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Original Research Article

STUDY OF SERUM FIBRINOGEN LEVELS IN PATIENTS WITH ACUTE ISCHEMIC STROKE AND CORRELATION WITH SEVERITY OF THE DISEASE

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Abstract:

Background: Serum Fibrinogen levels may be elevated in patients with acute Ischemic stroke and correlating with severity of the disease using NIHSS score is useful. **Objective.** To categorize the severity of ischemic stroke cases clinically, on admission by NIHSS score and to quantitatively assess serum fibrinogen levels and to correlate with clinical severity **Methods:** 118 patients presenting with acute ischemic stroke in Medicine department, KIMS hospital meeting inclusion criteria were considered for the study. Written and informed consent was obtained from the patients. The patient's clinical severity was assessed based on the NIHSS score, following which the patients venous blood is collected and tested for serum Fibrinogen levels and other appropriate investigations were performed and were correlated with clinical severity.

Result: In our study of 118 patients, 14% were in mild category followed by 40%, 20% and 28% in mild to moderate, severe and very severe categories based on NIHSS score. The mean serum fibrinogen level in our study is 558.2 mg/dl with SD of 218.2, and the mean serum fibrinogen was highest in very severe category (819.4$\pm$105.5 mg/dl) and lowest in mild category (259.2$\pm$ 69.6 mg/dl) the difference in mean across the four categories was statistically significant ($P < 0.001$).The mean

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serum fibrinogen was highest in age group more than 75 years, there was no statistical significance of fibrinogen levels between males and females. Our study showed that there is a positive correlation between smoking, tobacco use and increase in serum fibrinogen levels.

Conclusion: Serum fibrinogen levels were higher in patients with acute ischemic stroke. Among the patients with acute ischemic stroke, higher serum fibrinogen levels correlates with Clinical severity assessed by The National Institute of Health Stroke Scale. There is a positive correlation between serum fibrinogen levels with hypertension, smoking and tobacco use. Serum Fibrinogen levels can be used as predictor for severity of Acute Ischemic Stroke. Serum Fibrinogen levels can also be used to predict the prognosis in Acute Ischemic stroke

Keywords: Serum fibrinogen, NIHSS score, Acute ischemic Stroke

INTRODUCTION: Fibrinogen and fibrin play overlapping roles in blood clotting, fibrinolysis, cellular and matrix interactions, the inflammatory response, wound healing, and neoplasia. These functions are regulated by interactive sites on fibrinogen, some of which are masked or otherwise not available on fibrinogen, and they commonly evolve as a consequence of fibrin formation or fibrinogen surface interactions.

Fibrinogen has been identified as a major independent risk factor for cardiovascular disease. Fibrinogen has also been associated with traditional cardiovascular risk factors, suggesting that elevation of fibrinogen may be a pathway by which these risk factors exert their effect. There are several mechanisms by which fibrinogen may increase cardiovascular risk. First, it binds specifically to activated platelets via glycoprotein IIb/IIIa, contributing to platelet aggregation. Second, increased fibrinogen levels promote fibrin formation. Third, it is a major contributor to plasma viscosity. Finally, it is an acute-phase reactant that is increased in inflammatory states.[1]

Stroke is a global health problem and is a leading cause of adult disability. Stroke, the sudden death of some brain cells due to lack of oxygen when the blood flow to thebrain is lost by blockage or rupture of an artery to the brain, is also a leading cause of dementiaand

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depression.[2]

Globally, 70% of strokes and 87% of both stroke-related deaths and disability- adjusted life years occur in low- and middle-income countries. Over the last four decades, the stroke incidence in low- and middle-income countries has more than doubled. During these decades stroke incidence has declined by 42% in high- income countries.[2]

The risk factors for stroke are similar to those for coronary heart disease and other vascular diseases. Effective prevention strategies include targeting the key modifiable factors: hypertension, elevated lipids and diabetes. Risks due to lifestyle factors can also be addressed: smoking, low physical activity levels, unhealthy diet and abdominal obesity. Combinations ofsuch prevention strategies have proved effective in reducing stroke mortality even in some low- income settings.[3,4]

Fibrinogen, as a marker of thrombosis and inflammation, is associated with cardiovascular diseases (CVD). It has been demonstrated that elevated fibrinogen level is significantly associated with intima-media thickness and subclinical atherosclerosis.[5,6] previous studyrevealed that fibrinogen independently predicted future ischemic stroke risk and incident hypertension.[5,7]

Hence Measurement of plasma fibrinogen levels could potentially be more useful than thoseof other acute phase reactants such as C-reactive protein, as fibrinogen is probably more specific to vascular disease.

Material and Methods: This Single center and prospective observational study was conducted among patients presenting to KIMS hospital, IPD section with history of Acute ischemic stroke considering the inclusion and exclusion criteria. Study period was 2 years.

METHODS OF COLLECTION OF DATA:

108 patients presenting with history, characteristic clinical signs and symptoms of

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acute ischemicstroke were taken into the study and clinical severity score will be calculated based on that and the following investigations will be done in the selected patients –

- Complete hemogram
- Chest x-ray PA view
- Blood group
- Renal function test
- Serum Electrolytes
- HIV
- HBSAG
- Serum fibrinogen
- Lipid profile
- LFT
- ESR
- CT/MRI Brain

Sampling Size:

Based on the past year data in KIMS hospital total number of ischemic stroke in KIMS was 1148. After applying inclusion and exclusion criteria the sample size selected was 118 patients.

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Inclusion Criteria:

1. Patient above 18 years.
2. Patient giving informed consent.
3. Patients presenting with Acute ischemic Stroke.

Exclusion Criteria:

1. Patients with cerebral hemorrhage
2. Patients with acute infection.
3. Patients with inflammatory diseases
4. Patients with valvular heart disease
5. Patients on anticoagulant therapy
6. Patients with severe liver disease.
7. Pregnancy and Puerperium
8. Women on oral contraceptive pills
9. Patients undergone surgery within 3-6 months
10. Patients with acute myocardial infarction.

Statistical analysis:

Mean values of all parameters in subgroups were calculated by independent sample- t- test. To compare the distributions of dichotomous data viz., gender, age, smokers, presence of hypertension or diabetes and fibrinogen levels, Chi-square test was used. Association between acute ischemic stroke and fibrinogen level was assessed by logistic regression model. ANOVA test was used to assess the association between stroke scales and fibrinogen level.

All statistical analyses were performed using SPSS (software package used for statistical analysis) package. A p-value of less than 0.05 was considered to be statistically significant.

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Results:

In total, 118 patients were included in the study. 62/11. About 40% (n=47) were in the age group of 46-60 years, 37% in 61-75 years and 13% were above 75 years. Mean age was 62 years with a standard deviation of 11 years. Out of 118 study participants, 68 were male (58%) and the rest (42%) were female.

Out of 118 study participants, 14 (12%) were in mild NIHSS category followed by 40%, 20% and 28% in mild to moderate, severe and very severe categories respectively.

In mild NIHSS category, 28.6% belonged to >75 years of age compared to 2.1% in mild to moderate and severe NIHSS categories. In very severe category, this percentage was 27.3%. In all the NIHSS categories, most the participants were in 46-60 and 61-75-year age groups. Chi square test revealed a statistically significant association between age groups and NIHSS categories (P value=0.011).

The mean age was highest among those in mild (67.5 years) and very severe (65.8 years) categories. In mild to moderate and severe categories, the mean age was 58.1 years and 59.5 years respectively. There was statistically significant difference in mean age across NIHSS categories (P value=0.003).

The proportion of males was higher in all NIHSS categories except in severe category but this difference was not statistically significant (P value=0.298).

Table 1: Hypertension in different NIHSS categories

HTN	**Mild**		**Mild to moderate**		**Severe**		**Very severe**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Yes	7	50.0	22	47.8	15	62.5	28	84.8
No	7	50.0	24	52.2	9	37.5	5	15.2

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Total	14	100.0	46	100	24	100	33	100
Chi square p value=0.007(Significant)								

The prevalence of hypertension was higher in severe (62.5%) and very severe category (84.8%)compared to mild and mild to moderate NIHSS categories. This difference was statistically significant (P value=0.007).

Table 2: Diabetes mellitus in different NIHSS categories

DM	**Mild**		**Mild to moderate**		**Severe**		**Very severe**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Yes	5	35.7	20	42.6	15	62.5	18	54.5
No	9	64.3	27	57.4	9	37.5	15	45.5
Total	14	100.0	47	100	24	100	33	100
Chi square p value=0.270 (Not significant)								

The prevalence of DM was higher in severe (62.5%) and very severe category (54.5%) compared to mild and mild to moderate NIHSS categories. But this difference was not statistically significant (P value=0.270).

Smoking was reported higher by study participants in very severe category (54.5%) followed by32% in mild to moderate category followed by about 20% each in mild and severe NIHSS categories. This difference in smoking across categories was statistically significant (P value=0.029).

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Tobacco use was reported higher by study participants in severe category (33.3%) followed by 23% in mild to moderate category followed by about 21% in mild and 15% in very severe NIHSS category. This difference was not statistically significant (P value=0.453).

Alcohol use was reported higher by study participants in mild category (35.7%) followed by19.1% in mild to moderate category followed by 15% in very severe category and about 8%in severe NIHSS category. This difference in alcohol use across categories was not statistically significant (P value=0.424).

Table 3: Comparison of Mean cholesterol in different NIHSS categories

Total cholesterol	**Mean**	**SD**	**P value**
Mild	217.9	43.2	0.061
Mild to moderate	190.9	31.1	
Severe	191.4	38.1	
Very Severe	198.4	29.6	
One-way ANOVA test (Not Significant)			

The mean total cholesterol was highest in mild NIHSS category and the lowest was mild tomoderate category. The difference was not statistically significant (P=0.061).

Table 4: Comparison of Mean triglyceride in different NIHSS categories

TGL	**Mean**	**SD**	**P value**

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Mild	156.2	56.4	<0.001
Mild to moderate	108.8	46.8	
Severe	97.1	37.2	
Very Severe	102.5	30.2	
One-way ANOVA test (Significant)			

The mean TGL was highest in mild NIHSS category and the lowest was in severe NIHSScategory. The difference was statistically significant (P<0.001).

Table 5: Comparison of Mean LDL in different NIHSS categories

LDL	**Mean**	**SD**	**P value**
Mild	84.6	14.3	0.298
Mild to moderate	78.5	14.6	
Severe	75.8	12.4	
Very Severe	79.6	13.1	
One-way ANOVA test (Not Significant)			

The mean LDL was highest in mild NIHSS category and the lowest was in severe NIHSScategory. The difference was not statistically significant (P=0.298).

Table 6: Comparison of Mean HDL in different NIHSS categories

HDL	**Mean**	**SD**	**P value**
Mild	33.9	5.7	

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Mild to moderate	37.3	6.7	0.373
Severe	37.1	6.7	
Very Severe	36.8	5.9	
One-way ANOVA test (Not Significant)			

The mean HDL was highest in mild to moderate NIHSS category and the lowest was in mildNIHSS category. The difference was not statistically significant (P=0.373).

The mean TLC was highest in mild to moderate NIHSS category and the lowest was insevere NIHSS category. The difference was not statistically significant (P=0.186).

The mean hemoglobin was highest in mild to moderate NIHSS categoryand the lowest was in severe NIHSS category. The difference across the NIHSS categories was small and it notstatistically significant (P=0.734).

The mean platelet count was highest in mild to moderate and very severe NIHSS categoriesand the lowest was in severe NIHSS category. The difference in platelet counts across the categories was not statistically significant (P=0.437).

The mean serum creatinine level was same across all NIHSS categories and there was nodifference (P=0.938).

Table 7: Comparison of Serum Fibrinogen levels in different NIHSS categories

Serum fibrinogen	**Mean**	**SD**	**P value**
Mild	259.2	69.6	
Mild to moderate	438.7	107	<0.001

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Severe	608.6	130.2	
Very Severe	819.4	105.7	
One-Way ANOVA Test (Significant)			

There was difference in mean serum fibrinogen levels across the NIHSS categories. The mean was highest in very severe category (819.4 with a SD of 105.7) and lowest in mild category (259.2 with a SD of 69.6). The difference in means across the four categories was statistically significant (P <0.001).

Table 8: Comparison of HbA1c levels in different NIHSS categories

HbA1c	**Mean**	**SD**	**P value**
Mild	8.0	2.6	
Mild to moderate	7.4	2.3	
Severe	7.9	3	
Very Severe	8.3	2.9	0.507
One-way ANOVA test (Not Significant)			

The mean HbA1c was highest in very severe NIHSS category (8.3 gm%) and the lowest wasin mild to moderate NIHSS category (7.4gm%). The difference was not statistically significant (P=0.507).

The mean ESR levels was highest in very severe NIHSS category (74 with a SD of 25) andthe lowest was in mild NIHSS category (16.8 with a SD of 4.9). The difference was statistically significant (P<0.001).

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Table 9: Comparison of Serum Fibrinogen levels in different age groups

Age groups	Mean	SD	P value
≤45	589.5	177.5	0.232
46-60	551.7	215.9	
61-75	524.2	218.9	
>75	654.8	241.5	
One-way ANOVA test (Not Significant)			

The mean fibrinogen level was highest in >75 years age group and the lowest was in 61–75-years age group. The difference was not statistically significant (P=0.232)

The mean fibrinogen levels in male and female were 577.0 and 533.1 respectively. The difference in fibrinogen levels between male and female was not statistically significant (P=0.277).

The mean serum fibrinogen levels were higher in smokers compared to non- smokers and the difference was statistically significant (P<0.001).

The mean serum fibrinogen levels were higher in those who did not report alcohol use compared to alcohol users and the difference was not statistically significant (P=0.504).

The mean serum fibrinogen levels were higher in those who did not report tobacco usecompared to tobacco users; but the difference was not statistically significant (P=0.611).

The mean serum fibrinogen levels were higher in Hypertensive than non-hypertensive patients, the difference in mean was statistically significant.

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The mean serum fibrinogen levels were higher in Diabetic patients than non-diabetic patients, butthe difference in mean was not statistically significant.

Pearson correlation coefficient for the correlation between serum fibrinogen and ESR was0.794 (Good corelation) and it was statistically significant (P<0.001)

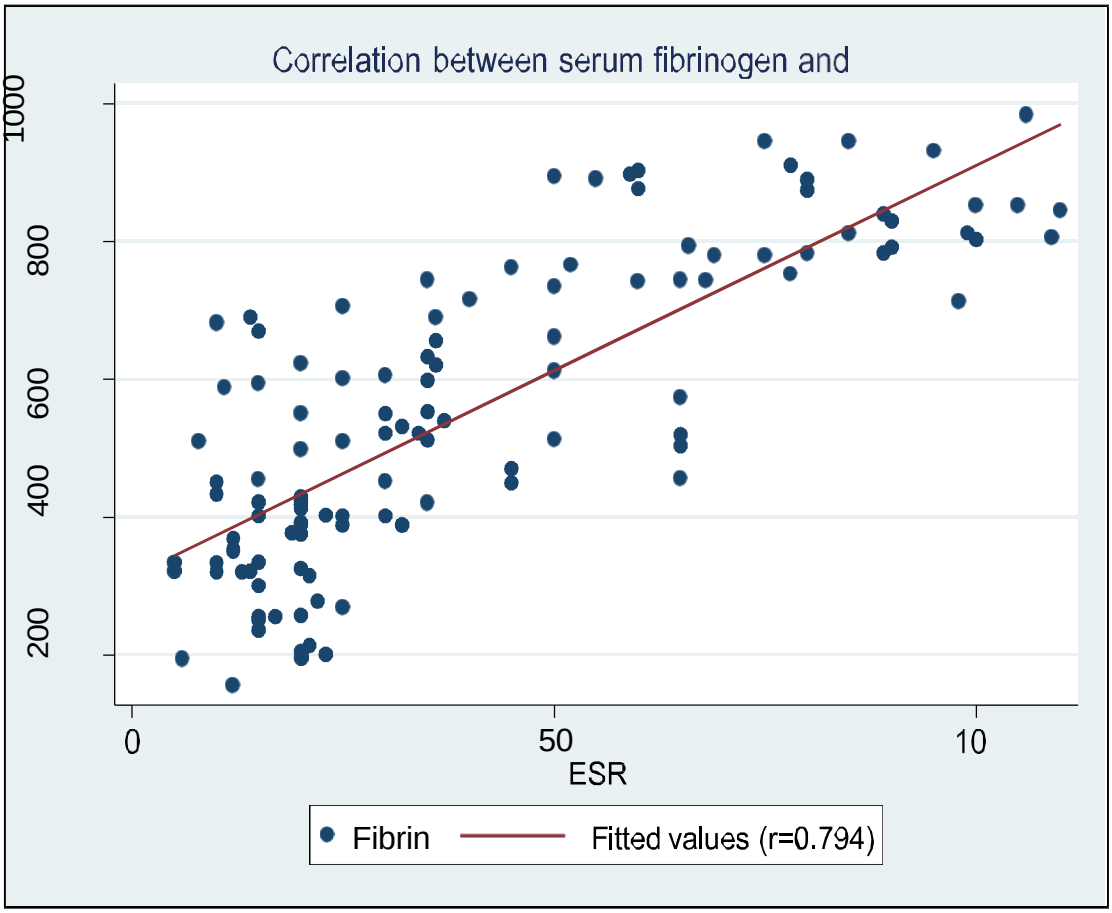

Figure 1 Correlation between serum fibrinogen and ESR

Discussion:

A total of 118 patients with acute ischemic stroke were enrolled in our study patients and they were studied dividing them into 4 groups namely mild (12%), mild to moderate (40%), severe (20%) and very severe (28%) based on NIHSS score.

Study subjects were also studied by determining serum fibrinogen levels in

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different age groups, habits like alcohol consumption and smoking, gender, comorbidities like hypertension and diabetes mellitus and fibrinogen levels were compared with severity using NIHSS score.

Samir et al[8] in their study demonstrated that increased fibrinogen levels in patients admitted to ICU for acute ischemic stroke with cutoff value >439 mg/dl showed sensitivity 92.31%, specificity 75.36%, and accuracy 84.34% for stroke. High serum fibrinogen levels in high-risk individuals, especially the diabetics, may be used as a predictor for the occurrence of acute ischemicstroke and mortality from stroke.

Dr Dhiraj Kumar et al[9] in their study showed all the stroke patients mean fibrinogen level was raised and it was 403.84 with a standard deviation of 85.73 and standard error of mean was 8.6, with a statistically significant p value (0.03). The minimum value observed was 179 among the patients andthe maximum was 530. 63% of the patients were having fibrinogen level >400 and 37% were having <400.

Srinivas B et al[10] study demonstrated plasma fibrinogen levels of cases were compared to fasting plasma fibrinogen levels of age-, sex-, and risk factor-matched controls selected randomly. Diabetic cases had significantly lower mean plasma fibrinogen than non-diabetic cases. Hypertensive cases had significantly high mean plasma fibrinogen levels than non-hypertensive cases. Non-alcoholic cases had significantly higher mean plasma fibrinogen levels than alcoholic cases. No significant difference found in mean plasma fibrinogen levels between smoker and non-smoker cases.

In our study the mean age of 62 years with SD of 11 years. The study group comprises of 68 male (57.6%) and 50 females (42.4%). Among the study group, 61.8 (73) were hypertensive, 53.33% (63) were diabetics,34.7% (41) were

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smokers,7.7% (21) were alcoholics and 22.8% (27) were having history of Tobacco use.

The mean fibrinogen level among patients was 558.4 with a standard deviation of 218.2 and standard error of mean 20.08. The mean fibrinogen level was highest in >75 years age group and the lowest was in 61–75-years age group. The mean fibrinogen levels in male and female were 577.0 and 533.1 respectively. The difference in fibrinogen levels between male and female was not statistically significant (P=0.277).

The mean serum fibrinogen levels were higher in smokers compared to non-smokers and the mean serum fibrinogen levels were higher in those who did not report alcohol use compared to alcohol users.

The mean serum fibrinogen levels were higher in those who did not report tobacco use compared to tobacco users.

In comparison with respect to gender distribution, it was found that in present study 60.19%were male and 39.81 were female. In Dhiraj Kumar et al study 56% were male 44% were female.

Mean age in present study is 62 years with SD of 11 years, it was 60.1± 9.2 in Dhiraj Kumar et al, 66.28±8.76 in M Samir et al study.

In the present Study 53.33% were hypertensive and 34.7% were diabetic. In Dhiraj kumar etal 60% hypertensive and 36% Diabetic, in M Samir et al study62.5% were hypertensive and 43.7 were diabetic.

In the present Study 34.7% were smokers and 22.8% alcoholic, In Dhiraj Kumar et al study 35.5% smokers and 41.4 % were alcoholic, M Samir et al studies showed 34% were smokers and 47% were alcoholic.

In our study the mean triglyceride is 110.27 ± 20.3 (SD), mean HDL is 36.7 ±

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9.34And mean cholesterol is 196.2 ± 31.56, which are comparable to M Samir et al studies.

The mean Serum fibrinogen levels in the present Study is 558.4 ±218.2, in Dhiraj Kumar et al 403.84 ± 85.73, and in M Samir et al538.31±42.57. Our study mean serum fibrinogen was comparable with Srinivas B et al and M Samir et al study.

In our study there was difference in mean serum fibrinogen levels across the NIHSS categories. The mean was highest in very severe category (819.4 with a SD of 105.7) and lowest in mild category (259.2 with a SD of 69.6). The difference in mean was statistically significant (P <0.001).

Similar to the above studies, the current study also demonstrated a significant increase in serum fibrinogen levels in ischemic stroke patients. The current study demonstrated that the serum fibrinogen levels corelates with severity of the disease.

Conclusion: Serum fibrinogen level was higher in patients with acute ischemic stroke. Among the patients with acute ischemic stroke, the higher serum fibrinogen level correlates with Clinical severity assessed by National Institute of Health Stroke Scale. There is a positive correlation between serum fibrinogen levels with hypertension, smoking and tobacco use. Serum Fibrinogen levels can be used as predictor for severity of Acute Ischemic Stroke. Serum Fibrinogen levels can also be used to predict the prognosis in Acute Ischemic stroke.

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