The Definition of Anemia in Older Persons

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ANEMIA IS DEFINED BY THE World Health Organization (WHO),1 but for older persons the criteria for anemia may not be as widely accepted as for younger people. The hemoglobin concentration is lower on average in people of older age and could therefore necessitate an adjustment of the criteria.1 On the other hand, the decline in hemoglobin concentration during aging is small and may not require unique criteria.2

The aim of this study was to investigate the association between hemoglobin concentration and mortality in older persons. We used mortality data to determine whether the WHO criteria for hemoglobin concentration and the WHO definition of anemia are appropriate for persons aged 85 years and older. We postulated that a low hemoglobin concentration represents underlying disease and supports evaluating the patient for possible causes of anemia.

METHODS

Study Sample
The subjects were participants of the community-based Leiden 85-plus Study. The primary goal of the study was to investigate the association between human leukocyte antigen (HLA) phenotypes and aging.3 Persons were included if they were inhabitants of Leiden, the Netherlands, and aged 85 years and older at the start of the study (December 1, 1986). There were no exclusion criteria. The study population comprised a total of 1258 persons of whom 73% were women. The Committee on Medical Ethics of the Leiden University Medical Center approved the study.

All persons were visited at their place of residence. The request for participation was made by telephone, a short home visit, or through relatives if the person was residing in a nursing home. After verbal informed consent, a physician interviewed the persons on their medical history and activities of daily living and tested their cognitive function with the Mini-Mental State Examination.4 At the end of the interview, permission was asked to collect a venous blood sample. The blood samples were drawn during a separate home call.

Laboratory Methods
The blood samples were collected in sterile, EDTA tubes (Becton Dickinson Vacutainer Systems, Meylan Cedex, France) and processed within 3 hours in the central laboratories of Leiden University Medical Center. The measurements were done with an automated system (Coulter counter, Coulter Electronics, Hialeah, Fla).

Context Whether hemoglobin concentrations defined as anemia by the World Health Organization (WHO) are associated with increased mortality in older persons is not known.

Objective To investigate the association between hemoglobin concentration and cause-specific mortality in older persons.

Design Community-based study conducted from 1986 to 1996 (follow-up period, 10 years).

Setting Leiden, the Netherlands.

Participants A total of 1016 community residents aged 85 years and older were eligible and 872 agreed to have a blood sample taken. Hemoglobin concentration was measured in 755 persons (74%).

Main Outcome Measures Hemoglobin concentration, 10-year survival, and primary cause of death. According to the WHO criteria, anemia was defined as a hemoglobin concentration below 7.5 mmol/L (120 g/L) in women and below 8.1 mmol/L (130 g/L) in men.

Results Compared with persons with a normal hemoglobin concentration, the mortality risk was 1.60 (95% confidence interval [CI], 1.24-2.06; P < .001) in women with anemia, and 2.29 (95% CI, 1.60-3.26; P < .001) in men with anemia. In both sexes, the mortality risk increased with lower hemoglobin concentrations. In persons without self-reported clinical disease at baseline, the mortality risk of anemia was 2.21 (95% CI, 1.37-3.57; P = .002). Mortality from malignant and infectious diseases was higher in persons with anemia.

Conclusions Anemia defined by the WHO criteria was associated with an increased mortality risk in persons aged 85 years and older. The criteria are thus appropriate for older persons. A low hemoglobin concentration at old age signifies disease.

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Anemia was defined by the criteria of the WHO. The reference interval for the hemoglobin concentration was set at 7.5 to 10.0 mmol/L (120-160 g/L) in women and at 8.1 to 11.2 mmol/L (130-180 g/L) in men. The reference interval for the red blood cell volume was set at 80 to 100 fL in both sexes.

**Mortality Data**
All participants were followed for mortality up to October 1, 1996, for a total follow-up period of 10 years. The places and dates of death and the numbers of the death certificates were obtained from the civic registries. Two persons who moved abroad during the study period were not included in the analysis.

**Causes of Death**
The primary causes of death were assessed by linking the death certificates to the causes of death coded by a physician of the Dutch Central Bureau of Statistics. The causes of death were classified according to the International Classification of Diseases, Ninth Revision. From 1996 onward, the death certificates were coded according to the International Classification of Diseases, 10th Revision. For purposes of the study, they were reclassified according to the ninth revision. The codes 390 to 459 were categorized as “cardiovascular disorders,” the codes 140 to 239 as “malignant neoplasms,” and the codes 460 to 519 as “respiratory diseases.” Selected respiratory tract infections (codes 460-466.1, 475, 480-487.8, 510.0-510.9, and 513.0-513.1) were included in the category “all infections.” The category “all infections” also included tuberculosis (codes 010-018.9 and 137-137.4), septicemia (codes 038-038.9), and infections of the kidney and urinary tract (codes 590-590.9 and 599.0). Other infectious diseases were not recorded in our study.

**Statistical Analyses**
Continuous data are presented as medians and interquartile ranges. The mortality risk of anemia and the 95% confidence interval (CI) was estimated by a Cox proportional hazards regression model. (A linear spline model produced very similar results; only the Cox model is presented here.) The mortality risk of persons with anemia was estimated in comparison to persons with a normal hemoglobin concentration. We used 4 regression models. In model 1, adjustment was made for age and sex. In model 2, adjustment was made for age, sex, and self-reported diseases at baseline associated with anemia: malignant neoplasm, infectious disease, thyroid disease, peptic ulcer, renal failure, and rheumatoid disease. In model 3, adjustment was made for age, sex, and functional status defined as any dependency in activities of daily living and cognitive impairment as measured by a Mini-Mental State Examination score below 24 points. In model 4, the mortality risk of anemia was estimated only for persons without self-reported clinical disease, after adjustment for age and sex.

Anemia was found in 17% of the women and in 8% of the men (Table 1). For both sexes, anemia was mostly normocytic (80% of all anemic women and 92% of all anemic men). The median age (interquartile range) was 90 years (88-92) in men and 89 years (88-92) in women. The reference interval for the hemoglobin concentration was set at 80 to 100 fL in both sexes.

**RESULTS**

**Study Sample**
During follow-up, 21 persons who were initially included were found to not fulfill the age criteria, and 221 persons died before the interview. Thus, 1016 persons were eligible for the study. Of these, 57 persons (6%) refused the interview, 2 persons were not traceable, and 1 person was erroneously not interviewed. A total of 956 persons (94%), of whom 872 persons (86% of the eligible number) approved of a blood sample, gave consent to the interview. If only a small amount of blood could be drawn, HLA typing was performed first because this was the primary goal of the study. The hemoglobin concentration was assessed in 755 persons (74% of the eligible number).

**Prevalence of Anemia**
Anemia was found in 17% of the women and in 8% of the men (Table 1). For both sexes, anemia was mostly normocytic (80% of all anemic women and 92% of all anemic men). The median age (interquartile range) was 90 years (88-93) years in persons with anemia and 89 years (88-91) years in persons with a normal hemoglobin concentration ($P = .003$).

**Diseases at Baseline**
At baseline, anemia was associated with diseases known to cause a decrease in hemoglobin concentration. Malignant neoplasms were found in 19 (13%) of the persons with anemia and in 28 (5%) of the persons with a normal hemoglobin concentration ($\chi^2 = 11.83, P < .001$). A history of peptic ulcer was present in...
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Table 2. Age- and Sex-Adjusted Mortality Risks in Persons With Anemia Compared With Persons With a Normal Hemoglobin Concentration in the Periods 0 to 5 Years and 5 to 10 Years After Blood Sampling*

<table>
<thead>
<tr>
<th></th>
<th>0-5 y Mortality Risk (95% Confidence Interval)</th>
<th>5-10 y Mortality Risk (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.84 (1.50-2.25)</td>
<td>0.99 (0.56-1.76)</td>
</tr>
<tr>
<td>Microcytic</td>
<td>1.84 (1.01-3.35)</td>
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<tr>
<td>Normocytic†</td>
<td>1.86 (1.51-2.31)</td>
<td>0.90 (0.52-1.79)</td>
</tr>
<tr>
<td>Macrocytic</td>
<td>1.52 (0.78-2.96)</td>
<td></td>
</tr>
<tr>
<td>Anemia, adjusted for disease‡</td>
<td>1.84 (1.49-2.27)</td>
<td>0.91 (0.50-1.64)</td>
</tr>
<tr>
<td>Anemia, adjusted for functional impairment§</td>
<td>1.74 (1.41-2.15)</td>
<td>1.07 (0.74-2.33)</td>
</tr>
<tr>
<td>Anemia, in persons without clinical disease</td>
<td>2.21 (1.37-3.57)</td>
<td>0.64 (0.15-2.68)</td>
</tr>
</tbody>
</table>

*World Health Organization criteria for a normal hemoglobin concentration: for women, 7.5 to 10.0 mmol/L (120-160 g/L); for men, 8.1 to 11.2 mmol/L (130-180 g/L). Ellipses indicate data not calculated because of small numbers.
†Defined as 80 to 100 g/L.
‡Diseases at baseline associated with anemia: malignant neoplasm, infectious disease, thyroid disease, peptic ulcer, renal failure, and rheumatoid disease.
§Functional impairment defined as any according to dependency in activities of daily living and cognitive impairment as measured by a Mini-Mental State Examination score below 24 points.

Figure 1. Mortality Risk by Hemoglobin Concentration in Women Aged 85 Years and Older 0 to 5 Years After Blood Sampling

The mortality risk of a category was calculated as the mortality risk for that category vs all other categories. Bars represent 95% confidence intervals.

Figure 2. Mortality Risk by Hemoglobin Concentration in Men Aged 85 Years and Older 0 to 5 Years After Blood Sampling

The mortality risk of a category was calculated as the mortality risk for that category vs all other categories. Bars represent 95% confidence intervals.

The mortality risk associated with anemia was similar after adjustment was made for diseases at baseline associated with anemia, and also if adjustment was made for functional impairments (Table 2). If the analysis was restricted to persons free from self-reported clinical disease at baseline, the mortality risk of anemia was higher (Table 2).

The mortality risk increased with lower hemoglobin concentrations for both sexes. In women, the mortality risk was increased in persons with a hemoglobin concentration below 8.0 mmol/L and was highest in persons with a hemoglobin concentration of 6.5 mmol/L: 2.20 (95% CI, 1.35-3.58; P = .002) compared with all other concentrations (Figure 1). In men, the mortality risk was increased in persons with a hemoglobin concentration below 8.5 mmol/L and was also highest in persons with a hemoglobin concentration of 6.5 mmol/L: 2.54 (95% CI, 1.33-4.87; P = .005) compared with all other concentrations (Figure 2).

In the period of 5 to 10 years after blood sampling, there were no differences in mortality risk (Table 2).

Causes of Death

During follow-up, 133 (86%) of the 151 persons with anemia had died compared with 390 (65%) of the 599 persons with a normal hemoglobin concentration. Malignant neoplasms and infections were more often noted as the primary cause of death in persons with anemia, whereas respiratory diseases were more often noted as the primary cause of death in persons with a normal hemoglobin concentration. The difference in the distribution of the primary causes of death was statistically significant ($\chi^2 = 9.89, P = .04$) (Table 3).

Validity

The hemoglobin concentration was not measured in 201 persons who gave consent to participate in the study. The mortality risk of these persons was 1.24 (95% CI, 1.03-1.48; P = .02) compared with the study sample.

3 (2%) of the persons with anemia compared with none of those with a normal hemoglobin concentration ($P = .03$). Any infection was found in 7 (5%) of the persons with anemia, and in 11 (2%) of the persons with a normal hemoglobin concentration ($P = .07$). There were no differences between persons with anemia and persons with a normal hemoglobin concentration for other diseases.

At baseline, 29 (21%) of the persons with anemia had no reported clinical disease compared with 148 persons (26%) with a normal hemoglobin concentration ($\chi^2 = 1.65, P = .20$).

The mortality risk for that category vs all other categories. Bars represent 95% confidence intervals.
COMMENT

The mortality risk in persons with anemia, defined according to the WHO criteria, was increased 2-fold compared with persons with a normal hemoglobin concentration. The mortality risk increased with lower hemoglobin concentrations. The association between a low hemoglobin concentration and increased mortality could not be explained by diseases at baseline or by functional impairment. Moreover, a low hemoglobin concentration was also associated with an increased mortality risk in older persons without clinical disease. Although clinical disease was determined by patient self-report, previous research has found self-report to be reasonably accurate.2,9

Although chosen arbitrarily, the WHO criteria for anemia were confirmed by our data. Anemia is defined by the WHO as a hemoglobin concentration below 7.5 mmol/L (120 g/L) in women and below 8.1 mmol/L (130 g/L) in men.4 These hemoglobin concentrations are based on data from young persons, but also were associated with an increased mortality risk in persons aged 85 years and older. Thus, the WHO criteria for anemia are also appropriate for persons aged 85 years and older, and age-dependent criteria are not necessary.

A cause for anemia is found in most older persons with a low hemoglobin concentration.10,11 In our study, anemia was also associated with a poor health status. As in other studies,10,11 malignant neoplasms and infections were more often found in older persons with anemia. These diseases were also more often marked as the primary cause of death. Thus, anemia at old age was probably due to disease. Because of this increased mortality risk, hemoglobin levels below normal are a reason for further investigation of older persons in clinical practice.

The higher prevalence of anemia in men was also described in other studies. The frequency of anemia varies between 27% to 40% in men aged 85 years and older and between 16% to 21% in women aged 85 years and older.12,13 The mortality risk of men in our cohort was slightly higher than in women.3 This suggests that the higher frequency of anemia in men can be explained by a higher prevalence of underlying diseases.12

A poor health status might also play a role if the hemoglobin concentration is high. Compared with the lowest mortality risk, a small increase in the mortality risk was seen in older persons with a high hemoglobin concentration. A higher hemoglobin concentration is caused, for example, by dehydration or obstructive pulmonary disease. In our study, respiratory diseases were more often noted as the primary cause of death in persons with a normal hemoglobin concentration than in persons with anemia. These disorders will lead both to a higher hemoglobin concentration and an increase in mortality risk.

In conclusion, the mortality risk was increased in older persons with anemia if anemia was defined by the WHO criteria.7 Thus, the WHO criteria are appropriate for older persons. Anemia in older persons is due to disease and not to aging. Therefore, further clinical investigation is warranted if an older person’s hemoglobin concentration is below the WHO normal values—even if the person is without apparent clinical disease.

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| Table 3. Causes of Death 0 to 5 Years After Blood Sampling According to Blood Cell Count |
|-----------------|-----------------|
| Cause of Death  | Anemia, No. (%) | Normocytopenia, No. (%) |
| Cardiovascular disorders | 133 (100) | 390 (100) |
| Ischemic heart disease | 60 (45) | 175 (45) |
| Cerebrovascular disease | 16 (12) | 51 (12) |
| Malignant neoplasms | 23 (17) | 57 (17) |
| Respiratory diseases | 2 (2) | 22 (6) |
| All infections | 16 (12) | 33 (8) |
| Others | 23 (17) | 95 (24) |

*World Health Organization criteria for a normal hemoglobin concentration: for women, 7.5 to 10.0 mmol/L (120-160 g/L); for men, 8.1 to 11.2 mmol/L (130-180 g/L).

†Test for the main categories cardiovascular disorders, malignant neoplasms, respiratory diseases, all infections, and others: χ² = 9.89, P = .04.

REFERENCES


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