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Investigating the relationship between serum levels of C-reactive protein (CRP) and different types of stroke and its severity

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ABSTRACT

Ischemic stroke is one of the major causes of death and disability, but predictive parameters such as CPR in this disease are not yet clear. The objective of this study was to investigate the relationship between serum levels of CRP and different types of CVA and its severity. In this case-control study, 161 patients with stroke (ischemic and hemorrhagic) were included. Stroke severity was measured based on NIHSS modified on admission and CRP was measured on admission (first 48 hours) and four days later. Then, T test and chi-square tests were used to compare the studied variables among various groups. The results showed that the highest and lowest CRP 48 hours after admission were seen respectively in severe stroke groups (22.56), minor ischemic (10.7), and hemorrhagic group (10.08) and the difference was statistically significant (P<0.001). Four days later, considering the CRP levels, the highest and lowest values were seen respectively in severe stroke (73) and mild (9.25) groups, which this difference was significant. In addition, significant difference (P<0.001) was seen between three severe, moderate and mild groups in terms of CRP rate (P<0.001). Studied groups characteristics including severity of CVA (severe, moderate, mild and hemorrhagic), age of patients, blood platelets, TG and CRP rate at first 48 hours and four days after admission to hospital were effective in MNIHSS amount of patients (P<0.05) .The results of this study indicated that the level of CRP on admission and four days after the admission of patients with stroke is closely correlated with ischemic stroke severity so that increasing severity of stroke causes an increase in level of CRP.

Key words: stroke, C-reactive protein (CRP), MNIHSS, ischemic, hemorrhagic

INTRODUCTION

Cerebrovascular accident [CVA] refers to anycerebral abnormality resulting from blood vessels pathological process, including duct obstruction by embolism or thrombosis, rupture of blood vessels, vascular wall permeability, or increased blood viscosity or any other change in quantity of blood flowing within cerebrovascular [1]. CVA is the third most common cause of death after heart disease and cancer [1, 2]. In 1930, two scientists, namely Francis and Tillet, found for the first time the that there is a protein in the serum of patients with pneumococcal that is able to react with polysaccharide C [C] of pneumococcal bacteria capsule in vitro, causing swelling in these bacteria. For this reason, the discovered protein was called CRP or C-reactive protein. CRP of this protein in serum and body fluids of healthy people has been reported in trace amounts, but in inflammatory reactions, the amount of CRP suddenly increases up to 3,000 times than its natural rate within 6 to 48 hours [3-5]. Serum CRP increases in several diseases:

As result of surgery, large amount of blood transfusion, vaccination, and pulmonary embolism, CRP level increases. In myocardial infarction, CRP measurement is the best and most sensitive method associated with signs of necrosis or inflammation of the heart muscle tissue. [6-9]. According to research in 2013 conducted in Nigeria, evidence suggests the correlation of inflammatory mediators, especially CRP level with prognosis of acute ischemic stroke. In addition, there is scattered information indicating the role of inflammatory markers such as CRP and stroke prognosis in Africans [10]. Additionally, in a study conducted in Egypt on 50 patients with CVA, CRP levels increased in response to stroke and it may be used as a predictor for prognosis of stroke [11 and 12]. According to a study conducted between 2004 and 2005 on 100 male and female patients with ischemic stroke in Imam Hospital of Tabriz, it was concluded that ischemic stroke is correlated with serum levels of CRP, although cutoff point varied from one patient to other patients. In this study, the importance of prognostic CRP in ischemic stroke [IS] has been taken for granted[13].

In other studies, it has been suggested that serum level of CRP increases in the first 48 hours after the onset of hemorrhagic stroke and high level of CRP was found correlated with disease serious prognosis. In this report, high CRP around the bleeding area in the brain and in neurons, and glial cells has been shown [14]. On the other hand, in a study conducted in 2012 in Japan on the relationship between high level of CRP and the heart stroke incidence of various brain cerebral strokes on 29786 healthy people, it was concluded that this relationship is positive and strong in the case of heart strokes, while it was weak in the case of cerebral strokes [15]. In other studies, it was found that high CRP level in plasma, independent of other risk factors for cardiovascular diseases, may be used as predictor risk of TIA and ischemic stroke in older adults [16].

However, there is much evidence on importance of predictive role of CRP in the course of cerebrovascular accident. Di Napoli et al conducted a study to investigate the value of CRP and its changes in different stages of ischemic stroke on admission and within 24 hours after a stroke, and after 48 to 72 hours and at discharge with prognosis during the year. They concluded that high CRP at different stages of ischemic stroke is associated with worse prognosis [17]. In other studies, high concentrations of CRP may be a prognostic factor in the incidence of ischemic stroke and its serious prognosis [18]. In some previous studies, high concentrations of CRP in the acute phase and in the course of ischemic vascular disease have been a sign of series prognosis [19]. In a study conducted in 2011 by Masoud and Daneshvar in Kashan, it was concluded that is no relationship between hs-CRP and age and involved side of body and between the severity of clinical symptoms either on admission or 41th day and gender and involved side of body.

In addition, there was no relationship between positive predictive value obtained for different values of hs-CRP and certain cut-off point for hs-CRP for predicting prognosis was not found [20]. A study was conducted by Faraji et al to examine the relationship between C-reactive protein and white blood cells, and the relationship between protein amount and severity of ischemic stroke and infarct volume. They showed that that was no correlation between infarct volume and C-reactive protein and white blood cells. In addition, significant relationship was not found between Canadian Neurological Scale score of cerebral stroke and amount of white blood cells [21].

Another study was conducted in 2014 by Iranmanesh et al to examine the correlation between serum levels of C-reactive protein and stenosis inside and outside the brain in patients with acute ischemic stroke. They concluded that there was a significant relationship between serum levels of CRP and stenosis ($p=0.003$).

In patients with abnormal CRP, most involved vessels were respectively internal carotid artery, the middle cerebral artery, and anterior cerebral artery and in patients with normal CRP, the most involved vessels were respectively anterior cerebral artery, the internal carotid artery and middle cerebral artery. There was significant correlation between serum levels of CRP and stenosis of the internal carotid artery ($p=0.015$) and middle cerebral artery ($p=006$) (22). Given high prevalence of CVA in Mashahd compared to western communities and as no study has been conducted on risk factors and correlation of CRP serum levels and CVA and its severity, we decided to take measure to collect data on gender, age, risk factors of hypertension, diabetes, arrhythmias (af), and specially serum CRP level and the severity of disease based on Modified NIHSS criteria. Accordingly, the present study was conducted to investigate the serum levels of CRP with a variety of CVA and short-term mortality and its severity. Therefore, by conducting this study, the impact of various factors on the CVA such as hypertension, diabetes mellitus, hyperlipidemia, arrhythmias such as af and others cases mentioned along with serum CRP level on CVA and its different types were identified in the patients of the region.

MATERIALS AND METHODS

This study was conducted by using case-control study. The study population included all patients with ischemic CVA, hospitalized in KashanShahidBeheshti Hospital from the beginning to the end of the sampling as well as patients with hemorrhagic CVA who met the exclusion criteria of the case group.

Inclusion and exclusion criteria were in this way that any patient with ischemic and hemorrhagic CVA diagnosed by a neurologist with age over 50 years and the disease severity has been determined during the first 48 hours were included in the study. in addition, patients that their increased CRP was due to the reasons of autoimmune diseases, infectious diseases, recent MI, malignancy, trauma, Crohn's disease, tissue necrosis, disposal of organ transplant were excluded from the study.Finally, 131 patients and 30 people with hemorrhagic CVA, which their number was determined to be 13 according to a study in Tabriz, were selected for the control group. After collecting data based on T tests, Fisher's exact test, and chi-square test in the mode of univariate and multivariate linear regression were used to respond the question of the study.

Findings:

The study was conducted on 161 patients with cerebral stroke (ischemic and hemorrhagic), which 116 (72%) of them male and 45 (28%) of them were female with an mean age of 74.51 ± 12.52 years, which the minimum age was 50 years and maximum age was 97 years. It was also found that out of 161 patients studied, 30 (18.6%) patients had severe ischemic stroke, 49 patients (30.4%) had moderate ischemic stroke, 52 patients (3/32%) had minor ischemic stroke, and 30 patients (18.6%) were diagnosed with hemorrhagic stroke.

Table 1: Mean and standard deviation of CRP in patients of four groups:

CVA / Variable	ischemic			HEMORRHAGIC (CONTROL)	P-value
	Severe	Moderate	Mild		
CRP	22.56 ± 12.084	13.98 ± 8.25	10.7±6.9	10.08 ±6.15	<0.001
CRP four days later	73 ± 31.017	32.23 ± 20.36	9.25 ±8.14	16.62 ±8.06	<0.001

ANOVA

According to Table 1, it was concluded that the highest and lowest CRP 48 hours after admission were respectively in severe stroke (22.56) mild ischemic group (10.7) hemorrhagic group (10.8), and the difference was statistically significant (P<0.001). Considering CRP level four days later, the highest and lowest values were related to severe stroke groups (73) and mild (9.25), which the difference was statistically significant. CRP level four days later was different in three groups of severe, moderate, and mild, which the difference was significant (P<0.001). Age and gender variables showed no statistically significant difference between the two groups (P> 0.19). Mean FBS was 101.8 mg/dl in patients with severe CVA and it was 117.7 mg/dl in hemorrhagic patients. However, no significant differences were seen in levels of FBS, BS, BUN, and Cr among four groups of patients with CVA (p>0.13).

Results showed that the highest amount of triglyceride was moderate in the group that had a stroke (154.82) and the lowest amount was in the hemorrhagic group (99/93), which the difference among the 4 groups was statistically significant (P=0.033). The highest amount of cholesterol was seen in the group with severe stroke (194.43) and lowest amount was seen in the control group (155.63), which the difference between the 4 groups was statistically significant (P=0.29).

In addition, the highest HDL level was seen in the group with severe stroke (40.27) and the lowest amount was seen in the hemorrhagic group (33.6) and the difference was statistically significant (P=0.019). In terms of the amount of LDL, difference was not observed among the 4 groups (P=0.088). This study found no significant correlation between coagulation factors and type of stroke (P.V> 0.24).

Table 2: Mean and standard deviation of MNIHSS in patients of four groups:

CVA / Variable	Ischemic			Hemorrhagic (Control)	P.value
	Severe	Moderate	Mild		
MNIHSS	20.2 ±3.881	8.76 ±2.213	2.62 ±1.051	6.72 ±3.872	<0.001

ANOVA

According to Table 2, it was concluded that the mean of MNIHSS in patients with severe stroke was 20.2, it was 8.76 in the moderate group, and it was 2.62 in group with mild stroke, and it was 6.72 in hemorrhagic stroke groups (P.V <0/001).

Table 3: The mean and SD of duration of hospitalization in patients of four groups:

CVA / Variable	Ischemic			Hemorrhagic (Control)	P. value
	Severe	Moderate	Mild		
duration of hospitalization	16.6± 4.39	8.96±3.34	7.55±3.79	9.76±4.56	<0.001
Number of people	30	49	52	30	-

ANOVA

Based on the table above, it was concluded that the duration of hospitalization was highest in severe stroke group (16.6 days), but the lowest hospitalization rate was seen in mild stroke group (7.55 days), which this difference was statistically significant. The mean of hospitalization in hemorrhagic group was slightly more than that in mild and moderate ischemic group, but the difference was not significant (P<0.001).The highest amount of platelet was seen in the group with severe stroke (268,900) and in the control group (280266.67) and the lowest amount was seen in the group was a mild stroke (223 500), which this difference was statistically significant (P=005). According to the results, it was concluded that there was no significant relationship between symptoms on admission and type of CVA (P.V>0.05).

However, it was found that the frequency of reduction in consciousness level of patients with acute ischemic stroke had the highest rate (56.7%), followed by hemorrhagic (36.7%) and the lowest rate was seen in patients with mild ischemic (0.2%), which the difference was significant. The frequency of dysarthria and imbalance in patients of hemorrhagic group was more than other groups (62.5%) and the lowest frequency was seen in patients with moderate stroke (10%) (PV = 0/01).

Additionally, only blood chronic disease history was significant among the groups studied, which 100% of patients were in the control group (P.V = 0.004). It was also found that none of the patients with a history of ESRD has antiphospholipid antibody, sickle cell, leukemia, and vasculitis. A significant relationship was not found between family history of stroke and stroke type. (P.V = 0/601). Significant relationship was not found between history of cerebral stroke and stroke type and TIA history (P.V> 0/05).

Table 4: Distribution of mortality in patients of four groups

Mortality / CVA		During hospitalization	Up to 6 months after the onset of symptoms (non-admission)	More than 6 months after the onset of symptoms	SURVIVORS	P-value
Ischemic	Severe	12 (42.85)	9 (32.14)	2 (7.1)	5 (17.85)	<0/001
	moderate	5 (11.36)	7 (15.9)	7 (15.9)	25 (56.81)	
	Mild	0	1 (4.3)	1 (4.3)	21 (91.3)	
Hemorrhagic (control)	Control	11 (64.7)	0	0	6 (35.29)	

Fisher's Exact Test

Based on the Table above, it was concluded that the highest rate of mortality during hospitalization was seen in patients with hemorrhagic CVA group (64.7%), followed by patients with severe ischemic CVA group (42.85%) and the lowest rate was seen in mild CVA (zero). Then, it was found that during the first 6 months after hospitalization, the highest rate of mortality was seen in patients with severe CVA (32.14%) and lowest rate was seen in patients with hemorrhagic CVA (zero). In the continuation of follow-up, it was revealed that during the first 6 months after hospitalization, the highest rate of mortality was seen in patients with severe CVA (32.14%) and lowest rate was seen in patients with hemorrhagic CVA (zero).

After 6 months, it was found that the highest rate of mortality WAS in patients with moderate CVA (15.9%) and lowest rate was seen in patients with hemorrhagic CVA (zero). Finally, it became clear that frequency of survivors in patients with mild stroke was more than that in others (91.3 %), followed by moderate stroke (56.81%), and hemorrhagic stroke (35.29%), and severe stroke (17.58%), which these differences were statistically significant (PV <0/001). A significant relationship was seen between Doppler result and type of stroke (P.V> 0/05). In addition, there is no relationship between CT scan result or MRI and type of stroke (P> 0/05), and finally there is no significant relationship between changes in ECG and type of stroke (P.V> 0/05).

Table 5: coefficients of linear regression model of factors affecting MNIHSS

Independent variable	Non-standard correlation coefficient		standard correlation coefficient	T	Significance
	B	Std. Error	Beta		
Age	0.09	0.023	0.629	3.99	<0.001
Groups	2.663	0.392	0.663	6.794	<0.001
Diastolic blood pressure	-0.073	0.022	-0.601	-3.416	0.001
Platelets	-6.505	2.455	-0.082	-2.65	0.009
triglyceride	-0.009	0.004	-0.14	-2.444	0.016
CRP in first day	0.149	0.047	0.215	3.135	0.002
CRP four days later	0.072	0.01	0.308	7.129	<0.001
Diabetes	1.541	0.667	0.098	2.308	0.022
CHF	-2.705	1.006	-0.084	-2.689	0.008
POLYCYTE	1.525	0.753	0.063	2.025	0.045
PR	0.037	0.017	0.278	2.158	0.033
HB	-0.359	0.115	-0.446	-3.114	0.002
TROP	-4.377	2.29	-0.055	-1.911	0.058

Results of table above show that various factors affect MNIHSS. As you can see, studied groups included severity of CVA (high, medium, mild and hemorrhagic). Along with age of patients, blood platelets, TG and CRP levels on admission and four days after hospitalization, diastolic blood pressure, diabetes, chronic heart failure, polycythemia, heart rate, and hemoglobin amount affect the MNIHSS level of patients. For diastolic blood pressure, platelet, triglycerides, heart failure and hemoglobin, this relationship is reversed ($P<0.05$). Explanatory power of the model is equal to 0.893 ($R2=0.902$ and Adjusted $R2=0.893$). In addition, most smoker patients were in the mild stroke group (47.6%), followed by patients with severe stroke (23.8%) and the lowest level was seen in the control group (7.1%) ($P=0.015$), but it was not significant with regard to addiction. The cigarette smoking in patients with severe stroke (12.58 years) and mild stroke (13.02 years) had the greatest duration, while the control group had the lowest duration (2 years) ($P=0.013$). However, duration of drug use among different groups was not significantly different ($P=0.474$). The findings showed that systolic and diastolic blood pressure was not significantly different among the four groups. The highest heart rate was in the group with severe stroke (85.67) and lowest rate was in the control group (71.5), which this difference was statistically significant ($P=0.002$).

CONCLUSION AND RECOMMENDATION

This study was conducted to investigate the relationship between serum levels of CRP with CVA and its severity. This study was conducted on 161 patients with cerebral stroke (ischemic and hemorrhagic). In a study conducted in Canada by Bob Siegerink et al on 101 patients with a diagnosis of a heart attack at the age of 39-16 years and the same number of patients with a diagnosis of stroke in this age group along with 202 people as a control group, 70% of cases were diagnosed with heart stroke, while 43% of them were diagnosed with cerebral stroke. High blood pressure had also high frequency in both patient groups compared to control group. A relationship was not found between arterial venous shunts in heart strike group, while significant correlation was found between large arterial venous shunts in the cerebral stroke group. In this study, migraine was associated with stroke significantly (23). In this study, it was found that smoking significantly increases the risk of severe ischemic cerebral strokes and the duration of smoking increased in patients with severe ischemic stroke. However, unlike the mentioned studies, significant relationship was not found between underlying diseases such as blood pressure and diabetes and ischemic severity. The difference in the results could be due to different populations studied and different sample size.
In a study conducted by Tiong et al on the effect of clot lysis time in cerebral stroke in young women, hypofibrinolysis (reduced activity of fibrinolytic, reduced clot lysis time) was not significantly associated with an increased risk of ischemic stroke (0.3-7.0 CI 95%; 5.1, or 2vs. T 3T) (24). The results of the mentioned study are consistent with findings of this study. In this study, it was found that there is no significant relationship between blood-clotting factors, which include PT, PTT, and INR and type and severity of ischemia. Although in most cases, lack of protein c is considered as a coagulopathy factor in the occurrence of venous thromboembolism, but recent reports has found that this factor is also effective in the development of arterial thrombosis.

In the report of Tanno K, et al., one case of white woman aged 26 with protein coagulopathy was introduced by diagnosis of cerebral stroke and it was recommended that investigation of disorders with coagulation increase modes to be part of the necessary studies in cerebral strokes among young people (25). Self-rated health (SRH) level can be a measure of factors determining mortality risk of people in the future, although its biologic basis is no clear. To evaluate the relation between self-rated health level and high levels of CRP, a study was conducted in Japan.In this

study, low level of self-rated health had direct correlation with high levels of CRP, and it has been suggested that measurement of biological indices including CRP could be a measure of general health of the person (26). The findings of the mentioned study are consistent with the findings of this study, since the present study found that with increasing severity of stroke, level of CRP on admission was significantly higher. On the other hand, by performing regression analysis, it was found that severity of stroke has a significant relationship with CRP four days after the admission. In other studies, high level of plasma CRP, independent of other risk factors of cardiovascular disease, can be used as a predictor of TIA and ischemic stroke in elderly patients (18).

In the present study, such relationship was not found. The reason for this difference might be using different population with demographically various people in two studies. It also may be differences in the exclusion criterion, since all diseases and disease conditions that increase CRP in these patients were excluded in the study, but in the mentioned study, only infectious diseases were excluded from the study, so the results of this study are more generalizable.

In the study conducted by Faraji. F et al, it was found that there was no significant correlation between infarct volume and C-reactive protein and white blood cells. Additionally, significant correlation was not found between Canadian Neurological Scale score of cerebral stroke and amount of white blood cells.

However, significant correlation was found between infarct volume and neurological Canadian Stroke Scale scores. Finally, significant correlation was not found between level of inflammatory factors, and volume and severity of infarct (21). Results of previous study were inconsistent with results of the current study, since it might be due to difference in sample size and exclusion criteria if the current study and mentioned studies. In the current study, we tried to eliminate all factors involved in increased CRP level so that only patients with cerebral stroke to be included in the study. In another study conducted in 2014 by Iranmanesh et al to examine the relationship between CRP serum levels and stenosis inside and outside of the brain, they showed that there was significant correlation between serum levels of CRP and stenosis ($p=0.003$).

In patients with abnormal CRP, the most involved vessels were respectively internal carotid artery, the middle cerebral artery, and anterior cerebral artery and in patients with normal CRP, the most involved vessels were respectively the anterior cerebral artery, the internal carotid artery, and middle cerebral artery. Significant correlation was not found between serum levels of CRP and stenosis of the internal carotid artery ($p=0.015$) and middle cerebral artery ($p=0.006$) (22). The findings of the mentioned study are consistent with the findings of this study.

The result of the study suggests that the level of CRP is high in ischemic patients compared with hemorrhagic group. CRP level has direct correlation with CVA severity according to MNIHSS criterion in ischemic patients, and as CRP level is high, the severity of CVA will be higher and vice versa.There is no correlation between CRP and severity of CVA in hemorrhagic CVA. Considering the various factors on MNIHSS, studied groups included severity of CVA (severe, moderate, mild and hemorrhagic), in which the age, blood platelets, TG and CRP levels on admission and four days after admission, diastolic blood pressure, diabetes, chronic heart failure, polycythemia, heart rate and amount of hemoglobin were effective on amount of MNIHSS in patients.

In the regard, direct impact of CRP level on admission and four days after the hospitalization, diabetes, and polycythemia was higher on MNIHSS and it has greater effect in CVA severity. Considering diastolic blood pressure, platelet, triglycerides, heart failure, hemoglobin, and troponin, this relationship is reversed ($p<0.05$) with explaining power of 0.893 ($R2=0.902$ and Adjusted $R2=0.893$). According to results of the current study, it is recommended that paraclinical tests of CRP on the admission, type, and severity of CVA to be performed. Holding meetings and providing information to doctors to introduce a variety of CRP relationships with ischemic stroke severity and variables reducing the risk of this disease and early referral of patients with high CRP up to the advanced centers are recommended to reduce mortality rate severe cerebral stroke complications. Due to the small number of studies conducted, conducting similar studies with larger sample size is recommended. Conducting another study to assess the effects of predicting effects of CRP to diagnose severity or type of CVA is also recommended.

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