Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Neurology

Association of Serum C- Reactive Protein with Severity of Acute Ischemic Stroke Patients

Muhammad Nazmul Alam[1*], Mahabubur Rahman[2], Tahrima Showkat[3], Paresh Chandra Halder[4], Biplab Kumar Das[5], Kartick Chandra Halder[6], Faruk Ahmed[7], Jasmin Akhtar[8], Sharmin Akter[9], Mohammad Maruf Reza[10]

[1]Assistant Professor (Neurology), Sheikh Sayera Khatun Medical College, Gopalganj, Bangladesh
[2]Assistant Professor (Neurology), Sheikh Sayera Khatun Medical College, Gopalganj, Bangladesh
[3]Medical Officer, National Institute of Neuroscience & Hospital, Agargaon, Dhaka, Bangladesh
[4]Assistant Professor (Anaesthasiology), Sheikh Sayera Khatun Medical College, Gopalganj, Bangladesh
[5]Assistant Professor (Cardiology), Sheikh Sayera Khatun Medical College, Gopalganj, Bangladesh
[6]Assistant Professor (Cardiology), Bangabandhu Sheikh Mujib Medical College, Faridpur, Bangladesh
[7]Assistant Professor (Paediatrics), Abdul Malek Ukil Medical College, Noakhali, Bangladesh
[8]Assistant Professor (Microbiology), National Institute of Traumatology and Orthopaedic Rehabilitation (NITOR), Dhaka, Bangladesh
[9]Medical Assistant, E-Z Medical Care, 85-50 118th Street, Kew Gardens, NY-11415, United States
[10]Quality Analyst (Endocrinology), Central Queens IPA, United States

DOI: 10.36347/sjams.2021.v09i12.016 | **Received:** 14.11.2021 | **Accepted:** 19.12.2021 | **Published:** 25.12.2021

***Corresponding author:** Muhammad Nazmul Alam **Email:** nazmul2411@hotmail.com

Abstract **Original Research Article**

Introduction: Stroke is a leading cause of death and long-term disability worldwide. Of the total number of prevalent strokes, more than 80% are ischemic. Atherosclerosis being an inflammatory condition is associated with raised serum level of CRP. Hence the possible role of serum CRP in pathogenesis of AIS is being studied. Many studies support that serum CRP is a marker of stroke severity and prognosis. ***Materials and Methods*:** The observational and prospective study was carried out at Department of Neurology, Sheikh Sayera Khatun Medical College, Gopalganj, Bangladesh from January to December-2020.The present study 'Serum C-reactive protein in Acute Ischemic stroke and its impact on stroke severity and prognosis. Total 51 neuroimaging confirmed cases of AIS were selected randomly for this non- interventional prospective study. Serum CRP was measured in all patients and NIHSSS was used for assessing stroke severity. ***Results*:** The mean CRP level was 21.93±3.60 mg/l and only 18% of cases were having normal CRP level. 60% of cases were having serum CRP level in the range of 3-30mg/L and 18% were having even the higher level. Age of the patient significantly correlated with the CRP level (r=0.294 at p-0.05) but the sex didn't affect the rise in CRP (p= 0.490). Serum CRP level was affecting the stroke severity significantly (r=0.643, p-0.000).The mean CRP level in discharged patients was 10.51 ± 13.21 mg/l whereas it was 44.11 ± 29.7 mg/l in those who died in the hospital. Thus CRP level affected mortality of acute ischemic stroke significantly. (p-0.00). ***Conclusion*:** CRP is raised in most of the patients of acute ischemic stroke and its elevation reveals the underlying inflammation causing atherosclerosis as well as CRP as a marker of brain injury. Serum C-reactive protein elevation is associated with more severe stroke and poor prognosis.

Keywords: Acute Ischemic Stroke, C-Reactive Protein, Prognostic Factors.

INTRODUCTION

Stroke is a leading cause of death and long-term disability worldwide [1]. Of the total number of prevalent strokes, more than 80% are ischemic [1]. Established risk factors include smoking, hypertension (HTN), high body mass index (BMI), atrial fibrillation, diabetes mellitus, and atherosclerosis [2]. Finding predictive markers for recurrent cardiovascular events could be vital in identifying potential preventive measures. There is evidence to suggest that stroke is associated with inflammation [3]. High sensitivity C-reactive protein (hs-CRP) detects low level inflammation and correlates with cardiovascular risk in the general population [4]. Acute ischemic stroke (AIS) is characterized by the sudden loss of blood circulation to an area of the brain, typically in a vascular territory, resulting in a corresponding loss of neurologic function [5]. Among various risk factors atherosclerosis is the most important. Many studies confirmed that early detection and prevention of atherosclerosis is very

effective in decreasing the risk of acute ischemic stroke. Atherosclerosis is considered a chronic inflammatory response by vascular endothelium [2]. C-reactive protein (CRP) is an acute phase reactant produced in response to inflammatory process and therefore it is considered a sensitive marker of inflammation and atherosclerosis. Cerebrovascular ischemia has been associated with bronchial and periodontal infections [3]. As a marker of infection and inflammation, high CRP has been associated with acute stroke. Several studies have assessed the value of CRP in the early phase of stroke as a prognostic factor of functional outcome. In one study, patients with CRP levels ≥7 mg/L had higher NIHSS scores on admission [4]. Patients with CRP levels ≥7 mg/L taken as a group had worse outcomes in terms of morbidity and mortality [5]. Interestingly, recent experimental studies have shown that CRP itself may contribute to secondary brain damage after focal cerebral ischemia, possibly via a complement-mediated exacerbation of tissue injury. Since infectious and inflammatory conditions are much prevalent in Bangladesh compared to developed countries, and only a few studies are available from Bangladesh on the association of CRP with ischemic stroke, aim of the present study was to assess the possible relationship of CRP in acute ischemic stroke and its impact on stroke severity and mortality. Clinical data relating CRP to prognosis after ischemic stroke are sparse; many patients with elevated CRP levels within 72 hours of stroke have an increased risk of death, with an excess of cardiovascular mortality [5]. However, there is no complete information regarding the independent value of this finding or the meaning of CRP determinations carried out at different times after stroke. Therefore, we performed a prospective study in patients with first-ever ischemic stroke to further analyze the relationship between CRP values measured immediately and at different times after stroke, and the 1-year outcome.

MATERIALS AND METHODS

The observational and prospective study was carried out at Department of Neurology, Sheikh Sayera Khatun Medical College, Gopalganj, Bangladesh from January to December-2020. Total 51 neuroimaging confirmed cases of AIS were selected randomly for this non- interventional prospective study. Serum CRP was measured in all patients and NIHSSS was used for assessing stroke severity. Diagnosis of stroke was confirmed by Brain imaging: CT-scan Or MRI. Venous blood samples for the estimation of C-reactive protein (CRP) and other biochemical parameters were collected within 72 hours of admission. Within one hour of collection, the samples were centrifuged to separate the serum and were kept in -70°C. CRP was measured using immunoturbidometric assays (VITROS 5.1).

As per the normative data from VITROS manual and current literature, the cardiovascular risk was determined as low risk with CRP levels < 1.0 mg/L, medium risk if 1.0-3.0 mg/L, high risk when > 3.0 mg/L [6]. For our study we considered CRP level of ≥ 3 mg/L as high risk and ≤ 3 mg/L as low risk. Detailed information about past medical and surgical history (in-particular infections, systemic inflammation) and other risk factors of cardiovascular and Cerebro-Vascular accident was collected from all patients. Erythrocyte sedimentation rate (ESR) was measured in all subjects. Other investigation included Serum total cholesterol, blood sugar, ECG, RFT etc. The severity of stroke was measured on admission by the NIH stroke severity scale. The NIHSS is composed of 11 items, each of which scores a specific ability between 0 and 4. For each item, a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0. Score <4 is having Minor stroke, 5-15 for moderate severity, 16-20 for moderate to severe stroke and 21-42 score shows very severe stroke. Patient's outcome/prognosis was recorded as either death in hospital or return home with partial/full recovery.

Inclusion Criteria

1. All the patients of acute ischemic stroke confirmed by cerebral imaging, admitted in the Department of Neurology, Sheikh Sayera Khatun Medical College, Gopalganj, Bangladesh from January to December-2020.
2. Presented within 72 hours of the onset of stroke.

Exclusion Criteria

1. Age <14 years
2. Impaired renal function
3. Elevated ESR value
4. Severe sepsis, peritonitis, pancreatitis and any other systemic inflammatory conditions
5. Patient unwilling to give informed consent.

Statistical Analysis

Categorical variables were analyzed using either the chi-square statistic or Fischer exact test, as appropriate. Continuous variables were expressed as mean and statistical significance was tested using Student's t-test. Patients were grouped as normal versus elevated based upon serum admission CRP levels. All other parameters like patient characteristics and risk factors as well as presenting symptoms were dichotomized into 'yes=1' or 'no=0' to make the analysis easy. Also the patient outcome was dichotomized into 'death=1' or 'discharged=0'. Multivariate logistic regression models were constructed to determine variables that predicted abnormal elevations in admission serum CRP. Similar models were constructed to identify variables that independently predicted long-term outcomes. Associations were considered significant if p value is less than 0.05. All analyses were performed with SPSS v 20.0.

RESULTS

In this study total 51 cases were taken. Among them most common age group was 50-60 years comprising 40% of the total. But among female the most common age group was 60-70 years. 72% of patients were from the age range of 50-70 years, the most vulnerable age group for stroke. (Fig 1). 52% of patients had hyperlipidemia, 42% had hypertension, 22% smoker, 34% alcoholic and 22% Diabetes. Atrial fibrillation was seen in 18% of cases, more common in female. 10% had CVA in past and 10% of patients were known case of CAD. Most common symptom at presentation was hemiplegia (92%) (Right sided >left). Facial palsy was the second most common (72%) presenting symptom. Headache, Vomiting and seizure were present in 22%, 4% and 10% of patients respectively. 44% had dysphasia. Most common artery affected was Middle cerebral artery (44%), followed by lacunar infarction (34%).12% of patients had bilateral lesion and this affected the prognosis and stroke severity significantly. Size of infarction significantly affected the mortality (p= 0.000) and stroke severity (p= 0.001). 44% of patients were having very severe stroke with NIHSS score in the range of 20-40.Mean NIHSS in discharged patients was 16.45 whereas mean score of those who died in hospital with stroke was 35.35. Thus NIHSS of the stroke patient at admission significantly affect mortality. (p=0.00).

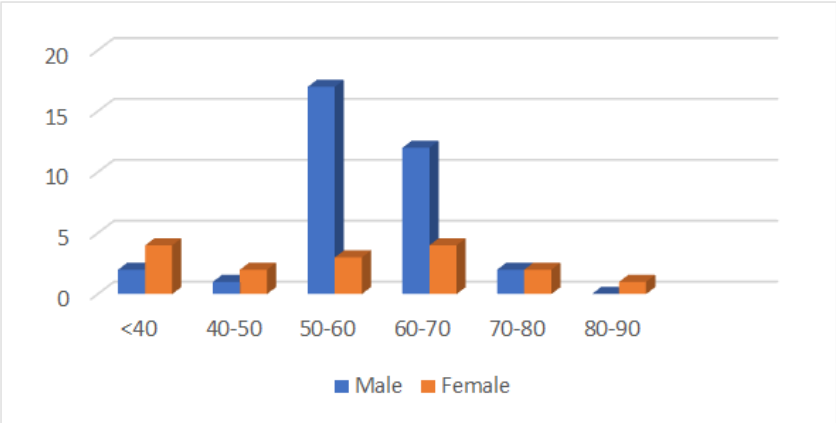

Fig-1: Age and sex distribution.

Table 1: CRP Statistics.

N	**51**
Mean (mg/L)	21.93
Std. Error of Mean	3.609
Median	13.10
Mode	4
Std. Deviation	25.523
Variance	651.401
Range	106
Minimum	2
Maximum	108

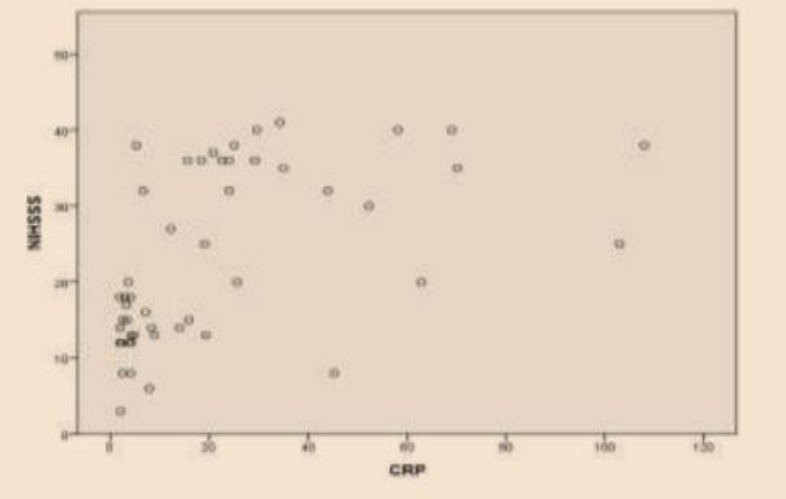

Fig-2: CRP vs. Stroke severity (NIHSS).

Table 2: CRP in Acute Ischemic stroke.

CRP range (mg/L)	Percentage
<3 (normal)	18%
3-10	30%
10-30	30%
>30	22%
Total	100%

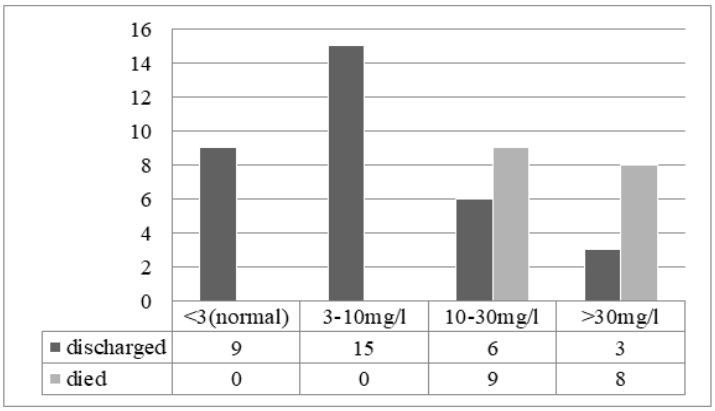

Figure 3: CRP vs. Mortality in acute Ischemic stroke.

Out of total 51 patients of Acute ischemic stroke (AIS) included in our study, 17 (33%) died. Difference in Mortality between female (5/16) and male (12/35) was not significant. (p= 0.778 by Pearson chi square test). Age of the patient significantly (p = 0.003) affect the mortality in AIS. The mean age of discharged patients was 55.06 years whereas the mean age of those who died was 65.18 years. Among the various risk factors, important determinants of mortality were: Hypertension (p=0.07), history of prior cerebrovascular accident (p=0.003), unconsciousness at admission (p=0.001) and ischemic changes in their ECG (p=0.000). DM, history of coronary artery disease (CAD), hyperlipidemia, and atrial fibrillation were not contributing to the prognosis/mortality although these are proven risk factor for the occurrence of ischemic stroke. The mean CRP level of patients included in this study was 21.93±3.60 mg/l. (Table 1) only 18% of cases were having normal CRP level. 60% of cases were having serum CRP level in the range of 3-30mg/L and 18% were having even the higher (>30mg/l) level maximum being 108mg/l (Table 2). Age of the patient significantly correlated with the CRP level (Spearman's correlation co-efficient 0.294 at p-value 0.05). But the sex didn't affect the rise in CRP (p= 0.490 by student t-test). The mean CRP level in discharged patients was 10.51 ± 13.21 mg/l whereas it was 44.11 ± 29.7 mg/l in those who died in the hospital. Thus CRP level affected mortality of acute ischemic stroke significantly. (p value<0.000, independent t-test and pearson chi quare) (Fig 2).

DISCUSSION

In general, in patients with major strokes, CRP levels correlate with stroke severity and can be a marker

of stroke etiology, with higher CRP in more severe cardio embolic or large artery disease stroke than in stroke caused by small artery disease [8] Age is the single most important risk factor for stroke. The most common age group among patients of 'Acute ischemic stroke (AIS)' in our study was 50-70 years covering 72% of total patients included in the study (Figure 2). Male to female ratio in our study was ~2.1:1 (Figure 1). US National Stroke Survey observed this as 1.44:1 [9]. 42% of stroke patients in this study had hypertension. 22% patients of acute ischemic stroke were Diabetic in this study. In Framingham, persons with glucose intolerance have double the risk of brain infarction of non-diabetic persons [10]. Mean CRP in patients of acute ischemic stroke in this study was 21.93mg/l much higher than the normal level of 3mg/l. Median value of CRP was 13.10 and maximum was 108 (Table 1). This signifies the inflammatory reactions asa mechanism of injury during acute ischemic stroke and possible role of anti- inflammatory molecules for the prevention and treatment of infarction. 22% of patients had CRP level above than 30 mg/l on the other hand 18% had normal CRP level. Winbeck *et al*., observed mean value of CRP in ischemic stroke as 17.5mg/l which corroborates our observations [12]. In the study of Abdul Kadir Kocer *et al*., mean CRP in cases of acute ischemic stroke was 31.2±4.4 whereas in control it was much lower, 3.9± 0.6 [13]. Keith W Muir *et al*., [14] also observed that mean CRP in cases were much higher than the control [14]. Rajput *et al*., had found that among stroke patients from Pakistan, 132 (88%) had elevated CRP (CRP > 10 mg/L) [5]. Moreover, in a study by Di Napoli *et al*., from Italy, 95 patients (74.2%) with acute ischemic stroke had high CRP levels (> 0.5 mg/dl) at admission [16]. Muir *et al.*, had detected CRP > 10 mg/L in 96 out of the 228 (42.1%) patients of acute ischemic stroke in UK [15]. CRP has evolved from being an association to a risk factor for vascular pathology of heart and brain. Zacho *et al.*, in his population based study, found a high frequency of ischemic heart disease (32%) and ischemic stroke (25%) among patients with high levels of CRP in Denmark [18]. Ridker *et al*., from the US, showed high CRP to be a predictor of risk for future myocardial infarction and stroke in healthy men [19]. Serum CRP level was affecting the stroke severity significantly (with the correlation coefficient >0.643, p-value 0.000) (Figure 2). Combined p value by ANOVA for this relation is 0.001. In one study, patients with CRP levels ≥7 mg/L had higher NIHSS scores on admission. Previous studies have shown that patients with increased CRP levels have larger infarctions [19]. Serum CRP level also correlates with the stroke prognosis. Mean CRP in discharged patient was 10.51mg/l whereas in those who died in hospital it was 44.11mg/l (p value 0.000) (Figure 3). Few studies in China and Nepal had similar findings [6]. A recent study showed that elevated CRP levels in young patients with ischemic stroke were associated with an increased risk of mortality, even 12 years after the CRP measurements [19]. Also Idicula *et al*., found a crude association between on admission high CRP and short-term (7 days) functional outcome in patients with acute ischemic stroke [7]. Song *et al*., in Korea demonstrated that elevated hs-CRP levels on the seventh hospital day, rather than within 24 h after stroke onset, could strongly predict the prognosis of functional disability [19]. Elevated CRP levels have been associated with poorer outcome in Malaysian patients with acute ischemic stroke [14]. Furthermore, we found a positive association between admission CRP and functional outcome. This is similar to the finding of Di Napoli *et al.*, [20] who demonstrated that increased levels of admission CRP are associated with worse outcome in patients with acute ischaemic stroke. Although the precise pathophysiological basis of this association is unclear, there are certain possible explanations.

CONCLUSION

Important risk factors for incidence of acute ischemic stroke are advance age, Hypertension, DM, atrial fibrillation, hyperlipidemia, prior stroke, alcohol and smoking. Determinants of stroke severity are: Age, ischemic changes in ECG, size of infarct and CRP level. Determinants of mortality are: Age, prior CVA, unconsciousness, ischemic changes in ECG, size of infarction, NIHSS score at admission and raised serum level of CRP. Serum CRP is raised in most of the patients of acute ischemic stroke and its elevation reveals the underlying inflammation causing atherosclerosis as well as CRP as a marker of brain injury. Serum C-reactive protein elevation is associated with more severe stroke and poor prognosis.

REFERENCES

1. Collaborators, G. B. D. S. (2019). GBD 2016 Stroke Collaborators: Global, regional, and national burden of stroke, 1990-2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol*, *18*, 439-458.
2. Gorelick, P. B. (2019). The global burden of stroke: persistent and disabling. *The Lancet Neurology*, *18*(5), 417-418.
3. Amarenco, P., Lavallée, P. C., Labreuche, J., Albers, G. W., Bornstein, N. M., Canhão, P., ... & Wong, L. K. (2016). One-year risk of stroke after transient ischemic attack or minor stroke. *New England Journal of Medicine*, *374*(16), 1533-1542.
4. Khanevski, A. N., Bjerkreim, A. T., Novotny, V., Næss, H., Thomassen, L., Logallo, N., ... & NOR-STROKE study group. (2019). Recurrent ischemic stroke: Incidence, predictors, and impact on mortality. *Acta Neurologica Scandinavica*, *140*(1), 3-8.
5. 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.
6. Huang, Y., Jing, J., Zhao, X. Q., Wang, C. X.,

Wang, Y. L., Liu, G. F., ... & Gu, W. K. (2012). High-sensitivity C-reactive protein is a strong risk factor for death after acute ischemic stroke among Chinese. *CNS neuroscience & therapeutics*, *18*(3), 261-266.

7. Adams, H. P., Davis, P. H., Leira, E. C., Chang, K. C., Bendixen, B. H., Clarke, W. R., ... & Hansen, M. D. (1999). Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*, *53*(1), 126-126-131.
8. Masotti, L., Ceccarelli, E., Forconi, S., & Cappelli, R. (2005). Prognostic role of C-reactive protein in very old patients with acute ischaemic stroke. *Journal of internal medicine*, *258*(2), 145-152.
9. American Heart Association Heart Disease and Stroke Statistics—2007 Update. 2007. Retrieved July 26, 2007, from www. americanheart.org/downloadable/heart/1166712318 459HS_ StatsInsideText.pdf.
10. Sacco, R. L., Benjamin, E. J., Broderick, J. P., Dyken, M., Easton, J. D., Feinberg, W. M., ... & Wolf, P. A. (1997). Risk factors. *Stroke*, *28*(7), 1507-1517.
11. Banerjee, T. K., & Das, S. K. (2016). Fifty years of stroke researches in India. *Annals of Indian Academy of Neurology*, *19*(1), 1-8.
12. 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.
13. Koçer, A., Canbulat, C., Gözke, E., & Ilhan, A. (2005). C-reactive protein is an indicator for fatal outcomes in first-time stroke patients. *Medical science monitor*, *11*(11), CR540-CR544.
14. Muir, K. W., Tyrrell, P., Sattar, N., & Warburton, E. (2007). Inflammation and ischaemic stroke. *Current opinion in neurology*, *20*(3), 334-342.
15. 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.
16. Di Napoli, M., Papa, F., & Bocola, V. (2001). C-reactive protein in ischemic stroke: an independent prognostic factor. *Stroke*, *32*(4), 917-924.
17. Den Hertog, H. M., Van Rossum, J. A., Van Der Worp, H. B., Van Gemert, H. M. A., de Jonge, R., Koudstaal, P. J., ... & PAIS investigators. (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.
18. Zacho, J., Tybjærg-Hansen, A., Jensen, J. S., Grande, P., Sillesen, H., & Nordestgaard, B. G. (2008). Genetically elevated C-reactive protein and ischemic vascular disease. *New England Journal of Medicine*, *359*(18), 1897-1908.
19. Chaudhuri, J. R., Mridula, K. R., Umamahesh, M., Swathi, A., Balaraju, B., & Bandaru, V. C. S. (2013). High sensitivity C-reactive protein levels in Acute Ischemic Stroke and subtypes: A study from a tertiary care center. *Iranian journal of neurology*, *12*(3), 92-97.
20. 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.