PROGNOSTIC SIGNIFICANCE OF C-REACTIVE PROTEIN IN ACUTE STROKE

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ABSTRACT

BACKGROUND

Cerebrovascular stroke is one of the leading cause of death and disability. C-Reactive Protein is an inflammatory marker that is increased in stroke. We intended to study the role of CRP in predicting severity and short-term outcome in stroke patients.

METHOD

The study included 60 patients with acute stroke admitted within 24 hours of symptom onset. All patients were subjected to detailed history taking and neurological evaluation. Severity of stroke on admission was assessed with National Institute of Health Stroke Scale (NIHSS), while seven days later outcome was assessed with modified Rankin Score (mRS) and Barthel ADL Index (BI). CRP levels and CT Brain was done in all patients within 24 hours of admission.

RESULTS

The mean age of the patients was 62.53±9.54. We found that CRP levels on admission was higher in ischaemic stroke patients (Mean=8.56±3.51) and there was positive correlation between CRP levels and severity assessed by NIHSS (r=0.44; p=0.004). There was positive correlation between CRP levels and short-term outcome assessed by mRS (r=0.35; p value=0.022). However, there was no positive correlation between CRP levels and severity or outcome in haemorrhagic stroke patients.

CONCLUSION

CRP levels on admission is a predictor of severity and short-term outcome in ischaemic stroke, but not haemorrhagic stroke.

KEYWORDS

C-Reactive Protein, Cerebrovascular Stroke, NIHSS.

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INTRODUCTION

C-reactive protein is a marker of inflammation. It is a glycoprotein synthesized by the liver in response to cytokines produced by macrophages. Recent evidences suggest that it is also associated with atherosclerosis. This led to studies focussing on CRP as an indicator of prognosis for vascular events.

Cerebrovascular Accidents, both ischaemic and haemorrhagic stroke have been one of the leading causes of mortality and morbidity in elderly populations.[1] However, markers predicting prognosis in these patients have not been established clearly.

The relationship between inflammation and atherosclerosis is well established. Thus, CRP being a marker of inflammation is identified as a marker for prognosis after vascular events. In addition elevated levels of CRP has also been used as an indicator of future vascular events.

The rise in CRP levels in stroke is not only due to its association with atherosclerosis, but also due to the inflammatory reaction that follows tissue damage.[2]

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Thus, explaining its potential to be a marker for prognosis following vascular events. The increased CRP levels causes activation of complement leading to secondary brain damage.[3]

Various studies have been done to establish correlation between CRP and stroke. Though it is less extensively studied when compared to CRP association in coronary artery disease, results from some of these studies show a positive association between CRP and stroke. The Framingham study found that high levels of CRP correlated with greater risk of ischaemic stroke or TIA.[4] The Rotterdam study found that CRP levels were not useful for future stroke prediction.[5]

Most of the studies were done in ischaemic stroke patients. The association between CRP levels and haemorrhagic stroke is not well studied. CRP levels in haemorrhagic stroke could be elevated due to inflammatory reaction elicited by haematoma.[6]

Thus, in pursuit of further knowledge into the role of C Reactive Protein in patients with stroke, we undertook this study.

AIM OF THE STUDY

This study is done to establish the role of CRP, measured within 24 hours of onset of stroke as an indicator for assessing stroke severity and its short-term outcome.

METHOD OF STUDY

The study included patients admitted with first episode of acute stroke within 24 hours of onset to the Department of Medicine, Government Vellore Medical College.

The study was conducted from February 2016 to March 2016. Patients with onset of symptoms more than 24 hours, recent history of traumatic brain injury, cerebrovascular events, acute coronary syndrome, liver cell failure and autoimmune diseases were excluded from the study.

The study design was submitted to the Institutional Ethical Committee and approval obtained. Informed written consent obtained from all patients or their relatives to participate and to publish the data.

Detailed history with emphasis on smoking (Number of packets of cigarette smoked per day times number of years-Pack Years), Hypertension (Patients who are on anti-hypertensives or documented Systolic BP ≥140 mmHg and/or Diastolic BP ≥90 mmHg), Dyslipidaemia and Diabetes mellitus (Patient on treatment for diabetes or diagnosed during hospital stay).

All patients underwent thorough neurologic examination and severity on admission was assessed using National Institute of Health Stroke Scale (NIHSS). Outcome was evaluated 7 days later using Modified Rankin Scale (mRS) and Barthel ADL Index (BI). Tables 1, 2 and 3 show the components of NIHSS, mRS and BI respectively.

CT-Brain was done to differentiate Ischaemic and Haemorrhagic stroke. Blood samples were taken on the day of admission for routine laboratory investigations and CRP assay. Solid phase ELISA was used to calculate CRP and normal reference value was less than 6 mg/L.

Instructions	Scale Definition	Score
1a. Level of Consciousness	0 = Alert 1 = Not alert; but arousable by minor stimulation to obey, answer or respond 2 = Not alert; requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (Not stereotyped) 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, and areflexic	……..
1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct	0 = Answers both questions correctly 1 = Answers one question correctly 2 = Answers neither question correctly	……..
1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used.	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly	……..
2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (Oculocephalic) eye movements will be scored, but caloric testing is not done.	0 = Normal 1 = Partial gaze palsy; gaze is abnormal in one or both eyes, but forced deviation and total gaze paresis is not present 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic manoeuver	……..
3. Visual: Visual fields (Upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patients may be encouraged, but if they look at the side of the moving fingers appropriately this can be scored as normal.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (Blind including cortical blindness)	……..
4. Facial Palsy	0 = Normal symmetrical movements 1 = Minor paralysis (Flattened nasolabial fold, asymmetry on smiling) 2 = Partial paralysis (Total or near-total paralysis of lower face) 3 = Complete paralysis of one or both sides (absence of facial movement in the upper and lower face)	……..
5. Motor Arm	0 = No drift; limb holds 90 (or 45) degrees for full 10s 1 = Drift; limb holds 90 (or 45) degrees, but drifts down before full 10 s; does not hit bed or other support 2 = Some effort against gravity; limb cannot get to or maintain (If cued) 90 (or 45) degrees, drifts down to bed, but has some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement UN = Amputation or joint fusion, explain	……..

Instructions	Scale Definition	Score
6. Motor Leg	0 = No drift; leg holds 30-degree position for full 5s 1 = Drift; leg falls by the end of the 5s period, but does not hit bed 2 = Some effort against gravity; leg falls to bed by 5s, but has some effort against gravity 3 = No effort against gravity; leg falls to bed immediately 4 = No movement UN = Amputation or joint fusion, explain:	……..
7. Limb Ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs UN = Amputation or joint fusion	……..
8. Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe-to-total sensory loss	……..
9. Best Language	0 = No aphasia; normal 1 = Mild-to-moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia; no usable speech or auditory comprehension	……..
10. Dysarthria	0 = Normal 1 = Mild-to-moderate dysarthria 2 = Severe dysarthria UN = Intubated or other physical barrier, explain:……	……..
11. Extinction and Inattention (Formerly Neglect)	0 = No abnormality 1 = Visual, tactile, auditory, spatial or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities 2 = Profound hemi-inattention or extinction to more than one modality; does not recognize own hand or orients to only one side of space	……..

Table 1: The Main Items of the NIHSS

Score	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead
Total (0–6)	

Table 2: The Main Items of the Modified Rankin Scale

Activity	Score
Feeding	
0 = Unable 5 = Needs help cutting, spreading butter, etc., or requires modified diet 10 = Independent	
Bathing	
0 = Dependent 5 = Independent (Or in shower)	
Grooming	
0 = Needs to help with personal care 5 = Independent face/hair/teeth/shaving (Implements provided)	
Activity	**Score**

Dressing	
0 =Dependent 5 = Needs help, but can do about half unaided 10 = Independent (Including buttons, zips, laces, etc.)	
Bowels	
0 = Incontinent (Or needs to be given enemas) 5 = Occasional accidents 10 = Continent	
Bladder	
0 = Incontinent (Or catheterized and unable to manage alone) 5 = Occasional accidents 10 = Continent	
Toilet Use	
0 = Dependent 5 = Needs some help, but can do something alone 10 = Independent (On and off, dressing, wiping)	
Transfers (Bed to Chair and Back)	
0 = Unable, no sitting balance 5 = Major help (One or two people, physical), can sit 10 = Minor help (Verbal or physical) 15 = Independent	
Mobility (On Level Surfaces)	
0 = Immobile or <50 yards 5 = Wheelchair independent, including corners, >50 yards 10 = Walks with help of one person (Verbal or physical) >50 yards 15 = Independent (But may use any aid; for example, stick) >50 yards	
Stairs	
0 = Unable 5 = Needs help (Verbal, physical, carrying aid) 10 = Independent	
Total (0–100): ——	

Table 3: The Main Items of the BI

Statistics

Data were prospectively collected and coded prior to analysis using the professional Statistical Package for Social Science (SPSS version 22). The description of data was in the form of mean (±) SD for quantitative data and frequency and proportion for qualitative data. Student-t Test (t) and one-way ANOVA was used for comparison between two groups and three groups regarding normally distributed (Parametric) quantitative data. Results were considered significant if p<=0.05.

RESULTS

The study involved 60 patients who were admitted within 24 hours of onset of acute stroke. Out of the 60 patients, 39 were male and 21 were female. The mean age of patients was 62.53±9.54. Based on CT Brain done at the time of admission, 41 patients had ischaemic stroke and 19 patients had haemorrhagic stroke. Table 4 and 5 shows the general characteristics of the study population.

Parameter	Mean±SD
Age	62.53±9.54
Pack years of smoking	8.48±11.44
Random blood sugar	165.9±53.15
Total cholesterol	182.43±37.76
CRP	8.05±4.33

Table 4: General Characteristics of Study Population

Parameter	Percentage
Male	65%
Female	35%
Hypertension	41.67%
Diabetes mellitus	28.33%
Dyslipidaemia	43.33%
CRP >6	70%
Ischaemic	68.33%
Haemorrhagic	31.67%

Table 5: General Characteristics of Study Population

Based on NIHSS scale, patients were classified as mild (0-7), moderate (8-14) and severe stroke (>14).[7,8] Short-term outcome was measured by modified Rankin scale and Barthel ADL Index (BI) at 7 days. Poor outcome was defined as mRS >2.[9-11] and BI <95.[12]

According to NIHSS scale, 13.3% of patients had mild stroke and 48.3% and 28.3% of patients had moderate and severe stroke respectively. Based on mRS done at 7 days, 21.67% of patients had favourable outcome and 78.3% of patients had poor outcome. The mean NIHSS score was 13.23±4.49. The mean mRS for the study population is 3.67±1.25. Based on BI, 18.33% of patients had favourable outcome and 81.67% of patients had poor outcome (Fig. 1).

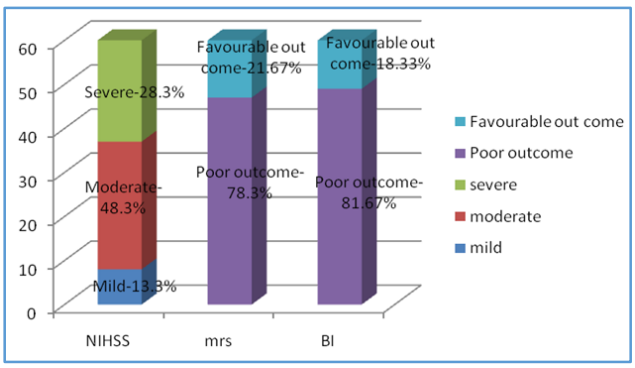


Fig. 1: Severity of Stroke in Study Population

The mean CRP levels in Ischaemic stroke was 8.56±3.51, while that of haemorrhagic stroke is 6.95±5.67. The demographic details of both ischaemic and haemorrhagic stroke is shown in Table 6.

	Ischaemic Stroke	Haemorrhagic Stroke
Age	63.1±9.59	61.32±9.59
Male	24	15
Female	17	4
Diabetes mellitus	12	5
Dyslipidaemia	16	10
Hypertension	11	14
Pack years of Smoking	7.68±10.96	10.21±12.54
Alcoholic	10	6
CRP	8.56±3.51	6.95±5.67
Total cholesterol	182.2±35.45	182.95±43.37
RBS	167.63±56.46	162.16±46.41

Table 6: Demographic Data in Ischaemic and Haemorrhagic Stroke

There was positive correlation between CRP levels and NIHSS in Ischaemic stroke (r=0.44; p=0.004 (Fig. 2)). CRP levels in severe ischaemic stroke based on NIHSS was 10.85±3.85, while in mild and moderate stroke it was 7.50±2.82 (p value= 0.012). MRS also had a positive correlation with CRP (r=0.35; p value=0.022) (Fig. 3), while BI had negative correlation with CRP in ischaemic stroke (r=0.54; p value <0.001) (Fig. 4).

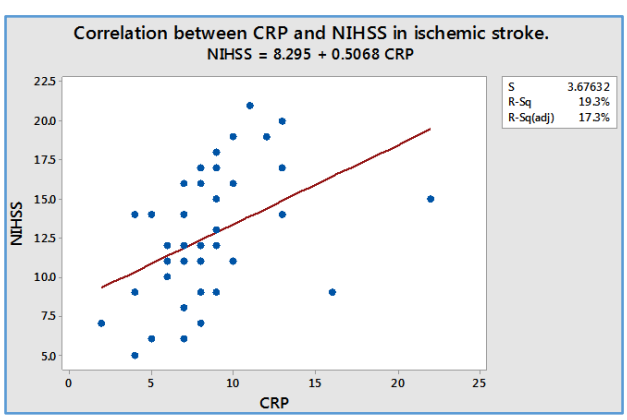
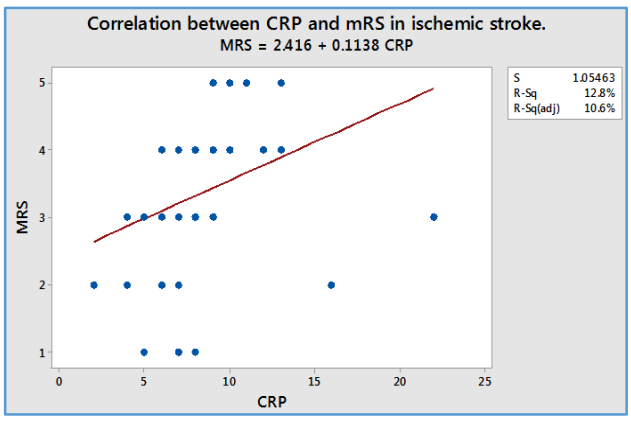


Fig. 2



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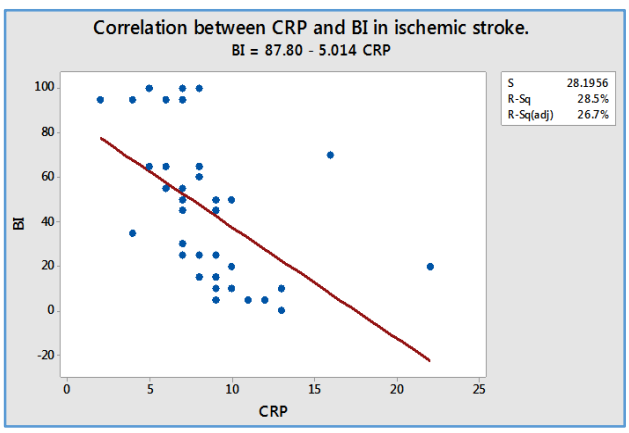
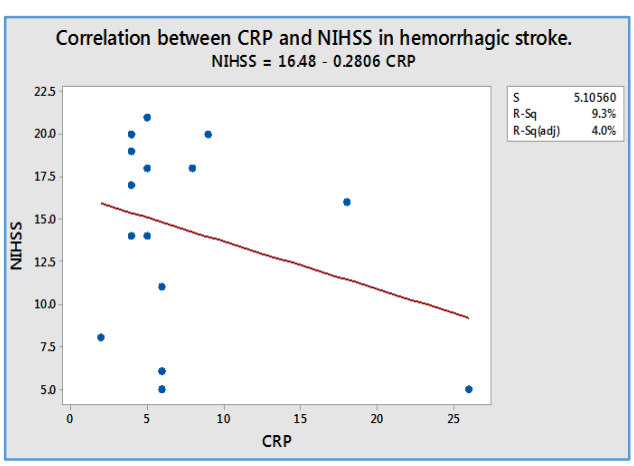


Fig. 4

In haemorrhagic stroke, the correlation between CRP and NIHSS was not significant (r=0.304; p value=0.203) (Fig. 5). The mean CRP levels in severe haemorrhagic stroke is 6.7±4.32, while in mild and moderate stroke it is 7.22±7.16 (p value=0.853). There was no significant correlation between mRS and CRP levels in haemorrhagic stroke (r=0.31; p value=0.201) (Fig. 6) as well as BI and CRP levels (Fig. 7).



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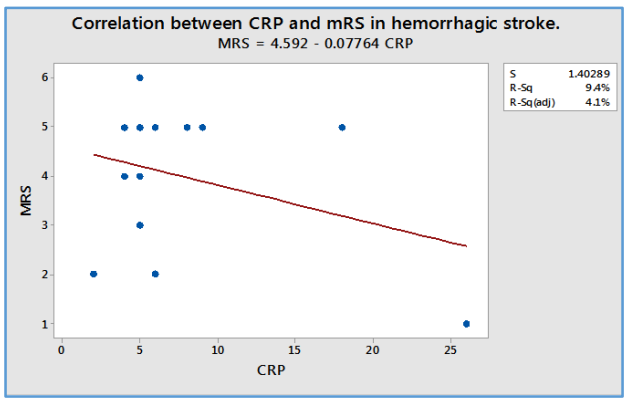

Fig. 6

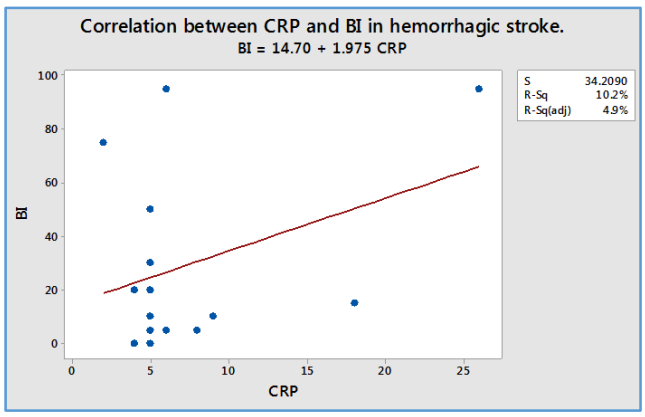

Fig. 7

Comparing both ischaemic and haemorrhagic stroke, CRP levels were higher in ischaemic stroke than haemorrhagic stroke. CRP levels significantly correlated with severity of stroke in ischaemic stroke, while in haemorrhagic stroke the association was not significant (Table 7).

Criteria		Ischaemic Stroke		Haemorrhagic Stroke	
		Mean with SD	P value	Mean with SD	P value
NIHSS	Mild and moderate	7.50+/-2.82	P-Value = 0.012	7.22 +/-7.16	P-Value = 0.853
	Severity	10.85 +/-3.85		6.70 +/-4.32	
MRS	Poor outcome	9.13+/-3.20	P-Value = 0.014	6.13+/-3.58	P-Value = 0.532
	Favourable outcome	6.56 +/-4.00		10.0+/-10.8	
BI	Poor outcome	9.33+/-3.37	P-Value < 0.001	5.88+/-3.61	P-Value = 0.419
	Favourable outcome	5.38 +/-2.00		12.7+/-11.5	

Table 7: CRP Levels with Severity in Ischaemic and Haemorrhagic Stroke

DISCUSSION

Stroke is the leading cause of disability in both developed and developing countries. It is the third most common cause of death.[13] Atherosclerosis with rupture of plaque is the most important cause of stroke. Inflammation is a central process in the initiation, development and subsequent rupture of plaques. As the plaques are developing, there is recruitment of immune cells such as macrophages and T cells. These cells produce various inflammatory mediators including cytokines, proteases and free radicals which ultimately cause rupture of plaque.[14] Brain damage further causes mobilization and migration of cells such as neutrophils and macrophages into the affected area and stimulates inflammatory response.

C-Reactive protein is produced by liver. It is usually absent in blood. Its production is stimulated by acute inflammation and usually rises within the first few hours of inflammation.[15] Our study was done to demonstrate the association between CRP levels and severity of stroke.

NIHSS was used in this study to assess severity. Various studies have concluded that it is predictive of stroke outcomes.[16-18] One study demonstrated that severity of stroke assessed by NIHSS at admission to be predictive of 3 month mortality and another study established it as an independent predictor of 30 days mortality.

We found that CRP levels is a predictor of severity and short-term outcome in ischaemic stroke patients. CRP levels did not correlate with severity in haemorrhagic stroke. CRP levels were positively correlated with NIHSS and mRS in ischaemic stroke. It had negative correlation with BI in ischaemic stroke.

Various studies have found an association between CRP levels and stroke. Di Napoli et al demonstrated in his study that concentration of CRP increased in the first 24 hours following stroke and this rise is associated with infarct size and hence associated with poor prognosis.[19]

Di Napoli in another study found that CRP cannot be used in the risk stratification of stroke.[20] Recent studies found that increased CRP levels predicted recurrence of stroke and transient ischaemic attack.

The exact mechanism for the elevation of CRP levels in severe stroke remains unexplained. Atherothrombosis being an inflammatory pathology could cause rise in acute phase reactants in the first few hours.[15] Also, cerebral tissue injury can cause elevated CRP.[21] Activation of coagulation by increased CRP through tissue factor expression has also been proposed as one of the possibilities.[22] CRP, being an inflammatory marker could be associated with other pathological processes that might cause severe stroke. Some studies have shown that CRP per se can cause secondary brain damage due to complement activation.[23]

In the above context, whether increased CRP leads to severe stroke or vice versa needs to be ascertained through larger population based studies.

The lack of inflammatory process preceding the onset of haemorrhagic stroke could well explain the finding in our study that there is no significant correlation between CRP and severity of haemorrhagic stroke. However, certain studies found as association between increased CRP and size of haematoma in haemorrhagic stroke. The probable mechanism could be the inflammatory response that occurs because of tissue injury as a result of haemorrhage.[24] This leads to IL6 production, one of the major stimulus for CRP synthesis.[25]

We found that although CRP levels are elevated in haemorrhagic stroke, there was no correlation with severity of stroke. Elevated CRP levels in haemorrhagic stroke is a consequence of tissue injury and does not involve in the pathogenesis. Our study revealed that rise in CRP level is more in ischaemic stroke than in haemorrhagic stroke. Other studies have also reached a similar conclusion.[26,27]

This study has few limitations. We did not correlate the radiologic finding of CT Brain such as the size of the haemorrhage with CRP levels, as we intended to find the clinical outcome.

Another limitation is that we used a single value of CRP at the time of admission for predicting severity rather than serial measurements, which could have been more informative. Another limitation is the use of regular CRP rather than using high sensitivity CRP. The regular CRP is commonly present and readily available in most ICU setups across our country.

CONCLUSION

CRP levels measured within 24 hours of admission are elevated in both ischaemic and haemorrhagic stroke. It is a predictor for severe stroke and unfavourable outcome in ischaemic stroke, but not in haemorrhagic stroke.

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