

## Predicting new silent cerebral infarction after intracerebral hemorrhage using serum white blood cell count

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### Abstract

**Background:** It has been confirmed that incidental silent cerebral infarctions (SCIs) found in healthy people may be risk factors for cerebrovascular diseases such as strokes and vascular dementia. The prospective study aimed to determine the utility of baseline serum white blood cell (WBC) counts to predict the emergence of new SCI after intracranial hemorrhage (ICH).

**Methods:** This is a prospective study. From January 2016 to December 2017, we recruited 171 patients admitted to the neurology department of the Affiliated Shuyang Hospital of Xuzhou Medical University with a first episode of ICH. Serum WBC count was measured on admission. SCI was detected by cranial magnetic resonance imaging (MRI) 14 days after the onset of the ICH. Receiver operating characteristic curve analysis was used to calculate the most appropriate cut-off values of the WBC count for differentiating patients with and without SCI at the end of the study period.

**Results:** New SCIs were detected in 28.07% of patients by cranial MRI. Multivariate logistic regression analysis showed that cerebral microbleeds (CMBs), raised WBC counts, and leukoaraiosis were independent risk factors for SCI. The most appropriate cut-off WBC count differentiating the two groups was  $7.65 \times 10^9/L$  (sensitivity: 77.08%, specificity: 63.41%).

**Conclusion:** Elevated levels of serum WBC counts in patients with ICH are associated with SCI. There is potential value in using serum WBC counts to predict new SCI after an acute hemorrhagic stroke.

**Keywords:** Cerebral infarction, Intracerebral hemorrhage, WBC count, Cerebral microbleed, Silent cerebral infarction.

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**D**iffusion weighted imaging (DWI) within 30 days of the onset of a spontaneous intracranial hemorrhage (ICH) can often find new silent cerebral infarctions (SCIs), which are mostly distributed in the subcortical and cortical areas. Some studies showed that 11.1–41.0% of patients who had undergone DWI during the acute stage of the ICH or within one month of its onset had SCIs (1, 2). It has been confirmed that incidental SCIs found in healthy people can be used to predict the development of cerebrovascular diseases such as strokes and vascular dementia (3, 4). In studies of ischemic strokes, SCIs appearing in the early stage of the disease were associated with increased risk of stroke recurrence, transient ischemic attacks (TIAs), and death due to vascular events (5). White blood cells (WBCs) make up part of the body's defense system. Physiologic elevation is most common after heavy meals and strenuous exercise. Pathologic elevation is common with infection, inflammation, and tissue necrosis.

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After ICH, the blood-brain barrier is damaged and WBCs infiltrate into the surrounding area of the hematoma (6). The infiltrated WBCs release pro-inflammatory cytokines, activate microglia, and further damage the blood-brain barrier (7). In recent years, the correlation between serum WBC counts and acute cerebrovascular diseases has been repeatedly demonstrated. Some researchers have found that the severity of neurological damage after ICH was directly proportional to elevated WBC count (8, 9). In our previous study of new SCIs following acute non-cerebral amyloid angiopathy (CAA), ICH independently correlated with elevated WBC count (10). Some scholars believe that the treatment of cerebrovascular diseases can significantly improve the prognosis after onset of the disease by reducing WBC counts (11).

The importance of predicting new SCIs after hemorrhagic strokes in clinical settings needs to be well established. To our knowledge, there are few data evaluating the ability to predict SCIs in patients with ICH using serum WBC counts. Therefore, the aim of the present study was to determine the ability of WBC counts to predict new SCIs following ICH.

## Methods

A total of 171 patients with ICH who were admitted to the neurology department of the Affiliated Shuyang Hospital of Xuzhou Medical University, in Shuyang, Jiangsu, China between January 2016 and December 2017 were considered for inclusion in our prospective study. The protocol was approved by the Academic Committee and Ethics Committee of our hospital (2015-SY-IRB-054). Written informed consent was obtained by all patients and/or their authorized signatories.

**Inclusion criteria:** We included patients with a first episode of acute ICH, whose diagnosis and neurological deficit scores were based on the criteria and scoring standards established by the Fourth National Conference on Cerebrovascular Diseases in 1996 and were confirmed using computed tomography (CT) or cranial magnetic resonance imaging (MRI). New SCIs were confirmed by MRI. The positions of hematoma including basal ganglia, thalamus, brainstem and cerebellum. Treatment of ICH strictly followed the guidelines for management of spontaneous intracerebral hemorrhage in 2015 (12).

**Exclusion criteria:** The exclusion criteria were as follows: clearly identifiable cerebral infarction or embolism;

symptomatic cerebral infarction after intracerebral hemorrhage; taking drugs that affect WBC; hemorrhagic cerebral infarction; recent active bleeding, bleeding disorders, or bleeding tendency; severe heart, liver, or kidney dysfunction; uncontrolled infectious diseases such as pneumonia, sepsis at or before onset; hematological diseases; platelet count  $< 100 \times 10^9/L$  or fibrinogen  $< 1.0$  g/L; recent surgical or traumatic injuries; obvious surgical indications such as cerebral lobe or shell nucleus hemorrhage  $> 30$  mL, cerebellar hemisphere hemorrhage  $> 15$  mL, and drainage for ventricular casting; definite vascular lesions such as aneurysm, arteriovenous malformations or cavernous hemangioma; and those with family members requiring craniotomy. ICHs likely caused by CAA were excluded based on the modified Boston standard criteria (13).

Boston Criteria for Diagnosis of CAA-Related Hemorrhage

### 1. Definite CAA

Full postmortem examination demonstrating:

- Lobar, cortical, or cortico-subcortical hemorrhage
- Severe CAA with vasculopathy†
- Absence of another diagnostic lesion

### 2. Probable CAA with supporting pathology

Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) demonstrating:

- Lobar, cortical, or cortico-subcortical hemorrhage
- Some degree of CAA in specimen
- Absence of another diagnostic lesion

### 3. Probable CAA

Clinical data and MRI or CT demonstrating:

• Multiple hemorrhages restricted to lobar, cortical, or cortico-subcortical regions (cerebellar hemorrhage allowed)

- Age  $\geq 55$  years
- Absence of other cause of hemorrhage

### 4. Possible CAA

Clinical data and MRI or CT demonstrating:

- Single lobar, cortical, or cortico-subcortical hemorrhage
- Age  $\geq 55$  years
- Absence of other cause of hemorrhage

**Data collection:** General clinical data, laboratory data, and imaging data were collected. Blood samples were taken upon presentation to hospital. The severity of the neurological impairment at the time of admission was evaluated using the National Institutes of Health Stroke Scale and the Glasgow Coma Scale. All patients were diagnosed with ICH on head CT examination within 3 days of admission, and head MRI

(Germany Siemens 3.0T MR) examination was performed on the 14th day after the onset of the ICH to detect new SCIs. MRI examination included T1-weighted, T2\*-weighted, DWI, and susceptibility-weighted imaging (SWI) sequences. All scans were performed by skilled radiologists, and image information, including SCI depicted by a high signal on DWI sequence, CMBs, and leukoaraiosis, were reported by two radiologists blinded to the clinical information.

**SCIs, CMBs, leukoaraiosis definitions and normal range of WBC:** SCI was defined as a high-signal intensity lesion on DWI with accompanying low-signal intensity on apparent diffusion coefficient (ADC). High-signal intensity lesions in the region of the hematoma and surrounding tissue were excluded (14). The asymptomatic state was defined as the absence of new symptoms such as abnormal sensation, limb weakness, or deterioration of the baseline nervous system function (15). CMBs were defined as circular and quasi-circular signal-reduction shadows with diameters of 2–5 mm on SWI with clear boundaries; no surrounding edema; and the exclusion of calcification, peripheral space, and venules (16, 17). Cerebral leukoaraiosis was defined as long spots, plaques, or fused long-T2 signal images of the white matter around the ventricle or the central part of the hemi-ovoid circle (18, 19). Normal WBC counts were measured using flow cytometer (Sysmex Corporation, Japan) and ranged from 4 to  $10 \times 10^9/L$ .

**Statistical analysis:** Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 17.0 (IBM, Armonk, NY, USA). Continuous

variables were expressed as mean±standard deviation and were analyzed using the independent-samples t-test. Categorical data, shown as count and percentage, were analyzed using either the chi-square test or the Fisher's exact test. Multivariate logistic regression analysis was used to determine the predictors of SCI. Receiver operating characteristic (ROC) curves were plotted and used to calculate the most appropriate cut-off values of WBC counts to differentiate patients with and without SCI. Two-tailed p values of < 0.05 were considered statistically significant.

## Results

1. Of the 171 patients with ICH, 48 (28.07%) were found to have SCI. Patients with SCI had lower levels of urea nitrogen ( $P=0.047$ ), higher WBC counts ( $P=0.000$ ), a higher number of CMBs ( $P=0.001$ ), increased leukoaraiosis severity ( $P=0.005$ ), and a higher number of lacunar infarctions ( $P=0.001$ ) than patients without SCI (table 1).

2. Multivariate logistic regression analysis showed that the presence of CMBs ( $P=0.021$ ), high WBC counts ( $P=0.000$ ), and the presence of leukoaraiosis ( $P=0.019$ ) were independent risk factors for SCI (table 2).

3. The most appropriate cut-off value used to differentiate the two groups was  $7.65 \times 10^9/L$  for WBC counts; the sensitivity and specificity of WBC counts were 77.08% and 63.41%, respectively; the area under the curve (AUC) was 0.736. The predictive ability of WBC counts was significant ( $P=0.000$ ) (table 3, figure 1).

**Table 1. Characteristics of patients with and without silent cerebral infarction**

Characteristic	NO SCI (123)	SCI (48)	t/ $\chi^2$ -value	P-value
Age (year)	60.15±11.42	63.18±9.52	1.631	0.105
Gender n			0.477	0.490
Male	83(67.48)	35(72.92)		
Female	40(32.52)	13(27.08)		
Hypertension n (%)	106 (86.18)	40 (83.33)	0.506	0.775
Diabetes n (%)	13(10.57)	10(20.83)	3.125	0.086
Smoking n (%)	57 (46.34)	23 (47.92)	0.034	0.853
Drinking n (%)	56 (45.53)	27 (56.25)	1.589	0.207
Leukoaraiosis n (%)	29 (23.58)	24 (50.00)	11.27	0.001
Atrial fibrillation n (%)	6 (4.87)	2 (4.17)	0.039	0.843
Coronary heart disease n (%)	6 (4.87)	4 (8.33)	0.749	0.387
Stroke history n (%)	33(26.19)	8(16.67)	1.956	0.162
Glucose mmol/L	7.11±2.07	7.19 ±2.59	0.231	0.818
Hematoma volume ml	11.73±10.39	10.78 ± 11.04	0.526	0.600
Systolic blood pressure mmHg	163.98±26.27	168.13±25.28	0.938	0.350

Diastolic blood pressure mmHg	97.07 ±17.82	98.33 ± 14.16	0.439	0.661
NIHSS score at admission	8.44±6.88	8.25±6.99	0.161	0.873
Glasgow Coma Score	13.76±2.60	14.08±2.04	0.763	0.447
Total bilirubin μmol/L	12.23±5.29	11.28 ±6.76	0.972	0.333
Direct bilirubin μmol /L	2.29±1.23	2.32±1.46	0.1	0.921
Cholesterol mmol/L	4.63±0.87	4.57±1.08	0.38	0.704
Triglyceride mmol/L	1.67 ±1.26	1.52 ±0.91	0.764	0.446
High-density lipoprotein mmol/L	1.17±0.29	1.20±0.32	0.55	0.583
Low-density lipoprotein mmol/l	2.29±0.60	2.44±0.71	1.379	0.170
Blood urea nitrogen mmol/l	5.44±1.66	4.86 ±1.78	1.997	0.047
Creatinine μmol /l	67.88±40.17	63.35±12.16	0.754	0.452
D dimer mg/L	0.21±0.252	0.24±0.21	0.349	0.728
White blood cell 10 <sup>9</sup> /L	7.29±1.96	8.79±1.63	2.874	0.000
fibrinogen g/L	3.13±0.88	3.42±0.99	1.879	0.062
C-reactive protein mg/L	6.48 ±6.38	5.95±4.69	0.433	0.666
Pneumonia after admission n (%)	18 (14.63)	12 (25.00)	2.565	0.121
Cerebral microbleed n (%)	48 (39.02)	32 (66.67)	10.596	0.001
Lacunar infarction n (%)	69 (56.09)	38 (79.17)	7.846	0.005

SCI, silent cerebral infarction; NIHSS, National Institute of Health stroke scale.

**Table 2. Multivariate logistic regression analysis showing that the presence of cerebral microbleeds, high white blood cell counts, and the presence of leukoaraiosis are independent risk factors for silent cerebral infarction**

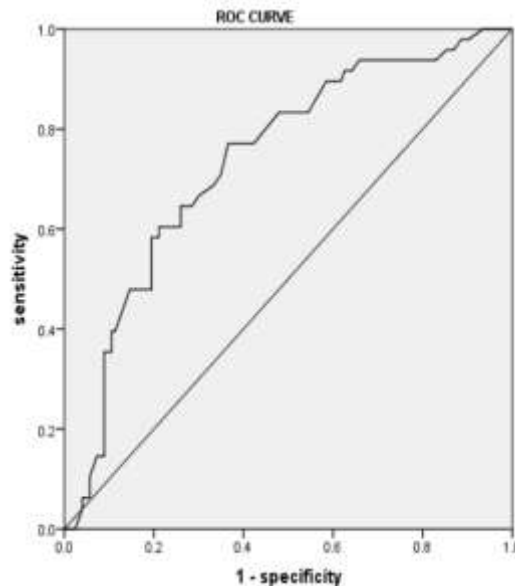
Factor	OR-value	95% CI	P-value
Cerebral microbleed	3.025	1.186–7.715	0.021
Blood urea nitrogen	0.788	0.617–1.005	0.055
White blood cell	1.635	1.308–2.043	0.000
Leukoaraiosis	3.917	1.194–7.602	0.019
Lacunar infarction	1.163	0.396–3.419	0.783

OR, odds ratio; CI, confidence interval.

**Table 3. AUC, Cutoff, Sensitivity, Specificity of WBC count.**

tems	AUC	95%CI	P-value	Cutoff	Sensitivity	Specificity
WBC	0.736	0.654-0.818	0.000	7.65×10 <sup>9</sup> /L	77.08	63.41

WBC, white blood cell.



### Figure 1. Receiver operating characteristic curve of WBC count

(WBC, white blood cell; ROC, receiver operating characteristic)

## Discussion

The presence of CMBs, high WBC counts, and the presence of leukoaraiosis were independent risk factors for SCI. WBC more than  $7.65 \times 10^9/L$  were the best cutoff value to predict new SCI. We speculate that interventions that reduce WBC counts or block their inflammatory cascades may improve outcomes in patients with ICH. An elevated WBC count after ICH is common. Related literature has reported that the WBC count in patients with ICH reached a peak on day three following the onset of the ICH and gradually decreased and reached a normal range after 1 -2 weeks from the onset of the ICH (7).

The main causes of the elevated WBC count after ICH are as follows: 1) The compression of the hematoma after ICH leads to swelling of brain tissue. This increased intracranial pressure results in endocrine changes in the hypothalamus-pituitary axis, an increase in cortisol hormone, and leucocyte proliferation. 2) The hematoma formed after ICH stimulates a stress response that promotes WBC proliferation.

We found that WBC counts were elevated in patients who developed new SCI after ICH when compared to those that did not develop SCI. This suggests that higher levels of WBC may lead to new SCI after ICH. We also found that CMBs and leukoaraiosis were significantly associated with new SCIs. Both usually indicate severe small-vessel diseases in patients with ICH. On the basis of severe cerebral small-vessel diseases, the soluble intercellular adhesion molecule-1 (sICAM-1) found in blood can cause WBCs to adhere to blood vessel walls (20), form WBC plugs that occlude blood vessels (21), affect local blood circulation, and cause tissue ischemia and hypoxia. In addition, WBCs can secrete vasoconstricting substances, further aggravating the vasoconstriction and tissue ischemia (22). Research suggested that the increased WBC counts after ICH could significantly increase mortality (23, 24). A study (25) confirmed that increased WBC counts were closely related to early mortality.

Many studies evaluating the prognosis of ICH have been carried out. The role of inflammation in the pathophysiological changes in ICH has gradually been recognized. Some scholars believe that treatments for cerebrovascular diseases that reduce WBC counts may

significantly improve the prognosis of patients with ICH (11). Therefore, we speculated that a reduction in WBC counts may reduce the incidence of SCI, thereby reducing the mortality rate in patients with ICH. Thus, it is possible to improve the prognosis of patients by determining the appropriate WBC count that allows for early detection and intervention of SCIs. Our study showed a suitable critical WBC cut-off value of  $7.65 \times 10^9/L$ , which has an acceptable sensitivity and specificity. Future interventions that reduce WBC counts or block their inflammatory cascades should be investigated to improve outcomes in patients with ICH. Except chemotherapy, receptor blockers of TNF- $\alpha$  and IL-1 $\beta$  maybe be used to improve outcomes.

## Conclusion

Although WBC can provide valuable information used to predict the occurrence of new SCI after acute ICH, its predictive ability is low. Further prospective studies are required to determine how to improve this predictive value and to determine whether there is a better predictor. WBC values higher than  $7.65 \times 10^9/L$  on admission in patients with acute ICH may predict new SCI.

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**Conflict of Interests:** The authors declare that they have no competing interests.

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