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The joint effects of inflammation and renal function status on in-hospital outcomes in patients with acute ischemic stroke treated with intravenous thrombolysis

Zhichao Huang^{1†}, Xiaoyue Zhu^{2†}, Xiuman Xu[†], Yi Wang¹, Yafang Zhu¹, Dongqin Chen¹, Yongjun Cao^{1*} and Xia Zhang^{1*}

Abstract

Objective We aimed to determine the predictive value of renal function status [estimating glomerular filtration rate (eGFR)] in conjunction with inflammatory biomarkers [white blood cell (WBC) and C-reactive protein (CRP)] for in-hospital outcomes in acute ischemic stroke (AIS) patients treated with intravenous thrombolysis (IVT).

Methods We retrospectively screened a total of 409 AIS patients treated with IVT. The study participants were classified into two groups according to post-stroke pneumonia or functional outcome. They were divided into four groups according to the cut-offs of inflammatory biomarkers and eGFR by receiver operating characteristics (ROC) curves for two outcomes of post-stroke pneumonia and functional status: WBC↓/eGFR↑, WBC↓/eGFR↓, WBC↑/eGFR↑, and WBC↑/eGFR↓ for post-stroke pneumonia; and CRP↓/eGFR↑, CRP↓/eGFR↓, CRP↑/eGFR↑, and CRP↑/eGFR↓ for functional outcome. Logistic regression models were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of post-stroke pneumonia or at-discharge functional outcome, using the WBC↓/eGFR↑ group or CRP↓/eGFR↑ group as the reference. The Net Reclassification Index (NRI) and the Integrated Discrimination Improvement (IDI) were calculated to analyze the combined predictive value.

Results Compared with patients in WBC↓/eGFR↑ group, those in WBC↑/eGFR↑ group had increased risk of post-stroke pneumonia (OR 5.15, 95% CI 1.67–15.87) and poor functional outcome (OR 5.95, 95% CI 2.25–15.74). Furthermore, patients in WBC↑/eGFR↓ group had the highest risk of clinical outcomes (all *P* value for trend < 0.001), the multivariable-adjusted ORs (95% CIs) were 7.04 (2.42–20.46) for post-stroke pneumonia and 8.64 (3.30–22.65) for poor functional outcome. The addition of WBC and eGFR to the basic model significantly improved risk prediction for post-stroke pneumonia (category-free NRI 69.0%, 95% CI 47.3%–90.7%; IDI 5.4%, 95% CI 2.6%–8.3%) and functional outcome (category-free NRI 59.4%, 95% CI 39.2%–79.9%; IDI 5.3%, 95% CI 2.9%–7.8%). Similarly, when we added CRP and eGFR to the basic model with conventional risk factors, the risk discrimination and prediction for post-stroke pneumonia and functional outcome was also significantly improved.

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Conclusion Combining renal function status and inflammatory biomarkers within 4.5 h after onset could better predict in-hospital outcomes of AIS patients with IVT.

Keywords Acute ischemic stroke, Estimating glomerular filtration rate, White blood cell, C-reactive protein, Intravenous thrombolysis, Prognosis, Joint prediction

Introduction

Intravenous thrombolytic therapy (IVT) with recombinant tissue plasminogen activator (rt-PA) has been shown to be the most effective treatment for acute ischemic stroke (AIS) patients within 4.5 h of the onset of symptoms [1], however, the prognosis for many patients receiving it is still poor due to the occurrence of complications. A number of studies have examined the association between poststroke medical complications and mortality. Pneumonia is the major early complication of stroke and is associated with high morbidity and mortality. Pneumonia by itself is also associated with longer hospital stays and poor functional outcomes [2, 3]. Meanwhile, more than one-third of stroke patients have renal dysfunction (CKD), presenting as a decrease of estimated glomerular filtration rate (eGFR, typically < 60 ml/min/1.73 m²) [4, 5]. Previous studies have shown that CKD is associated with poor prognosis, symptomatic intracranial hemorrhage (sICH) [3, 6] and death [7–10] in AIS patients. Both CKD and pneumonia are important factors contributing to the prognosis of AIS patients.

Moreover, inflammation plays an important role in ischemic stroke. Many inflammatory markers in peripheral blood are demonstrated to be correlated with ischemic stroke severity or prognosis. Furthermore, inflammation plays a critical role in the initiation and progression of CKD, and inflammation and CKD often co-exist in AIS patients. However, whether eGFR combined with inflammatory biomarkers can better predict the short-term prognosis of AIS patients has not been thoroughly investigated. This is important because a better understanding of risk factors and predictors of prognosis could enable clinicians to precisely identify patients at high risk and to give them appropriate treatments. Therefore in this paper, we aimed to determine the predictive value of eGFR and inflammatory biomarkers [white blood cell (WBC) or C-reactive protein (CRP)] for in-hospital outcomes in AIS patients treated with IVT.

Patients and methods

This study retrospectively selected consecutive AIS patients who received intravenous rt-PA within 4.5 h of symptom onset from the Stroke registry at the Suzhou Comprehensive Stroke Center between May 2018 and

May 2021. The inclusion criteria were based on indications for intravenous rt-PA thrombolysis [1]. The exclusion criteria were as follows: 1) patients with cerebral infarction sequelae and modified rankin scale (mRS) ≥ 1 ; 2) suffering from severe underlying diseases; 3) patients with stroke mimics; 4) missing mRS data; 5) patients without eGFR, WBC count, and CRP data collected within 4.5 h of symptoms of stroke onset. All patients were routinely given appropriate antithrombotic drugs and other conventional treatments 24 h after thrombolysis. The research program was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University and was conducted in accordance with the ethical standards set out in the 1964 Declaration of Helsinki and its later amendments (JDHG-2021-41). Informed consents were obtained from all participants or their caregivers.

Data on demographic characteristics, lifestyle, risk factors, medical history, clinical laboratory tests, and imagings were collected at admission. All information is obtained by trained staff through a standard management questionnaire. Baseline stroke severity was assessed by trained neurologists using the National Institutes of Health Stroke Scale (NIHSS) [11]. Oxfordshire Community Stroke Project (OCSP) classification [lacunar infarct (LACI), total anterior circulation infarcts (TACI), partial anterior circulation infarcts (PACI) and posterior circulation infarcts (POCI)], the Trial of Org 10,712 in Acute Stroke Treatment (TOAST) etiology [large artery atherosclerosis (LAA); cardioembolism (CE); small-artery occlusion (SAO); stroke of other determined cause (ODC)] were collected standardly. Blood samples were taken upon admission within 4.5 h of onset before IVT, and were tested using VITROS XT 3400 Chemistry Analyzer and Sysmex CS-5100 Coagulation Analyzer.

eGFR was calculated by the Chinese population Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with an adjustment coefficient of 1.1:

The CKD-EPI estimate of renal function was calculated as recommended [12]: For women with a plasma creatinine ≤ 0.7 , (plasma creatinine/0.7) $-0.329 \times (0.993)^{\text{age}} (\times 166$ if black; $\times 144$ if white or other); for women with a plasma creatinine > 0.7 , (plasma creatinine/0.7) $-1.209 \times (0.993)^{\text{age}} (\times 166$ if black; $\times 144$ if white or other); for men with a plasma creatinine ≤ 0.9 ; (plasma

creatinine/0.9) $-0.411 \times (0.993)^{\text{age}} (\times 163 \text{ if black}; \times 141 \text{ if white or other})$; for men with a plasma creatinine > 0.9 , (plasma creatinine/0.9) $-1.209 \times (0.993)^{\text{age}} (\times 163 \text{ if black}; \times 141 \text{ if white or other})$.

Post-stroke pneumonia was diagnosed within the first 7 days after admission, with reference to Centers for Disease control and Prevention (CDC) criteria.

Post-stroke pneumonia was diagnosed within the first 7 days after admission, with reference to Centers for Disease control and Prevention (CDC) criteria [13]. Diagnosis of post-stroke pneumonia was according to the following criteria: new or aggravated cough and expectoration; an increase in respiratory rate of more than 22 times/min; fever (body temperature $> 38^\circ\text{C}$); decreased WBC count ($< 4 \times 10^9/\text{L}$), increased WBC ($> 11 \times 10^9/\text{L}$), or increased neutrophil ratio; audible moist rales; and abnormal chest radiology (patchy infiltration, lobar consolidation, or pleural effusion). If the patient presented three or more of the above conditions, we diagnosed the patient with post-stroke pneumonia.

The primary endpoint was at-discharge functional outcome, which was evaluated by the mRS at-discharge, and a mRS Score of 3–6 was defined as unfavorable functional outcome.

Statistical analysis

Firstly, the study participants were classified into two groups in relation to post-stroke pneumonia status or functional outcome. The baseline characteristics of continuous variables were presented as means with SD or medians with interquartile ranges (IQRs), and were compared using Student's *t*-test or Wilcoxon rank-sum test. The categorical variables were expressed as a percentage and were compared using a χ^2 test.

In this study, we aimed to examine the combined effects of inflammatory biomarkers (WBC or CRP) and eGFR on the risk of post-stroke pneumonia and at-discharge functional outcome. Therefore, our participants were further divided into four groups in relation to inflammatory biomarkers and eGFR: WBC \downarrow /eGFR \uparrow , WBC \downarrow /eGFR \downarrow , WBC \uparrow /eGFR \uparrow , and WBC \uparrow /eGFR \downarrow ; or CRP \downarrow /eGFR \uparrow , CRP \downarrow /eGFR \downarrow , CRP \uparrow /eGFR \uparrow , and CRP \uparrow /eGFR \downarrow . Logistic regression models were used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs) of post-stroke pneumonia or at-discharge functional outcome, using the WBC \downarrow /eGFR \uparrow group or CRP \downarrow /eGFR \uparrow group as the reference. *P* trend < 0.05 indicated a significant change between groups. We constructed two logistic regression models: model 1 was an unadjusted logistic regression model; model 2 adjusted for age, sex, current smoking, admission NIHSS score, great vessels, medical history (hypertension, hyperglycemia, hyperlipidemia and coronary heart disease), history of stroke, ischemic

stroke syndrome, use of anticoagulant and antiplatelet medication, duration of hospitalization.

We further evaluated the predictive ability of the joint effects of inflammation and renal function status by adding WBC and eGFR, or CRP and eGFR to the basic model with established risk factors. Basic model included age, sex, current smoking, admission NIHSS score, great vessels, medical history (hypertension, hyperglycemia, hyperlipidemia and coronary heart disease), history of stroke, ischemic stroke syndrome, use of anticoagulant and antiplatelet medication, duration of hospitalization. We calculated C statistics, the net reclassification index (NRI), and integrated discrimination improvement (IDI) to evaluate the risk discrimination and prediction for post-stroke pneumonia and functional outcome.

All *P* values were 2-tailed, and a significance level of 0.05 was used. Statistical analysis was conducted using SAS statistical software (version 9.4; SAS Institute, Cary, NC).

Results

Baseline clinical characteristics

Figure 1 illustrated the flow chart of the patient inclusion process. After excluding patients with cerebral infarction sequelae and mRS ≥ 1 ($n = 21$), those with severe underlying diseases ($n = 23$), stroke mimics ($n = 4$), and missing mRS data ($n = 6$), and those without complete renal function and coagulation biomarker testing after IVT ($n = 21$), a total of 409 patients were included in the final analysis. The baseline clinical characteristics of participants were shown in Table 1. Compared with patients in non-pneumonia group, those in pneumonia group were older and had higher admission NIHSS scores with higher proportion of large vessel occlusion and TACI, lower proportion of PACI and longer duration of hospitalization (all $P < 0.05$). The levels of WBC and CRP were higher, while that of eGFR were lower in pneumonia group ($P < 0.05$). The same results were observed in patients with poor functional outcomes compared to those with good ones (all $P < 0.05$).

Joint effects of WBC and eGFR on in-hospital outcomes after IVT

According to the cutoffs of WBC and eGFR by ROC curves, the patients were divided into 4 groups. After adjustment for confounding factors including age, sex, NIHSS score, and medical history, compared with patients in WBC \downarrow /eGFR \uparrow group, those in WBC \uparrow /eGFR \uparrow group had increased risk of post-stroke pneumonia (OR 5.15, 95% CI 1.67–15.87) and poor functional outcome (OR 5.95, 95% CI 2.25–15.74). Furthermore, patients in WBC \uparrow /eGFR \downarrow group had the highest risk of clinical outcomes (all *P* value for trend < 0.001), the

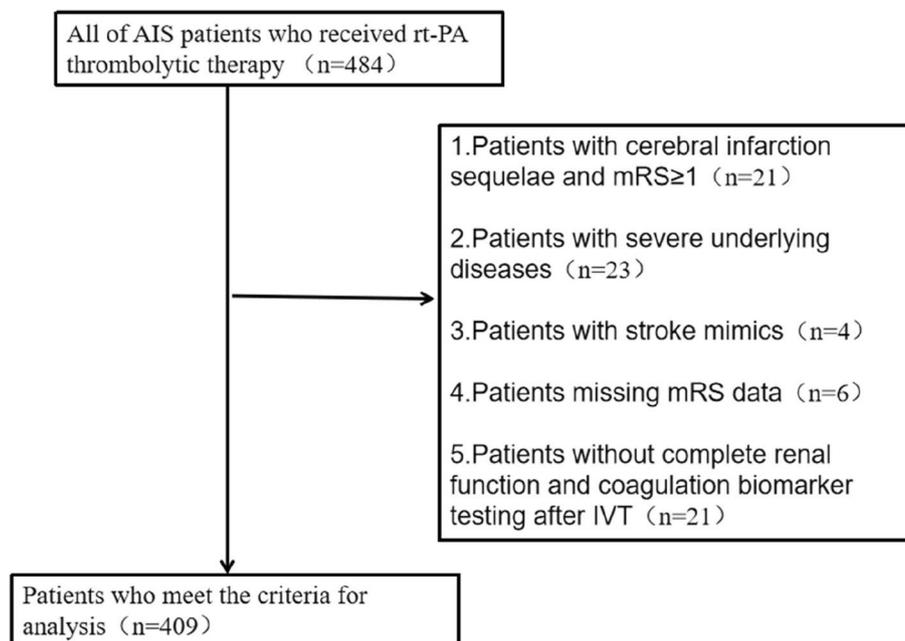


Fig. 1 Patient flowchart

multivariable-adjusted ORs (95% CIs) were 7.04 (2.42–20.46) for post-stroke pneumonia and 8.64 (3.30–22.65) for poor functional outcome, the results were shown in Table 2 and Fig. 2.

Joint effects of CRP and eGFR on in-hospital outcomes after IVT

Table 3 and Fig. 2 shows the relationships between CRP and eGFR with post-stroke pneumonia and functional outcome in patients with acute ischemic stroke treated with IVT. Patients in CRP[↑]/eGFR[↓] group had the highest risk of clinical outcomes (all P value for trend < 0.001). The ORs (95% CIs) of CRP[↑]/eGFR[↓] group were 7.90 (4.04–15.46) for post-stroke pneumonia and 12.54 (5.51–28.56) for poor functional outcome, compared with those in CRP[↓]/eGFR[↑] group. After adjustment for age, sex, NIHSS score, medical history, and other covariates in model 2, the ORs (95% CIs) were 4.76 (1.73–13.10) for post-stroke pneumonia and 5.51 (1.95–15.55) for poor functional outcome after acute ischemic stroke.

Predictive ability of inflammatory biomarkers and eGFR on study outcomes after ischemic stroke treated with IVT

We further assessed the incremental prediction utility of the combination of inflammatory biomarkers and eGFR beyond the basic model for clinical outcomes. The basic model included age, sex, NIHSS score, medical history, ischemic stroke syndrome and conventional risk factors. The fourth group demonstrated the highest predictive

value, having the largest auc after adding on to the base model (Fig. 3), as C statistics increased from 0.870 (95% CI: 0.834–0.901) to 0.889 (95% CI: 0.855–0.918) for post-stroke pneumonia, and from 0.861 (95% CI: 0.824–0.893) to 0.887 (95% CI: 0.852–0.916) for functional outcome. Furthermore, as shown in Table 4, the addition of WBC and eGFR to the basic model significantly improved risk prediction for post-stroke pneumonia (category-free NRI 69.0%, 95% CI 47.3%–90.7%; IDI 5.4%, 95% CI 2.6%–8.3%) and functional outcome (category-free NRI 59.4%, 95% CI 39.2%–79.9%; IDI 5.3%, 95% CI 2.9%–7.8%). Similarly, when we added CRP and eGFR to the basic model with conventional risk factors, the risk discrimination and prediction for post-stroke pneumonia and functional outcome was also significantly improved.

Discussion

In this study, we demonstrated that inflammation biomarkers and eGFR are important factors affecting in-hospital outcomes of patients with AIS after IVT treatment, and patients with WBC[↑]/eGFR[↓] and CRP[↑]/eGFR[↓] had the worst post-stroke pneumonia and poor functional outcomes compared with other groups. In addition, the addition of inflammatory biomarkers (WBC or CRP) combined with eGFR to the basic model with conventional risk factors significantly improved risk prediction for post-stroke pneumonia and functional outcome.

Previous studies have shown that CKD and stroke have similar risk factors and pathophysiological mechanisms,

Table 1 Baseline characteristics of study participants

Characteristics ^a	Post-stroke pneumonia			Functional outcome		
	Non-pneumonia	Pneumonia	P value	Good	Poor	P value
No. of patients	323 (79.0)	86 (21.0)		289 (70.7)	120 (29.3)	
Age, y	66.6 ± 12.8	73.1 ± 13.1	< 0.001	66.3 ± 12.9	71.9 ± 12.9	< 0.001
Male sex	189 (58.5)	44 (51.2)	0.22	176 (60.9)	57 (47.5)	0.01
Current cigarette smoking	116 (35.9)	25 (29.1)	0.24	109 (37.7)	32 (26.7)	0.03
Admission NIHSS score	3 (2–6)	12 (7–20)	< 0.001	3 (2–5)	11 (6–16)	< 0.001
Great vessels	45 (13.9)	51 (59.3)	< 0.001	32 (11.1)	64 (53.3)	< 0.001
Medical history						
Hypertension	208 (64.4)	59 (68.6)	0.47	180 (62.3)	87 (72.5)	0.05
Hyperglycemia	69 (21.4)	17 (19.8)	0.75	54 (18.7)	32 (26.7)	0.07
Hyperlipidemia	68 (21.1)	14 (16.3)	0.33	62 (21.5)	20 (16.7)	0.27
Coronary heart disease	21 (6.5)	6 (7.0)	0.87	18 (6.2)	9 (7.5)	0.64
History of stroke	44 (13.7)	13 (15.1)	0.73	42 (14.6)	15 (12.5)	0.58
Medications						
Anticoagulant	6 (1.9)	1 (1.2)	1.00	4 (1.4)	3 (2.5)	0.42
Antiplatelet	14 (4.3)	4 (4.7)	0.90	12 (4.2)	6 (5.0)	0.70
TOAST			< 0.001			< 0.001
LAA	252 (78.0)	46 (53.5)		226 (78.2)	72 (60.0)	
CE	18 (5.6)	3 (3.5)		19 (6.6)	2 (1.7)	
SAO	47 (14.6)	36 (41.9)		40 (13.8)	43 (35.8)	
ODS	6 (1.9)	1 (1.2)		4 (1.4)	3 (2.5)	
Stroke syndrome			< 0.001			< 0.001
TACI	37 (11.5)	39 (45.3)		27 (9.3)	49 (40.8)	
PACI	213 (65.9)	36 (41.9)		196 (67.8)	53 (44.2)	
POCI	63 (19.5)	11 (12.8)		56 (19.4)	18 (15.0)	
LACI	10 (3.1)	0		10 (3.5)	0	
Duration of hospitalization, d	8 (7–10)	13 (8–19)	< 0.001	8 (7–10)	11 (8–16)	< 0.001
WBC	7.1 ± 2.3	9.5 ± 3.4	< 0.001	6.9 ± 2.2	9.2 ± 3.3	< 0.001
CRP	6.9 ± 10.0	21.4 ± 31.4	< 0.001	7.4 ± 11.9	16.2 ± 26.4	< 0.001
eGFR	88.0 ± 20.3	80.5 ± 20.5	0.003	88.8 ± 17.6	80.7 ± 25.5	0.002

Abbreviations NIHSS National Institute of Health Stroke Scale, LAA Large-artery atherosclerosis, CE Cardioembolism, SAO Small-artery occlusion, ODC Stroke of other determined cause, TACI Total anterior circulation infarcts, PACI Partial anterior circulation infarcts, POCI Posterior circulation infarcts, LACI Lacunar infarcts, WBC White blood cell, CRP C-reactive protein, eGFR estimated glomerular filtration rate

^a Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as number (%)

and low eGFR is considered to be an independent risk factor for cardiovascular and cerebrovascular events and death in stroke patients [14, 15]. Cohort studies and meta-analyses have shown that eGFR reduction increases stroke risk by approximately 40% [16], and the presence of proteinuria increases stroke risk by up to 70% [17], even after adjusting for traditional cardiovascular risk factors. In this study, we determined the effect of renal function status on in-hospital clinical outcomes in AIS patients with rt-PA, similar to ENCHANTED's postmortem findings that baseline renal function status was associated with an increased 90-day risk of death [7]. While the exact mechanism by which eGFR reduction leads to harmful effects is not fully understood, it appears to be

a multifactorial process. First, traditional cardiovascular risk factors, including aging, high blood pressure, smoking, and dyslipidemia, were more prevalent in patients with CKD. Secondly, the greater burden of cardiovascular and cerebrovascular diseases caused by CKD may lead to poor peripheral collateral circulation and increased infarct volume, thus hindering vascular recanalization after stroke and leading to worse prognosis [18]. Third, non-conventional risk factors directly caused by kidney disease, such as chronic inflammation, oxidative stress and thrombosis factors, are also considered to be the cause of excessive cerebrovascular risk in patients with CKD, which can lead to vascular damage and endothelial dysfunction [19, 20].

Table 2 The joint effects of WBC and eGFR on clinical outcomes after ischemic stroke treated with IVT

	Groups by levels of baseline WBC and eGFR				P trend
	WBC↓/ eGFR↑	WBC↓/ eGFR↓	WBC↑/ eGFR↑	WBC↑/ eGFR↓	
Post-stroke Pneumonia					
No. (%) of cases	13 (8.7)	24 (15.5)	15 (34.1)	34 (56.7)	
Model 1	1.00	1.93 (0.93–3.95)	5.45 (2.34–12.68)	13.78 (6.42–29.60)	< 0.001
Model 2	1.00	0.90 (0.33–2.44)	5.15 (1.67–15.87)	7.04 (2.42–20.46)	< 0.001
Functional outcome					
No. (%) of cases	18 (12.1)	38 (24.7)	21 (46.7)	43 (70.5)	
Model 1	1.00	2.38 (1.29–4.40)	6.37 (2.96–13.69)	17.38 (8.31–36.38)	< 0.001
Model 2	1.00	1.69 (0.73–3.90)	5.95 (2.25–15.74)	8.64 (3.30–22.65)	< 0.001

Data are Odds ratios (95% confidence intervals)

Model 1: unadjusted logistic regression model

Model 2: adjusted for age, sex, current smoking, admission NIHSS score, great vessels, medical history (hypertension, hyperglycemia, hyperlipidemia and coronary heart disease), history of stroke, ischemic stroke syndrome, use of anticoagulant and antiplatelet medication, duration of hospitalization

Abbreviations: WBC White blood cell, eGFR estimated glomerular filtration rate

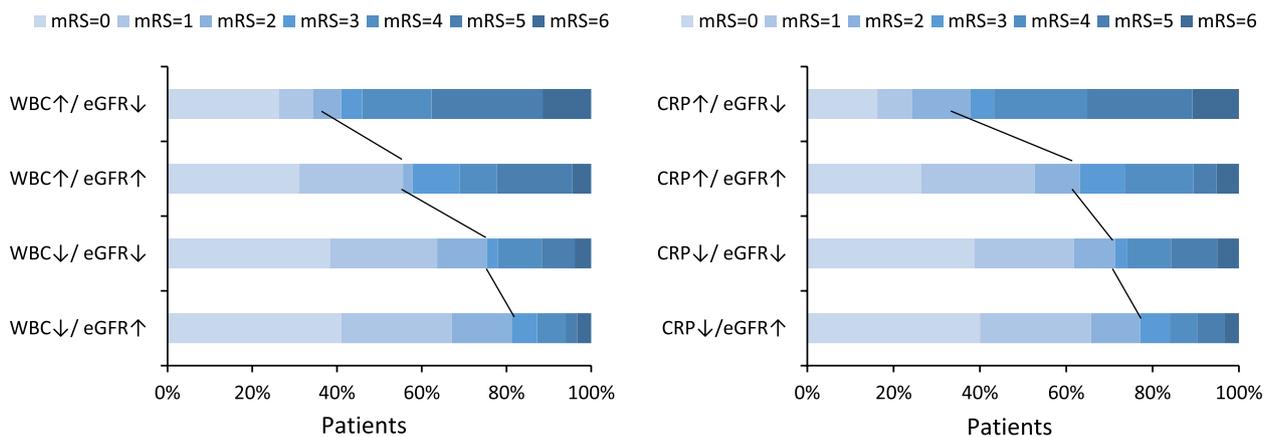


Fig. 2 The joint effects of WBC, CRP and eGFR on clinical outcomes after ischemic stroke treated with IVT

Table 3 The joint effects of CRP and eGFR on clinical outcomes after ischemic stroke treated with IVT

	Groups by levels of baseline CRP and eGFR				P trend
	CRP↓/eGFR↑	CRP↓/ eGFR↓	CRP↑/ eGFR↑	CRP↑/ eGFR↓	
Post-stroke Pneumonia					
No. (%) of cases	20 (12.8)	22 (14.9)	8 (21.1)	36 (53.7)	
Model 1	1.00	1.19 (0.62–2.28)	1.81 (0.73–4.51)	7.90 (4.04–15.46)	< 0.001
Model 2	1.00	0.57 (0.21–1.58)	1.18 (0.38–3.66)	4.76 (1.73–13.10)	< 0.001
Functional outcome					
No. (%) of cases	31 (17.7)	54 (30.3)	8 (42.1)	27 (73.0)	
Model 1	1.00	2.02 (1.22–3.34)	3.38 (1.26–9.09)	12.54 (5.51–28.56)	< 0.001
Model 2	1.00	1.73 (0.80–3.73)	1.75 (0.56–5.43)	5.51 (1.95–15.55)	0.002

Data are Odds ratios (95% confidence intervals)

Model 1: unadjusted logistic regression model

Model 2: adjusted for age, sex, current smoking, admission NIHSS score, great vessels, medical history (hypertension, hyperglycemia, hyperlipidemia and coronary heart disease), history of stroke, ischemic stroke syndrome, use of anticoagulant and antiplatelet medication, duration of hospitalization

Abbreviations CRP C-reactive protein, eGFR estimated glomerular filtration rate

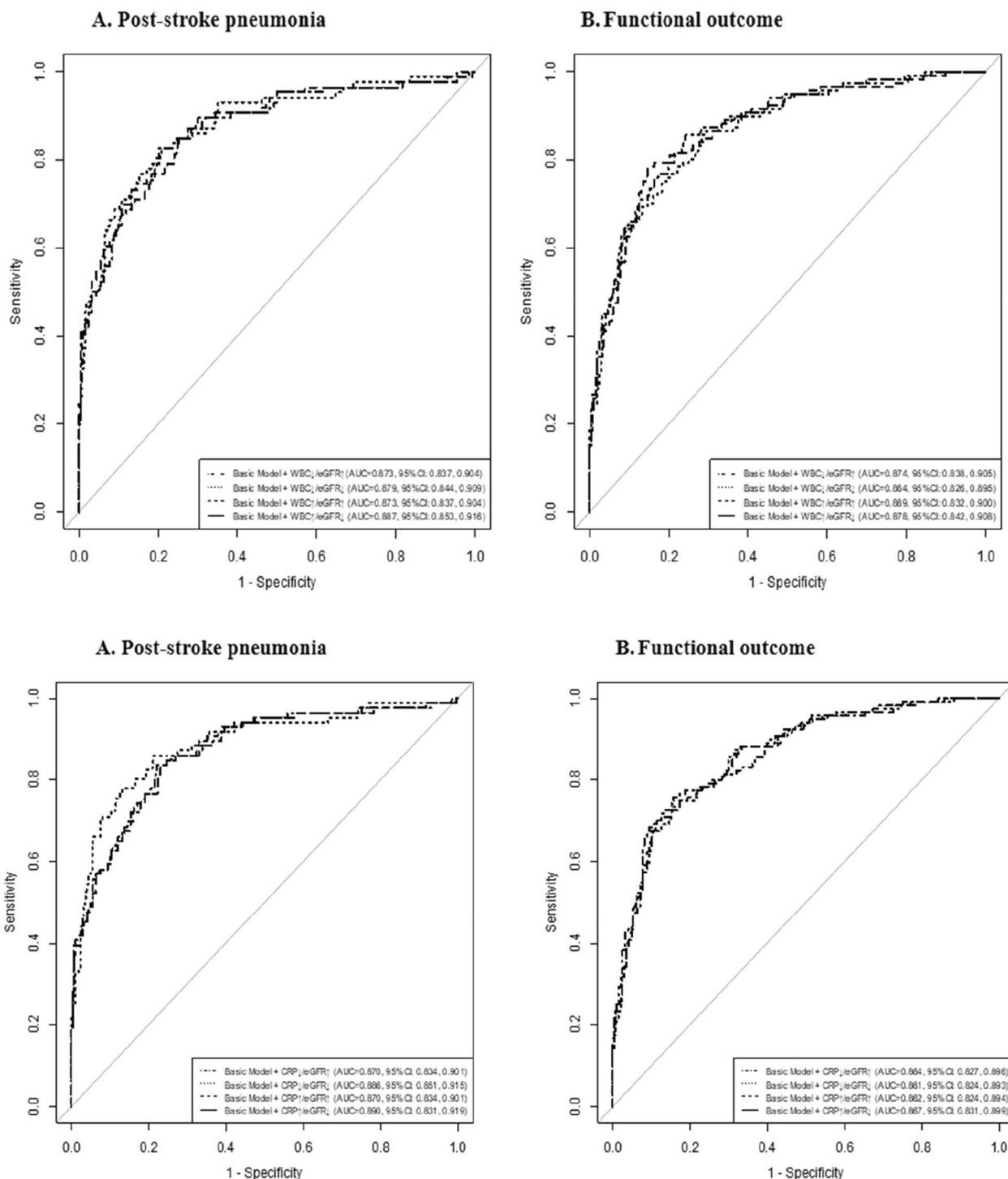


Fig. 3 Performance of models with inflammatory biomarkers and eGFR for clinical outcomes after ischemic stroke treated with IVT

In addition, CKD often alters the nature and structure of fibrin clots, which may lead to greater resistance to rt-PA thrombolysis [21]. CKD may also counteract the effects of rt-PA by impacting endothelial cell release

of tissue-type plasminogen activators, thereby reducing endothelial thrombolysis [22]. Therefore, for patients with cerebral infarction, it is feasible to actively improve renal function and thus be more beneficial to clinical

Table 4 Performance of models with inflammatory biomarkers and eGFR for clinical outcomes after ischemic stroke treated with IVT

	NRI (category free)		IDI	
	Estimate (95% CI), %	P value	Estimate (95% CI), %	P value
Post-stroke Pneumonia				
Basic model	Reference		Reference	
Basic model+WBC+eGFR	69.0 (47.3–90.7)	<0.001	5.4 (2.6–8.3)	<0.001
Basic model+CRP+eGFR	71.3 (49.1–93.4)	<0.001	8.4 (4.2–12.6)	<0.001
Functional outcome				
Basic model	Reference		Reference	
Basic model+WBC+eGFR	59.4 (39.2–79.7)	<0.001	5.3 (2.9–7.8)	<0.001
Basic model+CRP+eGFR	27.5 (71.3–47.9)	0.01	2.8 (0.8–4.9)	0.008

Basic model included age, sex, current smoking, admission NIHSS score, great vessels, medical history (hypertension, hyperglycemia, hyperlipidemia and coronary heart disease), history of stroke, ischemic stroke syndrome, use of anticoagulant and antiplatelet medication, duration of hospitalization

Abbreviations: WBC White blood cell, CRP C-reactive protein, eGFR estimated glomerular filtration rate, CI Confidence interval, IDI/Integrated discrimination improvement, NRI Net reclassification index

prognosis. In addition, the effect of gender on the results cannot be ruled out. A recent study showed that the early prognosis of women with cardiac embolism is worse than that of men [23]. We also found similar results, with higher rates in men among patients with a good prognosis. However, we found an interesting result: Among patients with a good prognosis, the proportion of current smokers was higher. This may be due to the small sample size of our study. In addition, we observed a higher incidence of pneumonia and a poorer prognosis in patients with large vessel occlusion.

Our study also confirmed the predictive value of inflammatory factors (WBC and CRP) combined with eGFR in in-hospital prognosis of patients with acute cerebral infarction, and patients in WBC \uparrow /eGFR \downarrow and CRP \uparrow /eGFR \downarrow groups had the worst short-term functional prognosis. It was previously believed that highly sensitive C-reactive protein (hs-CRP) can effectively reflect the inflammatory status of the body, and has a high sensitivity to mild aseptic inflammation, and has been widely used in clinical detection of inflammation in various diseases [24]. In patients with CKD, inflammatory biomarkers, including interleukin-6 (IL-6), tumor necrosis factor alpha (TNF- α), CRP, fibrinogen, and serum albumin, have been shown to be independently associated with atherosclerotic events and death, suggesting that inflammation may play a key role in cardiovascular events and stroke in patients with CKD [25]. Inflammatory cell damage in patients with CKD can also be demonstrated by the correlation between thrombomodulin (TM) and eGFR. TM is a vascular protective transmembrane glycoprotein with anticoagulant and anti-inflammatory activities [26]. It can be released and shed from the endothelium as an extracellular soluble form, leading to inflammatory cell damage, while studies have shown a moderate association

between TM and eGFR, even after adjusting for age. All the data implied a mutual role between inflammation and renal function status.

Previous studies have shown that hypertension patients with cerebral infarction ≥ 1.5 cm in diameter complicated with cerebral infarction have higher levels of inflammation-related factors in the body after onset, and hs-CRP and IL-6 are positively correlated with cerebral infarction diameter, which indicated the larger the diameter of cerebral infarction, the more obvious the inflammatory response of the body. 2 h after a cerebral infarction, significant pathophysiological changes occur in the brain tissue, leading to elevation of inflammation in the body [27]. With the increase of infarct size, especially in the area of cerebral ischemia and hypoxia, the above pathophysiological process became more obvious [28, 29]. Moreover, a large number of CRPs produced will further activate the complement system of the body, thus aggravating the damage of vascular endothelial cells, activating the coagulation system [30], leading to further expansion of thrombus [31], aggravating the progression of the disease and the disturbance of local blood circulation, resulting in poor prognosis [32]. Our results were consistent with the above conclusions, and the baseline NIHSS score and the proportion of large blood vessel occlusion in patients with pneumonia were significantly higher than those without pneumonia.

Our study has the following limitations. First, the prevalence of CKD in this study may have been overestimated because eGFR was estimated based on baseline creatinine at the time of vascular events, and acute kidney injury is a common complication after stroke [10]. Second, the majority of patients included in the non-inflammatory group had mild stroke with a baseline NIHSS score of 3, which is generally not associated with many systemic

sequelae. Third, only one measurement was performed for each parameter, which may weaken the relevance of the study results to some extent.

Conclusions

In this study, we demonstrated that elevated WBC or CRP levels combined with low eGFR were associated with highest risk of post-stroke pneumonia and unfavorable at-discharge functional outcome in AIS patients after IVT. The coexistence of inflammation and renal dysfunction improved risk prediction for clinical outcomes after acute ischemic stroke. In future studies, it is necessary to study the change trend of inflammatory factors and renal function in AIS patients after admission and their relationship with functional prognosis.

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Authors' contributions

Z.H. and X.Z. wrote and reviewed the draft. X.Z. and C.Z. designed the study. Y.W., Y.Z., D.C., and Z.H. collected the data and performed the statistical analysis. All authors read and approved the final manuscript.

Data availability

All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Declarations

Ethics approval and consent to participate

This study protocol was reviewed and approved by [Ethics Committee of the Second Affiliated Hospital of Soochow University], approval number [JD-LX-2018-022-05].

Consent for publication

Written informed consent was obtained from the patient for publication of this report and any accompanying images.

Competing interests

The authors declare no competing interests.

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