NRS 2002				0.443
<3	53/142 (37.32)	51/428 (11.92)	4.40 (2.81, 6.89)	
≥3	15/27 (55.56)	7/22 (31.82)	2.68 (0.83, 8.68)	

**Note:** The P value for interaction represents the likelihood of interaction between the variable and the hemoglobin concentrations.

**Abbreviations:** BMI, body mass index; CCI, Charlson Comorbidity Index; ADL, activities of daily living; NRS 2002, nutrition risk score 2002; OR, odds ratio; CI, confidence interval.

between hemoglobin levels and frailty was no longer significant after adjusting for confounding factors, however, compared with the lower hemoglobin group, the beta coefficient (95%) of the higher hemoglobin group were  $-0.616$  ( $-1.382, 0.151$ ) for frailty score, and the univariate analysis also showed the association between hemoglobin as a continuous variable and frailty was significant.<sup>16</sup> Lower hemoglobin levels could reduce the oxygen-carrying capacity, which could lead to tissue hypoxia and decreased muscular strength and physical mobility, further caused several adverse outcomes, including muscle atrophy and the development of frailty.<sup>33,34</sup> Current views suggest that the sharing of frailty and a low hemoglobin level is related to the pathological and physiological processes of chronic inflammation. A low hemoglobin level may result in muscle dysfunction through chronic

inflammation, making older adults develop symptoms of frailty. Frailty and low hemoglobin often exist in the same person.<sup>35,36</sup> In the stratified analysis, the association between hemoglobin levels and frailty was stable for different characteristics of the population, but no significant association was found in the group with BMI  $<18.5$ , mainly because there were only 24 people in this group. The smaller sample size may have affected the accuracy of the results. The relationship between hemoglobin concentration and frailty in the low BMI population needs further study.

Furthermore, we found there was an additive interaction effect for sex and hemoglobin on frailty. A study conducted in Brazil showed that the effect value of hemoglobin concentration associated with frailty was different between males and females, but the

**Table 4** Evaluation of the Interaction Effect of Sex with Anemia on Frailty

Characteristics	N(%)	Crude Model		Adjusted Model	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Sex with anemia					
Male & no anemia	249 (40.2)	Reference		Reference	
Male & anemia	85 (13.7)	3.37 (1.99, 5.72)	<0.001	1.77 (0.87, 3.59)	0.114
Female & no anemia	244 (39.4)	1.05 (0.68, 1.63)	0.821	1.36 (0.77, 2.41)	0.287
Female & anemia	41 (6.6)	9.62 (4.59, 20.17)	<0.001	6.43 (2.38, 17.34)	<0.001

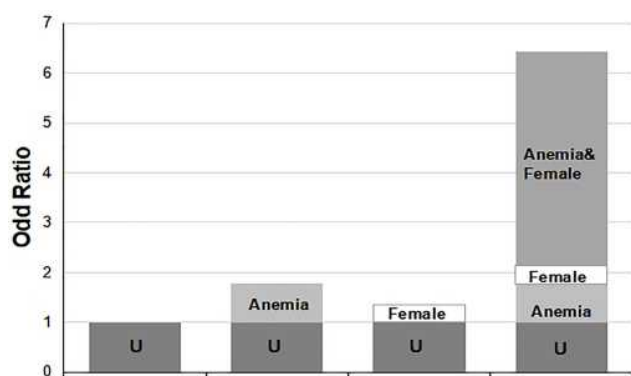
**Notes:** Adjusted Model: adjust for all of these variables, including age, BMI, current smoker, current drinker, hypertension, diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, malignant tumor, CCI, ADL, nutrition risk, albumin, prealbumin, cholesterol, RBC, WBC and lymphocytes.

**Abbreviations:** OR, odds ratio; CI, confidence interval; BMI, body mass index; CCI, Charlson Comorbidity Index; ADL, activities of daily living; RBC, red blood cell count; WBC, white cell count.

interaction between sex and hemoglobin levels was not analyzed.<sup>14</sup> The impact of lower hemoglobin or anemia on frailty was more obvious in females than males in the present study. Several possible explanations for the observed sex difference may be advanced. First, it is well known that females generally have longer life expectancy than males, but women tend to experience worse health, which called male–female health survival paradox.<sup>37</sup> Poorer health for women could be manifested as lower self-reported health, grip strength measurement and poor physical function, which are important parameters for the frailty assessment.<sup>38,39</sup> With aging, women could lose muscle mass rapidly.<sup>40</sup> A follow-up study found that muscle mass in postmenopausal women declined at a rate of six percent per year.<sup>41</sup> In addition, another possible explanation for this is that sex hormones may play some role in development of frailty. The MrOS (osteoporotic fractures in men) Sweden study reported that the decreased

estradiol was correlated with the lower hemoglobin (OR=1.61, 95% CI 1.34, 1.93) and anemia.<sup>42</sup> And the bioavailable testosterone which may contribute to the increase in muscle mass is decreased in elderly women.<sup>43,44</sup> Therefore, the decline of estrogen levels among elderly women and lower hemoglobin may have a synergistic effect on the health of muscle function and contributes to pathogenesis of frailty. However this possibility need more epidemiologic support.

The strengths of this study include the target participants and evidence for an association between hemoglobin concentration and frailty in hospitalized older patients in developing countries. The multiple regression model and interaction and stratified analyses were employed to examine the relationship between hemoglobin concentration and frailty. Meanwhile, to our best knowledge, this is the first study which determine the interaction of sex and hemoglobin in frailty. However, there are several limitations in this study. First, the data that we used in this study were collected from a comprehensive tertiary hospital and, therefore, our findings cannot be extended to all kinds of medical industries. Prospective studies in different environments are also needed to confirm the observed association. In addition, frailty status was assessed by frailty phenotype. Currently, there are dozens of frailty assessment tools and we cannot promise that consistent results will be found when applying different frailty evaluations. The frailty phenotype, however, is a very widely used tool throughout the world, and it has high credibility.<sup>45,46</sup> Additionally, our study had a cross-sectional design, which does not allow for drawing conclusions about a causative link for the reported associations. More longitudinal studies on this association should be conducted in the future.



**Figure 2** Interaction effect between sex and anemia in relation to frailty. U means the odds ratio was equal to 1.

**Note:** Females with lower hemoglobin had larger ORs, sex played a role in the association between lower hemoglobin and frailty.

## Conclusions and Implications

In summary, the hemoglobin concentration was independently and significantly associated with frailty among hospitalized older patients in mainland China and the results provide evidence that sex and lower hemoglobin have an interaction effect on frailty in elderly inpatients. Longitudinal studies are needed to evaluate the causal relationship between hemoglobin concentration, sex and frailty, as well as their predictive ability for the occurrence of frailty to help medical staff with sex-specific management decision-making.

## Highlights

- Frailty symptom is common in hospitalized older patients.
- Hemoglobin concentration and anemia were independently and significantly associated with frailty.
- Sex and anemia have an interaction effect on frailty.

## Data Sharing Statement

Data will be made available upon reasonable request to the corresponding author.

## Ethical Considerations

Participation was voluntary, and informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki, and ethical approval of this study was granted by the Institutional Review Board of Xuanwu hospital, Capital Medical University.

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## Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of

data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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