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C-REACTIVE PROTIEN AS A PROGNOSTIC INDICATOR FOR ISCHEMIC STROKE OUTCOMES.

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ABSTRACT

OBJECTIVES: To evaluate the value of CRP levels and their possible role in the pathogenesis of acute ischemic stroke.**PATIENTS AND METHODS:** This descriptive study was conducted at the medical wards of Liaquat University Hospital, Jamshoro, Hyderabad. Patients of either sex with their first-ever ischemic stroke were included. Blood samples were taken from all patients to measure the serum C-reactive protein. Blood samples were taken within 24 hours after an ischemic stroke, within 48 to 72 hours, and at hospital discharge. Relationship of C-reactive protein at different stages after acute ischemic stroke and also its role in the pathogenesis of acute ischemic stroke.**RESULTS:** A total of 100 patients with ischemic stroke were evaluated for CRP levels. There were 72 men and 28 women. 65% of patients had raised CRP levels at the time of admission within 12 to 24 hours after stroke, while 35% had a normal 0.5 mg/dl CRP level at the time of admission. Out of 65% of patients, the level of CRP persistently rose until discharge in 46% of patients, while the level dropped to normal in the remaining 19% of patients. Higher CRP levels at the time of admission were associated with large infarct sizes. Deaths were also observed in patients with a CRP level greater than 1.5mg/dl within 12 to 24 hours of stroke.**Conclusion:** CRP observed to be the helpful tool for assessing the prognosis of ischemic stroke patients. This is attributed to its capability to signify the systemic inflammatory response within the body, and its consistent link with unfavorable outcomes.

KEY WORDS: Inflammations, C-reactive protein, Ischemia, Stroke

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INTRODUCTION

Ischemic stroke is a significant contributor to both neurological mortality and morbidity. [1,2] In the US, approximately 700,000 people suffer from a new or recurring ischemic stroke each year. [3] This accounts for approximately 3% of the entire population of the country. Stroke stands as the primary cause of significant disabilities and ranking as the fifth most common cause of mortality in the nation.[3] Asia has seen an increase in the prevalence of ischemic stroke in the recent years, including Pakistan. This increase places a substantial burden on the country, leading to a significant expenditure of resources, finances, and healthcare professionals and impacting the overall economy. [4,5] In a recent extensive global study, physical inactivity, hypertension, and high serum lipid levels were identified as the most prominent risk factors for developing an acute stroke.[6] By addressing these factors along with other independent predictors such as smoking, obesity, diabetes mellitus, and the cardiovascular disease, the incidence of stroke has shown a decrease over the past three decades.[7] The importance of acute ischemic stroke as a public health concern is significant, and it will continue to gain relevance for future neurologists.[8] Timely reperfusion treatment remains crucial for effective stroke care. This entails prompt symptom recognition by the general public and first responders, appropriate triaging to a suitable stroke centre, and efficient evaluation and examination by the attending stroke team.[8] Serum biomarkers have the potential to aid in predicting the prognosis of critically ill patients and facilitate early treatment decisions. High-sensitivity CRP functions as a responsive marker for both inflammation and tissue injury occurring in the arterial wall.[8] Elevated levels of high-sensitive C-reactive protein, which indicate infection and inflammation, have been linked to the occurrence of acute stroke.[8,9] C-reactive protein CRP levels surge rapidly, increasing up to

50,000 times within two hours of inflammation onset, and reach their highest point at 48 hours. CRP serves as an indicator of inflammation, and its concentration is closely related to the rate and severity of the underlying cause that triggered the inflammation.[10] Previous research has indicated an association between CRP, an inflammatory marker, and stroke severity as well as long-term consequences.[11] This study has been done to estimate CRP levels and their potential contribution to the pathophysiology of acute ischemic stroke.

MATERIAL AND METHODS

This descriptive hospital-based study was conducted on 100 diagnosed patients of either sex with their first-ever ischemic stroke in medical wards at Liaquat University Hospital Hyderabad/ Jamshoro. Patients with a recent history of acute infection, including respiratory, urinary, or systemic infections, and individuals with known chronic inflammatory diseases like systemic lupus erythematosus, rheumatoid arthritis, or inflammatory bowel disease may be excluded due to the potential impact of these conditions on CRP levels, independent of acute ischemic stroke. All patients or their caregivers provided informed consent prior to participation in the study. A stringent protocol was followed to screen all patients, which included a comprehensive medical history assessment, a thorough neurological assessment, standardized blood investigations, and typically 1 or 2 CT scans or MRI of the brain. Transthoracic echocardiography and ECG were used for the detection of any underlying cardiac structural and functional abnormalities that could be associated with cardioembolic stroke. Neuroradiological findings were categorized into two types of lesions: large and small infarcts. Large infarcts were classified as such when the two-fold difference between the biggest transverse and sagittal diameters was greater than 1.5 cm. However, when the mean of the biggest transverse and sagittal diameters, dividing by 2, was less than 1.5 cm, minor infarcts were detected. Blood samples were taken from all patients to measure serum C-reactive protein. Blood samples were collected at specific time points: within 12 to 24 hours after the qualifying stroke, at 48 to 72 hours, and at discharge 12–5 days, or when an in-hospital end point occurred. The primary end point of the study was a combination of all-cause mortality and any new vascular event, whichever happened first during the hospitalization period. Data collection was performed using a study proforma, and the analysis of the data was conducted using SPSS version 26.

RESULTS

During the study period, a total of 214 patients presenting with clinical signs suggestive of ischemic stroke were identified. Following a thorough evaluation, 100 patients were included in the study. Among these cases, 72% were males, while 28 28% were females, resulting in a male-to-female ratio of 2.5:1. The levels of CRP measured within 12 to 24 hours, between 48 and 72 hours, and at hospital discharge or at the occurrence of an in-hospital end point. It is important to note that the normal CRP value is less than 0.5 mg/dL. The CRP levels exhibited changes from admission to discharge, indicating fluctuations in inflammation markers during the course of hospitalization. Out of the 100 patients diagnosed with ischemic stroke, 65% had CRP levels exceeding 0.5 mg/dL upon admission. Among these patients, 46% maintained elevated CRP levels until discharge or the primary end point, while 19% experienced a decrease in CRP levels, returning to normal. Among 35 individuals who were admitted with normal concentrations of CRP, 23 individuals continued to exhibit CRP levels below 0.5 mg/dL throughout their hospital stay. However, 12 patients from this group had abnormally elevated CRP levels during the time of discharge. In individuals with stroke, there was a significant incidence of cardioembolic stroke 40%, and 7% occurrence of stroke due to an unknown an etiology, while atherothrombotic stroke 53%. Table.2

It has been found that patients whose CRP levels were normal at the time of admission <0.5mg/dl and levels persisted at <0.5mg/dl throughout their hospital stay 23% had small infarcts and rapid and early improvement in their deficits from admission to discharge. While those patients whose CRP levels were elevated >0.5mg/dl at admission but dropped to normal 19% also showed better results in their deficits. Although the patients whose CRP levels were elevated >0.5mg/dl on admission and persistently remained elevated throughout their hospital stay in 46% faced subsequently vascular event or death, they were discharged without any significant improvement in their deficits. We also found that those patients whose CRP levels were higher at discharge were associated with larger infarcts without any significant improvement in their deficits.

24 patients had a primary end point during the study period; out of them, 10 patients died and 14 experienced a new vascular event transient ischemic attack, n = 3, recurrent stroke, n = 9, unstable angina, n = 2. Mortality occurred much more frequently in participants with a CRP level greater than 0.5 mg/dL within 12 to 24 hours of stroke. Table.3

Table. 1. Demographic characteristics of patients n=100

Variables	**Frequency**	**%**
Age groups		

40-45	25	25.0%
46-50	33	33.0%
51-55	18	18.0%
56-60	15	15.0%
61-65	09	09.0%
Gender		
Male	72	72.0%
Female	28	28.0%
Etiological distribution of stroke		
Stroke of unknown cases	07	7.0%
Cardio embolic stroke	40	40.0%
Athero thrombotic	53	53.0%

Table. 2. Patients' distribution according to CRP level n=100

Variables	**Frequency**	**%**
CRP level with in 12 to 24 hours after stroke		
<0.5 mg/dl	35	35.0%
>0.5 mg/dl	65	65.0%
CRP level after 48 to 72 hours		
>0.5 mg/dl	46	46.0%
<0.5 mg/dl	19	19.0%
CRP level changes from admission to discharge		
<0.5 mg/dl	23	23.0%
>0.5 mg/dl	12	12.0%

Table:3 Outcome and endpoint analysis n=24

Outcome	**Frequency**	**%**
Deaths	10	41.6%
TIA	3	1.25%
Recurrent stroke	9	37.5%
Unstable angina	2	8.3%

DISCUSSION

The occurrence of acute ischemic stroke can induce an inflammatory reaction, resulting in elevated levels of CRP. Higher CRP levels may be indicative of an unfavorable outcome, as they can reflect either an inflammatory response or tissue damage.[12] This study aimed to assess the potential role of CRP levels in the development of acute ischemic stroke, thereby evaluating their value in understanding its pathogenesis. Out of all 100 patients were included and out of these cases 72% were males and 28 28% were females, with a male to female ratio of 2.5:1. Consistently, Mahesar SA et al[13] reported that, out of all 132 cases males were 79 and females were 53. In the comparison of this study, Mahesar AH et al[14] reported that out of the total 85 participants included in the study, 73 individuals 85.9% were male, while 12 individuals 14.1% were female, resulting in a male-to-female ratio of 6 to 1. Differences in lifestyle and behavioral factors between males and females may contribute to the observed male dominance in ischemic stroke. For example, men are more prone to adopting unhealthy habits such as smoking, excessive consumption of alcohol, and a sedentary lifestyle, all of which are known risk factors for ischemic stroke.

In the current study of 100 individuals having ischemic stroke 65%, the concentration of CRP remained excessive until discharge or the primary end point in 46% of the participants and decreased to normal in 19%. The level of CRP remained at 0.5 mg/dL in 23 among the thirty-five individuals with normal CRP on admission and was significantly raised in the other twelve individuals after discharge. In the stroke patients, there was a high rate of cardioembolic stroke 40%, a low rate of stroke of unknown cause 7%, and atherothrombotic stroke 53%. In the comparison of this study, Giri N et al[15] demonstrated that a notable increase in CRP levels was observed among stroke patients upon admission, indicating a significant rise $p<0.001$. Over 73% of all cases demonstrated elevated CRP levels upon admission.[15] In the study by Reddy A et al[16] also C-reactive protein CRP levels were also measured

in patients admitted to the hospital who were confirmed to have ischemia through a CT scan conducted at the time of admission. CRP levels were assessed at two time points: 12 hours and within 72 hours from the onset of symptoms, and they observed that an increase in C-reactive protein CRP levels was found to be linked with an unfavorable outcome in individuals with acute ischemic stroke, indicating that elevated CRP serves as a poor prognostic indicator.[16] On the other hand, Chopda K et al[17] also reported that elevated levels of C-reactive protein CRP can be regarded as independent risk factors for stroke.

In this study, 24 patients had a primary end point during the study period; out of them, 10 patients died and 14 patients experience a new vascular event transient ischemic attack, n = 3, recurrent stroke, n = 9, unstable angina, n = 2. Mortality occurred much more frequently in participants with CRP levels greater than 0.5mg/dL within 12 to 24 hours of stroke. In the comparison of this study, Den Hertog HM et al[18] reported that individuals with C-reactive protein CRP levels equal to or higher than 7 mg/L were more frequently associated with unfavorable outcomes 57% versus 42%; p = 0.006 or mortality 23% versus 13%; p = 0.0007 compared to those with decreased CRP levels. Another study by Matsuo R et al[19] also reported a significant association between plasma hsCRP levels and unfavorable functional outcomes both at discharge and during the three-month follow-up period. Overall, the presence of raised CRP levels in ischemic stroke patients serves as an indicator of poor outcomes, including increased stroke severity, functional disability, and a heightened risk of recurrent stroke. Monitoring and managing CRP levels in these patients may aid in identifying those at higher risk and implementing appropriate interventions to improve their prognosis. The timing of CRP measurement may vary among studies, and this can impact the interpretation of results. CRP levels can fluctuate over time, and a single measurement may not accurately reflect the overall inflammatory status during the acute phase of stroke. CRP levels can be influenced by various factors, such as age, sex, comorbidities, medications, and lifestyle factors. Failure to account for these confounding variables adequately may affect the links between CRP levels and adverse outcomes, leading to potential bias in the result. Addressing these limitations through well-designed prospective studies with larger sample sizes, standardized protocols, adjustments for confounding factors, and diverse populations would enhance our understanding of the relationship between raised CRP levels and adverse outcomes in ischemic stroke patients.

CONCLUSION

It has been observed that the stroke patients whose CRP levels were persistently higher were more prone to develop subsequent vascular events or death, while those whose CRP levels were normal at admission or declined from a higher to a lower level during their hospital stay had much improvement in their neurological deficit. Patients who had elevated CRP levels showed a notable association with larger infarcts. An increase in CRP levels between 12 and 24 hours after the onset of stroke symptoms served as a significant predictor of an unfavorable outcome and was linked to an increased risk of subsequent vascular events or mortality. Through the use of sequential CRP measurements during the hyper-acute phase of stroke, it was observed that heightened CRP levels within 12 to 24 hours after the onset of stroke were strongly indicative of future cardiovascular or cerebrovascular events as well as an unfavorable outcome death. Conversely, elevated CRP concentrations measured 48 to 72 hours after the onset of stroke were not found to be correlated with the occurrence of endpoint events. It is not clear whether the association of CRP with cerebrovascular disease reflects its contributions to atherothrombosis, its acute phase condition, or both. However, more large-scale studies are needed to clarify the beneficial role of CRP as a routine test in stroke patients.

ETHICS APPROVAL: The ERC gave ethical review approval.

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin.

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