

ORIGINAL ARTICLE

Relationship between admission serum C-reactive protein and short term outcome following acute ischaemic stroke at a tertiary health institution in Nigeria

SA Abubakar, NU Okubadejo¹, OO Ojo¹, O Oladipo², FI Ojini¹, MA Danesi¹

Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria, Kaduna State, Nigeria, Department of ¹Medicine, ²Chemical Pathology, College of Medicine, University of Lagos and Lagos University Teaching Hospital, Idi-Araba, Lagos State

Abstract

Background: There is evidence of an association between mediators of inflammation, particularly C-reactive protein (CRP), and outcome of acute ischaemic stroke. This provides a potential opportunity for interventions aimed at improving outcome. There is sparse data exploring the role of inflammatory markers such as CRP and stroke outcome in Africans. The study objective was to determine the association between admission serum CRP levels and short-term outcome in the Nigerian patient presenting with acute ischaemic stroke.

Materials and Methods: Consecutive patients hospitalized for first-ever acute ischaemic stroke at the Lagos University Teaching Hospital, Lagos, Nigeria, were prospectively enrolled between October 2007 and June 2008. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS). Serum CRP was determined on samples obtained within 7 days of stroke onset. All stroke patients were followed up till day 30 post-stroke. Outcome measures were 30 day Glasgow outcome scale score and functional impairment on the modified Rankin Scale (mRS). An age- and gender-matched healthy control group had serum CRP determined at inclusion. Elevated CRP was defined as any level above the cutoff (mean +2 x standard deviation of CRP level of controls).

Results: Eighty patients with acute ischaemic stroke (47 men and 33 women) and 40 controls (27 male and 13 female) ($P=0.47$) were studied. Mean age in cases was 59.1 ± 15.0 years. Mean CRP was significantly higher in stroke cases than controls (17.7 ± 14.4 mg/L versus 1.1 ± 1.7 mg/L respectively) ($P < 0.00001$). The frequency of elevated CRP (>4.5 mg/L) was 76.3% in stroke ($N=61$) and 5% ($N=2$) in controls ($P < 0.0001$). The case fatality rate in stroke with elevated CRP (32.8%) was significantly higher than stroke with normal admission CRP (0%; $P=0.015$). The association of higher admission CRP with fatality (χ^2) was statistically significant ($P < 0.0001$). Amongst survivors, mean CRP levels were markedly higher in the patients with unfavorable motor outcome (moderate/severe disability; $n=22$; 21.5 ± 11.1) compared to those with favorable outcome (mild disability; $n=38$; 6.5 ± 6.2) ($P < 0.00001$). In multivariate regression analysis, only high NIHSS score ($P=0.004$) and admission CRP ($P=0.008$) were independently associated with case fatality.

Conclusions: Elevated admission CRP and high NIHSS score are independent predictors of short-term case fatality and adverse functional outcome following acute ischaemic stroke in Nigerians.

Key words: C-reactive protein, ischaemic stroke, outcome

Date of Acceptance: 17-Sept-2012

Address for correspondence:

Dr. S. A. Abubakar,
Department of Medicine, Ahmadu Bello University Teaching Hospital, Zaria, Kaduna State, Nigeria.
E-mail: abbatta1@yahoo.com

Access this article online

Quick Response Code:



Website: www.njcponline.com

DOI: 10.4103/1119-3077.113454

PMID: *****

Introduction

The burden of stroke in low and middle income countries is likely to rise substantially over the next few decades as a result of an increase in the prevalence of cardiovascular risk factors and a contemporaneous demographic transition. Stroke has been highlighted as a leading indication for medical emergency room admissions in sub Saharan Africa.^[1,2] At present, stroke mortality in sub Saharan Africa is high, with most hospital series reporting case fatality rates within the first month averaging 30%.^[3] Identifying overt and covert predictors of morbidity and mortality after stroke is thus a major concern for clinicians, as an initial step that can guide the implementation of strategies to improve outcome.

An increasing body of evidence has linked inflammation with the pathogenesis of atherothrombotic stroke. Infections and inflammation may promote atherosclerosis and thrombosis by elevating serum levels of fibrinogen, leucocytes, clotting factors, and cytokines, and altering the metabolism and function of endothelial cells and monocytes/macrophages.^[4-8] C-reactive protein (CRP) is an acute phase reactant and an indicator of underlying systemic inflammation that is a relatively novel plasma marker for atherothrombotic disease. The use of highly sensitive CRP assays has enhanced the usefulness of CRP as a reliable predictor of cardiovascular events. Large prospective studies in apparently healthy subjects have proposed that independent of other cardiovascular risk factors, elevated plasma CRP levels significantly predict the risk of future ischaemic stroke and transient ischaemic attack.^[9,10] The prognostic significance of serum CRP in acute ischaemic stroke among white populations has been evaluated in several studies.^[11-13] While most studies have found that increased levels of CRP are associated with worse clinical outcome in patients with acute ischaemic stroke, in one study, CRP was not found to be a useful marker to predict the outcome of an acute cerebrovascular event in hospitalized patients.^[11-13]

The role of CRP as a prognostic marker of stroke outcome in Nigerians is not known, and it is desirable to determine its significance considering the potential therapeutic implications. The present study was designed to evaluate the relationship between serum CRP levels determined at admission for acute ischemic stroke, and short-term stroke outcome in Nigerians.

Materials and Materials

The study was a prospective case-control study enrolling consecutive patients presenting with first-ever acute ischaemic stroke cases and hospitalized in the medical wards of the Lagos University Teaching Hospital (LUTH),

Lagos State, Nigeria. Approval of the study protocol was obtained from the Health Research Ethics committee of the institution. The inclusion criteria were: Admission within 7 days of onset of stroke symptoms, first-ever ischaemic stroke. Stroke was defined as '*rapidly developing symptoms or sign of focal and/or global cerebral dysfunction lasting more than 24 hrs or leading to death with no apparent cause other than of a vascular origin.*^[14] Brain computerized tomography (CT) scans were obtained in the majority of cases, and were reviewed by the study radiologists to document ischaemic strokes, exclude intracerebral haemorrhages and other conditions that may mimic stroke including intracranial space occupying lesions. In the few instances where brain CT was not available, ischaemic stroke was diagnosed using both the World Health Organization (WHO) clinical criteria, and the Siriraj stroke score criteria for ischaemic stroke.^[15] The study excluded patients with haemorrhagic stroke, underlying known chronic inflammatory conditions (e.g., connective tissue disease, inflammatory bowel diseases), recent history of fever (within last seven days prior to onset of symptoms of stroke, patients with history (within preceding three months) of myocardial infarction, surgery, angiography, malignancies, statin therapy, steroid or non-steroidal anti-inflammatory drug use. Control subjects (ratio 1 to 2 cases) were healthy volunteers and were age-(± 2 years) and sex-matched to cases. The same exclusion criteria were applied as for the cases. All cases were managed using a standardized protocol adapted from international guidelines for managing acute ischemic stroke, and incorporating our local standard of hospitalization of all strokes for 30 days. Thrombolytic therapy was not available.

Stroke severity on admission was assessed using the National Institute of Health Stroke Scale (NIHSS). The NIHSS is a 15-item impairment scale which provides a quantitative measure of key components of standard neurological examination.^[16] Admission NIHSS score was used to classify stroke severity as follows: Mild <8; moderate 8-16; and severe ≥ 17 .^[17]

Serum CRP determination

Blood samples were obtained by venepuncture at admission and serum was then separated by centrifugation at 3000 revolutions per minute for 10 minutes. The serum samples were refrigerated at the Central Research Laboratory of the institution at minus 30°C until batch analyzed. Serum CRP levels were determined using the particle-enhanced immunoturbidimetric test. This involved an antigen-antibody reaction between antibodies to human CRP bound to polystyrene particle and CRP in the sample and measured at a wavelength of 340 nm using the Hitachi @-905 auto analyzer. The first run of tests was done using universal application which allowed for an extremely wide measuring range of 0.3 mg/L to 350 mg/L. The samples with CRP values less than 0.3 mg/L were re-analyzed using a high sensitivity application (with the analyzer re-calibrated) with a measuring

range of 0.05 mg/L to 20 mg/L. The cutoff value for defining elevated CRP was set as any value two standard deviations above the mean serum CRP obtained for controls

Outcome evaluation

All cases were followed up for the entire 30 day period in-hospital. Outcome was determined using the Glasgow Outcome Scale. The functional status of patients who survived up to day 30 post-stroke was assessed using the modified Rankin scale (MRS). MRS score of 0-2 was graded favorable outcome (no symptoms/slight disability), while a score of 3-5 was graded as unfavorable outcome (moderate/severe disability).^[18]

Statistical analysis

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) ® version 13.0. Categorical data are summarized as frequencies and percentages while continuous data are described as mean values ± standard deviation (SD). Comparison of group differences in categorical variables was achieved using X² test, while the Student’s t-test and Mann Whitney U test were used to compare means of continuous normally distributed and non-normally distributed variables respectively. The relationship between admission CRP and outcome scores (MRS and GOS) was determined using linear regression analysis. Statistical significance was set at P < 0.05.

Results

The study recruited a total of 138 acute ischaemic stroke cases but only 80 fulfilled the predetermined inclusion criteria and were included in the analysis. 58 were excluded from the study for the following reasons: 20 ischemic strokes presented after 7 days of onset; 18 had documented fever at presentation; and 7 were on non-steroidal anti-inflammatory drugs/steroids at the time of the event. 13 of the cases who did not have brain CT scan and whose Siriraj stroke scores were between -1 and +1 were also excluded.

Baseline characteristics are shown in Table 1. The stroke cases comprised of 47 men (58.8%) and 33 women (41.3%), while the controls were 27 men (67.5%) and 13 women (32.5%). There was no significant difference in gender distribution of cases and controls (X² = 0.53; P = 0.47). The ages of the stroke cases ranged from 13 to 91 years, (mean age ± SD of 59.10 ± 15.02 years). The age range of the controls was 14 to 73 years (mean age ± SD of 56.13 ± 10.61) (T = 1.12; P = 0.27). Hypertension was the most common modifiable risk factor for stroke [Table 1].

Serum CRP levels and relationship to disease-related parameters

Based on the mean CRP in controls, elevated CRP was defined in this study as any value exceeding 4.5 mg/L.

The mean admission serum CRP level (mg/L) for stroke cases was 17.7 ± 14.4, compared to controls 1.1 ± 1.7 (P < 0.00001). Thus, the frequency of elevated CRP was 76.3% (n = 61) in stroke cases and 5% (n = 2) in controls. This difference was statistically significant (X² = 51.5, Fisher exact P < 0.00001).

The mean CRP in subgroups of stroke patients defined based on severity of stroke (NIHSS category) and stroke outcome measures (GOS and MRS) are shown in Table 2 and Figure 1. Overall case fatality rate was 25% (n = 20). Mean serum admission CRP was significantly higher in patients that died within the 30-day follow up period compared to survivors. Patients who recovered completely or had mild disability (favorable outcome) had significantly lower mean admission CRP levels compared to those with unfavorable outcome (moderate/severe disability).

Table 1: Baseline characteristics of ischaemic stroke patients enrolled in the study

Characteristics	Value
Age ± SD (years)	59.1 ± 15.0
Male/female	47/33
Mean blood pressure ± standard deviation (mmHg)	
Systolic	156.5 ± 30.4
Diastolic	91.4 ± 17.1
Risk factor profile N (%)	
Systemic hypertension	62 (77.5)
Diabetes mellitus	24 (30.0)
Cigarette smoking	9 (11.3)
Cardiac diseases*	2 (2.50)
Sickle cell anaemia	1 (1.3)
NIHSS score (mean ± SD)	8.1 ± 3.1
Stroke severity based on NIHSS score N (%)	
Mild	31 (38.8)
Moderate	48 (60)
Severe	1 (1.3)

*Dilated cardiomyopathy=1, atrial fibrillation=1

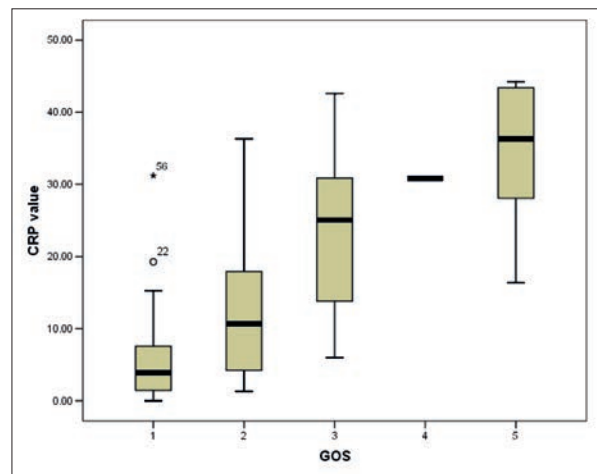


Figure 1: Admission serum CRP levels across the spectrum of outcomes on the Glasgow Outcome Scale at 30 days post-stroke

In multivariate regression analysis [Table 3], only high NIHSS score and admission CRP were predictors of case fatality. Other variables included in the model i.e., age at stroke onset, mean arterial pulse (MAP), pulse pressure (PP), duration prior to presentation were not found to be independent predictors of case fatality.

Discussion

This study found significantly higher CRP levels on admission in acute ischemic stroke patients compared to controls, and validates previous publications indicating that CRP levels tend to be elevated in the post-stroke period,^[11,12] typically representing an acute inflammatory phase reaction, and possibly reflecting the underlying role of inflammation in the pathogenesis of ischaemic stroke. Our study, conducted using a documented, from a prospective design incorporating population controls, documented a similarly high frequency of elevated CRP (76.3%) in acute ischemic stroke in Nigerians, comparable to data from other populations. Di Napoli *et al.*^[12] reported a frequency of elevated CRP of 74.2% in their Caucasian patients with acute ischaemic stroke. Genetic differences are known to modify CRP

concentrations post-stroke, as illustrated by Ben-Assayag *et al.* who showed that genetic variation in the promoter region of the CRP gene influences the triggered serum CRP concentration following acute stroke. During acute stroke, individuals with the CRP 717 AG/GG genotype have more significant elevation in CRP concentration compared to those with the 717 AA genotype.^[19]

Secondly, we found a positive association between admission CRP and severity of stroke at presentation. This may reflect the relationship between the magnitude of the acute inflammatory response and the extent of ischaemia. More profound necrosis results in a greater degree of inflammation and higher levels of circulating acute phase proteins. Human studies have shown a direct correlation of interleukin (IL) 6 levels with extent of tissue damage in stroke.^[20] This is also consistent with the finding that case fatality rate was highest in those with elevated CRP levels in this study, while none of the patients with normal CRP died within the study period, marking elevated CRP as a predictor of adverse outcome post-acute ischaemic stroke. Rallidis *et al.*^[21] also reported significantly higher mean CRP of 25.2 mg/L in stroke cases who died in their study, compared to survivors (3.2 mg/L).

Table 2: Mean admission serum CRP and relationship with 30-day post-stroke outcome

Characteristic	Mean CRP ± SD (mg/L)	t statistic	P value
Admission CRP values			
Stroke cases (n=80)	17.7 ± 14.4	7.22	<0.00001
Controls (n=40)	1.1 ± 1.7		
Admission stroke severity			
Mild stroke (n=31)	7.9 ± 8.5	5.72	<0.00001
Moderate/severe stroke (n=49)	23.9 ± 3.8		
30-day case fatality			
Died (n=20)	34.6 ± 8.9	8.33	<0.00001
Survived (n=60)	12.0 ± 11.0		
Length of survival			
Died ≤7 days (n=6)	43.6 ± 0.8	16.78	<0.00001
Died 8-14 days (n=5)	38.3 ± 3.3		
Died 15-21 days (n=5)	28.5 ± 6.8		
Died 22-30 days (n=4)	24.5 ± 6.7		
30-day functional outcome among survivors (n=60)			
Favorable outcome (MRS 0-2) (n=38)	6.5 ± 6.2	6.7	<0.00001
Unfavorable outcome (MRS 3-5) (n=22)	21.5 ± 11.1		

MRS = Modified Rankin scale. Boxplot showing increasing admission CRP levels (mg/L) (median and interquartile ranges) with worsening GOS score (from best outcome 1 to worst outcome 5). Numbers within background indicate outliers in the subcategory of patients with GOS 1

Table 3: Determinants of 30-day case fatality in multiple regression analysis

Parameter	Odds ratio	95% confidence interval	P value
Admission diastolic blood pressure	2.31	0.31-17.46	0.42
Admission mean arterial pressure	1.28	0.65-2.54	0.48
Admission pulse pressure	0.45	0.06-3.27	0.43
Age (years)	0.98	0.90-1.08	0.74
CRP value (mg/L)	1.24	1.06-1.44	0.008
Admission NIHSS score	3.43	1.49-7.94	0.004
Duration prior to presentation (hours)	1.01	0.98-1.05	0.49

Furthermore, we found a positive association between admission CRP and functional outcome. This is similar to the finding of Di Napoli *et al.*^[12] 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. Firstly, CRP concentration may reflect the degree of inflammation directly consequent upon cerebral infarction. Elevated CRP levels may reflect a greater extent of brain necrosis^[22] and a greater amount and activity of pro-inflammatory cytokines which may potentiate ischaemic brain injury through several mechanisms such as up regulation of adhesion molecules, recruitment and activation of leucocytes and potentiation of local pro-coagulant state.^[23] Secondly, CRP concentration on admission could also be predictive of outcome as baseline CRP may be indicative of underlying unstable atherosclerotic disease, the presence of which is a risk factor for other co-morbid states such as ischaemic heart disease which can worsen stroke outcome. Thirdly, CRP may be raised as a consequence of covert complications of stroke such as infections and aspiration. Even though strict inclusion criteria were applied, it is difficult to exclude, for instance, early asymptomatic stages of infection which could both compound stroke-specific CRP elevation and disease course.

Limitations

We acknowledge the modest size of the sample studied and indicate that our findings, though preliminary in nature, provide a thrust for larger, more elaborate studies. Also, a small minority of cases did not have a brain CT scan and clinical validated criteria were used for characterization as ischemic stroke. It was beyond the scope of this study to explore other covert contributions to elevated CRP levels, and we realize that these may exist. However, we have illustrated that elevated CRP is a frequent accompaniment of ischaemic stroke in our environment, correlates with stroke severity, and independently predicts adverse outcome including fatality and functional impairment. Our study buttresses the existing view that inflammation is a significant factor in ischemic stroke, and supports the need for scientific research focusing on establishing the relationship between inflammation and ischemic stroke.

References

- Ojini FI, Danesi MA. Pattern of neurological admissions at Lagos University Teaching Hospital. *Niger J. Clin. Pract.* 2003;5:38-41.
- Ogun SA, Adelowo OO, Familoni OB, Jaiyesimi AE, Fakoya EA. Pattern of medical admission at Ogun state University Teaching Hospital: A three year review. *West Afri J Med* 2000;19:304-8.
- Ogun SA, Ojini FI, Ogungbo B, Kolapo KO, Danesi MA. Stroke in south west

- Nigeria: A 10 year review. *Stroke* 2005;36:1120-2.
- Ernst E, Koenig W. Fibrinogen and cardiovascular risk. *Vasc Med* 1997;2:115-25.
- Ernst E, Hammerschmidt DE, Bagge U, Matrai A, Dormandy JA. Leucocytosis and risk of ischaemic diseases. *JAMA* 1987;257:2318-24.
- Juhan-Vague I, Pyke SD, Alessi MC, Jespersen J, Haverkate F, Thompson SG. Fibrinolytic factors and risk of myocardial infarction or sudden death in patients with angina pectoris. *Circulation* 1996;94:2057-63.
- Dinerman JL, Mehta JL, Saldeen TG, Emerson S, Wallin R, Davda R, *et al.* Increased neutrophil elastase release in unstable angina pectoris and acute myocardial infarction. *J Am Cardiol* 1990;15:1559-63.
- Mathla KJ, Valtonen VV, Neminen MS, Asikainen S. Role of infection as risk factor for atherosclerosis, myocardial infarction and stroke. *Clin Infect Dis* 1998;26:719-34.
- Rost NS, Wolf PA, Kase CS, Kelly-Hayes M, Silbershatz H, Massaro JM, *et al.* Plasma concentration of CRP and risk of ischaemic stroke and transient ischaemic attack: Framingham study. *Stroke* 2001;32:2575-9.
- Ross R. Atherosclerosis-an inflammatory disease. *N Eng J Med* 1999;340:115-26.
- Anuk T, Assayag EB, Rotstein R, Fusman R, Zeltser D, Berliner S, *et al.* Prognostic implications of admission inflammatory profile in acute ischaemic neurologic events. *Acta Neurol Scand* 2002;106:196-9.
- Di Napoli M, Papa F, Bocola V. Prognostic influence of increased C-Reactive protein and fibrinogen levels in ischaemic stroke. *Stroke* 2001;32:133-8.
- Canova CR, Courtin C, Reinhart WH. C-Reactive protein in cerebrovascular events. *Atherosclerosis* 1999;147:49-53.
- WHO MONICA project principal investigators. The World Health Organization MONICA project (monitoring trends and determinants in cardiovascular disease): A major collaboration. *J Clin Epidemiol* 1988;41:105-14.
- Poungvarin N, Viriyavejakul A, Komontri C. Siriraj stroke score and validation study to distinguish supratentorial intracerebral haemorrhage from infarction. *BMJ* 1991;302:1565-7.
- Appelros P, Terent A. Characteristics of the NIHSS results: Results from a population-based stroke cohort at baseline and after one year. *Cerebrovasc Dis* 2004;17:21-7.
- Briggs DE, Felberg RA, Malkoff MD, Bratina P, Grotta JC. Should mild or moderate stroke be admitted to an intensive care unit. *Stroke* 2001;32:871-6.
- Uyttenboogaart M, Stewart RE, Vroomen P, Keyser JD, Luijckx G. Optimizing cut off score for the Barthel index and Modified Rankin scale for defining outcome in stroke trials. *Stroke* 2005;36:1984-7.
- Ben-Assayag E, Shenhar-Tsarfaty S, Bova I, Berliner S, Shopin L, Peretz H, *et al.* Triggered CRP concentration and CRP gene-717 A>G polymorphism in acute stroke or TIA. *Eur J Neurol* 2007;14:315-20.
- Smith CJ, Emsley HC, Gavin CM, Georgiou RF, Vail A, Barberan EM, *et al.* Peak plasma interleukin-6 and other peripheral markers of inflammation in the first week of ischaemic stroke correlate with brain infarct volume, stroke severity and long-term outcome. *BMC Neurol* 2004;4:2.
- Rallidis LS, Vikelis M, Panagiotakos DB, Rizos I, Zolindaki MG, Kaliva K, *et al.* Inflammatory markers and in-hospital mortality in acute ischaemic stroke. *Atherosclerosis* 2006;189:193-7.
- Audebert HJ, Rott MM, Eck T, Haberl RL. Systemic inflammatory response depends on initial stroke severity but is attenuated by successful thrombolysis. *Stroke* 2004;35:2128-33.
- Kochanek PM, Hallenbeck JM. Polymorph nuclear leucocyte and monocyte/macrophage in pathogenesis of cerebral ischaemia and stroke. *Stroke* 1992;23:1367-79.

How to cite this article: Abubakar SA, Okubadejo NU, Ojo OO, Oladipo O, Ojini FI, Danesi MA. Relationship between admission serum C-reactive protein and short term outcome following acute ischaemic stroke at a tertiary health institution in Nigeria. *Niger J Clin Pract* 2013;16:320-4.
Source of Support: Nil, **Conflict of Interest:** None declared.