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Clinical Correlation Of Plasma Fibrinogen Level And Ischaemic Stroke

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Abstract

A definite association exists between fibrinogen and the process of atherothrombogenesis. However, the nature of the link is unclear. Although epidemiological and clinical studies suggest that the link is causal, no definite evidence exists. thrombogenesis is strongly linked to the process of atherogenesis, it follows that specific thrombogenic factors such as fibrinogen may play key roles in the process of atherosclerotic lesion formation, with subsequent effects on cardiovascular diseases. Hence impact of plasma fibrinogen levels on cardiovascular system needs to be focused on.

Keywords: Acute Ischemic stroke, Plasma fibrinogen levels

Introduction

Many prospective epidemiological studies have reported positive associations between the risk of cardiovascular disease and Plasma fibrinogen levels[1]. By mass, fibrinogen is one of the major coagulation proteins in the blood. It is also the precursor of fibrin and an important determinant of blood viscosity and platelet aggregation[2,3]. Because fibrinogen levels can be reduced considerably by lifestyle interventions that also affect levels of established risk factors (such as regular exercise, smoking cessation, and moderate alcohol consumption), there is interest in the possibility that measurement (or modification) of fibrinogen may help in disease prediction or prevention[4]. Despite that, the association of plasma fibrinogen levels with atherosclerosis and thrombosis is complicated. However, many paradoxes are present about the association of plasma fibrinogen with cardiovascular disease, and also the data and knowledge regarding the same are still incomplete.

Material And Methods

Patients admitted at Bharati Hospital in general wards and critical care units were taken, with episode of stroke first ever in life. The type of stroke being acute ischaemic non embolic with or without CT/MRI confirmation.

Study Design

A prospective, Observational study

Sample size calculation

Consecutive type of non-probability sampling was used in present study. A total of 100 consecutive diagnosed ischaemic stroke patients from our hospital were selected for study after informed consent.

Study duration

October 2018 - December 2019

Inclusion Criteria:

Patients admitted in our hospital with episode of stroke first ever in life. The type of stroke being acute

ischaemic non embolic with or without CT/MRI confirmation.

Exclusion Criteria:

1. Major renal, hepatic, and cancerous disease;
2. Surgery or major trauma in the previous month;
3. Obvious signs and clinical evidence of acquired in hospital infection;
4. Past history of coronary artery disease;
5. CT scan findings suggestive of hemorrhagic stroke
6. Old cases of cerebrovascular accidents

Transient ischaemic attack patients

Study Variables: Plasma fibrinogen levels, CT brain- plain + MR diffusion

Sample Size: Patient admitted in Bharati Hospital during study period

Sampling Technique: Convenient Sampling

Study Tools: Proforma and Laboratory Investigations along with CT brain- plain + MR diffusion

Results-

Table 1. Distribution of cases as per age group

Age Group (Years)	N	%
30-39	11	11.0
40-49	13	13.0
50-59	20	20.0
60-69	29	29.0
70-79	16	16.0
80-90	11	11.0
Total	100	100.0%
Mean Age- 64.76± 14.2 years		

Mean age of the study cases was 64.76 years with 56% of the cases being over 60 years of age.

Table 2. Distribution of cases as per gender

Gender	N	%
Male	40	40.0
Female	60	60.0
Total	100	100.0%

Male predominance was seen among study subjects with 60% males to 40% females.

Table 3. Laterality of cases as per Laterality of symptoms

Laterality	N	%
Left side weakness	68	68.0
Right side weakness	32	32.0
Total	100	100.0%

Out of 100 cases, 68% complained of left sided weakness while 32 % had right sided weakness

Plan For Analysis: Result will be analyzed with the help of biostatician using appropriate statistical test.

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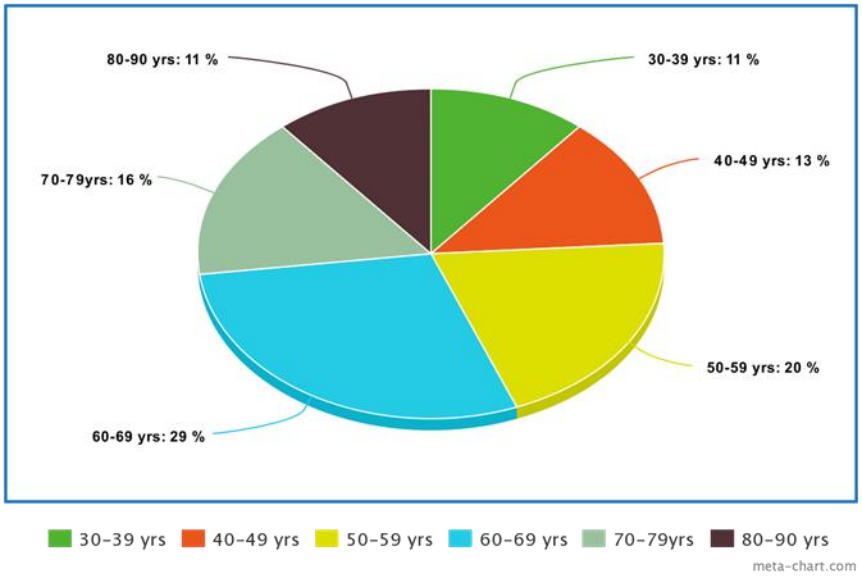
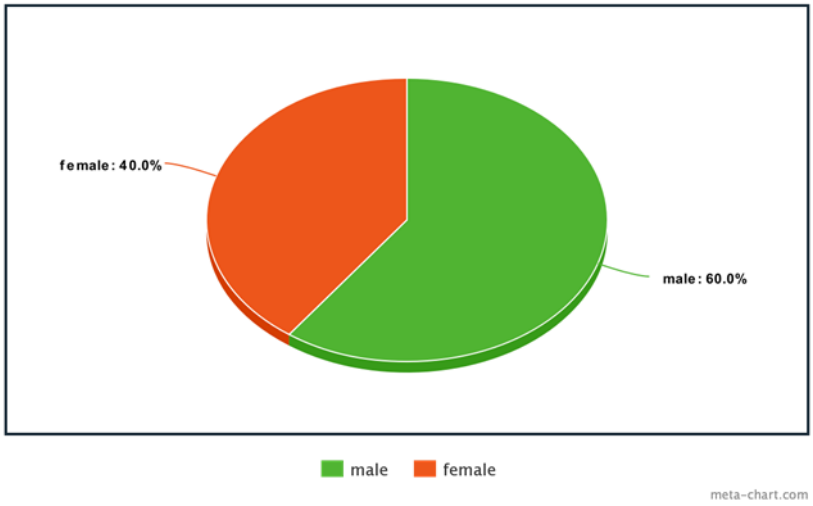
Expected Result: After analyzing the clinical profile and doing the laboratory investigation along with CT brain- plain + MR diffusion, I expect to find: The patients admitted to Acute ischemic stroke will be evaluated with reference to plasma fibrinogen levels. With above lab data, it will be interpreted whether there is any correlation between plasma fibrinogen levels and Acute ischemic stroke



gender based distribution of patients



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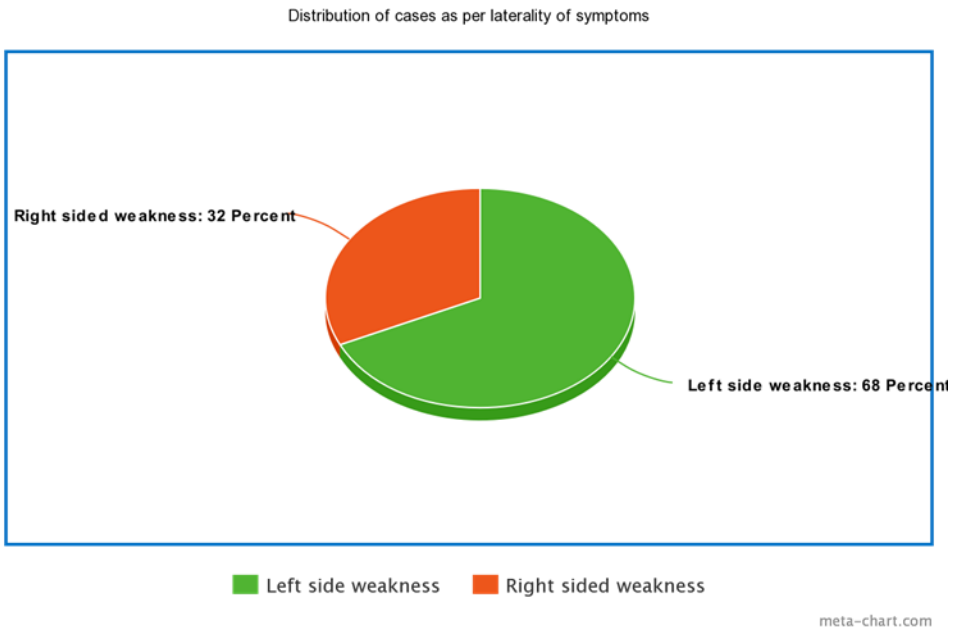

Table 4. distribution of cases as per associated co-morbidities

Co-morbidities	N	%
Diabetes mellitus	34	34.0
Hypertension	33	33.0

Out of 60 males 25 were diabetic, 8 were hypertensive while 9 male had both diabetes mellitus and hypertension, while out of 40 females, 6 had diabetes mellitus, 9 were hypertensive while 7 had both diabetes mellitus and hypertension.

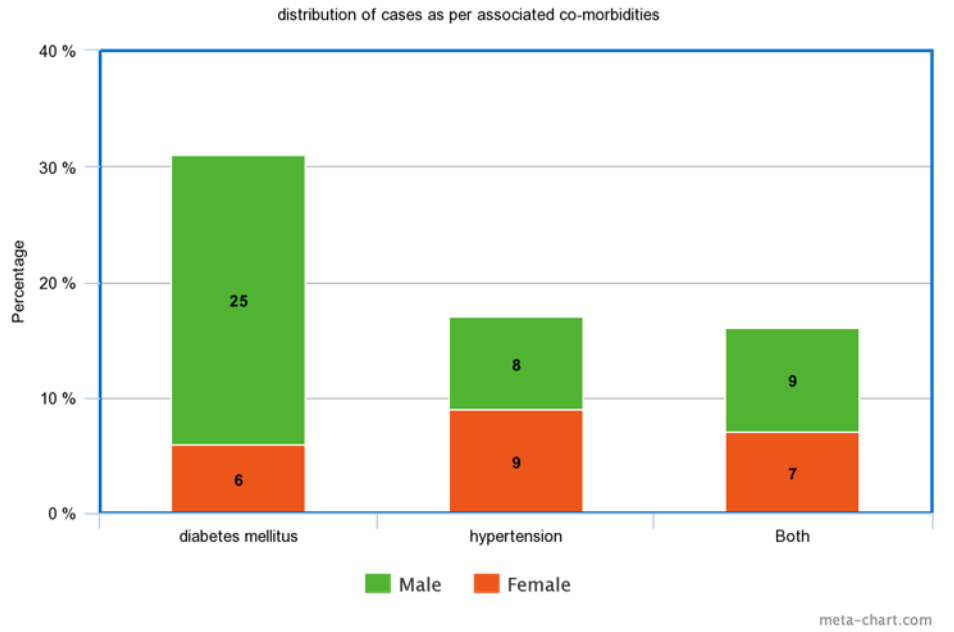

Table 5. Distribution of cases as per final outcomes

Outcome	N	%
Survived	89	89.0
Died	11	11.0

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Total	**100**	**100.0%**

Mortality rate among present study was observed to be 11%

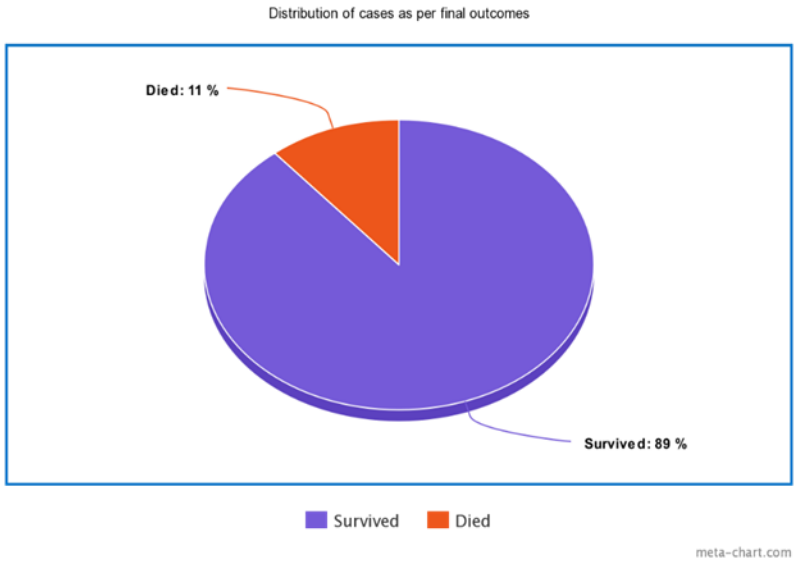

Table 6. Mean plasma fibrinogen levels among study cases

Plasma fibrinogen levels	Mean	SD	Minimum	Maximum
	414.27	**120.414**	**211**	**700**

Mean plasma fibrinogen levels among study cases was 414.27 mg/dL with standard deviation of 120.414, with variance of 14499.7371

A greater prevalence of high plasma fibrinogen level was observed in male sex (mean – 415.03 mg/dl) was noted while mean fibrinogen level in female were observed to be 414.55 mg/dl.

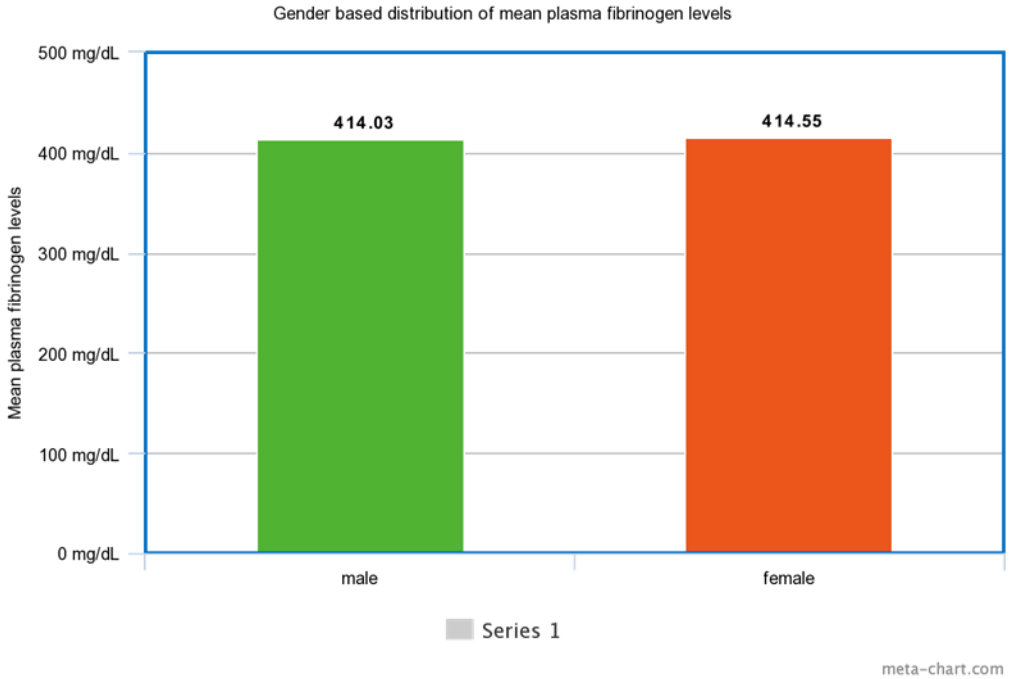

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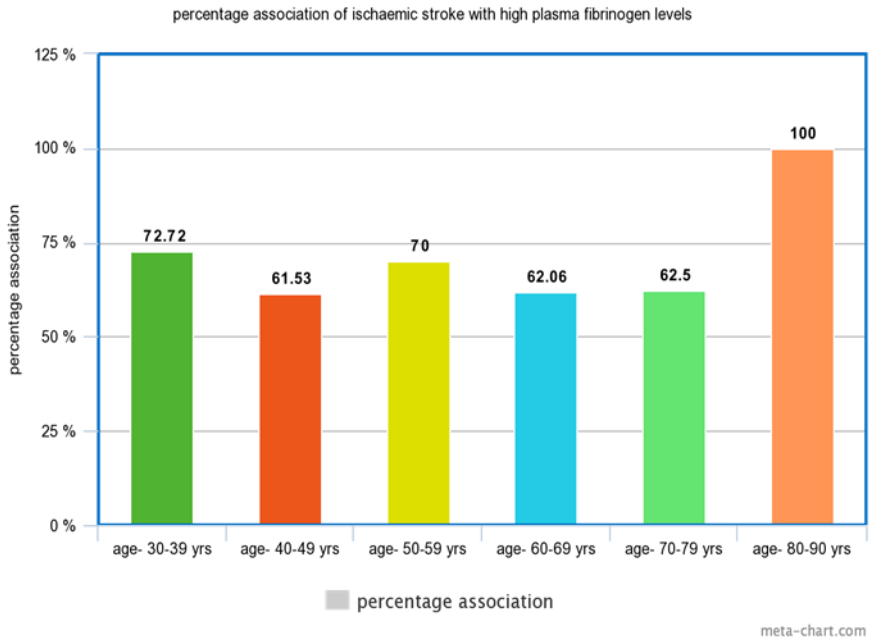
Table – 7. Percentage association of high plasma fibrinogen levels according to age groups

Age groupn[in years]	Percentage association
30-39	72.72
40-49	61.53
50-59	70
60-69	62.06
70-79	62.5
80-90	100



Percentage prediction of association of high plasma fibrinogen levels with ischaemic stroke was observed to be highest in age group 80 to 90 years – 100% association according to our study, while lowest association of around 61.53% was observed in age group 40-49 years.

Discussion

Pathophysiology

Fibrinogen's molecular weight is around 340 kDa and it is a soluble glycoprotein found in the plasma[5]. Fibrinogen has a biological half-life of about 100 h and is synthesized predominantly in the liver[6]. Fibrinogen, being the precursor of fibrin is an essential component of the blood coagulation system as a clotting factor. The minimum plasma fibrinogen level is 0.5 to 1 gm/L which is necessary for hemostasis. Many pathophysiological processes in the body, including inflammation, atherogenesis, and thrombogenesis require the presence of fibrinogen. Nevertheless, understanding of mechanics of the role of fibrinogen in thrombogenesis is less. Mechanisms proposed include the fibrinogen infiltrating the vessel wall, increasing the blood viscosity, promoting platelet aggregation and thrombus formation. Plasma fibrinogen is also a prominent acute phase reactant, and it perhaps helps in inflammation or infection (Chlamydophila pneumonia or Helicobacter pylori) implicated in cardiovascular risk may operate, in part, by increasing the reactivity of platelets. Degranulation of platelets in response to adenosine diphosphate (ADP), is augmented by fibrinogen.

Fibrinogen And Inflammation-

The interaction of integrins and leucocytes primarily mediates the inflammation. Leukocyte surface has 2 main receptors Mac-1(CD11b/CD18, α M β 2) and α X β 2 (CD11c/CD18, p150, 95). Binding of fibrinogen to MAC–1receptor results from the maturational changes occurring in the receptor during the process of cell differentiation, and is not seen in a

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resting leucocyte. Other integrins don't share the site on fibrinogen that interacts with MAC-1. Thus, ICAM-1 has a pivotal role in leukocyte adhesion to the vascular endothelium as it behaves as cell surface ligand for α-L β-2 and α-M β-2 (MAC-1) integrins, and. Fibrinogen also up-regulates and increases the concentration of ICAM-1 proteins leading to increased adhesion of leukocytes on the surface of endothelial cells, even at high shear rates inflow conditions. Moreover, the binding to ICAM-1 with fibrinogen mediates the adhesion of platelets. Cellular proliferation of cells expressing ICAM- 1 is facilitated by their interaction with fibrinogen. Fibrinogen facilitates the chemotaxis of leucocytes on binding to its integrin receptor on its surface. An increase in the free intracellular calcium and increased expression of neutrophil activation markers is one of the proposed mechanisms for the induction of pro-inflammatory changes in leukocytes. Cell-cell interaction and the interaction with an extracellular matrix such as collagen are also facilitated by fibrinogen. Hence, Fibrinogen facilitates the biomaterial provoked inflammatory response. Fibrinogen converts into 'pro-inflammatory' fibrinogen after interacting with the biomaterial, leading to the exposure of the epitope that interacts with the MAC-1 receptor for macrophages[7].

Fibrinogen And Atherogenesis-

The deposition of fibrin deposition can initiate atherogenesis and contribute to plaque formation[8]. Fibrinogen and its metabolites noticeably cause endothelial damage and dysfunction by numerous mechanisms. Many atherosclerotic lesions have shown deposition of fibrin in a large amount, which could either be in the form of mural thrombus on the intact surface of the plaque, in layers within the fibrous cap, in the lipid-rich core or distributed diffusely all over the plaque. This remarkable process appears to be compounded by reduced arterial intimal fibrinolytic activity and the plasminogen level as observed in various cardiovascular diseases[8]. Arterial intima cellular proliferation is stimulated by fibrin by providing a scaffold along which cells migrate, and by binding with fibronectin, hence stimulating the cell migration and adhesion. Intima contains fibrin degradation products, which stimulate collagen synthesis, mitogenesis, chemotactic for leukocytes, and alter endothelial permeability and vascular tone. Fibrin may be involved in the tight binding of LDL and accumulation of lipid which forms the lipid core of atherosclerotic lesions[9].

Fibrinogen And Thrombogenesis-

A fine balance between the coagulation and fibrinolytic pathways regulates thrombogenesis. Tissue thromboplastin is released from the sub-endothelium following vessel wall trauma which in turn triggers the extrinsic pathway of coagulation by activating factor VII to VIIa. The intrinsic pathway of coagulation is initiated following contact with the foreign surface, by activating factor XII to XIIa, as well as platelets. Aggregation of platelets doesn't provide adequate stability, and hence may not necessarily activate the coagulation pathway. The activation of factor X to Xa is crucial for the final common pathway of the coagulation cascade, and the further activation of prothrombin to thrombin, which facilitates fibrinogen cleavage into fibrin monomers. Sideways and end-to-end linking of these monomers leads to the formation of fibrin polymers. The stable fibrin clot is formed by the cross-linkage of fibrin polymers which is facilitated by the activated factor XIII. The final common pathway of aggregation of platelet also involved the presence of fibrinogen which helps in the cross-linking of the platelets by binding with the glycoprotein IIb-IIIa receptor on the surface of platelets. This phenomenon becomes more relevant with the advent of glycoprotein IIb-IIIa receptor inhibitors, blocking the final common pathway of platelet binding.

Conclusion

In our study there is a positive correlation between fibrinogen levels and male gender was found out. Similar data are available from epidemiological studies. But there is no significant two way interaction between fibrinogen and acute ischaemic in our study. ($p > .001$).

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