ORIGINAL ARTICLE

High-Sensitivity C-Reactive Protein is a Strong Risk Factor for Death after Acute Ischemic Stroke among Chinese

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Keywords

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SUMMARY

Background and purpose: Elevated plasma C-reactive protein (CRP) has been suggested as a risk factor for ischemic stroke (IS) and coronary ischemic disease. Evidence has shown that high-sensitivity CRP (hs-CRP) is related to a worsening prognosis after IS, but hs-CRP was rare in a large-sample study in a Chinese population. We investigated the associations between hs-CRP and outcome of Chinese patients after acute IS. **Methods:** Seven hundred and forty-one consecutive acute IS patients (74.9% male, mean age 60.9 years), with baseline characteristics and hs-CRP measured within 24 h after hospitalization, were admitted in this study. We also prospectively followed up for clinical outcome and death 3 months after disease onset. hs-CRP was divided into two categories: hs-CRP > 3 mg/L and hs-CRP ≤ 3 mg/L. Survival analysis using multivariable Cox regression was performed to analyze the association between hs-CRP and stroke outcomes after adjusting for potential confounding factors. **Results:** Compared with low hs-CRP, patients with high hs-CRP (> 3 mg/L) had a significantly higher rate of all-cause death (0.71% vs. 10.00%; $P < 0.001$) at 3 months after stroke onset. High hs-CRP was an independent risk factor for all-cause death (HR, 6.48; 95% CI, 1.41 to 29.8; $P = 0.016$), as well as history of atrial fibrillation (HR, 5.24; 95% CI, 1.83 to 15.0; $P = 0.002$), no statin therapy during hospitalization (HR, 4.56; 95% CI, 2.18 to 9.55; $P < 0.001$), high homocysteine (> 15.1 mmol/L) (HR, 2.66; 95% CI, 1.26 to 5.60; $P = 0.01$); fasting glucose (> 6.1 mmol/L) (HR, 9.14; 95% CI, 3.34 to 25.0; $P < 0.001$), NIHSS at admission (HR, 2.35; 95% CI, 1.35 to 4.09; $P = 0.003$) and history of coronary heart disease (CHD) (HR, 2.34; 95% CI, 1.06 to 5.17; $P = 0.035$). Kaplan–Meier survival curves showed a higher risk of death for patients with hs-CRP > 3 mg/L ($P = 0.016$). **Conclusion:** Elevated plasma hs-CRP independently predicted risk of all-cause death within 3 months after acute IS in Chinese patients.

Introduction

Much evidence has shown that inflammation plays a fundamental role in the pathogenesis of atherosclerosis [1,2]. C-reactive protein (CRP) is a known blood protein that increases in response to inflammation [3], and it is also one of the most extensively studied biomarkers of inflammation in cardiovascular disease and ischemic stroke (IS) [4,5]. CRP is clearly considered to be an established risk factor for cardiovascular disease [6]. Several prospective studies have demonstrated that elevated levels of CRP in apparently healthy individuals are associated with increased risk of all-cause mortality [7–10]. Also, multiple studies have demonstrated that CRP concentrations, in secondary prevention, are predictive of future mortality in stroke patients [11–16]. In

addition, data from large-sample studies in China about the relationship between high-sensitivity CRP (hs-CRP) and in stroke patients are rare [17,18], and evidences in statistically strong power are needed. Therefore, we sought to determine the relationship between hs-CRP and all-cause mortality after acute IS in a large cohort of Chinese patients.

Materials and Methods

Patients

Between October 1, 2009 and December 31, 2010, a series of consecutive acute IS inpatients (≥ 18 years old) less than 14 days after symptom onset were recruited at the Neurology

Department of Beijing Tiantan Hospital. Exclusion criteria were transient ischemic attack (TIA), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and lack of baseline data. Acute IS was defined as a sudden, focal, neurological deficit that persisted beyond 24 h with confirmation by brain CT or MRI examination. Participants signed informed consent forms, and the protocol for this study was approved by the Institutional Review Board at Tiantan Hospital.

Data Collection

The primary data collected were (1) patient demographics (age, sex); (2) vascular risk factors such as history of stroke (defined as a history of IS, TIA, or ICH confirmed by medical chart), hypertension (including self-reported history of hypertension, oral antihypertensive drugs, or two or more readings ≥ 140 mmHg and/or ≥ 90 mmHg before stroke), coronary heart disease (CHD), atrial fibrillation (history of atrial fibrillation, confirmed by at least one electrocardiogram (ECG) or the presence of arrhythmia during hospitalization), diabetes mellitus (including history of diabetes mellitus or oral hypoglycemic agents/insulin), current or previous smoking, peripheral vascular disease (intermittent claudication, critical leg ischemia or amputation, reconstructive vascular surgery or angioplasty because of atherosclerotic disease Ankle-Brachial Index < 0.9) and body mass index (calculated as measured weight divided by the square of measured height); (3) basic biochemistry tests such as hs-CRP, fasting blood glucose, total cholesterol, triglyceride, high-density lipoproteins, low-density lipoproteins, homocysteine, and blood creatinine with the blood sample the morning after being admitted; (4) usage of statins during hospitalization; (5) stroke etiologic subtype classified by the Chinese IS subclassification (CISS) [19] as large artery atherosclerosis, cardiogenic stroke, penetrating artery disease, other etiologies, or undetermined etiology.

Blood pressure (mmHg) and physical examination were determined after admission. Each patient received a CT scan or a brain MRI within 48 h of stroke to confirm the diagnosis of infarction. Carotid duplex ultrasound (CDU), transthoracic echocardiogram, and ECG were submitted to onset cardiological examination. Transesophageal echocardiogram and Holter monitor for 24 h were also used to examine potential heart abnormalities.

All patients were assessed 3 months after stroke by telephone follow-up for all-cause death (or modified Rankin Scale [mRS] = 6), dependency (mRS = 3–5), and recurrence of stroke (aggravated primary neurologic deficit; new signs; or rehospitalization with a diagnosis of IS, ICH, or SAH). The telephone follow-up was conducted centrally for all patients and was based on a standardized interview protocol. The interviewers were centrally trained with the interview protocol.

Measurement of hs-CRP

The level of hs-CRP was measured within 15 days after symptom onset. Blood was collected in vacutainers, which were immediately put on ice. Plasma hs-CRP levels were measured using the Ultrasensitive CRP kit (Cat. No. 68025) and control kit (Cat. No. 68257) from Orion Diagnostics (Espoo, Finland). An automated assay procedure was conducted on a Hitachi 911 analyzer (NY,

USA) according to the manufacturer's instructions. In brief, samples were clarified by centrifuging at 2000 *g* for 15 min before assay. Lyophilized reagent was reconstituted with 4 mL deionized water, mixed thoroughly, and left to stand for 35 min. The reconstituted reagent was then added to the Hitachi reagent vessel. Another 4 mL of deionized water were used to wash the reconstituting tube and then added to the Hitachi vessel. The reconstituted reagent was mixed thoroughly before assay. Buffer R1 was mixed with lyophilized reagent without reconstitution. Measurement and calibration parameters followed the instructions from Hitachi. To calculate hs-CRP content for each patient, a standard curve was made using the control kit following Hitachi's procedure.

Statistical Analysis

Demographic and clinical characteristics of stroke patients with hs-CRP > 3 mg/L were compared with those patients with hs-CRP ≤ 3 mg/L by using the χ^2 test and *t*-test for categorical and continuous variables, respectively. The associations between CRP and death were analyzed by univariate analysis. Furthermore, survival analysis by multivariable Cox regression was used to investigate the association of CRP and 3-month death after adjusting for potential confounders such as age, gender, National Institutes of Health Stroke Scale score (NIHSS), glucose level at admission, history of hypertension, coronary heart disease, and fasting glucose at admission. In the most parsimonious model, the association was adjusted for potential confounders including history of atrial fibrillation, statin therapy during hospitalization, high homocysteine, and fasting glucose. Survival time was estimated from Kaplan–Meier survival curves and tested for statistical significance with a log-rank test.

All data analyses were performed using SAS 9.1.3 (SAS Institute, Inc., Cary, NC, USA). For all tests, $P < 0.05$ was considered statistically significant.

Results

Of 846 consecutive admissions assessed, we had hs-CRP measurements and completed baseline information for 741 patients: 555 (74.9%) men and 186 (25.1%) women. Average age was 60.9 ± 13.3 years. Demographic data, medical history, risk factors, classification of stroke subtype, laboratory examinations, and 3-month outcomes are shown in Table 1. IS subtype was categorized according to the CISS [19]. After 3 months, we were able to follow up with 687 patients (92.7% of the total).

To examine the effect of levels of hs-CRP in the patients, we divided the patients into two groups: low hs-CRP group (hs-CRP ≤ 3 mg/L) and high hs-CRP group (hs-CRP > 3 mg/L; Table 2).

As shown in Table 3, death by the 3-month follow-up was associated with age, gender, history of atrial fibrillation, history of coronary heart disease, high homocystein, fasting glucose > 6.1 mmol/L, and blood creatinine. Although it is clear that death was associated with multiple factors, it is also clear that death was significantly associated with the level of hs-CRP. In the low hs-CRP group, death by 3 months was 49.1% whereas it increased tremendously to 93.8% in the hs-CRP high group ($P < 0.001$).

Table 1 Clinical characteristics of patients (n = 741)

Characteristic ^a	Value
Demographics	
Age, mean $\pm$ SD, (year)	60.9 $\pm$ 13.3
Male	555 (74.9)
Medical history and risk factors	
IS or TIA	199 (26.9)
ICH	23 (3.1)
Hypertension	485 (65.4)
Atrial fibrillation	42 (5.67)
Coronary heart disease	114 (15.4)
Peripheral vascular disease	8 (1.08)
Diabetes	207 (27.9)
Hypelipidemia	140 (18.9)
Smoking	
No smoking	275 (37.2)
Former smoker	158 (21.4)
Current smoker	306 (41.4)
Body mass index, mean (SD), kg/m ²	25.7 (5.1)
Total cholesterol, mean (SD), mmol/L	4.12 (1.08)
Triglyceride, mean (SD), mmol/L	1.56 (1.11)
High-density lipoproteins, mean (SD), mmol/L	1.05 (0.25)
Low-density lipoproteins, mean (SD), mmol/L	2.5 (0.86)
High homocysteine, mean (SD), mmol/L	17.1 (8.23)
hs-CRP, median (IQR), mg/L	3.3 (1.3–11.0)
Male	3.4 (1.2–11.2)
Female	3.1 (1.35–10.4)
Fasting glucose, mean (SD), mmol/L	6.28 (2.69)
Blood creatinine, mean (SD), mmol/L	74.6 (23.6)
Systolic blood pressure, mean (SD), mmHg	153 (27.2)
Distolic blood pressure, mean (SD), mmHg	89.0 (16.2)
Use of statin during of hospitalization	649 (87.6)
Etiology (CISS)	
Large-artery atherosclerosis	506 (68.3)
Cardioembolism	32 (4.32)
Perforating artery	62 (8.37)
Other determined etiology	14 (1.89)
Undetermined etiology	127 (17.1)
NIHSS at admission, median (IQR)	4 (2.0–10.0)
Outcome (n = 687)	
Death within 3 months	36 (5.25)
Male	21 (4.14)
Female	15 (8.38)
Recurrence at 3 months	12 (1.88)
Male	9 (1.9)
Female	3 (1.83)
mRS at 3 month	
0–2	469 (68.4)
3–5	181 (26.4)
6	36 (5.25)

IS, ischemic stroke; TIA, transient ischemic attack; ICH, intracranial hemorrhage; CISS, Chinese ischemic stroke subclassification.

^aData are given as number (percentage) except where otherwise indicated.

Table 2 Clinical characteristics of patients with low/high hs-CRP

Characteristic ^a	CRP $\leq$ 3	CRP >3	P value
Age, mean (SD), (year)	58.5 (12.1)	64.1 (13.1)	<0.001
Male	227 (75.7)	252 (77.1)	0.681
IS or TIA	74 (24.7)	97 (29.7)	0.160
ICH	9 (3.00)	10 (3.06)	0.966
Hypertension	184 (61.3)	227 (69.4)	0.033
Atrial fibrillation	9 (3.00)	25 (7.65)	0.010
Coronary heart disease	29 (9.67)	65 (19.9)	<0.001
Peripheral vascular disease	2 (0.67)	5 (1.53)	0.305
Diabetes	84 (28.0)	92 (28.1)	0.970
Hypelipidemia	67 (22.3)	51 (15.6)	0.031
Smoking			
No smoking	106 (35.3)	122 (37.5)	–
Former smoker	56 (18.7)	80 (24.6)	0.073
Current smoker	138 (46.0)	123 (37.8)	–
Body mass index, mean (SD), kg/m ²	25.9 (4.89)	25.4 (4.81)	0.188
Total cholesterol, mean (SD), mmol/L	4.25 (1.06)	3.97 (1.1)	0.001
Triglyceride, mean (SD), mmol/L	1.68 (1.29)	1.42 (0.97)	0.004
High-density lipoproteins, mean (SD), mmol/L	1.09 (0.25)	1.01 (0.25)	<0.001
Low-density lipoproteins, mean (SD), mmol/L	2.61 (0.87)	2.40 (0.86)	0.003
High homocysteine, mean (SD), mmol/L	16.7 (8.52)	17.2 (8.01)	0.408
High homocysteine >15.1 mmol/L	111 (37.0)	140 (42.8)	0.138
Fasting glucose, mean (SD), mmol/L	6.12 (2.56)	6.54 (2.94)	0.058
Fasting glucose >6.1 mmol/L	95 (31.7)	136 (41.6)	0.010
Blood creatinine, mean (SD), mmol/L	72.6 (18.2)	76.43 (27.0)	0.042
Systolic blood pressure, mean (SD), mmHg	154 (27.3)	153 (26.8)	0.835
Distolic blood pressure, mean (SD), mmHg	89.1 (16.8)	88.8 (15.5)	0.840
Use of statins during of hospitalization	31 (10.3)	48 (14.7)	0.101
Etiology (CISS)			
Large-artery atherosclerosis	218 (72.7)	209 (63.9)	–
Cardioembolism	9 (3.0)	21 (6.42)	–
Perforating artery	34 (11.3)	20 (6.12)	<0.001
Other determined etiology	3 (1.0)	6 (1.83)	–
Undetermined etiology	36 (12.0)	71 (21.7)	–
Death within 3 months	2 (0.71)	30 (10.00)	<0.001
Recurrence at 3 months	7 (2.54)	5 (1.92)	0.627
mRS at 3 month (score:3–5)	47 (16.8)	106 (39.3)	<0.001
mRS at 3 month (score:3–6)	49 (17.4)	136 (45.3)	<0.001

IS, ischemic stroke; TIA, transient ischemic attack; ICH, intracranial hemorrhage; CISS, Chinese ischemic stroke subclassification; mRS, modified Rankin scale.

^aData are given as number (percentage) except where otherwise indicated.

Table 3 Clinical characteristics of patients at 3-month follow-up

Characteristic ^a	Alive	Death	P value
Age, mean (SD) (year)	60.3 (13.0)	70.1 (16.0)	<0.001
Male	486 (74.8)	21 (58.3)	0.029
Hs-C reactive protein >3 mg/L	170 (49.1)	30 (93.8)	<0.001
Hs-C reactive protein, median (IQR), mg/L	3.00 (1.20–10.3)	12.65 (11.0–15.0)	<0.001
IS or TIA	172 (26.5)	10 (27.8)	0.862
ICH	19 (2.92)	2 (5.56)	0.372
Hypertension	423 (65.1)	22 (61.1)	0.627
Atrial fibrillation	32 (4.92)	7 (19.4)	<0.001
Coronary heart disease	94 (14.5)	15 (41.7)	<0.001
Peripheral vascular disease	7 (1.08)	1 (2.78)	0.355
Diabetes	178 (27.4)	14 (38.9)	0.134
Hyperlipidemia	130 (20.0)	2 (5.56)	0.032
Smoking			
No smoking	234 (36.1)	23 (65.7)	–
Former smoker	140 (21.6)	4 (11.43)	0.002
Current smoker	275 (42.4)	8 (22.86)	–
Body mass index, mean (SD), kg/m ²	25.8 (4.92)	25.2 (7.22)	0.569
Total cholesterol, mean (SD), mmol/L	4.14 (1.07)	3.99 (1.33)	0.415
Triglyceride, mean (SD), mmol/L	1.58 (1.15)	1.22 (0.53)	<0.001
High-density lipoproteins, mean (SD), mmol/L	1.05 (0.24)	1.08 (0.33)	0.563
Low-density lipoproteins, mean (SD), mmol/L	2.52 (0.86)	2.29 (0.99)	0.129
High homocysteine, mean (SD), mmol/L	16.7 (7.97)	21.0 (11.2)	0.004
High homocysteine >15.1 mmol/L	246 (37.8)	20 (55.6)	0.034
Fasting glucose, mean (SD), mmol/L	6.17 (2.63)	7.83 (2.27)	<0.001
Fasting glucose >6.1 mmol/L	219 (33.7)	29 (80.6)	<0.001
Blood creatinine, mean (SD), mmol/L	73.2 (21.1)	82.5 (41.0)	0.016
Systolic blood pressure, mean (SD), mmHg	153.0 (17.0)	155.0 (32.0)	0.717
Diastolic blood pressure, mean (SD), mmHg	88.9 (16.5)	88.1 (13.4)	0.76
Usage of statin during of hospitalization	577 (88.8)	23 (63.9)	<0.001
Etiology (CISS)			
Large-artery atherosclerosis	455 (70.0)	11 (30.6)	–
Cardioembolism	23 (3.54)	7 (19.4)	–
Perforating artery	60 (9.23)	0 (0)	<0.001
Other determined etiology	13 (2.0)	1 (2.78)	–
Undetermined etiology	99 (15.2)	17 (47.2)	–

IS, ischemic stroke; TIA, transient ischemic attack; ICH, intracranial hemorrhage; CISS, Chinese ischemic stroke subclassification.

^aData are given as number (percentage) except where otherwise indicated.

There was a negative association between smoking and death by 3 months. In nonsmokers, 36.1% were still alive, whereas 65.7% ($P = 0.002$) had died. The death rate was also negatively associated with usage of statin, history of hyperlipidemia, large-artery atherosclerosis and perforating artery. Accordingly, the death rate by 3 months was high in the subclasses of cardioembolism and undetermined etiology.

To further analyze the factors associated with death by 3 months, multivariate Cox regression analysis was conducted for hs-CRP >3 mg/L, history of atrial fibrillation, no statin therapy during hospitalization, high homocysteine (>15.1 mmol/L), fasting glucose (>6.1 mmol/L), NIHSS at admission and history of CHD. The associations of those factors with increased death rate in stroke patients have been reported [20–24]. As seen in Table 4, each of these factors was significantly associated with death by 3 months in our patient population. Kaplan–Meier survival curves

showed a higher risk of death for patients with hs-CRP >3 mg/L (Figure 1).

Table 4 Multiple analysis of association between hs-CRP and death by 3-month follow-up

	HR (95%CI)	P value
hs-CRP (>3 mg/L)	6.48 (1.41–29.8)	0.016
History of atrial fibrillation	5.24 (1.83–15.0)	0.002
No statin therapy during hospitalization	4.56 (2.18–9.55)	<0.001
High homocysteine (>15.1 mmol/L)	2.66 (1.26–5.6)	0.01
Fasting glucose (>6.1 mmol/L)	9.14 (3.34–25.0)	<0.001
NIHSS	2.35 (1.35–4.09)	0.003
History of CHD	2.34 (1.06–5.17)	0.035

Figure 1 Kaplan–Meier survival curves according to hs-CRP at admission.

Discussion

This study suggests that a high level of hs-CRP (>3 mg/L) within 15 days of IS onset strongly predicted all-cause death in our patient population in the first 3 months, even after adjusting for potential confounders. Although there was a tendency toward increased recurrence and dependency in patients with high hs-CRP, the degree was not as great as that of mortality.

In recent years, CRP, as part of a nonspecific, innate immune response, has been noted not only for its role in activating the classical complement pathway but also in predicting the incidence of cardiovascular events and death in primary and secondary prevention settings. Several prospective studies have demonstrated that elevated levels of CRP in apparently healthy individuals are associated with increased risk of all-cause death and cardiovascular events [7–10,25], and recent meta-analysis [26] clearly indicated that CRP concentration has continuous associations with the risk of coronary heart disease, IS, vascular mortality, and death in people without a history of vascular disease. Previous studies have proved that elevated levels of CRP in IS patients are associated with high in-hospital [27], short-term [28,29] and long-term mortality [11–14,30–33] even in those older than 90 years [34]. Recently, some research into the relationship between hs-CRP and prognosis in acute IS has been published [35–40], but there is very little data regarding the Chinese population [17,18].

Our research was a prospective study with integrated and detailed baseline, outcome, and blood sample data. The strengths of this study are its large sample size and robust outcome measures, both of which increase the relevance of our findings.

One distinguishing feature of this study is that all patients were categorized using CISS classification whereas previous studies used the Trial of Org 10172 in Acute Stroke Treatment [41] for patient classification [36,42].

Our results agree with data from previous reports. Mitchell *et al.* [36] admitted 467 patients with first IS; at 5-year follow-up, they concluded that hs-CRP was not associated with the risk

of recurrent stroke, myocardial infarction, or vascular death but was associated with risk of death. Similarly, several other reports have suggested that increased hs-CRP level is associated with high risk of death in cerebral infarction (CI) patients [11–13,28,30–34].

Our study has several limitations. The level of hs-CRP was measured only once for each patient. Therefore, our measurement was not able to reflect potentially dynamic changes of hs-CRP level. A previous study suggested that the level of hs-CRP in CI patients varies 7 days after symptom onset [39]. Because of variations in CRP levels, blood collection in most studies was done between 12 and 72 h after symptom onset [12,14,30,32,35,37,38,40]. And also, in our study, we collect blood sample as soon as possible after admission (median of 1 day among patient admitted to hospital) but not symptom onset, delay to blood draw window time was enlarged between 12 h and 15 days after symptom onset and not as previous studies collect blood sample within short time (from 12 to 72 h) [12,14,30,32,35,37,38,40]. However, it was surprising to see that, in our study, the level of hs-CRP collected various within 15 days after symptom onset still could predict risk of 3 months death. Recently, Whiteley *et al.* [33] analyzed the association between inflammation factors and long-term risk of 877 acute stroke patients (93% had a definite IS) and found that the high level of CRP various within 30 days of stroke had a strong predictability for long-term survival of patients (2.12 years). Accordingly, we feel that the hs-CRP level various from 12 h to 15 days of CI can still predict the death risk for a patient in short time.

Our study suggests that the level of hs-CRP has a stronger predictability of risk of death than for disease relapse. One explanation is that the number of patients with relapse was too small. CRP is one of the nonspecific immune response innate. Shortly after the onset of IS, increased CRP levels may reflect an accompanying inflammatory reaction. Elevated CRP levels may reflect the extent of brain injury. It is therefore conceivable that increased levels of CRP after stroke are not only a consequence of brain infarction but also contribute to ischemic damage. Accordingly, the death rate is increased with the elevated CRP level. We realized that, our result needs to be confirmed by future studies on long-term following up and data of survival rate.

Conclusion

Elevated hs-CRP levels of acute IS are independent prognostic factors for all-cause death within 3 months in Chinese patients.

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Conflict of Interest

The authors have no conflict of interest.

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