

INFLAMMATORY MARKERS IN ACUTE ISCHAEMIC STROKE IN RELATION TO CLINICAL SEVERITY AND EARLY OUTCOME

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ABSTRACT

BACKGROUND

Biochemical markers of inflammation could be useful to predict severity of stroke in acute phase. Stroke is the third cause of mortality and the first cause of disability. Recent literature have demonstrated that inflammation contributes to all phases of atherosclerosis. The results of researchers suggest that atherosclerosis is an inflammatory disease.

The aim of the study is to assess the-

1. Level of peripheral inflammatory markers in acute ischaemic stroke and their relation to severity of acute stroke.
2. Value of inflammatory markers in predicting the short-term outcome and disability at the end of six months.

MATERIALS AND METHODS

This is a prospective case control study for 6 months done from September 2014 to August 2016 in 100 patients of acute ischaemic stroke within first 5 days of symptom onset in comparison >18 years of age with 50 age and sex matched controls. Blood samples for all cases and controls were sent for erythrocyte sedimentation rate, Neutrophil-to-Lymphocyte Ratio (NLR), hs-C-reactive protein, mean platelet volume, serum ferritin, serum albumin and S. gamma-glutamyl transferase at admission.

RESULTS

The mean values of ESR, NLR, hs-CRP in all the cases are higher when compared to the controls and are statistically significant, whereas the mean values of MPV, S. ferritin, S. albumin and GGT in cases are lower when compared to controls, but are within normal range and difference is statistically significant except ferritin. ESR, hs-CRP has significant correlation with severity of acute ischaemic stroke. The mean values of these markers increased with increase in severity. Serum albumin has significant correlation with severity of acute ischaemic stroke with mean values of these markers decreasing with increase in severity of stroke. There is no significant correlation of the inflammatory markers in present study with the short-term outcome.

CONCLUSION

Inflammation plays an important role in the pathogenesis of non-cardioembolic ischaemic stroke. Management of acute ischaemic stroke in relation to inflammatory markers need to be well elucidated by further long-term study.

KEYWORDS

Inflammatory Markers, Acute Ischaemic Stroke, ESR, hs-CRP, GGT, NLR, Albumin, Ferritin, MPV.

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BACKGROUND

Stroke is the third cause of mortality and the first cause of disability. Recent literature have demonstrated that inflammation contributes to all phases of atherosclerosis. The results of researchers suggest that atherosclerosis is an inflammatory disease. In acute phase of cerebrovascular diseases, biochemical markers of inflammation could be useful to predict severity of stroke.

Many reports suggested that CRP was associated with risk of stroke,¹ whereas some reports did not find significant

relations. Recently, Liu et al² reported that elevated High Sensitivity-CRP (hs-CRP) concentrations were associated with a higher risk of ischaemic stroke, particularly for non-fatal stroke, males and hypertensive participants, but there were no significant associations between hs-CRP and intracranial haemorrhage and subarachnoid haemorrhage in a large prospective study.

Also, Erythrocyte Sedimentation Rate (ESR), a classical acute phase marker was often compared with CRP. Recently, there were a number of reports dealing with platelet indices such as Mean Platelet Volume (MPV); MPV/Platelet Count (PC) ratios have clinical indications in various conditions such as atherosclerosis,³ cerebral infarction⁴ and active inflammatory diseases and high MPV was even associated with fractures.⁵ Also, the Neutrophil-To-Lymphocyte Ratio (NLR) parameter was reported to be an important measure of systemic inflammation.⁶ However, platelet indices and NLR have not been fully investigated in roles as useful surrogate biomarkers of diagnosis in patients with cerebral infarction.

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In addition, most of the studies presently available are limited to 1 or 2 markers and expensive markers. A few studies have been done using simple, inexpensive, easily available markers like ESR, N/L ratio, GGT, MPV and serum albumin in resource limited setting like government hospitals in Andhra Pradesh up-to-date. To elucidate the significance of distinct markers to be part of the complex inflammatory response after stroke and to obtain insight into their interplay in this condition, this study was taken to assess the level of inexpensive, easily available peripheral inflammatory markers in acute ischaemic stroke and their relation with clinical severity at admission and their role in predicting short-term prognosis in acute ischaemic stroke.

Aims and Objectives of the Study-

- To assess the level of peripheral inflammatory markers in acute ischaemic stroke.
- To assess the relation of level of inflammatory markers under study with severity of acute stroke.
- To assess the value of inflammatory markers in predicting the short-term outcome and disability at the end of 6 months.

MATERIALS AND METHODS

Study Period- September 2014 to August 2017.
 Material- Our Study is a prospective case control study for 6 months involving hundred patients of acute ischaemic stroke presenting within first 5 days of onset of symptoms in comparison with 50 age and sex matched controls.

Case Definition- The AHA/ASA expert consensus document for an updated definition of stroke for the 21st century.

“Central nervous system infarction is defined as brain, spinal cord or retinal cell death attributable to ischaemia based on neuropathological, neuroimaging and/or clinical evidence of permanent injury.”

Inclusion Criteria- Patients above 18 years with first attack of acute ischaemic stroke as defined were included in the study.

Exclusion Criteria

- Patients with prior history of ischaemic stroke were excluded.
- Patients with transient ischaemic attacks and onset of stroke >5 days.
- Ischaemic stroke secondary to cardioembolism.
- Intracerebral haemorrhage.

- Systemic infections.
- Any infection requiring intravenous or oral antibiotics.
- All patients of stable or unstable angina, acute myocardial infarction and immunological disorders.
- Recent (less than 3 months) major trauma, surgery and burns.
- History of chronic liver or renal disease, endocrine and autoimmune diseases other than diabetes.
- Patients who were chronic alcoholics.
- Those who had undergone surgical interventions related to coronary, carotid or extremity arteries.
- Drug users, which might alter GGT test results (lipid-lowering drugs and antibiotics).

Methods- Complete history, neurological examination, assessment of stroke severity with NIHSS at baseline on admission was done along with routine laboratory investigation for all acute ischaemic stroke patients. CT scan or MRI of brain, ECG and cardiac echo, carotid Doppler of neck vessels, ultrasound abdomen and liver function tests were done and hundred patients fulfilling inclusion criteria mentioned were included in the study. Blood samples for all cases and controls were sent for erythrocyte sedimentation rate, neutrophil lymphocyte ratio, hs-C-reactive protein, mean platelet volume, serum ferritin, serum albumin, s. gamma-glutamyl transferase at admission.

Data Entry and Statistical Analysis-

- Data was entered into Microsoft Excel Sheet and analysed using IBM SPSS Statistics for Windows, Version 22.0.
- Descriptive statistics were expressed as means and percentages.
- Inferential statistical analysis was done using Chi-square tests for nominal and ordinal variables and ANOVA tests for interval variables.
- P-value of <0.05 will be considered statistically significant.

RESULTS

The mean values of ESR, NLR and hs-CRP in all the cases are higher when compared to the controls and are statistically significant, whereas the mean values of MPV, S. ferritin, S. albumin and GGT in cases are lower when compared to controls, but are within normal range and difference is statistically significant except ferritin.

Distribution of inflammatory markers in cases in relation to severity of acute ischaemic stroke.

Inflammatory Markers	Cases		Control		p value
	Mean	Standard Deviation	Mean	Standard Deviation	
ESR	34.490	23.4264	13.300	3.5355	0.000
NLR	4.4515	1.85616	2.3860	0.43893	0.000
MPV	11.359	1.2715	11.960	2.7027	0.000
S .ferritin	112.946	88.3452	127.98	78.88263	0.648
GGT	28.343	18.6410	34.180	7.1619	0.000
Hs-CRP	3.6520	2.78860	0.8974	0.18966	0.000
S. albumin	3.461	0.6970	4.082	0.4579	0.015

Table 1. Inflammatory Markers in Cases and Controls in the Present Study

Inflammatory Markers	NIHSS	Cases	Mean	Standard Deviation	p value
ESR	0-4	17	19.88	19.202	0.012
	5-14	75	36.83	22.719	
	>15	8	43.63	28.107	
		100			
NLR	0-4	17	3.8941	1.34837	0.319
	5-14	75	4.5207	1.92709	
	>15	8	4.9875	2.04411	
		100			
MPV	0-4	17	11.365	1.2046	0.708
	5-14	75	11.396	1.3241	
	>15	8	11.400	0.9227	
		100			
S. ferritin	0-4	17	101.4712	73.88509	0.706
	5-14	75	113.3912	89.51479	
	>15	8	133.1638	111.39515	
		100			
GGT	0-4	17	30.535	24.9016	0.869
	5-14	75	27.861	17.5158	
	>15	8	28.200	15.4783	
		100			
Hs-CRP	0-4	17	2.3106	2.70947	0.012
	5-14	75	3.7309	2.64453	
	>15	8	5.7625	3.12087	
		100			
S. albumin	0-4	17	3.412	0.6214	0.049
	5-14	75	3.461	0.7127	
	>15	8	4.413	0.4612	
		100			

Table 2. Relation of Inflammatory Markers with Clinical Severity in Present Study

Erythrocyte sedimentation rate, highly-sensitive C-reactive protein and has significant correlation with severity of acute ischaemic stroke. The mean values of these markers increased with increase in severity. Serum albumin has significant correlation with severity of acute ischaemic stroke with mean values of these markers decreasing with increase in severity of stroke distribution of inflammatory markers in cases as prognostic markers for short outcome.

Inflammatory Markers	mRS 6	Cases	Mean	Standard Deviation	p value
ESR	0-2	92	33.95	23.452	0.615
	3-6	8	40.75	23.729	
		100			
NLR	0-2	92	4.4098	1.85565	0.921
	3-6	8	4.9313	1.91739	
		100			
MPV	0-2	92	11.393	1.2982	0.284
	3-6	8	10.963	0.8733	
		100			
S. ferritin	0-2	92	116.5446	89.61521	0.384
	3-6	8	71.5700	62.08998	
		100			
GGT	0-2	92	28.479	18.9087	0.595
	3-6	8	26.775	16.2289	
		100			
Hs-CRP	0-2	92	3.5750	2.81053	0.251
	3-6	8	4.5375	2.51336	
		100			
S. albumin	0-2	92	3.888	0.7123	0.143
	3-6	8	3.550	0.3928	
		100			

Table 3. Relation of Inflammatory Markers with Short-Term Outcome

There is no significant correlation of the inflammatory markers in present study with the short-term outcome.

DISCUSSION

The present study focused on new-onset acute ischaemic stroke patients. In present study, there is no significant difference in cases and controls in respect to age and sex distribution.

Sex	Cases	Controls
Males	60	30
Females	40	20
Total	100	50

Table 4. Sex Distribution among Cases and Controls

Age Group	Cases	Controls
20-30	1	1
30-40	8	4
40-50	16	8
50-60	26	12
60-70	38	20
70-80	8	3
80-90	3	2
Total	100	50

Table 5. Age Distribution among Cases and Controls

Hs-CRP Values	Present Study	Yusuf Tamam et al	Mitchell SV Elkind, et al	Krishna Murthy H.A.	Agarwal et al Study	David Curb et al	SA Abubakar
AIS	3.65 ± 2.78	43.6 ± 56.7	1.67 ± 1.07	4.5 ± 2.58	25.0 ± 24.78	14.3	17.7 ± 14.4 mg/L
Controls	0.89 ± 0.19	1.4 ± 1.2	1.00 ± 1.18	0.88 ± 0.41	4.00 ± 1.48	11.6	1.1 ± 1.7 mg/L

Table 6. Comparison of Highly Sensitive C-Reactive Protein (hs-CRP) Distribution among Cases and Controls in Different Studies

Highly-Sensitive C-Reactive Protein- The mean CRP level in the present study 3.65 ± 2.78 mg/L among the cases and 0.89 ± 0.19 mg/L among the controls respectively, which is statistically significant with the p value of <0.001. These findings were comparable with studies done by David Curb et al,⁷ Mitchell et al, SV Elkind et al,⁸ Krishna Murthy H.A. et al,⁹ Yusuf Tamam et al and Agarwal et al.¹⁰

Hs-CRP	Present Study	Kouchaki Ebrahim et al ¹¹
Mild stroke	2.31 ± 2.71	10.7 ± 6.9
Moderate stroke	3.73 ± 2.65	13.98 ± 8.25
Severe stroke	5.76 ± 3.12	22.56 ± 12.084

Table 7. Comparison of Highly-Sensitive C-Reactive Protein (hs-CRP) as Marker of Stroke Severity with Other Study

The present study did not find any correlation between hs-CRP levels and short-term (6 months) functional outcome of ischaemic stroke. Similar to the present study, Canova et al and Modrego et al failed to conclude any relationship between CRP and outcome of acute cerebrovascular events such as ischaemic stroke. In contrast, CRP levels have been correlated positively with the size of the infarct and stroke severity.

	Present Study	Krishna Murthy et al ⁹	Kriti Gupta et al ¹²
Good outcome	1.57	3.2	4.6
Poor outcome	4.54	4.9	14.5

Table 8. Comparison of Highly-Sensitive C-Reactive Protein (hs-CRP) as a Prognostic Marker in Different Studies

Erythrocyte Sedimentation Rate (ESR)- The mean ESR level in the present study is 34.49 ± 23.42 mm/hour among the cases and 13.30 ± 3.53 mm/hour among the controls respectively, which is statistically significant with the p value of <0.001. These findings are comparable with studies done by Agarwal study et al and Aliaksei Kisialiou in AIS patients where the mean ESR level among the cases were higher when compared to controls and were statistically significant with p value of <0.001. The findings are not correlating with Ufuk Emre et al. The differences in results between studies could be attributed to different factors like differences in the study design (some of these studies followed the case control design, whereas others were cross-sectional comparative studies), the differences in sample sizes and the different ways of assessment of ischaemic stroke severity and outcome may be responsible for these contradictory results. There is a need for more studies to evaluate the use of the inflammatory markers as predictors of outcome in different types of ischaemic stroke.

ESR	Present Study	Agarwal Study et al ¹⁰	Ufuk Emre et al	Aliaksei Kisialiou et al
AIS	34.49 ± 23.42	33.92 ± 5.73	29.8 ± 16	21.3 ± 19.8
Controls	13.30 ± 3.53	14.08 ± 3.73	23.8 ± 13	19.20 ± 16.2
p value	<0.001	<0.05	>0.05	<0.05

Table 9. Comparison of Erythrocyte Sedimentation Rate (ESR) Distribution among Cases and Controls in Different Studies

Short Outcome Based on mRS	Baseline ESR at Admission				
	Present Study	Magdy et al ¹¹	Kriti Gupta et al ¹²	Krishna Murthy et al ⁹	Selim Selçuk et al ¹³
Good outcome	33.95	18	15.8	25	12
Poor outcome	40.75	29.5	23.3	34	14
P value	0.433	<0.05	0.254	<0.05	0.889

Table 10. Comparison of Erythrocyte Sedimentation Rate (ESR) as a Prognostic Marker in Different Studies

Serum Albumin- The mean albumin level in the present study is 3.46 ± 0.69 g/dL among the cases and 4.08 ± 0.45 g/dL among the controls respectively, which is statistically significant (p value <0.001). These findings are comparable with studies done by P.J. Kelly et al, Varga et al, F. J. Alvarez-Perez et al in AIS patients where the mean albumin level among the cases were lower when compared to controls and were statistically significant.

S. Albumin	Present Study	P.J. Kelly et al	Varga	F. J. Alvarez-Perez ¹⁴ (n=50)
AIS	3.46 ± 0.69	3.4 ± 0.48	4.02 ± 0.31	4 ± 0.4
Controls	4.08 ± 0.45	3.9 ± 0.4	3.55 ± 0.69	4.4 ± 0.2

Table 11. Serum Albumin Distribution among Cases and Controls in Different Studies

Albumin is the most abundant protein found in plasma functioning as a carrier molecule maintaining oncotic pressure and acting as a major antioxidant defender in inflammatory process.¹⁵ In addition, serum albumin level is one of the biochemical markers of nutritional status and it has been reported that protein energy malnutrition after acute stroke is a risk factor for poor outcome worsening the prognosis.¹⁶

Short-Term Outcome Based on mRS	Present Study	F. J. Alvarez-Perez	Sweileh et al	A. Vahedi et al	Dziedzic et al
Good outcome	3.88 ± 0.712	4.2 ± 0.4	4	3.6 ± 0.5	4.5
Poor outcome	3.55 ± 0.39	3.9 ± 0.5	3.1	3.1 ± 0.4	3.0
P value	0.190	<0.001	<0.001	<0.001	<0.001

Table 12. Comparison of Serum Albumin as a Prognostic Marker in Different Studies

Serum Gamma-Glutamyl Transferase (S. GGT)- The mean GGT level in the present study is 28.343 ± 18.6410 U/L among the cases and 34.180 ± 7.1619 U/L among the controls respectively, which is statistically significant with the (p value of <0.04). These findings are comparable with studies done by Emine Akinci et al, Antonio Muscari et al in AIS patients where the mean GGT level among the cases were lower when compared to controls and were statistically significant ($p <0.001$). In contrary to our findings, studies done by Nurbanu Gurbuzer et al,¹⁷ Umar Farooq Dar et al¹⁸ has shown GGT higher in cases compared to controls and the difference is statistically significant (p value <0.05).

S. GGT	Present Study	Nurbanu Gurbuzer	Emine Akinci	Antonio Muscari	Umar Farooq Dar
AIS	28.343 ± 18.6410	23.50 ± 9.910	21.5 (13-25)	22 (15-32)	26.7 ± 14.2
Controls	34.180 ± 7.1619	19.5 ± 12.4	23 ± 16.4	29 ± 15.3	18.5 ± 11.9
P value	0.001	<0.05	<0.001	<0.001	<0.05

Table 13. Serum Gamma-Glutamyl Transferase Distribution Among Cases and Controls in Different Studies

S. MPV	Present Study	Durdu Tamer	Kandan Muralidharan	Parvaiz A. Shah
AIS	11.539 ± 1.27	9.0 ± 2.4	10.33 ± 1.74	11.86 ± 0.96
Controls	11.960 ± 2.70	8.80 ± 2.1	9.2 ± 1.14	10.8 ± 1.14

Table 14. S. MPV Distribution among Cases and Controls in Different Studies

In our study, admission MPV has shown negative predictive value of 0.360 for short-term outcome following AIS, which is not statistically significant (p value = 0.190). These findings are in correlation with studies of O'Malley et al, Ntaios G et al, Du J, Wang Q et al, which were also not significant. In contrary to our study, Greisenegger's show significance for predicting short-term outcome following AIS.

Possible reasons for these divergent results could be small numbers of patients. The use of different outcome measures and variation in the timing of obtaining blood samples and their assessment in these studies. Also, it was suggested that increased MPV and higher platelet reactivity simply reflect a marker for a more severe stroke event and a more pronounced acute phase reaction, but in our present study, we included only patients whose MPV was determined mostly within the first 48-72 hours of admission.

mRS Disability Score	Present Study	Mayda-Domac F
0-2, good prognosis	11.393 ± 1.29	8.93 ± 0.93
3-6, poor prognosis	10.96 ± 0.873	11.26 ± 1.29
P value	<0.001	<0.001

Table 15. Comparison of Mean Platelet Volume (MPV) as a Prognostic Marker in Different Studies

Serum Ferritin- The mean level of S. ferritin in the present study is 112.94 ± 88.34 ng/mL among the cases, which is lower than controls of 127.98 ± 78.88 ng/mL respectively, which is statistically significant with the 'p' value of <0.001 .

These findings are not comparable to study done by Ufuk Emre et al, where cases have higher level values when compared to controls.

S. Ferritin	Present Study	Ufuk Emre et al
AIS	112.94 ± 88.34	102, 6 ± 7
Controls	127.98 ± 78.88	63 ± 5

Table 16. Serum Ferritin Distribution among Cases and Controls in Different Studies

Short Outcome Based on mRS	Ferritin at Admission				
	Present Study	Magdy et al ¹¹	Kriti Gupta et al ¹²	Krishna Murthy et al ⁹	Selim Selcuk et al ¹³
Good outcome	116.5446	18	15.8	25	12
Poor outcome	71.5	29.5	23.3	34	14
P value	0.16	<0.05	<0.05	<0.05	>0.05

Table 17. Comparison of Ferritin as a Prognostic Marker in Different Studies

Neutrophil Lymphocyte Ratio (NLR)- The mean NLR in the present study is 4.45 among the cases and 2.38 among the controls respectively, which is statistically significant with the p value of <0.001. These findings are comparable with studies done by Asuman Celikbilek in AIS patients where the mean NLR among the cases was higher when compared to controls and was statistically significant.

Short Outcome Based on mRS	Asuman Celikbilek et al	Present study	Ugur Lok et al	Dr. Ram Babu Gurjar
Good outcome	3.15 (2.20-4.10)	4.41 ± 1.85	2.7 ± 1.5	6.04 ± 5.03
Poor outcome	5.90 (2.70-10.00)	4.93 ± 1.917	12.1 ± 4.5	8.96 ± 7.98

Table 18. Comparison of Neutrophil Lymphocyte Ratio (NLR) as a Prognostic Marker in Different Studies

CONCLUSION

1. The inflammation plays an important role in the pathogenesis of non-cardioembolic ischaemic stroke.
2. Inflammatory mediators like erythrocyte sedimentation rate, highly-sensitive C-reactive protein and neutrophil lymphocyte ratio are significantly elevated, whereas serum albumin, mean platelet volume and serum ferritin are significantly decreased in cases compared to controls acute phase of acute ischaemic stroke in the present study.
3. Erythrocyte sedimentation rate, highly sensitive C-reactive protein and serum albumin have significant correlation with severity of acute ischaemic stroke.
4. All the inflammatory markers did not show significant prediction for short-term outcome in acute ischaemic stroke in the present study.
5. Management of acute ischaemic stroke in relation to inflammatory markers need to be well elucidated by further long-term study.

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