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G. Röhrig[1] · I. Becker[2] · M.C. Polidori[3] · R.-J. Schulz[4] · M. Noreik[4]

[1] University of Cologne, Medical Faculty and St. Marien-Hospital, University Hospital Cologne, Cologne, Germany
[2] Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Cologne, Germany
[3] University of Cologne, Medical Faculty, Cologne, Germany
[4] Department of Geriatric Medicine, St. Marien-Hospital, Cologne, Germany

Association of anemia and hypoalbuminemia in German geriatric inpatients

Relationship to nutritional status and comprehensive geriatric assessment

Introduction

Anemia and hypoalbuminemia (HA) have been shown to be associated with frailty in older people [19, 24, 36, 37] and frailty has been shown to be closely associated with nutritional status in the elderly [5, 20]. Low albumin blood levels have been previously shown to be associated with anemia [27, 29, 34, 35,] but comparable analyses among German inpatients are, however, currently lacking.

» Anemia is a common problem in older people

Anemia is a common problem in older people [3, 15]. Depending on the patient cohort, the prevalence may vary between 20 % among independent community-dwelling seniors and 40–60 % among inpatients [14, 15, 46]. Anemia in older people has been shown to be associated with increased morbidity and mortality as well as with a higher rate of hospitalization and longer hospital stay [9, 42]. Anemia also appears to be associated with impaired cognitive function in patients over 70 years of age [38]. A recent systematic review by Andro et al. identified several studies showing a significant association between anemia and cognitive decline, incidence of dementia and reduced executive functions [1]. Several risk factors for anemia have been identified in geriatric patients, such as chronic kidney disease [33, 45], iron deficiency and inflammation [30, 32].

» The association between nutritional status and frailty is widely acknowledged

» The role of albumin as a nutritional marker still remains controversial

Low serum albumin is also acknowledged to be a risk factor for mortality and morbidity [2, 13]. A recent study in older subjects with femoral neck fractures showed that albumin was a significant predictor of 12-month survival [23]. Similar findings could be shown by Kato et al. in cardiology patients undergoing heart surgery [22]. Furthermore, low serum albumin levels have been shown to be associated with anemia in smaller cohorts [27, 29, 34, 35]. The association of functional decline and serum albumin has been studied before. Isaia et al. could show an increased functional decline in Italian geriatric patients who had been admitted to hospital and presented with low serum albumin [18]. The association between nutritional status and frailty is widely acknowledged [5, 20]. Smit et al. showed a dependency of frailty on daily energy intake among older American adults and the authors additionally reported lower serum albumin levels in the frail than in the not frail subgroups of this patient cohort [37]; however, despite the fact that albumin was found to be associated with nutritional status in many studies [27, 35], the role of albumin as a nutritional marker still remains controversial [16, 25]. The present study aimed to fill the gap in knowledge on the relationship between anemia, HA and nutritional status in a typical geriatric inpatient population. Another aim of the study was to address the presence and degree of functional impairment as assessed by means of the comprehensive geriatric assessment (CGA), the cornerstone of geriatric methodology.

Patients and methods

The ethics commission of the Cologne University Faculty of Medicine approved the study (No 11-032) and it was performed in accordance with the 1964 Declaration of Helsinki and its later amendments. The study data was based on 1252 patients routinely evaluated by the clinical nutritionist between January and December 2011 at the Geriatric Department of the University Hospital at St. Marien Hos-

Table 1 Characteristics of the study population where values are given as mean (SD) or frequency (%)

Variable and pathological range	Total		Anemia			Hypoalbuminemia		
	N	Mean (± SD) or *N* (%)	No *N* =	Yes *N* =	*p*-value of t-test	No *N* =	Yes *N* =	*p*-value of t-test
Age (years)	626	81.09 ± 7.46	172	425	0.319	364	249	0.164
Body weight (kg) (median/range)	619	36.3–138.4	170	420	0.317	363	243	**0.001**
Barthel index ≤ 30(pts) (26)	622	43.31 ± 22.43	168	425	0.407	361	248	**0.000**
Clock drawing test > 3(pts)(42)	444	3.38 ± 1.41	118	306	0.160	260	177	0.142
GDS > 5(pts) (45)	483	4.39 ± 3.23	129	333	0.595	278	196	0.995
MMSE < 24(pts) (11)	529	22.57 ± 5.68	139	366	0.529	306	212	0.420
Tinetti < 20 (pts)(40)	264	16.49 ± 5.03	74	181	0.969	179	80	0.612
TUG (s) (31) ≤ 20 normal 20–30 probable > 30 pathological	240	30.84 ± 14.28	68	162	0.247	165	72	0.324
Hypoalbuminemia	613	249 (40.6 %)	171	415	**0.000**	/	/	/
Albumin (g/dl)[a]	613	3597.85 g/dl (± 433.69)	171	415	**0.000**	364	249	**0.000**
Folate ≤ 2,5(ng/ml)	588	8.08 ± 5.75	161	401	0.303	344	233	**0.004**
Hemoglobin (g/dl)	597	11.47 g/dl (± 1.69)	172	425	**0.000**	345	241	**0.000**
Anaemia (4)[b]	597	425 (71.2 %)	/	/	/	345	241	**0.000**
B12 ≤ 300(ng/l)	582	428.19 ± 222.05	163	393	0.598	342	230	**0.000**
Calcium (mmol/l) 2–2.6 normal < 2 > 2.6	622	2.23 ± 0.19	171	422	**0.000**	363	247	**0.000**
GFR (MDRD/ml/min) ≥ 90 normal 60–89 decreased < 60 pathological	622	71.96 ± 21.38	171	422	**0.005**	360	249	0.208
CRP ≥ 6 (mg/l)	626	2.14 ± 1.37	172	425	**0.000**	364	249	**0.000**
Ferritin ≤ 651(µg/l)	626	226.24 ± 147.72	172	425	0.729	364	249	**0.008**
Tranferrin saturation < 16 (%)	206	23.79 ± 24.94	60	143	0.828	117	88	0.239

B12 vitamin B12, *SD* standard deviation, *pts* points, *GDS* geriatric depression scale, *MMSE* mini-mental state examination, *TUG* timed up and go test, *GFR* glomerular filtration rate, *CRP* C-reactive protein

[a]Albumin 3.5–5.5 g/dl normal range, no values > 5.5 measured

[b]Anemia< 12 g/dl Hb (females), < 13 g/dl Hb (males)

Table 2 Frequencies of diagnoses causing admission

Diagnosis (ICD version 10)	Patients (%)
Reduced mobility (R26.8)	32.2
Fracture of the neck of femur (S72.01)	5.1
Fracture of the femur (S72.1)	4.6
(Embolic) stroke (I63.5)	3.8
Others	54.3

ICD international classification of diseases

pital in Cologne, Germany. Data were retrospectively collected on nutritional status, diagnosis on admission with the international classification of diseases version 10 (ICD 10), body mass index (BMI, kg/m^2, laboratory data and the CGA score. Patients with edema were excluded to avoid dilution-associated anemia and HA in the analysis. Patients with inflammation were also excluded from the analysis based on a C-reactive protein (CRP) value > 6 mg/l and a ferritin value > 651 ng/ml [7, 39] but patients with reduced glomerular filtration rate (GFR) were not excluded because approximately 60 % of the study patients showed a GFR < 90 ml/min and recent findings revealed that a reduction of GFR does not necessarily predispose to HA [12]. Due to a lack of data, liver disease as a possible reason for reduced albumin synthesis could not be excluded. A total of 626 patients could be included in the final analysis. Nutritional risk at hospital admission was assessed using the modified mini-nutritional assessment (m-MNA), a validated tool specially developed for older people [16]. The m-MNA includes the assessment of BMI, weight loss, mobility, food intake, number of main dishes consumed, fluid intake and self-assessment of health status. Based on the m-MNA scores, patients were divided into three groups: without malnutrition (group A), at risk for malnutrition (group B) and malnourished patients (group C) [21]. The CGA scores from all patients were included in the analysis. In this setting the CGA consisted of the Barthel index [26], Tinetti test [40] and timed up and go (TUG) test [31] for the functional assessment, mini-mental state examination (MMSE)

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Association of anemia and hypoalbuminemia in German geriatric inpatients. Relationship to nutritional status and comprehensive geriatric assessment

Abstract

Background. Anemia and hypoalbuminemia (HA) are acknowledged independent risk factors for morbidity and mortality in geriatric patients and are associated with nutritional status and frailty. Data exist regarding the association between albumin and frailty, anemia and frailty as well as frailty and nutritional status; however, there is a lack of information on the association between HA, anemia and nutritional status in older people.
Patients and methods. This study retrospectively analyzed 626 patients admitted to a German geriatrics department (average age 81.1 years, 68.2 % female and 31.8 % male) for anemia and HA. Data from the comprehensive geriatric assessment (CGA) and from the mini-nutritional assessment (MNA) were available in all patients.
Results. Patients with anemia suffered significantly more often from HA ($p < 0.001$) than patients without anemia, with an odds ratio (OR) of 1.99 (95 % confidence interval CI: 1.2-3.2) and of 5.41 (CI 95 %: 2.3-12.6) in patients at risk for malnutrition and in malnourished patients, respectively. A moderately significant association was seen between hemoglobin (Hb) and albumin values (Pearson's correlation $r = 0.330$; $p < 0.001$) as well as between albumin values and the Barthel index (Spearman's correlation $r = 0.210$; $p < 0.001$).
Conclusion. Anemia appears to be a risk factor for HA in inpatients with malnutrition and the observed association between albumin and Hb warrants further research. Geriatric inpatients with anemia should be evaluated in terms of the presence of malnutrition risk and HA.

Keywords

Anemia · Hemoglobin · Albumin · Nutritional status · Geriatrics

Zusammenhang von Anämie und Hypoalbuminämie bei deutschen stationär geriatrischen Patienten. Beziehung zum Ernährungsstatus und multidimensionalem geriatrischen Assessment („Comprehensive Geriatric Assessment")

Zusammenfassung

Hintergrund. Anämie und Hypoalbuminämie (HA) sind bei geriatrischen Patienten bekannte unabhängige Risikofaktoren für Morbidität und Mortalität, sie stehen im Zusammenhang mit Ernährungsstatus und Frailty. Es gibt Untersuchungen zum Zusammenhang zwischen Albumin und Frailty, Anämie und Frailty, sowie Frailty und dem Ernährungsstatus. Bisher fehlen jedoch Daten zu einem Zusammenhang zwischen HA, Anämie und Ernährungsstatus bei geriatrischen Patienten.
Patienten und Methoden. Retrospektive Datenanalyse von 626 stationären geriatrischen Patienten (mittleres Alter 81,1 Jahre, 68,2 % Frauen, 31,8 % Männer) hinsichtlich Anämie, HA und einem Zusammenhang mit dem Ernährungsstatus (Mini Nutritional Assessment, MNA) und dem multidimensionalen geriatrischen Assessment (Comprehensive Geriatric Assessment, CGA).
Ergebnisse. Patienten mit Anämie wiesen signifikant häufiger eine HA auf ($p < 0{,}001$) als Patienten ohne Anämie, wobei anämische Patienten mit einem Risiko für Mangelernährung eine erhöhte Chance auf eine HA hatten (OR I,9; 95 %-KI: 1,2-3,2) und Patienten mit einer Mangelernährung eine OR von 5,4 (95 %-KI: 2,3-12,6) aufwiesen. Ein moderater signifikanter Zusammenhang konnte gezeigt werden zwischen Hämoglobin (Hb) und Albumin (Pearsons Korrelationskoeffizient $r = 0{,}330$; $p < 0{,}001$) sowie zwischen Albumin und Barthel Index.
Schlussfolgerungen. Anämie scheint bei mangelernährten stationär geriatrischen Patienten ein Risikofaktor für HA zu sein, wobei der beobachtete Zusammenhang zwischen Albumin und Hb weiterer wissenschaftlicher Untersuchungen bedarf. Im klinischen Alltag sollte bei stationär geriatrischen Patienten mit Anämie eine Überprüfung auf HA erwogen werden, besonders bei drohender oder bereits bestehender Mangelernährung.

Schlüsselwörter

Anämie · Hämoglobin · Albumin · Ernährungsstatus · Geriatrie

[11] and clock drawing test [41] for the cognitive status and the geriatric depression scale (GDS) [44] to screen for major depression. Laboratory parameters included in the analysis comprised hemoglobin (Hb, g/dl) using the sodium lauryl sulphate (SLS) method (Sysmex® Analyzer XE-2100/XE-5000, Sysmex, Norderstedt Germany), serum albumin (g/dl, photometric method, Beckman Coulter® Analyzer, Beckmann Coulter, Krefeld Germany), CRP (mg/l) (immune turbidimetric method, Beckman Coulter® analyzer), folate (ng/ml, immunoassay, Cobas®, Roche, Mannheim, Germany), serum calcium (mmol/l, photometric arsenazo method, Beckman Coulter® analyzer), transferrin (mg/dl, immune turbidimetric method, Beckman Coulter® analyzer) with calculated transferrin saturation (%), ferritin (µg/l, immune turbidimetric method, Beckman Coulter® analyzer), vitamin B12 (ng/ml, electro-chemiluminescence ECLIA immunoassay, Cobas®) and creatinine/estimated GFR (ml/min), Jaffé method, Beckman Coulter® analyzer and modification of diet in renal disease formula (MDRD). While the estimated GFR could be considered in the statistical analysis, the absolute levels of creatinine were not available. For this study HA was defined as serum albumin< 3.5 g/dl, anemia was defined as Hb < 12 g/dl (females) and Hb < 13 g/dl (males) [4]. Statistical analysis was performed by means of the IBM SPSS statistical package Version 20.0 (IBM, Armonk NY). The main parameters Hb and albumin were analyzed as original metric data. Frequencies were compared by the χ^2-test, normally distributed variables by the t-test or ANOVA for more than two groups and two normally distributed variables by Pearson's correlations. For association between anemia and albumin odds ratios (OR) with 95 %

Table 3 Association between anemia, hypoalbuminemia, Barthel index and BMI according to mini-nutritional assessment group

	MNA group A (no malnutrition)	MNA group B (risk of malnutrition)	MNA group C (malnutrition)
Anemia	66 (66.7 %)	270 (72.8 %)	88 (69.8 %)
Hypoalbminemia	30 (28.8 %)	147 (38.9 %)	71 (54.6 %)
Hb (g/dl mean ± SD)	11.6 (± 1.8)	11.4 (± 1.6)	11.5 (± 1.7)
Albumin (mg/dl mean ± SD)	3753 (± 402)	3611 (± 417)	3439 (± 458)
Barthel score (mean ± SD)	51.0 (± 24.0)	45.2 (± 20.8)	31.1 (± 21.3)
BMI (mean ± SD)	28.6 (± 5.9)	25.8 (± 5.4)	23.2 (± 4.8)

Values are given as mean (SD) or frequency (%)
MNA mini-nutritional assessment, *BMI* body mass index, *Hb* hemoglobin

confidence intervals (CI) were calculated. Assessment tests and laboratory variables were analyzed as categorical data, distinguishing between pathological or normal values. The significance level was defined at 0.05.

Results

Descriptive characteristics of the 626 patients are shown in **Table 1** including 427 women (68.2 %) and 199 men (31.8 %). The most frequent diagnoses according to ICD 10 that were found in more than 3 % of study patients are shown in **Table 2**. The high number with the diagnosis reduced mobility (32.3 %) is related to the relatively low number of TUG and Tinetti test results on admission, which were often not possible to be conducted due to a reduced functional status of the patient. The prevalence of anemia in all 626 patients was 67.9 % (425) with 66.0 % (282 out of 427) in women and 71.9 % (143/199) in men. The prevalence of HA was 39.8 % (249/626), 40.5 % (173/427) in women and 38.2 % (76/199) in men (**Table 1**). Patients with HA had lower Hb levels, more often anemia, a lower Barthel index, lower BMI, higher vitamin B12 levels as well as lower levels of serum calcium than patients without HA. These differences were highly significant ($p < 0.001$) (**Table 1**). Ferritin and folate levels were significantly higher in hypoalbuminemic patients than in patients with normal albumin values ($p = 0.008$ and $p = 0.004$, respectively). In patients with anemia, HA was present significantly more often as well as lower albumin levels, lower serum calcium levels and higher CRP levels than in patients without anemia ($p < 0.001$). Anemic patients had significantly lower GFR values than patients without anemia ($p < 0.05$). No significant differences in CGA scores were seen among the groups. One-way ANOVA revealed that depending on the nutritional status according to the m-MNA, albumin levels, the BMI and Barthel index differed significantly ($p < 0.001$): the lowest albumin levels, BMI and Barthel index were found in patients with malnutrition (group C) compared to better nourished patients of m-MNA groups A and B. No statistically significant differences were seen for Hb levels (**Table 3**). A weak to moderately significant correlation was observed between albumin and Hb values (Pearson's correlation $r = 0.33$; $p < 0.001$) as well as between albumin values and the Barthel index ($r = 0.21$, $p < 0.001$). No other associations were observed. Patients with anemia had an elevated chance (OR 2.6, 95 % CI 1.8-3.9) to be hypoalbuminemic. Anemic patients at risk for malnutrition (m-MNA group B) showed an OR of 1.99 (95 % CI 1.2-3.2) to be hypoalbuminemic, reaching an OR of 5.41 (95 % CI 2.3-12.6) in malnourished patients belonging to m-MNA group C. No correlation between anemia and HA was found in m-MNA group A patients (OR 2.6, 95 % CI 0.95-7.3).

Discussion

The main result of this study is that anemia was found to be associated with HA and malnutrition in this geriatric population. Anemic patients at risk for malnutrition have an increased risk of hypoalbuminemia and this risk increases even more in malnourished patients. To the best of our knowledge this increase has not been described before among geriatric inpatients. An association between Hb and albumin values in older patients has been described before among geriatric patients outside of Germany but data are scarce and most of the studied patient cohorts are smaller than the present geriatric inpatient cohort [27, 29, 34, 35]. The prevalence of HA found in this patient cohort is similar to that found in previous studies. In the study of Mizrahi et al. HA was found in 38.8 % of geriatric patients on admission [28]. The high prevalence of anemia in the present study sample is comparable to the prevalence recently described by Chan et al. of 67 % in 812 old nursing home adults [8]. The data are also consistent with another recent study on 100 geriatric inpatients, in which a prevalence of 60 % was observed [46]. In this study cohort HA was associated with all abnormal laboratory values with the exception of GFR and transferrin saturation. Recent findings by Friedman et al. revealed that a reduction of GFR does not necessarily predispose to HA [12]. Bonilla-Palomas et al. described an independent association between HA and low transferrin values in patients with acute heart failure [6].

Different patient characteristics between the studies might be responsible for the different results. As hypoalbuminemic patients have a significantly lower body weight and significantly lower folate, vitamin B12 and serum calcium levels, an association between albumin and nutritional status might be assumed. In most of the studies albumin is associated with nutritional status [27, 35]; however, the role of albumin as a nutritional marker still remains controversial [16, 25]. The association between anemia, HA and nutritional status in this study cohort might suggest protein deficiency anemia but a causality cannot be proven due to a lack of variables of visceral protein storage (e.g. coagulation factors and liver function) and somatic protein storage (skeletal muscle mass). The association of HA with elevated levels of folate and vitamin B12 might be due to the role of albumin as a transport protein: a lack of albumin might result in higher levels of free folate and vitamin B12 [17]. Another important finding of this study is the observed association

of HA values with the Barthel index, lower body weight and anemia (**Table 1**) which are all factors that have been associated with frailty [10, 19]. Although the identification of frailty was not an aim of the present study, the findings are consistent with an earlier frailty study on a smaller patient cohort by Silva et al. [36]. In that study, an association between HA, nutrition status and functionality assessed by the Barthel index was found. Isaia et al. could also show a reduced functionality in relation to low serum albumin levels [18]. As ICD 10 does not include a code for frailty, in Germany medical controllers resort to disease codes describing symptoms of frailty, indicating the need for geriatric treatment, such as R15, R26.8, R29.6 and R32 [43]. In this patient cohort, the diagnosis code reduced mobility (R26.8, ICD 10) was found in one third of the patients as the main diagnosis (**Table 2**). This finding implies functional problems that are assumed to be caused by reasons other than the main diagnosis, such as hip fractures (S72.-) or stroke (I63.-) (**Table 2**). An association with frailty might be assumed but this assumption remains vague due to the lack of confirmatory data.

The strengths of this study include the size of the study population among geriatric inpatients in Germany. Moreover, the CGA including assessment of nutritional status was performed in a standardized manner by the application of validated tests [11, 26, 31, 40, 41, 44].

There are some shortcomings to this investigation. The retrospective nature and the broad, less precise selection of patients presenting to the nutritionist curtail an interpretation of the data.

Conclusion

This study shows that anemia and HA are highly prevalent in a typical German geriatric inpatient population. Anemia appears to be a risk factor for HA in malnourished geriatric inpatients, while HA is associated with reduced functionality based on the Barthel index. The study results support the assumption of an association between anemia and serum albumin which, to the knowledge of the authors, has not been shown before in a German geriatric inpatient cohort. These findings encourage further research in the complex field of frailty in association with nutritional status, anemia and HA and the effects on CGA in geriatric patients. A screening for HA should be considered in anemic geriatric inpatients, particularly if a nutritional risk screening (e.g. MNA) indicates malnutrition.

Corresponding address

Dr. G. Röhrig MPH
University of Cologne, Medical Faculty and St. Marien-Hospital, University Hospital Cologne, Kerpener Strasse 62, 50937 Cologne
gabriele.roehrig@uk-koeln.de

Compliance with ethical guidelines

Conflict of interest. G. Röhrig, I. Becker, M.C. Polidori, R.-J. Schulz and M. Noreik state that there are no conflicts of interest in connection with the content of this paper.

The ethics commission of the Cologne University Faculty of Medicine approved the study (No 11-032) and it was performed in accordance with the Helsinki Declaration of 1975, as revised in 2008. Informed consent was obtained from all patients included in this study.

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