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Predictive role of high sensitive C-reactive protein in early onset mortality after ischemic stroke

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Shahrzad Mohebbi[1], Mojdeh Ghabaee[2], Majid Ghaffarpour[3], Ali Pasha Meisami[4], Reza Shah Siah[5], Mohammad Reza Mousavi Mirkala[6], Maryam Pour Ashraf[7], Mahbubeh Yaghubi[1]

[1] Iranian Center of Neurological Research, Tehran University of Medical Sciences, Tehran, Iran
[2] Associate Professor, Iranian Center of Neurological Research, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[3] Professor, Iranian Center of Neurological Research, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
[4] Epidemiology and Preventive Medicine Department, Tehran University of Medical Sciences, Tehran, Iran
[5] Department of Pathology, Tehran University of Medical Sciences, Tehran, Iran
[6] Eye Research Center, Farabi Eye Hospital
[7] Department of Radiology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

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Inflammatory Biomarkers, High Sensitive C-reactive Protein, Acute Ischemic Stroke, Mortality

Abstract

Background: High sensitive C-reactive protein (hs-CRP) is a systemic inflammatory marker that is produced in a large amount by hepatocytes in response to interleukin-1 (IL-1), IL-6 and tumor necrosis factor after ischemic stroke.

Methods: Measurement of hs-CRP in the first 24 hours of onset in 162 patients suffering from ischemic stroke was done. Relation of CRP with the risk of early mortality, National Institutes of Health Stroke Scale (NIHSS), stroke subtypes and other factors was determined.

Results: Regarding to ROC curve analysis, appropriate cut-off point for predicting patients' short time mortality was equal to 2.15 mg/dl in this study. Significantly increased rate of mortality by 13.3 times was seen in patients with simultaneous CRP > 2.15 mg/dl and NIHSS > 10.

Conclusion: The Result of this study showed that there is a direct association between hs-CRP and mortality within the first week after stroke. Measuring hs-CRP within the first hours after stroke increases the predicting rate of early mortality risk with cut-off point of 2.15.

Introduction

In numerous industrial countries, cerebro-vascular accident (CVA) has been the third common cause of death after coronary arteries diseases (CAD) and cancers.[1] Systemic inflammatory response occurs after ischemic events and is responsible for thrombosis progression. Several studies have indicated that higher levels of inflammatory biomarkers such as C-reactive protein (CRP) and interlukin-6 (IL-6) have been associated with worsening ischemic events.[2]

CRP is a systemic inflammatory marker that is produced in a large amounts by hepatocytes in response to IL-1, IL-6 and TNF factor.[3,4] Rapid induction of CRP, its long half-life (19 hours)[5] and lack of alteration during day and night[6] in comparison with other acute phase reactants has introduced CRP as an important factor for evaluation in inflammatory and infectious diseases.

Nowadays, CRP is a confirmed diagnostic marker for the patients with CVA and recent prospective investigations showed that CRP is clinically helpful for predicting the risk of the next cardiovascular diseases.[7] Although many studies have been

Email: ijnl@tums.ac.ir

Corresponding Author: Mojdeh Ghabaee, MD
E mail: ghabaeem@tums.ac.ir

conducted on association of CRP and cardiac diseases; only few studies have evaluated its role in predicting mortality in stroke patients. In addition, it can be used as biomarker at early phases in diagnosis of stroke, determining prognostic value of therapeutic programs and secondary prevention strategies.

In this study, we intended to evaluate association of CRP as an inflammatory marker with acute cerebral ischemic attack characteristics, risk factors and to determine a cutoff point of hs-CRP in predicting early mortality.

Materials and Methods

This study was conducted on 200 patients with impression of stroke who had been referred to emergency ward of university hospital, Imam Khomeini Hospital, Tehran, Iran, within May 2009 – March 2011. Patients who had referred earlier than 24 hours after ischemic stroke were enrolled in the study. 38 patients with body temperature higher than 37.8 ^{o}C, hemorrhagic stroke and those with previous inflammatory or malignant diseases were excluded. Ethical committee of Tehran University of Medical Sciences accepted this project. Patients' information was recorded in the previously designed questionnaires.

Medical history was taken from the patient or his/her relatives if the patient was unconscious or not able to speak. Physical examination was performed by neurology residents. Patients were evaluated for age, sex, diabetes, hyperlipidemia, ischemic heart diseases, smoking and past history of stroke or hypertension. Routine laboratory tests, brain magnetic resonance imaging (MRI), transthoracic echocardiography (TTE) and carotid Doppler ultrasonography were done in all of the patients.

National Institutes of Health Stroke Scale (NIHSS) was used for assessing stroke severity. This scale consists of 15 items which is varied from 0 up to 42.[8-9] Type of stroke was determined based on TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification. This index is considered as an important source for determining stroke etiology in neurology.[10] It is able to demonstrate various types of acute ischemic stroke with different etiology and is consisted of 5 sub-groups: Large-vessel atherosclerosis, cardioembolic, small-vessel occlusion or lacunar, undetermined etiology, and non-atherosclerotic determined etiologies.

Informed consent was taken from the patients for obtaining additional blood samples. Venous blood samples were drawn in the first day of admission. Another sample for specific tests was stored in room temperature for 20 minutes until clotting. Then serum was isolated by 10 minutes centrifuging with 2500 Rpm speed. Serum was stored in -70 °C and sent to Heart Center Hospital of Tehran University of Medical Sciences and hs-CRP concentration was determined by turbidimetry method and Roche kit (manufactured in Swiss) with using Cobaf apparatus (model Integra400+).

Statistical analysis was done by SPSS software (version 15; SPSS Inc., Chicago, IL., USA) using chi-square test and Student's t-test for univariate analysis and Mantel Hansel analysis for multivariate analysis. Receiver operating characteristic (ROC) curve was drawn for demonstrating cut off point of CRP for predicting patients' mortality within the first week of admission.

Results

In this study, 162 patients with acute ischemic stroke were evaluated. They had been referred to emergency ward of Imam Khomeini Hospital within May 2009–March 2011**.** Mean age of the patients was 67 ± 12 years with a range of 33-95 years. Patients were classified into 3 age groups: 11 patients were younger than 50 years (6.8%), 81 cases were 50-70 years (50%) and 70 patients were older than 70 years (43.2%). They consisted of 81 females (50%) and 81 males (50%). Clinical demographic evaluation showed hypertension in 77 (47.5%) patients, diabetes in 50 (30.9%), hyperlipidemia in 56(35%), history of cardiovascular diseases in 46(24.8%), history of previous CVA in 33(20.4%) and cigarette smoking in 67(41.4%) patients. Sixteen (10%) patients died within the first week of admission.

Mean of NIHSS Score was 9.5 ± 8 (min 1 and max 30). According to NIHSS score, our patients were classified to 3 sub-groups: NIHSS score < 7 (mild neurologic disorders), NIHSS score 7-13 (moderate neurological disorders) and NIHSS score > 13 (severe neurological disorders).

According to TOAST classification criteria, large vessel atherosclerosis was seen in 95 subjects (58.6%), cardioembolic in 11 (6.8%) and small vessel occlusion in 56 patients (35%). No patient settled in unknown or other etiology groups. Mean of plasma hs-CRP concentration was 2.86 ± 5 mg/dl.

Regarding ROC curve analysis, appropriate cut-off point for predicting patients' short time mortality was determined as 2.15 in this study. In addition, NIHSS >10 was considered as appropriate score for predicting patients' short-term mortality (Fig. 1).

Association between hs-CRP and early mortality in the patients with acute CVA was significant. Mean of CRP in died patients was 8.9 ± 7 mg/dl and in survived patients was 2.2 ± 5 mg/dl (P = 0.0001). The hs-CRP amounts showed a significant association with early mortality, diabetes, IHD (ischemic heart diseases), smoking and NIHSS. Table 1 shows the summary of these findings.

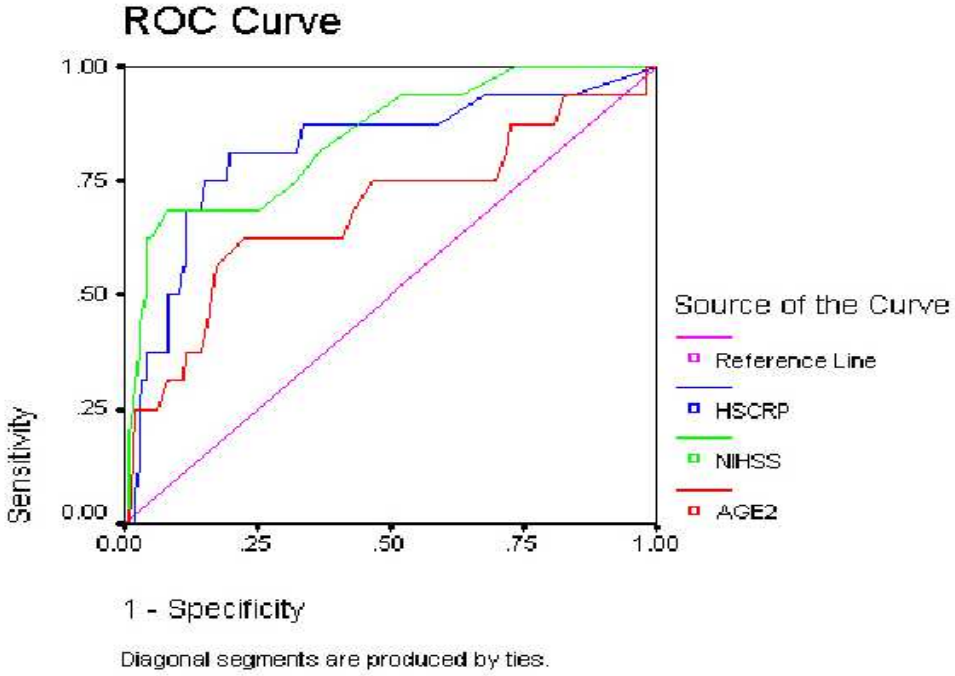

Figure 1. ROC curve of variables for predicting mortality in the patients with stroke

Table1. Incidence of early onset mortality based on sub-groups of evaluated demographic variables in the investigated patients with acute ischemic stroke

	Status (m)	**Mortality [n(%)] (95% CI)**	**P**	**RR (95% CI)**
Diabetes	Yes (50)	11(22.0%) 1(0.5%-33.5%)	0.001*	4.9 (1.8-13.4)
	No (112)	5(4.50%) (0.6%-8.3%)		
Ischemic heart disease	Yes (46)	14(30.4%) 1(7.1%-43.7%)	< 0.001*	17.6 (4.2-74.6)
	No (116)	2(1.70%) (0.0%-4.1%)		
Smoking	Yes (67)	11(16.4%) (7.5%-25.3%)	0.030*	3.1 (1.1-8.6)
	No (95)	5(5.30%) (0.8%-9.8%)		
NIHSS	<7 (71)	1(1.40%) (0.0%-4.1%)	< 0.001**	-
	7-13 (72)	4(5.60%) (0.3%-10.8%)		
	>13 (19)	11(57.9%) (35.7%-80.1%)		
NIHSS (cut-off point)	≤ 10 (103)	4(3.90%) (0.2%-7.6%)	0.002*	5.2 (1.8-15.6)
	>10 (59)	12(20.30%) (10.1%-30.6%)		
CRP (cut-off point) (mg/dl)	≤ 2.15 (120)	3(2.50%) (0.0%-5.3%)	< 0.001*	12.3 (3.7-41.7)
	> 2.15 (42)	13(31.00%) (17.0%-44.9%)		
Total (162)		16(9.90%) (5.3%-14.5%)	-	-

* Fisher Exact test ** Chi-square test

NIHSS: National Institutes of Health Stroke Scale; RR: Relative risk; CRP: C-reactive protein

After multivariate analysis and adjusting for sex, age, history of heart disease, NIHSS score and TOAST, we found hs-CRP as an independent factor in predicting early onset mortality. Significantly increased rate of mortality by 13.3 times was seen in patients by simultaneous CRP > 2.15 and NIHSS > 10 as cut-off points for predicting mortality, so that out of 23 patients possessing these conditions 11(47.8%) died.

In the patients who had simultaneously CRP > 2.15, neurological defect severity was more than 10 and diabetes and mortality rate increased about 19 times; so that out of 13 patients possessing these conditions, 10(76.90%) died. Therefore, co-existence of these three factors in a patient may strongly increase the risk of mortality. Determinant criteria for mortality risk in the patients with CVA and comparing them with each other are summarized in table 2.

Discussion

The results of present study showed that hs-CRP in the patients with acute ischemic CVA who had died within the first week after manifesting symptoms was significantly higher than survived patients. In addition, hs-CRP levels more than 2.15 mg/dl were considered as cut-off point for predicting mortality in this study. Poor outcomes have been recorded with elevated CRP or other inflammatory factors after stroke.[11,12] In addition, a large number of previous studies have reported that increasing CRP at the first hours after stroke was associated with risk of mortality.[12-14] Montaner et al. introduced CRP as a powerful factor for predicting mortality after CVA.[15]

Ischemic damage to brain resulted in disturbance in neuroglia activity especially astrocytes adhered to endothelial. Therefore, these cells release cytokines and inflammatory factors that resulted in neuron necrosis and vessels' endothelial permeability. At the same time by impaired blood brain barrier (BBB) permeability, neutrophils by exiting through endothelial cells, enters into tissues and increase inflammatory markers' concentration. As a consequence, neurons' death and apoptosis induction gradually increase.[16-18] It is considerable that numerous articles recommend application of NIHSS system for more accuracy in stroke severity.[13]

Cut-off point of > 10 for NIHSS was shown in present study that in combination with an elevated CRP > 2.15 was associated with 13 times increase in mortality. Similarly, studies performed by Basic et al.[19] and Shenhar et al.[20] showed association of NIHSS and increase in inflammatory factors.

Neurological defect severity and its association with elevated CRP were shown in ischemic cycles so that more ischemia resulted in more neurological defect severity.[16-18] Among 16 dead cases, 14 (30.4%) patients had history of heart diseases and

Table 2. Comparing of multivariate factors with early death in the patients with stroke

	Criteria (no of patients)	Mortality (%) (95% CI)	P	RR
CRP, NIHSS	CRP ≤ 2.15 mg/dl and NIHSS ≤ 10 (84)	2(2.40%) (0.0%-5.6%)	< 0.001**	-
	CRP > 2.15 mg/dl or NIHSS > 10 (55)	3(5.50%) (0.0%-11.5%)		
	CRP > 2.15 mg/dl and NIHSS > 10 (23)	11(47.8%) (27.4%-68.2%)		
CRP, NIHSS	CRP > 2.15 mg/dl and NIHSS > 10 (23)	11(47.8%) (27.4%-68.2%)	< 0.001*	13.3 (5.1-34.7)
	Others (139)	5(3.60%) (0.5%-6.7%)		
CRP + NIHSS + Diabetes	0 of CRP > 2.15 mg/dl or NIHSS > 10 or Diabetes (65)	2(3.10%) (0.0%-7.3%)	< 0.001**	-
	1 of CRP > 2.15 mg/dl or NIHSS > 10 or Diabetes (56)	2(3.60%) (0.0%-8.4%)		
	2 of CRP > 2.15 mg/dl or NIHSS > 10 or Diabetes (28)	2(7.10%) (0.0%-16.7%)		
	3 of CRP > 2.15 mg/dl or NIHSS > 10 or Diabetes (13)	10(76.90%) (54.0%-99.8%)		
CRP, NIHSS Diabetes	CRP > 2.15 mg/dl and NIHSS > 10 and diabetes (13)	10(76.90 %) (54.0%-99.8%)	< 0.001*	19.1 (8.3-44.2)
	Others (149)	6(4.00 %) (0.9%-7.2%)		

* Fisher Exact test ** Chi-square test

NIHSS: National Institutes of Health Stroke Scale; RR: Relative risk; CRP: C-reactive protein

significant association was seen between hs-CRP and mortality in relation to ischemic heart disease.

CRP is correlated with mortality due to cardiovascular diseases as well as stroke.[21] In addition, a Meta-analysis study indicated that CRP is directly associated with ischemic heart diseases, stroke and mortality risk.[22]

Time of hs-CRP evaluation was a determining factor in early predicting mortality in this study. Maximum of plasma CRP concentration has been usually reported within 36 to 48 hours after initiating signs of stroke. A study by Winbeck et al. showed that the most appropriate time for obtaining blood samples was 12-24 hours after initiating signs and can predict the risk of cardiac and cerebral vascular events.[23] In the present study, CRP was measured about 24 hours after the first attack.

Conclusion

This study showed that there was a direct association between hs-CRP and mortality within the first week after stroke. Cut-off point of CRP was 2.15 mg/dl and measuring hs-CRP within the first hours after stroke increase the predicting rate of early mortality risk. As up to now, a blood biomarker that can introduce accurate information about cause and outcome after stroke has not been known yet, cut-off point of hs-CRP can be used for therapeutic decision making. Prospective cohort studies are recommended for knowing various aspects of these subjects.

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