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No increased mortality risk in older persons with unexplained anaemia

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Abstract

Background: in older persons, anaemia is associated with a number of unfavourable outcomes. In approximately 30% of older persons with anaemia, the cause of the anaemia is unexplained. We assessed the clinical differences between subjects with explained and unexplained anaemia and investigated whether these subjects have different mortality patterns compared with subjects without anaemia.
Design: observational prospective follow-up study.
Setting: the Leiden 85-plus study.
Participants: four hundred and ninety-one persons aged 86 years.
Methods: the study population was divided in three groups: (i) no anaemia (reference group, $n = 377$), (ii) explained anaemia (iron deficiency, folate deficiency, vitamin B12 deficiency, signs of myelodysplastic syndrome or renal failure, $n = 74$) and (iii) unexplained anaemia, ($n = 40$). Mortality risks were estimated with Cox-proportional hazard models.
Results: haemoglobin levels were significantly lower in subjects with explained anaemia than in subjects with unexplained anaemia ($P < 0.01$). An increased risk for mortality was observed in subjects with explained anaemia [HR: 1.93 (95% CI: 1.47–2.52), $P < 0.001$], but not in subjects with unexplained anaemia [HR: 1.19 (95% CI: 0.85–1.69), $P = 0.31$]. Adjusted analyses (sex, co-morbidity, MMSE, institutionalised and smoking) did not change the observed associations for both explained and unexplained anaemic subjects.
Conclusion: older subjects with unexplained anaemia had similar survival compared with non-anaemic subjects. Increased mortality risks were observed in subjects with explained anaemia compared with non-anaemic subjects.

Keywords: *anaemia, elderly, mortality risk, unexplained*

Introduction

The incidence and prevalence of anaemia increase with age [1, 2]. In older subjects anaemia is associated with unfavourable events including death [3–6], dementia [7], cardiovascular diseases [8] and functional dependence [9, 10]. Clinical investigation into the cause of anaemia in older patients is often complicated by the co-morbidity characterising this patient group. Especially cognitive disorders and physical disabilities hamper reliable history taking and physical examinations, the cornerstones of medical practice. Therefore in clinical practice, the initial laboratory results are indicative for making the decision for further and often more invasive investigations in these patients. Since any procedure may lead to a deterioration of the current condition of the older patient invasive investigations should be limited to a minimum.

Chronic renal failure and iron deficiency are the most common causes for anaemia in older subjects [1, 11, 12], often caused by severe underlying diseases such as atherosclerosis and gastro-intestinal malignancies, respectively. Other well known causes in clinical practice for anaemia are folate and vitamin B12 deficiency. The role of vitamin B12 deficiency as predictor for the presence of anaemia in this population, however, is still subject to discussion [13, 14]. Another serious cause of anaemia in the elderly is myelodysplastic syndrome (MDS), a heterogeneous disorder characterised by ineffective haematopoiesis resulting in low peripheral blood counts [15, 16].

Several epidemiological studies have found that up to 30% of anaemia in the older population is unexplained, even when extensive clinical information is available [15, 17, 18]. The clinical relevance of unexplained anaemia is unclear. In the present study, we assessed clinical differences between explained and unexplained anaemia in older subjects and investigated how mortality risks differ by type of anaemia.

Methods

Study population

All data were derived from the Leiden 85-plus Study, a prospective follow-up study of subjects aged 85 years at baseline. At baseline, all individuals were living in Leiden, The Netherlands. There were no exclusion criteria for study participation. All subjects were visited at their place of residence where interviews took place and venous blood samples were drawn. Between 1997 and 1999, the Leiden 85-plus Study enrolled 599 subjects at baseline [19]. For the present analysis, we included 491 subjects aged 86 years. Of the 108 subjects that were not included in the present analysis, 47 died before the age of 86 years, 39 refused further participation, 16 refused blood sampling and in 6 subjects no erythropoietin measurement was available due to technical problems. The Medical Ethical Committee of the Leiden University Medical Center (LUMC) approved the study and all participants provided informed consent for study participation.

Laboratory measurements

All blood samples were collected in sterile EDTA tubes. Measurements of haemoglobin, mean corpuscular volume and erythrocyte count, white blood cell count and platelet count were done with a fully automated system (Sysmex XE-2100, TOA Medical Electronics, Kobe, Japan). Serum erythropoietin levels were measured using the enzyme immunoassay (EIA, Immulite 2500, Siemens Medical Diagnostics, Tarrytown, NY, USA), which had a sensitivity of 1.2 mU/ml and a coefficient of variation less than 6%. Creatinine was measured according to the Jaffe method (Hitachi 747, Tokyo, Japan). Creatinine clearance was estimated with the Modification of Diet in Renal Disease equation (MDRD) [20]. C-reactive protein (CRP) measurement was done in one batch using the Dual Count Solid Phase No Boil Assay (Diagnostic Products Corp, Los Angeles, CA, USA). Ferritin, folate and vitamin B12 were determined in one batch using the Dual Count Solid Phase No Boil Assay (Diagnostic Products Corp, Los Angeles, CA, USA).

Mortality

All subjects were followed up for mortality until 1 February 2008. For the deceased participants, the cause of death was obtained from Statistics Netherlands. Only the primary cause of death on the death certificate was used in our analyses. The international classification of diseases (ICD) codes I00-I99 were used for cardiovascular mortality. For non-vascular mortality, all ICD codes except I00-I99 were used.

Study groups

For the present study, the study population was divided in three groups: a group with no anaemia (reference group), a group with a known cause for anaemia (explained anaemia) and a group with an unknown cause for anaemia (unexplained anaemia). Explained and unexplained anaemia are two different identities; explained anaemia, often due to chronic diseases or malignancies, is characterised by significant higher CRP, Interleukin-6 levels or higher erythropoietin levels. In persons with unexplained anaemia, lower CRP, lower lymphocyte counts and EPO levels are found, assuming a totally different pathophysiological form of anaemia. Anaemia was defined according to the criteria of the World Health Organization [21] as haemoglobin levels lower than 12.0 g/dl (7.5 mmol/l) for women and 13.0 g/dl (8.1 mmol/l) for men. Explained anaemia was defined as anaemia in the presence of iron deficiency (ferritin <20 ng/ml), renal failure (MDRD <50 ml/min/m^2), vitamin B12 deficiency (<150 pmol/ml), folate deficiency (<7.0 nmol/ml) or signs of MDS. MDS was defined as anaemia

together with leucopenia (white blood cell count less than 3.5×10^9) or thrombopenia (platelet count less than 150×10^9). Unexplained anaemia was defined as the presence of anaemia with normal ferritin, vitamin B12, folate and creatinine concentrations.

Additional study parameters

Information on the presence of chronic disease (diabetes mellitus, chronic obstructive pulmonary disease (COPD), arthritis, myocardial infarction, heart failure, stroke and malignancy) was obtained from general practitioners, nursing home physicians and pharmacy records [22]. Cognitive function was measured with the Mini-Mental State Examination (MMSE) [23]. All participants were interviewed about current and former smoking habits.

Statistical analyses

Data are presented as number (percentages) for dichotomous parameters and as a median (inter-quartile range) for continuous parameters. Differences in laboratory values between anaemic (both explained and unexplained) and non-anaemic subjects (the reference group) were determined by Mann–Whitney *U* test. Mortality differences between anaemic and non-anaemic subjects were assessed with Cox regression analysis, adjusted for gender, co-morbidity, MMSE, institutionalisation, smoking and haemoglobin level. Mortality was visually depicted with Kaplan–Meier survival curves. Mortality differences between subjects with explained and unexplained anaemia were additionally adjusted for the haemoglobin level.

Since previous results from the Leiden 85-plus Study showed no association between vitamin B12 deficiency and anaemia [13], we repeated all analyses excluding vitamin B12 deficiency from the explained anaemic group.

The SPSS software (version 16.0.1, SPSS, Inc, Chicago, IL, USA) was used for all statistical analyses. *P*-values lower than 0.05 were considered statistically significant.

Results

Baseline characteristics of the 491 subjects are presented in Table 1. A total of 108 (22%) subjects were institutionalised in a nursing home or care home for older persons, 315 (64%) had one or more chronic diseases, 49 (10%) had a history of myocardial infarction and 58 (12%) a history of stroke. A total of 131 subjects (27%) had renal insufficiency with an estimated glomerular filtration rate <50 ml/min/1.73 m^2 (MDRD). Of the 114 (23%) cases of anaemia, 74 (65%) were explained and 40 (35%) were unexplained. Of the 74 subjects with explained anaemia, 13 (19%) had iron deficiency, 42 (56%) had renal failure, 4 (5%) folate deficiency, 11 (15%) vitamin B12 deficiency and 4 (5%) MDS.

Table 2 shows the haematological characteristics of the subjects with explained anaemia, unexplained anaemia and their counterparts without anaemia. Haemoglobin levels were significantly lower in the subjects with explained anaemia than in the subjects with unexplained anaemia ($P < 0.01$) As expected, median erythropoietin levels were significantly higher in the subjects with anaemia than in the subjects without anaemia (9.6 mIU/ml) ($P < 0.01$). However, median erythropoietin levels were similar in subjects with explained anaemia and those with unexplained anaemia, (11.5 mIU/ml versus 12.1 mIU/ml, $P = 0.88$). Only in the group with explained anaemia, CRP was significantly higher than in those without anaemia ($P < 0.05$). No differences in comorbid illnesses (malignancies, diabetes mellitus, COPD, arthritis, myocardial infarction and stroke), smoking, MMSE and institutionalisation were found between the explained and unexplained anaemic groups (data not shown).

Survival differences between subjects with explained anaemia, unexplained anaemia and without anaemia from age 86 onwards are visually depicted in Figure 1. An increased risk for all-cause mortality was found in the

Table 1. Baseline characteristics of the subjects at age 86

	n = 491
Women (%)	331 (67)
Institutionalised (%)	108 (22)
MMSE score (median, IQR)	26 (22–28)
Current and/or past smoking (%)	231 (47)
Chronic diseases (%)	315 (64)
Malignancies (%)	92 (19)
Diabetes mellitus (%)	73 (15)
COPD (%)	49 (10)
Arthritis[a] (%)	162 (33)
Renal insufficiency[b] (%)	131 (27)
Myocardial infarction (%)	49 (10)
Stroke (%)	58 (12)
Anaemia (%)	114 (23)
Explained anaemia (%)	74 (15)
Iron deficiency[c] (%)	13 (19)
Renal anaemia[d] (%)	42 (57)
Vitamin B12 deficiency[e] (%)	11 (15)
Folate deficiency[f] (%)	4 (5)
Myelodysplastic syndrome[g] (%)	4 (5)
Unexplained anaemia (%)	40 (8)
Follow-up time (years)	6 (3–9)

MMSE, Mini Mental State Examination; COPD, chronic obstructive pulmonary disease.
Continuous parameters are presented as median (inter-quartile range).
Categorial data are presented as numbers (percentages).
[a]Arthritis was defined as polymyalgia rheumatica, rheumatoid arthritis and osteoarthrosis.
[b]Renal insufficiency was defined as creatinine clearance <50 ml/min/1.73 m^2 calculated by the Modification of Diet in Renal Disease formula.
[c]Iron deficiency was defined as ferritin <20 ng/ml.
[d]Renal anaemia was defined as having anaemia and creatinine clearance <50 ml/min/1.73 m^2.
[e]Vitamin B12 deficiency was defined as <150 pmol/ml.
[f]Folate deficiency was defined as <7.0 nmol/ml.
[g]Myelodysplastic syndrome vitamin was defined as anaemia together with leucopenia (white blood cell count less than 3.5×10^9), and thrombopenia (platelet count less than 150×10^9).

Table 2. Clinical characteristics of study participants by anaemia status

	Explained anaemia ($n = 74$)	Unexplained anaemia ($n = 40$)	Without anaemia ($n = 377$)
Haemoglobin (g/dl)	11.4 (10.4–11.8)**	11.7 (11.2–12.2)**	13.4 (12.8–14.1)
Haematocrit (%)	0.35 (0.32–0.36)**	0.36 (0.34–0.37)**	0.41 (0.38–0.43)
MCV (fL)	90 (86–93)**	91 (88–94)	91 (89–94)
Erythrocytes ($\times 10^9$/l)	3.9 (3.6–4.1)**	3.9 (3.7–4.1)**	4.5 (4.3–4.7)
Leucocytes ($\times 10^9$/l)	6.5 (5.1–7.6)	6.0 (5.0–7.1)	6.3 (5.3–7.5)
Platelets ($\times 10^9$/l)	225 (172–272)	235 (194–282)	227 (191–267)
Erythropoietin (mIU/ml)	11.5 (8.8–17.2)**	12.1 (9.7–15.0)**	9.6 (7.5–12.8)
Creatinine (μmol/l)	105 (88–135)**	93 (79–100)	91 (80–106)
MDRD (ml/min/1.73 m^2)	48 (37–66)**	62 (54–68)	58 (50–68)
Albumin (g/l)	39 (36–41)**	39 (36–41)**	41 (39–43)
CRP (mg/l)	6.0 (2.0–12.0)**	4.0 (1.0–8.0)	3.0 (0.0–7.0)
Ferritin (mg/l)	103 (37–229)*	93 (49–190)	118 (64–202)
Vitamin B12 (pmol/l)	282 (190–339)	302 (209–451)	256 (204–338)
Folic acid (nmol/l)	11 (9–14)**	13 (11–17)	13 (10–16)

MCV, mean corpuscular volume; CRP, C-reactive protein.
Data are presented in median (inter-quartile range). *P*-value calculated by the Mann–Whitney *U* test.
*$P < 0.05$, **$P \leq 0.01$ compared with subjects without anaemia.

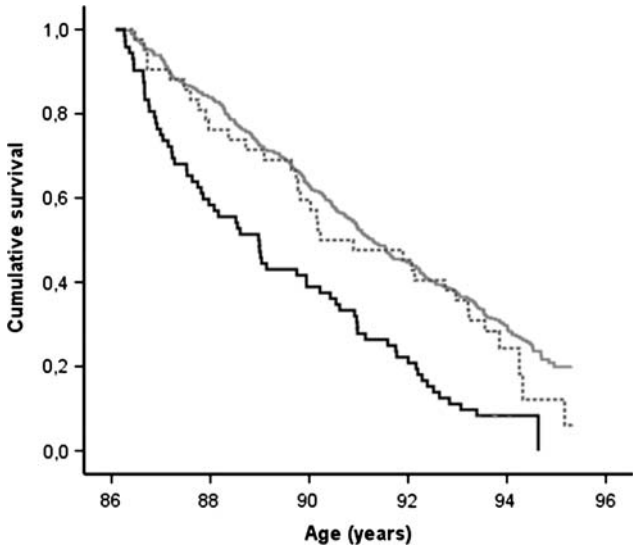

Figure 1. Survival of subjects with no anaemia ($n = 377$), explained anaemia ($n = 74$) and unexplained anaemia ($n = 40$) from age 86.

group of subjects with explained anaemia (HR: 1.93, 95% CI: 1.47–2.52), $P < 0.001$) compared with the group of subjects without anaemia. Subjects with unexplained anaemia had no increased risk for all-cause mortality compared with non-anaemic subjects (HR: 1.19 (95% CI: 0.85–1.69), $P = 0.31$). Adjustment for sex, co-morbidity, MMSE, institutionalisation and smoking did not change these associations for subjects with explained anaemia [HR: 1.93 (95% CI: 1.23–3.02), $P = 0.004$] and for subjects with unexplained anaemia [HR: 1.19 (95% CI: 0.79–1.79), $P = 0.39$]. When we repeated all analyses excluding vitamin B12 deficiency from the explained anaemic group, the results were not materially different.

Subjects with explained anaemia had an increased mortality risk compared with subjects with unexplained anaemia [HR: 1.61 (95% CI: 1.09–2.21), $P = 0.04$]. Adjustment for sex, co-morbidity, MMSE, institutionalisation, smoking and haemoglobin did not change this association. In this analysis, sex [HR: 2.15 (95% CI: 1.59–2.90), $P < 0.0001$], haemoglobin level [HR: 1.41 (95% CI: 1.16–1.73), $P = 0.001$], CRP [HR: 1.02 (95% CI: 1.00–1.02), $P = 0.001$] and MMSE [HR: 1.07 (95% CI: 1.04–1.09), $P = 0.0001$] were independently associated with mortality risk.

Furthermore, the all-cause, cardiovascular and non-cardiovascular mortality risks for participants with explained and unexplained anaemia were studied. No statistically significant differences were found in cardiovascular mortality risk between the explained and unexplained anaemic group [HR: 1.83 (95% CI: 0.90–3.74), $P = 0.09$]. However, no difference was found in non-cardiovascular mortality risk between these two groups [HR: 1.36 (95% CI: 0.81–2.32), $P = 0.24$] (data not shown).

Discussion

The main finding of this study is that older subjects with explained anaemia had an almost twofold increased mortality risk compared with subjects without anaemia, whereas in subjects with unexplained anaemia no excess mortality was found. These findings possibly suggest that in older persons anaemia is only relevant for survival when a clinical explanation for the cause of anaemia can be demonstrated.

In our study sample, we found that in 37% of anaemic subjects no clinical explanation for anaemia could be found similar to earlier reports. Data from a non-institutionalised US population assessed in the third National Health and Nutrition Examination Survey (1988–94) showed that unexplained anaemia was present in one-third of the older adults (>65 years) with anaemia [1]. Another study reported that no evident cause for anaemia in a representative sample of older Europeans (>65 years) was found in

36.8% of the anaemic participants [18]. Moreover, in a study conducted among subjects of a nursing facility almost one-third of the anaemic subjects qualified as clinically unexplained [17]. Hence, our findings on the prevalence of explained and unexplained anaemia in elderly subjects corresponds well with the prevalences reported in the literature.

We found a twofold increased mortality risk in older persons with explained anaemia compared with the non-anaemic subjects. We regarded subjects as having explained anaemia when they met obvious clinical criteria as causes for anaemia, i.e. iron, folate, vitamin B12 deficiency, renal failure and MDS. Because of the design of our study, we were not informed about the specific underlying diseases causing these types of anaemia. The reason for the observed difference in mortality between the subjects with explained anaemia and unexplained anaemia or without anaemia is not obvious from our study. Between the three groups no differences in the cause of death were found. It is tempting to speculate that persons with iron deficiency would have an increased mortality risk because of the presence of intestinal malignancy and that persons with a renal anaemia would preferably die because of cardiovascular disease. However, further analysis of our data failed to demonstrate such relationships, probably because of the small number of subjects.

Higher serum CRP levels were found in the group of subjects with explained anaemia when compared with subjects with unexplained anaemia and subjects without anaemia. It may therefore be suggested that the underlying cause of the anaemia is associated with a chronic inflammatory response that may contribute to the observed increased mortality. Since there was significant predominance of renal insufficiency and myocardial infarction in the explained group the observed elevated CRP may be the result of the inflammatory status due to underlying atherosclerotic disease.

In contrast to the group of subjects with known causes for anaemia, the group with unexplained anaemia had no increased mortality risk. To our knowledge, this is a new finding with potentially important clinical implications. It possibly suggests that when in older persons no cause for an anaemia can be demonstrated by laboratory measurements, no further clinical investigations might be necessary. Anaemia in general is associated with an increased mortality risk, also in the oldest old [4–6]. An explanation for the present observation is still subject to speculation. It can be hypothesised that in subjects with unexplained anaemia, a relatively low haemoglobin level is part of their 'normal' phenotype. However, the fact that erythropoietin levels in the subjects with unexplained anaemia were similar to the level in the group with explained anaemia, might suggest a physiological response to a relatively low haemoglobin level in these subjects. Based on the selection criteria used for this group, the absence of increased co-morbidity and the relatively normal CRP levels, it could be suggested that anaemia in this group might be caused by impaired erythrocyte production due to an age-associated diminished haematopoietic stem cell proliferative capacity or, as suggested earlier, or by an one lineage MDS presenting as anaemia without white blood cell or platelet features with a very low risk of further deterioration [15]. However, new studies are required to shed light on this clinically important finding.

Our study contributes to the extensive discussion about the relationship between ageing and anaemia. A strong point of our study is its prospective follow-up setting, permitting us to analyse survival of the oldest old subjects aged 86 years. A limitation of the study is the relatively limited sample size of subjects with explained and unexplained anaemia. However, as mentioned, the prevalence of the subjects with unexplained anaemia is remarkably similar to those reported in other studies [1, 17]. Therefore, we believe that our findings may have a high external validity. Another limitation is that we were only able to draw conclusions of subjects of 86 years or older who were still alive, more research have to be done on the impact of unexplained anaemia and mortality of subjects younger than 86 years.

In conclusion, the present findings show that in contrast to older subjects with explained cause for anaemia, older subjects with unexplained anaemia based on initial laboratory measurements have no increased mortality risk compared with subjects without anaemia, suggesting that further clinical and often invasive evaluation to the cause of anaemia is possibly not necessary in this very old group of patients. This observation should be confirmed in other prospective observational studies and in dedicated intervention studies.

Key points

- Increased mortality risks were found in older subjects with explained anaemia.
- Older subjects with unexplained anaemia had similar survival compared with non-anaemic subjects.
- Further clinical invasive evaluation to the cause of anaemia is possibly not necessary in older patients with unexplained anaemia.

Conflicts of interest

None declared.

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Temporal relationship between handgrip strength and cognitive performance in oldest old people

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