Anemia in relation to ischemic stroke outcomes

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ASTRACT: Objective: Acute ischemic stroke patients with anemia have worse outcomes compared to those non-anemia patients. Since many researches in European and America have found that patients with anemia have worse outcomes after stroke, we examined whether anemia associate with ischemic stroke outcome in our country. **Methods:** We prospectively studied 459 patients enrolled in Neurology department of First Affiliated Hospital to Zhengzhou University, China. Our study started from September 2011 to August 2012 and follow-up was completed in February 2013. We explored the relationship of anemia with clinical outcome at 6 months, as measured by the modified Rankin Scale (mRS). Logistic regression was used to evaluate the independent effect of anemia on clinical outcome. **Results:** Anemia was associated with worse 6-month outcomes in univariate analysis ($p<0.001$). Anemia remained independently associated with poor outcome after adjustment for comorbid disease, stroke severity, age, and sex. **Conclusions:** Anemia by World Health Organization criteria was independently associated with worse 6-month outcomes after acute ischemic stroke.

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Low hemoglobin, or anemia is a common condition among older adults, with prevalence increasing with age. Anemia is associated with increased mortality [1-4], disability, and poorer physical performance [5] regardless of the underlying cause of the low hemoglobin. Accumulating evidence suggests that anemia may be an important risk factors for the outcome of stroke[6].The World Health Organization (WHO)[7] defines anemia as a hemoglobin concentration of less than 12 g/dL for women and less than 13 g/dL for men. Many studies in Europe and America[8-10] have assessed the association of anemia with clinical outcomes in the elderly populations, while in our country there is less known about the association between anemia and outcomes of acute ischemic stroke. During the worldwide, previous studies have shown that hemoglobin level correlates with worse neuroimaging outcomes[11]. This raises the possibility that a portion of the worse outcome may be mediated by hemoglobin level. The purpose of this study was to assess whether anemia was associated with neurological outcomes.

METHODS: We prospectively analyzed the clinical data collected at our department, used CT angiography and MRI to improve prediction of stroke and outcome. Clinical outcomes status was determined using the modified Rankin Scale (mRS) obtained by telephone interview at 6 months. The study started in September 2011 and follow-up was completed in February 2013. For the present analysis, patients were eligible if they had a discharge diagnosis of stroke, had a 6-month mRS recorded, and were not treated with thrombolytic or investigational treatments. Patients with prestroke disability (mRS≥2) were excluded. All patients underwent a standardized evaluation by the same team of neurologists and were given an individualized treatment before discharge.

Admission National Institutes of Health Stroke Scale (NIHSS) score, and clinical outcome at 6 months as defined by mRS were collected prospectively. Clinical characteristics including time of stroke onset (defined as the last time the patient was known to be well) and demographic and medical information were ascertained for each patient through chart review. The hemoglobin level during hospitalization was abstracted retrospectively and used for analysis. Analysis was performed using anemia and non-anemia, based on the WHO sex-specific definitions[12]. We classified the patients in our research to anemia group and non-anemia group by WHO criteria. And the patients were dibvided into two group: well-outcome(mRS<3) and worse-outcome (mRS≥3) by mRS score[13].

Differences in clinical and laboratory variables according to outcome were compared using *Student t*, Wilcoxon rank-sum, or Fisher exact test, Kruskal-Wallis, or χ^2 test as appropriate. Logistic regression analysis was performed with outcome as the dependent variable and the above clinical characteristics as independent variables. All numeric variables were expressed as mean±SD ,and categorical variables were expressed as median and interquartile range (IQR). A level of $p<0.05$ was considered statistically significant. Statistical analyses were

performed using SPSS 15.0 statistical software.

RESULTS:

Table 1 shows the relationship of clinical characteristics to 6-month outcome. Anemia was associated with worse neurologic impairment, there were 130 patients in the worse-outcome group, and anemia ones took the percentage of 56.2, while 117 anemia patients took a percentage of 35.6 in well-outcome group, there was significant difference ($p < 0.001$). Increased age was associated with more severe functional deficits, the mean age of patients in worse-outcome group was 69±8, higher than that in the well-outcome group's 63±8 by 6 ($p<0.001$).

The NIHSS also predicted 6-month outcome the interquartile range of well-outcome group was 3(0,6), less than that of the other group ($p<0.001$), as did blood glucose anemia ($p < 0.001$). We also evaluated common comorbidities and the relationship to outcome (table 1), and found that higher rates of diabetes predicted worse recovery ($p=0.028$), as did atrial fibrillation ($p=0.005$), and pulmonary infection ($p < 0.001$). On the other hand, tobacco use was associated with better outcome ($p < 0.01$). Other individual comorbidities were not associated with neurologic outcome.

From the Table 1, we got age, anemia, tobacco use, pulmonary infection, NIHSS score, diabetes, atrial fibrillation, blood glucose that 8 variables had statistical significance. Then we used these 8 predictors to explore the independent relationship between them and outcomes in multivariable logistic regression (table 2).There was an independent association of anemia with neurological outcome ($p<0.001$), with an adjusted odds ratio (OR) of 1.842 (95% confidence interval [CI] 1.036-1.108) .We could see that the risk for patients with anemia getting worse outcome was 0.842 times higher than those non-anemia patients. Other independent predictors included age, NIHSS score, and tobacco use. We could get the conclusion that age, NIHSS score were risk factors for outcomes after acute ischemic stroke. Tobacco use was kind of protective factors.

Table 1. Distribution of clinical characteristics according to outcome.

	Well-outcome n=329	Worse-outcome n=130	p
Variables			
Anemia	117（35.6%）	73（56.2%）	＜0.001
Sex（female）	176（53.8%）	67（51.5%）	0.705
NIHSS score（IQR）	3(0,6)	7(4,10)	＜0.001
Blood glucose ($\bar{x}$ ±s)	6.01±2.66	6.45±2.41	＜0.001
Age（$\bar{x}$ ±s）	63±8	69±8	＜0.001
TIA history	32(9.7%)	12（9.2%）	0.386
Comorbidities n(%)			
Atrial fibrillation	7（2.1%）	9（6.9%）	0.005
Myocardial infarction	12（3.6%）	2（1.5%）	0.237
Diabetes	86（26.1%）	45（34.6%）	0.028
Coronary heart disease	112（34.0%）	58（44.6%）	0.070
Tobacco use	111(33.8%)	29(22.3%)	0.017
Hypertension	206（62.6%）	87（66.9%）	0.588
Pulmonary infection	14（4.3%）	22 (16.9%)	＜0.001

IQR=interquartile range; mRS=modified Rankin Scale

Table 2 Predictors of 6-month outcomes

Variables	*β*	*Wals*	*P*	*OR*	*95%CI*
Age	0.069	16.414	0.001	1.072	1.036-1.108
Tobacco use	-0.707	4.905	0.027	0.493	0.483-0.922
Anemia	0.611	4.632	0.031	1.842	1.056-3.011
Pulmonaryinfection	1.528	5.779	0.052	4.610	1.326-12.024
NIHSS score	0.290	17.525	0.001	1.336	1.248-1.429
Diabetes	0.373	1.810	0.178	1.453	0.843-2.503
Atrial fibrillation	0.894	1.417	0.234	2.444	0.561-10.650
Blood glucose	0.029	0.375	0.550	1.029	0.936-1.131

CI=confidence interval; OR =odds ratio.

DISCUSSION

The results from this study show that anemia is inversely associated with neurologic outcome after acute ischemic stroke. However, underlying diseases (like pulmonary infection, diabetes et al) may induce anemia through increased inflammation suppressing erythropoiesis, or malnutrition[14,15].So we adjusted for age, NIHSS score, blood glucose, and several common comorbidities, after that this association remains significant. A study from Massachusetts General Hospital, America, suggested that lower hemoglobin values are associated with larger acute infarcts and an increased degree of infarct growth. This effect is independent of recognized variables that contribute to infarct size, including age, sex, admission blood glucose, NIHSS score[16]. Some studies have identified a U-shaped relationship between hemoglobin and outcome[17].So we may draw the conclusion that low and a highly elevated hemoglobin may contribute to the poor outcomes after acute ischemic stroke. In the present study, anemia was a risk factor for outcome after acute ischemic stroke. And along with our observational findings, there are many other studies[18-23], suggest that anemia is causally related to adverse outcomes after acute ischemic stroke. Accumulating evidence suggests that a low hemoglobin level adversely affects the cerebrovascular system[24-26]. However this studies are mostly American and European. In China, there few studies explored the association between anemia and outcomes after ischemic stroke. A study from Taiwan[27], China, suggested that hemoglobin and albumin were risk factors for persistent neurological deterioration during hospitalization following acute ischemic stroke, suggesting that hemoglobin level may be related to neurological deterioration. Further studies are necessary to sort out the pathophysiologic mechanism that may account for our findings.

The major limitations of this study are that it was a prospective study of patients in our hospital, and the participants toward patients with less severe stroke (median NIHSS 4), may not represent a cross-section of the elderly population. Furthermore, the study also used 6-month outcome by phone, which may also bias toward less severe stroke, limiting the generalization of our findings in severe stroke populations. Although we adjusted for potential comorbidities, we do not have information on the etiology of anemia (vitamin B12, folate, ferritin concentrations, and red blood cell indices) and cannot speculate on the magnitude of this effect. And there is another question that it remains possible that exist unrecognized concomitant diseases that may influence the level of patients' hemoglobin.

Our data demonstrate that lower anemia is independently associated with worse neurologic outcome. As the key oxygen-carrying molecule in the body[28,29], hemoglobin may play a director indirect role in influencing brain recovery and neurologic function. The mechanism by which lower hemoglobin associates with poor outcomes after ischemic stroke is still unknown. However, one possible explanation may be through its influence on energy supply. Hemoglobin carries 98% of the total blood oxygen, yet within one standard deviation of the normal range that level may vary by as much as 20%[30]. If a 20% reduced oxygen-carrying capacity occurs in the context of normally functioning cerebrovasculature, autoregulatory mechanisms typically compensate by augmenting cerebral blood flow[31]. However, in the context of ischemia, autoregulatory compensation is significantly impaired in the ischemic brain3[2], with limited ability of the brain to increase the extraction of available oxygen[33]. The fact that anemia independently predicted worse outcome after ischemic stroke suggest that it may contribute to long-term adverse physiologic changes. Future studies that explore association between anemia and outcome after stroke should include more detailed anemia grade and more potential concomitant diseases.

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