# *Association of anemia with functional and nutritional status in the German multicenter study "GeriAnaemie2013"*

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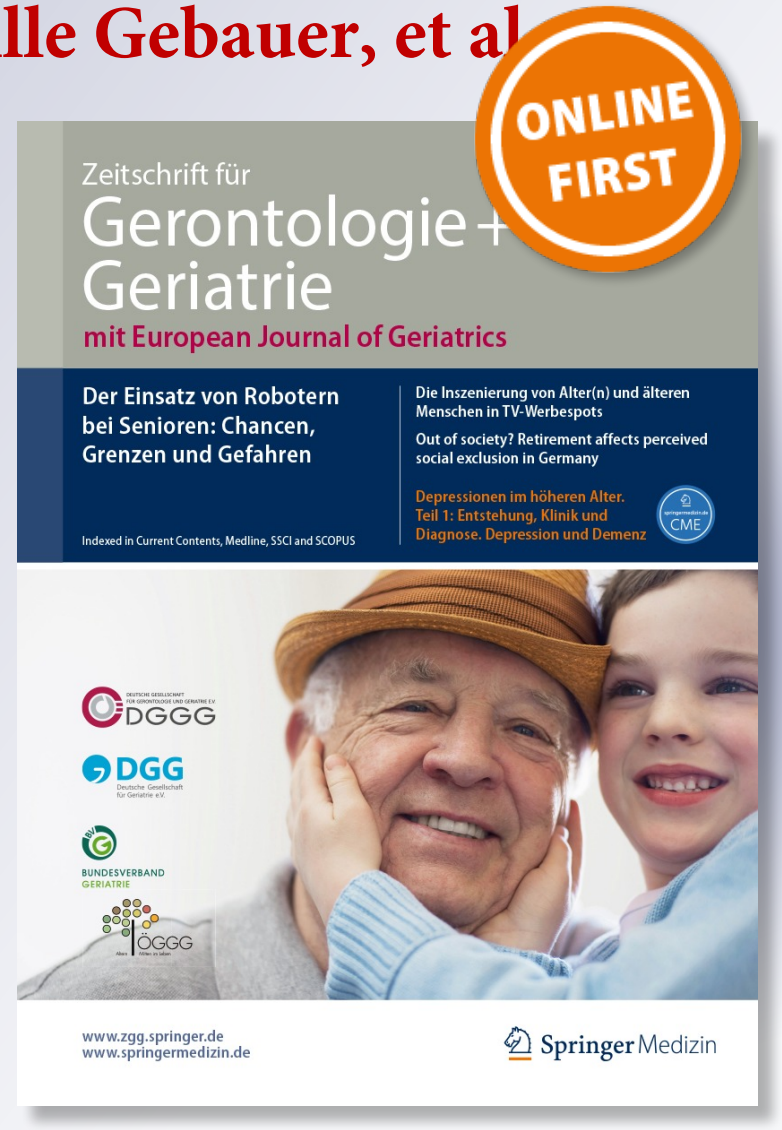


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## Introduction

Anemia is a common finding in older patients and is associated with increased mortality, increased morbidity and functional decline [6, 22, 30]. Several international studies have shown that the prevalence of anemia varies depending on the population studied. 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 [8]. A more recent study among home dwelling people in rural India was consistent with this finding [21]. A systematic review by Gaskell et al. [7] among geriatric inpatients > 65 years living in developed countries found an anemia prevalence of 40 %. Bach et al. [2] showed a comparable prevalence of anemia among geriatric inpatients aged 90+ years; however, data concerning anemia prevalence among German geriatric inpatients are still rare and mostly derived from monocentric studies. The German Geriatric Society therefore decided to initiate the first multicentric study on anemia prevalence among geriatric inpatients. The primary objective of this study was to evaluate the prevalence of anemia. Further study objectives comprised the impact of anemia on functional ability measured by the Barthel index (BI) and the evaluation of nutritional status and drug intake in anemic patients. In a recent study from India anemia, risk of malnutrition and physical disability have been associated in community dwelling patients aged 60+ years [21]. Previous international studies were found to be associated anemia and malnutrition with functional decline and frailty [11, 12, 25, 26]; therefore, this first multicenter study on German geriatric inpatients is intended to provide data with respect to anemia prevalence, its impact on functional ability and its association with nutritional status and drug intake in this increasing population.

## Patients and methods

Between June 2013 and December 2014 a total of 579 geriatric inpatients were consecutively recruited on admission in 6 participating German study centers (5 geriatric centers and 1 general emergency department of a university hospital). The recruitment interval was 4–6 weeks in every study center. Included were patients > 70 years admitted to the geriatric department or, in the case of the general emergency department, with the intention of being admitted to a geriatric department. All study patients gave informed consent. Patients with current cancer disease or cancer-associated treatment were not included in the study. Functional status was measured by the Hamburg classification manual [16] based on the BI [17]. Handgrip strength was measured with a GLS Martin® Vigorimeter (Gebrüder Martin GmbH & Co KG, Tuttlingen, Germany) and the reference values for reduced handgrip were males < 66 kPa and females < 38 kPa [30]. Nutritional status was assessed by patient self-

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**Table 1** Characteristics of study patients with and without anemia: metric variables

| Metric study parameters | All patients (*n*) | Non-anemic patients | Mean ± SD or median (IQR) | Anemic patients | Mean ± SD or median (IQR) | *p*-value |
|---|---|---|---|---|---|---|
| Age (years) | 579 | 260 | 81.7 ± 6.4 | 319 | 82.0 ± 6.0 | 0.60 |
| Hemoglobin (g/dl) | 579 | 260 | 13.5 ± 1.1 | 319 | 10.5 ± 1.2 | **<0.001** |
| Folic acid (ng/ml) | 468 | 203 | 5.8 (4.2–8.5) | 265 | 5.7 (4.2–9.2) | 0.3 |
| Vitamin B12 (ng/l) | 469 | 205 | 430.8 (308.9–611.1) | 264 | 437 (313–690.7) | 0.4 |
| Serum albumin (g/dl) | 462 | 201 | 3.3 ± 0.5 | 261 | 3.1 ± 0.6 | **<0.001** |
| Handgrip strength (kPa) | 90 | 38 | 35.1 ± 17.1 | 52 | 42.9 ± 15.9 | 0.53 |
| Barthel index (points) | 573 | 256 | 54.3 ± 27.1 | 317 | 47.9 ± 25.1 | **0.004** |

*p*-value for statistical differences between anemic and non-anemic patients, *SD* standard deviation, *IQR* interquartile range, statistically significant *p*-values are printed in bold type

reporting: patients were asked for information on loss of appetite (yes or no), food intake (normal or less than normal) and weight loss (≤3 kg or >3 kg) within the last 4 weeks and prescribed medication was assessed by the pill count based on the World Health Organization (WHO) criteria for polymedication (<5 drugs per day or ≥ 5 drugs per day). As different laboratories were involved in this multicenter study, laboratory parameters were converted into uniform units of measurement for better analysis: hemoglobin (Hb, anemic if males <13 g/dl and females < 12 g/dl), serum folic acid (deficient if < 3 ng/ml) [31], serum vitamin B12 (deficient if < 200 ng/l) and serum albumin (hypoalbuminemia if < 3.5 g/dl). Anemia was defined according to the WHO criteria. Risk of malnutrition was defined if loss of appetite and decreased food intake were present without unchanged or increased weight. Completed Case Report Forms (CRF) were sent to the study central in Cologne for evaluation. The database was created by means of Research Electronic Data Capture (REDCap®), Harvard Catalyst, Harvard, Boston, USA). Statistical analysis was carried out by means of the IBM Statistical Package for the Social Sciences (SPSS) version 22. Groups were compared using the t-test for normally distributed data, Mann-Whitney U-test for abnormal distributions and nominal data by the $\chi^2$-test. Descriptive numbers are given as the mean ± standard deviation, median (interquartile range, IQR) or frequencies, accordingly. Binary logistic regression was applied for multivariate analysis and calculating adjusted odds ratios (OR). Multivariate binary logistic regression was executed both with the enter and backward methods and an inclusion criterion of $p < 0.05$. The results were only deemed meaningful and presented if both methods yielded consistent results. Adjusted odds ratios (OR) were calculated with 95 % confidence intervals.

This study "GeriAnaemie2013" is registered in the German Clinical Trials Register (DRKS, Freiburg) with No. DRKS00004617. The local ethics committee of the University Hospital Cologne approved 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.

## Results

In this study 579 patients fulfilling the inclusion criteria were recruited and included 391 females (67.5 %) and 188 males (32.5 %). Study patients had a mean Hb level of 11.9 ± 1.9 g/dl and a mean BI of 50.8 ± 26.2 points. Anemia was found in 319 out of the 579 (55.1 %) patients including 205 female (64.3 %) and 114 male (35.7 %) patients (**Table 2**). The mean age of the study patients was 81.9 years (range 70–97 years, standard deviation SD ± 6.2). Anemic patients had a mean age of 82.0 years (range 70–96 years, SD ± 6.0) (**Table 1**) Patient characteristics are shown in **Table 1 and 2** with respect to differences between anemic and non-anemic patients.

Anemic patients had a lower BI, took > 5 drugs/day significantly more often, had significantly lower serum albumin levels and were hypoalbuminemic significantly more often (**Table 1 and 2**) than non-anemic patients. Handgrip strength did not significantly differ between anemic and non-anemic patients.

The significant factors were included in a multivariate logistic regression analysis. Here, the BI showed no significant association with anemia, adjusted for albumin and drug intake but the significant dependency of anemia on drug intake and albumin persisted. A drug intake of > 5 drugs/day doubles a patient's chance to be anemic with an adjusted OR of 2.17 (range 1.28–3.68, $p = 0.004$), as well as a serum albumin below 3.5 g/dl with an adjusted OR of 2.11 (range 1.40–3.19, $p < 0.001$) (**Table 3**).

Of the patients 176 (30.3 %) were at risk of malnutrition according to the study criteria. They had a lower BI significantly more often (mean ± SD 45 ± 26.5, $p = 0.001$) and significantly lower serum albumin levels (mean ± SD 3.0 ± 0.6, $p < 0.001$) than patients without risk of malnutrition, while Hb levels and handgrip did not significantly differ between the patient groups. No significant correlation between anemia and malnutritionwas found. Mann-Whitney-U-tests revealed significantly lower levels of folic acid with a median and IQR of 5.3 (range 4.0–7.9) and significantly higher levels of vitamin B12 with a median and IQR of 481.0 (range 318.4–712.7) in patients with risk of malnutrition ($p = 0.017$ and $p = 0.029$, respectively) than in patients with no risk, folic acid median and IQR 5.9 (range 4.3–9.2) and vitamin B12 median and IQR of 420.0 (range 307.7–603.6). Multivariate logistic regression, however, yielded no clear result.

## Discussion

The results of this multicenter study on German geriatric inpatients revealed a high prevalence of anemia and hypoalbuminemia, in accordance with previous data. A recent study from Spain among geriatric inpatients admitted to an acute geriatric unit showed an anemia prevalence of 64.13 % [25] corresponding with previous data by our study group of 60 % [32]. Comparable results could also be shown among institutionalized geriatric patients from China [4]. Beghé et al. in an earlier review article underlined the variability of anemia prevalence depending on patient cohort, health status and cut-off levels applied for the definition of anemia [3]. Most studies refer to the WHO cut-off levels for anemia although these values are controversial [18, 20]. For better comparability with other studies, however, we also applied the WHO cut-off levels for the definition of anemia in this study.

In our patient cohort anemia was significantly associated with hypoalbuminemia. Data on the prevalence of hypoalbuminemia among geriatric inpatients are scarce [24] although the associated risk of morbidity and mortality is acknowledged [13, 12]. An association between albumin and nutritional status has been demonstrated in many studies [19, 27] but the role of albumin as a nutritional marker is still controversial as it also correlates with inflammation [9, 14]. Analysis of patients with risk of malnutrition according to study criteria revealed significantly lower levels of serum albumin; however, the prevalence of hypoalbuminemia was not significantly higher in patients with a risk of malnutrition than in patients with no risk. In this patient cohort one might therefore be inclined to assume that albumin does not seem to be a specific nutritional marker.

Data from a number of previous studies have shown that anemia, low serum albumin and deficient physical performance are risk factors for frailty in aged patients [10, 11]. The results of an earlier Japanese study on impairment of activities of daily living (ADL) and low serum albumin suggest a mutual interference [14], leading to the hypothesis

## Abstract · Zusammenfassung

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# Association of anemia with functional and nutritional status in the German multicenter study "GeriAnaemie2013"

### Abstract

**Objectives.** Anemia and malnutrition are risk factors for frailty in older people but data from multicenter studies among German geriatric inpatients are lacking. This analysis evaluated data from the multicenter study "GerAnaemie2013" commissioned by the German Geriatric Society.

**Patients and methods.** The study involved an analysis of the 579 geriatric inpatients recruited in the context of the German multicenter study "GeriAnaemie2013". Study parameters: Barthel index (BI), handgrip strength, nutritional data (e.g. loss of appetite, loss of weight and decreased food intake). Inclusion criteria: in-patient age ≥70 years, exclusion criteria: current cancer disease or cancer-associated treatment. Anemia was defined according to the World Health Organization (WHO) criteria.

**Results.** The mean age of patients was 81.9 years, overall prevalence of anemia 55.1 %, mean hemoglobin (Hb) level 11.9 g/dl, average BI 50.8 points and 30.3 % of all patients were at risk of malnutrition. While univariate analysis revealed a significantly lower BI in anemic patients, this association was no longer seen in multivariate analysis. Regression analysis revealed that a drug intake of > 5 drugs/day doubles the chance of suffering from anemia with an adjusted odds ratio (OR) of 2.17 (confidence interval (CI) 1.28–3.68, $p = 0.004$) as well as a serum albumin level below 3.5 g/dl with an adjusted OR of 2.11 (range 1.40–3.19, $p < 0.001$).

**Conclusion.** Polymedication and low serum albumin were independent risk factors for anemia in geriatric patients, probably reflecting disease severity.

### Keywords

Barthel index · Albumin · Geriatrics · Malnutrition · Polymedication

# Assoziation von Anämie mit dem Ernährungszustand und funktionellen Status in der deutschen Multizenterstudie „GeriAnaemie2013"

### Zusammenfassung

**Hintergrund.** Anämie und Mangelernährung sind Risikofaktoren für Frailty bei alten Patienten, doch bisher fehlen deutsche Daten aus Multizenterstudien. Die vorliegende Untersuchung basiert auf Daten der multizentrischen Studie „GeriAnaemie2013" der Deutschen Gesellschaft für Geriatrie.

**Patienten und Methoden.** Es erfolgte eine Analyse der 579 stationär geriatrischen Patienten anhand folgender Studienparameter: Barthel-Index (BI), Handkraft, Appetitverlust, Gewichtsverlust, reduzierte Nahrungszufuhr. Einschlusskriterien: stationär geriatrischer Patient ≥ 70 Jahre; Ausschlusskriterien: aktuelle Tumorerkrankung oder Tumortherapie. Anämie wurde gemäß den WHO Kriterien definiert.

**Ergebnisse.** Das mittlere Alter der Patienten betrug 81,9 Jahren. Die Anämieprävalenz lag bei 55,1 %,der mittlere Hb-Wert bei 11,9 g/dl und der mittlere bei BI 50,8 Punkten. 30,3 % der Patienten hatten ein Risiko für Mangelernährung. In der univariaten Analyse zeigten anämische Patienten einen signifikant niedrigeren BI, jedoch war dieser Effekt in der multivariaten Analyse nicht mehr zusehen. Die binär logistische Regression zeigte bei Einnahme von > 5 Medikamenten/Tag bzw. einem erniedrigten Serumalbumin ein zweifach erhöhtes Risiko anämisch zu sein mit einer angepassten Odds Ratio (OR) von 2,17 (Range: 1,28–3,68); $p = 0,004$) bzw. einer angepassten OR von 2,11 (Range: 1,40–3,19; $p < 0,001$).

**Schlussfolgerung.** Polymedikation und niedriges Serumalbumin sind unabhängige Risikofaktoren für Anämie bei geriatrischen Patienten, wobei sie vermutlich die Schwere der jeweiligen Grunderkrankung spiegeln.

### Schlüsselwörter

Barthel-Index · Albumin · Geriatrie · Mangelernährung · Polymedikation

**Table 2** Characteristics of study patients with and without anemia (study definitions based on nominal parameters, *p*-value for statistical differences between anemic and non-anemic patients)

| Nominal study parameters | All patients (*n*) | Non-anemic patients | Non-anemic patients % | Anemic patients | Anemic patients % | *p*-value |
|---|---|---|---|---|---|---|
| Gender<br>Female<br>Male | <br>391<br>188 | <br>186<br>74 | <br>71.5<br>28.4 | <br>205<br>114 | <br>64.3<br>35.7 | <br>0.07 |
| Hypoalbuminemia (<3.5 g/dl) | 462 | 125 | 62.2 | 203 | 77.8 | **<0.001** |
| Folic acid deficiency (<3 ng/ml) | 469 | 12 | 5.9 | 16 | 6 | 0.9 |
| Vitamin B12 deficiency (<200 ng/l) | 469 | 14 | 6.8 | 13 | 4.9 | 0.3 |
| Reduced handgrip strength (males < 66 kPa, females < 38 kPa) | 90 | 19 | 50 | 27 | 51.9 | 0.8 |
| Loss of appetite (yes) | 579 | 109 | 41.9 | 154 | 48.3 | 0.1 |
| Reduced food intake (less than normal) | 579 | 119 | 45.8 | 159 | 49.8 | 0.3 |
| Weight loss (>3 kg/in previous 4 weeks) | 460 | 82 | 40.2 | 86 | 33.6 | 0.1 |
| Drug intake (>5/day) | 579 | 206 | 79.2 | 281 | 88.1 | **0.004** |
| Reduced BI (<100 points) | 573 | 241 | 94.1 | 310 | 97.8 | **0.02** |
| Risk of malnutrition (loss of appetite + lower food intake but no unchanged or increased weight) | 579 | 77 | 29.6 | 99 | 31.0 | 0.7 |

*BI* Barthel index, statistically significant ***p***-values are printed in bold type

**Table 3** Results of multivariate logistic regression analysis for the outcome anemia: after adjustment for albumin and drug intake, *BI* showed no significant association with anemia (*dash*); howevere, the significant dependency of anemia on drug intake and albumin persisted

| | Final model | |
|---|---|---|
| **Factors in the initial model** | **Odds ratio (CI)** | ***p*-value** |
| Barthel index | – | – |
| Hypoalbuminemia (<3.5 g/dl) | 2.11 (1.40–3.19) | <0.001 |
| Drug intake (>5/day) | 2.17 (1.28–3.68) | 0.004 |

that physical activity may have a stimulating effect on the maintenance of serum albumin due to an increase of hepatic albumin production [13]; however, this hypothesis remains to be proven. A recent prospective cohort study from Hong Kong showed that the serum level of albumin may serve as a predictor for accidents and emergency department attendance in outpatients > 60 years, with similar findings for Hb levels [15]. Kitamura et al. [12] analyzed risk factors for short-term mortality in elderly patients with a mean age of 83.6 years and could show that a lower BI, lower hemoglobin and lower serum albumin levels were associated with mortality in this patient group.

Univariate analysis of our study results also revealed a lower BI in anemic patients, which is in accordance with previous findings from a Spanish study [25]; however, after application of multivariate analysis the BI was no longer a significant influence on anemia. This is in contrast to the results of the Ocatabaix study group [5], who evaluated seniors living independently in Spain. This controversy might be due to the different study designs with a 3-year follow-up and a larger study population in the Octabaix study [5] than in our multicenter study. Nonetheless, multivariate data on an association between anemia and the BI are rare and further research is required.

The percentage of patients at risk of malnutrition was lower in our study than that described in the German hospital malnutrition study by Pirlich et al. [23]: Based on the subjective global assessment (SGA) tool Pirlich et al. reported more than 50 % of geriatric inpatients to be malnourished [23]. In our study, however, nutritional status was assessed only by patient self-reporting. An established assessment tool for nutritional status was not applied due to the limited time available for recruitment in an emergency room setting on admission; therefore, only risk of malnutrition was assessed and the comparability of findings is limited. A recent Swiss review on nutritional surveys in the United States, Germany, the Netherlands and the United Kingdom revealed that 50–75 % of the German population have a folic acid intake below the recommended levels based on the results of the German National Nutrition Survey II (NVS II) [29]. Our findings of significantly lower folic acid levels in patients at risk of malnutrition may support these previous data; however, the discrepancy in our study results, with malnourished patients having elevated levels of vitamin B12 compared to patients without risk of malnutrition remains unclear. A substitutional proportion of preclinical treatment with vitamin B12 might be assumed but our data cannot prove this. While a previous cohort-based study by Paul and Abraham [21] revealed an association between anemia and risk of malnutrition, our data failed to show such a significant association. This discrepancy might possibly be due to the fact that Paul and Abraham applied the mini nutritional assessment (MNA) [21] while we could only refer to patient self-report for the reasons already mentioned.

Polymedication is a common problem in older patients and associated drug interactions have been described as leading to severe undesired side-effects [1, 28]. Based on the WHO criteria (>5 drugs per day) our results on polymedication

in this study cohort are in accordance with previous data by Ahmed et al. [1] who reported that 70 % of the study patients were on polymedication according to WHO criteria. In our study cohort anemic patients were on polymedication significantly more often. Hematotoxic side effects associated with polymedication are conceivable but an association of anemia with multimorbidity, reflected by polymedication is also possible.

This study has a number of shortcomings: study parameters, such as handgrip strength, vitamin B12 and folic acid were not available from all study centers. Due to this lack of data, the results only have a limited informative value. The lack of consistent laboratory analyses for all study centers may also be responsible for the variability of results. Due to the fact that study parameters were collected on admission in an emergency room setting, time was too limited for a comprehensive geriatric assessment. Lack of an established nutritional assessment, such as the MNA or the SAG may have led to an underestimation of patients with a risk of malnutrition and patients with malnutrition were overlooked.

## Conclusion

This analysis of the multicenter study "GeriAnaemie2013" on German geriatric inpatients revealed an important association of anemia with hypoalbuminemia and polymedication. The assumed association of anemia with impaired functionality based on the BI could not be confirmed in this study. Nevertheless, pathogenetic causes of anemia in older patients should be evaluated by clinicians before starting a cause-related treatment.


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## Compliance with ethical guidelines

**Conflicts of interest.** G. Röhrig, Y. Rücker, I. Becker, R.-J. Schulz, R. Lenzen-Großimlinghaus, P. Willschrei, S. Gebauer, M. Modreker, M. Jäger and R. Wirth state that there are no conflicts of interest.

The local ethics committee of the University Hospital Cologne approved the study (No. 12–322 from 13.02.2013). All studies on humans were carried out in accordance with national laws and the current version of the Declaration of Helsinki from 2013. Informed consent was obtained from all patients included in the studies.

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