A Prospective Study of Anemia Status, Hemoglobin Concentration, and Mortality in an Elderly Cohort

The Cardiovascular Health Study

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Background: Anemia is viewed as a negative prognostic factor in the elderly population; its independent impact on survival is unclear.

Methods: Baseline hemoglobin quintiles and anemia, as defined by the World Health Organization criteria, were assessed in relation to mortality in the Cardiovascular Health Study, a prospective cohort study with 11.2 years of follow-up of 5888 community-dwelling men and women 65 years or older, enrolled in 1989-1990 or 1992-1993 in 4 US communities.

Results: A total of 1205 participants were in the lowest hemoglobin quintile (<13.7 g/dL for men; <12.6 g/dL for women), and 498 (8.5%) were anemic (<13 g/dL for men; <12 g/dL for women). A reverse J-shaped relationship with mortality was observed; age-, sex-, and race-adjusted hazard ratios (95% confidence interval [CI]) in the first and fifth quintiles, compared with the fourth quintile, were 1.42 (95% CI, 1.25-1.62) and 1.24 (95% CI, 1.09-1.42). After multivariate adjustment, these hazard ratios were 1.33 (95% CI, 1.15-1.54) and 1.17 (95% CI, 1.01-1.36). The demographic- and fully-adjusted hazard ratios of anemia for mortality were 1.57 (95% CI, 1.38-1.78) and 1.38 (95% CI, 1.19-1.54). Adjustment for causes and consequences of anemia (renal function, inflammation, or frailty) did not reduce associations.

Conclusions: Lower and higher hemoglobin concentrations and anemia by World Health Organization criteria were independently associated with increased mortality. The World Health Organization criteria did not identify risk as well as a lower hemoglobin value. Additional study is needed on the clinically valid definition for and causes of anemia in the elderly and on the increased mortality at the extremes of hemoglobin concentrations.

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A NEMIA IS USUALLY REGARDED as an abnormal laboratory value, with its associated morbidity and mortality related to underlying diseases.1 However, increasing evidence indicates that anemia is common in the elderly population and adversely affects morbidity and mortality.2,7 The prevalence of anemia among elderly individuals and its independent impact on survival remain unclear.

The number of elderly individuals is increasing in America and is projected to reach 50 million by 2050.5-6 Estimates of the prevalence of anemia among the elderly population vary widely (2.9%-61% of men and 3.3%-41% of women) depending on the population studied and the definition of anemia that is used.6-7 The World Health Organization (WHO)4 defines anemia as a hemoglobin concentration of less than 12 g/dL for women and less than 13 g/dL for men. These criteria have physiological correlates in younger individuals, although their appropriateness for elderly individuals is debated; there is evidence of increased morbidity and mortality across the healthy reference range of hemoglobin concentration defined by the WHO.1,5,8,9

See also pages 2187, 2222, 2229, and 2237

Few studies have assessed the association of anemia with clinical outcomes in the elderly population; a meta-analysis6 cited only 4 articles related to outcomes (1 specifically to mortality). Several small studies2,3 evaluated anemia and mortality in elderly individuals, adjusting only for age and sex. In select groups, such as patients with renal10-12 or cardiac diseases,13,14 human immunodeficiency virus,15 and other chronic diseases,5,16 anemia adversely influences survival.
In this analysis from the Cardiovascular Health Study (CHS) cohort of community-dwelling elderly individuals, we compared the association of hemoglobin concentration and anemia status with subsequent mortality over 11 years. We evaluated whether hemoglobin was an independent predictor of mortality and investigated possible causal pathways using exploratory modeling.

METHODS

SUBJECTS

The CHS is a prospective, observational study of risk factors and consequences of cardiovascular disease in older community-dwelling adults. In 1989 and 1990, 5201 men and women 65 years or older were recruited from 4 US communities (Forsyth County, North Carolina; Sacramento County, California; Washington County, Maryland; and Allegheny County, Pennsylvania). An additional cohort of 687 black men and women were recruited in 1992 and 1993, giving a total cohort of 5888. Prospective participants and age-eligible household members were identified by Medicare eligibility lists of the Health Care Financing Administration. Exclusion criteria included being wheelchair-bound, receiving treatment for cancer, and being institutionalized. Anemia was identified by Medicare eligibility lists of the Health Care Financing Administration. Exclusion criteria included being wheelchair-bound, receiving treatment for cancer, and being institutionalized. Among those screened for participation, 9.6% were ineligible, and 37.3% of those eligible enrolled. Enrollment interviews and physical examinations were conducted with standardized interviews that assessed health history, physical function, physical activity, noninvasive measures of vascular disease, spirometry, height, weight, blood pressure, grip strength, and gait speed. Informed consent was established using methods approved by institutional review committees at each study site.

LABORATORY ANALYSIS

Fasting blood tests were performed in the morning at enrollment. Hemoglobin concentration and platelet and white blood cell counts were measured on automated instruments at local hematology laboratories near each field center. Internal and external quality-assurance reports were examined, and concurrently obtained duplicate samples were analyzed for 3% of participants. Fibrinogen, albumin, creatinine, and C-reactive protein concentrations were measured as described elsewhere.

DEFINITIONS

Anemia was defined by the WHO criteria as a hemoglobin concentration of less than 13 g/dL in men and less than 12 g/dL in women. Because of differences among ethnic groups, ethnicity was assessed and defined by participant self-report from the following list: white, black, American Indian/Alaskan Native, Asian/Pacific Islander, and other. Health status was assessed by self-report, and activity level was assessed by questionnaire. Baseline coronary heart disease consisted of myocardial infarction, angina, angioplasty, or coronary bypass surgery prior to enrollment and was confirmed by a committee using medical record review. Renal insufficiency was defined as a creatinine concentration of at least 1.5 mg/dL (132.6 µmol/L) for men and at least 1.3 mg/dL (114.9 µmol/L) for women. Frailty was defined as having 3 of the 5 following characteristics: unintentional weight loss of at least 10% of body weight in the previous year; being in the lowest quintile for grip strength, timed walk, or physical activity level; and self-reported poor endurance or energy. Presence of inflammation was defined as any 2 of the following: an albumin concentration in the bottom tertile or C-reactive protein, white blood cell count, or fibrinogen concentration in the top tertile of the distribution. Prior cancer was determined by questionnaire and defined as cancer in the past 5 years. Hypertension was defined as a blood pressure greater than 140/90 mm Hg or use of antihypertensive medications with a physician’s diagnosis of hypertension. Chronic obstructive pulmonary disease was defined as self-reported physician diagnosis of chronic bronchitis, asthma, or emphysema.

OUTCOMES AND FOLLOW-UP

Participants were contacted biannually; telephone interviews and clinic examinations were conducted alternately. Periodic searches of the Health Care Financing Administration Medicare utilization files were compiled to identify events missed by other methods. All deaths were reviewed and classified by a committee using information from death certificates, autopsy and coroners’ forms, hospital records, and interviews with physicians, next of kin, and witnesses. Deaths were classified as cardiovascular or noncardiovascular. Complete follow-up was available through June 2001.

STATISTICAL ANALYSIS

Hemoglobin was analyzed in 2 ways: by dividing the distribution into sex-specific quintiles (to assess linearity between hemoglobin and mortality) and by the WHO criteria. Cross-sectional associations of baseline risk factors with hemoglobin quintiles and anemia were performed using χ² analysis, 2-tailed t tests, or Wilcoxon rank sum tests as appropriate. Staged Cox proportional hazards models were used to assess the independent association of baseline hemoglobin quintiles or anemia with subsequent mortality. The first model (A) included no potential confounders. Model B was adjusted for age, sex, and race (black vs white plus other). We then considered predictors of 5-year mortality in the CHS cohort, namely, cardiovascular disease, chronic obstructive pulmonary disease, congestive heart failure, diabetes mellitus, prevalent stroke or transient ischemic attack, hypertension, prior cancer, ankle-arm index of 0.9 or lower, body mass index (calculated as weight in kilograms divided by the square of height in meters), fair or poor self-reported health status, physical activity concentration (kilocalories expended per week), alcohol use (number of drinks per week), history of cigarette use, and forced vital capacity (in liters). A final model (C) was selected that included all covariates that changed the coefficient for hemoglobin in model B by at least 5%. All-cause mortality, cardiovascular mortality, and noncardiovascular mortality were examined separately. Another exploratory model evaluated the addition of potential causes and consequences of anemia to model C (renal function, inflammation status, and frailty). Renal function was expressed as the reciprocal of creatinine to achieve a normal distribution. Using an age-, sex-, and race-adjusted model, stratified models were explored to assess the impact of baseline inflammation, renal insufficiency, and cardiovascular disease on the association of hemoglobin concentration with mortality.

RESULTS

PREVALENCE OF ANEMIA

Of 5888 participants, 5797 (98.5%) had baseline hemoglobin concentration determined. The mean (SD) hemoglobin concentration was 14.0 (1.4) g/dL. Men had a higher mean hemoglobin concentration than women (14.7
The median follow-up period was 11.2 years with 53,866 person-years of observation. The overall mortality rate was 43.6 per 1000 person-years. When mortality was examined by hemoglobin quintiles, a reverse J-shaped relation was observed (Figure 1). Mortality was highest in the first quintile (49%), decreasing over the second, third, and fourth quintiles but increasing in the fifth quintile (41%). This pattern was also apparent for cardiovascular mortality over the five quintiles, with the lowest quintile's HR being 1.22 (95% CI, 1.07-1.42) and the highest quintile's HR being 1.29 (95% CI, 1.17-1.44). Although the pattern was similar, cardiovascular mortality was slightly greater than noncardiovascular mortality (36% vs 23%; **P** < .001). Based on the WHO criteria, the age-, race-, and sex-adjusted HR for mortality was 1.57 (95% CI, 1.38-1.78) for persons with anemia.

### MULTIVARIATE ANALYSIS

Table 3 presents the multivariate analyses relating hemoglobin to mortality. Hemoglobin quintiles and anemia status were independently associated with mortality. Compared with the unadjusted analysis (model A), the HR for the lowest quintile was modestly attenuated with demographic adjustment, whereas the highest quintile's was less changed (Table 3). In contrast, adjustment for comorbid conditions had a larger relative effect on the HR for the fifth quintile than the first and lessened the difference between the fourth and fifth quintiles.

The effect of multivariate adjustment in the models for anemia based on the WHO criteria was similar to that for the lowest hemoglobin quintile. In model C, the association of anemia with mortality, with a HR of 1.38, was slightly greater than associations of other established risk factors for mortality in this model, such as smoking (HR, 1.25; 95% CI, 1.14-1.38) and baseline cardiovascular disease (HR, 1.19; 95% CI, 1.07-1.33), but not as strong as for male sex (HR, 2.14; 95% CI, 1.90-2.42), diabetes (HR, 1.57; 95% CI, 1.41-1.75), congestive heart failure (HR, 1.67; 95% CI, 1.41-1.98), and prior cancer (HR, 2.18; 95% CI, 1.95-2.44).

We explored the effect of adding covariates to model C that might be causes or consequences of lower hemoglobin concentrations. When the reciprocal of creatinine, inflammation status, and frailty were added to model C, the HRs for mortality for the first quintile compared with the fourth, or for anemia based on the WHO criteria, were similar to the HRs in model C: 1.25 (95% CI, 1.07-1.47) and 1.20 (95% CI, 1.02-1.42). For the fifth hemoglobin quintile, the HR compared with the fourth quintile remained elevated at 1.22 (95% CI, 1.04-1.42). When we added the components of inflammation (C-reactive protein, white blood cell count, and fibrinogen and albumin concentrations) as continuous variables to model C, the HRs for the first hemoglobin quintile compared with the fourth and for anemia were 1.27 (95% CI, 1.09-1.47) and 1.35 (95% CI, 1.15-1.53), respectively.

Table 4 shows the associations of lower hemoglobin concentration or anemia with cardiovascular and noncardiovascular mortality. After adjustment for demographic factors and in subsequent models, there was a weaker association of hemoglobin concentration or anemia with cardiovascular than noncardiovascular mortality.

There were no significant differences in mortality by hemoglobin in groups stratified by inflammation status, coronary heart disease, renal insufficiency, or race (**P** values for interaction were 0.77, 0.35, 0.09, and 0.3, respectively).

### COMMENT

In this elderly cohort, the prevalence of anemia was 7.0% among white and 17.6% among black individuals. After 11.2 years of follow-up, lower hemoglobin concentra-
tions were associated with increased mortality risk, independent of many potentially confounding factors. The magnitude of this association was similar whether the lowest quintile of hemoglobin or the WHO criteria for anemia were used; however, the number of participants was much larger when considering the lowest quintile of hemoglobin concentration. The attributable risk for mortality was 3.3% for anemia based on the WHO criteria and 6.5% based on the lowest hemoglobin quintile. Associations were present between hemoglobin and all-cause and noncardiovascular mortality but not cardiovascular mortality. No differences existed in the associations between low hemoglobin and mortality based on the presence of coronary disease, inflammation, renal impairment, or race. Furthermore, before and after

Table 2. Prevalence of Risk Factors for Mortality by Hemoglobin Quintiles*

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Hemoglobin Quintiles</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (n = 1205)</td>
<td>2 (n = 1131)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>74.1 (6.2)</td>
<td>73.1 (5.8)</td>
</tr>
<tr>
<td>Black race</td>
<td>310 (26)</td>
<td>218 (19)</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>252 (21)</td>
<td>233 (21)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>141 (12)</td>
<td>149 (14)</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>248 (21)</td>
<td>120 (11)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>95 (8)</td>
<td>53 (5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>194 (16)</td>
<td>176 (16)</td>
</tr>
<tr>
<td>Frailty</td>
<td>114 (11)</td>
<td>72 (7)</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>103 (9)</td>
<td>75 (7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>704 (58)</td>
<td>634 (56)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>547 (45)</td>
<td>450 (40)</td>
</tr>
<tr>
<td>Prebaseline cancer</td>
<td>185 (15)</td>
<td>151 (13)</td>
</tr>
<tr>
<td>Body mass index,† mean (SD)</td>
<td>179 (15)</td>
<td>154 (14)</td>
</tr>
<tr>
<td>Self-reported health status fair or poor</td>
<td>26.1 (4.9)</td>
<td>26.6 (4.7)</td>
</tr>
<tr>
<td>Activity level, median (IQR), kcal/wk</td>
<td>580 (1369)</td>
<td>1105 (1853)</td>
</tr>
<tr>
<td>Alcohol use, mean (SD), drinks/wk</td>
<td>1.7 (4.6)</td>
<td>2.1 (5.8)</td>
</tr>
<tr>
<td>History of cigarette use</td>
<td>585 (49)</td>
<td>578 (51)</td>
</tr>
<tr>
<td>Forced vital capacity, mean (SD), L</td>
<td>2.83 (0.88)</td>
<td>2.94 (0.89)</td>
</tr>
<tr>
<td>Albumin, mean (SD), mg/dL</td>
<td>3.88 (0.29)</td>
<td>3.95 (0.28)</td>
</tr>
<tr>
<td>C-reactive protein, median (IQR), mg/L</td>
<td>2.10 (3.52)</td>
<td>1.83 (2.44)</td>
</tr>
<tr>
<td>Creatinine, mean (SD), mg/dL</td>
<td>1.19 (0.67)</td>
<td>1.05 (0.29)</td>
</tr>
<tr>
<td>Fibrinogen, mean (SD), mg/dL</td>
<td>335 (77)</td>
<td>323 (68)</td>
</tr>
<tr>
<td>White blood cell count, mean (SD), $10^3$/µL</td>
<td>6.1 (2.9)</td>
<td>6.1 (1.9)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.
SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; to convert fibrinogen to micromoles per liter, multiply by 0.0294.
*All values are given as number (percentage) unless otherwise indicated. Hemoglobin quintiles were defined in a sex-specific manner and rounded to the nearest tenth. Values in women were 12.6, 12.7 to 13.2, 13.3 to 13.8, 13.9 to 14.4, and >14.4 g/dL, respectively. In men, these were 13.7, 13.8 to 14.4, 14.5 to 15.0, 15.1 to 15.6, and >15.6 g/dL.
†Calculated as weight in kilograms divided by the square of height in meters.

Figure 1. Unadjusted mortality over 11.2 years by hemoglobin quintiles ($P$ values for trend across quintiles are <.001, <.001, and .002, respectively).

Figure 2. Kaplan-Meier curve of survival over 11.2 years by anemia status (based on World Health Organization criteria) ($P$<.001).
multivariate adjustment, higher hemoglobin concentrations were associated with increased mortality.

Anemia is common among elderly individuals, and its prevalence in this cohort, based on the WHO criteria, adds to previous findings.5-7,23 The CHS as a community-dwelling cohort may underestimate the prevalence of anemia in the elderly population because up to 40% of individuals in long-term care facilities may be anemic.24 Little previous available data exist on hemoglobin concentrations or the prevalence of anemia among elderly black individuals. In a recent report from the Third National Health and Nutrition Examination Survey,7 27.8% of non-Hispanic black participants had anemia as defined by the WHO criteria. This was nearly 3 times higher than for white participants.

Our findings agree with other studies relating anemia to mortality. In one study of 3957 elderly patients treated at an ambulatory care clinic, a physician diagnosis code of anemia was associated with an adjusted HR of 1.44 (95% CI, 1.16-1.79) for 1-year mortality.23 Izaks et al2 investigated subjects 85 years and older in the Netherlands. In age- and sex-adjusted models, the 10-year HR for mortality with anemia using the WHO criteria was 1.84 (95% CI, 1.49-2.27), although extensive adjustment for other risk factors was not done. In a 5-year study2 of 618 residents of Olmstead County, Minnesota, the age- and sex-adjusted HR for mortality with anemia (<12 g/dL for men and <11 g/dL for women) was 1.8 (95% CI, 1.6-2.0). In studies of specific patient populations, including patients with cardiac13,14 and renal10,25,26 disease, the risk of death related to anemia was similar to that reported herein. In sum, the data suggest that anemia itself, regardless of the patient group studied, is a marker for mortality. These studies are diverse; limitations included reliance on physician diagnosis codes for anemia, small sample size, or low generalizability resulting from inclusion of specific patient populations.

The Atherosclerosis Risk in Communities (ARIC) study investigators27 showed findings similar to ours in middle-aged individuals, such as weaker associations of anemia with cardiovascular than noncardiovascular mortality. They observed an adjusted HR of 1.65 (95% CI, 1.30-2.10) for all-cause mortality and an adjusted HR of 1.41 (95% CI, 1.01-1.95) for cardiovascular mortality in those with anemia. A larger association of anemia with noncardiovascular mortality might be the result of a greater propensity for inflammatory conditions (such as cancer or infections) to cause anemia than subclinical cardiovascular disease; however, this would be speculation because we do not know the cause of anemia in either cohort.

An intriguing finding in our study was the elevated mortality among those in the highest hemoglobin quintile, even after extensive adjustment for other factors. Although the 95% CI approached 1, this result suggests that a hemoglobin concentration at the upper range of normal (>15.6 g/dL for men and >14.4 g/dL for women) may confer an increased risk of mortality. It remains unclear whether the impact of hemoglobin on mortality operates through the same or different causal pathways at higher vs lower values. Participants with higher hemoglobin concentrations appeared to be healthier at base-
line compared with those in the lowest hemoglobin quintile; they had lower concentrations of inflammation markers and creatinine and lower prevalences of congestive heart failure and frailty. Although they smoked more, they were not more likely to have lung disease. Similar findings have been reported in elderly women and patients with renal disease. Hypotheses suggest that higher hemoglobin concentrations lead to increased blood viscosity, blood pressure, and dialysis-access thrombosis. Many studies have not shown a reverse J-shaped relationship between hemoglobin concentration and mortality, and reported increased mortality only with lower hemoglobin concentrations. Additional study of this phenomenon is needed.

Along with our observational findings and those of other studies, current data suggest a hypothesis that low hemoglobin concentrations are causally related to adverse outcomes. Underlying diseases may induce anemia through increased inflammation suppressing erythropoiesis, and a low hemoglobin concentration as a marker for heart or renal failure or malnutrition. In the present study, a lower hemoglobin concentration was a risk factor for mortality independent of these factors that might modify the effect of anemia and independent of factors that might be involved in the causal pathways between anemia and mortality (e.g., inflammation or renal function). Accumulating evidence suggests that a low hemoglobin concentration adversely affects the cardiovascular system and that correction of anemia in renal patients may reduce mortality by up to 20% and reverse mild left ventricular dilation.

The major limitations of this study are that it was an observational study of a community-dwelling population; participants may not represent a cross-section of the elderly population. Furthermore, observational studies cannot determine causality. It could be argued that transient anemia from gastrointestinal losses would not confer as great a risk of mortality as a persistently low hemoglobin concentration. We do not have information on the etiology of anemia (vitamin B12, folate, ferritin concentrations, and red blood cell indices) and cannot speculate on the magnitude of this effect. The fact that anemia independently predicted mortality over a long period and the linearity of the Kaplan-Meier survival curve (Figure 2) suggest that it may contribute to long-term adverse physiologic changes rather than serve as a proxy for another, unmeasured condition. Because this was a study assessing cardiovascular risk, some confounding variables, such as malignancy, may not have been adequately assessed.

In conclusion, a lower hemoglobin concentration was independently associated with mortality in this elderly cohort. The bottom hemoglobin quintile defined a larger group at risk than anemia status based on the WHO criteria. Future areas of investigation should determine the optimal hemoglobin value that defines an abnormal concentration in elderly individuals, study the causes of low hemoglobin concentrations in elderly individuals and how these relate differentially to outcomes, evaluate the causes of increased mortality in individuals with low and high hemoglobin concentrations, and assess whether treatment of low hemoglobin in the general population reduces mortality.

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Group Members: A full list of participating Cardiovascular Health Study investigators and institutions can be found at http://www.chs-nhlbi.org.

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Additional Information: Dr Cushman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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