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Research paper

Anemia prevalence and hematologic findings in German geriatric inpatients – results of the prospective cross-sectional multicenter study "GeriAnaemie 2013"

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ABSTRACT

Objectives: Anemia is a frequent finding in older patients, associated with increased morbidity. Hematologic data of German geriatric inpatients are scarce. This cross-sectional multicenter study was issued by the German Geriatric Society to evaluate hematologic findings and possible causes of anemia in German geriatric inpatients.
Methods: Five hundred and seventy-nine geriatric inpatients, consecutively recruited in 6 participating German study centers; patient characteristics and laboratory parameters were obtained on admission. Inclusion criteria: geriatric in-patient ≥70 years; exclusion criteria: actual cancer disease or cancer associated treatment. Anemia definition according to WHO criteria. Definition of anemia severity according to National Cancer Institute reference values. Anemia subtypes were defined and divided into renal anemia, anemia of chronic diseases, iron deficiency anemia and anemia associated with vitamin B12 deficiency or deficiency of folic acid. Myelodysplastic syndrome (MDS) was suspected in case of anemia in combination with leucopenia or low platelets.
Results: Overall, prevalence of anemia was 55.1% (319/579 patients), mean serum hemoglobin value 11.9 g/dL. Anemia was mainly mild (72.7%) and normocytic (70.2%). MDS was suspected in 27 patients (8.5%), with 10 being macrocytic. Anemia of chronic diseases (ACD) was the most prevalent subtype of anemia (8.2%); multicausality can be assumed in many patients. MCV based classification was heterogenous in all anemia subtypes.
Conclusion: Anemia was mainly normocytic, mild and highly prevalent in this patient cohort, could not always be specified; multicausality was supposed; MCV appeared to be inappropriate for pathogenetical assignment of anemia subtypes in older patients. Further research in geriatric hematologic particularities is needed.

Abbreviations: Absolute ID, Absolute iron deficiency; ACD, Anemia of chronic disease; CRP, C-reactive protein; Ery, Erythrocyte count; FA, Folic acid; FAA, Folic acid associated anemia; Functional ID, Functional iron deficiency; GFR, Glomerular filtration rate; Hb, Hemoglobin; IDA, Iron deficient anemia; MCV, Mean corpuscular volume; MDS, Myelodysplastic syndrome; NAA, Not assigned anemia; RA, Renal anemia; RPI, Reticulocyte production index; TSAT, Transferrin saturation; VB12A, Vitamin B12 associated anemia; VitB12, VitaminB12.

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1. Introduction

Anemia is a frequent finding in older patients and is associated with increased mortality, increased morbidity and risk of frailty [1–3]. Several international studies have shown that prevalence of anemia varies depending on the population considered. A study of the third National Health and Nutrition Examination survey (NHANES 1991–1994) showed an anemia prevalence of > 20% among community dwelling seniors > 85 years [4]. A more recent study among Indian home-dwelling people was consistent with this finding [5]. A systematic review by Gaskell et al. [6] among geriatric inpatients > 65 years living in developed countries found an anemia prevalence of 40%. Bach et al. [7] showed a comparable prevalence of anemia among Austrian geriatric in-patients aged ≥90. In their study cohort, anemia of chronic disease (ACD) prevailed and anemia was predominantly normocytic and mild [7]. However, data respecting anemia prevalence and hematologic findings like anemia severity or type of anemia among German geriatric inpatients are still rare and mostly derive from monocentric studies. The presumed high prevalence of anemia [8,9] with associated comorbidities among the increasing population of aged patients will be a challenge for clinicians in the near future. Until now, there is no general recommendation for diagnostic and therapeutic steps in connection with anemia in geriatric patients [10]. The German Geriatric Society therefore decided to initiate the first multicenter study on anemia prevalence among German geriatric inpatients. Primary objective of this study was to evaluate the prevalence of anemia. Further objectives were the analysis of hematological parameters and red blood cell indices to assess type and severity of anemia and possible causes for anemia.

2. Patients and methods

Between June 2013 and December 2014, a number of 598 geriatric inpatients were consecutively recruited on admission in six participating German study centers (5 geriatric centers and 1 general emergency department of a university hospital). Recruitment interval was 4 to 6 weeks in every study center at varying seasonal times. Included were patients > 70 years admitted to the geriatric department or – in case of the general emergency department – purposed to be admitted to a geriatric department. The patient cohort was broadly based on geriatric inpatients, who were transferred from other departments (e.g. after having undergone surgery) or admitted to the geriatric department either by practicing doctors or as an emergency. All study patients gave written informed consent. Patients with actual cancer disease or actual cancer associated treatment were not included in the study. Of the 598 patients, 579 met with study criteria and were included in the study. Of the 19 excluded patients, 4 had no written informed consent and 15 were < 70 years old. Hematologic relevant parameters were analysed in every center-associated laboratory department. They included: hemoglobin (Hb) (g/dL), erythrocyte count (ery) (mio/μL), reticulocytes (‰), hematocrite (%), mean corpuscular volume (MCV) (fL), serum iron (μg/dL), ferritin (μg/L), c-reactive protein (CRP) (mg/L), folic acid (FA) (ng/mL), creatinine (mg/dL), vitamin B12 (vitB12) (ng/L), and transferrin saturation (TSAT) (%). Additional data was gathered concerning patients' gender and age. Reference values for definition of anemia and subtype characteristics were taken from published literature: anemia was defined according to WHO criteria (females < 12 g/dL, males < 13 g/dL); severity of anemia was defined according to National Cancer Institute (NCI) scale (> 10–12 g/dL [women] and > 10–14 g/dL (men) "mild", 8–10 g/dL "moderate", 6.5–7.9 g/dL "severe", < 6.5 g/dL "very severe"). Based on MCV, anemia was classified microcytic (MCV < 78 fL), normocytic (78 fL < MCV ≤ 94 fL) or macrocytic (MCV > 94 fL). Definitions of anemia subtypes were rather restrictive to avoid overlap and exclude multifactorial pathogenesis: iron deficient anemia (IDA) was defined if ferritin < 30 μg/L and TSAT < 16% ([12]; for the definition of ACD we required ferritin > 650 μg/L in addition to CRP > 5 mg/L to exclude overlap with IDA and avoid an overestimation of ACD due to age-associated higher levels of ferritin [11,12]. Due to the increasing prevalence of chronic kidney disease (CKD) among patients > 70 years, interpretability of TSAT becomes difficult in connection with ACD and renal anemia (RA) and was therefore not considered [13], As glomerular filtration rate (GFR) was not estimated routinely in the study centers, it was calculated based on MDRD short formula (GFR = 170 × creatinine – 1.154 × age – 0.203 × (0.742 [females]) [12]. RA was defined GFR < 30 mLl/min and ferritin > 30 μg/L to exclude overlap with IDA.

Folic acid (FAA) or vitamin B12 (VB12A) associated anemia were defined if folic acid was < 3 ng/mL [14] or vitamin B12 < 200 ng/L and GFR > 30 mL/min and CRP < 5 mg/L to avoid overlap with RA and ACD. Not assigned anemia (NAA) was defined if study parameters did not allow assignment to any form of anemia. Absolute iron deficiency (absolute ID) was defined ferritin < 30 μg/L, TSAT < 16% and absence of anemia; functional iron deficiency (functional ID) was defined ferritin > 650 μg/L, TSAT < 16%, CRP > 5 mg/L and absence of anemia [12]. In functional ID, we had to consider TSAT due to lack of other iron parameters in these study patients. Myelodysplastic syndrome (MDS) was suspected if anemia was associated with either leucopenia (< 4.000/μL) or low platelet count (< 150.000/μL) according to the characteristics of this malignant bonemarrow disorder [15]. For the definition of anemia types, we did not consider MCV because of previous findings, showing that MCV is not an adequate parameter for pathogenetic assignment of anemia in older patients [7]. Reticulocyte production index (RPI) was calculated (RPI = [reticulocytes (%) * hematocrit]/[45 * shift]) to esteem bone marrow insufficiency, defined RPI < 2. For calculation, reticulocyte count in ‰ was converted to %.

Completed CRFs were sent to study central in Cologne for evaluation. Database was created by means of Research Electronic Data Capture (REDCap®). Statistical analysis was carried out by means of the IBM SPSS statistics version 22.

Centers were compared by Anova for normally distributed data, Kruskal-Wallis-test for not normal distributions and nominal data by Chi^2 test. Descriptive numbers are mean ± standard deviation or median with inter quartile range (IQR). Categorical variables were analysed by Chi^2 or Fisher-test, as appropriate, if group totals were > 5. A P-value < 0.05 was defined as significant.

This study is registered in the German Clinical Trials Registry (DRKS, Freiburg) with no. DRKS00004617. The Ethics Committee of the University Hospital Cologne approved of the study (no. 12-322; 13.2.2013). The study was carried out in accordance with the current version of the Declaration of Helsinki of 2013.

3. Results

The study patient cohort consisted of 579 patients with 391 females (67.5%) and 188 males (32.5%). Anemia was found in 319 of 579 (55.1%) patients, with 205 females (64.3%) and 114 males (35.7%) (Tables 1a and 1b). Mean age of study patients was 81.9 years (70 to 97 years, standard deviation [SD]: 6.2). Anemic patients had a mean age of 82.0 years (70 to 96 years; SD: 6.1). Most patients had normocytic, mild anemia. According to study definition, ACD was the most common form of anemia found in this study population. Due to restrictive definitions and lack of hematologic and anemia related parameters in the 319 anemic

Table 1a
Characteristics of anemic study patients: metric variables evaluated in 319 anemic patients; *P*-value for statistical differences between study centers.

Metric study parameter ($n = 319$) including reference values	Number of patients	Mean ± SD or median (IQR)	*P*-value
Age (years)	319	82.0 ± 6.1	< 0.001
Hemoglobin (g/dL)	319	10.6 ± 1.2	0.24
Hematocrite (%)	319	32.0 ± 3.7	0.65
Leucocytes (tsd/μL)	319	7.5 (6.2-9.5)	0.09
Platelets (tsd/μL)	319	283 (216-399)	< 0.001
Erythrocytes (mio/μL)	319	3.6 ± 0.5	0.045
MCV (fL)	319	90.4 ± 7.2	< 0.001
MCH (pg)	319	29.9 ± 2.7	0.001
Ferritin (mg/L)	258	166.8 (85.0-308.8)	0.24
Transferrin saturation (%)	244	19 (13-27)	0.19
Serum iron (μg/dL)	268	48 (34-66)	0.12
CRP (mg/L)	315	22.0 (7.8-50.5)	0.008
Creatinine (mg/dL)	318	1.13 (0.88-1.13)	< 0.001
GFR (mL/min)	318	48.9 (35.1-68.2)	< 0.001
Folic acid (ng/mL)	265	5.9 (4.2-9.3)	< 0.001
Vitamin B12 (ng/L)	264	438 (313-691)	0.68
Reticulocytes (‰)	249	22.0 ‰ (12.3-37.8)	< 0.001
Reticulocyte production index	249	1.13 (0.07-8.7)	<$0.001

SD: standard deviation; IQR: interquartile range.

Table 1b
Characteristics of anemic study patients: study definitions based on nominal parameters available and evaluated in anemic patients.

Nominal study parameters (n)	Number of patients	%	*P*-value
Gender (319)			
Female	205	64.3	0.005
Male	114	35.7	
Iron deficiency anemia (available in 271 patients)	5	1.80	n.d.
(Ferritin < 30 μg/L, TSAT < 16%)			
Anemia of chronic diseases (available in 290 patients)	24	8.2	0.5
(ferritin > 650 μg/L, CRP > 5 mg/L)			
Renal anemia (available in 260 patients)	4	1.5	n.d.
(GFR < 30 mL/min, ferritin > 30 μg/L)			
Folic acid deficiency anemia (available 313 patients)	2	0.6	n.d
(Folic acid < 3 ng/mL, GFR > 30 mL/min, CRP < 5 mg/L)			
Vitamin B12 deficiency anemia (available in 313 patients)	2	0.6	n.d.
(Vitamin B12 < 200 ng/L, GFR > 30 mL/min, CRP < 5 mg/L)			
Not pathogenetically assigned anemia (255)	223	87.4	0.1
(Neither of the anemia subtype criteria fulfilled)			
Anemia severity (available in 319 patients)			
Mild (> 10 g/dL)	232	72.7	
Moderate (8.9–10 g/dL)	76	23.8	0.223
Severe (6.5–7.9 g/dL)	11	3.4	
MCV-based classification (available in 319 patients)			
Microcytic (< 78 fL)	10	3.1	
Normocytic (78 fL < MCV < = 94 fL)	222	69.6	0.001
Macrocytic (> 94 fL)	87	26.3	
Bonemarrow insufficiency suspected (available in 249 patients)	194	77.9	< 0.001
RPI < 2			
MDS suspected (available in 319 patients)	27	8.4	< 0.001
Anemia + leucopenia (< 4.000/μL) or anemia + low platelet count (< 150.000/μL)			

Number in brackets: number of patients where parameters were available; *P*-value for statistical differences between study centers; SD: standard deviation; n.d.: not done. Only group totals > 5 were tested.

patients (Table 1a, metric parameters), assignment to anemia type was only possible in a small number of 37 patients, while 223 could not be assigned (Table 1b, nominal parameters).

Significant differences between study centers for nominal variables were seen for gender, MCV-based cytology, suspected MDS and suspected bone marrow insufficiency. Among metric parameters significant differences between study centers were revealed for age, MCV, MCH, creatinine, CRP, GFR, platelets, folic acid, reticulocytes and RPI (Table 1a).

Overlap was seen in almost all anemia types: Among IDA patients, in one (20%) patient, MDS was suspected. Among ACD patients, in five patients (20.8%), MDS was suspected and four (16%) showed overlap with RA. Among the two VB12A patients, one patient overlapped with FAA and in both patients MDS was suspected. In one IDA patient and in one FAA patient, MDS was suspected, respectively.

Of all patients with available RPI, bone marrow insufficiency with RPI < 2 was suspected in 77.9% (194/249) and in 13 (86%) of all patients with suspected MDS. Among NAA, 11 (4.9%) patients were suspected to have MDS.

Analysis of MCV-based classification is shown in Table 2. Crosstab analysis of MCV-based classification and different types of anemia revealed that every type of anemia was associated with several types of erythrocyte cytology (Table 2). In IDA, significantly more patients were normocytic than microcytic ($P < 0.007$). Crosstab analysis of MCV-based classification and MCH revealed that microcytic cells were all hypochromatic, normocytic cells were significantly more often normochromatic than hypochromatic ($P < 0.001$) and macrocytic cells were significantly more often normochromatic than hyperchromatic ($P < 0.001$). No hyperchromatic microcytic and no hypochromatic macrocytic erythrocytes were seen in this study population.

Table 2
MCV-based cytology in different types of anemia.

	MCV-based cytology			Total	*P*-value
	Microcytic	Normocytic	Macrocytic		
Iron deficiency anemia	2	3	0	5	n.d.
Anemia of chronic diseases	0	14	10	24	0.3
Renal anemia	0	2	2	4	n.d
Folic acid deficient anemia	0	1	1	2	n.d.
VitB12 deficient anemia	0	1	1	2	n.d.
Not assigned anemia	6	156	61	223	0.2

*Fisher-test; n.d.: not done. Only group totals > 5 were tested.

Functional and absolute ID were seen in 1 (0.2%) and 4 (0.8%) patients, respectively. All patients were normocytic.

4. Discussion

Results of this cross-sectional multicenter study on German geriatric in-patients revealed a high prevalence of anemia, which has been described earlier [8,16]. Anemia in our study population was mainly mild and normocytic. These findings are in accordance with results of previous studies among older people: Callera et al. [17] saw that the great majority of anemia in their Brazilian study population of independent dwelling aged persons > 65 years was mild and normocytic. Similar findings were made among Italian [18] and Austrian [7] geriatric in-patients.

Reasons for significant differences of study parameter values between study centers can be assumed to be partly due to local reasons: patients recruited in the universitarian emergency department were generally not transferred by another hospital but admitted for emergency reasons with optional transfer to a geriatric department after consultation by a geriatrician. Possibly, they therefore tend to be younger. Significant differences in GFR might be due to presence of a nephrologic department with a hemodialysis unit in the given study center. However, significant differences among many other variables remain unexplained. They possibly point to a complex hematopathogenesis in the aged. A further reason for significant differences of study parameter values between study centers might be the seasonal time of recruitment with possibly increased dehydration prevalence in hot months or increased gastrointestinal infections during autumn and winter months.

Definition of types of anemia was based on study criteria. Definition relevant parameters were present in 255 of 319 anemic patients (79.9%). Thirty-seven patients (14.3%) could be assigned a cause of anemia, (including 5 patients with overlap), while 223 patients (85.7%) could not be assigned to a special type of anemia (NAA). This rather high percentage of NAA is assumed to be due to the restrictive study criteria for the assigned types of anemia, intended to exclude overlap with multifactorial anemia.

FAA and VB12A were seen in only a small number of study patients (0.6%, respectively). Results of our study can be compared with the findings by Bach et al. [7]. In their large study cohort of about 4000 anemic patients, they also found only small numbers of FFA (6.7%) and VB12A (2%) [7]. In contrast to Bach et al., we again applied more restrictive criteria for the definition of FAA and VB12A. This might explain why our results are even lower than the results by Bach et al. [7].

Like in our study, ACD was seen in the majority of their study patients and anemia was mostly mild and normocytic [7]. While Bach et al. saw more RA patients than IDA patients in their study cohort, in our study, the number of RA patients and IDA patients was comparable. The differing prevalence rates between the two studies might be due to the smaller number of exclusively geriatric in-patients in our study, but also due to differing definition criteria for types of anemia. For defining ACD, Bach et al. chose an elevated CRP level as only criterion [7]. Considering the underlying hypothesis of hyperinflammation, a complex system of inflammatory cytokines and parameters is assumed to be responsible for functional iron deficiency in ACD. However, in practice, routinely estimation of all parameters relevant for inflammation is impossible and therefore mostly limited to CRP. In our definition of ACD, we additionally required ferritin because of its role of acute phase protein. Bearing in mind an age-associated increase of ferritin [12], we chose the recommended upper reference value of ferritin for aged persons [11]. A restrictively high ferritin cut-off by 650 µg/L for the definition of ACD resulted in lower prevalence rates of ACD than seen by Bach et al. [7]. We did not require TSAT for defining ACD because of its difficult interpretability in connection with inflammation. TSAT has some acute phase reactivity due to the elevation of transferrin in the setting of inflammation. In the setting of malnutrition and chronic inflammation, however, transferrin can be reduced [13]. Given the prevalence of malnutrition and risk of malnutrition among geriatric patients in connection with protein deficiency, we did not include TSAT to avoid misinterpretation. In connection with functional ID, however, we had to consider TSAT to avoid overlap with absolute ID due to absence of any other iron parameter in this study group. The soluble transferrin receptor or the soluble transferrin receptor-ferritin index would have been a more reliable parameter to discern ACD from IDA and functional ID from absolute ID [19]. However, this study was based on hematologic parameters, routinely assessed in the study centers and neither the soluble transferrin receptor nor the soluble transferrin receptor-ferritin index were routinely assessed in any of the study centers. The lower prevalence of ACD in this study compared to the Bach et al. [7] may also be due to the restrictive definition criteria for ACD with the high cut-off levels for ferritin and GFR to avoid overlap with RA. The definition of ACD based on ferritin levels and CRP levels did not allow a discernability between chronic inflammatory diseases (e.g. rheumatoid arthritis or chronic inflammatory bowel disease) and acute bacterial infections [20]. ACD is usually associated with increased cytokine and hepcidin levels, which are responsible for functional iron deficiency [19,20]. However, neither hepcidin levels nor cytokine levels were routinely assessed hematologic parameters in the study centers and could not be evaluated in this study. While ACD was found to be the most frequent type of anemia in our cross-sectional study as well as in the large cohort study by Bach et al. [7], a Turkish study revealed a high prevalence of vitB12 deficiency to be the most frequent cause for anemia in their study population [21]. These controversial findings underline the hypothesis that anemia of the aged is not a monocausal problem. Rather, a multifactorial pathogenesis can be suggested [7] as well as a dependence on the patient cohort considered. The assumption of multicausality is further underlined by the finding of overlapping anemia causes: in our study population, patients assigned to a special cause of anemia often showed also further potential causes for anemia. This finding was also shown by [7]. The problem that clear definitions for anemia subtypes lack and general definition of anemia in older patients is still controversial [7] contributes to the assumption of multicausality.

While MCV is a routinely assessed and recommended parameter for anemia diagnostic in younger patient cohorts [22], in geriatric patients, the morphologic classification based on MCV appears to be inadequate regarding pathogenesis: microcytosis is associated with IDA or thalassaemia in younger patients, while macrocytosis is associated with deficiency of vitB12 or folic acid and normocytosis is associated with RA. In our study patients, however, we found a heterogenous distribution of MCV

size among the different causes of anemia (Table 2) with macrocytosis seen in ACD, RA and NAA, while FAA and VB12A were partly normocytic. Interestingly, some functional ID patients without anemia also showed macrocytosis, but only one of them was deficient of vitamin B12. This heterogeneity of MCV was also described by Bach et al. [7] and they came to the conclusion that MCV appears to be an inadequate parameter for pathogenetic assignment of anemia in geriatric patients. This conclusion is sustained by our findings, even though the underlying resaons remain unclear. A recent Spanish study [23] described an increase of the red cell distribution width, a marker of erythrocyte volume, during the last 5 years of geriatric patients. However, if this observation can be transferred to all anemic patients and might explain the assumed inappropriateness of MCV for anemia type assignment, remains subject to further studies. MDS in older patients is frequently seen with a rising prevalence [24] and often associated with unexplained anemia. Peripheral blood cytopenias are frequent findings in MDS, while macrocytosis is not obligatory [25,26] In our patient cohort, macrocytosis was found in 10 of 27 patients (37.0%) suspected of MDS. Thus, the estimated number of occult MDS with and without macrocytosis was 8.5% (27/319) in our patient cohort. This finding is also consistent with previous data [7]. However, the strict definition criteria for ACD can also be made responsible for the fact that ACD and MDS have a comparable prevalence in this study, which is inconsistent with the findings by Bach et al, who revealed a higher prevalence of ACD patients than of MDS patients due to less restrictive definitions for ACD [7]. Evaluation of RPI among patients suspected to have MDS revealed that 86% showed a RPI < 2, which underlines the suspicion of bonemarrow insufficiency.

This study has also a number of shortcomings: GFR was estimated based on MDRD with its known limits of interpretability [27]. Another shortcoming is the lack of consistent laboratory analysis for all study centers, which may also be made responsible for result variability. This lack of parameters can also be made responsible for the fact that of 319 anemic patients only between 260 and 313 patients could be characterized (Table 1b). A further shortcoming was the regional imbalance of study centers without any recruited patients from the south of Germany. This might impair representativeness of data. A general problem affecting most studies among geriatric patients is the lack of hematologic reference values for older patients including hemoglobin [28], ferritin [11] or TSAT [13] and the lack of general definitions for IDA and ACD [4,7] as well as RA [29]. Therefore, prevalence rates are assumed to be either over- or underestimated. These shortcomings have to be taken into account during preparation of further studies.

5. Conclusion

In conclusion, anemia is mainly normocytic and mild but highly prevalent in these German geriatric inpatients. Anemia cannot always be specified, supporting the hypothesis of multicausality in anemia of the aged. Causes and prevalence seem to vary in dependence on the patient cohort. MCV appears to be not an appropriate diagnostic parameter for pathogenetical assignment of anemia subtypes in older patients. Further research is needed in hematologic particularities of geriatric patients for a better understanding of the complex hematopathogenesis of anemia in the aged.

Disclosure of interest

The authors declare that they have no competing interest.

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