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Original Article

C-Reactive Protein Levels and Clinical Outcomes in Stroke Patients: A Prospective Cohort Study

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Abstract

Background: The C-reactive protein (CRP) level, as an early prognostic factor of functional outcome after stroke, may be of clinical importance. The aim of this study was to determine the prognostic value of CRP on functional outcome and death in stroke patients.

Methods: This prospective study was conducted from 2015 to 2016 in Hamadan province, Iran. Patients with both ischemic and hemorrhagic stroke who were admitted in the first 12 hours were enrolled. The clinical characteristics of the patients were recorded at time of admission as well as on the fourth and the 90th day after stroke. Blood sample was taken and CRP levels were measured at time of admission.

Results: From 186 admitted patients, 155 patients remained in this study for analysis. Mean time between stroke onset and admission was 4.42 hours. Mean level of CRP was 20.03 mg/L. CRP levels in 68 patients (43.8%) were 7 mg/L or above. Prevalence of diabetes ($P=0.001$), angina pectoris ($P=0.001$), death ($P=0.001$), pneumonia ($P=0.004$), and DVT ($P=0.002$) was significantly higher among patients with CRP levels ≥7 mg/L than patients with CRP levels <7 mg/L. A CRP level ≥7 was associated with poor clinical outcome, including the National Institutes of Health Stroke Scale (NIHSS) ≥13 ($P=0.001$) as well as modified Rankin Scale (mRS) >2 ($P=0.004$) and Barthel Index (BI) <70 on the first (0.047, 0.001), fourth (0.005, 0.001), and 90th day (0.001, 0.001), respectively.

Conclusion: Our findings indicated that elevated CRP levels in the very early phase of both ischemic and hemorrhagic stroke were associated with poor clinical outcomes and prognosis.

Keywords: C-reactive protein, Cohort study, Prognosis, Stroke

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Introduction

Inflammation plays a key role in pathogenesis of cerebrovascular disease via mechanisms including development of atherosclerosis, plaque instability, and triggering of plaque rupture.[1-3] Among peripheral blood marker of inflammation, C-reactive protein (CRP), an acute phase protein, is the most extensively used and established marker.[4-7] Increases in CRP may reflect systemic inflammatory response following stroke, tissue damage and its extent, or concurrent infections.[8]

Verification of CRP as an early prognostic factor of functional outcome after stroke may be of clinical importance because it is an easily measured and readily available inflammatory marker.[9-13] Several studies have assessed CRP value in the very early phase of stroke as a prognostic factor of functional outcome. The studies only tested the relation between CRP levels and mortality instead of functional outcome. However, the results were inconsistent.[9,14] The aim of this study was to determine the association between CRP levels in stroke patients and poor functional outcomes and death.

Materials and Methods

Study Subjects and Design

This prospective cohort study was conducted from February 2015 to December 2016 at Sina hospital, affiliated with Hamadan University of Medical Sciences, Hamadan, Iran. Informed consent was taken either from the patients or their relatives. Patients with a diagnosis of both ischemic and hemorrhagic stroke, who were admitted in the first 12 hours, were enrolled. Patients with a previous history of stroke, cancer, active infections, hepatic or renal failures, and vasculitis disorders, including systemic lupus erythematosus and Sjogren's disease, which might affect the study results, were excluded. Of 186 admitted patients during the study period, 31 patients were excluded from the study because they were not eligible or declined to participate. Therefore, 155 remained for analysis. Patient information was obtained on the first and fourth day of hospitalization and three

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months later by phone call.

Disease Definitions

Demographic data were evaluated, including age, gender, onset of symptoms, type of stroke, and risk factors such as hypertension, diabetes mellitus, heart disease, hyperlipidemia, cigarette smoking and body temperature. Hypertension was characterized with blood pressure >140/90 mm Hg or a history of antihypertensive drug consumption. Diabetes mellitus was defined with blood sugar >200 mg/dL or fasting blood sugar >120 mg/dL or use of anti-diabetes drugs. Cardiac disease was characterized with a history of previous myocardial infarction or angina pectoris and cardiac dysrhythmia (e.g. atrial fibrillation) or use of related medications. Hyperlipidemia was diagnosed with serum cholesterol level >200 mg/dL or serum triglyceride level >150 mg/dL or use of lipid-lowering drugs. Cigarette smoking was defined as the current use of a minimum of one cigarette per day for at least three months currently (current smoker) or previously (former smoker).

Patients with ischemic stroke received anti-platelet medications plus routine treatments. Patients with hemorrhagic stroke only received routine treatments according to the clinical signs and symptoms and associated baseline diseases. Disease severity was determined by using the National Institutes of Health Stroke Scale (NIHSS) at onset of stroke. The severity of the disease was determined based on level of consciousness, eye movements and field, facial and limb motors, equilibrium, and speech. Disabilities caused by stroke, in the course of disease, was evaluated by an expert neurologist using modified Rankin Scale (MRS) and Barthel Index (BI) on the first, fourth, and 90th day after stroke. Disabilities included incontinency and inability to walk, bath, and dress.

Laboratory Assessments

Blood samples were taken to check CRP levels, white blood cell (WBC) counts, lipid profile and blood sugar levels within the first 12 hours of symptom onset. CRP level was measured by immunoturbidometry with automatic analyzer. CRP values were dichotomized into low levels (CRP <7 mg/L) and high levels (CRP ≥7 mg/L).[8]

Statistical Analyses

The independent *t* test was used for analysis of continuous variables and the chi-square test for nominal variables. In addition, odd ratio (OR) was calculated using simple and multiple logistic regression to explore the association between CRP levels and MRS, BI, and NIHSS. All statistical analyses were performed at a significance level of 0.05 using Stata version 14.2. (StataCopr, US, TX).

Results

Of 186 patients admitted during the study period, 10 patients were excluded because they entered this study beyond 12 hours after stroke and 19 patients refused to participate in this study. The analysis was done based on the remaining 155 eligible patients. The average level of CRP on the first day of admission was 20.03 mg/L. Of 155 stroke patients, 68 (43.8%) had CRP ≥7 mg/L. The average interval time between stroke onset and admission was 4.42 hours (ranged from 0.5 to 12 hours).

Tables 1 and 2 show the baseline characteristics of the patients by CRP levels <7 mg/L or ≥7 mg/L. Majority of strokes were ischemic. Infarction was the most common finding on CT-scan evaluation. Prevalence of diabetes (P = 0.001), angina pectoris (P = 0.001), death (P = 0.001), pneumonia (P = 0.004), and DVT (P = 0.002) was significantly higher in patients with CRP levels ≥7 mg/L than patients with CRP levels <7 mg/L. There was no significant difference between the two groups in term of age (P = 0.367), gender (P = 0.316), smoking (P = 0.325), type of stroke (P = 0.500), hypertension (P = 0.545), hyperlipidemia (P = 0.628), history of myocardial infarction (P = 0.059) or atrial fibrillation (0.361), and urinary tract infection (P = 0.072).

Associations between CRP levels and stroke outcome scores based on MRS, BI, and NIHSS are given in Table 3. There was significant association between CRP and MRS, BI, and NIHSS. According to these results, patients with CRP ≥7 mg/L were at higher risk of MRS >2 on the first day (OR [odds ratio] = 4.73 [95% CI: 1.08, 20.56]), on the fourth day (OR = 5.16 [95% CI: 1.05, 25.27]), and on the 90th day (OR = 17.14 [95% CI: 5.49, 53.49]). In addition, patients with elevated CRP were at higher risk of having BI <70 on the first day (OR = 5.95 [95% CI: 1.24, 28.47]), on the fourth day (OR=7.65 [95% CI: 2.06, 28.39]), and on the 90th day (OR = 7.95 [95% CI: 3.07, 20.57]). Furthermore, risk of NIHSS being between 7–13 and >13 at baseline was much higher in patients with elevated CRP (OR=16.24 [95% CI: 5.03, 52.43] and 4.53 [1.24, 16.52], respectively).

Discussion

Our study showed that elevated CRP levels within 12 hours of stroke onset was associated with poor short-term clinical outcomes, including NIHSS ≥13, MRS >2, and BI <70 in all patients studied. Ischemic damage to brain resulted in neuroglia activity disturbance especially in regards to astrocytes adhering to the endothelia. Therefore, these cells release cytokines and inflammatory factors that may result in neuron necrosis and endothelial vessel permeability. At the same time, by impaired blood

Table 1. Characteristics of the Study Population by C-Reactive Protein (CRP) Levels

Variables	CRP <7 mg/L, n = 65		CRP ≥7 mg/L, n = 90		*P* Value
	Number	Percentage	Number	Percentage	
Gender					
Male	33	38.4	53	61.6	0.316
Female	32	46.4	37	53.6	
Type of stroke					
Hemorrhagic	26	60.5	17	39.5	0.500
Ischemic	61	54.5	51	45.5	
CT-scan findings at baseline					
Normal	42	44.2	52	55.8	0.532
Hemorrhage	5	29.4	12	70.6	
Infarction	18	41.9	25	58.1	
Hypertension at baseline					
No	18	38.3	29	61.7	0.545
Yes	47	43.5	61	56.5	
Diabetes mellitus at baseline					
No	51	55.4	41	44.6	0.001
Type 1	1	25.0	3	75.0	
Type 2	13	22.1	46	77.9	
Angina pectoris at baseline					
No	60	55.6	48	44.4	0.001
Yes	5	10.6	42	89.4	
A history of myocardial infarction					
No	57	45.6	68	54.4	0.059
Yes	8	26.7	22	73.3	
A history of atrial fibrillation					
No	52	40.3	77	59.7	0.361
Yes	13	50.0	13	50.0	
Smoking status					
Never smoker	38	38.0	62	62.0	0.325
Former smoker	14	53.9	12	46.4	
Current smoker	13	44.8	16	55.2	
Hyperlipidemia at baseline					
No	54	42.9	72	57.1	0.628
Yes	11	37.9	18	62.1	
Death during the study period					
No	52	47.7	57	52.3	0.001
Yes	13	14.9	33	48.5	
Pneumonia at baseline					
No	57	48.3	51.7		0.004
Yes	8	21.6	29	78.4	
Urinary tract infection at baseline					
No	49	38.6	78	61.4	0.072
Yes	16	57.1	12	42.9	
Deep vein thrombosis during the study period					
No	65	42.2	89	57.8	0.002
Yes	0	0.0	1	10.0	

Table 2. Characteristics of the Study Population by C-Reactive Protein (CRP) Levels

Variables	CRP <7 mg/L, n = 65		CRP ≥7 mg/L, n = 90		*P* Value
	Mean	SD	Mean	SD	
Age (y)	70.51	10.46	72.07	10.83	0.367
White blood cell count at baseline	7725.28	2442.56	9925.0	9784.26	0.045

brain barrier (BBB) permeability, neutrophils that are exiting through endothelial cells, enter into tissues and increase inflammatory marker concentration. As consequence, neuron death and apoptosis induction increase gradually.[9]

Several studies have reported an association between increased CRP levels and clinical outcomes in a time window between 12 and 72 hours after ischemic stroke.[10-12] However, results of previous studies that assessed the prognostic value of CRP in the very early

Table 3. Association Between CRP Levels and Stroke Outcome Scores Using MRS, BI, and NIHSS

Variables	CRP <7 mg/L	CRP ≥7 mg/L	OR (95% CI)	*P* Value	Adjusted OR (95% CI) [a]	*P* Value
MRS on the 1st day						
≤2	9	4	1.00		1.00	
>2	56	86	3.45 (1.01, 11.76)	0.047	4.73 (1.08, 20.56)	0.038
MRS on the 4th day						
≤2	12	3	1.00		1.00	
>2	53	87	6.56 (1.77, 24.34)	0.005	5.16 (1.05, 25.27)	0.043
MRS on the 90th day						
≤2	51	22	1.00		1.00	
>2	14	68	11.25 (5.25, 24.12)	0.001	17.14 (5.49, 53.49)	0.001
BI on the 1st day						
≥70	15	3	1.00		1.00	
<70	50	87	8.70 (2.40, 31.52)	0.001	5.95 (1.24, 28.47)	0.026
BI on the 4th day						
≥70	25	6	1.00		1.00	
<70	40	84	8.75 (3.32, 23.02)	0.001	7.65 (2.06, 28.39)	0.002
BI on the 90th day						
≥70	47	24	1.00		1.00	
<70	18	66	7.18 (3.50, 14.70)	0.001	7.95 (3.07, 20.57)	0.001
NIHSS at baseline						
<7	35	2	1.00		1.00	
7–13	15	51	17.00 (6.28, 45.97)	0.001	16.24 (5.03, 52.43)	0.001
≥13	15	32	10.66 (3.85, 45.97)	0.001	4.53 (1.24, 16.52)	0.022
Death after stroke						
No	52	57	-	-	-	-
Yes	13	33	-	-	-	-

Abbreviations: CRP, C-reactive protein; MRS, Modified Rankin Scale; BI, Barthel Index; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.
[a] Odds ratio adjusted for age, sex, diabetes, angina pectoris, pneumonia, and deep vein thrombosis.

phase of stroke are inconsistent. Two prospective studies reported no relationship between CRP levels obtained within 6 or 12 hours after symptom onset and death or patients' dependency to others for doing their daily activities during follow-up.[12,13] Both studies had small sample sizes (127 and 111 patients) and might therefore have low statistical power to detect a true association. In addition, one of these studies included only patients treated with rt-PA.[13]

Along with the study of den Hertog et al, we found an association between increased levels of CRP and diabetes mellitus and blood leukocytes but no association with AF, cigarette smoking and hypertension.[8] According to the results of the study conducted by Idicula et al, elevated levels of CRP were associated with NIHSS ≥14, diabetes mellitus and MRS >2. They reported no association between elevated levels of CRP and sex, age, smoking and admission time.[14] In the study conducted by Matsuo et al, in addition to diabetes mellitus, elevated levels of CRP was associated with NIHSS, acute infection, hypertension, atrial fibrillation and drinking.[15] Based on our results, increased CRP associated with MRS >2, BI <7 and NIHSS ≥13 at admission with pulmonary infection and deep vein thrombosis but no association with UTI. A study by Winbeck et al showed that the most appropriate time for obtaining blood samples was 12–24 hours after onset of stroke. This can predict risk of cardiac and cerebral vascular event.[12] In our study, CRP was measured within 12 hours after stroke.

Association between CRP levels and post-stroke clinical outcomes is still controversial. Although some studies showed a positive association,[16] number of the patients was limited and the effect of confounding factors was not controlled. In fact, other studies reported that the association of CRP with clinical outcomes (3-month mortality)[10] disappeared after adjusting for confounders. Nonetheless, in our study, the association between CRP and MRS, BI and NIHSS was statistically significant after adjusting for several potential confounders such as age, sex, diabetes, angina pectoris, pneumonia, and deep vein thrombosis.

The main limitation of this study was a short follow-up period. We followed study patients for three months. Thus, associations between CRP and clinical outcomes after ischemic stroke needs further evaluation. We suggest that this study be repeated and follow-ups to be conducted for at least a year. The neurology ward of Sina hospital is not a referral center for the entire province,

therefore, generalization of these results to the entire province should be done with caution.

In conclusion, this study indicated that elevated CRP levels in the very early phase of both ischemic and hemorrhagic stroke was associated with poor functional outcomes, prognosis, and death three months after stroke.

Authors' Contribution

SM contributed to study conception and design, and interpretation of data, and drafting of the manuscript. ER contributed to study conception and design and critical revision. JP contributed to study conception and design, analysis and interpretation of data, and critical revision. MG contributed to study conception and design and critical revision.

Conflict of Interest Disclosures

The authors have no conflict of interest to declare.

Ethical Statement

The Ethics Committee of the Hamadan University of Medical Sciences approved the study. The patients participated voluntarily in the study giving a verbal informed consent.

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