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Original Article

Relationship between leukocyte and neutrophil counts and early prognosis after acute ischemic stroke

Jin Liang[1], Xinyi Gu[1], Wenbo Liu[1], Jianping Sun[1], Qiang Ma[1], Weijun Tong[2]

[1]*Department of Neurology, The Affiliated Zhongshan Hospital of Dalian University, Dalian 116001, China;*
[2]*Department of Teaching and Research Section, Institute of Epidemiology and Health Statistics, School of Public Health, Suzhou University, Suzhou 215123, China*

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Abstract: This study aims to investigate the relationship between leukocyte and neutrophil counts on admission to the hospital and early prognosis after acute ischemic stroke, in order to provide a scientific basis for improving prevention and treatment. Data were collected from 2,557 cases of acute ischemic stroke in the Affiliated Zhongshan Hospital of Dalian University from January 2009 to December 2012. The data included demographic characteristics, lifestyle-related risk factors, clinical features, and other characteristics for all the participants. The outcomes were defined by Modified Rankin scale scores (MRs) at discharge or on the 14th day. According to MRs, the subjects were divided into three groups: $0 \leq MRs \leq 2$, the control group; $3 \leq MRs \leq 5$, the disability group; $MRs = 6$, the death group; and $3 \leq MRs \leq 6$, the composite outcome group. The general conditions in the control, disability, and death groups were compared. Logistic regression analysis was used to evaluate the risk factors for short-term prognosis. Admission leukocyte count (odds ratio [OR]: 1.73) and neutrophil ratio (OR: 3.17) were related to early adverse prognosis after acute ischemic stroke. With an increase in leukocyte count and neutrophil ratio on admission, the risk of early adverse prognosis in patients increased accordingly. The leukocyte and neutrophil ratio are risk factors for early prognosis after acute ischemic stroke.

Keywords: Acute ischemic stroke, prognosis, leukocyte, neutrophil

Introduction

Globally, about 15 million new stroke events occur every year, two-thirds of which occur in people living in low- and middle-income countries. By the year 2020, stroke is projected to be the second leading cause of death and disability in developed regions of the world [1-3]. With societal aging in China, the incidence of acute ischemic stroke is rising. Demographic transition resulting from adoption of a westernized lifestyle is also likely to increase the burden of stroke in developing economies [1-3].

Given the high prevalence, disability rate, and mortality of acute ischemic stroke, prognosis has been closely evaluated. The ability to accurately predict the outcome in stroke victims is very important for clinical management [4-6], and can also be used to select specific management strategies, set realistic therapeutic goals, improve discharge planning, and anticipate the need for rehabilitation and community support [4, 5, 7].

Many studies have shown that the total leukocyte count is a marker of acute or chronic inflammation. An increase in total leukocytes is also an independent risk factor for atherosclerotic disease. Leukocytes trigger a series of reactions by phagocytes, leading to blood vessel damage and the progression of atherosclerosis.

Many studies have shown that leukocyte and neutrophil counts are independent risk factors for acute cerebral infarction [8, 9].

However, there have been few studies about the relationship between leukocyte counts and their components and early prognosis after acute ischemic stroke.

Table 1. Distribution of subtypes and outcomes

Subtypes	No outcome group		Disability group		Death group		Total
	Frequency	Percentage (%)	Frequency	Percentage (%)	Frequency	Percentage (%)	
Cerebral infaction	1455	77.72	373	19.93	44	2.35	1872
Cerebral embolism	164	63.08	81	31.15	15	5.77	260
Lacunar infarction	369	86.82	47	11.06	9	2.12	425
Total	1988	77.75	501	19.59	68	2.66	2557

In this paper, we retrospectively reviewed 2,557 cases of acute ischemic stroke and analyzed the relationship between leukocyte and neutrophil counts and early prognosis after acute ischemic stroke, in order to provide a scientific basis for prevention and treatment.

Materials and methods

Subjects

A total of 2,557 patients with acute ischemic stroke, who were hospitalized in the Neurology Department of the Affiliated Zhongshan Hospital of Dalian University from January 1, 2009 to December 31, 2012, were enrolled in this study. The subjects were surveyed with a questionnaire. This study was conducted in accordance with the Declaration of Helsinki, and with approval from the Ethics Committee of the Affiliated Zhongshan Hospital. Written informed consent was obtained from all participants.

Diagnostic criteria

1) Chinese guidelines for cerebrovascular disease prevention and treatment (2005); 2) diagnostic criteria for hypertension: systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg; 3) diagnostic criteria for high blood glucose: fasting plasma glucose > 5.6 mmol/L (110 mg/dL); and 4) diagnostic criteria for dyslipidemia: serum total cholesterol (TC) ≥ 5.72 mmol/L, triglycerides (TG) ≥ 1.7 mmol/L, high-density lipoprotein cholesterol (HDL-C) < 1.04 mmol/L, and low-density lipoprotein cholesterol (LDL-C) ≥ 4.14 mmol/L. Dyslipidemia included any abnormally elevated levels of the above lipids.

Inclusion criteria

1) Initial or recurrent acute ischemic stroke; 2) acute cerebral infarction diagnosed with computed tomography (CT) or magnetic resonance imaging (MRI); and 3) age 40 years or older.

Exclusion criteria

1) A documented history of cancer or autoimmune disease; 2) infection prior to hospitalization; 3) severe liver or kidney disease; or 4) disability or difficulty with daily activities due to any cause before the onset of acute ischemic stroke.

Study information

Demographic data, lifestyle, clinical manifestations, medical history, past history, physical examination, secondary examinations, laboratory tests, imaging results, and others. Definition of smoking: one or more cigarettes per day on average, continuously for one or more years. Definition of drinking: consumption of 50 g or more of alcohol weekly (beer and fruit wine were calculated according to equivalent alcohol content), continuously for one or more years.

Laboratory tests

Routine blood tests (XE-2100 automated blood cell analyzer, Sysmex, Japan), biochemical indices (ADVIA2400, automated biochemistry analyzer, Siemens, Germany), and blood coagulation tests (Destiny Max, automated coagulation analyzer, Trinity Biotech, Ireland) were performed within 24 h after the patients were admitted to the hospital.

Definition of outcomes

At discharge, the patients were assessed by an experienced neurologist, using the Modified Rankin scale score (MRs). If the hospital stay was longer than 14 days, the score on the 14th day would be evaluated as the outcome. If a patient survived until discharge, MRs ≥ 3 indi-

Table 2. The baseline data of patients with different outcomes

	No outcome group		Disability group		Death group	
Age[1]	1965	68.82 (10.89)	499	71.27 (10.85)*	68	75.38 (9.94)#
Gender (male)[3]	1965	1186 (60.36)	499	296 (59.32)	68	33 (48.53)
Onset-admission time (H)[2]	1965	48 (24, 96)	499	31 (7, 80)	68	19.5(4.0, 110.5)^
Hospital stay (day)[2]	1965	11 (10, 13)	499	13 (10, 16)	68	10.0 (4.5, 15.5)^
Breath (n)[1]	1965	17.76 (1.06)	499	18.13 (1.99)*	68	18.82 (3.55)#
Body temperature (°C)[1]	1965	36.48 (0.26)	499	36.54 (0.41)	68	36.55 (0.42)
Sbp (mmHg)[1]	1965	150.35 (21.40)	499	151.56 (22.82)	68	160.47 (28.41)#
Dbp (mmHg)[1]	1965	87.92 (10.99)	499	87.80 (12.46)	68	89.87 (16.13)
Heart rate (n/min)[1]	1965	76.71 (7.22)	499	78.16 (11.78)	68	82.37 (15.78)#
Blood glucose (mmol/l)[1]	1965	6.50 (2.63)	499	7.31 (3.34)*	68	7.54 (3.62)#
Cr (mmol/l)[1]	1963	78.16 (41.52)	498	78.86 (45.11)	68	101.36 (96.07)#
Urea (mmol/l)[1]	1952	6.45 (4.05)	497	6.90 (5.32)	68	9.08 (9.13)#
White blood cell count (10^9/l)[2]	1965	6.40 (5.40, 7.80)	499	7.10 (5.60, 8.90)	68	8.25 (5.80, 12.90)^
Monocyte count (10^9/l)[2]	1965	0.40 (0.30, 0.52)	499	0.41 (0.30, 0.57)	68	0.40 (0.27, 0.60)
Neutrophil ratio (%)[2]	1965	61.10 (54.50, 57.95)	499	67.50 (59.50, 75.00)	68	72.20 (62.70, 86.50)^
Thrombocytocrit (fl)[2]	1965	10.60 (10.00, 11.20)	499	10.60 (10.10, 11.20)	68	10.90 (10.00, 11.85)
Tc (mmol/l)[2]	1965	4.80 (4.065, 5.64)	499	4.77 (3.99, 5.46)	68	4.80 (3.93, 5.28)
Tg (mmol/l)[2]	1965	1.42 (1.05, 2.03)	499	1.40 (1.00, 2.02)	68	1.38 (0.99, 1.89)
Ldlc (mmol/l)[2]	1965	2.85 (2.30, 3.58)	499	2,87 (2.22, 3.50)	68	2.82 (2.26, 3.38)
hdlc (mmol/l)[2]	1965	1.13 (0.94, 1.35)	499	1.10 (0.93, 1.31)	68	1.14 (0.98, 1.38)
Tbil (umol/l)[2]	1963	15.80 (12.50, 20.00)	499	16.50 (12.80, 21.40)	68	19.50 (14.20, 24.90)^
Dbil (umol/l)[2]	1963	4.50 (2.00, 7.00)	499	4.80 (2.00, 7.60)	68	6.00 (3.70, 8.75)^
Ibil (umol/l)[2]	1963	11.0 (7.90, 15.00)	499	11.60 (7.40, 16.20)	68	12.00 (8.65, 17.45)
Blood uric acid (mmol/l)[2]	1965	318.65 (259.20, 387.05)	498	304.95 (245.00, 377.00)	68	350.60 (271.60, 420.70)^
Fb (g/l)[2]	1961	3.03 (2.61, 3.47)	499	3.17 (2.76, 3.85)	68	3.28 (2.67, 4.06)^
The history of hypertension (n, %)	1959	1442 (73.61)	499	365 (73.15)	68	45 (66.18)
The history of diabetes mellitus (n, %)	1953	616 (31.54)	496	194 (39.11)	68	27 (39.71)&
The history of heart disease (non-atrial fibrillation) (n, %)	1951	183 (9.38)	495	59 (11.92)	68	12 (17.65)&
The history of atrial fibrillation (n, %)	1950	138 (7.08)	494	67 (13.56)	68	18 (26.47)&
The history of stroke (n, %)[3]	1963	522 (26.59)	499	153 (30.66)	68	25 (36.76)&
The history of smoking (n, %)[3]	1962	254 (12.95)	498	46 (9.24)	68	14 (20.59)&
The history of drinking (n, %)[3]	1961	149 (7.60)	498	19 (3.81)	68	6 (8.83)&

Notes: Missing value is existence in the no outcome group and disability group. [1]indicate that when the variable is normal distribution of measurement data, we count the mean value and standard deviation in every group. [2]indicate that when the variable is not normal distribution of measurement data, we count the median and range interquartile in every group. [3]indicate that when the variable is enumeration data, we count the constituent ratios in every group. *The disability group was significantly different from the non-outcome group ($P < 0.05$); #The death group was significantly different from the non-outcome group ($P < 0.05$); ^Population distribution is different in the 3 groups, $P < 0.05$; &Constituent ratio is different in the 3 groups, $P < 0.05$.

Table 3. Distribution of leukocyte count, mononuclear count, neutrophils ratio

	Non-outcome group	%	Composite outcome group	%	*P*
Leukocyte count					< 0.0001
≤ 5.45	510	25.95%	123	21.69%	
5.45~6.60	512	26.06%	110	19.40%	
6.60~8.10	521	26.51%	120	21.16%	
≥ 8.10	422	21.48%	214	37.74%	
Mononuclear count					0.0084
≤ 0.30	447	22.75%	144	25.40%	
0.30~0.40	499	25.39%	115	20.28%	
0.40~0.54	544	27.68%	142	25.04%	
≥ 0.54	475	24.17%	166	29.28%	
Neutrophils ratio					< 0.0001
≤ 55.60	555	28.24%	79	13.93%	
55.60~62.40	519	26.41%	109	19.22%	
62.40~70.00	495	25.19%	133	23.46%	
≥ 70.00	396	20.15%	246	43.39%	

cated disability. If a patient died, the cause of death would be determined by the Identification Committee of our hospital. The attending physician filled out a registration form for death cases and a death certificate, and death-related information in a case report form. Disability or death was defined as a composite outcome.

Statistical analysis

We established a database with EpiData3.1 software. The database was separately verified twice by professional staff. Inconsistent data, once identified, would be corrected by specified personnel according to the original questionnaire. A score of 0 ≤ MRs ≤ 2 was categorized as the control (no outcome) group, 3 ≤ MRs ≤ 5 was the disability group, and MRs = 6 was the death group; 3 ≤ MRs ≤ 6 was the composite death and disability outcome group. We compared the general conditions of patients in the control, disability, and death groups. Analysis of variance was used for continuous data with normal distribution. A nonparametric test was used for data with skewed distribution. Counted data were compared with the chi-square test. Univariate and multivariate logistic regression analyses were applied to calculate the odds ratio (OR) and 95% confidence interval (95% CI) for different risk factors when the composite group was compared with the control group. Composite outcome was defined as a dependent variable, and some variables, including age, onset-admission time, hospital stay (days), body temperature (°C), history of stroke, and blood glucose, were defined as independent variables. SAS9.2 software was applied for statistical analysis. Two-tailed $P < 0.05$ indicated a significant difference.

Results

Distribution of subtypes and outcomes

A total of 2,557 cases of acute ischemic stroke were recruited in this study. The control group included 1,988 cases (77.75%), with a mean age of 68.82 ± 10.89 years. The disability group included 501 cases (19.59%), with a mean age of 71.27 ± 10.85 years. Sixty-eight patients (2.66%) died; their mean age was 75.38 ± 9.94 years. A total of 569 cases (22.25%) had composite outcomes (**Table 1**).

Baseline data

The baseline data for patients with different outcomes included the following information: age, gender, onset-admission time (H), hospital stay, body temperature, SBP, DBP, heart rate, blood glucose level, blood urea level, serum creatinine level, white blood cell count, monocyte count, neutrophil ratio, thrombocytocrit, TC level, TG level, LDL-C level, HDL-C level, total bilirubin level, direct bilirubin level, indirect bilirubin level, uric acid level, fibrinogen level, history of hypertension, history of diabetes melli-

Table 4. Multivariate analysis of the leukocyte count, neutrophils ratio associated with composite outcomes of acute ischemic stroke. Non-conditional logistic analysis

	B	S.E.	Wald	OR	OR 95% CI	*P*
Leukocyte count						
≤ 5.45	-	-	76.4332	-	-	
5.45~6.60	-0.1424	0.1505	0.8956	0.87	0.65~1.66	0.3440
6.60~8.10	-0.1223	0.1472	0.6899	0.88	0.66~1.18	0.4062
≥ 8.10	0.5463	0.1378	15.7223	1.73	1.32~2.26	< 0.0001
Continuous	0.1862	0.0456	16.6888	1.20	1.10~1.32	< 0.0001
Neutrophils ratio						
≤ 55.60	-	-	111.3961	-	-	
55.60~62.40	0.3224	0.1649	3.8234	1.38	1.00~1.91	0.0505
62.40~70.00	0.4734	0.1604	8.7116	1.60	1.17~2.20	0.0032
≥ 70.00	1.1529	0.1521	57.4925	3.17	2.35~4.27	< 0.0001
Continuous	0.3808	0.0481	62.5991	1.46	1.33~1.61	< 0.0001

tus, history of heart disease (other than atrial fibrillation), history of atrial fibrillation, history of stroke, smoking, and drinking.

The disability group was significantly different from the non-outcome group in mean age and fasting plasma glucose ($P < 0.05$). The death group and the non-outcome group were significantly different in mean age, fasting plasma glucose, SBP, heart rate, serum creatinine, and uric acid ($P < 0.05$). The three groups were significantly different in the distribution of onset-admission time, hospital stay, white blood cell count, neutrophil ratio, total bilirubin, direct bilirubin, urea, and fibrinogen ($P < 0.05$). The three groups were significantly different in the constituent ratio of the history of diabetes, atrial fibrillation, stroke, smoking, and drinking ($P < 0.05$) (**Table 2**).

Distribution of leukocyte count, mononuclear count, and neutrophil ratio

On admission, in the composite outcome group, the number of patients with a leukocyte count 0-5.45 × 10^9/L was 123, and the ratio was 21.69%; the number of patients with a leukocyte count ≥ 8.1 × 10^9/L was 214, and the ratio was 37.74%. There were significant differences between the two subgroups ($P < 0.0001$).

The number of patients with a neutrophil ratio 0-0.556 was 79, and the ratio was 13.93%; the number of patients with a neutrophil ratio ≥ 0.7 was 246, and the ratio was 43.39%. There were significant differences between the two subgroups ($P < 0.0001$) (**Table 3**).

Multivariate analysis

On multivariate analysis, compared with the group of patients with leukocyte count on admission of 0-5.45 × 10^9/L, the group with leukocyte count on admission ≥ 8.1 × 10^9/L had 1.73 times the risk of an early adverse prognosis. The risk of early adverse prognosis during the period of hospitalization in patients with a neutrophil ratio on admission ≥ 0.70 was 3.17 times greater than that in patients with a neutrophil ratio between 0-0.556. Trend testing showed that with an increased leukocyte count and neutrophil ratio on admission, the risk of early adverse prognosis increased accordingly ($P < 0.0001$) (**Table 4**).

Discussion

Many studies have shown that total leukocyte count is a marker for acute or chronic inflammation. An increase in total leukocytes is also an independent risk factor for atherosclerotic disease. Leukocytes trigger a series of reactions by phagocytes, leading to blood vessel damage and the progression of atherosclerosis. Many studies have shown that leukocyte and neutrophil counts are independent risk factors for acute cerebral infarction and acute myocardial infarction [8, 9].

However, there have been few studies about the relationship between leukocyte counts and their components and early prognosis after acute ischemic stroke. Large-sample research is especially lacking in China. This research showed that when we adjusted for age, onset-admission time, hospital stay, body temperature, blood glucose, and history of stroke, the leukocyte count (OR: 1.73) and neutrophil ratio (OR: 3.17) correlated with early adverse prognosis after acute ischemic stroke. With an increase in leukocyte count and neutrophil ratio on admission, the risk of early adverse

prognosis increased accordingly. Results showed that the leukocyte count in the study group was significantly higher than in the control group.

On multivariate analysis, compared with the group with a leukocyte count on admission of 0-5.45 × 10^9/L, the risk of early adverse prognosis was 1.73 times greater in the group with a leukocyte count on admission of ≥ 8.1 × 10^9/L. The risk of early adverse prognosis during the period of hospitalization in patients with a neutrophil ratio on admission ≥ 0.70 was 3.17 times greater than that in patients with a neutrophil ratio between 0-0.556. Trend testing showed that with an increased leukocyte count and neutrophil rate on admission, the risk of early adverse prognosis in patients increased accordingly ($P < 0.0001$). The results indicate that leukocyte count and neutrophil ratio on admission can be used as adverse outcome predictors in patients hospitalized with acute cerebral infarction.

Other authors showed similar results [10]. Furlan [11] conducted a study on 170 cases with acute cerebral infarction from 2003 to 2008, and found that for every increase of 1 × 10^9 in leukocyte count on admission, the risk of stroke leading to disability at discharge was 1.04 times greater (95% CI 1.07-1.10; $P < 0.0001$), and that mortality at 30 days also increased (risk ratio 1.07, 95% CI 1.05-1.08; $P < 0.0001$). Survival curves showed that an increased leukocyte count worsened the 30-day mortality in patients with acute ischemic stroke.

Elkind [12] conducted a prospective cohort study in an urban population in the USA. The risk of poor prognosis during the period of hospitalization was 1.75 times greater for the highest vs. the lowest quartile of acute ischemic stroke patients. The study found that elevated leukocyte count can be used as a predictor of poor prognosis in acute cerebral infarction.

Nardi [13] studied the National Institutes of Health Stroke Scale (NIHSS) score within 12 and 72 hours of stroke onset, and the MRs score on discharge, and found that an elevated leukocyte count on admission is an independent risk factor for poor prognosis in acute cerebral infarction patients. Neutrophils played the same role [14].

Grau [15] conducted a study on 18,558 cases of cerebral ischemic stroke, myocardial infarction, and peripheral arterial disease. Patients were stratified according to quartiles of leukocyte count on admission. Multivariate analysis showed that for the highest versus the lowest quartile of acute ischemic stroke patients, the risk of poor prognosis during the period of hospitalization was 1.3 times greater. The study found that elevated leukocyte count on admission can be used as a predictor of poor prognosis in acute cerebral infarction. Leukocyte count was positively correlated with poor prognosis in acute cerebral infarction.

The causes may be found early after the acute onset of cerebral infarction. Due to reasons such as tissue edema, the deformation capacity of leukocytes decreases significantly, and functions of adhesion and aggregation increase significantly, inducing cerebral microcirculation disorders and limiting collateral circulation. Leukocyte adhesion to the surface of vascular endothelial cells causes formation of small emboli, blocks small vessels, induces a microcirculatory disorder, and a decrease in cerebral blood flow. Two types of leukocytes adhere to the surface of vascular endothelial cells and activate each other in brain tissue; this results in generation and release of oxygen free radicals, vasoactive substances such as leukotrienes, and platelet activating factors, in turn decreasing endothelial cell viability, inducing platelet aggregation and vasoconstriction, and directly damaging brain cells. At the same time, these substances damage the blood-brain barrier, further worsening brain edema, resulting in more severe brain injury [16, 17].

However, another large sample multivariate analysis showed that elevated leukocyte count on admission may be an expression of inflammation and the intensity of a stress reaction, reflecting the severity of tissue damage. There is no single factor with a direct and leading role in the pathophysiology of stroke [18]. Another study showed that increased leukocyte counts in patients with recurrent stroke do not increase the risk of a poor prognosis [19]. Thus, the relationship between leukocytes and neutrophils and early prognosis after acute ischemic stroke should be studied further. This study adjusted for the influence of factors that may affect the prognosis in patients with cerebral infarction,

including age, onset-admission time, hospital stay, body temperature, blood glucose, and history of stroke. The study found that elevated leukocyte count and neutrophil ratio can be used as predictors of poor prognosis in acute cerebral infarction.

This study had limitations. It was a retrospective study, and only analyzed cases with short-term outcome data. A comprehensive study on the relationship between leukocyte count and neutrophil ratio and early prognosis after acute ischemic stroke requires a long-term prospective cohort study. Research is ongoing.

In conclusion, this study showed that leukocyte count and neutrophil ratio on admission are associated with and predictive of early poor prognosis after acute ischemic stroke. Moreover, the determination method is simple and convenient.

Disclosure of conflict of interest

None.

Address correspondence to: Qiang Ma, Department of Neurology, The Affiliated Zhongshan Hospital of Dalian University, No. 6 Jiefang Street, Dalian 116001, China. Tel: +86 411 62893579; E-mail: qiangmacn@126.com

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