

Anemia on admission and long-term mortality risk in patients with acute ischemic stroke

Tanja Hojs Fabjan^{1,4,A–F}, Meta Penko^{2,A–C,E,F}, Radovan Hojs^{3,4,A,C,E,F}

¹ Department of Neurology, University Medical Centre, Maribor, Slovenia

² Clinic of Internal Medicine, Department of Cardiology, University Medical Centre, Maribor, Slovenia

³ Clinic of Internal Medicine, Department of Nephrology, University Medical Centre, Maribor, Slovenia

⁴ Faculty of Medicine, University of Maribor, Slovenia

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;

D – writing the article; E – critical revision of the article; F – final approval of the article

Advances in Clinical and Experimental Medicine, ISSN 1899–5276 (print), ISSN 2451–2680 (online)

Adv Clin Exp Med. 2019;28(10):1419–1424

Address for correspondence

Tanja Hojs Fabjan

E-mail: tanja.hojs@gmail.com

Funding sources

This work was partly supported by Slovenian Research Agency (ARRS); project “Chronic renal failure – new risk factor for stroke” (grant No. L3-9376).

Conflict of interest

None declared

Received on January 16, 2018

Reviewed on September 9, 2018

Accepted on February 18, 2019

Published online on September 16, 2019

Abstract

Background. Anemia is associated with adverse outcomes in patients with acute myocardial infarction and congestive heart failure. Additionally, it has been shown that anemia increases the short-term mortality risk in patients with acute stroke.

Objectives. The aim of our study was to determine the importance of anemia as a long-term mortality risk factor by itself or in combination with other risk factors.

Material and methods. We included 390 Caucasian patients with acute ischemic stroke in our study. Their progress was followed from the day of their admission until their death or a max. of 1,669 days. Stroke and anemia were defined according to the World Health Organization (WHO) criteria.

Results. Anemia was present in 57 (14.6%) patients. The patients with anemia were older ($p < 0.01$) and more likely to be female ($p < 0.001$). They had higher NIHSS scores on admission ($p < 0.001$) and discharge ($p < 0.001$), lower estimated glomerular filtration rates (eGFRs) ($p < 0.001$), lower serum LDL cholesterol ($p < 0.01$) and lower serum albumin levels ($p < 0.001$), while their serum C-reactive protein (CRP) levels were higher ($p < 0.001$). The Kaplan–Meier curves showed that patients with anemia had higher mortality ($p < 0.001$). Cox’s regression analysis revealed that anemia at admission was a predictor of long-term mortality in these patients (hazard ratio (HR) = 2.448, 95% confidence interval (95% CI) = 1.773–3.490; $p < 0.001$). Anemia remained a strong predictor of mortality after adjusting for other risk factors as well.

Conclusions. Anemia was frequent among our patients and was an independent predictor of long-term mortality even after adjusting for other risk factors.

Key words: risk factors, acute ischemic stroke, anemia, long-term mortality

Cite as

Hojs Fabjan T, Penko M, Hojs R. Anemia on admission and long-term mortality risk in patients with acute ischemic stroke. *Adv Clin Exp Med.* 2019;28(10):1419–1424. doi:10.17219/acem/104540

DOI

10.17219/acem/104540

Copyright

Copyright by Author(s)

This is an article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

Introduction

Cerebral oxygen delivery depends on cerebral blood flow and arterial oxygen content.¹ Arterial oxygen content is primarily determined by hemoglobin levels.¹ Anemia, defined as low hemoglobin levels, may further impair oxygen delivery to the brain as well as, being associated with decreased oxygen-carrying ability, cause an inflammatory response, impaired cerebrovascular autoregulation and alterations in blood viscosity.^{1,2} Anemia is associated with decreased physical performance or disability and increased mortality regardless of the underlying cause of the low hemoglobin.^{3,4}

In previous studies, it has been shown that anemia is associated with adverse outcomes in patients with acute myocardial infarction and congestive heart failure.^{5–7} Additionally, it has been found that anemia increases the short-term mortality risk in patients with stroke. Li et al. in a meta-analysis of 13 cohort studies, found that anemia was an independent predictor of unfavorable outcomes in patients who have had a stroke.⁸ In 11 studies of this meta-analysis, patients were followed-up after a period of 48 h to 1 year, while in the remaining studies they were followed-up for 2 or 3 years.⁸ The latter 2 studies were from Taiwan and included a Chinese population.^{9,10} Data about the effect of anemia on long-term mortality (over 3 years) in patients with acute ischemic stroke is lacking, especially among Caucasians.

The aim of our study was to evaluate the influence of anemia on long-term mortality in patients suffering from acute ischemic stroke. The importance of other traditional and non-traditional factors on mortality risk was also evaluated.

Patients and methods

We included 390 Caucasian patients with acute ischemic stroke who were hospitalized at our department from January 2005 to January 2006. Patients were followed from the day of their admission until their death or for a max. of 56 months (from 1 to 1,669 days). No patient was lost to follow-up. Ischemic stroke was defined according to World Health Organization (WHO) criteria¹¹ and was diagnosed if the patient had had an appropriate clinical event and had a brain computed tomography (CT) that was either normal or showed a compatible low-density lesion. Events resolving completely within 24 h were diagnosed as a transitory ischemic attack (TIA) and these patients were excluded from the study. A neurologist reviewed all cases. During admission, a quantitative measurement of neurological deficit was performed according to the National Institutes of Health Stroke Scale (NIHSS1).¹² The same measurement was done on the day of discharge from the hospital (NIHSS2).

We collected blood samples from all patients. At admission, hemoglobin and serum creatinine were measured with routine laboratory methods. Anemia was defined using

the WHO criteria as a blood hemoglobin level <120 g/L in women and <130 g/L in men.¹³ The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.¹⁴ All other blood samples were taken in the first 24 h. Serum cholesterol (low-density-lipoprotein cholesterol (LDL cholesterol)), serum triglyceride, serum glycated hemoglobin (HbA1c), serum high-sensitivity C-reactive protein (hsCRP), serum albumin, serum lipoprotein(a), and serum homocysteine levels were measured with routine laboratory methods.

Diabetes mellitus was diagnosed if the patient had already been treated for diabetes mellitus (such information was obtained using a questionnaire from the patients and/or their relatives) or if their fasting glucose level during their hospitalization was higher than 7 mmol/L.¹⁵ Arterial hypertension was diagnosed if the patient had already been treated for hypertension (according to a questionnaire and/or their relatives) or if their average blood pressure value was ≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic, based on 3 different measurements during hospitalization.¹⁶ In the questionnaire, we also gathered data on smoking habits in order to divide the patients into 2 subgroups: current smokers and non-smokers. Atrial fibrillation was confirmed with a standard 12-lead electrocardiogram.

The study was approved by the National Ethics Committee of the Republic of Slovenia. Informed consent was obtained from each patient. The study was carried out in adherence with the Declaration of Helsinki.

Statistical analysis

SPSS for Windows software v. 24.0.0.0 (IBM Corp., Armonk, USA) was used to analyze the data. Arithmetic mean values and standard deviations (SD) were calculated. Characteristics of patients with and without anemia were compared using the t-test or the χ^2 test, where appropriate. Survival rates in patients with and without anemia were analyzed using Kaplan–Meier survival curves. A Cox multivariable regression analysis was used to discover predictors of long-term mortality. In the 1st model, variables which are known to be associated with higher mortality in the general population and/or in stroke patients were included: anemia; age; gender; presence of hypertension, diabetes or atrial fibrillation; smoking status; NIHSS1 and NIHSS2 scores; serum lipid (LDL cholesterol and triglycerides) and serum HbA1c levels; and eGFRs (CKD-EPI equation). In the 2nd model, along with the previous variables, serum hsCRP and serum albumin levels were included, since they – as markers of inflammation/malnutrition – have been associated with higher mortality in previous studies of stroke patients. In the 3rd model, serum lipoprotein(a) and serum homocysteine were added to all of the variables from the 2nd model. Serum lipoprotein(a) and serum homocysteine are accepted as newer non-traditional mortality risk factors. A value of $p < 0.05$ was considered to be statistically significant.

Results

In our study, 390 patients with acute ischemic stroke were included; 183 (46.9%) women and 207 (53.1%) men. Anemia was present in 57 (14.6%) patients. The baseline characteristics of all patients and patients with and without anemia are presented in Table 1.

Patients with anemia were older ($p < 0.01$) at the onset of stroke and more likely to be female ($p < 0.001$); they had higher NIHSS scores on admission ($p < 0.001$) and discharge ($p < 0.001$), and they had lower eGFRs ($p < 0.001$) and lower serum LDL cholesterol ($p < 0.01$), lower serum albumin ($p < 0.001$) and higher serum hsCRP levels ($p < 0.001$). There was no significant difference in smoking status, the presence of diabetes, hypertension or atrial fibrillation or serum HbA1c, serum triglyceride, serum lipoprotein(a), or serum homocysteine levels.

All patients were followed-up from the day of their admission to the hospital until their death or for a max. of 1,669 days. During the follow-up period, 191 (49%) patients died. The Kaplan–Meier survival analysis for patients with and without anemia showed statistically different survival curves; patients with anemia had higher mortality in the observation period (log-rank test; $p < 0.001$) (Fig. 1).

The patients who died were more likely to have anemia ($p < 0.001$) at the onset of their stroke; they were older ($p < 0.001$) and more likely to be female ($p < 0.025$); they had higher NIHSS scores on admission ($p < 0.001$) and discharge ($p < 0.001$), lower eGFRs ($p < 0.001$), lower serum LDL cholesterol ($p < 0.007$) and serum albumin levels

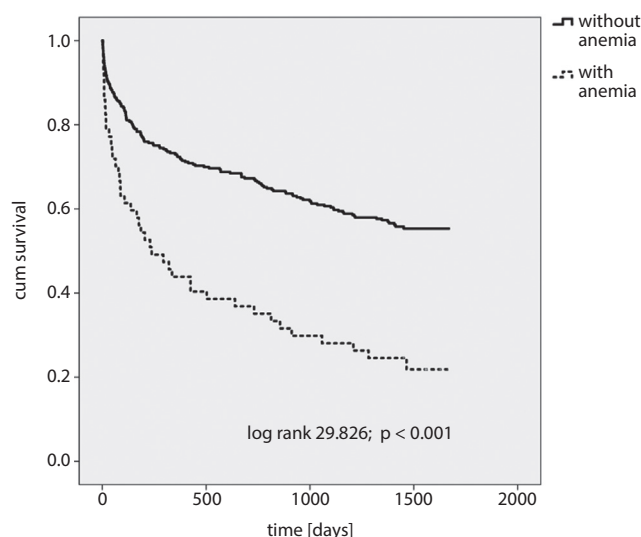


Fig. 1. Kaplan–Meier estimates for the survival of patients with anemia (broken line) and without anemia (solid line)

($p < 0.001$), while they had higher serum hsCRP ($p < 0.001$) and serum homocysteine levels ($p < 0.001$) (Table 2).

There was no significant difference in smoking status, the presence of diabetes, hypertension or atrial fibrillation or serum HbA1c, serum triglyceride, or serum lipoprotein(a) levels (Table 2).

According to the Cox regression analysis, anemia at admission was associated with long-term mortality in patients suffering from acute ischemic stroke (hazard ratio (HR) = 2.448, 95% confidence interval (95% CI) = 1.773–3.490; $p < 0.001$). Anemia also remained a strong

Table 1. Baseline characteristics of the patients included in our study (all patients grouped by presence of anemia)

Variable	All patients	With anemia	Without anemia
Age [years], mean \pm SD	70.97 \pm 11.64	74.63 \pm 12.09	70.35 \pm 11.46*
Gender (women/men), n (%)	183/207 (46.9)	44/13 (77.2)	139/194 (41.7)*
Hypertension (yes/no (%))	313/77 (80.3)	47/10 (82.5)	266/67 (79.9)
Diabetes mellitus/presence (yes/no (%))	100/290 (25.6)	12/42 (21.1)	88/245 (26.4)
HbA1c [mmol/L], mean \pm SD	6.39 \pm 1.43	6.43 \pm 1.54	6.38 \pm 1.42
Smoking/presence (yes/no (%))	61/329 (15.6)	6/52 (10.5)	55/278 (16.5)
Atrial fibrillation/presence (yes/no (%))	81/309 (20.8)	9/48 (15.8)	72/261 (21.6)
NIHSS1 (score), mean \pm SD	9.60 \pm 5.31	11.86 \pm 6.52	9.21 \pm 4.98*
NIHSS2 (score), mean \pm SD	8.07 \pm 7.44	11.28 \pm 7.99	7.53 \pm 7.21*
LDL cholesterol [mmol/L], mean \pm SD	3.17 \pm 1.08	2.73 \pm 0.98	3.25 \pm 1.08*
Triglycerides [mmol/L], mean \pm SD	1.92 \pm 2.23	1.71 \pm 1.54	1.96 \pm 2.32
eGFR [mL/min/1.73 m ²], mean \pm SD	63.38 \pm 20.16	54.04 \pm 25.83	64.98 \pm 18.60*
hsCRP [mg/L], mean \pm SD	17.68 \pm 35.91	34.87 \pm 44.49	14.73 \pm 33.42*
Albumin [g/L], mean \pm SD	40.08 \pm 5.05	34.61 \pm 5.27	41.01 \pm 4.38*
Lipoprotein(a) [g/L], mean \pm SD	0.29 \pm 0.36	0.33 \pm 0.40	0.28 \pm 0.35
Homocysteine [μ mol/L], mean \pm SD	13.18 \pm 6.23	13.96 \pm 5.41	13.05 \pm 6.35

* – statistically significant difference between patients with and without anemia; SD – standard deviation; LDL – low-density lipoprotein; HbA1c – glycated hemoglobin; NIHSS1 – National Institutes of Health Stroke Scale at admission; NIHSS2 – National Institutes of Health Stroke Scale at discharge; eGFR – estimated glomerular filtration rate; hsCRP – high-sensitivity C-reactive protein.

Table 2. Data of patients included in our study grouped by survival

Variable	Died	Survived	p-value
Anemia (yes/no (%))	44/147 (23.0)	13/186 (6.5)	0.001
Age [years], mean \pm SD	74.93 \pm 10.39	67.18 \pm 11.53	0.001
Gender (women/men), n (%)	101/90 (52.9)	82/117 (46.2)	0.025
Hypertension (yes/no (%))	155/36 (81.2)	158/41 (79.4)	NS
Diabetes mellitus (yes/no (%))	52/139 (27.2)	48/151 (24.1)	NS
HbA1c [mmol/L], mean \pm SD	6.43 \pm 1.36	6.34 \pm 1.50	NS
Smoking (yes/no (%))	25/166 (13.1)	36/163 (18.1)	NS
Atrial fibrillation (yes/no (%))	53/138 (27.7)	28/171 (14.1)	NS
NIHSS1 (score), mean \pm SD	11.95 \pm 8.56	7.78 \pm 3.91	0.001
NIHSS2 (score), mean \pm SD	11.95 \pm 8.56	4.36 \pm 3.17	0.001
LDL cholesterol [mmol/L], mean \pm SD	3.02 \pm 0.96	3.32 \pm 1.17	0.007
Triglycerides [mmol/L], mean \pm SD	1.73 \pm 1.80	2.11 \pm 2.56	NS
eGFR [mL/min/1.73 m ²], mean \pm SD	58.95 \pm 21.47	67.63 \pm 17.87	0.001
hsCRP [mg/L], mean \pm SD	25.67 \pm 37.87	10.00 \pm 32.18	0.001
Albumin [g/L], mean \pm SD	38.22 \pm 5.36	41.86 \pm 3.99	0.001
Lipoprotein(a) [g/L], mean \pm SD	0.28 \pm 0.36	0.29 \pm 0.35	NS
Homocysteine [μ mol/L], mean \pm SD	14.25 \pm 7.05	12.16 \pm 5.13	0.001

SD – standard deviation; LDL – low-density lipoprotein; HbA1c – glycated hemoglobin; NIHSS1 – National Institutes of Health Stroke Scale at admission; NIHSS2 – National Institutes of Health Stroke Scale at discharge; eGFR – estimated glomerular filtration rate; hsCRP – high-sensitivity C-reactive protein; NS – not statistically significant.

Table 3. Predictors of mortality in Cox regression analysis models

Variable	Model 1		Model 2		Model 3	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Anemia	1.949 (1.235–3.077)	0.004	1.721 (1.056–2.805)	0.029	1.718 (1.055–2.800)	0.03
Age	1.047 (1.024–1.069)	0.001	1.045 (1.023–1.068)	0.001	1.044 (1.021–1.067)	0.001
Female gender	1.689 (1.146–2.490)	0.008	1.745 (1.181–2.580)	0.005	1.700 (1.145–2.523)	0.008
LDL cholesterol	0.831 (0.706–0.978)	0.026	–	–	–	–
eGFR	0.989 (0.980–0.998)	0.021	0.991 (0.981–1.000)	0.049	–	–
NIHSS1	0.950 (0.918–0.982)	0.003	0.946 (0.914–0.980)	0.022	0.946 (0.914–0.980)	0.002
NIHSS2	1.226 (1.188–1.265)	0.001	1.223 (1.185–1.263)	0.001	1.224 (1.185–1.263)	0.001

HR – hazard ratio; 95% CI – 95% confidence interval; LDL – low-density lipoprotein; eGFR – estimated glomerular filtration rate; NIHSS1 – National Institutes of Health Stroke Scale at admission; NIHSS2 – National Institutes of Health Stroke Scale at discharge.

Model 1 included anemia, age, gender, the presence of hypertension, diabetes and atrial fibrillation, smoking status and NIHSS1, NIHSS2, serum LDL cholesterol, serum triglyceride, eGFR (CKD-EPI equation), and serum HbA1c levels. Model 2 included the previous variables plus serum hsCRP and serum albumin levels. Model 3 included the variables from the 2nd model plus serum lipoprotein(a) and serum homocysteine levels.

predictor of mortality in all 3 adjusted Cox regression models (Table 3).

With the Cox multivariable regression analysis in the 1st model, anemia, age, female gender, eGFR, NIHSS1 and NIHSS2 scores, and serum LDL cholesterol level were predictors of long-term mortality (Table 3). In the 2nd model, anemia, age, female gender, eGFR, and NIHSS1 and NIHSS2 scores remained predictors of long-term mortality (Table 3). In the 3rd

model, anemia, age, female gender, and NIHSS1 and NIHSS2 scores were predictors of long-term mortality (Table 3).

Discussion

To the best of our knowledge, this is the first study to demonstrate the importance of anemia in predicting long-term

mortality in patients with acute ischemic stroke. In our study, patients were followed-up from their admission to the hospital until their death or for a max. of 56 months (up to 1,669 days). Anemia at admission was more common among patients who later died than among the patients who survived. The Kaplan–Meier survival analysis showed higher mortality among patients with anemia in the observation period. The stroke patients with anemia had an increased risk of mortality compared to the patients without anemia in a univariate analysis (HR = 1.949; 95% CI = 1.235–3.077). Anemia remained an independent predictor of long-term mortality even after adjustments for known traditional – and some novel, non-traditional – risk factors (HR = 1.721–1.718) (Table 3).

In some previous studies, inconsistent results about the impact of anemia on mortality in patients with stroke have been reported.^{10,17,18} In 2016, a meta-analysis of cohort studies was published and it was clearly shown that anemia is an independent risk factor of unfavorable short-term outcomes in patients who have had a stroke.⁸ Thirteen studies were included in that meta-analysis.⁸ Patients with acute ischemic or acute hemorrhagic strokes – or both – were included.⁸ It is also important to note that 2 of 11 studies found that anemia is not always associated with mortality. Sico et al. found that anemia is independently associated with an outcome only in patients with a less severe stroke, defined as NIHSS < 10 at admission.¹⁹ They suggested a J-shaped relationship between hematocrit level and a poor prognosis in patients with severe stroke.¹⁹ In a study by Hao et al., anemia was not an independent predictor of the combined outcome of death and disability at 12 months.²⁰ In 11 of the studies included in the meta-analysis, patients were followed-up from 48 h up to 1 year.⁸ In the other 2 studies, patients were followed-up for 2 or 3 years and the authors concluded that there were still no long-term effects of anemia at that point.^{8–10} Both of the latter, longer studies were from Taiwan and studied a Chinese population.^{9,10}

In 2016, a paper by Barlas et al. was published.²¹ The authors analyzed their own data and conducted a meta-analysis of some previously published studies. They included in their retrospective analysis 8,013 stroke patients consecutively admitted over 11 years (86.7% had an ischemic stroke).²¹ Follow-up was obtained by electronic linkage and was ended at 365 days for all patients.²¹ Anemia was associated with an increased risk of short-term mortality.²¹ They included 20 studies in their meta-analysis; in 9 of them, the patients had ischemic stroke, in 6 studies the patients had hemorrhagic stroke, and in 5 the patients had suffered both types of stroke.²¹ In one study, the patients were followed-up on for 3 years, while in all the others the follow-up period was up to 1 year. The study that lasted for 3 years was from Taiwan and included a Chinese population. Meta-analyses of pooled results showed that anemia is associated with an increased risk of mortality in patients with ischemic stroke.²¹ In our study, the patients were followed for much longer and this is the only study where Caucasian patients were followed-up on for more than 1 year.

The prevalence of anemia in acute stroke patients varies from 0.11% to 39.40%. In a meta-analysis by Li et al., the pooled prevalence of anemia was 21.9%.⁸ In our study, the prevalence of anemia was 14.6%. This is still significantly higher than the reported prevalence of 7% in the general elderly population.²² The patients with anemia at admission were older and more likely to be female and with a higher neurological deficit (visible in NIHSS). Similar results were found in some but not all previous studies.^{10,20,23} In a laboratory analysis, patients with anemia had significantly lower eGFRs and lower serum LDL cholesterol, lower serum albumin and higher serum CRP levels. This laboratory data suggests that anemia is possibly part of the malnutrition-inflammation syndrome that is associated with advanced atherosclerosis.²⁴ This is frequently seen in patients with renal dysfunction, which was also more common in our study among patients with anemia.^{24,25} Old age and renal dysfunction were also found more frequently in patients with anemia than in those without, in some previous studies.^{10,20} In a study by Milionis et al., old age, lower eGFRs and lower total cholesterol and higher CRP levels were found in patients with anemia.²⁰ There was no significant difference in smoking status or the presence of diabetes, hypertension or atrial fibrillation in patients with or without anemia in our study. Similar results were found in most previous studies.^{10,19,20} In a study by Milionis et al., there was no difference in the presence of hypertension and smoking but patients with anemia more frequently suffered from diabetes and atrial fibrillation.²³

During the follow-up period, 49% of our patients died. Anemia was significantly more frequent among the patients who died. The patients who died were older and more likely to be female, they had higher NIHSS scores, lower eGFRs, lower serum LDL cholesterol and serum albumin levels, while they had higher serum hsCRP and serum homocysteine levels. In many previous studies where anemia was not included in the analysis, old age, higher NIHSS scores and renal dysfunction were predictors of short- and long-term mortality in patients with acute ischemic stroke.^{25–27} Laboratory data from our study – and some previous ones – suggests that mortality, like anemia, is associated with malnutrition-inflammation syndrome.^{8,24} Some other explanations about how anemia is associated with the outcome of acute ischemic stroke have also been proposed. Anemia leads to low blood oxygen content, which may cause subsequent cerebral ischemia.²⁸ Furthermore, anemia may induce a hyperkinetic circulatory state and upregulate the endothelial adhesion molecule genes, which may lead to a thrombus.²⁹ In addition, blood flow augmentation and turbulence may result in the migration of an existing thrombus, thus producing an artery-to-artery embolism.²⁹ Further studies are needed about the mechanism behind how anemia influences short- and long-term mortality in patients with acute ischemic stroke. There is only a single study examining the relationship between a specific morphological type

of anemia and mortality.³⁰ In that study, normochromic normocytic anemia was associated with inpatient mortality, 90-day mortality and a longer length of hospital stay in patients with ischemic stroke.³⁰ The study also found an association between hypochromic microcytic anemia and both 90-day mortality and longer length of stay in these patients.³⁰ The exact causes of normochromic normocytic and hypochromic microcytic anemia were not explained in this study.

Our study had some limitations which should be considered. Firstly, this is a single-center study. Secondly, only Caucasians were included in our study, thus limiting the generalizability of our findings. Thirdly, we had no information on the etiology or duration of anemia prior to the stroke or on further treatment during the follow-up period. The subtypes of anemia were not analyzed. Finally, the effect of unmeasured confounding variables (frailty, cognitive function, etc.) or complex interactions between covariates cannot be ruled out.

Conclusions

Anemia was frequent in patients who suffered from an acute ischemic stroke. Patients with anemia at admission had higher mortality during the observation period. Anemia was an independent predictor of long-term mortality in a univariate analysis and after adjustments for many other risk factors.

References

- Dhar R, Zazulia AR, Videen TO, Zipfel GJ, Derdeyn CP, Diringner MN. Red blood cell transfusion increases cerebral oxygen delivery in anemic patients with subarachnoid hemorrhage. *Stroke*. 2009;40(9):3039–3044.
- Ferrucci L, Guralnik JM, Woodman RC, et al. Proinflammatory state and circulating erythropoietin in persons with and without anemia. *Am J Med*. 2005;118(11):1288.
- Culleton BF, Manns BJ, Zhang J, Tonelli M, Klarenbach S, Hemmelgarn BR. Impact of anemia on hospitalization and mortality in older adults. *Blood*. 2006;107(10):3841–3846.
- Penninx BW, Pahor M, Cesari M, et al. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc*. 2004;52(5):719–724.
- Salisbury AC, Alexander KP, Reid KJ, et al. Incidence, correlates, and outcomes of acute, hospital-acquired anemia in patients with acute myocardial infarction. *Circ Cardiovasc Qual Outcomes*. 2010;3(4):337–346.
- Younge JO, Nauta ST, Akkerhuis KM, Deckers JW, van Domburg RT. Effect of anemia on short- and long-term outcome in patients hospitalized for acute coronary syndromes. *Am J Cardiol*. 2012;109(4):506–510.
- Kosiborod M, Smith GL, Radford MJ, Foody JM, Krumholz HM. The prognostic importance of anemia in patients with heart failure. *Am J Med*. 2003;114(2):112–119.
- Li Z, Zhou T, Li Y, Chen P, Chen L. Anemia increases the mortality risk in patients with stroke: A meta-analysis of cohort studies. *Sci Rep*. 2016;6:26636.
- Huang WY, Weng WC, Chien YY, Wu CL, Peng TI, Chen KH. Predictive factors of outcome and stroke recurrence in patients with unilateral atherosclerosis-related internal carotid artery occlusion. *Neurol India*. 2008;56(2):173–178.
- Huang WY, Chen IC, Meng L, Weng WC, Peng TI. The influence of anemia on clinical presentation and outcome of patients with first-ever atherosclerosis-related ischemic stroke. *J Clin Neurosci*. 2009;16(5):645–649.
- Thorvaldsen P, Asplund K, Kuulasmaa K, Rajakangas AM, Schroll M. Stroke incidence, case fatality, and mortality in the WHO MONICA Project. *Stroke*. 1995;26(3):361–367.
- Muir KW, Weir CJ, Murray GD, Povey C, Lees KR. Comparison of neurological scales and scoring systems for acute stroke prognosis. *Stroke*. 1996;27(10):1817–1820.
- Nutritional anemias. Report of a WHO scientific group. *World Health Organ Tech Rep Ser*. 1968;405:5–37.
- Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604–612.
- Ryden L, Grant PJ, Anker SD, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2013;34(39):3035–3087.
- Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *Eur Heart J*. 2013;34(28):2159–2219.
- Del Fabbro P, Luthi JC, Carrera E, Michel P, Burnier M, Burnand B. Anemia and chronic kidney disease are potential risk factors for mortality in stroke patients: A historic cohort study. *BMC Nephrol*. 2010;11:27.
- Nybo M, Kristensen SR, Mickley H, Jensen JK. The influence of anemia on stroke prognosis and its relation to N-terminal pro-brain natriuretic peptide. *Eur J Neurol*. 2007;14(5):477–482.
- Sico JJ, Concato J, Wells CK, et al. Anemia is associated with poor outcomes in patients with less severe ischemic stroke. *J Stroke Cerebrovasc Dis*. 2013;22(3):271–278.
- Hao Z, Wu B, Wang D, Lin S, Tao W, Liu M. A cohort study of patients with anemia on admission and fatality after acute ischemic stroke. *J Clin Neurosci*. 2013;20(1):37–42.
- Barlas RS, Honney K, Loke YK, et al. Impact of hemoglobin levels and anemia on mortality in acute stroke: Analysis of UK regional registry data, systematic review, and meta-analysis. *J Am Heart Assoc*. 2016;5(8):pii: e003019.
- Corona LP, Duarte YA, Lebrão ML. Prevalence of anemia and associated factors in older adults: Evidence from the SABE Study. *Rev Saude Publica*. 2014;48(5):723–731.
- Milionis H, Papavasileiou V, Eskandari A, D'Ambrogio-Remillard S, Ntaios G, Michel P. Anemia on admission predicts short- and long-term outcomes in patients with acute ischemic stroke. *Int J Stroke*. 2015;10(2):224–230.
- Stenvinkel P, Heimbürger O, Paultre F, et al. Strong association between malnutrition, inflammation and atherosclerosis in chronic renal failure. *Kidney Int*. 1999;55(5):1899–1911.
- Hojs Fabjan T, Hojs R, Tetickovic E, Pecovnik Balon B. Ischaemic stroke – impact of renal dysfunction on in-hospital mortality. *Eur J Neurol*. 2007;14(12):1351–1356.
- MacWalter RS, Wong SYS, Wong KYK. Does renal dysfunction predict mortality after acute stroke? A 7-year follow-up study. *Stroke*. 2002;33(6):130–135.
- Tsagalas G, Akrivos T, Alevizaki M, et al. Renal dysfunction in acute stroke: An independent predictor of long-term all combined vascular events and overall mortality. *Nephrol Dial Transplant*. 2009;24(1):194–200.
- Dexter F, Hindman BJ. Effect of haemoglobin concentration on brain oxygenation in focal stroke: A mathematical modelling study. *Br J Anaesth*. 1997;79(3):346–351.
- Kim JS, Kang SY. Bleeding and subsequent anemia: A precipitant for cerebral infarction. *Eur Neurol*. 2000;43(4):201–208.
- Barles RS, McCall SJ, Bettencourt-Silva JH, et al. Impact of anemia on acute stroke outcomes depends on the type of anemia: Evidence from a UK stroke register. *J Neurol Sci*. 2017;383:26–30.