IMPACT OF COVID-19 ON COAGULATION

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***Abstract*: The patients who were hospitalized with COVID-19 are those who especially suffering from severe respiratory and systemic manifestations, come under the spectrum of the acutely ill medical population, there is increased risk of coagulation of blood & shown to cause various thrombic disorders in the patients. Thrombotic complications seem to emerge as an important issue in patients infected with COVID-19. Preliminary reports, clinical and laboratory findings on COVID-19 patients include thrombocytopenia, elevated D-dimer, prolonged prothrombin time, and disseminated intravascular coagulation. Present review is about impact of coagulation on COVID-19 infected patients basing upon the past review of previous coronavirus epidemics caused by the severe acute respiratory syndrome coronavirus (SARS-CoV-1) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) associated cogulation disorders and its implications for treatment.**

***Keywords*: Coagulation, SARS-CoV-1, MERS-CoV, Disseminated Intravascular Coagulation (DIC), Thrombic Micro Angiopathy (TMA), coagulopathy, thrombosis.**

INTRODUCTION:

Covid-19 has shown its Thrombotic complications which seem to emerge as an important issue in patients suffering with COVID-19. Preliminary reports have shown that infected patients commonly develop thrombocytopenia about 36.2% and they may have elevated D-dimer about 46.4%.These rates are even higher in patients with severe COVID-19 disease about 57.7% and 59.6%, respectively [1]. Emerging of these coagulation data supports that patients who are infected by this novel coronavirus are at risk of developing Disseminated Intravascular Coagulation (DIC) [1,2,3]. The Increased D-dimer and fibrin degradation products levels, and prolonged prothrombin time have been associated with poor prognosis in patients affected by the novel coronavirus[3] Both thrombocytopenia and elevated D-dimer have excessive activation of the coagulation cascade and platelets. Viral infections produce systemic inflammatory response and cause an imbalance between procoagulant and anticoagulant homeostatic mechanisms[4] . There are Multiple pathogenetic mechanisms involved, which includes endothelial dysfunction, , Tolllike receptor activation, von Willebrand factor elevation and tissue-factor pathway activation [4–6]. Platelets, upon antigen recognition, become activated and interact with white blood cells and facilitates clearance to pathogen through white blood cell activation and clot formation[7] . Platelets are key mediators of inflammation and sensors of infectious agents through the interaction of cell surface receptors and pathogens having pathogen pattern recognition receptor or immune system derivatives having immunoglobulin Fc receptors and complement receptors The activation of and the interactions between macrophages, monocytes, endothelial cells, platelets and lymphocytes play a critical role in the procoagulant effect of viral infections [6,8].

Infection due to viral, fungal, or bacterial pathogens initiates complex systemic inflammatory responses as part of innate immunity. Activation of host defense systems results in subsequent activation of coagulation and thrombin generation as critical communication components among humoral and cellular amplification pathways, a term called thrombo inflammation or immune thrombosis. [9-12]

The inflammatory response is activated through several procoagulant pathways. Polyphosphates, derived from microorganisms, activates platelets, mast cells, and FXII in the contact pathway of coagulation, and exhibit other downstream roles in amplifying the procoagulant response of the intrinsic coagulation pathway.[13] Complement pathways also contribute to activation of coagulation factors.[14]

Important aspects of the complex interactions between the immune response and coagulation and in sepsis is Pathogen-associated molecular mechanisms (PAMPs). The inflammatory effects of cytokines also result in activated vascular endothelial cells and endothelial injury with resultant prothrombotic properties[15,16]

SARS-CoV-1 associated coagulation disorders

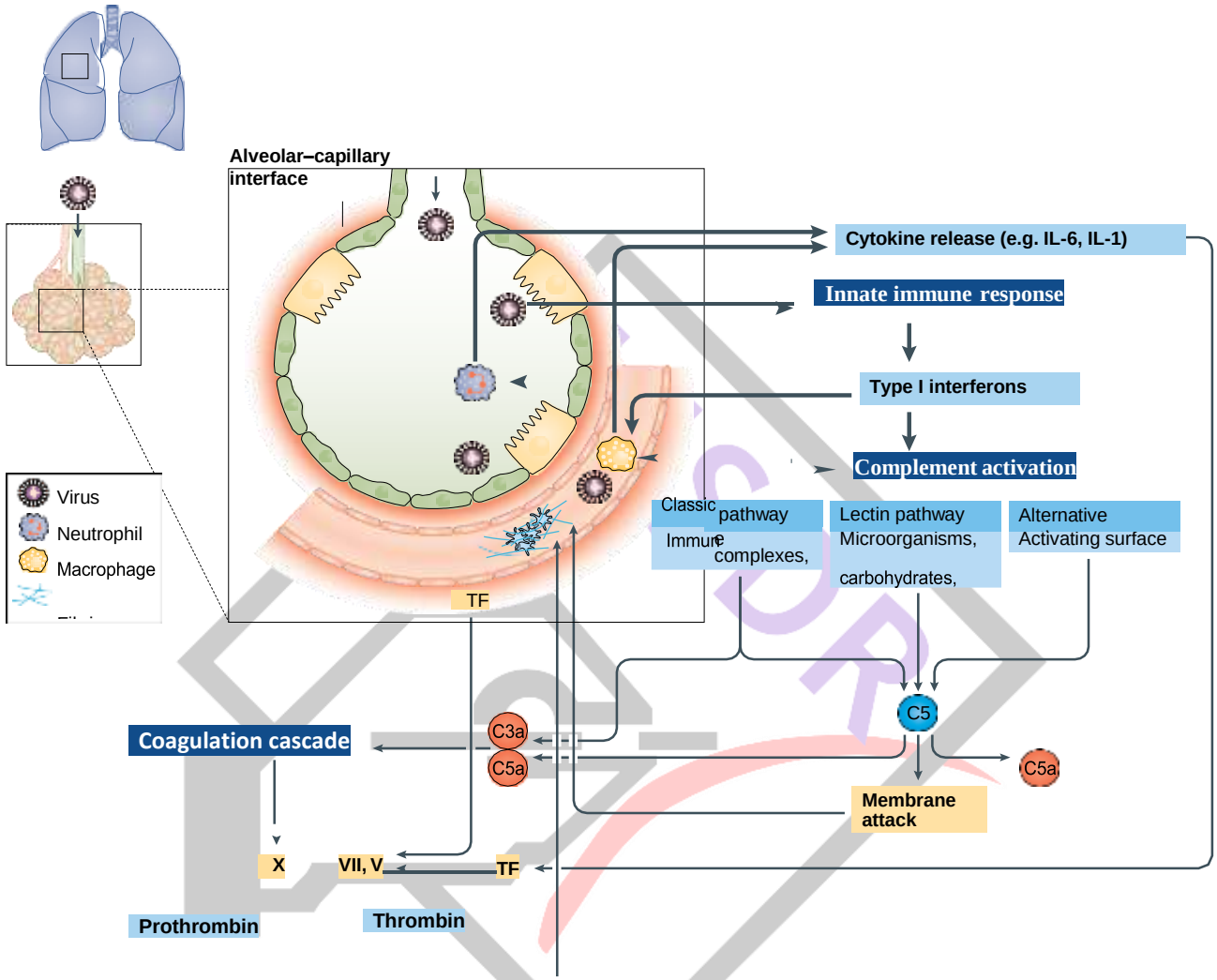
Multiple organ thrombosis, associated with polyangiitis and microcirculation disturbance[17] ischemic strokes, critically ill patients had venous thromboembolism[10] SARS-CoV-1 has also been associated with fetal complications such as oligohydramnios, intrauterine growth delay, and small fetal size due to placental circulation dysfunction, mainly attributed to intervillous and subchorionic fibrin deposition, avascular and fibrotic villi formation, and prothrombotic tendency[18]

The effects of SARS-CoV-1 in human hepatoma cells (Huh7) analysis revealed upregulation in the expression of five genes that are associated with the coagulation pathway includes, tissue factor pathway inhibitor 2 -TFPI2, early growth response 1-EGR1, plasminogen activator inhibitor 1-PAI1/SERPINE1, the phospholipid scramblase 1-PLSCR1, and thrombospondin 1-THBS1. TFPI2 inactivates the tissue factor-VIIa complex and thrombin generation, but its expression upregulation corresponds most probably to a counteractive mechanism that inhibits overt coagulation cascade activation in response to inflammation. PAI1 gene upregulation inhibits fibrinolysis and promotes fibrin deposition during inflammatory states.[19,20,21]

MERS-CoV associated coagulation disorders:

"Middle East respiratory syndrome" (MERS-CoV). MERS-CoV disease, similar to COVID-19 and SARS-CoV-1 disease, was associated with thrombotic complications and hematologic manifestations.

Thrombocytopenia, disseminated intravascular coagulopathy (DIC) is one of the major complications reported in fatal MERS-CoV cases , MERS-induced DIC, intracerebral hemorrhage, and multiorgan failure, a fatal case associated with DIC, hyperkalemia, ventricular tachycardia, and cardiac arrest has been reported.[22,23,24] Histopathologic examination revealed microthrombi present on day 4 of infection in the pulmonary vasculature and parenchymal consolidation, alveolar edema, and cellular infiltrates as the main findings of the MERS-CoV infection[25]



A substantial patients with COVID-19 mortality associated with coagulation is due to severe Thrombic Micro Angiopathy(TMA), arising in association with viral invasion of endothelial cells and triggering a robust innate immune response with widespread activation of immune cells, cytokines and complement activation. The range of clinical, laboratory and pathological findings reviewed here confirms a diffuse, small-vessel microangiopathy similar to complement-associated TMA syndromes. This COVID-19-associated TMA can be accompanied by full-blown viral sepsis, cytokine storm and/or advanced inflammation in the lungs, which would probably synergistically increase the risk of thrombosis. The COVID-19-associated thrombotic syndrome is a novel condition, which might be described as SARS-CoV-2- incited, complement-mediated TMA with or without cytokine storm.[26-29] .

Table: Comparison of COVID-19 coagulopathy and other TMA syndromes

Feature	COVID-19	CAPS	HUS[a]	Atypical HUS[b]	TTP or autoimmune (SLE) TTP	DIC
Microthromboses	Yes	Yes	Yes	Yes	Yes	Yes
Multi-organ involvement	Yes	Yes	Yes	Yes	Yes	Yes
Complement activation	Yes	Yes	Yes	Yes	Yes	No
Low platelet counts	Mild	Mild	Low	Low	Very Low	Very Low
Schistocytes	No	Rare	Yes	Yes	Yes	Yes

Neurological involvement	Yes	Yes	Rare	Rare	More common	Yes
Renal involvement	Yes	Yes	Yes	Yes	Yes	Rare
Gastrointestinal symptoms	Yes	Yes	Yes	Yes	Yes	Rare
Cardiac involvement	Yes	Yes	Rare	Rare	Yes	Rare
High LDH	Yes	Yes	Yes	Yes	Yes	Yes
Prolonged coagulation time	Sometimes	Sometimes	No	No	No	Yes
High concentrations of D-dimer	Yes	Yes	Yes	Yes	Yes	Yes
Lupus anticoagulant or aPL	Preliminary reports	Yes	Rare	Rare	Yes	Rare
Fibrinogen concentration	High	Normal	Normal	Normal	Normal	Low
Bleeding	No	No	No	No	Rare	Yes
Association with known infection	Yes	Sometimes	Yes	Sometimes	Rare	Yes
Response to plasmapheresis or plasma exchange	Preliminary reports	Yes	Yes	Yes	Yes	Not used
Treatments	Anticoagulation, resolution of underlying cause if possible, targeted complement inhibition, steroids, other immune suppression, plasma exchange, IVIG					Anticoagulation plus resolution of the underlying cause

The above table summarizes the similarities and differences between COVID-19-associated coagulopathy, DIC and other TMAs, including catastrophic antiphospholipid syndrome (CAPS), haemolytic uraemic syndrome (HUS), atypical HUS (aHUS) and thrombotic thrombocytopenic purpura (TTP).

Disseminated Intravascular Coagulation DIC typically involves disorders at multiple levels of the coagulation and fibrinolytic systems, which lead to a consumptive coagulopathy that is characterized by both excessive thrombotic activity and low levels of fibrinolytic and anticoagulant factors[30]The finding of SARS-CoV-2 in specific regions where microangiopathy was observed. [31,32]suggests that this virus might be directly participating in the thrombotic diathesis, similar to the well-established pathology of Shiga toxin-mediated HUS[33,34]

IMPLICATIONS OF TREATMENT / MANAGEMENT OF COAGULATION ISSUES:

the effects of immune suppression in patients Owing to concerns with SARS-CoV-2 infection at high risk of severe disease,the implications include the use of potent, targeted immune modulators or globally immunosuppressive treatments have largely been considered only for patients with advanced disease[35].

The standards of care for patients with non-DIC TMA syndromes includes strategies to modulate the immune– coagulation axis such as plasma exchange and intravenous immunoglobulin (IVIG)) and frank immunosuppressive strategies .

for example, treatment with steroids, rituximab or complement inhibitors[36-39]

It is suggested that patients with severe disease and pre-existing deposits of fibrin in the lungs, inducing local fibrinolysis .[40] Two anecdotal reports suggest that tissue plasminogen activator seems to be clinically helpful as a treatment for COVID-19-associated ARDS [41-43]. Currently available antiviral treatments have also demonstrated modest efficacy. In an uncontrolled case series of hospitalized patients with COVID-19 who had hypoxia, clinical improvement was documented in 36 of 53 patients treated with remdesivir[44]. A press release, an NIAID trial of remdesivir met its primary efficacy end point, but the benefits were limited to the achievement of faster recovery time without affecting the rate of death[45]

The theories supporting the use of targeted immunomodulatory treatments are:

✓ good outcomes in patients with COVID-19 after use of the C5 inhibitor eculizumab, the C3 inhibitor AMY-101 or an anti-C5a antibody[46-48]

✓ The use of IVIG for the treatment of COVID-19 has also been reported anecdotally, and several patients have been reported to have recovered promptly after receiving IVIG during a stage of rapid deterioration[49]

✓ Receiving plasma exchange followed by IVIG106. Plasma exchange is a safe and effective treatment for a compromised population and is standard of care in those with complement-mediated TMA syndromes.

PLASMA THERAPY:

The purpose of plasma exchange is to remove thrombogenic and anti-fibrinolytic molecules and cytokines associated with a TMA condition. Replacing the removed volume of plasma with normal plasma might also replenish any deficiency of natural anticoagulant or pro-fibrinolytic molecules that are depleted in DIC-like consumptive coagulopathy[50,51] plasma exchange was associated with faster resolution of organ failure and improved survival, suggesting that the replacement of plasma might be an important aspect of the treatment, which simply removes pathogenic elements from a patient's own plasma which is then put back into the patient. Plasma exchange can also specifically reduce IL-6 and IL-1β in patients with septic shock it a feasible and safe supplement or even alternative to global immune suppression for a range of patients with COVID-19 and hypoxia due to

microangiopathy and/or full blown ARDS.Plasma exchange might provide a particularly attractive vehicle for a multi-therapeutic approach by using plasma from convalescent patients with COVID-19 as the replacement source. [52-55]

Coagulation Test Surveillance: Hospitalized patients with newly confirmed or presumptive COVID-19 infection should have coagulation testing performed on admission, including D-dimer, PT, aPTT, fibrinogen, and platelet count, testing that can provide useful prognostic information. The rising D-dimer associated with non-survivors, and the rapid drop in fibrinogen associated with DIC, can be seen within 7-11 days after onset of symptoms or 4-10 days after hospitalization.

VTE Prophylaxis All confirmed or suspected COVID-19 patients admitted to the hospital should be treated with pharmacologic VTE prophylaxis, given the high inflammatory state, unless there are specific contraindications.
For obese patients, enoxaparin 40 mg twice daily Increased heparin doses may also be necessary for prophylaxis to overcome the increases in procoagulant proteins that has been observed, including high levels of fibrinogen, FVIII, and vWF, levels which are not encountered in post orthopedic joint replacement surgery or typical medically ill patients. At this time, individual patient assessment incorporating baseline VTE risk factors and bleeding risk factors with clinical judgment is required.[56]

Microvascular Thrombosis and its implications for Treatment
The physiologic anticoagulants that include activated protein C, thrombomodulin, and antithrombin have been previously studied in randomized clinical trials also demonstrated limited efficacy, however, all patients with sepsis were included, not just those with sepsis-associated coagulopathy and DIC. Post-hoc database analyses examining septic patients with laboratory proven DIC report decreased mortality examining antithrombin and thrombomodulin supplementation, and a trend towards improved survival in septic patients. [57-60]

CONCLUSION:
The present review is about the impact of covid-19 on cogulation disorders that are associated with pandemic deadly viruses including SARS & MERS .The cogulation disorders associated with include, Disseminated Intravascular Coagulation (DIC), Thrombic Micro Angiopathy(TMA), ischemic strokes, venous thromboembolism etc has to be dignosied proper in order to reduce the lethal conditions & mortality rates in population and to take atmost care in treatment so as to reduce the cause of impact of coagulation on covid-19 disease.

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