ORIGINAL ARTICLE

Combination of Hs-CRP and Homocysteine Levels as Predictors of Short-term Outcome in Acute Ischemic Stroke

Gaurab Bhaduri[1], Chanchal K Jana[2], Shatavisa Mukherjee[3], Shambo S Samajdar[4]

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Abstract

Background: Apart from the traditional risk factors associated with stroke, several newer independent risk markers that are promising targets for modification, such as hyperhomocysteinemia, and elevated high-sensitive C-reactive protein (hs-CRP), may contribute significantly to the stroke risk. The role of elevated levels of inflammatory markers in predicting prognosis after a first ischemic stroke has been a gray area. The present study aimed to assess the clinical outcome of acute ischemic stroke patients in particular relation to hs-CRP and homocysteine (Hcy) levels within 48 hours of presentation.

Methods: A prospective, observational study was carried out among admitted and diagnosed patients with acute ischemic stroke confirmed by CT/MRI scans where included patients were subjected to detailed history taking using pretested and predesigned pro forma along with thorough clinical examination using CT scan brain (non-contrast)/MRI brain. High-sensitive C-reactive protein and Hcy levels and other blood parameters were done within 48 hrs of hospital admission. Patients were scored based on the National Institute of Health Stroke Scale (NIHSS) at specified time points to assess the clinical outcome. Results were statistically analyzed.

Results: Patients of cerebral infarction with elevated hs-CRP had a lower improvement score in contrast to those with non-elevated hs-CRP, who had a higher improvement. Also, patients with an elevated Hcy level had a lower mean improvement score at day 30 compared to those with normal Hcy levels. With the increasing size of the infarct, there was a lower improvement score. The higher the admission NIHSS score, the lower the improvement score in the study. High-sensitive C-reactive protein proved to be the strongest predictor for score improvement with other predictor variables like infarct size, NIHSS baseline score and Hcys also showing positive association.

Conclusion: High-sensitive C-reactive protein alone comes out as the strongest predictor for the improvement in NIHSS score from the time of admission to a 30-day progress period with a prediction power of 98%.

Keywords: Acute ischemic stroke, High-sensitive C-reactive protein, Homocysteine, Outcome.

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Introduction

Worldwide, strokes, also known as cerebrovascular accidents (CVA), rank third in mortality rates following coronary artery disease and cancer. They hold the highest prevalence and significance among adult neurological conditions, constituting at least half of all admissions to general hospitals for neurological issues. Furthermore, strokes are a significant contributor to disability.[1,2] Of all stroke varieties, 80% are ischemic, with the remaining attributed to hemorrhagic causes. Ischemic strokes, commonly perceived as a singular condition, can stem from various underlying diseases. In instances of ischemic stroke, the primary anomaly is a disruption in cerebral blood flow and metabolic function.[1,3,4] Numerous elements influence the aftermath of a stroke. Research suggests that inflammatory processes are crucial in the development and advancement of atherosclerosis, plaque rupture, thrombosis, and stroke itself. Inflammatory indicators like high-sensitivity C-reactive protein (hs-CRP) have been recognized as a prognostic factor post-stroke. Studies using experimental stroke models indicate that increased hs-CRP levels negatively impact prognosis, a correlation supported by a growing body of clinical research linking elevated hs-CRP levels with functional outcomes.[5,6]

Hyperhomocysteinemia, a modifiable risk factor for stroke, may have a significant negative impact on the disease outcome. The amino acid homocysteine (Hcy) is a sulfhydryl-containing compound that is produced when the liver and other proliferating cells metabolically demethylate methionine, an amino acid that is required in diet.[7] Genetic causes of hyperhomocysteinemia include mutations in cystathione β-synthase or methylene tetrahydrofolate reductase, whereas acquired causes include renal impairment, nutrition, medications, and comorbid conditions including leukemia.[8] Although there has been evidence linking hyperhomocysteinemia to atherosclerotic disease for more than 30 years, attention to this connection has just lately become focused. Increased thrombogenicity, modified endothelial function,

[1]Department of Diabetes and Endocrinology, Apollo Sugar Clinic, Kolkata, West Bengal, India

[2]Department of Internal Medicine, Apollo Clinic, Kolkata, West Bengal, India

[3,4]Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India

Corresponding Author: Shatavisa Mukherjee, Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India, Phone: +91 9830529192, e-mail: shatavisa100@gmail.com

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and vascular smooth muscle proliferation are some of the ways that hyperhomocysteinemia can exacerbate oxidative damage to the vascular bed.[9,10] Multiple epidemiological studies have proven a positive dose-dependent connection between plasma Hcy level and cardiovascular risks, including stroke.[9,11] High and moderately elevated Hcy levels, regardless of the impact of confounders like blood pressure, smoking, and cholesterol, have been demonstrated in studies to be a potentially modifiable risk factor for stroke in all age-groups.[12] Elevated levels of Hcy in the bloodstream are likely to adversely affect the outcome of ischemic stroke, substantially heightening the likelihood of a poor recovery.[9,13] Research is still needed because of the contentious relationship between Hcy levels and stroke outcomes.

Recent studies suggest that the predictive value of functional outcome increases when both hs-CRP and Hcy are taken into consideration.[14–16] So, there is a need to study whether hs-CRP and Hcy are independent prognostic markers in acute ischemic stroke and whether their combination increases the predictive value in determining functional outcomes. Although a research has been done to find out a biochemical parameter like hs-CRP and Hcy for stoke outcomes across the globe, such information from India is very scanty. Therefore, the present study aimed to study the admission of hs-CRP and Hcy and their effect on infarct size and severity using the National Institute of Health Stroke Scale (NIHSS) in cases of cerebral infarction. The study aimed to assess the clinical profile, infarct size on CT/MRI scans, and clinical outcome of acute ischemic stroke in relation to hs-CRP and Hcy levels within 48 hours of presentation.

Methods

A prospective, observational study was carried out for 18 months in the Department of General Medicine and Neuromedicine in a Tertiary Care Teaching Hospital in Eastern India. Permission was obtained from the Institutional Ethical Committee for the conduct of the study before study initiation. All adult patients of either sex admitted in the general medicine and neuromedicine unit within 48 hours of presentation and diagnosed with acute ischemic stroke confirmed by CT/MRI scans were included in the study. Patients with transient ischemic attack, hemorrhagic stroke, cerebellar/brainstem infarctions, cerebral venous thrombosis, known cases of sols, or having a previous history of stroke were excluded from the study.

Included patients were subjected to detailed history taking using pretested and predesigned pro forma along with thorough clinical examination using CT scan brain (non-contrast)/MRI brain. hs-CRP and Hcy levels and other blood parameters were done within 48 hours of hospital admission. At the time of discharge on day 1 and again on day 30, patients were rated using the NIHSS to evaluate the clinical outcome. Homocysteine levels of more than 15 µmol/L were considered elevated, while hs-CRP levels of more than 3 mg/L were considered elevated. A hs-CRP level of less than 1 mg/L was normal, and 1–3 mg/L was considered intermediate. Infarct size on CT scan brain <3 cm^2 was considered small, 3–5 cm^2 moderate, and >5 cm^2 large. Routine investigations including complete hemogram, urinalysis, liver, kidney, and lipid profile were looked at along with other special investigations like hs-CRP, Hcy, fasting and postprandial blood sugar, electrocardiogram, and echocardiography.

After the acquired data was verified as complete, statistical analysis was performed. A variety of statistical software programs, including Microsoft Excel and the Statistical Package for the Social Sciences (Windows version 21.0; SPSS Inc., Chicago [IL], USA), were used to do all statistical analyses for the various measures.

Table 1: Basic demographics

Age-groups (in years)	*Number of cases (%)*
18–20	0 (0%)
21–30	5 (6%)
31–40	5 (6%)
41–50	14 (18%)
51–60	23 (29%)
61–70	24 (30%)
71–80	9 (11%)
Gender	
Female	30 (37%)
Male	50 (63%)
Comorbid conditions	
Atrial fibrillation	2 (2.5%)
Acute myocardial infarction	3 (3.75%)
Chronic obstructive pulmonary disease	2 (2.5%)
Diabetes mellitus	21 (26.25%)
Dyslipidemia	22 (27.5%)
Hypertension	32 (40%)
Ischemic heart disease	15 (18.75%)
Mitral stenosis	2 (2.5%)
Mitral valve prolapse	2 (2.5%)

Results

A total of 80 patients with cerebral infarction were included in the study. While the mean age of the study population was 56 ± 12.5 years, the majority belonged to age-group 61–70 years and 51–60 years. A male preponderance with male-female ratio of 1.66:1 was noted. Hemiplegia, cranial nerve dysfunction mainly VII CN, altered sensorium, language disturbances, and sensory symptoms were common presenting symptoms. The common comorbid conditions in the study group were hypertension, diabetes, dyslipidemia, and ischemic heart disease. The other conditions included valvular heart disease (mitral stenosis and mitral valve prolapse), atrial fibrillation, COPD and AMI (Table 1).

In our study, 30% of the patients had normal hs-CRP, 48% of patients had hs-CRP in the intermediate range and 22% elevated. About 67.5% ($n = 26$) of patients had an elevated Hcy, while the rest had a normal Hcy level. Analyzing gender distribution, 66% of males and 70% of females had an elevated Hcys level (Table 2).

In our study, patients with cerebral infarction with elevated hs-CRP had a lower improvement score, and patients with non-elevated hs-CRP had a higher improvement, with a maximum improvement score in patients with normal hs-CRP. In this study, patients with an elevated Hcy level had a lower mean improvement score at day 30 and patients with normal Hcy had a higher mean improvement score at day 30 (Table 3).

The prediction power of hs-CRP in determining the short-term outcome (improvement score at day 30) is 98.4% ($p < 0.001$). Patients with elevated Hcy had a worse outcome demonstrated by a poor improvement score with a prediction power of 38% ($p < 0.001$) (Figs 1 and 2).

Table 2: Distribution of hs-CRP and Hcys levels

	Males	*Females*	*Total*
Hs-CRP levels			
Hs-CRP normal (<1)	15 (30%)	9 (30%)	24 (30%)
Hs-CRP intermediate (1–3)	24 (48%)	14 (47%)	38 (48%)
Hs-CRP elevated (>3)	11 (22%)	7 (23%)	18 (22%)
Hcys levels			
Hcys normal (≤15)	17 (34%)	9 (30%)	26 (32.5%)
Hcys elevated (>15)	33 (66%)	21 (70%)	54 (67.5%)

Table 3: NIHSS scoring in different levels of hs-CRP and Hcys

	Hs-CRP levels			*Hcys levels*	
	Normal	*Intermediate*	*Elevated*	*Normal*	*Elevated*
Mean NIHSS score					
During admission	14	20	28	14	23
During follow-up	7	15	25	7	18
After 30 days	2	11	23	2	16
Mean improvement in score	12	8	5	12	7

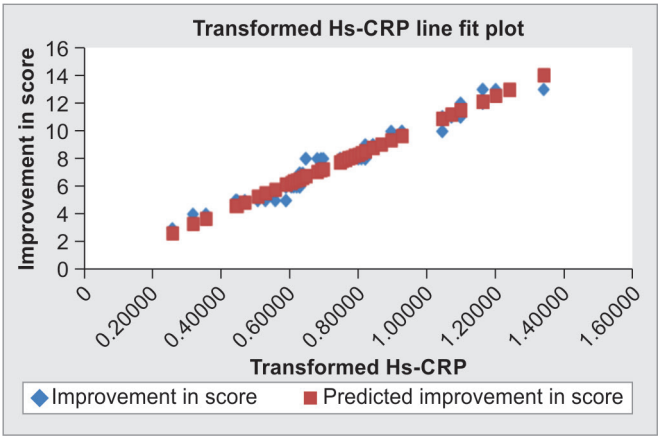

Fig. 1: Prediction power of hs-CRP

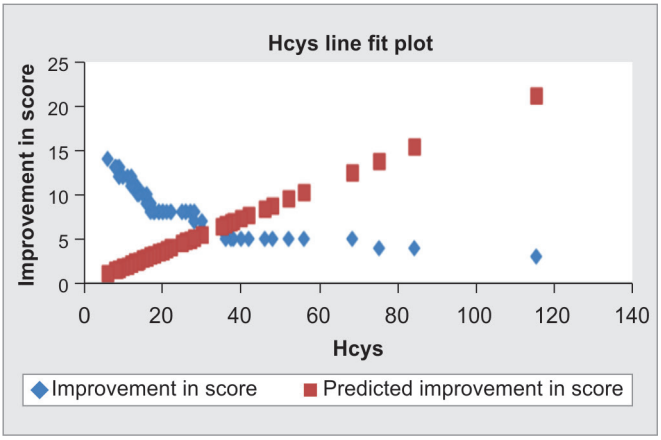

Fig. 2: Prediction power of Hcys

Table 4: Infarct size vs hs-CRP levels

	Number of cases (%)		
Infarct size grade	*Hs-CRP normal (<1)*	*Hs-CRP intermediate (1–3)*	*Hs-CRP elevated (>3)*
A	24 (30%)	3 (4%)	
B	–	31 (39%)	–
C	–	4 (5%)	18 (22%)

Table 5: NIHSS scores by infarct size levels

Infarct sizes	*Mean NIHSS score during admission*	*Mean NIHSS score during follow-up*	*Mean NIHSS score after 30 days*	*Mean improvement in score*
A	14	7	2	12
B	19	14	11	8
C	28	25	23	5

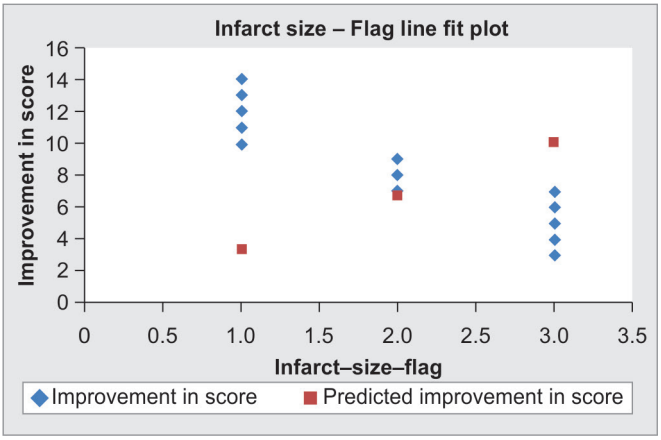

Fig. 3: Prediction power of infarct size

Infarct size was noted as another outcome measure. Medium infarct size 'B' was noted in a total of 39% of cases ($n = 31$), followed by small-sized infarct 'A' in 34% of cases ($n = 27$) and large-sized infarct "C" in 27% ($n = 22$) cases. High-sensitivity C-reactive protein was noted as a covariate for the infarct size measure. It was observed that patients with small-sized infarcts either had a normal or intermediate hs-CRP but no elevated hs-CRP was noted. While medium-sized infarct cases mostly had intermediate-leveled hs-CRP, the large-sized infarct group had either hs-CRP in the intermediate range (5%) or elevated (22%), with notably no cases of normal hs-CRP (Table 4).

The mean improvement in NIHSS score was lowest for large infarcts, highest for small infarcts, and intermediate for medium-sized infarcts. The study showed that with the increasing size of the infarct, there was a lower improvement score. The mean NIHSS score at admission was even highest for large infarct cases and lowest for small infarcts (Table 5). Analysis suggests that the prediction power of infarct size in determining short-term outcomes (improvement at day 30) was 60% ($p < 0.001$) (Fig. 3). The higher the baseline NIHSS score, the lower the improvement score in the study ($p < 0.001$). When infarct size and baseline NIHSS score were both taken into account together the prediction power in determining short-term outcome (improvement at day 30) increased to 82% (Fig. 4). Alone infarct size had a prediction power of 60% in determining outcome.

From this analysis, hs-CRP alone comes out as the strongest predictor for the improvement in NIHSS score from the time of admission to a 30-day progress period with a prediction power of 98%. The other factors that showed a positive influence on the score improvement are infarct size, NIHSS baseline score, and Hcys. But either these independently or their combination failed to predict the improvement scale to the extent hs-CRP does. The closest competitor to this prediction model was the combined impact of infarct size and baseline scores obtained during admission with a prediction power of 82%. But while these would give a good direction, hs-CRP alone shows the best and independent prediction for the score improvement (Fig. 5).

Discussion

In developed and increasingly low-middle-income nations, stroke is a major cause of both mortality and morbidity. The burden of stroke is increasing in India with a gradual increase in life expectancy to over 60 years, thus leading to age-related diseases. Stroke is currently the fifth most common cause of disability and the fourth most common cause of death in India.[17,18] Stroke prevention is facilitated by the identification of risk factors, understanding of their relative importance, and comprehension of how they interact. Among various risk factors, some notable ones are hypertension, diabetes, obesity, blood lipids, clotting factors, coronary heart disease, atrial fibrillation, migraine, abnormal ECG pattern, familial history of stroke, cigarette smoking, alcohol consumption, use of oral contraceptives, hormone replacement therapy, physical activity, and diet.[19] In addition to the conventional risk factors linked to stroke, several recent independent risk markers, like hyperhomocysteinemia, show promise as targets for adjustment and may considerably raise the risk of stroke. The role of elevated levels of inflammatory markers in predicting prognosis after a first ischemic stroke is again a gray area. It is possible to hypothesize that a more severe stroke is linked to a higher inflammatory response because there is evidence that an ischemic stroke includes an inflammatory response. Though there have been some studies showing CRP as a prognosticator of future stroke attacks and some assessing post-ischemic CRP's contribution to stroke patients' long-term mortality, studies on the potential function of CRP as a predictor of functional prognosis following a stroke event are scarce.[20,21] The present study aimed to assess the clinical outcome of acute ischemic stroke patients in particular relation to hs-CRP and Hcy levels within 48 hours of presentation. 80 individuals who met the study's inclusion criteria and had an acute cerebral infarction as determined by computed tomography were enrolled. The age-group of the patients ranged from 20 to 80 years, with the mean age being 56 ± 12.5 years, the maximum distribution of cases was in the sixth and seventh decades. This finding was comparable to Guillermo et al. where the mean age was 59 ± 4 years.[22] There were 63% male and 37% female patients. There was a male preponderance of a male: female ratio of 1.66:1, comparable to a study conducted by Kushner et al. which had an M:F ratio of 1.7:1.5.[23] According to the UKPDS study, male sex is a significant risk factor for stroke. The study group had ischemic heart disease, diabetes, dyslipidemia, and hypertension as prevalent comorbid diseases. Atrial fibrillation, COPD, AMI, and valvular heart disease (mitral stenosis and mitral valve prolapse) were among the other conditions. These are similar to research on stroke risk factors.

Two important factors in the pathogenesis of atherosclerosis are inflammation and infections.[24] The development of atherosclerotic symptoms in the heart and brain circulation is significantly influenced by CRP. An accurate marker of artery wall inflammation and tissue damage is hs-CRP.[25] Bronchial and periodontal infections have been linked to cerebral ischemia. Elevated hs-CRP, an indicator of inflammation and infection, has been linked to acute stroke.[26] In our study, 30% of the patients had normal hs-CRP, 48% of patients had hs-CRP in the intermediate range and 22% elevated. About 67.5% of patients had an elevated and 32.5% had normal Hcy levels. Patients with elevated Hcy levels had a lower mean improvement score at day 30, while patients with normal Hcy had a higher mean improvement score at day 30. Patients with elevated Hcy even had a worse outcome demonstrated by poor improvement scores. Similar

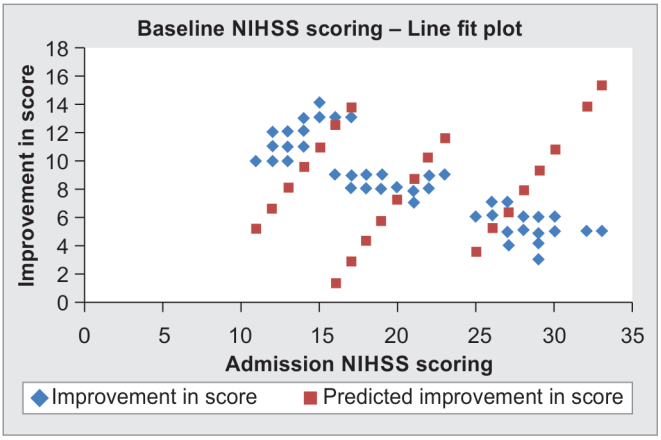

Fig. 4: Prediction power of infarct size and baseline NIHSS scoring

Prediction table

Factors	Prediction score	Comments
Infarct Size	60%	
Infarct size + NIHSS score during admission	82%	
Hcys	38%	
Hcys + Hs-CRP	59%	
Hcys + Hs-CRP (Mathematical transformation)	0%	*Model not valid*
Hs_CRP (Mathematical transformation)	98%	

Transformed Hs-CRP = *Hs-CRP^[–1×(1/2.367)]*

Fig. 5: Prediction table for factors

results were shown by Pniewski J et al. in their study of plasma Hcy and the course of ischemic stroke.[13]

Two radiologists independently verified the size of the infarct, which was quantified on CT as small, medium, and large-sized infarcts. This infarct categorization corroborated with findings of Yadav nd Chaudhary.[27] In this study, the patients with small-sized infarcts either had a normal or intermediate hs-CRP level, but no elevated cases. While the thing was exactly the reverse for large-sized infarcts.

The NIHSS is a graded neurologic assessment tool designed to quantify deficits resulting from a stroke.[28] The motor function, visual fields, ataxia, speech, language, cognition, and motor and sensory deficits are all considered in this scale. Each degree of functioning in these areas is assigned a score, which is then added together to provide the final cumulative score. The severity of the neurologic deficits that appear after a stroke is indicated by a higher score on the scale. This score is a somewhat accurate indicator that can be applied to explore novel treatment modalities in this field as well as treatment evaluation. The patient's clinical presentation and the final score may also be related. Neurologic impairment is classified as light if the score is less than 5, mild to moderately severe if the score is between 5 and 15, severe if the score is between 15 and 25, and very severe if the score is greater than 25.[29] The present study showed that with increasing size of the infarct, there was a lower improvement in scores ($p < 0.001$). The prediction power of infarct size in determining the short-term outcome was 60%. In this study, the mean NIHSS score at admission was highest for large infarcts and lowest for small. The higher the admission NIHSS score, the lower the improvement score in the study. This finding corroborates with the study conducted by Adams et al. where it was shown that baseline NIHSS score strongly predicts outcome after stroke.[30] When infarct size and baseline NIHSS score were both taken into account together the prediction power in determining short-term outcome increased to 82% while infarct size as singly had a prediction power of only 60% in determining outcome. The research conducted by Vogt G et al. also found that the initial size of the lesion serves as a standalone predictor for the clinical outcome of stroke.[31]

The study had some obvious limitations. The study had a limited sample size. A total of 80 cases is inadequate for this type of research. The patients' 30-day follow-up was insufficient; if the patients had been followed up for the third, sixth, and 12 months in a row, a stronger long-term association might have been achieved. However, future research should overcome these limitations.

Conclusion

High-sensitive C-reactive protein alone comes out as the strongest predictor for the improvement in NIHSS score from the time of admission to a 30-day progress period with a prediction power of 98%. Other factors like infarct size, NIHSS baseline score, and Hcys also showed a positive influence on the score improvement.

Orcid

Shatavisa Mukherjee https://orcid.org/0000-0001-9524-1525

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