


# Predictive Values of White Blood Cell Count in Peripheral Blood at Admission on In-Hospital Complications and 90-Day Outcomes of Patients with Aneurysmal Subarachnoid Hemorrhage: Insights from the LongTEAM Registry

Runting Li <sup>1</sup>, Yuanli Zhao<sup>1-4</sup>, Xiaolin Chen<sup>1,3,4</sup>, Qiang Hao<sup>1</sup>

<sup>1</sup>Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, Beijing, People's Republic of China; <sup>2</sup>China National Clinical Research Center for Neurological Diseases, Beijing, People's Republic of China; <sup>3</sup>Stroke Center, Beijing Institute for Brain Disorders, Beijing, People's Republic of China; <sup>4</sup>Beijing Key Laboratory of Translational Medicine for Cerebrovascular Disease, Beijing, People's Republic of China

Correspondence: Qiang Hao; Xiaolin Chen, Department of Neurosurgery, Beijing Tiantan Hospital, Capital Medical University, No. 119 South Fourth Ring West Road, Fengtai District, Beijing, 100070, People's Republic of China, Email haoqiang713@163.com; chenxiaolin@bjtth.org

**Purpose:** This study aimed to explore the relationship between white blood cells (WBCs) at admission and clinical outcomes in patients with aneurysmal subarachnoid hemorrhage (aSAH).

**Patients and Methods:** We analyzed data from patients with aSAH between January 2015 and September 2021 who were included in the LongTEAM (Long-term Prognosis of Emergency Aneurysmal Subarachnoid Hemorrhage) registry study. WBC is classified into four groups according to the quartile. We used the logistic model for in-hospital complications, mortality, modified Rankin scale (mRS) at discharge and 90 days to examine the relationship between WBC and clinical outcomes. We used WBC levels near odds ratio (OR) = 1 (Q1) in restricted cubic splines as the reference to evaluate whether there is a nonlinear relationship between WBC and clinical outcomes. Another Kaplan–Meier method was used to analyze the relationship between WBC levels and the risk of developing pneumonia.

**Results:** Of the 988 patients included, the results showed that compared with patients in the Q1 group, patients in the highest quartile (Q4) had an increased incidence of 90-day unfavorable outcomes after adjusting the confounders (adjusted OR = 1.81, 95% CI = 1.02–3.20,  $p = 0.042$ ), which may be caused by the increased incidence and risk of pneumonia (adjusted OR = 2.06, 95% CI = 1.30–3.29,  $p = 0.002$ ; adjusted hazard ratio [HR]=1.63, 95% CI = 1.13–2.36,  $p < 0.001$ ). The restricted cubic spline indicated that the incidence of developing pneumonia and 90-day unfavorable outcomes rises with increasing WBC levels ( $p$  for nonlinear = 0.135 and 0.113).

**Conclusion:** Patients with higher WBC at admission were associated with an increased incidence of 90-day unfavorable outcomes, which might be related to pneumonia.

**Keywords:** aneurysmal subarachnoid hemorrhage, white blood cell, pneumonia, functional outcome

## Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a common neurological emergency with high mortality and disability.<sup>1,2</sup> Researchers believe early brain injury (EBI) might be responsible for severe complications after aneurysm rupture, leading to poor patient outcomes.<sup>3</sup> Within 72 hours after aneurysm rupture, the brain will undergo various pathophysiological events such as energy failure, ionic changes, increased endothelin-1, depletion of nitric oxide, inflammation, oxidative stress, etc.<sup>4,5</sup> Among these events, the inflammatory response after bleeding has always been the research hot spot.

Like many other diseases, aSAH has been demonstrated as a state of systemic inflammation and immunosuppression.<sup>6</sup> Our previous study developed a prognostic model named “TAPS” for aSAH that included white blood cells (WBCs) at admission, further emphasizing preoperative inflammation’s impact on prognosis.<sup>7</sup> WBC is the most abundant immune cell in peripheral blood and can reflect the systemic inflammatory status. Up to now, little is known about how early abnormal WBC levels contribute to unfavorable outcomes, even though three studies indicated that delayed cerebral ischemia (DCI) might be the potential cause.<sup>8–10</sup> However, considering the limited clinical evidence available, we hypothesized that other complications could also be involved in the poor prognosis of patients mediated by abnormal WBC levels. Therefore, in this study, we aimed to divide WBC at admission into four groups according to the quartile to analyze the relationship between WBC and different clinical outcomes in aSAH patients.

## Materials and Methods

### Study Design

All patient data between January 2015 and September 2021 were drawn from the LongTEAM registry study (Registration No. NCT 04785976), a large, single-center, observational cohort conducted at Beijing Tiantan Hospital in China. In this study, all patients had angiographically documented aneurysms with subarachnoid hemorrhage (SAH), which were confirmed by either computed tomography or lumbar puncture. We set the inclusion criteria as follows: (1) age  $\geq 18$  years old; (2) emergency admission; (3) single aneurysm; (4) treated with surgical clipping or endovascular coiling; (5) less than 72 hours from the rupture to the admission and less than 72 hours from the admission to treatment; (6) complete 90-day follow-up. The main exclusion criteria were as follows: (1) previous SAH; (2) history of neurosurgery due to any reasons; (3) physical disability due to any previous disease; (4) treatment including external ventricular drainage, lumbar puncture, angiography, intubation, and/or mechanical ventilation at other hospitals before presentation to our hospital; (5) missing data, including medical records, radiological, and laboratory information.

This study was approved by the Institutional Review Board of Beijing Tiantan Hospital (KY 2021–008-01). Informed consent for clinical analysis was obtained from all individual participants or their authorized representatives. All the analysis was performed according to the Declaration of Helsinki and the local ethics policies. All patients were managed according to the guidelines.<sup>11</sup>

### Data Collection

We gathered patient baseline data on (1) demographics, including age and sex; (2) medical history, including hypertension, hyperlipidemia, diabetes mellitus, and heart disease; (3) lifestyle risk factors, including current smoking and drinking; (4) location and size of aneurysm; (5) early seizures, early loss of consciousness; (6) clinical status, including World Federation of Neurological Societies (WFNS) grade; (7) first CT-related information, including modified Fisher scale (mFS), Graeb score, Subarachnoid Hemorrhage Early Brain Edema Score (SEBES), and acute hydrocephalus; (8) laboratory examination, including WBC count (normal range:  $[3.5–9.5] \times 10^9/L$ ), neutrophil-to-lymphocyte ratio (NLR); (9) treatment modality, including surgical clipping and endovascular coiling.

Besides, we collected eleven in-hospital complications such as cardiac event, DCI, intracranial infection, stress ulcer bleeding, urinary tract infection, anemia, hypoproteinemia, pneumonia, muscular calf vein thrombosis (MCVT), deep vein thrombosis (DVT), and lipid metabolism disorder. [Supplementary Table 1](#) shows the detailed diagnostic criteria for the associated complications.

### Outcome Assessment

The primary outcome was the modified Rankin scale (mRS) at 90 days after discharge (the neurosurgeon followed up with patients via telephone or an outpatient appointment). We defined the unfavorable outcome as mRS score  $\geq 3$ . The secondary outcomes were the occurrence of in-hospital complications, mortality at discharge, and unfavorable outcomes at discharge.

## Statistical Analysis

WBC was classified into four groups according to the quartile. Categorical variables were presented as percentages and continuous variables as mean with standard deviation (normal distribution) or median with interquartile range (IQR) (skewed distribution). One-way ANOVA with post hoc (Bonferroni correction factor) analysis was applied to compare the baseline characteristics of four groups. The relationship between baseline WBC levels and in-hospital complications, mortality, and outcomes was estimated by a logistic model, using restricted cube bar graphs of WBC levels near odds ratio (OR) = 1 (Q1) as the reference. Adjusted ORs with their 95% confidence intervals (CIs) were estimated for each quartile of the WBC level. For each outcome, two multivariable models were constructed. In Model 1, we only adjusted the variables for age, sex, and treatment modality. In Model 2, we additionally adjusted for early loss of consciousness, WFNS grade 4–5, mFS grade 3–4, Graeb score 5–12, SEBES score 3–4, acute hydrocephalus, and neutrophil-to-lymphocyte ratio.

Besides, we evaluated the pattern and magnitude of associations between the WBC levels at admission and the risk of outcome events by constructing logistic regression models with restricted cubic splines for WBC levels (continuous variable), adjusting for all potential covariates (Model 2). The Q1 of the WBC level was treated as the reference, and five knots for the spline were placed at the WBC level's 5th, 25th, 50th, 75th, and 95th percentiles.

The hazard ratio (HR) with 95% CI for the Cox regression model was calculated to examine the relationship between WBC levels and the risk of developing in-hospital pneumonia. In addition, subgroup analysis stratified by age (>55 and ≤55 years), sex (male and female), current smoking (yes and no), hypertension (yes and no), WFNS grade (1–3 and 4–5), and treatment modality (surgical clipping and endovascular coiling) were performed to assess whether there was any significant interaction between these factors and WBC levels when analyzing pneumonia and 90-day outcomes.

The analysis was performed with SPSS Statistics 26.0 (IBM, Armonk, New York, USA), R software (Version 4.1.2), and GraphPad PRISM 8.3.0 (GraphPad Software Inc., San Diego, CA, USA). Significance was set at  $p < 0.05$ .

## Results

### Study Patients

A total of 988 consecutive patients with aSAH enrolled in the LongTEAM study. Of the patients included, 583 (59.0%) were female patients, and the mean age was 54.8 years old.

The median WBC level was  $12.40 \times 10^9/L$  ([IQR] 9.87–15.41,  $10^9/L$ ). Patients with higher WBC levels had a higher incidence of early loss of consciousness, higher proportions of WFNS 4–5, mFS 3–4, Graeb 5–12, and SEBES 3–4, a higher rate of acute hydrocephalus, and a higher level of NLR (Shown in Table 1).

### WBC Levels and Clinical Outcomes

Table 2 shows the detailed information about association of WBC and outcomes. There were 376 (38.1%) patients with cardiac events, 268 (27.1%) patients with DCI, 125 (12.7%) patients with intracranial infection, 209 (21.2%) patients with stress ulcer bleeding, 28 (2.8%) patients with urinary tract infection, 315 (31.9%) patients with anemia, 345 (34.9%) patients with hypoproteinemia, 309 (31.3%) patients with pneumonia, 252 (25.5%) patients with MCVT, 85 (8.6%) patients with DVT, 245 (24.8%) patients with lipid metabolism disorder, 16 (1.6%) patients dead at discharge, 416 (42.1%) patients with mRS ≥3 at discharge, and 181 (18.3%) patients with mRS ≥3 at 90 days after discharge.

After adjusting age, sex, and treatment modality (Model 1), compared with the reference group (Q1), patients in the higher WBC level categories (Q3, Q4) had a higher incidence of DCI (adjusted OR = 1.64, 95% CI = 1.08–2.50,  $p = 0.021$ ; adjusted OR = 1.99, 95% CI = 1.32–3.02,  $p = 0.001$ ), patients in the highest WBC level category (Q4) had a higher incidence of hypoproteinemia (adjusted OR = 2.07, 95% CI = 1.39–3.08,  $p < 0.001$ ), patients in the higher WBC level categories (Q2, Q3, Q4) had a higher incidence of pneumonia (adjusted OR = 1.67, 95% CI = 1.09–2.56,  $p = 0.019$ ; adjusted OR = 1.91, 95% CI = 1.25–2.91,  $p = 0.003$ ; adjusted OR = 4.16, 95% CI = 2.75–6.31,  $p < 0.001$ ), patients in the highest WBC level category (Q4) had a higher incidence of MCVT (adjusted OR = 1.55, 95% CI = 1.01–2.37,  $p = 0.043$ ), patients in the highest WBC level category (Q4) had a higher incidence of DVT (adjusted OR = 2.01, 95% CI = 1.05–3.85,  $p = 0.036$ ), patients in the highest WBC level categories (Q4) had a higher proportion of mRS ≥3 at discharge (adjusted OR = 2.72, 95% CI = 1.85–4.00,  $p < 0.001$ ), and patients in the higher WBC

**Table I** Baseline Information

Characteristics	Total	WBC <sup>a</sup> Level				p <sup>c</sup>
		Q1 (<9.87)	Q2 (9.87–12.40)	Q3 (12.40–15.41)	Q4 (≥15.41)	
No. of patients	988	246	248	246	248	
Age, years, mean±SD	54.8±11.0	56.3±11.2	54.8±10.6	54.7±10.7	53.5±11.5	0.051
Female, n (%)	583 (59.0)	144 (58.5)	147 (59.3)	143 (58.1)	149 (60.1)	0.973
Hypertension, n (%)	581 (58.8)	146 (59.3)	150 (60.5)	129 (52.4)	156 (62.9)	0.104
Hyperlipidemia, n (%)	78 (7.9)	22 (8.9)	21 (8.5)	17 (6.9)	18 (7.3)	0.813
Diabetes mellitus, n (%)	92 (9.3)	24 (9.8)	30 (12.1)	15 (6.1)	23 (9.3)	0.148
Heart disease, n (%)	74 (7.5)	16 (6.5)	17 (6.9)	15 (6.1)	26 (10.5)	0.223
Current smoking, n (%)	263 (26.6)	58 (23.6)	70 (28.2)	68 (27.6)	67 (27.0)	0.649
Current drinking, n (%)	198 (20.0)	57 (23.2)	49 (19.8)	44 (17.9)	48 (19.4)	0.512
Posterior circulation, n (%)	106 (10.7)	29 (11.8)	26 (10.5)	23 (9.3)	28 (11.3)	0.832
Maximum diameter of aneurysm <sup>b</sup> , mean±SD	6.56±5.40	6.58±6.42	6.57±5.60	6.77±6.60	6.33±3.64	0.917
Early seizures, n (%)	54 (5.5)	10 (4.1)	14 (5.6)	7 (2.8)	23 (9.3)	0.011
Early loss of consciousness, n (%)	304 (30.8)	42 (17.1)	60 (24.2)	77 (31.3)	125 (50.4)	<0.001
WFNS grade 4–5, n (%)	222 (22.5)	26 (10.6)	37 (14.9)	56 (22.8)	103 (41.5)	<0.001
mFS grade 3–4, n (%)	718 (72.7)	155 (63.0)	176 (71.0)	178 (72.4)	209 (84.3)	<0.001
Graeb score 5–12, n (%)	84 (8.5)	9 (3.7)	13 (5.2)	20 (8.1)	42 (16.9)	<0.001
SEBES score 3–4, n (%)	491 (49.7)	83 (33.7)	118 (47.6)	122 (49.6)	168 (67.7)	<0.001
Acute hydrocephalus, n (%)	387 (39.2)	73 (29.7)	78 (31.5)	104 (42.3)	132 (53.2)	<0.001
Neutrophil-to-lymphocyte ratio, median (IQR)	11.69 (7.54–17.40)	6.98 (4.44–11.48)	10.22 (7.17–14.46)	13.99 (9.44–19.78)	15.88 (10.71–23.58)	<0.001
Treatment modality						0.959
Surgical clipping, n (%)	507 (51.3)	123 (50.0)	127 (51.2)	129 (52.4)	128 (51.6)	
Endovascular coiling, n (%)	481 (48.7)	123 (50.0)	121 (48.8)	117 (47.6)	120 (48.4)	

**Notes:** <sup>a</sup>Unit of measurement: 10<sup>9</sup>/L. <sup>b</sup>Unit of measurement: mm. <sup>c</sup>Denotes significance after applying a Bonferroni correction, significance was set at p<0.00833.

**Abbreviations:** WFNS, world federation of neurological societies; mFS, modified Fisher; SEBES, subarachnoid hemorrhage early brain edema score.

**Table 2** Adjusted Odds Ratios of In-Hospital Complications and Functional Outcomes According to WBC Levels at Admission

Variables	WBC <sup>a</sup> Level	No.	Model 1			Model 2	
			Events, n (%)	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Cardiac event	Q1	246	88 (35.8)	–	–	–	–
	Q2	248	91 (36.7)	1.11 (0.76–1.62)	0.585	1.01 (0.69–1.48)	0.963
	Q3	246	94 (38.2)	1.20 (0.82–1.75)	0.345	1.01 (0.68–1.49)	0.980
	Q4	248	103 (41.5)	1.45 (0.99–2.10)	0.054	1.01 (0.66–1.53)	0.971
DCI	Q1	246	51 (20.7)	–	–	–	–
	Q2	248	64 (25.8)	1.38 (0.90–2.11)	0.141	1.27 (0.83–1.97)	0.275
	Q3	246	72 (29.3)	1.64 (1.08–2.50)	0.021	1.41 (0.92–2.18)	0.118
	Q4	248	81 (32.7)	1.99 (1.32–3.02)	0.001	1.43 (0.90–2.26)	0.132
Intracranial infection	Q1	246	31 (12.6)	–	–	–	–
	Q2	248	28 (11.3)	0.83 (0.48–1.48)	0.528	0.82 (0.45–1.47)	0.504
	Q3	246	36 (14.6)	1.15 (0.67–2.00)	0.611	1.11 (0.63–1.97)	0.714
	Q4	248	30 (12.1)	0.93 (0.53–1.64)	0.798	0.85 (0.45–1.60)	0.613
Stress ulcer bleeding	Q1	246	46 (18.7)	–	–	–	–
	Q2	248	58 (23.4)	1.39 (0.90–2.16)	0.139	1.27 (0.81–2.00)	0.292
	Q3	246	48 (19.5)	1.11 (0.70–1.74)	0.660	0.89 (0.55–1.43)	0.621
	Q4	248	57 (23.0)	1.41 (0.90–2.19)	0.130	0.86 (0.52–1.43)	0.567
Urinary tract infection	Q1	246	6 (2.4)	–	–	–	–
	Q2	248	5 (2.0)	0.85 (0.26–2.86)	0.798	0.81 (0.24–2.76)	0.732
	Q3	246	5 (2.0)	0.88 (0.26–2.92)	0.829	0.88 (0.25–3.16)	0.850
	Q4	248	12 (4.8)	2.21 (0.81–6.05)	0.124	1.91 (0.59–6.19)	0.280
Anemia	Q1	246	75 (30.5)	–	–	–	–
	Q2	248	71 (28.6)	0.94 (0.62–1.41)	0.750	0.85 (0.56–1.30)	0.457
	Q3	246	76 (30.9)	1.05 (0.69–1.58)	0.834	0.84 (0.54–1.29)	0.428
	Q4	248	93 (37.5)	1.50 (0.99–2.25)	0.051	0.94 (0.60–1.49)	0.792
Hypoproteinemia	Q1	246	73 (29.7)	–	–	–	–
	Q2	248	83 (33.5)	1.28 (0.86–1.92)	0.226	1.16 (0.77–1.76)	0.471
	Q3	246	84 (34.1)	1.31 (0.88–1.97)	0.184	1.08 (0.71–1.64)	0.732
	Q4	248	105 (42.3)	2.07 (1.39–3.08)	<0.001	1.30 (0.83–2.02)	0.253
Pneumonia	Q1	246	49 (19.9)	–	–	–	–
	Q2	248	69 (27.8)	1.67 (1.09–2.56)	0.019	1.45 (0.93–2.27)	0.104
	Q3	246	75 (30.5)	1.91 (1.25–2.91)	0.003	1.39 (0.88–2.19)	0.156
	Q4	248	116 (46.8)	4.16 (2.75–6.31)	<0.001	2.06 (1.30–3.29)	0.002

(Continued)

**Table 2** (Continued).

Variables	WBC <sup>a</sup> Level	No.	Model 1			Model 2	
			Events, n (%)	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
MCVT	Q1	246	57 (23.2)	–	–	–	–
	Q2	248	60 (24.2)	1.16 (0.75–1.78)	0.509	1.10 (0.71–1.72)	0.664
	Q3	246	64 (26.0)	1.29 (0.84–1.98)	0.250	1.17 (0.74–1.83)	0.515
	Q4	248	71 (28.6)	1.55 (1.01–2.37)	0.043	1.15 (0.71–1.88)	0.567
DVT	Q1	246	16 (6.5)	–	–	–	–
	Q2	248	21 (8.5)	1.41 (0.72–2.80)	0.320	1.45 (0.72–2.91)	0.301
	Q3	246	20 (8.1)	1.34 (0.68–2.68)	0.400	1.42 (0.68–2.98)	0.350
	Q4	248	28 (11.3)	2.01 (1.05–3.85)	0.036	1.98 (0.93–4.20)	0.077
Lipid metabolism disorder	Q1	246	64 (26.0)	–	–	–	–
	Q2	248	57 (23.0)	0.86 (0.57–1.30)	0.472	0.86 (0.56–1.31)	0.472
	Q3	246	67 (27.2)	1.09 (0.73–1.62)	0.693	1.09 (0.72–1.66)	0.681
	Q4	248	57 (23.0)	0.87 (0.57–1.31)	0.496	0.90 (0.57–1.43)	0.654
Mortality at discharge	Q1	246	4 (1.6)	–	–	–	–
	Q2	248	3 (1.2)	0.78 (0.17–3.54)	0.748	0.86 (0.57–1.31)	0.492
	Q3	246	4 (1.6)	1.04 (0.26–4.24)	0.954	0.98 (0.64–1.50)	0.909
	Q4	248	5 (2.0)	1.33 (0.35–5.05)	0.677	1.21 (0.76–1.92)	0.422
Unfavorable outcome at discharge	Q1	246	89 (36.2)	–	–	–	–
	Q2	248	88 (35.5)	1.04 (0.71–1.53)	0.832	0.86 (0.57–1.31)	0.493
	Q3	246	102 (41.5)	1.37 (0.94–2.01)	0.103	0.98 (0.64–1.50)	0.922
	Q4	248	137 (55.2)	2.72 (1.85–4.00)	<0.001	1.21 (0.76–1.92)	0.420
90-day unfavorable outcome	Q1	246	28 (11.4)	–	–	–	–
	Q2	248	29 (11.7)	1.16 (0.65–2.04)	0.620	0.92 (0.51–1.68)	0.786
	Q3	246	51 (20.7)	2.40 (1.43–4.05)	0.001	1.60 (0.91–2.80)	0.102
	Q4	248	73 (29.4)	4.30 (2.59–7.15)	<0.001	1.81 (1.02–3.20)	0.042

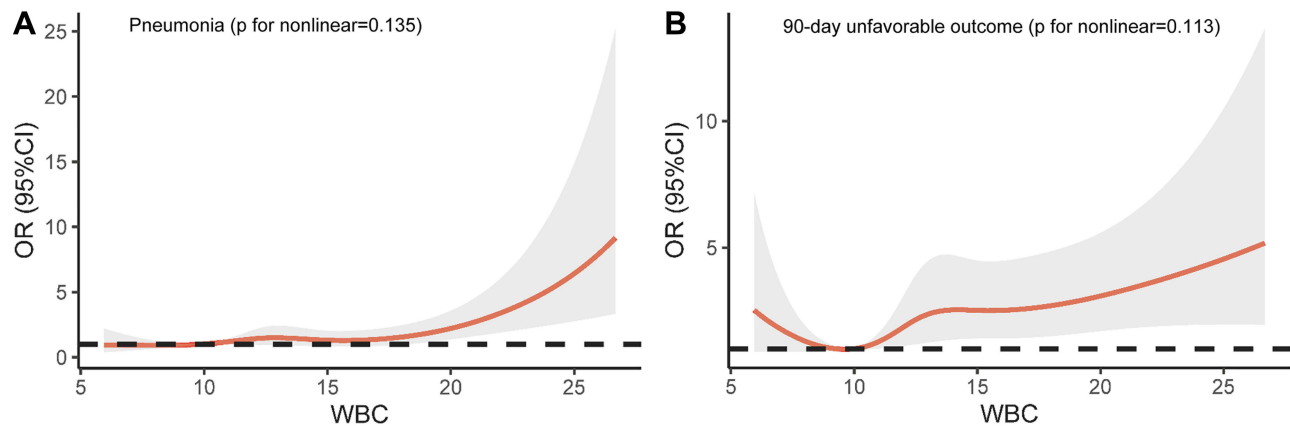
**Notes:** Model 1: adjusted for age, sex, and treatment modality. Model 2: adjusted for Model 1+Early loss of consciousness+WFNS grade 4–5+mFS grade 3–4+Graeb score 5–12+SEBES score 3–4+Acute hydrocephalus+Neutrophil-to-lymphocyte ratio. <sup>a</sup>Unit of measurement: 10<sup>9</sup>/L.

**Abbreviations:** DCI, delayed cerebral ischemia; MCVT, muscular calf vein thrombosis; DVT, deep vein thrombosis.

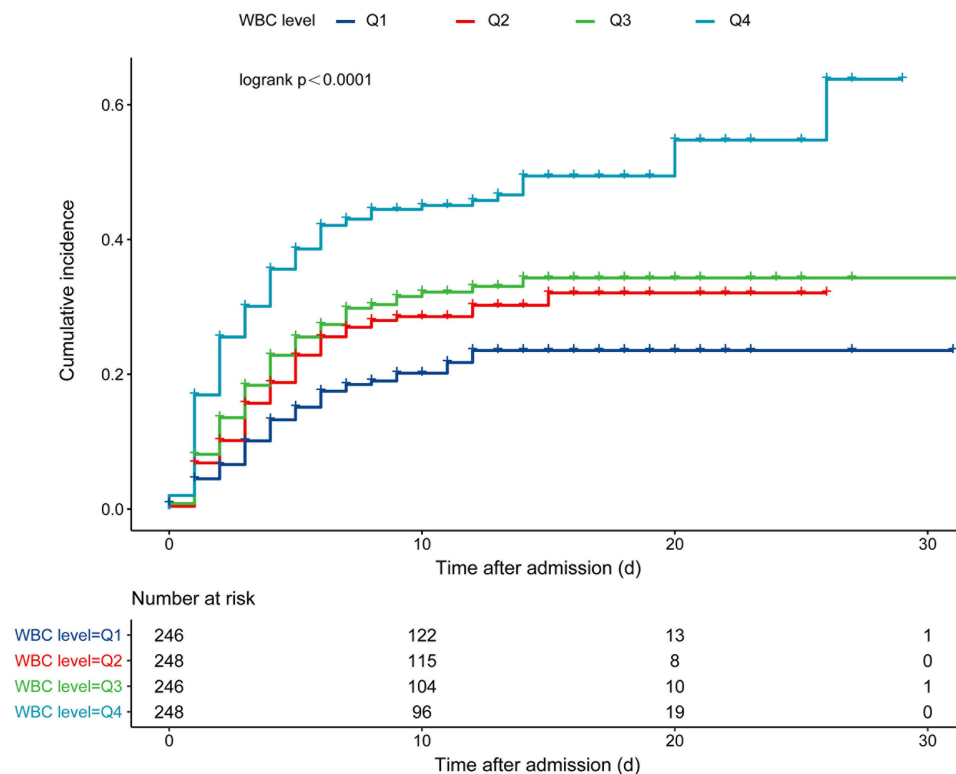
level categories (Q3, Q4) had a higher proportion of mRS  $\geq 3$  at 90 days after discharge (adjusted OR = 2.40, 95% CI = 1.43–4.05,  $p = 0.001$ ; adjusted OR = 4.30, 95% CI = 2.59–7.15,  $p < 0.001$ ). After further adjustment for related risk factors (Model 2), the highest quartile of WBC level remained associated with an increased risk of pneumonia (adjusted OR = 2.06, 95% CI = 1.30–3.29,  $p = 0.002$ ), and 90-day unfavorable outcomes (adjusted OR = 1.81, 95% CI = 1.02–3.20,  $p = 0.042$ ) compared with patients in the Q1 group.

Using logistic regression models with restricted cubic spline, we found that compared with Q1 group, higher levels of WBC were associated with an increased risk of pneumonia ( $p$  for nonlinear = 0.135) and 90-day unfavorable outcomes ( $p$  for nonlinear = 0.113) (Shown in Figure 1).

Figure 2 depicts the cumulative incidence of pneumonia by WBC levels. Compared with Q1 group, the adjusted regression model (model 2) suggested that Q4 (adjusted HR = 1.63, 95% CI = 1.13–2.36,  $p < 0.001$ ) was associated with a higher risk of pneumonia.



**Figure 1** Adjusted odds ratios of (A) pneumonia and (B) 90-day unfavorable outcomes according to baseline WBC level. The reference is the Q1 of the baseline WBC level ( $9.87 \times 10^9/L$ ). Data were fitted using a logistic regression model of the restricted cubic spline with five knots (the 5th, 25th, 50th, 75th, 95th percentiles) for baseline WBC level, adjusting for potential covariates.



**Figure 2** Kaplan–Meier curves for in-hospital pneumonia.

## Subgroup Analysis

After adjusting for all potential confounding variables according to model 2, subgroup analysis only showed a significant interaction between WBC levels and age when analyzing pneumonia. The effect of WBC levels on the prevalence of pneumonia was stronger in patients with age  $\leq 55$  than in those patients with age  $> 55$  in the fully adjusted model ( $p$  for interaction = 0.040) (Shown in Tables 3 and 4).

**Table 3** Subgroup Analysis of Association Between WBC Groups and In-Hospital Pneumonia

Subgroup	WBC Level	No. of Patients	Events, n (%)	Adjusted OR (95% CI)	p	p for Interaction
Age						0.040
$\leq 55$	Q1	118	18 (15.3)	–		
	Q2	130	37 (28.5)	1.83 (0.92–3.62)	0.084	
	Q3	129	25 (19.4)	0.94 (0.45–1.95)	0.862	
	Q4	146	66 (45.2)	2.21 (1.10–4.41)	0.025	
$> 55$	Q1	128	31 (24.2)	–		
	Q2	118	32 (27.1)	1.06 (0.58–1.95)	0.843	
	Q3	117	50 (42.7)	1.75 (0.96–3.19)	0.067	
	Q4	102	50 (49.0)	1.63 (0.85–3.12)	0.143	
Sex						0.616
Male	Q1	102	20 (19.6)	–		
	Q2	101	35 (34.7)	2.19 (1.08–4.45)	0.029	
	Q3	103	32 (31.1)	1.70 (0.80–3.61)	0.168	
	Q4	99	50 (50.5)	2.56 (1.16–5.62)	0.020	
Female	Q1	144	29 (20.1)	–		
	Q2	147	34 (23.1)	1.17 (0.64–2.13)	0.603	
	Q3	143	43 (30.1)	1.29 (0.72–2.33)	0.399	
	Q4	149	66 (44.3)	1.93 (1.06–3.53)	0.032	
Current smoking						0.493
Yes	Q1	58	11 (19.0)	–		
	Q2	70	20 (28.6)	2.03 (0.78–5.32)	0.148	
	Q3	68	21 (30.9)	1.79 (0.65–4.92)	0.257	
	Q4	67	38 (56.7)	4.10 (1.44–11.71)	0.008	
No	Q1	188	38 (20.2)	–		
	Q2	178	49 (27.5)	1.37 (0.82–2.31)	0.235	
	Q3	178	54 (30.3)	1.38 (0.82–2.33)	0.225	
	Q4	181	78 (43.1)	1.81 (1.06–3.10)	0.031	

(Continued)



Table 3 (Continued).

Subgroup	WBC Level	No. of Patients	Events, n (%)	Adjusted OR (95% CI)	p	p for Interaction
Hypertension						0.265
Yes	Q1	146	37 (25.3)	–		
	Q2	150	43 (28.7)	1.05 (0.60–1.84)	0.855	
	Q3	129	44 (34.1)	1.20 (0.67–2.14)	0.536	
	Q4	156	83 (53.2)	1.86 (1.06–3.29)	0.032	
No	Q1	100	12 (12.0)	–		
	Q2	98	26 (26.5)	3.04 (1.34–6.91)	0.008	
	Q3	117	31 (26.5)	2.67 (1.16–6.15)	0.021	
	Q4	92	33 (35.9)	3.35 (1.34–8.35)	0.010	
WFNS grade						0.314
1–3	Q1	220	36 (16.4)	–		
	Q2	211	49 (23.2)	1.54 (0.93–2.54)	0.094	
	Q3	190	48 (25.3)	1.63 (0.97–2.72)	0.065	
	Q4	145	43 (29.7)	1.85 (1.06–3.22)	0.030	
4–5	Q1	26	13 (50.0)	–		
	Q2	37	20 (54.1)	1.26 (0.41–3.87)	0.689	
	Q3	56	27 (48.2)	0.97 (0.33–2.83)	0.956	
	Q4	103	73 (70.9)	2.81 (0.97–8.14)	0.057	
Treatment modality						0.329
Surgical clipping	Q1	123	27 (22.0)	–		
	Q2	127	45 (35.4)	1.70 (0.94–3.08)	0.080	
	Q3	129	40 (31.0)	1.23 (0.67–2.27)	0.504	
	Q4	128	67 (52.3)	2.38 (1.28–4.43)	0.006	
Endovascular coiling	Q1	123	22 (17.9)	–		
	Q2	121	24 (19.8)	1.28 (0.63–2.62)	0.499	
	Q3	117	35 (29.9)	1.76 (0.87–3.54)	0.115	
	Q4	120	49 (40.8)	1.87 (0.90–3.85)	0.092	

**Abbreviations:** WBC, white blood cell; WFNS, world federation of neurological societies.

## Time of Developing Pneumonia in Different Groups, and the Relationship Between Pneumonia and Length of Hospital Stay, Number of Complications, and Total Hospital Charges

The median time after admission of developing pneumonia did not differ between patients in the Q1, Q2, Q3, Q4, and overall groups (2.0 [4.0–6.0] vs 3.0 [1.0–5.0] vs 3.0 [1.0–5.0] vs 2.0 [1.0–4.8] vs 3.0 [1.0–5.0],  $p = 0.223$ ). Compared

**Table 4** Subgroup Analysis of Association Between WBC Groups and 90-Day Outcomes

Subgroup	WBC Level	No. of Patients	Events, n (%)	Adjusted OR (95% CI)	p	p for Interaction
Age						0.513
≤55	Q1	118	9 (7.6)	–		
	Q2	130	7 (5.4)	0.42 (0.14–1.26)	0.123	
	Q3	129	15 (11.6)	1.01 (0.39–2.63)	0.985	
	Q4	146	33 (22.6)	1.24 (0.50–3.12)	0.642	
>55	Q1	128	19 (14.8)	–		
	Q2	118	22 (18.6)	1.15 (0.56–2.35)	0.700	
	Q3	117	36 (30.8)	1.60 (0.80–3.22)	0.187	
	Q4	102	40 (39.2)	1.73 (0.83–3.64)	0.146	
Sex						0.932
Male	Q1	102	10 (9.8)	–		
	Q2	101	13 (12.9)	1.16 (0.43–3.15)	0.766	
	Q3	103	20 (19.4)	2.35 (0.87–6.36)	0.093	
	Q4	99	29 (29.3)	2.39 (0.86–6.68)	0.096	
Female	Q1	144	18 (12.5)	–		
	Q2	147	16 (10.9)	0.85 (0.39–1.86)	0.691	
	Q3	143	31 (21.7)	1.55 (0.76–3.15)	0.228	
	Q4	149	44 (29.5)	1.85 (0.90–3.82)	0.097	
Current smoking						0.724
Yes	Q1	58	5 (8.6)	–		
	Q2	70	7 (10.0)	1.55 (0.36–6.63)	0.557	
	Q3	68	14 (20.6)	2.95 (0.72–12.02)	0.132	
	Q4	67	18 (26.9)	1.89 (0.45–7.90)	0.383	
No	Q1	188	23 (12.2)	–		
	Q2	178	22 (12.4)	0.92 (0.46–1.82)	0.803	
	Q3	178	37 (20.8)	1.56 (0.82–2.96)	0.173	
	Q4	181	55 (30.4)	2.19 (1.14–4.19)	0.018	
Hypertension						0.436
Yes	Q1	146	21 (14.4)	–		
	Q2	150	21 (14.0)	0.85 (0.42–1.73)	0.652	
	Q3	129	29 (22.5)	1.41 (0.71–2.83)	0.329	
	Q4	156	56 (35.9)	2.11 (1.08–4.13)	0.028	

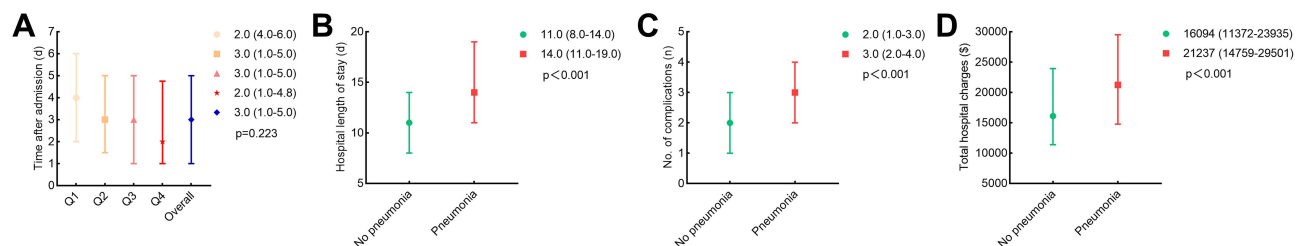
(Continued)

Table 4 (Continued).

Subgroup	WBC Level	No. of Patients	Events, n (%)	Adjusted OR (95% CI)	p	p for Interaction
No	Q1	100	7 (7.0)	–		
	Q2	98	8 (8.2)	1.48 (0.44–4.99)	0.527	
	Q3	117	22 (18.8)	3.07 (1.02–9.26)	0.047	
	Q4	92	17 (18.5)	2.23 (0.63–7.91)	0.212	
WFNS grade						0.433
1–3	Q1	220	20 (9.1)	–		
	Q2	211	19 (9.0)	1.06 (0.53–2.15)	0.869	
	Q3	190	21 (11.1)	1.31 (0.64–2.66)	0.461	
	Q4	145	21 (14.5)	1.84 (0.88–3.85)	0.107	
4–5	Q1	26	8 (30.8)	–		
	Q2	37	10 (27.0)	0.69 (0.21–2.28)	0.539	
	Q3	56	30 (53.6)	2.52 (0.85–7.46)	0.094	
	Q4	103	52 (50.5)	2.25 (0.79–6.43)	0.130	
Treatment modality						0.573
Surgical clipping	Q1	123	15 (12.2)	–		
	Q2	127	22 (17.3)	1.25 (0.57–2.72)	0.582	
	Q3	129	33 (25.6)	1.84 (0.87–3.90)	0.110	
	Q4	128	46 (35.9)	2.12 (0.99–4.54)	0.054	
Endovascular coiling	Q1	123	13 (10.6)	–		
	Q2	121	7 (5.8)	0.57 (0.20–1.62)	0.295	
	Q3	117	18 (15.4)	1.37 (0.57–3.30)	0.485	
	Q4	120	27 (22.5)	1.64 (0.67–4.05)	0.280	

**Abbreviations:** WBC, white blood cell; WFNS, world federation of neurological societies.

with patients without pneumonia, patients with pneumonia had longer hospital length of stays (14.0 [11.0–19.0] vs 11.0 [8.0–14.0],  $p < 0.001$ ), more complications (3.0 [2.0–4.0] vs 2.0 [1.0–3.0],  $p < 0.001$ ), and more hospital charges (21237 [14759–29501] vs 16094 [11372–23935],  $p < 0.001$ ) (shown in Figure 3).



**Figure 3** (A) The timing of pneumonia formation. (B) Relationship between the length of stays and pneumonia. (C) Relationship between the number of complications and pneumonia. (D) Relationship between the total hospital charges and pneumonia (US dollar = 7.11 renminbi [updated on October 10, 2022]).

## Discussion

The earliest reports describing WBC and outcomes in patients with hemorrhagic stroke can date back to 1987, with two clinical studies illustrating the relationship between WBC and vasospasm and death, respectively.<sup>12,13</sup> However, in the following decades, reports on WBC came more frequently from patients with ischemic stroke.<sup>14–18</sup> One meta-analysis in 2021 indicated although confirms the association between WBC and unfavorable outcomes in aSAH patients, a strong conclusion cannot be made due to the limitation of the small study number, between-study heterogeneity, and suspicion of uncontrolled factors.<sup>19</sup> Therefore, whether WBC at admission can be regarded as a prognostic marker needs more investigation.

In this large observational cohort study conducted in China, we divided WBC levels at admission according to the quartile. We found that the preoperative WBC levels were associated with an increased risk of in-hospital pneumonia and 90-day unfavorable outcomes for aSAH patients. Moreover, such risk rises with increasing WBC levels.

Three previous studies showed that elevated WBC might be associated with the development of DCI during hospitalization, leading to unfavorable outcomes.<sup>8–10</sup> There are several mechanisms by which WBC contributes to cerebral injury. On the one hand, the brain will experience early hypoperfusion after an aneurysm rupture, in this period, the capillaries may behave like a sieve and trap the leukocytes to increase the WBC count. Aggregates of WBC adherent to each other can occlude the microcirculation, aggravating tissue hypoperfusion and ischemia injury.<sup>20</sup> On the other hand, WBC could release cytotoxic mediators such as some interleukins to increase WBC-endothelial interactions and damage the vessel wall or other viable tissues.<sup>21</sup> In our study, when adjusting for age, sex, and treatment modality, the elevated WBC correlates with the development of DCI, but when adjusting for more preoperative confounders, the results showed that elevated WBC appears to be associated only with pneumonia, not DCI. The similar conclusion was addressed in a 2018 study where they considered NLR (also an inflammatory biomarker thought to be associated with the development of DCI) only to be associated with pneumonia rather than DCI after adjusting preoperative confounders.<sup>22</sup>

We suppose there are several reasons leading to this controversial conclusion. First, is the study population the same? Is there any consideration given to the effect of preoperative grading on DCI? In other words, patients with high-grade aSAH have a higher level of inflammation and a higher probability of developing DCI, and the effect of confounding factors on DCI should be appropriately adjusted. Second, there may be differences in the sensitivity of WBC levels in peripheral blood for predicting DCI compared with local (cerebrospinal fluid), and how the consistency of WBC levels in peripheral blood and cerebrospinal fluid remains to be explored. Third, the time at which WBC was collected may influence the results.

Our previous study indicated that pneumonia might have a long-lasting impact on the prognosis of aSAH patients and is even more devastating than DCI since some DCI is asymptomatic, whereas the development of pneumonia can cause damage to multiple systems throughout the body.<sup>23</sup> Another study in 2011 similarly pointed out that pneumonia is a leading cause of poor prognosis in patients with aSAH.<sup>24</sup> Fortunately, there are increasing studies focusing on preventing and treating postoperative pneumonia. One study in 2022 revealed that age, WFNS 4–5, heart disease, higher WBC levels, and mFS 3–4 were independent risk factors for pneumonia, and the reason for WBC leading to pneumonia might be due to its ability to reflect the disease severity (patients with high WBC levels had higher WFNS grade and mFS grade at admission, which can prolong the bedridden time and increase the risk of hypostatic pneumonia and aspiration pneumonia).<sup>25</sup> Another study in 2022 developed a novel risk score for predicting pneumonia containing WFNS grade, high neutrophil, the need for RBC transfusion, and tracheostomy.<sup>26</sup> Besides, NLR, lactate dehydrogenase, and neutrophil-to-albumin ratio were also reported to be associated with pneumonia.<sup>27–29</sup>

Interestingly, in addition to DCI and pneumonia, the inflammatory response following aSAH can induce hypoproteinemia, leading to muscle dystrophy, of which temporal muscle thickness has been reported to predict patient outcomes, further highlighting the importance of controlling inflammation.<sup>30–32</sup> Up to now, we have found many ongoing clinical trials on inflammation, and the interventions used in these clinical trials include dexamethasone, dexmedetomidine, lycopene, hydrogen gas, etc. We look forward to the results of these clinical trials. After all, there are currently very limited measures to improve outcomes in patients with aSAH.

Our study provides evidence for the involvement of WBC after aSAH and highlights the significance of preoperative inflammatory biomarkers for predicting prognosis and complications. As we know, WBC is the most accessible inflammatory indicator regardless of the hospital level. Exploring the relationship between WBC and outcomes can help clinicians better understand the role of inflammatory response in the early brain injury stage.

## Limitation

There are several limitations of our study. First, it is unclear whether the patient had a preoperative infection. Second, the conclusions from this study are only based on WBC levels in peripheral blood. Third, the population we studied came from northern China, and it is unclear whether racial differences exist in this phenomenon. Fourth, we did not collect data for daily WBC count in the early hospital course. Fifth, the data used for analysis only include patients with single aneurysms.

## Conclusion

In this large, single-center, observational cohort in China, WBC levels at admission were associated with an increased risk of in-hospital pneumonia and 90-day unfavorable outcomes in patients with aSAH. Moreover, such risk rises with increasing WBC levels. Our findings can help clinicians better understand the role of inflammatory response in early brain injury.

## Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

## Ethics Approval

This study has obtained approval from the Institutional Review Board of Beijing Tiantan Hospital (KY 2021-008-01). Informed consent for clinical analysis was obtained from all individual participants or their authorized representatives. All the analysis was performed according to the Declaration of Helsinki and the local ethics policies.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors have no personal, financial, or institutional interest in any of the materials or methods used in this study or the findings specified in this paper.

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