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Original Article

Acute and chronic anemia and short- and long-term outcome of patients with peripheral arterial disease and critical limb ischemia

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ABSTRACT

Background: Evident data about the additive effect of "the fifth cardiovascular risk factor" (anemia) and peripheral arterial disease (PAD) focused on morbidity and outcome of patients with PAD are currently still missing.
Methods and results: A total of 41,882 PAD patients were included. Of these, 5566 (13.3%) suffered from anemia. Patients with anemia were older ($P < 0.001$), suffered more often from chronic kidney disease ($P < 0.001$), coronary artery disease ($P < 0.001$), and more severe PAD ($P < 0.001$). However, they received significantly less endovascular revascularizations ($P < 0.001$), had higher amputation rates (acute anemia: 3.7-fold, $P < 0.001$; nutritional, aplastic, and anemia in chronic disease: 2.9-fold, $P < 0.001$), higher in-hospital mortality rates (acute anemia: 6.4-fold, $P < 0.001$; nutritional, aplastic, and anemia in chronic disease: 4.6-fold; $P < 0.001$), had significantly higher in-hospital complications ($P < 0.001$) compared to those without anemia. During a follow-up time up to 4 years (until Dec. 31st, 2012, median 775 days, 25th–75th percentiles 469–1120 days) nutritional, aplastic, and anemia in chronic disease and acute anemia were high significant predictors of long-term mortality and amputation (each $P < 0.001$). Lengths of hospital stay and reimbursement costs were higher (nutritional, aplastic, and anemia in chronic disease: 2-fold higher ($P < 0.001$), acute anemia: 3-fold higher ($P < 0.001$)) than in patients without anemia.
Conclusion: This study illustrates from a large, comprehensive database the association of acute, nutritional, aplastic, and anemia in chronic disease on morbidity, in-hospital treatment and complications, short- and long term outcome, and costs of patients with PAD.

1. Introduction

Anemia is a frequent condition in patients with cardiovascular disease [1], especially in patients with critical limb ischemia (CLI) [2,3], who suffer from chronic inflammation caused by ulceration and gangrene [4]. Moreover, it may be caused by numerous comorbidities such as active bleeding, chronic kidney disease and blood disorders [5,6]. However, although the primary effect of anemia is tissue hypoxia, this induces a complex vicious circle and impacts multiple cardiovascular pathways. Thus, it leads to increased activity of the sympathetic nervous and renin–angiotensin–aldosterone-system, to hypertension, and finally chronic kidney disease and heart failure [7–11]. Therefore, anemia has been shown to be associated with markedly reduced clinical outcome in patients with coronary heart disease [12–14], chronic heart failure [11], chronic kidney disease [15], and also after several types of surgical procedures and interventions [13,16,17].

However, data about its association with the outcome of patients with peripheral artery disease (PAD) are scarce; although it is conceivable that tissue hypoxia by anemia might enhance the symptoms and severity of PAD, especially in those with CLI. Recently, a small registry study [18] showed that one year rates of death and amputations were significantly higher in anemic PAD patients compared to patients without anemia. Furthermore, in other cohorts anemia also increased the risk of postoperative complications, mortality and prolongs hospital stay [2,16,17].

We assessed the influence of anemia on in-hospital treatment and complications, short- and long term outcome, and costs in a large contemporary population-based cohort study. Depending on the large scale of our data we were also able to assess the association of anemia with the different Rutherford categories, and moreover to analyse any

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differences concerning the influence of acute, bleeding related anemia compared to nutritional, aplastic, and anemia in chronic disease.

2. Methods

2.1. Data source, study population, inclusion-criteria

We evaluated comprehensive anonymized data of a large public health insurance company in Germany (Barmer GEK) as described elsewhere in detail [19,20]. Currently, it is the largest public German health insurance company, responsible for more than 8 million people representing about 10% of the entire German population.

Patients were included in this analysis with an index hospitalization between Jan. 1st, 2009 and Dec. 31st, 2011, with the diagnosis of lower limb PAD (ICD-10 codes I70.20 to I70.24), as main or a secondary diagnosis in combination with the diagnosis chronic anemia (ICD-10 codes D50–D53, D60–61, D63–64) or acute anemia (ICD-10 code D62).

2.2. Codes and reimbursement

All main or additional diagnoses were coded according to the German Modification of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10-GM). Annual adaptations of the ICD-10-GM did not affect any of the analyzed diagnoses in this study. Patients were classified according to PAD as Rutherford 6 if I70.24 was coded, I70.23 as Rutherford 5, I70.22 as Rutherford 4 and I70.20 or I70.21 as Rutherford 1–3; anemia was classified as follows: Anemia after intra- and postoperative bleeding (D62), nutritional anemia (D50–D53), aplastic anemia (D60–D61), anemia in chronic disease classified elsewhere and other anemia (D63–D64).

Additionally, operation procedure codes (OPS) for diagnostic angiography (OPS codes: 3–605.0, 3–607.0) and endovascular treatment (OPS codes: 8–836*, 8–84*), vascular surgery (OPS codes: 5–380*, 5–381*, 5–383*, 5–386*, 5–388*, 5–393*, 5–395*), amputations (OPS codes: 5–864.*, 5–865.*) were analyzed. Amputations of the upper extremities or amputations due to other reasons than limb ischemia were not included. In-hospital complications were assessed from specific secondary diagnoses.

All in-hospital costs including drugs, catheters, and blood products are presented in this study. Any costs resulting from outpatient care are not included in this analysis.

2.3. Follow-up data

Additionally, all in- and outpatient cardiovascular diagnoses and procedure codes were recorded a minimum period of 24 months after the index-hospitalization until Dec. 31st, 2012 as follow-up.

2.4. Statistics

Categorical variables are presented as absolute numbers (n) and percentages (%) of the total numbers for each Rutherford subgroup; statistical comparisons for these were made by the chi-square test. Continuous variables were presented as mean ± standard deviation (SD) and compared by the ANOVA-F-test. Relative risks for death and amputation including the baseline parameters concerning short-term outcome after 30 days were analyzed by multivariable binary logistic regression. Additionally, long-term outcomes of those without such an event within the first 30 days after discharge over a follow-up time up to 4 years were analyzed and displayed graphically by multivariable Cox regression models; results were displayed as hazard ratios (HRR) and 95% confidence intervals (CI) (with the covariates: age, gender, hypertension, obesity, dyslipidemia, smoking, diabetes, PAD, coronary artery disease, chronic heart failure and malignancies). All tests were performed two-sided, and P-values of <0.05 were considered statistically significant.

3. Results

A total of 41,882 patients fulfilled the inclusion criteria and defined the cohort for this analysis. Of these, 5566 (13.3%) suffered from anemia (acute anemia 3745 (8.9%); nutritional anemia (1.6%), aplastic anemia (0.1%), anemia in chronic disease (2.7%). Baseline characteristics and comorbidities of all patients in relation to acute, nutritional, aplastic, and anemia in chronic disease anemia are presented in Table 1. The ratio women-to-men was 1:1.3.

Compared to patients without anemia, patients with anemia were older ($P < 0.001$), had more often diabetes ($P < 0.001$), chronic kidney disease ($P < 0.001$), coronary artery disease ($P < 0.001$) and chronic heart failure ($P < 0.001$), and showed more severe peripheral arterial disease, critical limb ischemia inclusively (Table 1). The proportions of patients with obesity ($P < 0.001$), dyslipidemia ($P < 0.001$) and smoking ($P < 0.001$) were lower in patients with anemia, compared to those without anemia.

Patients with nutritional, aplastic, and anemia in chronic disease suffered more often from diabetes ($P < 0.001$), chronic kidney disease ($P < 0.001$), coronary artery disease ($P < 0.001$) and chronic heart failure ($P < 0.001$) compared to those with acute anemia.

3.1. In-hospital treatment, complications and outcome

PAD patients with nutritional, aplastic, and anemia in chronic disease received significantly less revascularizations procedures compared to those without anemia ($P < 0.001$). This applied to endovascular procedures ($P < 0.001$). In-hospital treatment, complications and outcome of all patients in relation to acute, nutritional, aplastic, and anemia in chronic disease are presented in Table 2.

Acute anemia occurred 2.6-fold more often in surgical procedures (2514; 67.1%, $P < 0.001$), 1.6-fold more often in bypass surgery (1561; 41.7%, $P < 0.001$), and 1.1-fold more often in thromboendarterectomy procedures (TEA) (1063; 28.4%, $P < 0.001$) compared to endovascular procedures.

A total of 4401 (10.5%) patients were amputated during their index-hospitalization. Patients with nutritional, aplastic, and anemia in chronic disease had a 2.9-fold higher amputation rate (413; 22.7%; $P < 0.001$) compared to those without anemia (2884; 7.9%). Acute anemia occurred in 1.104 (29.5%) amputations. Thus, the amputation rate in patients with acute anemia was 3.7-fold higher ($P < 0.001$) compared to patients without anemia.

The leading complication during index hospitalization in the entire cohort was infectious disease (5749; 13.7%), followed by death (1217; 2.9%) and sepsis (983; 2.4%). Acute renal failure occurred in 511 patients (1.2%), myocardial infarction in 317 patients (0.76%), and ischemic stroke in 146 patients (0.4%). Patients with nutritional, aplastic, and anemia in chronic disease had distinctly higher frequencies of all observed in-hospital complications compared to those without anemia: 2.8-fold higher infection-rate ($P < 0.001$), 4.6-fold higher in-hospital mortality ($P < 0.001$), 3.8-fold higher sepsis-rate ($P < 0.001$) and 6.2-fold higher rate of acute renal failure ($P < 0.001$), 4-fold higher myocardial infarction rate ($P < 0.001$) and 5.5-fold higher rate of ischemic stroke ($P < 0.001$). Patients with an acute anemia had 2.7-fold higher infection-rate ($P < 0.001$), 6.4-fold higher in-hospital mortality ($P < 0.001$), 3.4-fold higher sepsis-rate ($P < 0.001$) and 10-fold higher rate of acute renal failure ($P < 0.001$), 5.4-fold higher myocardial infarction rate ($P < 0.001$) and a 5-fold higher rate of ischemic stroke ($P < 0.001$), compared to those without anemia.

3.2. Long term outcome

The 30-day outcome of the entire cohort was evaluated. In the comorbidities and baseline parameters adjusted staged binary logistic regression analysis (Table 3), acute anemia and anemia in chronic disease,