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REVIEW ARTICLE

Fibrinogen in COVID-19: Interpreting From Current Evidence

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ABSTRACT

COVID 19 has emerged as a global pandemic with high morbidity and mortality. Continuous research and understanding of the disease has led to formulation of various guidelines for the patient management. Fibrinogen plays an essential role in pathology, both as an acute phase reactant and a procoagulant. Baseline and the monitoring of the levels may help in prediction of the prothrombotic or the pro hemorrhagic states. And hence, the interpretation of fibrinogen along with clinical picture, d dimers and coagulation parameters may help in better judgement of the patient situation.

COVID 19 due SARSCoV2 has emerged to be a global pandemic affecting millions and causing significant mortality and morbidity. Caused by a positive sense RNA virus, the virus interacts with human cells via receptors like ACE2, TMPRSS2, CD147 and sialic acid receptor. With a strong ability to evade our immune system, the virus participates in proinflammatory reactions and may indirectly lead to the fatal cytokine storm. The virus is also known to cause endotheliopathy thereby causing vascular leakage, promotion of inflammation and initiation of the coagulation cascade leading to thrombosis.

The balance between thrombogenic and antithrombogenic components is essential for the maintenance of the fluidic state of the circulating blood (1). Coagulation factors, part of thrombogenic components are essential for the blood homeostasis and are normally present in an inactivated state. On encounter with appropriate stimulus like endothelial injury or tissue damage, these participate in the coagulation cascade.

COVID 19 has been a disease with varied clinical, pathological and biochemical presentations; and with better understanding of the disease various guidelines have been written to aid the management and improve the survival and morbidity. We the authors wish to review one of the ubiquitous guide markers, fibrinogen which serves as an important coagulation factor and an acute phase reactant; for its versatile role relating to coagulation, inflammation, blood viscosity and the related implications in COVID 19 management. Fibrinogen (coagulation factor I), a large glycoprotein (340kDa) is essential for the clot formation. Thrombin mediated proteolysis converts the soluble fibrinogen to insoluble fibrin which provides a structural integrity to the clots. Further, it stimulates platelet aggregation by binding to the gpIIb/IIIa receptors. A

hexameric homodimer composed of 2 Aα, 2Bβ and 2γ is encoded by a gene on long arm of chromosome 4 and is shown to have heritable changes (2). An almost exclusive product of liver synthesis, the expression is regulated both transcriptionally and post transcriptionally; thereby rendering a both constitutive and inducible expression (3). Bβ and γ polypeptide chains of fibrinogen are encoded by a three gene cluster on human chromosome four. The fibrinogen genes (FGB-FGA-FGG The normal adult range of fibrinogen is 2-5 mg/mL with a circulating half-life of about 4 days. In addition to its procoagulant role, fibrinogen affects the inflammatory response by modulating the leukocyte migration; and hence serves as an acute inflammatory reactant (4, 5). Fibrinogen along with its cleaved products like fibrinopeptide B have a proinflammatory role and have been implicated in a myriad of diseases like multiple sclerosis, Alzheimer's disease, colitis, rheumatoid arthritis. These can serve as chemoattractants, activators of NF-kB pathway, stimulate the secretion of various cytokines or interact with various adhesion molecules; and hence can play a role of DAMP(damage associated molecular pattern) in the innate immunity (6,7). In addition, its expression is modulated by a variety of cytokines and importantly IL-6 (3). Bβ and γ polypeptide chains of fibrinogen are encoded by a three gene cluster on human chromosome four. The fibrinogen genes (FGB-FGA-FGG Inappropriate activation of inflammation by coagulation cascade can misbalance the see-saw of blood homeostasis and have unfavorable outcomes (8).

Over the year of pandemic, with increasing understanding about the etiopathogenesis, the management and research to tide over the crisis has improved dramatically.

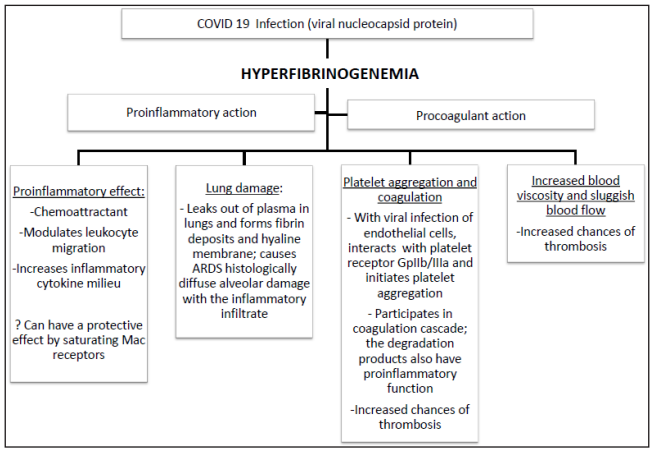

Fig. 1: Effects of hyperfibrinogenemia in COVID 19 patients ©Dr. Surabhi Jain,AIIMS, New Delhi

Fibrinogen and inflammatory state of COVID 19

Due to the infectious etiology, the fibrinogen levels are expected to rise in the COVID 19 patients as an acute phase reactant. They are proinflammatory and contribute to the innate immunity. According to Thachil, fibrinogen may have a protective effect rather than a prothrombotic effect since it saturates the Mac 1 receptor which is required for binding of the RNA virus. Increased soluble fibrinogen may antagonize neutrophil adhesion and thereby limit the inflammation (9). And hence the initial phase is marked by an elevated fibrinogen levels with a minimal rise in D-dimers.

Though for other members of the family, in vitro models have suggested the enhanced expression of fibrinogen (FGB, FGG) in the coronavirus infected cells with probable effect of SARS CoV nucleocapsid protein and hence contributing to the innate immunity (10,11).

It is believed that the leaked plasma fibrinogen on action by various inflammatory cells and thrombin, forms fibrin which gets deposited along the alveolar wall and causes fibrosis. However, studies suggest that lung alveoli may also serve as a potential local source of fibrinogen secretion during the infection. Hence, cause more inflammation along with decreased surfactant and fibrosis contributing to the defective repair of lung (12). Being a systemic inflammatory marker, fibrinogen is known to rise and serve as a marker of chronic obstructive pulmonary disease exacerbations along with metabolic syndrome and peripheral vascular disease; and hence with the predominant lung attack, COVID 19 patients with prior comorbidities may exhibit an added rise in the marker (13).

Interleukins like IL-6 and IL-1 contribute to an increasing fibrinogen levels and thereby may be indicative of an impending cytokine storm (14). Though its interaction with fibrinogen genes (FGA, FGB, FGG. A simplified way of interpreting hyperfibrinogenemea has been outlined in the figure 1.

Fibrinogen and procoagulant state of COVID 19

Varied studies have indicated the deranged higher fibrinogen profile in COVID 19 patients; however have failed to ascertain the definite prognostic and predictive role of fibrinogen. One of the meta-analysis showed the poor prognostic outcome of higher fibrinogen levels at the admission (15). In the initial phase, the acute phase reactant action of fibrinogen dominates and there is minimal thrombosis like physiological states of pregnancy or trauma.

However, with setting in of thrombosis due to inflammation and endotheliopathy, the D-dimers begin to rise and with uncontrolled thrombosis, fibrinogen levels and platelet counts begin to drop. (9) With minor thrombotic events in the early phases, disseminated intravascular coagulation can set in later leading to consumptive coagulopathy. In the early stages of the infection, coagulopathy is manifested by increased fibrinogen levels, mildly increased D-dimers, normal PT, apTT and platelet counts. Though debated, coagulopathy is thought to be associated with the thromboinflammation and the severity of the disease and not the intrinsic viral activity; and hence assessment of fibrinogen levels serves as a guide marker in many of the guidelines (16). Interpretation of fibrinogen levels in context of D-dimer levels in COVID19 hence is important before taking a judgment regarding the thrombotic state of the patient.

Han *et al.,* suggested the prognostic implication of FDPs and D-Dimers where rising levels required a more aggressive approach. Though the levels of fibrinogen were higher than the normal individuals and increased with the severity of disease; however they did not help in prognostication (17). Zou *et al.,* also suggested the higher prevalence of raised fibrinogen levels (>7g/L) in patients with severe disease(19.1%) vs mild disease (5.7%) (18).

In the study by Tang *et al.,* though the fibrinogen levels were slightly higher in the non survivors; the difference was not significant. A fraction of the non survivors (6%) showed a decreased fibrinogen levels (<1 g/L) which increased the grade of the DIC according to the guidelines of International Society on Thrombosis and Haemostasis (ISTH) (19,20).

And hence, when the decline in fibrinogen is interpreted in accordance to the rising trend of D-Dimers; a clue to the impending DIC can be hinted upon (21) named by the World Health Organization (WHO). This is unlike the classical DIC wherein the fibrinogen levels are markedly reduced. The higher levels of fibrinogen was reiterated by Li *et al.,* (median 4.3 in non survivors compared to 3.6 in survivors); however the least values were also seen in the non survivors in the later stages indicative of consumptive coagulopathy (22). Therefore a careful assessment of fibrinogen levels is required along with the D-dimers and clinical attributes in order to designate the patient in COVID19 coagulopathy or DIC; both of which can have fatal outcomes. A bleeding, anemic, hemolytic scenario with a thrombocytopenic blood picture may point towards DIC (23).

Fibrinogen assays might not be feasible in many laboratories, however monitoring the trend may play a role in the management along with the other parameters like D-dimers, platelet count and prothrombin time. A D-dimer: Fibrinogen ratio (ug/mL: mg/dL)×100 may prove as a better marker to predict thromboembolism. Studies have suggested a value>1 may hint towards a possible embolism (23, 24).

Ranucci *et al.,* studied the procoagulant pattern along with the administration of thromboembolic prophylaxis. They measured the viscoelasticity of blood with Quantra Hemostasis analyzer and attributed the higher clot firmness to the increased platelet (60%) and fibrinogen (100%) contribution to the clot strength. With the thromboembolic prophylaxis, there was a significant decrease in the fibrinogen levels and contribution of fibrinogen to the clot strength. Also, the effect of IL6 on fibrinogen synthesis was demonstrated (26).

Thromboelastography in COVID 19 patients also showed a hypercoagulable state (27,28). Further, fibrinogen proved to be a strong predictor of maximum amplitude when >441 mg/dL and hence, the chances of macrothrombosis (29).

The blood viscosity is also known to increase in critically ill COVID 19 patients which may be attributed to the high fibrinogen levels which cause erythrocyte aggregation and may lead to increased tendency of thrombosis (30).

The fibrinogen levels should be read with caution in patients with other comorbidities and on medications. Direct thrombin inhibitors can spuriously cause a low fibrinogen level measurement (31).

On the other hand, few of the antiviral drugs like nafamostat may have an anticoagulant effect and lead to decreased fibrinogen levels (32).

The level of rise in fibrinogen levels has been studied across various study groups with a range of 3-9 g/L at baseline (normal = 2-4 g/L) with a decrease at follow up in the absence of secondary infections, coagulopathies and disease progression (18, 26). Though not necessarily for COLVID 19, levels > 4 g/L pose an important risk for thrombotic events particularly deep venous and pulmonary thrombosis and hence requires thromboprophylaxis (33,34) collectively termed venous thromboembolism (VTE A fibrinogen level of <2g/L requires daily monitoring along with prophylaxis with low molecular weight heparin to alleviate the progression to DIC and it is advisable to keep the level of >1.5 g/L in bleeding individuals (35,36). Levels of <1 g/L contributes to the DIC score and patients with levels <0.5 g/L need to be spared off the thromboprophylaxis. However, the patients with other factors responsible for thrombosis like obesity, prolonged immobilization, on oral

Table 1: Interpretation of fibrinogen levels along with platelets, d-dimers, PT, apTT in accordance to the patient state in COVID-19 ©Dr. Surabhi Jain, Dr Arvind Kumar, AIIMS, New Delhi.PT- Prothrombin time, apTT-activated partial thromboplastin time, DIC-disseminated intravascular coagulation

Platelets	Fibrinogen	D-Dimers	PT, apTT	Interpretation	Management
Normal	↑↑	Normal	Normal/ ↓	Acute phase	Appropriate therapy
Normal	↔	↔	Normal	Resolution	Monitor
↓↓	↓	↑↑	↑↑	Impending DIC/DIC	Appropriate therapy
↓	↑↑↑	↑	↓/ Normal	Thrombotic predilection	Thromboprophylaxis

contraceptive may require thromboprophylaxis earlier in the disease process. A simplified approach of fibrinogen interpretation and management has been outlined in the table 1.

Fibrinogen in Pregnancy and Geriatric Age group

Fibrinogen increases in pregnancy normally and its values may as high as 370 mg/dl to 670 mg/dl (37). In the same context, Fibrinogen increases by 25 mg/dl per decade in general and reaches more than 320 mg/dl at 60 yrs and so while interpreting in COVID in these subject adequate caution should be taken (38).

Fibrinogen serves as an acute phase reactant along with a procoagulant in the COVID-19 scenario. None of the guidelines suggest it to be interpreted in isolation for COVID-19 thromboprophylaxis. It serves as a sensitive marker for the systemic inflammation; however its role in predicting overall survival is uncertain. When interpreted as an adjunct to other markers like D-dimer and FDPs along with clinical variables, it may be of an additional value and provide clue towards the shift of a prothrombotic to a pro-hemorrhagic profile; and hence requires continuous monitoring and cautious interpretation along with clinical and other lab parameters.

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