ORIGINAL RESEARCH

Yanbo Peng MD^{1,2}
Dali Wang MD²
Jiang Zhang MD²
Xinhong Xue MD²
Zhuo Wang MD³
Weijun Tong MD¹
Tan Xu MD, PhD¹
Yonghong Zhang MD, PhD¹

¹ Department of Epidemiology, School of Radiation Medicine and Public Health, Medical College of Soochow University, Suzhou, China.

² Department of Neurology, Affiliated Hospital of Hebei United University, Tangshan, China.

³ International Education Center, Hebei United University, Tangshan, China.

Relationship between white blood cell count at admission and short term outcome in patients with acute cerebral infarction

Abstract

Purpose: We studied the association between admission white blood cell (WBC) count and short term outcome in patients with acute cerebral infarction.

Methods: 2808 patients with acute cerebral infarction were included in the study. WBC count and other variables were collected within the first 24 hours of admission. Clinical outcomes (death or dependency) were evaluated by neurologists during hospitalization. The associations between WBC count and in-hospital death or dependency at discharge were analyzed using a multiple logistic model.

Result: Multivariate-adjusted odds ratio (95% confidence intervals) of dependency associated with patients with WBC of $10.0\text{--}10.9 \times 10^9/\text{L}$, $11.0\text{--}11.9 \times 10^9/\text{L}$, $\geq 12.0 \times 10^9/\text{L}$ were 1.46(0. 87-2. 45), 6.21(3. 70-10. 42) and 7.01(4. 53-10. 87), respectively, when compared with patients with admission WBC counts $<10.0 \times 10^9/\text{L}$. Multivariate-adjusted odds ratio (95% confidence intervals) of death associated with WBC $10.0\text{--}10.9 \times 10^9/\text{L}$, $11.0\text{--}11.9 \times 10^9/\text{L}$ and $\geq 12.0 \times 10^9/\text{L}$ were 2.098(0. 96-4. 58), 4.79(2. 24-10. 22) and 5.59(3. 14-9. 98), respectively.

Conclusion: Increased WBC count at admission was significantly and positively associated with in-hospital death or dependency at discharge among patients with acute cerebral infarction.

Manuscript submitted 10th April, 2011

Manuscript accepted 20th June, 2011

Clin Invest Med 2011; 34 (4): E249-E254.

Correspondence to:

Yonghong Zhang, MD, PhD
Department of Epidemiology, School of Radiation Medicine and Public Health,
Medical College of Soochow University
199 Renai Road, Industrial Park District,
Suzhou, China. 215123
E-mail: yhzhang@suda.edu.cn

Stroke is the leading cause of death and long-term disability worldwide [1]. In China, stroke is the third leading cause of death for males and the second leading cause for females, and the morbidity and mortality of stroke are higher compared with other countries [2]. Atherosclerosis is one of the major mechanisms of stroke [3]. Recent evidence suggests that atherosclerosis is an inflammatory condition [4]. White blood cells (WBC) play an important role in the initiation and propagation of the atherosclerotic process and WBC count has been shown to be associated with an increased risk of stroke [5]. A study showed that WBC count was predictive of first ischemic stroke, after adjustment for vascular risk factors [6]; however, there was no consensus about the relationship between WBC count and the prognosis after onset of cerebral infarction. Some studies had found that increased WBC count in the first day of acute ischemic stroke is a prognostic factor of disease progression [7], and the WBC count was an important predictive factor of in-hospital death [8]. There were also some studies [9-11] that did not find an association between the admission WBC count and clinical outcome. In China, there has been no large-sample data on the relationship between WBC count at admission and short term clinical outcomes among patients with acute cerebral infarction. The purpose of the present study is to examine the association between WBC count at admission and short term clinical outcomes, including death and dependency, among acute cerebral infarction patients in China.

Participants and Methods

Study participants

Acute cerebral infarction patients were recruited from the affiliated hospital of Hebei United University, China. Written informed consent was obtained for all study participants or their family members. All the patients with a clinical diagnosis of acute cerebral infarction admitted to the hospital from January 1, 2003 to December 31, 2009 were potentially eligible for the study; however, only those whose diagnosis was confirmed by a computed tomography (CT) scan or magnetic resonance imaging (MRI) and whose admission times from onset were less than 72 hours were included. A team of investigators, including neurologists, reviewed the eligibility of study participants. Among the 3256 acute cerebral infarction patients admitted to the hospital during the study period, all of whom had a CT or MRI confirmed cerebral infarction, only 2808 patients were included in our analysis. A total of 448 patients were excluded from our analysis according to the following exclusion criteria: recent acute infection including prior to admission,

history of active leukemia/lymphoma, use of thrombolysis after admission, use of medications that could affect blood cell counts such as prednisone or chemotherapeutic agents. This study was approved by Soochow University and Hebei United University Ethics Committees.

Data collection

Baseline data were collected within the first 24 hours of admission during an interview with patients or their family members (if patients were not able to communicate). Data on demographic characteristics, lifestyle risk factors, medical history, complications, NIH stroke score (NIHSS), clinical laboratory tests and imaging data (CT and MRI) were obtained by trained staffs for all participants. Cigarette smokers were defined as having smoked at least 1 cigarette per day for 1 year or more. Details on the amount and type of alcohol consumption during the past year were collected. Alcohol consumption was defined as consuming one or more alcoholic drinks per week during the past year. Complications included myocardial infarction, heart failure, renal failure and pneumonia at admission.

The WBC count was measured using a fully automated hematology analyzer (ABX PENTRA 60, France). Fasting plasma glucose levels were measured using a modified hexokinase enzymatic method. Total cholesterol, high-density lipoprotein(HDL)-cholesterol and triglycerides were analyzed enzymatically using a Beckman Synchron CX5 Delta Clinical System (Beckman Coulter, Fullerton, USA) using commercial reagents. Low-density lipoprotein (LDL)-cholesterol levels were calculated by the use of the Friedewald equation for the participants.

The study outcomes included in-hospital death and dependency at discharge. If a patient died in the hospital, a study staff member recorded the death on the event form and obtained the death certificate. If a patient survived the acute stroke, the neurologists conducted a comprehensive clinical evaluation at discharge. Dependency was defined as moderate or severe disability at discharge using a modified Rankin Scale (mRS) > 2 [12].

Statistical analysis

The mean and standard deviation of continuous variables and proportion of categorical variables at admission were calculated for the death, dependency and non-dependency (mRS ≤ 2) participants. The participants were grouped by the WBC count level (<10.0×10⁹/L, 10.0-10.9×10⁹/L, 11.0-11.9×10⁹/L and ≥12.0×10⁹/L), multivariate logistic regression analysis was

TABLE 1. Characteristics of acute cerebral infraction patients at hospital admission

	Death	Dependency	Non-dependency
N	117	713	1978
Age(<i>mean±sd</i>)	75.57±9.72* [#]	68.86±11.56 [#]	62.87±11.46
Male, %(N)	54.7(64)	53.8(384)	57.4(1135)
History of hypertension, %(N)	71.8(84)* [#]	55.1(393)	55.1(1090)
History of diabetes, %(N)	43.6(51)* [#]	40.3(287) [#]	18.8(371)
History of coronary heart diseases, %(N)	24.8(29)* [#]	36.5(260) [#]	14.5(286)
History of stroke, %(N)	41.9(49)* [#]	25.7(183) [#]	18.9(373)
Cigarette smoking, %(N)	65.8(77)* [#]	28.2(201) [#]	22.5(445)
Alcohol drinking, %(N)	67.5(79)* [#]	26.5(187) [#]	15.8(313)
Dyslipidemia, %(N)	32.8(38)* [#]	18.8(134)	20.3(402)
Hyperglycemia, %(N)	53.0 (62) * [#]	40.8(291) [#]	21.0(416)
Complications, %(N)	11.1(13) * [#]	2.7(19) [#]	1.7(34)
NIHSS (<i>mean±sd</i>)	13.39±7.92* [#]	11.71±7.63* [#]	3.38±3.22* [#]
WBC count (mean ± sd) ×10 ⁹ /L	12.16±5.18* [#]	9.17±3.27 [#]	7.19±2.59

Dyslipidemia: total cholesterol≥6.22mmol/L or LDL≥4.14mmol/L or triglyceride ≥1.72mmol/L.

Hyperglycemia: fasting plasma glucose ≥6.1mmol/L

WBC: White blood cell. Complications including myocardial infarction, heart failure, renal failure and pneumonia at admission. sd: standard deviation

*Compared with dependency, P<0.05; [#]compared with no dependency, P<0.05

TABLE 2. Odds ratio (OR) and 95% confidence intervals (CI) of study outcomes associated with admission white blood cell count

	Unadjusted OR(95%CI)	P	Adjusted* OR(95%CI)	P
Dependency				
<<10.0×10 ⁹ /L	1.00 (ref)	-	1.00 (ref)	
10.0-10.9×10 ⁹ /L	1.99(1.13-3.55)	0.018	1.46 (0.87-2.45)	0.148
11.0-11.9×10 ⁹ /L	3.78(2.12-6.73)	<0.001	6.21(3.70-10.42)	<0.001
≥12.0×10 ⁹ /L	10.08(5.16-19.68)	<0.001	7.01(4.53-10.87)	<0.001
P-value for trend	<0.001		<0.001	
Death				
<<10.0×10 ⁹ /L	1.00 (ref)	-	1.00 (ref)	
10.0-10.9×10 ⁹ /L	4.10(1.38-12.23)	0.011	2.098 (0.96-4.58)	0.063
11.0-11.9×10 ⁹ /L	17.52(6.09-50.33)	<0.001	4.79(2.24-10.22)	<0.001
≥12.0×10 ⁹ /L	19.02(9.81-36.73)	<0.001	5.59(3.14-9.98)	<0.001
P-value for trend	<0.001		<0.001	0.001
Combined outcomes				
<<10.0×10 ⁹ /L	1.00(ref)	-	1.00 (ref)	
10.0-10.9×10 ⁹ /L	3.99(2.16-7.37)	<0.001	1.98(1.34-2.93)	0.001
11.0-11.9×10 ⁹ /L	4.28(1.59-11.5)	0.004	3.60(2.45-5.29)	<0.001
≥12.0×10 ⁹ /L	17.23(11.0-26.9)	<0.001	11.54(7.64-17.43)	<0.001
P-value for trend	<0.001		<0.001	

*Adjusted for age, time from stroke onset to admission, hypertension, history of diabetes, coronary heart diseases and stroke, smoking and drinking, dyslipidemia, hyperglycemia, NIHSS and complications at admission.

used to examine the association between WBC count and study outcomes (death or dependency), adjusted for age, time from stroke onset to admission, hypertension, history of diabetes, coronary heart diseases and stroke, smoking and drinking, dyslipidemia, hyperglycemia, NIHSS and complications at admission.

Odds ratio (OR) and 95% confidence interval (95% CI) were calculated for each group, using the group with the lowest WBC count as a reference. Statistical analyses were conducted using SPSS statistical software (version 13.0).

Results

A total of 117 death cases, 713 dependency cases and 1978 non-dependency cases were included in the present analysis. The median time from onset of symptom to admission was 24 hours; the median duration of hospitalization was 15 days. The demographic and clinical characteristics of acute cerebral infarction patients at admission by the study outcomes are presented in Table 1. Deaths were more likely to occur in older patients, and those with hypertension, histories of diabetes, stroke, coronary heart diseases, smoking and drinking, dyslipidemia, hyperglycemia, complications at admission, and higher NIHSS and WBC count at admission compared with survivors. The dependency cases were more likely to be older, have histories of diabetes, coronary heart diseases and stroke, smoking, drinking, hyperglycemia, have complications at admission, and have higher NIHSS and WBC count at admission compared with those without dependency. There was no significant difference in gender among the death, dependency and non-dependent patients.

There was positive and significant association between WBC count at admission and study outcome (Table 2). Compared with those with $\text{WBC} < 10.0 \times 10^9/\text{L}$, unadjusted ORs of dependency were all positive and significant for the patients with WBC count of $10.0\text{--}10.9 \times 10^9/\text{L}$, $11.0\text{--}11.9 \times 10^9/\text{L}$, $\geq 12.0 \times 10^9/\text{L}$. The ORs of dependency associated with WBC count of $11.0\text{--}11.9 \times 10^9/\text{L}$ and $\geq 12.0 \times 10^9/\text{L}$ remained significant after adjustment for multivariate, the risk of dependency in the patients with $\text{WBC} \geq 12.0 \times 10^9/\text{L}$ was 7.01 times those with $\text{WBC} < 10.0 \times 10^9/\text{L}$. unadjusted ORs of death were all positive and significant for the patients with WBC count of $10.0\text{--}10.9 \times 10^9/\text{L}$, $11.0\text{--}11.9 \times 10^9/\text{L}$ and $\geq 12.0 \times 10^9/\text{L}$. The ORs of death associated with WBC count of $11.0\text{--}11.9 \times 10^9/\text{L}$ and $\geq 12.0 \times 10^9/\text{L}$ remained significant after adjustment for multivariate, the risk of death in the patients with WBC count of $11.0\text{--}11.9 \times 10^9/\text{L}$ and $\geq 12.0 \times 10^9/\text{L}$ was 4.79 and 5.59, respectively, compared with those with $\text{WBC} < 10.0 \times 10^9/\text{L}$.

Discussion

We conducted a large-sample study on the relationship between WBC count at admission and short term clinical outcomes among acute cerebral infarction patients. Increased WBC count at admission was found to be independently associated with in-hospital death and dependency at discharge among patients with acute cerebral infarction. WBC count was higher in the death cases than in the dependency cases and higher in the death and dependency cases than in non-dependent cases. Furthermore, admission WBC counts of $11.0\text{--}11.9 \times 10^9/\text{L}$, $\geq 12.0 \times 10^9/\text{L}$ were associated with 6.21 and 7.01-fold increase in the risk of dependency, and 4.79 and 5.59-fold increase in the risk of death among acute cerebral infarction patients compared with WBC counts $< 10.0 \times 10^9/\text{L}$. Some factors, including age, time from stroke onset to admission, histories of hypertension, diabetes, coronary heart diseases and stroke, NIHSS and complications at admission, were adjusted by using a multiple logistic model. The observational findings suggest that WBC count at admission maybe predict the occurrence of poor outcome in short term among acute cerebral infarction patients.

Some studies have showed that inflammatory biomarkers are associated with the risk of future ischemic events in the general population. In a meta-analysis, Danesh *et al.* reported that relative risk of cardiovascular disease associated with upper tertiles of leukocyte count, CRP and fibrinogen was 1.4, 1.7 and 1.8, respectively, compared with lowest tertiles [13]. Elkind's study [6] showed that increased baseline leukocyte counts might independently predict occurrence of first cerebral infarction, and Armin *et al.* [14] reported that elevated baseline leukocyte counts were independently associated with ischemic events in the high-risk populations with ischemic stroke, myocardial infarction or peripheral arterial disease. Brown [15] reported that elevated WBC may predict mortality from cerebrovascular disease after adjustment for the effects of smoking and other cardiovascular disease risk factors. There are two studies [16,17] of patients in whom bacterial infections lead to increased WBC counts, which suggest that acute bacterial infections may be associated with ischemic events. There are, however, conflicting reports about the association between WBC count and the prognosis after onset of cerebral infarction [8-11]. In 763 unselected patients with stroke, admitted within 24 hours from onset, Kammersgaard *et al.* [9] prospectively studied the relationship between leukocyte count and clinical outcome. Their findings showed that leukocytosis at admission was related to initial stroke severity but not to outcome; leukocyte count at admission seems merely to reflect initial stroke severity and is most likely a stress response with

no independent influence on outcome. Kazmierski's study [8] showed that an increased WBC count within the first 12 h of onset of an ischemic stroke was a strong prognostic factor for in-hospital mortality in 400 consecutive acute stroke patients. In the Northern Manhattan Stroke Study [18], 655 patients with first ischemic stroke were prospectively followed for 5 years for the occurrence of recurrent stroke, myocardial infarction or death. Their findings indicated that elevated leukocyte count at the time of ischemic stroke predicts future recurrent stroke, myocardial infarction or death. Turaj's study [19] showed that the WBC count was an independent predictor of one-year case-fatality among 900 patients with ischemic stroke admitted to the hospital within 24 h after onset of symptoms. Compared with previous studies, our study is a larger survey sample, which includes 2808 ischemic cerebral infarction patients unselected from 2003 to 2009 in a hospital. Although data about infarct size, associated with severity of stroke, was not collected in this study, some important covariates were adjusted for, including NIHSS and complications at admission, which might reflect severity of stroke and were related to the prognosis. The time length from stroke onset to admission may complicate the analysis, however, the time length from stroke onset to admission was adjusted for. Our findings, therefore, support the concept that an elevated WBC count is an independent risk factor for in-hospital death, or short term poor outcomes, in ischemic cerebral infarction patients.

The mechanisms linking WBC count to clinical outcome are insufficiently understood. Buck *et al.* [20] reported that, in acute ischemic stroke, early elevation of total leukocyte count and neutrophil count is associated with a larger volume of early ischemic tissue. A study by Audebert *et al.* [21] showed that an increase in inflammatory parameters (C-reactive protein and WBC count) correlated significantly with lesion volume and stroke severity. Increased WBC count may make a major contribution to the rheologic properties of blood, alter adhesive properties under stress, including the stress of ischemia, and participate in endothelial injury, both acutely and chronically, by adhering to endothelium and damaging it with toxic oxygen compounds and proteolytic enzymes [22].

Our study has some limitations. Firstly, the study is an observational study and not a multicenter clinical study. Secondly, the participants included some patients whose time from onset to admission exceeded 24 hours, and whose WBC count at admission maybe not accurately reflect the levels of WBC at stroke onset. Thirdly, the data of long term outcomes after the discharge was not collected; therefore, these findings are limited to explanations of short term outcomes.

In summary, our study found that increased WBC count at admission was significantly and positively associated with in-hospital death and with dependency at discharge. Our findings suggest that increased WBC is an independent risk factor for short term poor outcomes among patients with acute cerebral infarction.

Acknowledgments

This study was supported by National Natural Science Foundation of China (Grant No. 30972531).

References

1. WHO. Global Burden of Disease 2002: Deaths by age, sex, and cause for the year 2002. Geneva, Switzerland: World Health Organization 2003.
2. Zhang LF, Gu D, Wu X, et al. Proportion of different subtypes of stroke in China. *Stroke*. 2003; 34:2091-6.
3. Bakhai A. The burden of coronary, cerebrovascular and peripheral arterial disease. *Pharmacoeconomics*. 2004;22(suppl 4):11-18.
4. Stoll G, Bendszus M. Inflammation and atherosclerosis: novel insights into plaque formation and destabilization. *Stroke*. 2006;37:1923-32.
5. Grau AJ, Boddy AW, Dukovic DA, Buggle F, Lichy C, Brandt T, Hacke W; CAPRIE Investigators. Leukocyte count as an independent predictor of recurrent ischemic events. *Stroke*. 2004;35:1147-52.
6. Elkind MSV, Sciacca R, Boden-Albala B, Rundek T, Paik MC, Sacco RL. Relative elevation in leukocyte count predicts first cerebral infarction. *Neurology*. 2005;64:2121-5.
7. Kaźmierski R, Guzik P, Ambrosius W, et al. Leukocytosis in the first day of acute ischemic stroke as a prognostic factor of disease progression. *Wiad Lek*. 2001; 54: 143-51
8. Kazmierski R, Guzik P, Ambrosius W, Ciesielska A, Moskal J, Kozubski W. Predictive value of white blood cell count on admission for in-hospital mortality in acute stroke patients. *Clin Neurol Neurosurg*. 2004 ;107:38-43.
9. Kammersgaard LP, Jørgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Leukocytosis in acute stroke: Relation to initial stroke severity, infarct size, and outcome: The Copenhagen stroke study. *Stroke Cerebrovasc Dis*. 1999; 8: 259-63.
10. Christensen H, Boysen G. C-reactive protein and white blood cell count increases in the first 24 hours after acute stroke. *Cerebrovasc Dis*. 2004; 18: 214-9.
11. Zuliani G, Cherubini A, Ranzini M, Ruggiero C, Atti AR, Fellin R. Risk Factors for Short-Term Mortality in Older Subjects with Acute Ischemic Stroke. *Gerontology*. 2006; 52: 231-236.
12. Bonita R, Beaglehole R. Modification of Rankin Scale: recovery of motor function after stroke. *Stroke*. 1988;19:1497-1500.

13. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA*. 1998;279:1477-82.
14. Grau AJ, Boddy AW, Dukovic DA, Bugge F, Lichy C, Brandt T, Hacke W. Leukocyte Count as an Independent Predictor of Recurrent ischemic Events. *Stroke*. 2004;1147-52.
15. Brown DW, Ford ES, Giles WH, Croft JB, Balluz LS, Mokdad AH.. Associations between white blood cell count and risk for cerebrovascular disease mortality: NHANES II Mortality Study, 1976-1992. *Ann Epidemiol*. 2004;14:425-30.
16. Grau AJ, Bugge F, Becher H, Zimmermann E, Spiel M, Fent T, Maiwald M, Werle E, Zorn M, Hengel H, Hacke W. Recent bacterial and viral infection is a risk-factor for cerebrovascular ischemia: clinical and biochemical studies. *Neurology*. 1998; 50: 196-203.
17. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Valance P. Risk of myocardial infarction and stroke after infection or vaccination. *N Engl J Med*. 2004 ;351:2611-8.
18. Elkind MSV, Cheng J, Rundek T, Boden-Albala B, Sacco RL. Leukocyte count predicts outcome after ischemic stroke: the Northern Manhattan Stroke Study. *J Stroke Cerebrovasc Dis*. 2004;13:220-7.
19. Turaj W, Słowik A, Dziedzic T, Pułyk R, Adamski M, Strojny J, Szczudlik A. Increased plasma fibrinogen predicts one-year mortality in patients with acute ischemic stroke. *J Neurol Sci*. 2006; 246: 13-19.
20. Buck BH, Liebeskind DS, Saver JL, Bang OY, Yun SW, Starkman S, Ali LK, Kim D, Villablanca JP, Salamon N, Razinia T, Ovbiagele B. Early neutrophilia is associated with volume of ischemic tissue in acute stroke. *Stroke*. 2008 ;39:355-60.
21. Audebert HJ, Rott MM, Eck T, Haberl RL. Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. *Stroke*. 2004 ;35:2128-33.
22. Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leukocytes and the risk of ischemic diseases. *JAMA*. 1987; 257:2318-24.