

## Association Of Peripheral Inflammatory Markers With Clinical Severity Following Stroke

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### Abstract:

**Background:** The role of inflammation in the pathogenesis of ischemic and haemorrhagic stroke has been well established. We studied the prognostic value of peripheral markers of inflammation in determining the functional outcome 28 days following stroke.

**Method:** Two hundred and five (205) cases of acute stroke confirmed by CT were evaluated for body temperature, TLC, blood glucose, platelet count, CRP and ESR on admission. Functional outcome was determined after a 28 day period by the modified Rankin scale.

**Results:** A higher TLC (p 0.044), blood glucose (p 0.002) and CRP (p 0.003) was found in patients of ischemic stroke with a poor functional outcome. In patients of haemorrhagic stroke, higher blood glucose (0.001) and CRP (p 0.008) were associated with poor functional outcome after a 28 day period.

**Conclusion:** Peripheral markers of inflammation can be used to assess the clinical severity following both ischemic and haemorrhagic stroke

**Key words:** stroke, hemorrhagic, ischemic, CRP, inflammation

### Introduction

Stroke has often being highlighted as the 3<sup>rd</sup> highest cause of mortality<sup>1</sup>, but little is known about the burden of the disease on survivors in developing countries.

The need for better planning of care of stroke survivors is being realized now more than ever. Recently, neurologists have started to identify the need of markers to reliably predict prognosis promptly following stroke.

Keeping the need of easily available, inexpensive and expedient markers in mind, peripheral markers of inflammation, such as WBC count, CRP, ESR and platelet count are now being considered.

How inflammation is involved in the pathogenesis of ischemic stroke is now being extensively studied. An increasing body of evidence has suggested that early inflammation is an important factor contributing to unfavourable prognosis following stroke<sup>2</sup>. This has been

attributed to elevated levels of triglyceride rich lipoproteins and increased plaque volume in stroke patients with elevated acute phase reactants<sup>3</sup>. The Insulin Resistance Atherosclerosis Study<sup>4</sup> found an association between acute inflammatory markers and insulin resistance, suggesting chronic subclinical inflammation as a part of insulin resistance syndrome.

On the other hand, the role of inflammation in intracerebral haemorrhage (ICH) is a poorly understood issue. Statistical evidence indicate that inflammatory processes play a role in the severity of ICH induced brain injury<sup>5</sup>. A small number of studies report the association of inflammatory markers and mortality following ICH, but there is limited data on the effect of this inflammation on functional outcome<sup>6,7</sup>.

This study was performed to assess the role of systemic inflammatory markers in stroke and their association with clinical severity.

**Aim:**

To study the association of body temperature, blood glucose, TLC, Platelet count, CRP and ESR levels with clinical severity following stroke.

## Methods

This prospective cross-sectional study was conducted in AVBRH, 1300 bedded rural hospital in central India. This patient population fairly represents the disease pattern in this region. Consent was taken from the institutional ethical committee. Written informed consent was obtained from all patients or from a relative.

From the period of January 2013 to December 2014, all patients admitted to the hospital with a diagnosis of acute stroke were included and data was collected in a prospective manner for routine inflammatory markers.

**Case definition :**  
Acute stroke was defined as rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin.<sup>8</sup>

**Neuro-radiological diagnosis:**  
The diagnosis of stroke was confirmed by CT scan performed within 24 hours after admission and patients diagnosed with brain infarction (ischemic stroke) or brain haemorrhage (intracerebral haemorrhage) according to the Stroke Data Bank Subtype Classification were studied<sup>9</sup>.

**Exclusion criteria:**  
Patients suffering from pre-existing infectious diseases, chronic inflammatory, malignant diseases or coagulation disorders, and patients on anti-inflammatory treatment. Patients were classified as suffering from pre-existing infectious disease if there was amnesic history of fever  $\leq 4$  weeks before the onset of stroke. Patients with ICH secondary to trauma, or any secondary haemorrhage including cerebral aneurysms and tumours. Patients diagnosed with sub arachnoid haemorrhage following CT scan. Diabetic patients.

**Peripheral inflammatory markers in blood:**  
Venous blood samples were taken at the time of admission, or as soon as possible within 24 hours of admission. Blood was collected and analysed for ESR using an automated Westergren, total WBC count using the Coulter principle method, absolute platelet count, and C reactive protein levels.

**Blood Glucose:**  
Venous blood samples collected before the administration of

fluids and blood glucose level was estimated. Diabetic patients were excluded based on the following criteria: past history of diabetes, or random blood glucose level of  $>200$ mg/dl, or patients on hypoglycaemic agents.<sup>10</sup>

**Clinical Evaluation:**  
Body temperature was recorded orally at baseline. Rectal temperature was taken if oral temperature could not be taken.

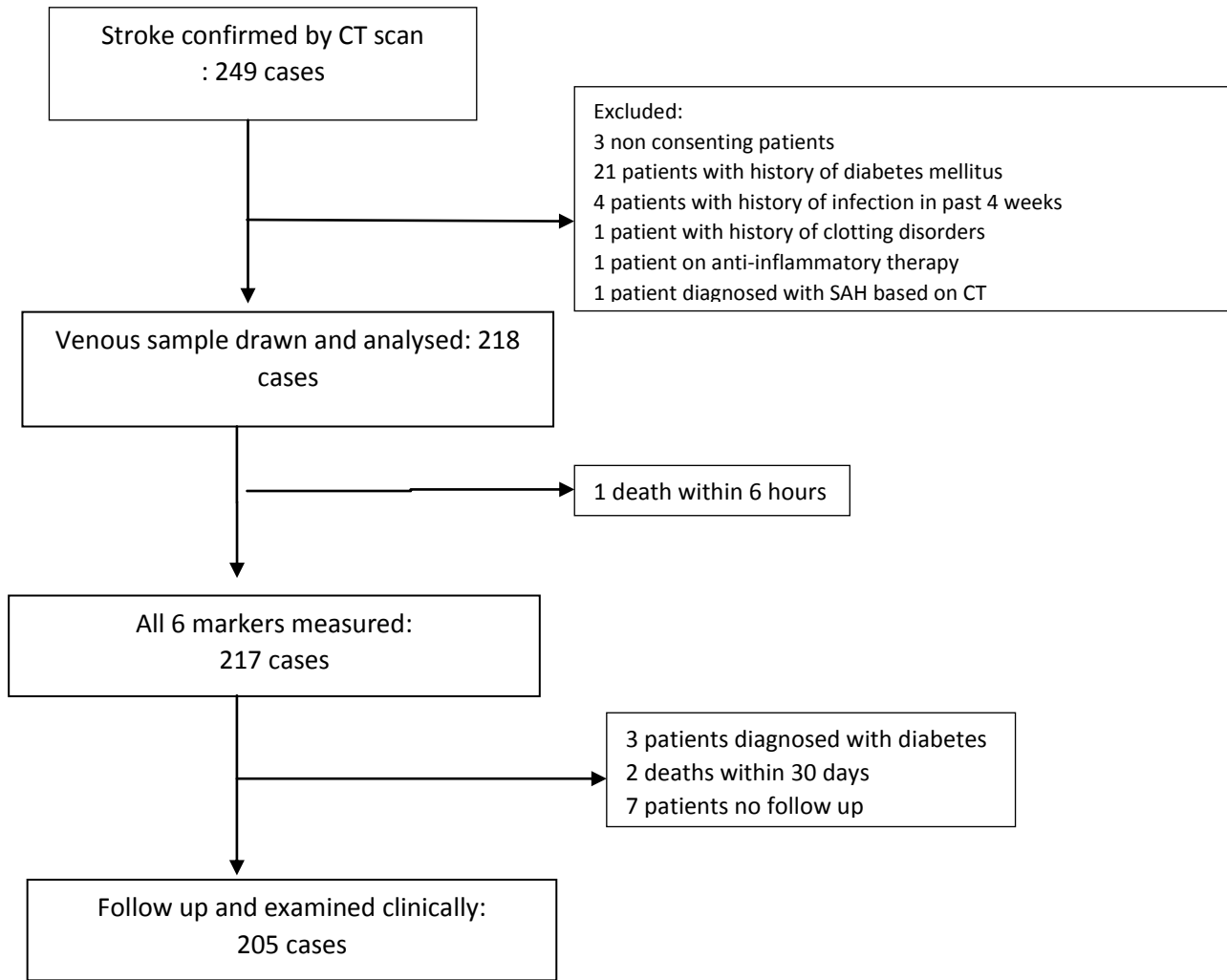
Improvement in clinical severity was evaluated at 28 days following admission. Patients who were discharged before 28 days were called to the OPD for follow up. The severity of clinical features was graded by the modified Rankin Score. The scale graded from 0-6, from perfectly healthy asymptomatic patients to death.<sup>11</sup> Patients were divided into two groups based on the degree of impairment. Patients without significant impairment (i.e.  $\leq$  grade 2 on mRS) were classified as group A. Those with significant impairment (i.e.  $>$  grade 2 in mRS) were classified as group B.

**Statistical Analysis:**  
Normally distributed baseline characteristics were compared with Student's t-tests, from which p value was calculated.

## Results

In the 2 year period, there were a total of 249 confirmed cases of stroke. Consent could be obtained from 246 of these cases. 21 patients with history of diabetes mellitus, 4 patients with documented history of infection in the past 4 weeks and 1 patient with clotting disorder and were excluded from the study. 1 patient on anti-inflammatory treatment was also excluded. Blood was drawn from 218 patients at the time of admission. 3 patients were diagnosed with diabetes mellitus after review of reports of the blood analyses. There was 1 death at the time of admission and 2 deaths due to complications arising from stroke (recurrent stroke and infection) within 28 days following admission.

The functional outcome at 28 days was assessed in 205 patients. An outline of data compilation is illustrated in Figure 1. The mean delay between the time of admission and drawing blood sample was 3 hours.



**Figure 1:** Flowchart showing the study design and data collection scheme

The mean age was found to be 60±8. Mean age for males was 57±5 and females was 63±3years. Males constitutes 65% (n=133) of the cases, whereas the females were 35% (n=72). The age and sex distribution of the population is shown in the table 1:

AGE	Male		Female	
	N	%	N	%
40-50	17	8.0	5	2.5
50-60	22	10.7	15	7.4
60-70	54	26.3	22	10.8
70-80	40	19.6	30	14.7
<b>Total</b>	<b>133</b>	<b>64.6%</b>	<b>72</b>	<b>35.4%</b>

**Table 1.** Sex distribution of patients according to age groups

The diagnosis of stroke was confirmed by CT and subtyping was done according to stroke data bank criteria in 205 patients. The diagnosis of ischemic stroke was made in 78% of the patients (n=160). Haemorrhagic stroke accounted for 22% of the cases (n=45). Table 2 summarizes the distribution of patients based on subtypes.

					Ischemic stroke		ICH	
					N	%	N	%
<b>Male</b>					106	51.7	27	13.3
<b>Females</b>					54	26.3	18	8.7
<b>Total</b>	<b>160</b>	<b>78%</b>	<b>45</b>	<b>22%</b>				

**Table 2.** Frequency and percentage of stroke subtypes

Baseline investigations for peripheral markers of inflammation were analysed at admission. After a 28 days post admission follow up, degree of clinical impairment was determined using the mRS scale. Out of the 205 patients that were assessed clinically, 112 (55%) had good functional outcome (mRS score  $\leq 2$ ) and 93 (45%) had poor functional outcome (mRS score  $> 2$ ). The relationship between the body temperature, total leucocyte count, absolute platelet count, blood glucose, ESR and CRP and the degree of clinical impairment was studied.

As illustrated in Table 3, all variables were higher in ischemic stroke patients with significant clinical impairment at 28 days (group A patients). This difference is statistically significant for TLC, blood glucose and CRP. In group B patients, the mean TLC (per  $\text{mm}^3$ ) on admission was  $9,200 \pm 2,300$  (p 0.044), whereas the mean blood glucose (mg/dl) was  $177.2 \pm 23.2$  (p 0.002) and mean CRP level (mg/dl) was  $14.5 \pm 5.6$  (p 0.003).

	Group A (mRS score $\leq 2$ )	Group B (mRS score $> 2$ )	P value
Body temperature (°C)	36.2 (3.3)	39.2 (2.8)	0.388
TLC ( $\times 10^3/\text{mm}^3$ )	5.7 (3.3)	9.2 (2.3)	0.044
Blood glucose (mg/dl)	121 (22.1)	177.2 (23.2)	0.002
Platelet ( $\times 10^5/\text{mm}^3$ )	194.6(74.1)	184.2(70.0)	0.413
CRP (mg/dl)	4.6(3.5)	14.5(5.6)	0.003
ESR	19.4(12.3)	25.9(17.2)	0.254

**Table 3.** Indicators of inflammation and degree of clinical impairment in ischemic stroke

For patients with haemorrhagic stroke, a significant association between inflammatory markers and clinical impairment at 28 days was found with CRP and blood glucose only. ICH patients with significant clinical impairment were found to have an admission mean blood glucose value (mg/dl) of  $174 \pm 11.9$  (p=0.001) and mean CRP levels (mg/dl) of  $13.21 \pm 2.5$  (p 0.008). The variables for group A and B patients diagnosed with ICH is shown in Table 4.

	Group A (mRS score $\leq 2$ )	Group B (mRS score $> 2$ )	P value
Body temperature (°C)	36.9 (1.9)	38.2 (1.4)	0.131
TLC ( $\times 10^3/\text{mm}^3$ )	7.8 (2.0)	8.4 (1.3)	0.287
Blood glucose (mg/dl)	128 (22.5)	174 (11.9)	0.001
Platelet ( $\times 10^5/\text{mm}^3$ )	160.8(42.2)	181.8(40.4)	0.222
CRP (mg/dl)	5.52(2.8)	13.41(2.5)	0.008
ESR	15.8(3.6)	23.3(9.6)	0.072

**Table 4.** Indicators of inflammation and degree of clinical impairment in ICH patients

**Discussion**

In a 24 months period, there were a total of 205 cases of diagnosed acute stroke evaluated for this study. Out of these, the most common subtype was found to be ischemic stroke (78%) followed by ICH (22%). This distribution is similar to those found in stroke registries of other parts of countries as cited in Trivandrum Stroke Registry<sup>12</sup> and that of western countries<sup>13,14</sup>, but lower as compared to other parts of Asia<sup>15</sup>. This can be attributed to ethnic differences owing to a predominantly Chinese population in the other studies. The average age of the patients was found to be 57±8 years.

Several studies support the conclusion that increase in inflammatory markers in the acute phase following stroke are associated with poor outcome<sup>21-25</sup>. The link between high admission blood glucose and hematoma expansion as well as high inflammatory markers and poor functional outcome in ICH patients has also been established<sup>26,27</sup>. We have discussed the role of the variables studied in the clinical outcome following both ischemic and haemorrhagic stroke.

Although the predictive value of elevated body temperature in early neurological deterioration following ICH has been suggested<sup>28</sup>, we found that the body temperature on admission did not correlate significantly with the degree of clinical impairment in patients of either ischemic or haemorrhagic stroke at 28 days.

Our study found a significant association between high WBC count and poor functional outcome following ischemic stroke. A prospective study of inflammatory markers and poor outcome after stroke concluded that peripheral markers of inflammation were associated with poor outcome at 6 months. However an independent association could only be established for IL6<sup>29</sup>. The Northern Manhattan Stroke Study confirmed the role of increased mean WBC count in acute phase following ischemic stroke as a poor prognostic marker<sup>30</sup>. Nardi et al also reported TLC as a significant independent predictor for poor outcome at 72 hours and discharge disability<sup>31</sup>. When it came to ICH, high neutrophil count has been demonstrated as predictor of early neurological deterioration<sup>32</sup>. High WBC count has also been associated with increased risk of 30-day mortality<sup>27</sup>. In contrast, this current study could not establish any such associations.

We found a significant increase in RBS measured on admission in patients with worse neurological outcome at 28 days for patients with ischemic stroke. These findings are consistent with several studies that suggest a worse prognosis in non-diabetic hyperglycaemic patients, compared to normoglycaemic patients<sup>33</sup>. Murros et al found that FBS in

This is similar to results obtained from other studies in Middle East and East Asia<sup>16</sup>, but lower than that of reported in the western world<sup>17</sup>. This could be explained by the lower life expectancy in the developing countries compared to the western world<sup>18</sup>.

The male: female ratio was 3:1. Male predominance is particularly seen in the age group of 60-70 years, but a female predominance exists in age group above 70 years, probably due to the lower life expectancy and earlier death in men, and the protective effect of oestrogen in females. These findings are consistent with other reports<sup>19,20</sup>.

non-diabetics strongly correlated with the severity of hemiparesis and predicted poorer outcome<sup>34</sup>. Likewise, Candilise et al found a correlation between RBS and both functional score and size of lesion on CT<sup>35</sup>. A large prospective study in Hong Kong showed a positive correlation between admission glucose level and neurological outcome. However, no such correlation could be established in ICH patients<sup>36</sup>. Cox and Corain reported acute hyperglycaemia to be more important than diabetes mellitus in determining prognosis in stroke patients<sup>37</sup>. In contrast, there is also evidence denying any prognostic significance of acute hyperglycaemia after stroke<sup>38,39</sup>. Furthermore, Toni et al suggested a variable influence of acute hyperglycaemia on ischemic stroke depending on pattern of residual flow after arterial occlusion<sup>40</sup>. Studies conducted to relate poor functional outcome with higher RBS at admission in ICH patients have shown mixed results. On one hand, the value admission hyperglycaemia in predicting increased risk of mortality following ICH has been documented<sup>26,41,42</sup>. Conversely, conclusions drawn by Tuhir et al, and Tetri et al contradict this finding<sup>43,44</sup>. We found that higher glucose on admission in non-diabetic patients is significantly associated with poor functional outcome at 28 days in ICH patients. These findings can be justified by experiments that have proven that the acute stress hyperglycaemia following stroke increases tissue lactic acidosis which impairs post infarction recovery<sup>45</sup>.

Low platelet count has been identified as a predictor of fatal outcome in ICH<sup>46</sup>. Moreover, others have suggested a relationship between platelet dysfunction and expansion of ICH volume<sup>47</sup>. Our study did not find any such association between platelet count and outcome from both ischemic and haemorrhagic stroke.

Studies have suggested the role of CRP in predicting the degree of neurological dysfunction in the period following acute stroke<sup>48</sup>.

Our study supports the hypothesis that elevated CRP levels on admission can predict poor prognosis in terms of functional outcome following stroke. Abubakar et al, in his

study on CRP levels on admission in 209 stroke patients reached similar conclusion<sup>49</sup>. The role of CRP level on discharge as an independent prognostic factor has been studied by Napoli et al<sup>25</sup>. One explanation offered for this is the association between elevated CRP levels and the large size of infarct<sup>50</sup> and a larger area of brain necrosis<sup>51</sup>. An increased CRP also mediates proinflammatory cytokines and maintains a local prothrombotic state<sup>52</sup>. High CRP is also found to be an independent predictor of death following ICH<sup>26</sup>. This is in accordance with our findings, as patients suffering from poor functional outcome following ICH were found to have higher admission CRP levels.

An association between increased ESR and functional outcome has been claimed in previous studies<sup>53-55</sup>. Castellanos et al found such associations in patients of ICH as well<sup>27</sup>. However, no such association could be established in our study.

The finding of this study were adversely effected by certain factors. The sample based on the patient population of a single centre limits the usefulness of the results on a more racially and ethnically diverse population. A delay in blood collection for some patients could have affected the strength of association between the variables measured. Additional factors, including the size of the lesion on CT were not accounted for.

All stages of development of an atherosclerotic plaque involve cells characteristic of inflammation<sup>56</sup>. But whether the rise in inflammatory markers after stroke is owing to a non-specific systemic inflammatory response to stroke, or does it reflect the extent of brain damage has always been a question of debate. Nevertheless, peripheral markers of inflammation can serve as mean to assess risk stratification and identify patients who may benefit from ancillary lifestyle modification or drug therapy.

## Conclusion

Peripheral markers of inflammation can be used to predict the functional outcome in stroke patients. A higher level of TLC count, blood glucose and CRP were associated with poor functional outcome in patients of ischemic stroke, whereas higher TLC count and blood glucose are association with poor functional outcome following haemorrhagic stroke. Current management guidelines of ICH patients are based on decreasing BP and hematoma size, and have shown no decrease in mortality or morbidity. Easily measurable acute phase reactants can be used to predict morbidity following stroke and provide more accurate information to patients. Further studies need to be done to study

neuroinflammation as a potential target of treatment in the management of stroke.

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