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Combined Effect of White Blood Cell and Platelet Count for Predicting In-Hospital Mortality and Pneumonia in Acute Ischemic Stroke

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Abstract

Background: High white blood cell (WBC) count was the risk factors for mortality and pneumonia after acute ischemic stroke (AIS). Low platelet count increased the risk of mortality. We investigated the combined effect of WBC count and platelet count on hospital admission and in-hospital mortality and pneumonia in acute AIS patients.

Methods: A total of 3,265 AIS patients enrolled from December 2013 to May 2014 across 22 hospitals in Suzhou city were included in the present study. We divided patients into four groups according to their level of WBC count and platelet count: LWHP (low WBC and high platelet), LWLP (low WBC and low platelet), HWHP (high WBC and high platelet) and HWLP (high WBC and low platelet). Cox proportional logistic regression model were used to estimate the combined effect of WBC count and platelet count on all cause in-hospital mortality and pneumonia in AIS patients.

Results: HWLP was associated with a 2.07-fold increase in the risk of in-hospital mortality in comparison to LWHP (adjusted odds ratio [OR] 2.07; 95% confidence interval [CI], 1.02-4.18; *P*-trend =0.020). The risk of pneumonia was significantly higher in patients with HWLP compared to those with LWHP (adjusted OR 2.29; 95% CI, 1.57-3.35; *P*-trend <0.001). The C-statistic for the combined WBC count and platelet count was higher than WBC count or platelet count alone for prediction of in-hospital mortality and pneumonia (all $p < 0.01$).

Conclusions: High WBC count combined with low platelet count level at admission was independently associated with in-hospital mortality and pneumonia in AIS patients. Moreover, the combination of WBC count and platelet count level appeared to be a better predictor than WBC count or platelet count alone.

Introduction

Pneumonia was the common infection among acute ischemic stroke patients during hospitalization, which accounts for poor functional outcome[1]. The stroke associated with in-hospital mortality is still high, although reduce throughout the years based on reperfusion therapies and supportive care[2].

Increased white blood cell (WBC) count are frequently and associated with high odds of pneumonia, poor functional outcome, and mortality among acute ischemic stroke (AIS) patients[3–5]. Several studies reported that low platelet count or thrombocytopenia at baseline were significant associated with a high risk of poor outcome and mortality in patients with AIS[6–8]. More recently, some studies indicated that platelet play extremely role of regulation inflammation and associated with infection disease[9–12]. A study from china shown low platelet count is an independent risk factor of postoperative pneumonia in patients with type A acute aortic dissection (AAAD)[12]. There was a stronger interaction between platelets and WBC and relevance in the regulation of both hemostatic and inflammatory processes from the basic researches[9]. Given that, maybe there was a combine effect of platelets and WBC for predict clinical outcome. Two studies have noted that the baseline low platelet to white blood cell ratio (PWR) was

increased the risk of 90 days poor outcome and mortality[13, 14]. However, whether there was a combine effect of platelets and WBC on in-hospital mortality still uncertain. And the evidence on the association between combined effect of platelets and WBC at admission and pneumonia in AIS patients are remain unclear.

In the present study, we aimed to investigate the possible association between combined effect of platelets and WBC and in-hospital mortality and pneumonia in a large multicenter study of patients from Suzhou, China.

Methods

Study participants

We recruited patients with AIS or transient ischemic attack (TIA) from 22 hospitals in Suzhou, China from December 2013 to May 2014. Patients aged ≥18 years with a clinical diagnosis of AIS or TIA were considered eligible[15]. Diagnosis of ischemic stroke was made according to World Health Organization-defined criteria based on patient history, clinical data, and neuroimaging results (computed tomography [CT] or magnetic resonance imaging [MRI]). A team of investigators, including neurologists, reviewed the eligibility of study participants. Additional exclusion criteria were as follows: (1) diagnosis of TIA based on completely revised of symptoms and no acute infract on the MRI or follow-up CT scans; (2) lack of data on admission serum WBC or platelet levels; (3) time from onset to admission over 7 days. Finally, 3265 patients were potentially eligible for this analysis. (flowchart of participants selection; Fig. 1).

Data Collection And Outcome Assessment

Baseline information were collected, including patient demographics, vascular risk factors, stroke severity (as measured by the National Institutes of Health Stroke Scale, NIHSS; and modified Rankin Scale, mRS), medication use, imaging data and other diagnosis-related information. Vascular risk factors included history of hypertension, history of diabetes mellitus, history of atrial fibrillation, history of stroke, history of coronary heart disease, current or previous smoking status, and alcohol consumption. Information on the aforementioned factors were obtained by interviews with patients or their family members (if patients were not able to communicate). Current smoking status was defined as having smoked at least one cigarette per day for the previous year or more. Data on the amount and type of alcohol consumed during the past year was collected. Alcohol consumption was defined as having consumed at least one alcoholic drink per day during the last year. Hypertension was defined as having a systolic blood pressure (BP) ≥140 mmHg and/or diastolic BP ≥90 mmHg, or use of antihypertensive medications. Diabetes mellitus was defined as having fasting glucose ≥7.0 mmol/L (126 mg/dL), non-fasting glucose ≥11.1 mmol/L (200 mg/dL) with classic symptoms of hyperglycemia or hyperglycemic crisis, use of glucose-lowering drugs. Atrial fibrillation was defined as having a history of atrial fibrillation, confirmed by ≥1 electrocardiograms or the presence of arrhythmia during hospitalization. Pneumonia after AIS was

diagnosed by treating physicians according to the criteria of US Center for Disease Control and Prevention for hospital-acquired pneumonia, based on clinical and laboratory test[16]. Blood samples were collected within 24 hours of hospital admission. The WBC count and platelet count were determined at hospital admission by automated cell counters at local laboratories. The outcome of this study was all-cause in-hospital mortality and pneumonia.

Statistical analysis

Receiver-operating characteristic (ROC) curve analysis was performed to determine the best WBC count and platelet count cut-off value for the prediction of all-cause mortality were $8.3*10^9$/L and $162 *10^9$/L while maximizing sensitivity and specificity. Than study participants were divided into four groups, based on WBC count and platelet count at admission: low WBC count and high platelet count, LWHP (WBC count < $8.3*10^9$/L and platelet count ≥ $162 *10^9$/L), low WBC count and low platelet count, LWLP (WBC count < $8.3*10^9$/L and platelet count < $162 *10^9$/L), high WBC count and high platelet count, HWHP (WBC count ≥ $8.3*10^9$/L and platelet count ≥ $162 *10^9$/L), and high WBC count and low platelet count, HWLP (WBC count ≥ $8.3*10^9$/L and platelet count < $162 *10^9$/L). Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]) and were compared using the analysis of variance or Wilcoxon rank-sum test. Categorical variables were expressed as frequency (%) and were compared using the chi-square test.

The crude cumulative risks of in-hospital mortality for each patient group based on admission serum WBC count and platelet count were shown in a Kaplan-Meier plot and compared using the log-rank test. Crude and multivariable logistic regression models was used to estimate the risk of in-hospital mortality and the odds of in-hospital pneumonia respectively. Odds ratios (ORs) and 95% confidence interval (CIs) were calculated for each group with the LWHP as reference. Potential confounders that were adjusted in the multivariable models included age, sex, time from onset to admission, systolic BP, cigarette smoking status, alcohol drinking, history of hypertension, history of diabetes mellitus, history of coronary heart disease, history of atrial fibrillation, history of stroke, thrombolysis treatment, baseline NIHSS score, estimated glomerular filtration rate (eGFR) levels, Oxfordshire Community Stroke Project (OCSP) classification. For the outcome of in-hospital mortality, pneumonia was also as confounder in multivariable models.

To assess the robustness of the association between different serum WBC count and platelet count and in-hospital mortality and pneumonia, we also performed sensitivity analyses (by restricting to patients with age < 80 years old, and those with time from onset to admission ≤ 24 hours). In addition, we tested the discriminatory ability of WBC count and platelet count (combined and separately) to predict in-hospital mortality and pneumonia by calculating C-statistics (areas under ROC curves). Moreover, we also performed sensitivity analyses based on quartiles of platelet to white blood cell count ratio (PWR), which defined by the count ratio of platelets to white blood cell[13, 14]. All *P* values were two-tailed, and a

significance level of 0.05 was used. All analyses were conducted using the SPSS Version 17.0 statistical software.

Results

There were 3265 patients with complete data on conventional risk factors and WBC count and platelet count at admission were enrolled. Whose mean age was 68.6 years (± 12.9), with a median NIHSS score of 4.0 (IQR, 2.0–7.0). Baseline characteristics are presented in Table 1. In comparison to LWHP participants, those with HWLP were more likely to be older, had more severe stroke (higher NIHSS) and other co-morbidities including coronary heart disease and atrial fibrillation. HWLP patients also differed in metabolic profile (higher fasting glucose levels, high-density lipoprotein cholesterol and WBC count level, lower serum total cholesterol, triglycerides, low-density lipoprotein cholesterol, platelet count and eGFR level and higher baseline systolic BP, diastolic BP, and shorter time from onset to hospital). (Table 1)

Table 1
Baseline characteristics of 3,265 acute ischemic stroke patients according to white blood cell count and platelet count

Characteristics [a]	LWHP	LWLP	HWHP	HWLP	*P*-value
Number of subjects	1395	970	662	238	
Demographics					
Age, y	68.8 ± 12.7	72.1 ± 11.4	66.0 ± 14.3	71.9 ± 12.6	< 0.001
Male sex	782 (56.1)	563 (58.0)	408 (61.6)	132 (55.5)	0.099
Cigarette smoking status	289 (20.7)	171 (17.6)	148 (22.4)	42 (17.6)	0.072
Alcohol consumption	133 (9.5)	93 (9.6)	69 (10.4)	20 (8.4)	0.824
Clinical features					
Time from onset to hospital, h	24.0 (6.0–72.0)	24.0 (5.0–48.0)	24.0 (5.0–48.0)	7.0 (3.0–26.0)	< 0.001
Hospital stay, day	10.0 (8.0–13.0)	10.0 (8.0–14.0)	11.0 (8.0–15.0)	11.5 (8.0–16.0)	< 0.001
Baseline systolic BP, mm Hg	152.3 ± 22.2	151.1 ± 22.1	154.5 ± 24.0	151.9 ± 24.7	0.029
Baseline diastolic BP, mm Hg	85.8 ± 13.3	84.2 ± 11.9	86.9 ± 13.8	84.4 ± 15.0	< 0.001
TG, mmol/L	1.3 (0.9–1.8)	1.1 (0.8–1.6)	1.3 (0.9–1.8)	1.1 (0.8–1.5)	< 0.001
TC, mmol/L	4.7 (4.0–5.3)	4.3 (3.7–5.0)	4.7 (4.1–5.5)	4.4 (3.7–5.0)	< 0.001
LDL-C, mmol/L	2.8 (2.3–3.3)	2.4 (2.0–3.0)	2.9 (2.3–3.5)	2.6 (2.1–3.1)	< 0.001
HDL-C, mmol/L	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (1.0–1.4)	1.2 (1.0–1.5)	< 0.001

*Continuous variables are expressed as mean ± standard deviation or as median (interquartile range). Categorical variables are expressed as frequency (percent).

Abbreviations: BP, blood pressure; HWHP, High WBC and high platelet; HWLP, High WBC and low platelet; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale; TACS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; LACS, lacunar syndrome; LWHP, Low WBC and high platelet; LWLP, Low WBC and low platelet; Q, quartile.

Characteristics [a]	LWHP	LWLP	HWHP	HWLP	*P*-value
FPG, mmol/L	5.6 (5.0–6.8)	5.6 (5.0–6.9)	6.0 (5.2–7.8)	6.4 (5.5–8.6)	< 0.001
Platelet, 10^3/uL	202 (182–233)	131 (110–148)	222 (192–263)	143 (122–153)	< 0.001
WBC, 10^3/uL	6.4 (5.4–7.2)	5.6 (4.7–6.6)	9.9 (8.9–11.5)	9.8 (8.8–11.2)	< 0.001
eGFR, ml/min/1.73 m^2	100.5 (80.2–120.8)	90.3 (73.2–110.7)	98.0 (75.7–120.4)	83.7 (65.9–106.9)	< 0.001
Baseline NIHSS score	3.0 (2.0–5.0)	3.0 (2.0–6.0)	5.0 (2.0–9.0)	7.5 (3.0–15.0)	< 0.001
Medical history					
History of hypertension	1112 (79.7)	724 (74.6)	549 (82.9)	182 (76.5)	< 0.001
History of diabetes mellitus	364 (26.1)	232 (23.9)	187 (28.2)	60 (25.2)	0.265
History of coronary heart disease	63 (4.5)	71 (7.3)	29 (4.4)	21 (8.8)	0.002
History of atrial fibrillation	136 (9.7)	194 (20.0)	98 (14.8)	76 (31.9)	< 0.001
History of stroke	324 (23.2)	216 (22.3)	149 (22.5)	44 (18.5)	0.449
Medication history					
Antihypertensive therapy	841 (60.3)	536 (55.3)	403 (60.9)	141 (59.2)	0.058
Antiplatelet therapy	112 (8.0)	79 (8.1)	41 (6.2)	13 (5.5)	0.241
Anticoagulation therapy	13 (0.9)	11(1.1)	8 (1.2)	4 (1.7)	0.758
Antiglycemic therapy	273 (19.6)	172 (17.7)	133 (20.1)	40 (16.8)	0.465
Statin therapy	44 (3.2)	38 (3.9)	14 (2.1)	5 (2.1)	0.164

*Continuous variables are expressed as mean ± standard deviation or as median (interquartile range). Categorical variables are expressed as frequency (percent).

Abbreviations: BP, blood pressure; HWHP, High WBC and high platelet; HWLP, High WBC and low platelet; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale; TACS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; LACS, lacunar syndrome; LWHP, Low WBC and high platelet; LWLP, Low WBC and low platelet; Q, quartile.

Characteristics [a]	LWHP	LWLP	HWHP	HWLP	*P*-value
Thrombolysis treatment	27 (1.9)	18 (1.9)	27 (4.1)	9 (3.8)	0.008
Stroke syndrome					< 0.001
TACS	72 (5.2)	80 (8.2)	91 (13.7)	71 (29.8)	
PACS	720 (51.6)	511(52.7)	320 (48.3)	90 (37.8)	
POCS	329 (23.6)	197 (20.3)	180 (27.2)	59 (24.8)	
LACS	274 (19.6)	182 (18.8)	71 (10.7)	18 (7.6)	

*Continuous variables are expressed as mean ± standard deviation or as median (interquartile range). Categorical variables are expressed as frequency (percent).

Abbreviations: BP, blood pressure; HWHP, High WBC and high platelet; HWLP, High WBC and low platelet; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; eGFR, estimated glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale; TACS, total anterior circulation syndrome; PACS, partial anterior circulation syndrome; POCS, posterior circulation syndrome; LACS, lacunar syndrome; LWHP, Low WBC and high platelet; LWLP, Low WBC and low platelet; Q, quartile.

During hospitalization, 111 patients (3.4%) died from all causes. HWLP patients had the highest cumulative incidence of in-hospital mortality (log-rank $P < 0.001$; Fig. 2). In the unadjusted model, the OR of in-hospital mortality was significantly higher among study participants with admission HWHP and HWLP compared with LWHP (P-trend < 0.001). After adjusting for age, sex, time from onset to admission, baseline NIHSS score, pneumonia and other confounders, the OR (95% CI) of admission HWLP was 2.07 (1.02–4.18) for all-cause mortality as compared with LWHP (P-trend = 0.020) (Table 2). HWLP was also shown to be associated with a higher risk of in-hospital mortality in patients with age < 80 years old, and those with time from onset to admission ≤ 24 hours (Table 2).

Table 2
Odds ratios and 95% confidence intervals of in-hospital mortality according to level of white blood cell count and platelet count

	LWHP	LWLP	HWHP	HWLP	*P*-trend
No.	1395	970	662	238	
No. of deaths	21(1.5)	23(2.4)	28(4.2)	39(16.4)	
Crude	1.00	1.59 (0.87–2.89)	2.89 (1.63–5.13)	12.82 (7.39–22.25)	< 0.001
Model 1	1.00	1.19 (0.65–2.18)	2.89 (1.62–5.16)	9.90 (5.63–17.42)	< 0.001
Model 2	1.00	0.70 (0.34–1.45)	1.06 (0.53–2.11)	2.07 (1.02–4.18)	0.020
Sensitivity analysis					
Model 3	1.00	0.87 (0.40–1.91)	1.30 (0.61–2.79)	2.34 (1.08–5.04)	0.014
Model 4	1.00	0.80 (0.24–2.64)	1.92 (0.69–5.38)	3.78 (1.29–11.07)	0.004
Model 1, adjusted for age and sex;					
Model 2, adjusted for age, sex, systolic BP, time from onset to admission, cigarette smoking status, alcohol drinking, history of hypertension, history of diabetes mellitus, history of coronary heart disease, history of atrial fibrillation, history of stroke, thrombolysis treatment, baseline National Institutes of Health Stroke Scale score, eGFR levels, Oxfordshire Community Stroke Project classification, and pneumonia.					
Model 3, adjusted for model 2 and further restricted to patients with time from onset to admission ≤ 24 hours.					
Model 4, adjusted for model 2 and further restricted to patients with age < 80 years old.					

There were 563 patients (17.2%) had pneumonia during hospitalization. The risk of pneumonia was significantly higher among LWLP, HWHP and HWLP participants compared with LWHP patients (*P*-trend < 0.001) in the unadjusted regression model. In multivariable regression models, the odds of pneumonia for the HWLP group was 2.29 (95% CI 1.57–3.35) and HWHP group was 2.17 (95% CI 1.64–2.87) as compared with the LWHP group (*P*-trend < 0.001) (Table 3). Similar associations between HWLP, HWHP and pneumonia were shown when patients restricting to with age < 80 years old, and those with time from onset to admission ≤ 24 hours (Table 3).

Table 3
Odds ratios and 95% confidence intervals of pneumonia according to level of white blood cell count and platelet count

	LWHP	LWLP	HWHP	HWLP	*P*-trend
No.	1395	970	662	238	
No. of Pneumonia	153(11.0)	145(14.9)	168(25.4)	97(40.8)	
Crude	1.00	1.43 (1.12–1.82)	2.76 (2.17–3.52)	5.58 (4.10–7.60)	< 0.001
Model 1	1.00	1.09 (0.85–1.40)	3.01 (2.34–3.88)	4.73 (3.42–6.53)	< 0.001
Model 2	1.00	0.98 (0.75–1.30)	2.17 (1.64–2.87)	2.29 (1.57–3.35)	< 0.001
Sensitivity analysis					
Model 3	1.00	1.11 (0.80–1.55)	2.06 (1.46–2.91)	2.02 (1.30–3.14)	< 0.001
Model 4	1.00	1.06 (0.75–1.49)	2.21 (1.58–3.10)	2.43 (1.54–3.85)	< 0.001
Model 1, adjusted for age and sex;					
Model 2, adjusted for age, sex, systolic BP, time from onset to admission, cigarette smoking status, alcohol drinking, history of hypertension, history of diabetes mellitus, history of coronary heart disease, history of atrial fibrillation, history of stroke, thrombolysis treatment, baseline National Institutes of Health Stroke Scale score, Oxfordshire Community Stroke Project classification, and eGFR levels.					
Model 3, adjusted for model 2 and further restricted to patients with time from onset to admission ≤ 24 hours.					
Model 4, adjusted for model 2 and further restricted to patients with age < 80 years old.					

We also performed sensitivity analyses based on quartiles of PWR. A lowest PWR (Q1) was associated with a 6.81-fold increase in the risk of in-hospital mortality (OR 6.81; 95% CI, 3.66–12.67; *P*-trend < 0.001) and pneumonia (OR 3.70; 95% CI, 2.84–4.84; *P*-trend < 0.001) in comparison to highest group (Q4) in the unadjusted model (Table 4). The risk of pneumonia was still significantly higher in lowest PWR participants compared with highest PWR patients (OR 1.73; 95% CI, 1.26–2.37; *P*-trend < 0.001) but not in-hospital mortality (*P*-trend = 0.416) after adjust potential confounders (Table 4).

Table 4
Odds ratios and 95% confidence intervals for in-hospital outcomes according to quartiles of platelet to white blood cell count

		Unadjusted		Model 1		Model 2	
	Cases (%)	OR (95% CI)	*P*-trend	OR (95% CI)	*P*-trend	OR (95% CI)	*P*-trend
In-hospital mortality			< 0.001		< 0.001		0.416*
< 20	69 (8.8)	6.81 (3.66–12.67)		5.50 (2.92–10.35)		1.12 (0.52–2.40)	
20–26	17 (2.1)	1.49 (0.71–3.13)		1.27 (0.60–2.69)		0.61 (0.25–1.44)	
26–33	13 (1.6)	1.15 (0.52–2.53)		1.04 (0.47–2.31)		0.73 (0.29–1.83)	
≥ 33	12 (1.4)	1.00 (reference)		1.00 (reference)		1.00 (reference)	
In-hospital pneumonia			< 0.001		< 0.001		< 0.001
< 20	235 (30.1)	3.70 (2.84–4.84)		3.16 (2.40–4.17)		1.73 (1.26–2.37)	
20–26	138 (16.8)	1.74 (1.31–2.32)		1.52 (1.13–2.04)		1.24 (0.90–1.70)	
26–33	101 (12.5)	1.23 (0.91–1.66)		1.13 (0.83–1.53)		1.02 (0.73–1.43)	
≥ 33	89 (10.4)	1.00 (reference)		1.00 (reference)		1.00 (reference)	

Model 1, adjusted for age and sex;

Model 2, adjusted for age, sex, systolic BP, time from onset to admission, cigarette smoking status, alcohol drinking, history of hypertension, history of diabetes mellitus, history of coronary heart disease, history of atrial fibrillation, history of stroke, thrombolysis treatment, baseline National Institutes of Health Stroke Scale score, Oxfordshire Community Stroke Project classification, and eGFR levels.

* Adjusted for all the confounders in model 2 and pneumonia.

We compared the predictive ability of combined WBC count and platelet count, WBC count or platelet count alone on pneumonia and in-hospital mortality are shown in Fig. 3A and Fig. 3B by ROC curves. The C-statistic was significantly greater for the combined effect of WBC count and platelet count than WBC count or platelet count alone for both outcomes (all $p < 0.01$).

Discussion

This study of 3265 patients shows that the independently combined effect of high WBC count and low platelet count on in-hospital mortality and pneumonia among AIS patients. Patients with high WBC count ($\geq 8.3*10^9$/L) and low platelet count ($< 162 *10^9$/L) tended to be associated with a 2.07-fold and 2.29-fold increase in the risk of in-hospital mortality and pneumonia respectively. Moreover, the lowest PWR participants was associated with greater risk of pneumonia. Furthermore, the predictive value of combined WBC and platelet count on in-hospital mortality and pneumonia appear to be better than WBC or platelet alone.

A growing body of studies have demonstrated that a high WBC count or low platelet count at baseline were significantly increased the risk of poor functional outcome and mortality after AIS[3, 6–8]. Data from the registry of the Canadian Stroke Network of 8829 AIS patients indicated higher WBC at baseline associated with greater risk of disability at hospital discharge as well as 30 days mortality[3]. Yang et al study of 101527 AIS patient with thrombolysis treatment found the baseline platelet $< 150 *10^9$/L was associated with higher in-hospital mortality and a higher incidence of intracranial hemorrhage[6]. For the significant interaction between platelets and WBC on regulation of both hemostatic and inflammatory processes[9], two studies seen the combined effect of platelets and WBC for predict clinical outcome among AIS patients[13, 14]. A study of 168 AIS patients given thrombolysis treatment indicated patients with low PWR was associated with poor outcome at 90 days[13]. Cao et al study enrolled 633 AIS patients shown low PWR as well as other marker were increased the risk of 90 days mortality[14]. In present large multicenter study, we found the combined effect of high WBC count and low platelet count on in-hospital mortality. AIS patients with baseline WBC count $\geq 8.3*10^9$/L and platelet count $< 162 *10^9$/L associated with a 2.07-fold risk of in-hospital mortality. We also found the predictive value of combined WBC count and platelet count for in-hospital mortality was better than WBC count or platelet count alone.

It is well known that increased WBC was the marker of inflammation and prior studies had shown the significant association between increased WBC and pneumonia after AIS[5,17]. The role of platelets in hemostasis is well established and more recently studies indicated platelets also play a key role of regulation inflammatory processes[9]. The interaction to leukocyte or monocyte and secreted mediators were the underlying mechanisms of platelets regulation inflammatory processes[9, 18–21]. Some studies have been indicated low platelet was increased the risk as well as the severity of pneumonia[11,12]. A study from china shown low platelet count is an independent risk factor of postoperative pneumonia in patients with type A acute aortic dissection (AAAD) [12]. As for coronavirus disease 2019 (COVID-19), a meta-analysis of nine studies with 1779 COVID-19 patients indicated low platelet count was associated with increased risk of severe disease[11]. Additionally, a study from Canada found the low PWR was significantly increased the risk of pneumonia in patients undergoing radical nephrectomy for renal malignancy[22]. However, no studies investigate the prognostic of the combined of WBC count and platelet on pneumonia after AIS. In present study, we found patients with baseline WBC count $\geq 8.3*10^9$/L and platelet count $< 162 *10^9$/L associated with a 2.29-fold risk of pneumonia. Moreover, we noted the

predictive value of combined WBC count and platelet count for pneumonia was better than WBC count or platelet count alone.

In present study, we also do sensitivity analyses evaluate the relationship between PWR and in-hospital mortality and pneumonia. We noted patients with lowest PWR was significant associated with a high risk of pneumonia but not in-hospital mortality in comparison to highest group after adjust potential confounders. The positive association between low PWR and pneumonia support the combined effect of WBC count and platelet count on predict the risk of pneumonia. While the relationship between low PWR and high risk of in-hospital mortality was not significant after adjust potential confounders, which indicated combined WBC count and platelet count with cutoff value is better and feasibility in clinical practice. Early two studies[13, 14] shown low PWR was associated with high risk of 90 days mortality and poor outcome, which different with our study. Different outcomes definition, different study sample size and different cofounders in the models may cause the difference findings.

The strengths of this study include having a large dataset of patients from multiple centers and being the first study to evaluate the combination effect of WBC count and platelet count on in-hospital mortality and pneumonia. However, this study has several limitations. First, a proportion of patients were excluded due to a lack of WBC and platelet count data, which may cause selection bias. Secondly, this cohort included some patients whose time from onset to admission exceeded 24 hours, therefore, the levels of WBC and platelet count at admission might not accurately reflect the levels at stroke onset. However, our sensitivity analysis showed that the significance of the association remained when we restricted to patients with time from onset to admission ≤ 24 hours. Thirdly, we were precluded investigating the possible mechanism between WBC count and platelet count and in-hospital mortality as we lacked information on exact cause of death. Also, we lack the data of previous anti-platelet drug use, which may affect the platelet function. Finally, the follow-up period of our study is relatively short, thus we were unable to evaluate the combined long-term effect of WBC count and platelet count on AIS outcomes.

Conclusion

Combined high WBC count with low platelet count at admission was independently associated with in-hospital mortality and pneumonia in acute stroke patients and its predictive value is better than WBC count and platelet count alone. Our findings may helpful to early assess a high-risk patient tend to be pneumonia and mortality.

List Of Abbreviations

AIS, Acute ischemic stroke; AAAD, A acute aortic dissection; BP, Blood pressure; CI, Confidence interval; CT, computed tomography; COVID-19, Coronavirus disease 2019; eGFR, estimated glomerular filtration rate; HWHP, High WBC and high platelet; HWLP, High WBC and low platelet; IQR, Interquartile range; LWHP, Low WBC and high platelet; LWLP, Low WBC and low platelet; mRS, Modified Rankin Scale score; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; WBC, White blood cell;

OR, Odds ratio; OCSP, Oxfordshire Community Stroke Project; PWR, Platelet to white blood cell ratio; ROC, Receiver operating characteristic; SD, Standard deviation; TIA, Transient ischemic attack.

Declarations

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Availability of data and materials

The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SJY, YJC, and WQZ contributed to the concept and rationale for the study. SJY and GLX were responsible for the first draft; SJY and CKZ contributed statistical analyses. YZ, SJY and JPC performed the data collection; YJC and CFL for the first revision; All authors read and approved the final manuscript.

Competing interests

The authors declare no competing interests

Consent for publication

Not applicable

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University, as well as ethical committees at the participating hospitals. Written consent was obtained from all study participants or their immediate family members.

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Figures

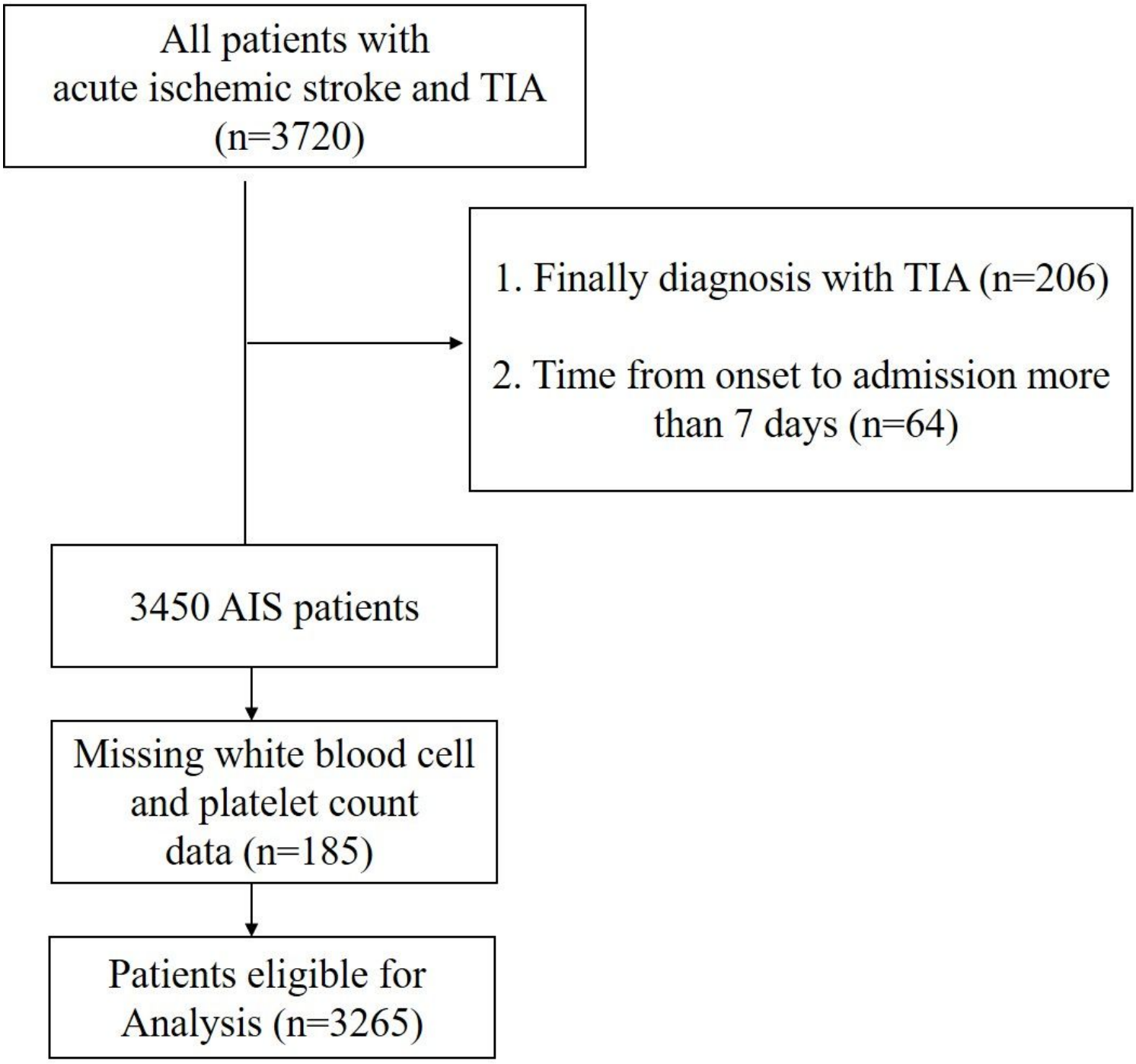

Figure 1

Patient flowchart.

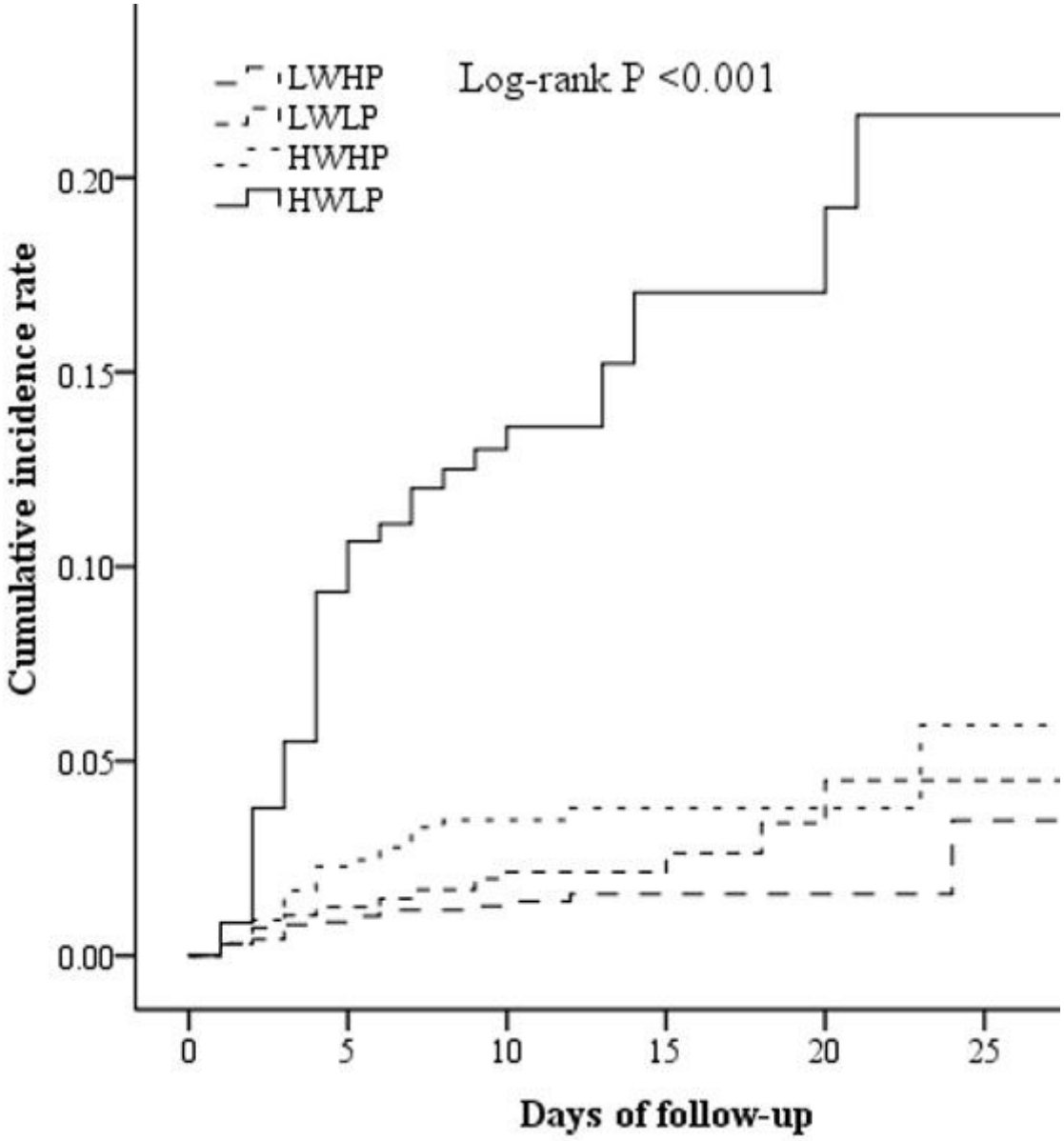

Figure 2

Cumulative incidence curves of in-hospital mortality by WBC count and platelet count

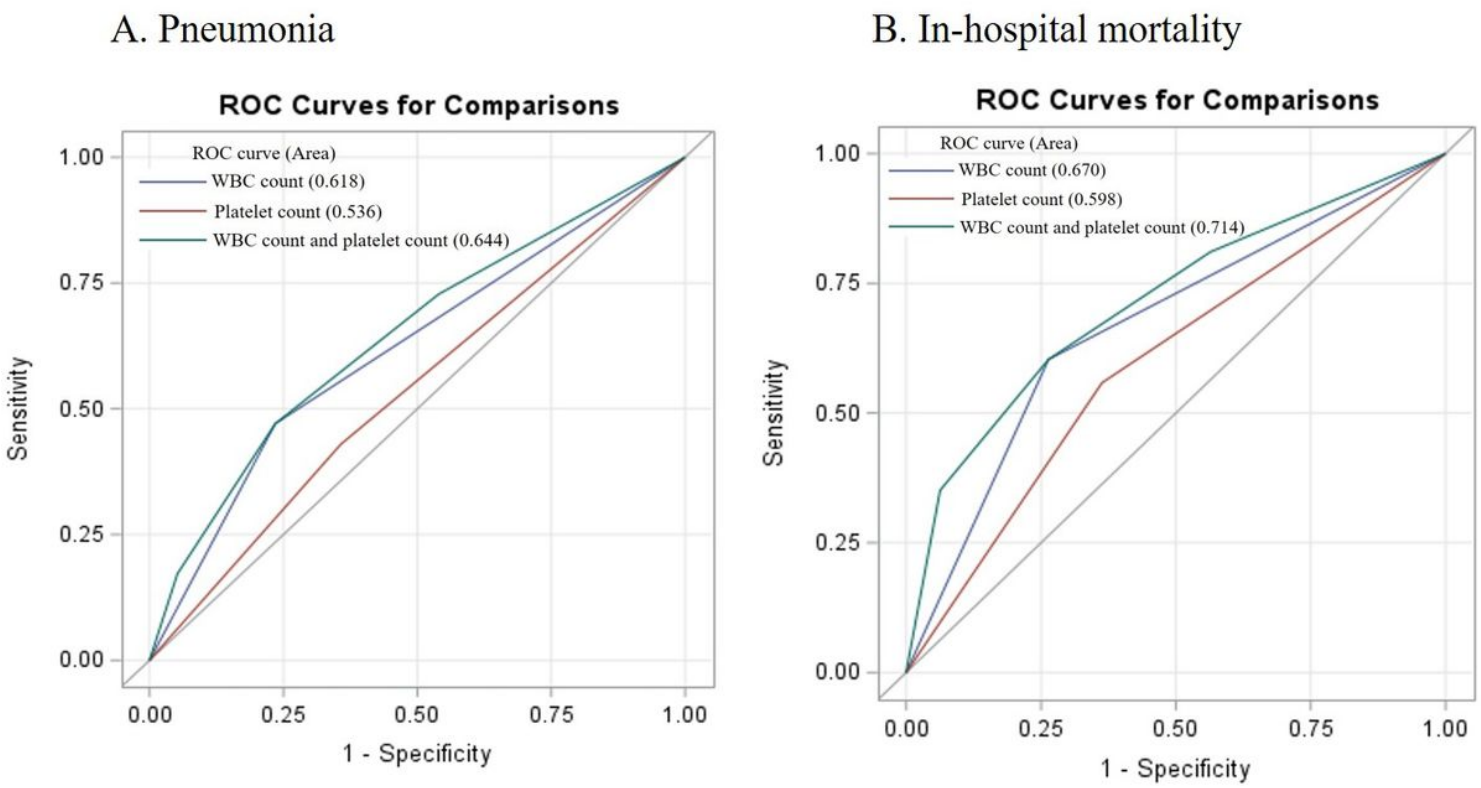

Figure 3

A. ROC curve of combined WBC count and platelet count on in-hospital pneumonia. B. ROC curves of combined WBC count and platelet count on in-hospital mortality.

Supplementary Files

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