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Original Research Article

Correlation between CRP Level and Stroke Volume

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Abstract: ***Background:*** Stroke is an important health issue for individuals and society. Early identification of risk factors of stroke patients helps take measures to prevent the development of further stroke. C-reactive protein is a marker of acute infection as well as acute inflammation. A high level of CRP may be associated with poor outcomes because they reflect either an inflammatory reaction or tissue damage (den Hertog HM *et al*., 2009). Increase in inflammatory parameters correlated significantly with lesion volume and stroke severity (Audebert HJ *et al*., 2004). ***Aim of the study:*** To see the Correlation between CRP level and stroke volume. And to see the CRP level as a prognostic marker in 3 months follow-ups in ischemic stroke. ***Methods*****:** This was a descriptive cross-sectional study undertaken in the neurology department of a medical college hospital in Bangladesh. A total of 130 patients were included in the study group who met the inclusion and exclusion criteria. Out of 130 patients, 63 were ischemic strokes and 67 were hemorrhagic strokes. ***Results:*** In our study, the estimated level of mean CRP level in acute haemorrhagic stroke was 8.6 mg/L. and in acute ischemic stroke was 21.6mg/L. In this study, there was a statistically significant relationship between the size of the infarct and the level of estimated CRP in ischemic stroke**.** There was no correlation between CRP level and volume of hemorrhage in hemorrhagic stroke. In this study, the mean CRP value was 19.1 mg/L in those patients who were alive and 28.4 mg/L in those patients who died of ischemic stroke. The difference between the two groups was not statistically significant (p-value 0.30) though the mean CRP in patients who died were much higher than in those who were alive. ***Conclusion:*** In conclusion, we believe that these data support two main conclusions. First, the elevation of CRP is common in ischemic stroke. Second, advanced CRP levels were associated with larger infarct size in cases with acute ischemic stroke. These results suggest that elevated CRP levels, reflecting a large infarct size, may serve as a helpful serologic marker in the evaluation of inflexibility of acute ischemic stroke*.*

Keywords: C-Reactive Protein Level, Mortality, Acute Stroke.

INTRODUCTION

World health organization (who) defined stroke as a clinical syndrome occurring due to sudden cerebral dysfunction, producing focal or global neurological deficit, persisting for more than 24 hours, or the patient dies within 24 hours, vascular in origin, non-epileptic, non-traumatic (Aho *et al*., 1980). Stroke is the most prevalent neurological disorder under the age of 65 years. It causes 9% of all deaths around the world and is the second most common cause of death after ischaemic

heart disease. (Donnan GA *et al*., 2008). About two-thirds or more stroke deaths occur in the developing world (Philip B 2002). About eighty-five percent of all first-ever strokes are ischemic, ten percent are due to intracerebral haemorrhage, and five percent are due to subarachnoid haemorrhage. The burden of stroke is higher in blacks than white for both ischemic and haemorrhagic strokes (Rothwell P 2009). C-Reactive Protein (CRP) is a trace protein in the circulation of healthy subjects, with a median concentration of about 1 mg/ L. CRP is the most reliable marker of inflammation. It is produced mostly by liver hepatocytes in response to cytokines such as IL-2, IL-6 and tissue necrosis factor (TNF). It activates the classical complement pathway as a response to the inflammatory reaction. Induction of CRP is rapid and the half-life (19 hours) is long enough for a steady time course in repeated measurement. CRP is associated with endothelial cell dysfunction and progression of atherosclerosis, possibly by nitric oxide synthesis (Napoli MD *et al*., 2005). Elevated serum levels of CRP are found in up to three-quarters of patients with ischemic stroke. Increases in CRP may reflect a systemic inflammatory response following ischemic stroke, the extent of tissue injury, or concurrent infections (den Hertog HM *et al*., 2009). A high level of CRP may be associated with poor outcomes because they reflect either an inflammatory reaction or tissue damage (den Hertog HM *et al*., 2009). Increase in inflammatory parameters correlated significantly with lesion volume and stroke severity (Audebert HJ *et al*., 2004). C-reactive protein has proven to be a sensitive systemic marker of inflammation and to be involved in the endothelial inflammatory response (EJ van Dijk *et al*., 2005).

METHODS AND MATERIALS

This was a descriptive cross-sectional study undertaken in the department of Neuromedicine, Rajshahi medical college hospital, during the period from July 2010 to June 2011 After taking a detailed history and physical examination a total of 200 patients were included in the study. A CT scan was done on all the patients. Among them, 28 patients were excluded due to tumor, abscess and other metabolic abnormalities. Among the remaining 172 patients, 22 patients were excluded from the study due to evidence of infection, rheumatological disorder, recurrent stroke, major renal diseases and history of acute MI. Among the remaining 150 patients, 20 patients dropped out of the study. Eventually, a total of 130 patients were included in the study group who met the inclusion and exclusion criteria.

Inclusion criteria were:

- Age- between 40 to 70 years
- Sex- male and female
- Patient with clinical features suggestive of stroke
- Stroke within 24 hours. (excluding TIA)
- Neuroimaging features consistent with a diagnosis of stroke

Exclusion criteria were:

- Recurrent stroke
- After acute MI
- Patient suffering from an acute infectious disease
- Patient suffering from connective tissue diseases. e.g., vasculitis.
- Concurrent major renal, hepatic or cancerous diseases
- Recent surgery or major trauma.

Before the commencement of this study, the research protocol was approved by the Institutional Review Board of RMC. A signed informed consent described in the Bengali Language was taken from the parents after explaining to them the nature, objective, procedure, risks and benefits and implications of the study. Detail history was taken about age, hypertension, diabetes, smoking habit, cardiac disease, oral contraceptive pill, history of stroke, convulsion, vomiting, headache, speech abnormality, swallowing difficulty, onset and progression of symptoms and any abnormal movement. General examination was done and detailed neurological examinations such as level of consciousness, motor weakness, respiratory pattern, reflexes, gaze palsy and fundoscopic examination were done. They were clinically evaluated for the presence of any valvular and ischemic heart disease. All of them were routinely investigated for CRP, complete blood count, urine R/M/E, serum creatinine, RBS and ECG. By definition, large infarcts were so designated when the sum of the largest transverse and sagittal diameter divided by 2 was >1.5 cm; small infarcts, when the sum of the largest transverse and sagittal diameter divided by 2 was <1.5 cm (Napoli MD 2001). C-reactive protein in serum was estimated by a vitros-350 auto analyzer in a private diagnostic center near the Rajshahi Medical College Hospital. The results were evaluated automatically by the analyzer and were represented in mg/L. CT scan was done in the radiology and imaging department of Rajshahi Medical College Hospital, Rajshahi and also some private diagnostic centers. Computer-based software; a statistical package for social sciences (SPSS) was used to analyze the collected data. Appropriate analyses, such as the Unpaired Students 't-test, Chi-square

test, Z-test, etc., were carried out. P-value <0.05 was taken as a minimum level of significance.

RESULTS

There were 130 patients of whom 68 were male and 62 females. 67(51.5%) patients had haemorrhagic and 63(48.5%) patients had ischemic stock. The mean value of C-reactive protein in ischemic stroke and the mean value of C-reactive protein in a normal Bangladeshi population were 21.6 mg/L and 4.3 mg/L respectively. The significance of the difference in mean CRP between the two groups was statistically significant (<0.001). The mean value of C-reactive protein in hemorrhagic stroke and the mean value of C-reactive protein in a normal Bangladeshi population were 8.6 mg/L and 4.3 mg/L respectively. The significance of the difference in mean CRP between the two groups was statistically significant (<0.046). This table shows mean CRP value was 19.1mg/L among alive patients and 28.4 mg/L among dead patients with ischemic stroke. The mean difference between the alive and dead groups was not statistically significant (p=0.30). This presentation shows that there was a correlation between CRP level and the size of the infarct in ischemic stroke and the association was statistically significant. This graphical presentation shows that there was a correlation between CRP level and the size of the infarct in ischemic stroke and the association was statistically significant.

Table-1: Relationship of CRP level in patients of acute haemorrhagic stroke with that of normal population

Types of stroke	Number	CRP level (mg/L)		df	t-value	p-value
		Mean(±SD)	Mean diff.			
Ischemic	63	21.6(23.97)	17.300	91	3.9409	<0.001
Normal	30	4.30(0.72)				

Table-2: Association between CRP level and 3 months' mortality in ischemic stroke

Status	Number	CRP level (mg/L)		df	t-value	p-value
		Mean(±SD)	Mean diff.			
Alive	46	19.1(18.70)	9.31	61	1.06	0.3
Dead	17	28.4(34.28)				

Table-3: Correlation between CRP level and size of infarct in ischemic stroke

Correlations			
		C-reactive protein (mg/L)	CT scan size of infarction in cm
C-reactive protein (mg/L)	Pearson correlation	1	0.309*
	Sig. 2-tailed		0.014
	N	130	63
CT scan size of infarction in cm	Pearson correlation	0.309	1
	Sig. 2-tailed	0.014	
	N	63	63
* Correlation is significant at the 0.05 level (2-tailed).			

Table-4: Correlation between CRP level and volume of hemorrhage in hemorrhagic stroke

Correlations			
		C-reactive protein (mg/L)	CT scan in haemorrhage (ml)
C-reactive protein (mg/L)	Pearson correlation	1	-0.081
	Sig. (2-tailed)		0.586
	N	130	48
CT scan in haemorrhage (ml)	Pearson correlation	-0.081	1
	Sig. (2-tailed)	0.586	
	N	48	48

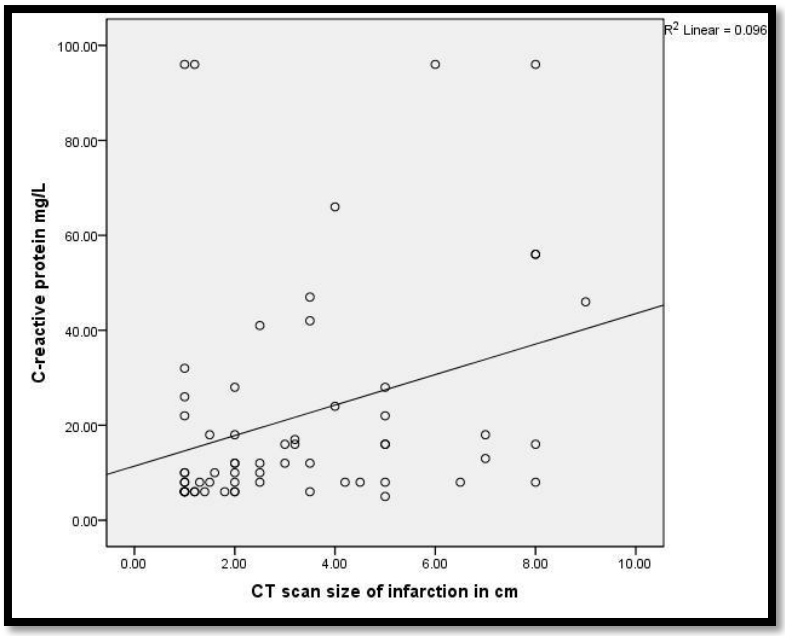

Figure-1: This graphical presentation shows that there was a correlation between CRP level with the size of the infarct in ischemic stroke and the association was statistically significant

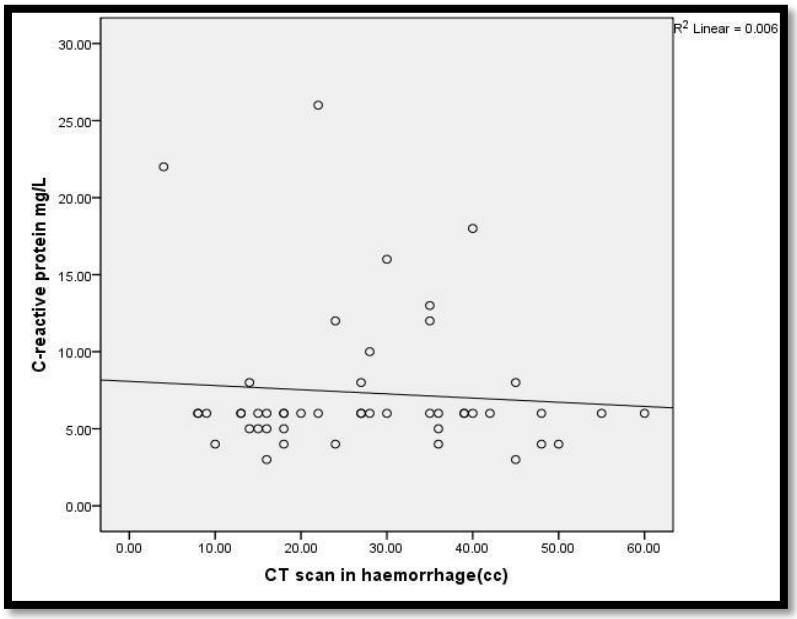

Figure-2: This graphical presentation shows that there was no correlation between CRP level and volume of hemorrhage in hemorrhagic stroke

DISCUSSION

This is a prospective descriptive study in which the CRP level was estimated in patients with acute stroke, Both ischaemic and hemorrhagic. There were 130 patients of whom 68 were males and 62 were females. 67(51.5%) patients had hemorrhagic and 63(48.5%) patients had an ischemic stroke. In our study, the estimated level of mean CRP level in acute haemorrhagic stroke was 8.6 mg/L, while in patients with ischemic stroke it was 21.6 mg/L. In this study, the mean CRP value was 19.1 mg/L in those patients who were alive and 28.4 mg/L in those patients who died of ischemic stroke. The difference between the two groups was not statistically significant (p-value 0.30) though the mean in patients who died was much higher than in those who were alive. CRP levels have been monitored to find their relationship with mortality and most studies done elsewhere has found significantly higher CRP levels in patients of ischemic stroke who had died. Shantikumar *et al*.,

(2009) followed up 394 patients for a median of 7.4 years and during follow-up, 231 patients (59%) died. CRP levels were significantly higher in those who subsequently died (10.8 mg/L) compared with those who survived (3.8 mg/L). So authors of this study concluded that CRP remained predictive for mortality after adjusting for conventional clinical and demographic risk factors. Muir *et al*., (1999) diagnosed ischemic stroke in 228 consecutive admissions and the median follow-up was 959 days. Survival in those with CRP >10.1 mg/L was significantly worse than in those with CRP <10.1 mg/L. In their study higher CRP concentration was an independent predictor of mortality, together with age and stroke severity on the National Institutes of Health Stroke Scale. Napoli *et al*., (2001) included 128 patients with ischemic stroke in their study and measured their CRP levels within 24 hours. Stratification of the patients into tertiles based on CRP (<5, 5 to 33, and > 33 mg/L) revealed an increased probability of death or new vascular event in patients with increased CRP levels (12.1%, 29.7%, and 54.8%). Thus they concluded that increased levels of CRP are associated with a worse outcome in patients with ischemic stroke. Idicula *et al*., (2009) studied 498 patients with ischemic stroke who were admitted within 24 hours after the onset of symptoms and their CRP was measured at the time of admission. Patients were followed up for 2.5 years for mortality. High CRP was associated with high mortality (p=0.002). The authors of this study concluded that CRP is an independent predictor of mortality after ischemic stroke. The result of the studies quoted above clearly demonstrates that higher CRP levels were associated with a poor outcome, after adjusting for other confounding factors which may affect mortality. In our study also the mean CRP level was higher (28.4 to 19.1 mg/L) in those patients who died compared to those who were alive so the results of this study are similar to what has been reported elsewhere. In this study, there was a statistically significant relationship between the size of the infarct and the level of estimated CRP. Napoli (2001) included 193 patients with ischemic stroke in their study. The C reactive protein concentrations increased in about three-quarters of patients within 24 hours after ischemic stroke, and higher values were significantly associated with large infarct size and worse outcomes. Audebert (2004) studied 346 patients out of 1500 consecutive acute ischemic stroke patients of which 43 patients underwent thrombolysis. Patients with a larger stroke volume and more severe stroke deficits had higher CRP in the acute phase after stroke. Youn *et al*., (2010) studied 96 patients with ischemic stroke who underwent MRI scans. Infarct volumes were estimated by diffusion-weighted imaging. There was a significant correlation between hs-CRP and DWI volumes so the authors concluded that higher hs-CRP levels were associated with larger infarct volumes in patients with acute ischemic stroke. So findings of this study correlate well with the findings of other studies.

Limitations of the study

The number of cases in this study was small. The cases were collected from indoor unit of Medicine and the Neuromedicine department of Rajshahi Medical College Hospital. So there is some selection bias regarding the severity of stroke (most patients were moderate to severe in severity) and socioeconomic condition (mostly middle class and poor socioeconomic background). Only a single blood level was checked. Single CRP measurement can be influenced by many factors such as infection, stress, the timing of measurement, and lab error. Another limitation of this study was substantial heterogeneity in stroke. Unavailability of case-specific survival data.

CONCLUSION AND RECOMMENDATIONS

CRP is a widely recognized indicator of inflammation and is known to play important role in atherogenesis. As a sensitive but non-specific marker of inflammation, CRP concentration should always be interpreted in the context of the patient's clinical history, preferably with a review of previous results. High CRP in ischemic stroke patients is clearly associated with severe stroke and poor outcomes. The clinical implications of these findings are unclear at present. It remains to be seen whether CRP is a marker of stroke severity, or is a response to stroke, or a mixture of both. A broad-based prospective study is required to substantiate the present observation.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee.

REFERENCES

1. Ahmed, K. G. U. (2009). `Study of C-reactive Protein in Acute Ischemic stroke'. Accepted thesis in Department of Neurology; Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.
2. Aho, K., Harmsen, P., Hatano, S., Marquardsen, J., Smirnov, V. E., & Strasser, T. (1980). Cerebrovascular disease in the community: results of a WHO collaborative study. *Bulletin of the World Health Organization*, *58*(1), 113-130.

3. Audebert, H. J., Rott, M. M., Eck, T., & Haberl, R. L. (2004). Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. *Stroke*, *35*(9), 2128-2133.
4. Bos, M. J., Schipper, C. M. A., Koudstaal, P. J., Witteman, J. C., Hofman, A., & Breteler, M. M. (2006). High serum C-reactive protein level is not an independent predictor for stroke: the Rotterdam Study. *Circulation*, *114*(15), 1591-1598.
5. Den Hertog, H. M., Van Rossum, J. A., Van Der Worp, H. B., Van Gemert, H. M. A., de Jonge, R., Koudstaal, P. J., & Dippel, D. W. J. (2009). C-reactive protein in the very early phase of acute ischemic stroke: association with poor outcome and death. *Journal of neurology*, *256*(12), 2003-2008.
6. Ga, D. (2008). Fisher m, macleod m, Davis Sm. *Stroke. Lancet*, *371*(9624), 1612-23.
7. Van Dijk, E. J., Prins, N. D., Vermeer, S. E., Vrooman, H. A., Hofman, A., Koudstaal, P. J., & Breteler, M. M. B. (2005). C-reactive protein and cerebral small-vessel disease: the Rotterdam Scan Study. *Circulation*, *112*(6), 900-905.
8. Gorelick, P. B. (2002). Stroke prevention therapy beyond antithrombotics: unifying mechanisms in ischemic stroke pathogenesis and implications for therapy: an invited review. *Stroke*, *33*(3), 862-875.
9. Greenberg, M. S. (2006). Cerebral hemorrhage. Handbook of Neurosurgery, sixth edition; Thieme Medical Publisher, New York, pp 856.
10. Hirschfield, G. M., & Pepys, M. B. (2003). C-reactive protein and cardiovascular disease: new insights from an old molecule. *Qjm*, *96*(11), 793-807.
11. Idicula, T. T., Brogger, J., Naess, H., Waje-Andreassen, U., & Thomassen, L. (2009). Admission C–reactive protein after acute ischemic stroke is associated with stroke severity and mortality: The'Bergen stroke study'. *BMC neurology*, *9*(1), 1-9. doi:10.1186/1471-2377-9-18.
12. Ledue, T. B., & Rifai, N. (2003). Preanalytic and analytic sources of variations in C-reactive protein measurement: implications for cardiovascular disease risk assessment. *Clinical Chemistry*, *49*(8), 1258-1271.
13. Lindsberg, P. J., & Grau, A. J. (2003). Inflammation and infections as risk factors for ischemic stroke. *Stroke*, *34*(10), 2518-2532.
14. Mary, K., Louise, D., & Turgon, G. (1996). 'Immunology and serology in laboratory medicine, 2nd and. Mosby-yearbook, pp. 48-55.
15. Modrego, P. J., Boned, B., Berlanga, J. J., & Serrano, M. (2008). Plasmatic B-type natriuretic peptide and C-reactive protein in hyperacute stroke as markers of CT-evidence of brain edema. *International journal of medical sciences*, *5*(1), 18-23.
16. Muir, K. W., Weir, C. J., Alwan, W., Squire, I. B., & Lees, K. R. (1999). C-reactive protein and outcome after ischemic stroke. *Stroke*, *30*(5), 981-985.
17. Di Napoli, M., Day, R., & Gilroy, F. (2001). C reactive protein and acute phase of ischaemic stroke. *British Medical Journal*, *322*(7302), 1605-1606.
18. Di Napoli, M. (2001). Systemic complement activation in ischemic stroke. *Stroke*, *32*(6), 1443-1448.
19. Di Napoli, M., & Papa, F. (2003). Clinical use of C-reactive protein for prognostic stratification in ischemic stroke: has the time come for including it in the patient risk profile?. *Stroke*, *34*(2), 375-376.
20. Di Napoli, M., Papa, F., & Bocola, V. (2001). C-reactive protein in ischemic stroke: an independent prognostic factor. *Stroke*, *32*(4), 917-924.
21. Di Napoli, M., Papa, F., & Bocola, V. (2001). Prognostic influence of increased C-reactive protein and fibrinogen levels in ischemic stroke. *Stroke*, *32*(1), 133-138.
22. Di Napoli, M., Schwaninger, M., Cappelli, R., Ceccarelli, E., Di Gianfilippo, G., Donati, C., ... & Weber, D. (2005). Evaluation of C-reactive protein measurement for assessing the risk and prognosis in ischemic stroke: a statement for health care professionals from the CRP Pooling Project members. *Stroke*, *36*(6), 1316-1329.
23. Di Napoli, M., & Papa, F. (2003). Association between blood pressure and C-reactive protein levels in acute ischemic stroke. *Hypertension*, *42*(6), 1117-1123.
24. Ridker, P. M., Cushman, M., Stampfer, M. J., Tracy, R. P., & Hennekens, C. H. (1997). Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *New England journal of medicine*, *336*(14), 973-979.
25. Gorelick, P. B. (2002). Stroke prevention therapy beyond antithrombotics: unifying mechanisms in ischemic stroke pathogenesis and implications for therapy: an invited review. *Stroke*, *33*(3), 862-875.
26. Prasad, K. (2006). C-reactive protein (CRP)-lowering agents. *Cardiovascular drug reviews*, *24*(1), 33-50.
27. Rallidis, L. S., Vikelis, M., Panagiotakos, D. B., Rizos, I., Zolindaki, M. G., Kaliva, K., & Kremastinos, D. T. (2006). Inflammatory markers and in-hospital mortality in acute

ischaemic stroke. *Atherosclerosis*, *189*(1), 193-197.
28. Ropper, A. H., & Samuels, M. A. (2009). Cerebrovascular diseases. In: Adams and Victor's. 9th edition. McGraw-Hill companies Inc. Printed in the United States of America; 776-806.
29. Rothwell, P. (2009). Cerebrovascular diseases. In: Brain's Diseases of the Nervous System 12th edition. Ed. Michael Donaghy. Oxford University Press, Oxford, pp–1004-1007.
30. Shantikumar, S., Grant, P. J., Catto, A. J., Bamford, J. M., & Carter, A. M. (2009). Elevated C-reactive protein and long-term mortality after ischaemic stroke: relationship with markers of endothelial cell and platelet activation. *Stroke*, *40*(3), 977-979.
31. Tillett, W. S., & Francis Jr, T. (1930). Serological reactions in pneumonia with a non-protein somatic fraction of pneumococcus. *The Journal of experimental medicine*, *52*(4), 561-571.
32. Verma, S., & Yeh, E. T. (2003). C-reactive protein and atherothrombosis—beyond a biomarker: an actual partaker of lesion formation. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, *285*(5), R1253-R1256.
33. Wakugawa, Y., Kiyohara, Y., Tanizaki, Y., Kubo, M., Ninomiya, T., Hata, J., ... & Iida, M. (2006). C-reactive protein and risk of first-ever ischemic and hemorrhagic stroke in a general Japanese population: the Hisayama Study. *Stroke*, *37*(1), 27-32.
34. Winbeck, K., Poppert, H., Etgen, T., Conrad, B., & Sander, D. (2002). Prognostic relevance of early serial C-reactive protein measurements after first ischemic stroke. *Stroke*, *33*(10), 2459-2464.
35. Youn, C. S., Choi, S. P., Kim, S. H., Oh, S. H., Jeong, W. J., Kim, H. J., & Park, K. N. (2012). Serum highly selective C-reactive protein concentration is associated with the volume of ischemic tissue in acute ischemic stroke. *The American journal of emergency medicine*, *30*(1), 124-128.