Associations Between Anemia, Cognitive Impairment, and All-Cause Mortality in Oldest-Old Adults: A Prospective Population-Based Cohort Study

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Objective: To evaluate the combined effects of anemia and cognitive function on the risk of all-cause mortality in oldest-old individuals.

Design: Prospective population-based cohort study.

Setting and Participants: We included 1,212 oldest-old individuals (men, 416; mean age, 93.3 years).

Methods: Blood tests, physical examinations, and health questionnaire surveys were conducted in 2012 were used for baseline data. Mortality was assessed in the subsequent 2014 and 2018 survey waves. Cox proportional hazards models were used to evaluate anemia, cognitive impairment, and mortality risk. We used restricted cubic splines to analyze and visualize the association between hemoglobin (Hb) levels and mortality risk.

Results: A total of 801 (66.1%) deaths were identified during the 6-year follow-up. We noted a significant association between anemia and mortality [HR 1.32, 95% confidence interval [CI] 1.14–1.54] after adjusting for confounding variables. We also observed a dose-response relationship between the severity of anemia and mortality (P < 0.001). In the restricted cubic spline models, Hb levels had a reverse J-shaped association with mortality risk (HR 0.88, 95% CI 0.84–0.93 per 10 g/L-increase in Hb levels below 130 g/L). The reverse J-shaped association persisted in individuals without cognitive impairment (HR 0.88, 95% CI 0.79–0.98 per 10 g/L-increase in Hb levels below 110 g/L). For people with cognitive impairment, Hb levels were inversely associated with mortality risk (HR 0.83, 95% CI 0.78–0.89 per 10 g/L-increase in Hb levels below 150 g/L). People with anemia and cognitive impairment had the highest risk of mortality (HR 2.60, 95% CI 2.06–3.27).
INTRODUCTION

Anemia is a common clinical condition among older adults. The prevalence of anemia increases with age, reaching 30.7% in individuals aged 80+ years, 37% in those aged 90+ years, and >50% in centenarians (1–4). The population of oldest-old (aged ≥80 years) is rapidly growing worldwide (5). Thus, the number of the oldest-old with anemia will dramatically increase with the aging population. Anemia in older adults has significant clinical relevance. Many epidemiological studies have shown that anemia is associated with an increased risk of mortality (6–12). However, very few studies have been conducted to determine the association between anemia and mortality in oldest-old people, especially in middle-income countries.

Cognitive impairment is another condition that commonly affects older adults. This condition is burdensome and it poses a heavy burden on the public health system (13). Several studies have shown an association between cognitive impairment and increased mortality (13–15). Interestingly, anemia is a known risk factor for cognitive impairment (12, 16, 17). However, whether anemia and cognitive impairment have combined effects on mortality is still unclear. Furthermore, whether the association between anemia and mortality is influenced by cognitive status is not known. Clarifying these associations may be very relevant for clinical screening.

Thus, we conducted this study to evaluate the combined effects of anemia and cognitive impairment on the risk of all-cause mortality among oldest-old people. We also investigated whether the association between anemia and mortality is potentially modified by cognitive impairment.

METHODS

Study Design and Participants

This study used data from the Chinese Longitudinal Healthy Longevity Survey (CLHLS), which is a prospective community-based nationwide cohort study of older people in China. Details of the CLHLS have been previously described (5, 18, 19). Briefly, this nationwide survey, conducted in 23 provinces, collected representative and widespread data to explore the determinants for healthy aging among older people in China.

Participants were recruited from the biomarker sub-study of the 6th wave (2012) of the CLHLS and followed in the 7th (2014) and the 8th (2018) wave in eight longevity areas. We included 1,427 participants aged 80 or above who had biomarker data and cognition assessments in the baseline survey. We then excluded 215 participants who were lost to follow-up. Thus, in the final analysis we included 1,212 oldest-old individuals.

Conclusion: Our results indicate that anemia is associated with an increased risk of mortality in oldest-old people. Cognitive impairment modifies the association between Hb levels and mortality.

Keywords: anemia, hemoglobin, cognition, mortality, CLHLS

The study was approved by the Ethics Committee of Duke University and Peking University (Ethics Number: IRB00001052-13074). Informed consent was signed by all participants or their legal representatives in the baseline and follow-up surveys.

Assessment of Mortality

Mortality was ascertained during the subsequent 7th (2014) and the 8th (2018) wave of the CLHLS. The date of death was collected from local doctors or participants’ close family members. The survival time was measured from the date of the first interview to the date of death or the date of the last follow-up (which occurred first).

Anemia and Cognition Impairment

Fasting venous blood samples were drawn by medical staff, and concentration of hemoglobin (Hb) was measured with the commercially available diagnostic kits (Roche Diagnostic) in the Automatic Biochemistry Analyzer (Hitachi 7180, Tokyo, Japan). Quality control measures and more details were described previously (20). According to the World Health Organization (WHO) criteria, we defined anemia as Hb <130.0 g/L in men and <120.0 g/L in women. Anemia was further classified into three groups as follows (8): mild anemia (Hb 120–129 g/L in men and 110–119 g/L in women); moderate anemia (Hb 110–119 g/L in men and 100–109 g/L in women); severe anemia (Hb <110 g/L in men and <100 g/L in women). Based on the mean corpuscular volume (MCV), anemia was characterized as normocytic (MCV 80–100 fl) macrocytic (MCV >100 fl), or microcytic (MCV < 80 fl).

The Mini-Mental Status Examination (MMSE) is a sensitive, valid, and reliable instrument that is used extensively in clinical and research settings to measure cognitive impairment (21). Cognitive impairment was assessed by the Chinese version of the MMSE (Supplementary Table 1) (22), of which the validity and reliability have been verified (13, 23, 24). Based on the MMSE score combined with the educational time, cognition impairment was defined as an MMSE score <18 in illiterate participants, <21 in those with 1–6 education years, or <25 in those with over 6 education years (13, 25).

Covariates

Data for covariates information were collected during home interviews and biochemistry tests. Based on the literature (13, 24, 26–28), we selected the following covariates: age at the baseline, sex, marital status (married and living with spouse/other), education years (0/1–6/>6), ethnicity (Han/others), smoking (yes/no), drinking (yes/no), body mass index (BMI) as defined as the body mass divided by the square of the body height, and is universally expressed in units of kg/m²). Chronic conditions...
(hypertension, diabetes mellitus, chronic kidney disease (CKD), albumin, fasting blood glucose (FBG), high sensitivity C-reactive protein (hs-CRP), and lipid profile. Hypertension patients were defined as those with systolic blood pressure $\geq$140 mmHg or diastolic blood pressure $\geq$90 mmHg, or self-reporters (29). Diabetes mellitus patients were defined as those with FBG level $\geq$7.0 mmol/L, or self-reporters (30). CKD patients were defined as those with estimated glomerular filtration rate (eGFR) $<$60 mL/min/1.73 m$^2$ (26). The Chinese modified version of the Modification of Diet in Renal Disease (MDRD) equation was used to calculate eGFR: $175 \times$ serum creatinine (mg/dL)$^{-1.234} \times$ age (years)$^{-0.179} \times 0.79$ (if female) (31).

**Statistical Analyses**

Baseline characteristics were presented as counts (%) for categorical variables and as means (standard deviations) or medians (interquartile range) for continuous variables. Student's t-tests or Mann–Whitney U-test were applied to compare the differences in the continuous variables of the two groups. Chi-square tests or Fisher's exact test were used to explore the differences in categorical variables. The association of anemia and cognitive function with all-cause mortality was analyzed using Cox proportional hazard models, including model one and two. We adjusted for age and sex in model one, and further controlled for more potential confounders such as education, marital status, BMI, albumin, hs-CRP, and chronic conditions in model two. We assessed the proportional hazards assumption using the Schoenfeld residuals technique and ascertained it had not been violated.

We use restricted cubic splines to analyze and visualize the association of Hb levels with mortality risk in all participants and participants with/without cognitive impairment. The likelihood ratio test was used to test for potential non-linearity (32, 33). If the associations of Hb levels with mortality were non-linear, we additionally calculated hazard ratios (HR) and 95% CI per 10 g/L increase in Hb based on a two-line piecewise linear model.

To observe the combined effect of anemia and cognition impairment on mortality, we created the four-level joint anemia/cognition impairment groups (group one: non-anemic and normal cognition, group two: anemic and normal cognition, group three: non-anemic and cognition impairment, group four: anemic and cognition impairment) and repeated the above analysis. The survival curve was estimated using the Kaplan–Meier and the log-rank test. The subgroup analyses of the association of four groups with mortality were conducted by age (80–89 years or $\geq$90 years) and sex. The interactions were tested to evaluate whether the combined effect was similar in different subgroups.

**TABLE 1 | General characteristics of the 1,212 participants with and without anemia.**

| Characteristic                  | Overall (n = 1,212) | Without anemia (n = 501) | With anemia (n = 711) | P-value |
|--------------------------------|---------------------|--------------------------|-----------------------|---------|
| Age, mean (SD)                 | 93.3 (8.1)          | 91.9 (8.4)               | 94.3 (7.6)            | <0.001  |
| Male, %                        | 416 (34.3)          | 175 (34.9)               | 241 (33.9)            | 0.755   |
| Married and living with spouse, % | 245 (20.2)        | 112 (22.4)               | 133 (18.7)            | 0.137   |
| Education time, years, %       |                     |                          |                       |         |
| 0                              | 945 (78.0)          | 375 (74.9)               | 570 (80.2)            | 0.048   |
| 1–6                            | 195 (16.1)          | 96 (19.2)                | 99 (13.9)             |         |
| >6                             | 72 (5.9)            | 30 (6.0)                 | 42 (5.9)              |         |
| Han ethnicity, %               | 1,118 (92.2)        | 466 (93.0)               | 652 (91.7)            | 0.464   |
| Current smoker, %              | 126 (10.5)          | 58 (11.7)                | 68 (9.6)              | 0.294   |
| Current drinker, %             | 150 (12.4)          | 79 (15.8)                | 71 (10.0)             | 0.003   |
| Hypertension, %                | 737 (60.8)          | 302 (60.3)               | 435 (61.2)            | 0.797   |
| Diabetes mellitus, %           | 97 (8.0)            | 50 (10.0)                | 47 (6.6)              | 0.043   |
| CKD, %                         | 233 (19.2)          | 46 (9.2)                 | 187 (26.3)            | <0.001  |
| Cognitive impairment, %        | 421 (34.7)          | 175 (34.9)               | 246 (34.6)            | 0.954   |
| Hemoglobin, g/L, mean (SD)     | 118.78 (20.72)      | 136.81 (14.52)           | 106.07 (13.88)        | <0.001  |
| MMSE score, mean (SD)          | 24.00 (12.00–28.00) | 24.00 (14.00–28.00)      | 24.00 (12.00–28.00)   | 0.505   |
| BMI, kg/m$^2$, mean (SD)       | 20.38 (3.88)        | 21.23 (3.77)             | 19.74 (3.85)          | <0.001  |
| eGFR, mL/min/1.73 m$^2$, mean (SD) | 79.46 (63.79–98.36) | 85.23 (72.76–102.36)    | 73.91 (59.10–93.59)   | <0.001  |
| Albumin, g/L, mean (SD)        | 39.27 (4.94)        | 39.92 (4.84)             | 38.80 (4.96)          | <0.001  |
| Hs-CRP, mg/L, median (QR)      | 1.01 (0.41–2.97)    | 0.90 (0.42–0.62)         | 1.08 (0.39–3.44)      | 0.319   |
| Glucose, mmol/L, mean (SD)     | 4.67 (2.04)         | 5.02 (2.31)              | 4.43 (1.79)           | <0.001  |
| Total cholesterol, mmol/L, mean (SD) | 4.23 (0.97)      | 4.43 (0.92)              | 4.09 (0.99)           | <0.001  |
| Triglycerides, mmol/L, mean (SD) | 0.93 (0.53)       | 0.96 (0.55)              | 0.90 (0.52)           | 0.062   |

SD, standard deviations; CKD, chronic kidney disease; MMSE, Mini-Mental State Examination; BMI, body mass index; eGFR, estimated glomerular filtration rate; Hs-CRP, high-sensitivity C-reactive protein; IQR, interquartile range.
To test the robustness of the primary results, the following three sensitivity analyses were performed (24, 34): (1) excluding deaths in the first 6 months for alleviating potential confounding effects. (2) excluding deaths in the 1st year. (3) excluding participants with four kinds of self-reported diseases, such as cancer, respiratory disease, heart disease, cerebrovascular disease. (4) additionally, adjusting for the above four kinds of self-reported diseases.

These analyses were performed using Stata (version 16.0) and the R software (version 3.6.3). A \( P < 0.05 \) (2-tailed) was considered statistically significant.

**RESULTS**

**Baseline Characteristics**

Table 1 shows the baseline characteristics of the participants. The mean age (standard deviation) of the 1,212 participants was 93.3 (8.1) years, and 34.3% of the participants were male. The prevalence of anemia was 58.7% (males, 59.0%; females, 57.9%). There were significant differences \( (P < 0.05) \) between the participants who had anemia and those who did not have anemia in terms of age, diabetes mellitus, CKD, BMI, eGFR, albumin, glucose, total cholesterol.

**Anemia and All-Cause Mortality**

A total of 801 (66.1%) deaths were identified (men, 268; women, 533) during the 6-year follow-up. Participants who had anemia had a significantly higher mortality rate than those who did not (68.8 and 62.3%, respectively; \( P = 0.019 \)). Table 2 presents the association between anemia and mortality. We noted a significant association between anemia and mortality (HR = 1.32; 95% CI, 1.14–1.54) after adjusting for confounding variables in Model two. Furthermore, participants who had severe anemia had a 51% (95% CI, 1.23–1.85) higher risk of mortality than those who did not have anemia. A dose-response relationship between the severity of anemia and mortality was also observed \( (P < 0.001) \). In addition, the association between anemia and mortality remained similar in normocytic, macrocytic, and microcytic anemia.

**Hb Levels and All-Cause Mortality**

Figure 1 shows the smoothed spline curve of HRs for Hb as continuous variables. Hb levels and mortality showed a nearly reverse J-shaped relationship \( (P \text{ for non-linearity} < 0.001) \). Below 130 g/L, the HR per 10 g/L increase in Hb levels was 0.88 (95% CI, 0.84–0.93).

The shape of the curve for the association between Hb concentration and mortality was significantly modified by cognitive function (all \( P \text{ for non-linearity} < 0.001 \) (Figure 2). For participants without cognitive impairment, there was a steep decrease in the risk of mortality with increasing Hb concentrations <110 g/L \( (HR = 0.88; 95\% \text{ CI}, 0.79–0.98) \); for Hb concentrations above 110 g/L, the relationship was flattened \( (HR = 0.99; 95\% \text{ CI}, 0.92–1.06) \) (Figure 2A). For participants who had cognitive impairment, Hb levels were inversely associated with mortality for concentrations <150 g/L \( (HR = 0.83; 95\% \text{ CI}, 0.78–0.89) \); a positive but not significant association was noted for concentrations above 150 g/L \( (HR = 1.23; 95\% \text{ CI}, 0.99–1.53) \) (Figure 2B).

**Combined Effect of Anemia and Cognitive Status on Mortality**

Figure 3 shows the survival curves for four categories of participants stratified according to their anemia and cognitive function records at baseline. The median survival durations the four anemia/cognition impairment groups were 61.8, 51.1, 29.4, and 17.2 months, respectively. Compared with individuals who did not have anemia and cognitive impairment, people who had...
anemia and cognitive impairment had more than double the mortality risk (adjusted HR = 2.60; 95% CI, 2.06–3.27) (Table 3). In the cognitive impairment subgroup, we noted a significant association between anemia and mortality (HR = 1.86; 95% CI, 1.48–2.34) after adjusting for the confounding variables in Model two (Table 4). Significant interaction between anemia and cognitive impairment was observed in terms of mortality risk (P = 0.005).

The stratified results for different age and sex subgroups are presented in Figure 4. Interestingly, the estimated risk of mortality was stronger in participants aged 80–90 years than participants aged ≥90 years (P for interaction = 0.032). This association between anemia, cognitive function, and mortality had a sex-specific between-group difference (P for interaction = 0.047). Regarding sensitivity analyses, there was almost no change in the combined associations between anemia, cognitive impairment, and all-cause mortality (Supplementary Table 2).

**DISCUSSION**

In this large prospective, community-based cohort of oldest-old adults, we evaluated the combined effects of anemia and cognitive impairment on the risk of mortality. We also investigated whether the association between anemia and mortality is potentially modified by cognitive impairment. After adjusting for potential confounders, we observed a dose-response relationship between the severity of anemia and all-cause mortality. Interestingly, we also found that the shape of curve indicating the association and Hb and mortality differs according to cognitive function. Participants who had anemia and cognitive impairment had a higher risk of mortality, and the association between anemia, cognitive function, and mortality was stronger among relatively younger oldest-old participants (aged 80–90 years).

Our results showed a significant association between anemia and increased mortality, a finding which is consistent with those of previous studies (6–12). In a large (n = 562) population-based study of people aged 85 years in Leiden, the Netherlands, it was estimated that anemia was associated with an increased risk of...
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FIGURE 3 | Kaplan-Meier survival curves by the 4-level joint anemia/cognition impairment groups in oldest-old adults (N = 1,212). Log-rank P < 0.0001.

TABLE 3 | Hazard ratios for the combined associations of anemia and cognitive impairment with all-cause mortality.

| Group | Crude model | | Model 1 | | Model 2 |
|-------|-------------|-----------------|-----------|-----------------|-----------|
|       | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Non-anemic and normal cognition (n = 326) | 1 | | 1 | | 1 | |
| Anemic and normal cognition (n = 463) | 1.28 (1.05, 1.56) | 0.013 | 1.14 (0.94, 1.39) | 0.195 | 1.06(0.86, 1.30) | 0.609 |
| Non-anemic and cognition impairment (n = 175) | 2.42 (1.93, 3.02) | <0.001 | 1.69 (1.33, 2.15) | <0.001 | 1.53 (1.20, 1.96) | <0.001 |
| Anemic and cognition impairment (n = 248) | 4.21 (3.43, 5.16) | <0.001 | 2.85 (2.28, 3.56) | <0.001 | 2.60 (2.06, 3.27) | <0.001 |
| P for trend | < 0.001 | | < 0.001 | | < 0.001 | |

Model 1: adjusted for age, sex. Model 2: further adjusted for education, marital status, ethnicity, current smoker, current drinker, body mass index, cognitive impairment, albumin, high-sensitivity C-reactive protein, and chronic conditions (hypertension, diabetes mellitus, and chronic kidney disease).

We found a non-linear relationship between Hb levels and mortality, which was consistent with previous studies (9, 35). Chaves et al. (9) observed a curvilinear slope of steady mortality decrease up to the Hb threshold of 139 g/L in 686 subjects aged ≥65 years. Zakai et al. (35) found a reversed J-shaped relationship between Hb levels and mortality in a prospective cohort study that included 11.2 years of follow-up of 5,888 participants aged ≥65 years. Further, the consideration of cognitive function in the present study expands on the findings of previous studies. Interestingly, we found that the shape of the curve depicting the association between Hb levels and mortality differed according to cognitive function. Our results provide evidence that supports screening for anemia and cognitive function in oldest-old people.

Anemia and cognitive impairment may be surrogate markers for mortality (36), although the cause pathway remains unclear. For people without cognitive impairment, the 110 g/L threshold of Hb levels may be more suitable for the oldest-old than the WHO criterion. However, even Hb levels were within the WHO criterion normal ranges, low-normal Hb levels when coexisting with cognitive impairment, predicted mortality during the 6-year follow-up. Many studies have shown that anemia and cognitive impairment are associated with increased mortality (6–15). People who have anemia and cognitive impairment may have a greater risk of mortality, as indicated by our results. Careful screening of Hb levels and cognitive impairment, as well as adequate treatment for underlying subclinical and clinical diseases, may be especially important for the oldest-old as a means of improving survival.

We also found that the association between anemia, cognitive function, and mortality appeared to be stronger among relatively younger oldest-old adults (aged 80–90 years) participants than among relatively older adults (aged 90 years or older). Robert et al. also observed the typical pattern of a decreasing relative risk (RR) with age in analyses of the effect of anemia on mortality, (ages 50–59, RR = 2.89; 60–69, RR = 2.13; 70–79, RR = 1.52; ≥80, RR = 1.34) (37). This may be partially due to survival bias (38). Survival bias, also commonly called selection bias due to loss to follow-up, can distort study results in geriatric
TABLE 4 | Hazard ratios for the association between anemia and all-cause mortality by cognition impairment or not.

| Group                        | Crude model | Model 1 | Model 2 |
|------------------------------|-------------|---------|---------|
|                              | HR (95% CI) | P-value | HR (95% CI) | P-value | HR (95% CI) | P-value |
| **Normal cognition**         |             |         |         |         |             |         |
| No anemia (n = 326)          | 1           |         | 1       |         | 1           |         |
| Anemia (n = 463)             | 1.29 (1.06, 1.56) | 0.01 | 1.09 (0.90, 1.33) | 0.39 | 1.13 (0.85, 1.50) | 0.39 |
| **Cognitive impairment**     |             |         |         |         |             |         |
| No anemia (n = 175)          | 1           |         | 1       |         | 1           |         |
| Anemia (n = 248)             | 1.72 (1.39, 2.12) | <0.001 | 1.70 (1.48, 2.34) | <0.001 | 1.86 (1.48, 2.34) | <0.001 |

Model 1: adjusted for age, sex. Model 2: further adjusted for education, marital status, ethnicity, current smoker, current drinker, body mass index, albumin, high-sensitivity C-reactive protein, and chronic conditions (hypertension, diabetes mellitus, and chronic kidney disease).

FIGURE 4 | Hazard ratios (HRs) for the combined associations of anemia and cognition impairment with mortality according to age and sex subgroups. All models were adjusted for age (not in age subgroup) and sex (not in sex subgroup), education, marital status, ethnicity, current smoker, current drinker, body mass index, cognitive impairment, albumin, high-sensitivity C-reactive protein, and chronic conditions (hypertension, diabetes mellitus, and chronic kidney disease). The estimated HRs for each group are compared with individuals who did not have anemia and cognition impairment (HR = 1.0, not shown).

CONCLUSIONS AND IMPLICATIONS

In summary, our findings indicate that anemia in oldest-old people is associated with an increased risk of mortality. We also found that cognitive impairment modified the association between Hb levels and mortality. This study provides evidence that indicates the importance of screening for anemia and cognitive function in oldest-old people. Further research should focus on the best way to translate the interaction between Hb levels and cognitive impairment into health-related screening tools for oldest-old people.
DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://opendata.pku.edu.cn/dataverse/CHA DS.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Duke University and Peking University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JW, LM, and HY contributed to the conception and design of the study. WS, YS, SY, and HK managed the data and provided help in the data analysis. JW, CW, and HK performed the statistical analysis and wrote the first draft of the manuscript. All authors contributed to the study design, critically reviewed draft versions and provided important intellectual content during revisions, and accept accountability for the overall work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.613426/full#supplementary-material
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**Conflicts of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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