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REVIEW ARTICLE

MECHANISM OF COAGULOPATHY IN COVID 19

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ABSTRACT:

COVID 19 is a highly contagious disease caused by SARS COV2 (Severe acute respiratory syndrome coronavirus- 2). A new viral pandemic with wide range of symptoms from asymptomatic to severe respiratory failure. Some of the moderate to severe affected patients with SARSCOV2 shows derangement of coagulation system causing thrombosis and hemorrhage. What lead to these wide ranges of coagulation disorders is explained by pro coagulant state seen in patients with severe COVID 19, including inflammatory cytokine storm, activation of the complement and coagulation system, viral binding to different receptors, direct endothelial damage caused by a virus. Hence major complications of COVID 19 results from deranged clotting mechanisms such as cerebrovascular accident, pulmonary embolism, multi organ dysfunction leading to death.

KEY WORDS: Angiotensin converting enzyme 2 receptors, Cytokine storm, Hypercoagulability, Hemorrhage, Multi organ failure, Pulmonary Embolism

INTRODUCTION

Coronavirus is single stranded RNA viruses belonging to the Coronaviridae family comprising of a subfamily Orthocoronavirinae consisting of four genera: Alpha coronavirus, Beta coronavirus, Gamma coronavirus and Delta coronavirus. Of these Alpha and Beta coronaviruses particularly infect mammalian species. Gamma and delta coronaviruses infect a wide range of hosts including avian species. [1], [2].

Human coronaviruses examples HCOV-229E and HCOV-OC43 cause mild respiratory tract infection such as the common cold, in contrast with Middle East respiratory syndrome coronavirus (MERS-COV), severe acute respiratory syndrome coronavirus SARS- COV and SARS-COV-2 are highly pathogenic causing severe pneumonia. Coronaviruses infect the bronchial epithelial cells, pneumocytes and upper respiratory tract cells developing life threatening lung disease. [3]

DISCUSSION:

Novel coronavirus was first detected in late December 2019 in Wuhan, china as a case of unidentified pneumonia. WHO named the disease as COVID-19. [4]

Genomic Analysis and Receptor Binding Of SARS-COV2:

Genomic analysis reveals that there is approximately 79% homology of genetic sequence between Bat SAR CORONAVIRUS and human SARCOV2[5]. This indicates that SAR COV2 probably have originated from Bats. [6]

In addition to the respiratory system COVID 19 affects coagulation in severely infected patients, which is a major cause of mortality. [7], [8], [9]Coronavirus enter the lung via binding to ACE2 receptors. ACE2 receptors are also located over endothelial cells lining the blood vessels and lymphatic vessels. [10]

Various coagulopathies resulting from COVID 19 infection include bleeding, thrombocytopenia, hyper coagulation, pulmonary intravascular coagulation, Microangiopathy, venous thromboembolism and disseminated intravascular coagulation. [11], [12]

Other receptors to which SARSCOV2 binds include neuropilin-1 receptor, CD147 (also known as Basigin or EMMPRIN)[13], [14], CD209 (DC-SIGN), CD209L (L-SIGN, encoded by gene C type lectin domain family 4 member M - CLEC4M). Later, two promote viral dissemination. [15]and CDA209L has 80% sequence homology with CD209.[16], [17]CD 209L and ACE2 receptors are present over type ii alveolar cells and lung endothelial cells.

Thus, gene encoding L SIGN (CD209L, CLEC4M), [18] is significant because CLEC4M not only act as viral receptor, but it is also one of the three distinct receptor which determines VWF plasma level. CLEC4M has an intrinsic capacity to recognize Von Willi brand Factor glycan structure, therefore it internalizes VWF and clear it. [19]However its possible mechanism in coagulation needs further studies. Derangement of coagulation mechanism in COVID 19 is due to interplay between inflammatory Cytokine storm, Complement system and Coagulation system.

Inflammatory- Cytokine Storm:

SARS COV2 initially manifest as dry cough, sore throat, fever, malaise, myalgia, gastrointestinal symptoms like anorexia, nausea, diarrhea,[4],[20]temporary loss of taste and smell. [21]During the later period of infection, patients develop shortness of breath, dyspnoea, haematological complications like neutrophilia, lymphopenia, coagulation disturbances.[22]

Patients with severe infection can develop the cytokine storm as because when SARSCOV2 enters the body, it activates TH1cells (T helper cell 1) which upon activation release inflammatory cytokines like GM-CSF (Granulocyte Macrophage colony stimulating factor), IL6. GM CSF also activates CD14+ and CD16+ inflammatory monocytes which in turn produce IL6, TNF, and IL1.[23], [24].These cytokines also seen in patients with sepsis.IL6 has a key role in causing hyper coagulation because IL6 induces

Tissue factor expression in inflamed tissue and in bone marrow it stimulates megakaryopoiesis. [25] IL6 also stimulate production of Fibrinogen and Factor 8 which increases vascular permeability by inducing vascular endothelial growth factor production acting on the endothelial cells.[26], [27], [28]. Alveolar macrophages and other immune cells in infected tissue causes chemotaxis of neutrophils and other immunomodulatory cells at site of infection in order to resolve the infection and cause healing.

Neutrophil phagocytes the pathogen by releasing reactive oxygen species (Respiratory Burst) and by forming Neutrophil Extracellular Traps (NET). NET is the extracellular web like network of DNA and proteins formed when the nuclei of neutrophils are lost causing death of cells. NET provides a high concentration of antimicrobial substances at the site of infection and prevent the spread of the pathogen by trapping them in the web like fibrils. [29], [30], [31], [32], [33].

IL1β secreted from alveolar macrophages and the enzyme neutrophil elastase present at the site of infection are key factors contributing NET formation. Excess NET formation destroy surrounding tissue and result in micro thrombosis, thus NET histones and platelet phospholipids result in activation of coagulation process.[34], [35], [36].

Complement and Coagulation System Activation:

Following injury or infection, complement system and coagulation system activated in synchrony to regulate the invading pathogen and to limit hemorrhage.[37],[38], [39], [40].

Complement system comprises of about 30 different circulating proteins in blood. [41] It increases the humoral antibody mediated immune response and enhances the ability of phagocytic cells like macrophages and neutrophils to eliminate pathogenic organisms.[42]

Following infection, complement system gets activated and releases C5a, one of the most potent pro-coagulant factors which activates tissue factor and mannose associates serine protease 1 (mannose associated serine protease 1 – MASP1). They cleave fibrinogen and factor xiii thus activates coagulation.MASP2 further amplifies complement activity thus creating a circular loop. [40], [43], [44], [45]. Above evidence result from post-mortem studies of COVID 19 patients showing increased intra-alveolar deposit of MASP1,2, C4b, C3b, C5b-9.[46],[47],[48].

Coagulation system comprising of platelets, endothelial cells, and soluble blood proteins initiates coagulation at the site of infection. [49] Coagulation process contains two pathways Extrinsic and Intrinsic pathway, both pathways lead to common pathway Factor x activation.[50] Platelet provides the surface on which coagulation factor acts along with Platelets release mediators which favours hemostasis.[39]

Extrinsic pathway is activated by external injury or trauma it involves tissue factor and coagulation factors I, II, VII. Whereas the intrinsic pathway is activated by exposure of endothelial collagen following in vivo injury to vascular endothelium and involves the clotting factors XII, XI, IX, and VIII. [51]

Under normal circumstances human body maintains balance in procoagulant and anticoagulant activity. [51] Following infections or inflammations there is activation of

immune system with secretion of immunoglobins and secretion of complement protein via complement system activation leading to procoagulant activity in body.[51] Recent studies show that patients with COVID 19 have elevated levels of D-dimer and fibrin/fibrin degradation products.[52], [53].

Increase D- DIMER in COVID 19:

Severe COVID 19 patients show hypo fibrinolysis with resultant increase in fibrinogen levels. A recent study done on 44 patients with severe COVID 19 suggests Fibrinolysis shutdown utilizing Thromboelastography (TEG) and showed elevated maximum amplitude with hypercoagulable state and lysis at 30 min. This indicates fibrinolysis shutdown in severe COVID19 patients. However, the mechanism of a shutdown is poorly understood. [54] Liver primarily produces Fibrinogen and distributes it to plasma[55], [56]where fibrinogen gets converted into Fibrin, which is further cleaved by plasmin into D- dimer.[57]

As discussed, SARS COV2 binds to ACE2 receptors which reduce Angiotensin converting enzyme 2 (ACE2) expression leading to activation of Renin Angiotensin system (RAS) and leads to platelet adhesion and aggregation. [58] It also causes direct endothelial dysfunction leading to formation of platelet plug. [59]Increase in Angiotensin-II levels cause release of Reactive Oxygen species which oxidises the non-oxidised β2 glycoprotein 1 (which binds to VWF) to oxidised β2 glycoprotein 1. Thus resulting in the cascade of platelet adhesion, activation and aggregation. [60]

Angiotensin 2 excess also causes increase in level of plasminogen activator inhibitor (PAI-1) which is main inhibitor of fibrinolysis. [61], [62]. PAI-1 is also increased by C5a complement component.[63] A pilot observation study done on COVID 19 patients which are divided into two groups Non surviving septic patients and Septic patients with Multiorgan failure. Both groups' shows increase level of PAI-1 with Fibrinolytic shutdown throughout the observation period. [64]

Severe inflammation in COVID 19 patients causes increase in Bradykinin resulting in upregulation of Kinin Bradykinin pathway and increase in production of tissue plasminogen activator (TPA) which favours bleeding. However this increase in TPA has not been proven to counterbalance the effect of increase PAI-1.[65] Thus possible explanation why severe COVID 19 patients show both haemorrhage and thrombosis because of different sites that express either increase in tissue plasminogen activator (causing intra alveolar haemorrhage) or increase in plasminogen activator inhibitor-1 (causing micro thrombosis).[66]

C type lectin receptors CLEC4M to which SARSCOV2 bind not only act as clearance receptor for VWF but also bind and internalizes the clotting factor VIII. Thus in type I VWF disease which affects CLEC4M causes alteration of VWF levels.[67], [68] Viral infections induced inflammation increases production of thrombin and activated factor VIII also result in pro-coagulant state.[69]

Endothelial Injury:

Severe inflammation causes endothelial injury and resulting thrombosis. Activated endothelial cells causes exocytosis, microvascular inflammation and thrombosis mediated by VWF, p selectin and cytokines which are produced during exocytosis.[64] Among them as already discussed VWF causes platelet adhesion and aggregation, p selectin causes leucocyte adhesion to vessel wall.[70]

SARSCOV2 causes endothelial exocytosis by direct viral binding to ACE2 receptors present on endothelial surface, also by direct injury to endothelial cells by virus and indirectly via cytokines release.[64] Inflammatory cytokine IL6 inhibits ADAMTS13 thus increases platelet adhesion and aggregation.[71] Deficiency of ADAMST13, increases VWF further causing coagulation.[72]

LIMITATION:

Above review article mainly focussed on data collected from different literature reviews. Hence coagulopathy in C0VID 19 needs further study and mechanism of derangement in coagulation system require further experimental studies.

CONCLUSION:

SARSCOV2 infection in patients not only causes respiratory disease but also result in derangement of coagulation system in moderate to severely affected patients leading to increase clotting with resulting micro thrombi formation and increase bleeding or haemorrhage, along with their possible complications like cerebrovascular accident, pulmonary embolism, disseminated intravascular coagulation and multi organ failure.

Several hypotheses has been put forward to explain the possible mechanisms of above coagulation disorders like inflammation induces cytokine storm, complement and coagulation system activation and interaction of virus with different receptors. However, this needs further research to explain the exact mechanism of abnormal coagulation in severe COVID19 patients.

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