International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 11; Issue 03 (C); March 2022; Page No.520-523
DOI: http://dx.doi.org/10.24327/ijcar.2022.523.0115

Review Article

HAEMOSTATIC ABNORMALITIES IN COVID 19: A REVIEW

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A R T I C L E I N F O

Article History:
Received 13th December, 2021
Received in revised form 11th January, 2022
Accepted 8th February, 2022
Published online 28th March, 2022

Key words:
Covid 19; haemostatic; coagulopathy

A B S T R A C T

Background: Covid 19 pandemic caused by severe acute respiratory syndrome corona virus 2, mainly affects the lungs. Deranged homeostasis has been observed in patients suffering from it. Covid 19 associated coagulopathy (CAC) can cause thrombo-embolic complications in critically ill patients.
Body: The pathogenesis is likely due to endothelial injury, immobilization & an increase in circulating pro-thrombotic factors. Routine thrombo-prophylaxis with low molecular weight heparin is recommended in all patients to reduce the incidence of thrombosis.
Conclusions:
The authors present a review of the current literature available on CAC highlighting pathogenesis, clinical features & management of CAC. Systemic inflammatory response, platelet activation and endothelial dysfunction go side by side to disturb the balance between the pro and anticoagulant pathways in covid 19 disease.
Covid 19 associated coagulopathy is associated with high risk of morbidity and mortality.
This pandemic posed numerous challenges to our current medical knowledge, health care delivery and laboratory systems across the world. This review has emphasized on the various mechanisms of thrombosis, haematological aspects of the disease and anticoagulation prophylaxis in covid-19 patients.

INTRODUCTION

Covid 19 was first reported in the city of Wuhan, China in December of 2019 and has since been rapidly spreading throughout the world causing a pandemic[1]. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS COV-2). [2] Bats and birds are known viral reservoirs and are known for animal-to-animal-to human transmission. [3] This pandemic is attributed to human-to-human transmission caused by respiratory droplets such as coughing, sneezing and by indirect contact with contaminated surfaces or objects including thermometer and stethoscope. [4]

Other studies also show that the virus is found in saliva, faeces, urine and semen. [5] The most common symptoms are respiratory but gastrointestinal, neurological and other atypical symptoms can also be seen. [6]

The SARS- COV2) results in novel coronavirus pneumonia which is accompanied with excessive inflammation, hypoxia, immobilization and disseminated intravascular coagulation. These conditions may predispose a patient to venous and arterial thromboembolism. Coagulation dysfunction is a major cause of death in severe covid-19 patients. [7]

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After respiratory infection, SARS COV2 accesses the lung by infecting the pulmonary epithelial cells. In the first step the SARS COV2 Spike glycoprotein binds with angiotensin converting enzyme 2. [8]

The next step is the cleavage of viral protein which is done by host cellular proteases. After proteolytic processing the viral S protein undergoes irreversible conformational changes that facilitates virus entry via the merge of the virus to the host cell membrane. [9]

In the absence of the exogenous or membrane bound protease SARS COV-2 is internalized via clatharin or non clathrin mediated endocytosis. After the entry of the virus the pH in the endosomes decreases and then low pH activated cathepsins which triggers the fusion pathway and releases the SARS COV-2 genome. [10]
The release of viral RNA is followed by active transcription and translation of viral proteins. The rapid production of virus by the cells induces the production of several proinflammatory cytokines. [11]

The increase of inflammatoryinfilterates in the lungs provides the accumulation of immune cells. The immune cells increase interleukin[IL-1β], tumor necrosis factor, IL-6, IL-8 and chemokinase. [12]

These newly released cytokines and chemokines are responsible for the activation of inflammatory cells to the infection site which is the characteristic of the severe acute respiratory syndrome. [13]

During the onset of inflammation in the airways, the presence of abundant exudate containing fibrinogen promotes the generation of persistent intra-alveolar fibrin deposits formed by the proteolytic activity of coagulation factors and local thrombin generation. Excessive deposits of fibrin in the lungs provides an ideal environment for fibroblast adhesion and collagen deposition in the alveolar space, replacement of functional parenchyma by stromal cells and development of pulmonary fibrosis. Fibrin can also directly impair lung function, inactivating the surfactant leading to loss of lung compliance and eventually respiratory failure and fatality. [14, 15]

In the present review we are focussing on the association between the pathophysiology of coagulation and covid-19 and strategies that help in the management and treatment of covid 19 associated coagulopathy.

Pathogenesis

The proposed pathogenesis of hypercoagulability in covid-19 is that all the three components of the Virchow's triad appear to be involved i.e endothelial injury, stasis and hypercoagulable state. Endothelial injury is evident from the direct invasion of endothelial cells by SARS COV-2. [16]

Increased angiogenesis was also seen in these patients. [17] Increased cytokines like IL-6 and various acute phase reactants in covid-19 are also released which leads to endothelial injury. [18]

There is also activation of alternate and lecithin complement pathways, CD4 and mannose-bindings protein associated serine protease 2 leading to further endothelial cells injury. [19]

The use of intravascular catheters can also cause direct endothelial cell injury. Stasis is due to immobilization in all hospitalized patients. A hypercoagulable state is seen due to several coagulation abnormalities from elevated von Willebrand factor, factor VIII, D-dimer, fibrinogen, neutrophil extracellular traps, prothrombotic mucoparticles and anionic phospholipids. [20]

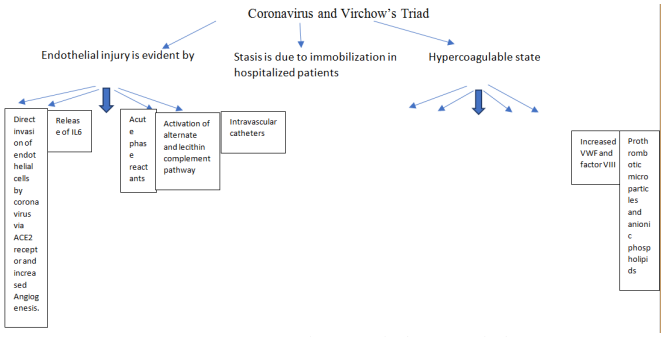

Figure 1 Coronavirus & Virchow's Triad
Increased d-dimer increased fibrinogen & neutrophil extracellular traps

Elevated levels of D-dimer have been observed to correlate with severity of illness and 28-day mortality. [21] The overproduction of pro-inflammatory cytokines and the overactivation of immune cells during covid infection is known as a cytokine storm. [22] Proinflammatory cytokines like IL-1, TNF AND IL6 further enhances local procoagulant responses by inducing TF expression in monocytes. [23]

Clinical manifestation and complications of covid 19 coagulopathy The emergence of thromboembolic complications and subsequent dysfunction is common in covid-19. [24] In covid 19 patients, over inflammatory responses due to systemic infection are linked to endothelial dysfunction and mainly affect both the venous and the arterial vascular disease. [25] A recent study on 1026 covid patients showed that 40% of cases were at risk of venous thromboembolism when they were referred to the hospital. [26]

Another study on 184 covid-19 patients showed incidence of venous and arterial thrombosis. [27] Wichmann etal described autopsy findings in 12 covid 19 patients revealing deep venous thrombosis in 7 of 12 unsuspected patients (58%). Pulmonary embolism was the direct cause of death in 4 patients. In all patients SARS COV-2 RNA was detected in lungs in high concentrations, Viremia in 6 out of 10 and 5out of 12 patients demonstrated high viral RNA titers in the liver, Kidney and heart. [28]

Coagulation abnormalities

Covid 19 is associated with a hypercoagulable state. Coagulation anomalies and clinical features observed in covid 19 associated coagulopathy are different from DIC. [29] Abnormal coagulative parameters are associated with poor prognosis in patients with novel coronavirus pneumonia.

Table 1 comparison between features and investigations of covid 19 coagulopathy and DIC

Features	Covid 19 coagulopathy	Disseminated intravascular coagulation
Major clinical findings	Thrombosis	Bleeding
Pulmonary involvement	++++	++
Prothrombin time	Normal/↑	↑
APTT (activated partial thromboplastin time)	Normal/↑	↑
Platelet count	Normal/↓	↓↓↓
Fibrinogen	↑	↓
D Dimer	↑↑↑	↑
VWF and F VIII activity	↑	↑
Antithrombin	↑	↓
Anticardiolipin antibody	Positive	Negative
Protein C	↑	↓

Management and treatment of coagulation disorders in covid-19 It is recommended to start prophylactic dose with low molecular weight heparin (LMWH) in all acutely ill hospitalized patients unless contraindicated. [30] The recommended prophylactic dose of LMWH for patients with creatinine clearance > 30ml/min is 40mg once daily and 30 mg once daily for creatinine clearance 15-30 ml/min.

Several studies showed D-Dimer levels being positively correlated with risk for VTE or illness severely. D-dimer levels were in the range of 1600-40,000 mg/ml. (Normal range<500ng/ml). [31]

Tissue plasminogen activators can be used in cases of arterial thrombosis. Patients with documented VTE due to covid need at least 3 months of anticoagulation post discharge from the hospital with appropriate follow up. Rivaroxaban 10mg daily for 31-39 days is considered as an alternative as outpatients prophylaxis in such high risk patients.[32]

Anti-inflammatory agents like tocilizumab (inhibiting IL-6 pathway and complement cascade activation) is used in initial days of severe covid 19 patients. [33] Corticosteroids are used to reduce the risk of deaths in covid 19 patients with ARDS. [34]

CONCLUSION

Systemic inflammatory response, platelet activation and endothelial dysfunction go side by side to disturb the balance between the pro and anticoagulant pathways in covid 19 disease. Covid 19 associated coagulopathy is associated with high risk of morbidity and mortality. The author also contrtacted covid 19 in April 2021 and had high raised d-dimer levels for over six months.

This pandemic posed numerous challenges to our current medical knowledge, health care delivery and laboratory systems across the world. This review has emphasized on the various mechanisms of thrombosis, haematological aspects of the disease and anticoagulation prophylaxis in covid-19 patients. Participation in clinical trials is encouraged to improve our understanding of pathogenesis and management of coagulopathy in covid-19.

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How to cite this article:

Geetanjali Sharma and Sushrut Sharma (2022) 'Haemostatic Abnormalities in Covid 19: A Review', *International Journal of Current Advanced Research,* 11(03), pp. 520-523. DOI: http://dx.doi.org/10.24327/ijcar.2022. 523.0115

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