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High-sensitive C-reactive protein and stroke outcomes in patients with and without atrial fibrillation.

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Abstract

Aims: The purpose of this study was to examine and compare the association of baseline high-sensitive C-reactive protein (hsCRP) levels with Early Neurological Deterioration (END) in acute ischemic stroke with and without Atrial Fibrillation (AF).

Methods: Consecutive ischemic stroke patients admitted to our center within 24 h of symptom onset were prospectively recruited. Plasma hsCRP levels were measured after admission and categorized into three groups (low risk, <1.0 mg/L; average risk, 1-3 mg/L; and high risk, >3 mg/L). END was defined as a National Institutes of Health Stroke Scale (NIHSS) score increased ≥ 2 during the first 72 h compared with the initial NIHSS score.

Results: A total of 811 patients with ischemic stroke including 348 female with average age of 66.44 ± 12.54 y were enrolled in the analysis. Of them, AF was found in 226 (27.9%) patients. During the first 72 h after admission, 81 (35.8%) patients with AF and 181 (30.9%) patients without AF developed END, respectively. After adjusting the confounding factors whose P value<0.1 in univariate analysis, multiple logistic regression analysis demonstrated that high risk level of hsCRP (OR=2.39, 95% CI: 1.06-5.40) was the independent predictors of END in AF-related stroke. However, any level of hsCRP was found to be independently related to END in patients without AF.

Conclusion: Our study demonstrated that high level of hsCRP independently correlated with END in AF-related ischemic stroke.

Keywords: Stroke, C-reactive protein, Early neurological deterioration, Inflammation.

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Introduction

Atrial Fibrillation (AF) is associated with an increased risk of ischemic stroke and AF-related stroke is related to more disabling and unfavorable outcomes compared with those caused by other stroke pathophysiology [1,2]. Previous studies had suggested increased risk of thrombogenesis in participates with AF [3]. And this thrombogenic tendency was considered to be related to systemic inflammatory conditions [4]. As a blood marker of inflammation, high-sensitive C-reactive protein (hsCRP), an acutephase protein, had been reported to be increased in AF, and predict new-onset AF and AF recurrence after cardioversion or catheter ablation [5-7]. Furthermore, hsCRP had been reported to predict mid- and long-term prognosis in patients with ischemic stroke [8-10]. Early Neurological Deterioration (END), a known complication of stroke in general, commonly occurs in hours or even days after symptom onset and often leads to worse clinical outcome, may also be related to hsCRP [11,12]. However, this finding still lacks confirmation by other groups. And whether hsCRP predicts END differently in AF-related versus non-AF-related stroke is largely unknown. Currently, precise pathophysiology of END is yet incompletely elucidated. Thus, identification of various predictors for END in a certain population might help in mitigating its occurrence and influence on functional outcome. Therefore, we sought to examine and compare the association between baseline hsCRP level and END in acute ischemic stroke with and without AF.

Materials and Methods

Subjects

This study reviewed consecutive patients with a diagnosis of ischemic stroke who were admitted to our hospital within 24 h of symptom onset between January 2014 and January 2016. All patients included in this study were more than 18 years old. For those patients with stroke on awakening, stroke onset was

designated as the halfway point between the time when the patient was last symptom-free and when the neurologic deficits became apparent. Ischemic stroke was defined as the presence of focal neurologic deficits explained by the relevant lesions detected on brain Magnetic Resonance Imaging (MRI) performed within 24 h after admission. Reasons for exclusion from the study included intracranial hemorrhage, tumors and infections and intravenous or intra-arterial thrombolysis, incomplete medical records, and early discharge from the hospital (within 3 or fewer days). The study was approved by Ethics Committees of the First People's Hospital of Yangzhou and all subjects provided written informed consent before entering the study.

Clinical course assessment

Detailed data were prospectively recorded including demographics, medical history and associated cardiovascular risk factors, stroke mechanism and laboratory findings. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg in the chronic stage, or as a previous history of treatment with antihypertensive drugs. Diabetes mellitus was determined by a fasting blood glucose ≥ 126 mg/dl, positive ≥ 75 g oral glucose tolerance test result, or use of insulin or oral hypoglycemic agents. Smoking was defined as current or former cigarette smoking, and alcohol intake was defined as habitual consumption of alcohol beverages before onset of stroke. Data on history of stroke was also collected.

Information of AF was evaluated by the study cardiologist, and AF was diagnosed based on electrocardiographic findings on admission or during hospitalization, or a self-reported history of AF [13,14]. When AF was strongly suspected from the clinical presentation and brain imaging findings, repeated electrocardiogram or 24 h Holter electrocardiographic monitoring was conducted during hospital stay.

Levels of hsCRP, total cholesterol, triglycerides, Low-Density Lipoprotein (LDL), and High Density Lipoprotein (HDL), Fasting Blood-Glucose (FBG), Blood Urea Nitrogen (BUN) and Creatinine (Cr) were also analysed from fasting blood samples obtained within 24 h of admission. hsCRP level was analysed and divided into three categories based on the relative risk category recommended by the Centers for Disease Control and American Heart Association (low risk, <1.0 mg/L; average risk, 1-3 mg/L; and high risk, >3 mg/L), originally recommended for the risk assessment of cardiovascular disease [15].

Imaging analysis

A comprehensive MRI protocol including T1WI, T2WI, DWI, fluid-attenuated inversion recovery (FLAIR), and 3D time-of-flight Magnetic Resonance Angiography (MRA) was carried out by either 1.5 T (Signa; GE; USA) or a 3.0 T (Magnetom Avanto; Siemens, Germany) system largely depending on which one was available to achieve quick evaluation during the first 24 h after admission. Then Computer Tomography Angiography (CTA) was also performed to evaluate the status of craniocervical artery. Catheter-based Digital Subtraction Angiography (DSA) was performed only if these noninvasive angiographies were unable to provide sufficient information for conclusive diagnosis. Based on these imaging data, two experienced neuroradiologists, who were blinded to the patients' clinical details, independently evaluated the size of the infarction and the status of craniocervical artery. The size of the lesion was represented by the largest diameter of the lesion on DWI. The intracranial stenosis and extracranial stenosis were evaluated according to WASID criteria and NASCET criteria, respectively [16,17]. Consensus was reached over inter-observer discrepancies through consultation.

Treatment protocol and neurological deficits assessment

Once admitted in the stroke unit, guideline-based treatments were immediately started. Two basic of antithrombotic therapies including antiplatelet and anticoagulation were selected largely based on the stoke mechanisms and stroke unit's therapeutic and diagnostic protocol [18,19]. Oral stain was mandatory administrated in case of no contradictions. In addition, other treatments such as blood pressure, glucose management were also carried out as appropriate.

Neurological deficits assessment was performed using the National Institutes of Health Stroke Scale (NIHSS) at admission and continued at the following 72 h by a certified neurologist blind to clinical and imaging information. END was defined as the subsequent NIHSS score increasing ≥ 2 points compared with initial one [20,21].

Statistical analysis

All statistical analyses were performed using SPSS version 16.0. A P value<0.05 was considered significant. Continuous data were described by their mean ± SD or median (Interquartile Range (IQR)) and categorical data as proportions (percentage). For univariate analysis, student t-test, variance analysis, Mann-Whitney test, χ^2-test or Fisher's exact test was performed as appropriate. Multiple logistic regression model was performed using variables with P value ≤ 0.1 in univariate analysis to determine the independent predictors of END. The results were calculated as adjusted Odds Ratios (ORs) with 95% Confidence Intervals (CIs).

Results

A total of 811 patients with ischemic stroke including 348 female with average age of 66.44 ± 12.54 y were enrolled in the analysis. The median NIHSS score at admission was 7 (interquartile range, 3 to 11). Of them, AF was found in 226 (27.9%) patients. Other risk factors included hypertension 559 (68.9%), diabetes mellitus in 202 (24.9%), smoking in 230 (28.4%), and drinking in 137 (16.9%). Patients with responsible artery occlusion were found in 120 (14.8) patients

and responsible artery stenosis in 375 (46.2). Previous TIA or stroke was founded in 109 (13.4%) patients (Table 1).

Table 1. *Basic clinical data of patients.*

Characteristics	All patients (N=811)	Patients with AF (N=226)	Patients without AF (N=585)
General clinical characteristics			
Age, years, mean (SD)	66.44 ± 12.54	68.79 ± 10.96	65.33 ± 13.09
Female, N (%)	348 (42.9)	96 (42.5)	252 (43.13)
Hypertension, N (%)	559 (68.9)	162 (71.7)	397 (67.9)
Diabetes mellitus, N (%)	202 (24.9)	52 (23.0)	150 (25.6)
Previous TIA or stroke, N (%)	109 (13.4)	46 (20.4)	63 (10.8)
Smoking, N (%)	230 (28.4)	60 (26.5)	170 (29.1)
Drinking, N (%)	137 (16.9)	35 (15.5)	102 (17.4)
Initial NIHSS, median (IQR)	7 (3-11)	8 (5-12)	6 (3-11)
Hematological parameters			
WBC (10^9, $\bar{x} \pm s$)	6.87 ± 2.36	6.92 ± 2.03	6.84 ± 2.48
RBC (10^{12}, $\bar{x} \pm s$)	4.52 ± 0.64	4.55 ± 0.72	4.51 ± 0.59
BUN (mmol/l, $\bar{x} \pm s$)	5.44 ± 2.76	5.54 ± 3.84	5.39 ± 2.00
Cr (mmol/l, $\bar{x} \pm s$)	76.64 ± 34.97	77.55 ± 36.62	76.21 ± 34.18
FBG (mmol/l, $\bar{x} \pm s$)	6.48 ± 2.33	6.44 ± 2.49	6.49 ± 2.27
Total cholesterol (mmol/l, $\bar{x} \pm s$)	4.68 ± 1.17	4.77 ± 1.28	4.63 ± 1.11
Triglycerides (mmol/l, $\bar{x} \pm s$)	1.61 ± 1.08	1.62 ± 1.24	1.60 ± 1.00
LDL-cholesterol (mmol/l, $\bar{x} \pm s$)	2.67 ± 0.91	2.86 ± 0.91	2.60 ± 0.89
HDL-cholesterol (mmol/l, $\bar{x} \pm s$)	1.19 ± 0.31	1.20 ± 0.32	1.19 ± 0.31
hsCRP			
Low risk, N (%)	305 (37.6)	64 (28.3)	241 (41.2)
Average risk, N (%)	239 (29.5)	70 (31.5)	169 (28.9)
High risk, N (%)	267 (32.9)	92 (40.7)	175 (29.9)
Imaging indexes			
Lesion ≥ 20 mm, N (%)	272 (33.5)	80 (35.4)	192 (32.8)
Multiple lesion, N (%)	173 (21.3)	57 (25.2)	116 (19.8)
Responsible artery occlusion, N (%)	120 (14.8)	49 (21.7)	71 (12.1)
Responsible artery stenosis, N (%)	375 (46.2)	105 (46.5)	270 (46.2)
Current medications			
Antiplatelet age, N (%)	681 (84.0)	182 (80.5)	499 (85.3)
Anticoagulants, N (%)	42 (5.2)	29 (12.8)	13 (2.2)
END, N (%)	262 (32.3)	81 (35.8)	181 (30.9)

AF: Atrial Fibrillation; hsCRP: High-Sensitivity C-Reactive Protein; WBC: White Blood Cell; RBC: Red Blood Cell; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; FBG: Fasting Blood-Glucose; BUN: Blood Urea Nitrogen; Cr: Creatinine; END: Early Neurological Deterioration.

Low risk level of hsCRP was found in 305 (37.6%) patients. Average risk and high risk level of hsCRP were found in 239 (29.5%) and 267 (32.9%) patients, respectively. Table 2 shows the clinical characteristics of patients according to the hsCRP

risk level. The age, initial NIHSS score, FBG and END were significantly different between patients with different level of hsCRP (P<0.05).

Table 2. Comparisons of basic characteristics of patients according to hsCRP level.

Characteristics	hsCRP<1 mg/L N=305	hsCRP 1-3 mg/L N=239	hsCRP>3 mg/L N=267
General clinical characteristics			
Age, years, mean (SD)	64.88 ± 12.58	66.67 ± 11.59	68.03 ± 2.46*
Female, N (%)	125 (41.0)	101 (42.3)	122 (45.7)
Hypertension, N (%)	204 (66.9)	162 (67.8)	193 (72.3)
Diabetes mellitus, N (%)	64 (21.0)	62 (25.9)	76 (28.5)
Previous TIA or stroke, N (%)	35 (11.5)	27 (11.3)	47 (17.6)**
Smoking, N (%)	77 (25.2)	73 (30.5)	80 (30.0)
Drinking, N (%)	51 (16.7)	45 (18.8)	41 (15.4)
Initial NIHSS, median (IQR)	5 (2-9)	7 (4-12)	9 (4-12)*
Hematological parameters			
WBC (10^9, $\bar{x} \pm s$)	6.77 ± 2.41	6.76 ± 2.26	7.08 ± 2.38**
RBC (10^{12}, $\bar{x} \pm s$)	4.52 ± 0.66	4.52 ± 0.65	4.53 ± 0.60
BUN (mmol/l, $\bar{x} \pm s$)	5.52 ± 3.75	5.16 ± 1.65	5.60 ± 2.13
Cr (mmol/l, $\bar{x} \pm s$)	77.04 ± 37.20	72.69 ± 23.94	79.72 ± 40.06**
FBG (mmol/l, $\bar{x} \pm s$)	6.33 ± 2.16	6.33 ± 2.26	6.78 ± 2.54*
Total cholesterol (mmol/l, $\bar{x} \pm s$)	4.70 ± 1.16	4.63 ± 1.28	4.69 ± 1.08
Triglycerides (mmol/l, $\bar{x} \pm s$)	1.63 ± 1.21	1.60 ± 0.87	1.60 ± 1.11
LDL-cholesterol (mmol/l, $\bar{x} \pm s$)	2.64 ± 0.88	2.66 ± 0.97	2.71 ± 0.88
HDL-cholesterol (mmol/l, $\bar{x} \pm s$)	1.21 ± 0.30	1.17 ± 0.27	1.19 ± 0.35
Imaging indexes			
Lesion ≥ 20 mm, N (%)	105 (34.4)	70 (29.3)	97 (36.3)
Multiple lesion, N (%)	65 (21.3)	48 (20.1)	60 (22.5)
Responsible artery occlusion, N (%)	40 (13.1)	33 (13.8)	47 (17.6)
Responsible artery stenosis, N (%)	149 (48.9)	104 (43.5)	122 (45.7)
Current medications			
Antiplatelet age, N (%)	249 (81.6)	204 (85.4)	228 (85.4)
Anticoagulants, N (%)	21 (6.9)	11 (4.6)	10 (3.7)
END, N (%)	75 (24.6)	80 (33.5)	107 (40.1)*

AF: Atrial Fibrillation; hsCRP: High-Sensitivity C-Reactive Protein; WBC: White Blood Cell; RBC: Red Blood Cell; LDL: Low-Density Lipoprotein; HDL: High-Density Lipoprotein; FBG: Fasting Blood-Glucose; BUN: Blood Urea Nitrogen; Cr: Creatinine; END: Early Neurological Deterioration.

*P<0.05; **P<0.01

Of the 811 subjects included in the study, 226 patients were diagnosed with AF. During the first 72 h after admission, 81 (35.8%) patients with AF and 181 (30.9%) patients without AF developed END, respectively. After adjusting the confounding factors (including age, sex, previous TIA or stroke, baseline NIHSS, LDL, FBG and responsible artery occlusion) whose P value ≤ 0.1 in univariate analysis, multiple logistic regression analysis demonstrated that, compared with low risk level of hsCRP, high risk level of hsCRP (OR=2.39, 95% CI: 1.06-5.40) was the independent predictors of END in AF-related ischemic stroke. For those without AF, however, any level of hsCRP was found to be independently related to END

after adjusting the age, sex, diabetes mellitus, smoking, baseline NIHSS, LDL, FBG and responsible artery occlusion (Table 3).

Table 3. Multivariable analysis of the associations between hsCRP levels and the development of END.

	Patients with AF		Patients without AF	
	Unadjusted OR (95% CI)	Adjusted† OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR‡ (95% CI)
hsCRP				
Low risk	Ref	Ref		
Average risk	2.32 (1.06-5.05)	1.97 (0.86-4.54)	1.36 (0.88-2.09)	1.28 (0.81-2.02)
High risk	3.30 (1.58-6.87)	2.39 (1.06-5.40)	1.71 (1.12-2.60)	1.37 (0.88-2.15)

†Adjustment by age, sex, previous TIA or stroke, baseline NIHSS, LDL, FBG and responsible artery occlusion. ‡Adjustment by age, sex, diabetes mellitus, smoking, baseline NIHSS, LDL, FBG and responsible artery occlusion.

Discussion

The present study analysed a large series of consecutive stroke patients to investigate the role of hsCRP in the prediction of END. We showed that high risk level of hsCRP measured at admission was an independent predictor of END in patients with AF, but not in patients without AF. To prove these associations, we adopted a relatively stringent definition of END as a ≥ 2-point increase in NIHSS score within 72 h after admission, which was more likely to be related to hemodynamic and thrombotic causes. Whereas the deterioration in the later stage of ischemic stroke was more association with systemic reasons such as aspiration, infection and electrolyte disturbances. Due to the diverse diagnostic criteria for END and the time interval to evaluation among studies, the rate of END in hospitalized ischemic stroke patients ranged from 12% to 43% [20-23]. In the present study, END was present in 32.3% of the subjects analysed, which was consistent with previous studies.

Inflammation is increasingly considered as playing a central role in the process of atherosclerosis and cardiovascular disease. As one of the most investigated inflammatory makers in cardiovascular researches, hsCRP had been shown to be a useful prognostic indicator for such vascular diseases as myocardial infarction, coronary artery disease, and ischemic stroke [5]. An influence of elevated levels of the CRP on cardiovascular or stroke functional outcome had also been reported [6-10]. In the Framingham Study, elevated plasma CRP levels were shown to be significantly associated with future ischemic stroke and transient ischemic attack independent of conventional risk factors [24]. In addition, a study from the Third National Health and Nutrition Examination Survey investigated the relationship between hsCRP and stroke risk in 880 participants. Baseline hsCRP levels were shown to be predictive of mortality and vascular death in AF but not stroke [25]. However, in another study consisted of biracial US population, baseline hsCRP was shown to be a marker of increased risk of stroke but not in participants with AF despite the fact of having higher levels of hs-CRP [7]. In a word, it was controversy whether the predictive effects of hsCRP on clinical outcome were the same in patients with AF and those with non-AF. The findings of this study support the different predictive effects of hsCRP on the END within 72 h in AF versus non-AF. To our best knowledge, few studies had examined and compared the relationship between baseline hsCRP level and END in acute ischemic stroke with and without AF.

Currently, the precise mechanisms underlying the association between plasma hsCRP and clinical outcomes after ischemic stroke had not yet been sufficiently studied. As we all know, once an ischemic event occurs, the expression of inflammatory molecules and activation of quiescent inflammatory cells leads to inflammatory state for several months after initial insult [26]. Furthermore, AF itself may lead to an inflammatory state. And previous studies had already shown that patients with AF-related stroke compared with other subtypes have significantly higher median levels of multiple inflammatory markers like tumor necrosis factor-alpha, IL-6, and IL-1b [27]. Therefore, the predictive effect of hsCRP on END might be markedly magnified in patients with AF. As expected, we found that high level of hsCRP was associated with END in AF-related stroke. Although the precise mechanisms underlying this association were unclear, there are two possible explanations. The first involves the fluid accumulation and edema, which might lead to exacerbation of brain infarction [5,12]. Alternatively, patients with AF were reported to be with increased risk of thrombogenesis. This thrombogenic tendency was considered to be related to abnormal changes in inflammatory biomarkers like hsCRP [5,11]. Therefore, hsCRP might further increase the risk of thrombogenesis in patients with AF, which could lead to a infarct expansion or a new thromboembolic events. However, further researches are needed to confirm our result.

We acknowledge certain limitations of our study. First, the present study was limited by its observational study in a single hospital, which might have generated selection bias compared with a population-wide setting. Second, venous blood was collected after an overnight fast when patients had already

taken the first dosage of antiplatelet drug. However, we supposed that the administration of first dosage of antiplatelet drug may have little impact on hsCRP according current several published studies [28,29]. Third, AF in our study was ascertained by electrocardiographic findings and a self-reported history. Although the self-report of a previous physician diagnosis of AF could be subject to recall and ascertainment bias. Previous study had shown that self-report of a previous physician diagnosis of AF has similar stroke predictive value as electrocardiogram [7,13]. Forth, we had not conducted the second imaging examination after END, so the specific mechanisms of END were not evidently demonstrated. Further researches were needed to elaborate the underlying mechanisms of END.

In conclusion, we found that high level of hsCRP independently correlated with END in AF-related ischemic stroke, which to some degree demonstrated that hsCRP might be a target for intervention during the acute phase of ischemic stroke, especially of the AF-related ischemic stroke. Development of specific human hsCRP inhibitors might further help elaborate the precise mechanisms underlying this association.

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All the authors listed have approved the submitted manuscript and we declare that we have no conflict of interest.

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