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# The impact of anemia on the course and short-term prognosis in patients with first ever ischemic stroke

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ABSTRACT

*Background:* Anemia is the risk factor for cerebrovascular events. The aim of this study was to evaluate the prevalence of anemia among patients with first-ever stroke and its impact on neurological state in the acute phase of the disease and the degree of disability in short-term follow-up.

*Patients and methods:* The prospective study included 107 patients aged 72.81 ± 11.12 with the first-ever stroke. Each patient underwent CT of the head and blood tests, including Hb concentration on the first day of hospitalization. We have analyzed the neurological state on the first day of stroke by NIHSS and the functional status on the 14th day after the onset of stroke by mRankin scale in patients with and without anemia. Patients with anemia were additionally divided according to Hb level (less or over 11 g/dl).

*Results:* Patients with Hb ≤ 11 g/dl significantly more often achieved a score of 4–5 points on mRankin scale on the 14th day of stroke compared to patients with anemia and Hb > 11 g/dl. Independent predictors of a worse functional status on the 14th day of stroke in patients with anemia include the neurological state on the 1st day and the hemispheric location of stroke; an independent predictor of death was the neurological state on the 1st day of onset.

*Conclusion:* Mild anemia did not influence significantly the neurological condition in acute phase of stroke but worsened the functional status in subacute phase of stroke.

The neurological state on the first day of stroke and the hemispheric location of cerebral ischemia are independent factors of poor prognosis in patients with anemia in short-term follow-up.



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## 1. Introduction

Anemia is the most common hematologic disorder which incidence increases with the patient's age. It is a risk factor for cardiovascular events, including cerebrovascular ones. Anemia is associated with increased disability and mortality. However, it is considered an independent risk factor for stroke in children; children's anemia has been observed in more than half of the cases without the presence of other risk factors for stroke [1–5]. The relationship between the entire range of low hemoglobin concentrations and the outcome after stroke in adults is ambiguous. Whereas hypertension, diabetes, smoking habit, old age and dyslipidemia are well-known vascular risk factors for stroke, the role of hemoglobin (Hb) value is still up for debate [6]. In 1972, the Framingham Study conducted on more than 5000 patients concluded that the pathogenetic, preventive and therapeutic implications of the interrelationship between hemoglobin level and stroke would have required further exploration [7]. Close attention is paid to the relationship between stroke and anemia in patients with sickle cell anemia. Emphasis has been put on the importance of genetic and molecular factors underlying nerve structure ischemia in this patient group [8]. It has been observed that in subjects without primary hematologic disorders anemia has a negative impact on the course of stroke, especially hemorrhagic one, and its prognosis. Disorders of oxygen distribution to the neural tissue induce hypoxia in the brain region affected by impaired blood flow. Independently from the traditional risk factors for stroke, thrombocytosis secondary to iron deficiency may be an additional factor causing deterioration in blood supply to the brain.

Recently published studies found a relationship between anemia during stroke and the size of infarct territory, over 1-year mortality and worse long-term outcomes [9–11]. To date, no studies have been conducted in relation to the effect of anemia on the course of the acute phase of stroke and prognosis in the short-term follow-up in adults.

The aim of this study was to evaluate the prevalence of anemia among patients with first ever stroke and its impact on their neurological state in the acute phase of the disease and the degree of disability in short-term follow-up.

## 2. Patients and methods

The prospective study conducted between November 2012 and February 2013 included 107 patients aged $72.81 \pm 11.12$ (median 75, min 29, max 92) on the first day of the patient's first-ever ischemic stroke diagnosed according to the WHO criteria and based on radiological images (computed tomography (CT) and/or magnetic resonance (MRI) of the head) [12]. All patients were hospitalized during the acute phase of stroke in the Department of Neurology of the Academic Medical Center, where diagnostics and therapy were conducted in accordance with the current guidelines [13,14]. Ethical committee approval was not required because the study was based on a routine laboratory tests performed in every patients with a stroke – no patient identification was recorded and thus the study did not fulfill the criterion of a medical experiment.

Each patient was interviewed and underwent physical examination, CT of the head and blood tests, including Hb concentration on the first day of hospitalization.

On the basis of the existing patients' records and examination results, the presence of comorbidities generally recognized as certain and probable risk factors for stroke was found during hospitalization.

The following criteria were used to diagnose the selected comorbidities:

- Arterial hypertension – patient diagnosed or treated for arterial hypertension before the stroke or the in-hospital blood pressure values were above 140/90 mmHg.
- Diabetes – patient diagnosed or treated for diabetes before the stroke, any in-hospital glycemia was above 200 mg/dl, fasting plasma glucose measured on 2 different days was above 126 mg/dl or the 2-h oral glucose tolerance test (OGTT) glucose was above 200 mg/dl.
- Coronary artery disease – diagnosis made before the hospitalization, history of typical symptoms (including relatives), typical ECG changes (prior myocardial infarction, ischemic abnormalities in ECG) or typical echocardiographic findings (regional wall motion abnormality, lowered ejection fraction).
- Atrial fibrillation or flutter – arrhythmias documented earlier or present in ECG during the present hospitalization.
- Lipid disorder – LDL level >130 mg/dl in patients without ischemic heart disease or >100 mg/dl in patients with coronary artery disease or triglyceride level >150 mg/dl or patient already treated for hyperlipidemia (statins, fibrates, ezetimibe).
- Myocardial infarction – increase in TnI on the second day of stroke by at least 25% in relation to the baseline assay, CK-MB > 25 UI (on the 1st day of stroke), ST-T elevation or depression in the ECG ≥ 0.1 mV or formation of a new pathological Q-wave.
- Heart failure–was recognized as a clinical syndrome characterized by specific symptoms (dyspnea and fatigue) in the medical history and signs (edema, rales) on the physical examination.

The above-mentioned conditions were confirmed by a cardiologist or internal medicine specialist.

The following definitions of anemia were applied: Hb serum level <13.5 g/dl in men and <12 g/dl in women [15]. The incidence of anemia was examined in the entire group of patients, then the subjects were divided by sex and age (≤ and >65 years)

The following parameters were compared between in patients with anemia (Group 1) and in patients with normal hemoglobin serum level (Group 2): neurological state on the first day of stroke (by National Institute Health Stroke Scale, NIHSS), the functional status on the 14th day after the onset of stroke (by mRankin scale, mRS) and death incidence within a month after stroke, and the incidence of selected comorbidities and biochemical parameters.

The analysis of the neurological state on the 1st day of stroke (NIHSS) in both groups has also included, the differentiation between a ''slight'' (NIHSS 0–4) and moderate/severe (NIHSS > 4) neurological deficit.

The patients with anemia were divided into 2 subgroups according to Hb serum level (Hb ≤ and >11 g/dl). The following parameters were compared between selected subgroups: state according to NIHSS, the functional status (mRS) on the 14th day and death incidence within a month after stroke.

The statistical analysis was performed by the means of Statistica 5.0 software. For the comparison of the nonparametric values the $Chi^2$ test and *U* Mann–Whitney test were used. Parametric data analysis was based on the *t*-Student test and *p* value of <0.05 was considered as a statistically significant.

Logistic regression analysis was performed in order to determine independent factors of worse prognosis (acc. to mRS, a state of 3–5 and death) among analyzed patients. Analysis concerned the importance of the following factors: gender, age, arterial hypertension, diabetes, ischemic heart disease, lipid disorders, heart failure, atrial fibrillation, stroke location (hemisphere or brainstem).

## 3. Results

Anemia was diagnosed in 15 women (28.30%) and 17 men (31.48%), in 8 patients (26.67%) aged ≤65 years and in 24 (31.17%) patients >65 years. Differences in the prevalence of anemia by gender and age were not statistically significant; $p = 0.71$ and 0.64, respectively. In women aged >65 years anemia occurred more frequently than in younger women (29.72% vs 25% respectively; $p = 0.77$). Similarly, in men >65 years anemia occurred more frequently (33.33%) than in the younger age group (27.78%, $p = 0.67$).

The causes of anemia are presented in Table 2.

Among patients with anemia (Group 1) type 2 diabetes and abnormal renal parameters (creatinine and/or estimate glomerular filtration rate, eGFR) were significantly more common; however, lipid disorders and past myocardial infarction were observed significantly more often in patients without anemia (Group 2). The incidence of other parameters selected for the analysis in Groups 1 and 2 showed no statistically significant differences.

The characteristics of patients with anemia and normal hemoglobin level are shown in Table 1.

The mean serum concentration of hemoglobin among patients with anemia was 11.08 g/dl ± 1.12 (median 1.22, min 8.37, max 12.86).

The mean serum concentration of hemoglobin in women was: 13.00 g/dl ± 1.73 (median 13.14, min 8.37, max 17.47).

The mean serum concentration of hemoglobin in men was: 13.65 g/dl ± 2.02 (median 14.06, min 8.61, max 18.18).

There were no significant differences in neurological deficit on 1st day (NIHSS), functional status at the level of 3–5 (mRS) on 14th day and death within first month between analyzed groups (1 vs 2) (Tables 3 and 4).

Patients with Hb ≤ 11 g/dl significantly more often achieved a score of 4–5 points on mRankin scale on the 14th day of stroke compared to patients with anemia and Hb > 11 g/dl ($p = 0.0167$). There were no statistically significant differences in the neurological state according to NIHSS ($p = 0.0979$) and in

**Table 1 – The characteristics of patients from Group 1 and Group 2.**

| | Patients with anemia *n* = 32 | Patients without anemia *n* = 75 | *p* ($Chi^2$) |
|---|---|---|---|
| Sex (F) | 15 (46.9%) | 38 (50.7%) | 0.7195 |
| Age | 74.47 ± 10.58 | 71.16 ± 11.66 | 0.1703[a] |
| | Mediana 78 | Mediana 72 | |
| | Min 54 max 89 | Min 29 max 92 | |
| Hemispheric location | 22 (68.8%) | 47 (62.7%) | 0.5472 |
| Thrombolytic therapy | 1 (3.1%) | 8 (10.7%) | 0.1982 |
| $Na^+$ | 138.33 ± 4.11 | 138.09 ± 3.81 | 0.7764[a] |
| $K^+$ | 4.03 ± 0.41 | 3.95 ± 0.48 | 0.3910[a] |
| eGFR | 58.59 ± 26.14 | 71.95 ± 16.11 | 0.0227[b] |
| CrCl | 1.28 ± 0.67 | 0.93 ± 0.24 | 0.0002[a] |
| NIHSS | 5.47 ± 4.88 | 4.96 ± 4.83 | 0.5059[b] |
| | Mediana 3.50 | Mediana 3 | |
| | Min 0 max 16 | Min 0 max 18 | |
| mRS | 2.78 ± 1.96 | 2.37 ± 1.94 | 0.3148[b] |
| | Mediana 3 | Mediana 2 | |
| | Min 0 max 6 | Min 0 max 6 | |
| mRS 3–5 | 16 (50%) | 33 (44%) | 0.5684 |
| Mortality | 2 (6.3%) | 3 (4.0%) | 0.6136 |
| AH | 27 (84.4%) | 68 (90.7%) | 0.3450 |
| DM | 15 (46.9%) | 19 (25.3%) | 0.0284 |
| AF | 12 (37.5%) | 22 (29.3%) | 0.4062 |
| LD | 2 (6.3%) | 17 (22.7%) | 0.0419 |
| HF | 22 (68.8%) | 44 (58.7%) | 0.3260 |
| Past MI | 1 (3.1%) | 16 (21.3%) | 0.0183 |

eGFR – estimated glomerular filtration rate, CrCl – creatinine clearance, NIHSS – National Institutes of Health Stroke Scale, mRS – modified Rankin scale, AH – arterial hypertension, DM – diabetes mellitus, AF – atrial fibrillation, LD – lipid disorders, HF – heart failure

[a] *t*-Student's test.

[b] *U* Mann–Whitney test.

**Table 2 – Causes of anemia.**

| Cause of anemia | *n* (%) |
|---|---|
| Chronic urinary tract infection | 3 (9.37) |
| Neoplasmatic disease | 3 (9.37) |
| Rheumatoid arthritis | 1 (3.12) |
| Iron insufficiency | 19 (59.37) |
| Postbleeding anemia | 1 (3.12) |
| Undefined | 5 (15.62) |

**Table 3 – The neurological state according to NIHSS in Groups 1 and 2.**

| | Patients with anemia *n* = 32 | Patients without anemia *n* = 75 | *p* |
|---|---|---|---|
| NIHSS 0–4 | 18 (56.25%) | 48 (64%) | 0.4503 |
| NIHSS >5 | 14 (43.75%) | 27 (36%) | |

NIHSS – National Institutes of Health Stroke Scale.

**Table 4 – The functioning state according to mRS in Groups 1 and 2.**

| | Patients with anemia *n* = 32 | Patients without anemia *n* = 75 | *p* |
|---|---|---|---|
| mRS 0–2 | 14 (43.75%) | 39 (52%) | 0.4345 |
| mRS 3–5 | 16 (50%) | 33 (44%) | 0.5684 |
| mRS 6 | 2 (6.25%) | 3 (4%) | 0.6136 |

mRS – modified Rankin scale.

the incidence of deaths within the first month after stroke ($p = 0.1931$).

Independent predictors of a worse functional status (3–5 points by mRankin) on the 14th day of stroke among patients with anemia include the neurological state on the 1st day of stroke (NIHSS) and the hemispheric location of stroke; an independent predictor of death was the neurological state on the 1st day of onset (Table 5).

**Table 5 – The risk of functioning state at level 3–5 points in mRS and death in patients with anemia.**

| Risk factor for 3–5 mRS | *p* (model) | *p* (factor) | RR |
|---|---|---|---|
| Hemispheric location | 0.0000 | 0.0132 | 3.37<br>95% CI<br>[1.27–8.92] |
| NIHSS | | 0.0003 | 1.23<br>95% CI<br>[1.10–1.37] |
| Risk factor for death | *p* (model) | *p* (factor) | RR |
| NIHSS | 0.0004 | 0.024 | 1.28<br>95% CI<br>[1.03–1.59] |

mRS – modified Rankin Scale, NIHSS – National Institutes of Health Stroke Scale.
The following co-variables were analyzed: sex, age, NIHSS, arterial hypertension, diabetes, lipid disorders, atrial fibrillation, coronary heart disease, heart failure, past myocardial infarct, $Na^+$, $K^+$, estimated glomerular filtration rate, creatinine clearance.

**Table 6 – The risk of functioning state at level 3–5 points in mRS and death in patients without anemia.**

| Risk factor for 3–5 mRS | *p* (model) | *p* (factor) | RR |
|---|---|---|---|
| NIHSS | 0.0001 | 0.0068 | 1.19<br>95% CI<br>[1.05–1.35] |
| Risk factor for death | *p* (model) | *p* (factor) | RR |
| NIHSS | 0.0095 | 0.00292 | 1.33<br>95% CI<br>[1.02–1.73] |

NIHSS – National Institutes of Health Stroke Scale.
The following co-variables were analyzed: sex, age, NIHSS, arterial hypertension, diabetes, lipid disorders, atrial fibrillation, coronary heart disease, heart failure, past myocardial infarct, $Na^+$, $K^+$, estimated glomerular filtration rate, creatinine clearance.

The neurological condition on the first day of onset was recognized as an independent predictor of a worse functional status (3–5 points by mRankin or death) among the patients with normal serum hemoglobin level (Table 6).

## 4. Discussion

Anemia accompanies cardiovascular diseases and is associated with the occurrence of cerebrovascular events [16–18]. It has been shown that anemia influences increased mortality, disability, susceptibility to falls and intellectual deficit in the elderly, and acute cerebral ischemia in children [19–24]. It was found that in patients with hemorrhagic stroke low hemoglobin concentration at admission and Hb nadir in the acute phase of disease are independent predictors of neurological deficit [25,26]. Association of anemia and the size of hemorrhagic focus in brain structures has been previously confirmed [27,28].

Except for patients with sickle cell anemia, the importance of anemia for cerebral ischemia in adults has not been definitely established. It is believed that the physiological regulation of cerebral blood flow should meet the brain's demand for oxygen in pathological state, including profound anemia. Given the incidence of both stroke and anemia in the population, the problem of a possible cause-and-effect relationship or the influence of anemia on the course of stroke in adults is relatively rarely discussed, especially in relation to ischemic stroke.

In the present study anemia was recognized in almost 30% of patients with ischemic stroke, particularly in subjects >65 years of age. No significant relationship was found between anemia and the subjects' gender. Tanne et al. observed a reverse correlation between hemoglobin concentration and age [29]. Dubyk et al. found that among patients with first-ever stroke or transient ischemic attack (TIA) in patients >65 years anemia occurs more often than established in the population registers (NHANESS III) [30]. In the current study, anemia was found significantly more often in patients with abnormal renal parameters and diabetes.

In the present study, anemia was associated with a worse neurological state on the 1st day of stroke and a more serious

degree of disability and dependence on the caretaker on the 14th day after stroke. However, as compared to subjects with normal Hb concentration, the differences were not statistically significant.

The neurological state on the 1st day of stroke and stroke location in the brain hemisphere. turned out to be an independent factors of a worse prognosis in the short-term follow-up after stroke in patients with anemia like age, the patients' state by NIHSS is a significant predictor of disability and death during hospitalization of patients with cerebral stroke [26,31]. The other known factors affecting the patients in the acute phase of stroke and influencing prognosis include the time of therapy inclusion, the vascular territories involved, arterial pressure, blood glucose concentration and body temperature [32]. They may negatively impact the cerebral circulation, decreasing oxygen-carrying capacity and promoting rapid deterioration of ischemic penumbra. Anemia may induce a hyperkinetic circulatory state and upregulate the endothelial adhesion molecule genes, which may lead to thrombus generation [33]. Furthermore, blood flow augmentation and turbulence may result in the migration of a thrombus that had already existed in the diseased vessel, thus producing artery-to-artery embolism [33].

The negative impact of anemia on the course of stroke and the outcome after stroke was observed by other investigators [34–36]. However, the authors presented the results of long-term follow-ups.

In the present study in patients with anemia, as compared to those with normal hemoglobin concentration, there were no significant differences in the neurological state and functioning in the acute phase of stroke. Additionally, anemia did not cause a significantly higher mortality rate. Such a relationship has been already proven in the short and long-term follow-up but in patients with coronary heart disease [16,17]. However, it should be noted that in the present study the mean concentration of hemoglobin in patients with anemia was above 10 g/dl. It is likely that within the patients' level of anemia the mechanisms which compensate for the negative impact of anemia in the acute period of stroke were efficient. I Interestingly, anemia was proved to be a risk factor for death. A mathematical modeling study in rabbit's brain found that penumbral extraction reserve was nearly exhausted at a hemoglobin concentration of approximately 10 g/dl and oxygen uptake in the ischemic penumbra decreased progressively when hemoglobin concentration further decreases. Therefore, a hemoglobin concentration of 10 g/dl might represent the rational transfusion ''trigger'' for the acutely anemic stroke patients, although a suitable randomized clinical study has to be performed before validation of the proposed model [37].

The evaluation of hemoglobin concentration allows to identify those patients who may suffer from the more serious consequences of stroke. Further studies are required in patients with anemia in the acute phase of stroke in order to better understand the importance of anemia in that period and the pathophysiological relevance of abnormal morphology parameters and other factors active in the acute period of cerebral ischemia.

## 5. Limitations

The study has some limitations, the main was the lack of analysis related to the impact of the condition before stroke on the degree of post-stroke disability.

## 6. Conclusion

Mild anemia did not influence significantly the neurological condition in acute phase of stroke but worsened the functional status in subacute phase of stroke.

The neurological state on the first day of stroke and the hemispheric location of cerebral ischemia are independent factors of bad prognosis in patients with anemia in short-term follow-up.

## Conflict of interest

None declared.

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None declared.

## Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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