International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

A Detailed View on COVID-19 and Coagulopathy

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Abstract: ***Background: Corona Virus disease (COVID-19) rapidly spreading pandemic was initially found as a cluster of severe pneumonia cases in December 2019 reported in Wuhan, Hubei province, China. Infection with the virus, can be asymptomatic or mild to severe symptomatic disease causing Acute viral pneumonia like symptoms leading to fatality in the least possible time if untreated. The pathological cause of this is severe coagulopathies in the microvasculature primarily in the lungs causing hypoxia and later multiorgan failure. Though thrombolytics play an important role, it fail to recover the patient completely, and if so may have thrombolytic effects in other organs too which lead to complications. Objectives: The primary focus of this presentation article is on causation of coagulation mechanism in COVID-19 disease, resulting in multiorgan failure. Conclusion: The COVID-19-associated coagulopathy (CAC) are distinct from those seen with bacterial Sepsis-Induced Coagulopathy (SIC) and disseminated intravascular coagulation (DIC). The CAC usually shows increased D-dimer and fibrinogen levels with minimal abnormalities in Prothrombin time and platelet count.***

Keywords: Coagulation mechanism, COVID-19 coagulopathy

1. Introduction

Corona virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is an ongoing global health emergency. The disease name was subsequently recommended as COVID-19 by the World Health Organization. Meanwhile 2019-ncov was renamed SARS-CoV-2 by the International Committee on Taxonomy of Viruses. The transmission of this virus is via droplets and close contact and Feaco-oral transmission. [1] The median duration of RNA detection in the stool was 22 days in the sputum and saliva- 28days and in the serum 16 days. SARS-Cov-2 binds to host endothelial cells via the Angiotensin converting enzyme (ACE-2) receptor(R)-a metallo peptidase which is present in all major organs particularly high in the lungs, heart, veins and arteries. Its protein Expression causes macro and micro vascular thrombosis are formed through the gap junctions between pericytes of blood vessels in all major organs [2]. Platelets after getting exposed to Covid infection triggers the release of Platelet microbial proteins, peptides, Platelet factor (PF)-4, RANTES, and fibrino peptide B. The induction of a cytokine storm, suppression of antiviral immunity and the activation of proinflammatory response is the root cause of pathogenecity both in SARS and COVID-19. CoV-2 differs from SARS-CoV in interferon-antagonizing and inflammasome-activating properties [3].

Clotting Mechanism [4].

After injury to endothelium, there is activation of pericytes and fibroblasts. Simultaneously Activated factor VIIa circulating in blood binds with tissue factor (TF) and activates the factor X to Xa generating thrombin. This thrombin activates platelets via Protease activated receptors. The platelets adhere to Subendothelial collagen via Glycoprotein IB (GP IB) receptors. Gp IB receptors in turn bind to factor XI which helps in localising factor VIII to site of endothelial disruption via carrier protein VWF. Factor XIa mediates activation of factor IX to IXa, wherein Factor VIIIa serves as cofactor in this mechanism. Factor IXa mediates activation of X to Xa where in Factor Va serves as a cofactor for this mechanism. Meanwhile partially activated Factor V is released from Platelet Granules upon platelet activation. Factors V, VIII, XI are involved in sustained procoagulant responses (Intrinsic pathway). Single thrombin activated platelet exposes 12000 copies of receptors that concentrate fibrinogen for fibrin formation. The Fibrinogen with factor XIII is the final thrombin substrates that stabilize Haemostatic plug. To avoid interruption in microvasculature of various organs an *inhibitory* mechanism for coagulation is regulated by factors like – i) TF pathway inhibitor which Neutralises factor Xa when in complex with TF-FVIIa and ii) Antithrombin Neutralises Xa & thrombin. These inhibitors are increased only when TF is exposed at high level [4].

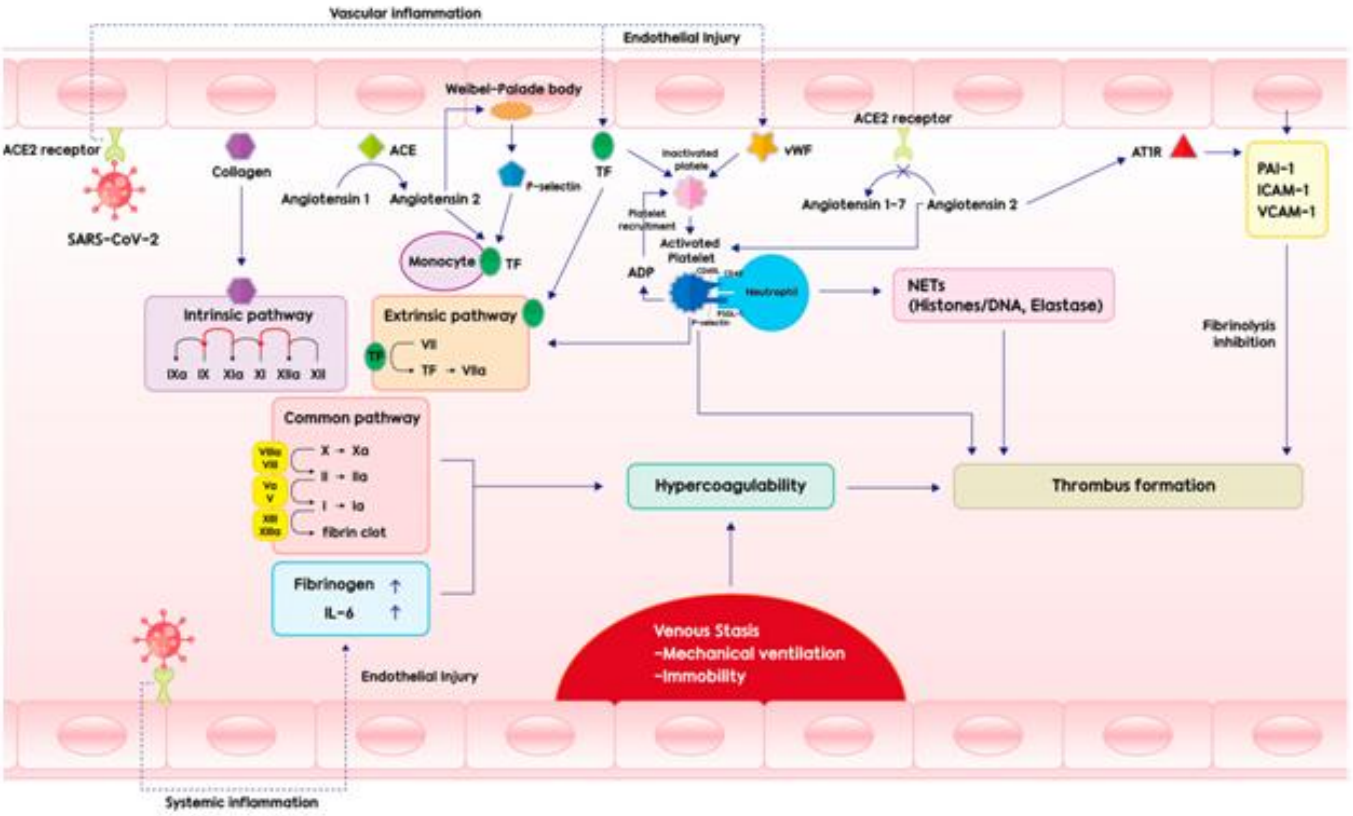

Figure 1: Pathophysiology of thrombosis in patients with COVID-19. Abbreviations: ACE, angiotensin-converting enzyme; TF, tissue factor; vWF, von Willebrand factor; ADP, adenosine diphosphate; ACE2 receptor, angiotensin-converting enzyme 2 receptor; AT1R, angiotensin II type 1 receptor; NETs, neutrophil extracellular traps; PAI-I, plasminogen activator-1; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; IL-6, interleukin-6.[16]

Fibrin and D-Dimers [5, 6]

During clotting mechanism plasma fibrinogen is converted into fibrin monomers by enzymatic thrombin. These Monomers are linked at C terminal appendages of the γ chains by factor XIIIa resulting in dimerisations and form the clot. Later as a part of thrombolysis by plasmin, proteolysis of this "crosslinked" fibrin generates fragments D-Dimers and E as terminal products. If proteolysis occurs in direct fibrinogen or non-cross linked fibrin, (non-XL-Fg) it results in formation of monomer fragment D. Hence the dimeric D-domain therefore may serve as indicator of *in vivo* fibrin formation.

The values of D-Dimers are an index of fibrin turnover in the circulation and a single measurement is adequate to assess the fibrinolytic status. As D-Dimers are not artificially generated *in vitro* during blood collection, its measurement more consistently reflects *in vivo* haemostatic activity. Its absence excludes the presence of intravascular thrombus. [7]

Coagulopathy activation in COVID-19: Pulmonary vascular thrombosis may occur as a result of hypoxia, which stimulates coagulation. Within hours of infection with Covid infection proinflammatory reactions takes place resulting in anaphylatoxins (c3a and c5a) release, and C5a signaling protein activates cytokine storm. A hypercoagulable inflammatory state in small vessels of lungs causes diffuse alveolar damage. Later lymphocyte exhaustion, immune paresis, Imbalances between complement, extrinsic and intrinsic coagulation pathways contributes to a net procoagulant state in the microvasculature of various critical organs leading to multi organ damage [8]. Most cases of COVID -19 lung infections showed signs of pale areas with firm, reddish-blue areas with high capillary-to-fiber ratios [9].

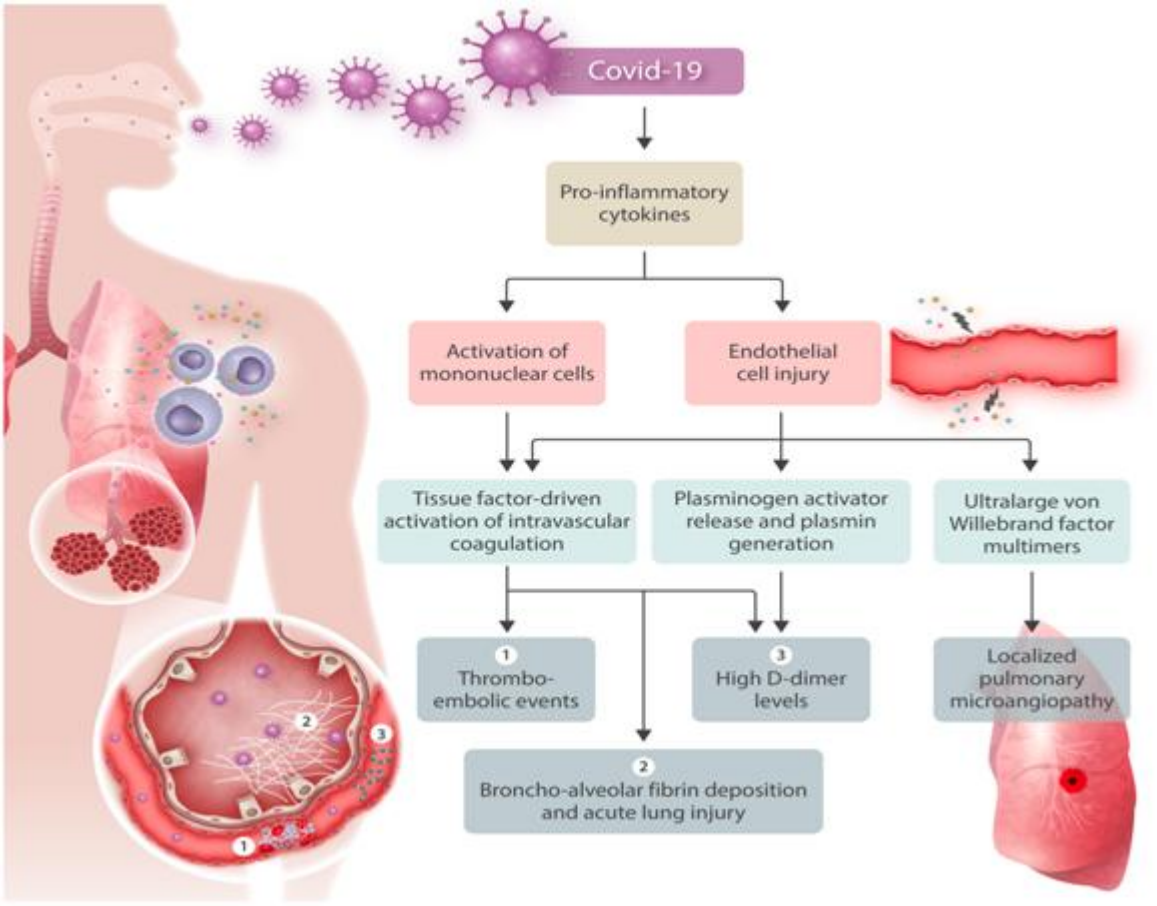

Figure 2

In many cases laboratory tests showed elevated levels of D-dimer, Raised C-reactive protein, increased Lactate Dehydrogenase (indicating tissue Damage) as well as mild thrombocytopenia. But abnormalities in prothrombin time, partial thromboplastin time, and platelet counts are relatively uncommon in initial presentations. The NLRP3* inflammasome is a critical component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines (IL-1β/IL-18) in response to microbial infection and cellular damage play a key role in coagulopathy. Elevated cardiac enzyme concentrations with normal fibrinogen and platelet levels are early features of severe pulmonary intravascular coagulopathy [9, 10, 11]. Elevated D-dimer at admission is associated with increased mortality. Rising D-dimer after admission precedes multiorgan failure &Longer duration of hospital stay associated with increasing D-dimer indicates development of Sepsis physiology.

Various reports have been published regarding the levels of D-dimer and the severity of COVID-19. While in some studies in-hospital mortality was associated with a high level of D-dimer (> 1μg/ml) on admission, other studies found no significant difference in D-dimer level between severe and non-severe patients (*4,5,6*). It should be considered that D-dimer assays are not necessarily comparable due to different calibrators, detection antibodies and methods (*6*). High levels of D-dimer have been associated with 28-day mortality among patients with infection or sepsis. The systemic pro-inflammatory cytokines contribute to plaque rupture through local inflammation, induced procoagulant pathway at multiple levels, such as induction of coagulation activation by proinflammatory cytokines of TNF, IL-1, IL-6 and IL- 12, and haemodynamic alterations are mechanisms involved in predisposition to ischaemia and thrombosis (*17*). The most haemostatic abnormalities in patients with COVID-19 requiring greater mechanical ventilation, ICU admission, or death, were mild thrombocytopenia and increased levels of D-dimer, indicating the presence of some forms of coagulopathy with increased risk of thrombotic events [(17).]

Investigations and assesment of coagulopathy [12].
Coagulopathy defined as spontaneous prolongation of the prothrombin time > 3 seconds or activated partial thromboplastin time > 5 seconds as independent predictors of thrombotic complications. Coagulopathy reflects resultant thrombo inflammation and not intrinsic viral activity.

Evaluation of Coagulopathy in COVID-19 case [13].
The routine investigations for COVID-19 coagulopathies to be followed are:

- Hemostasis function
- Lymphocyte count
- Significantly elevated D-dimer level.
- Prolonged prothrombin time
- Platlet count
- Fibrinogen

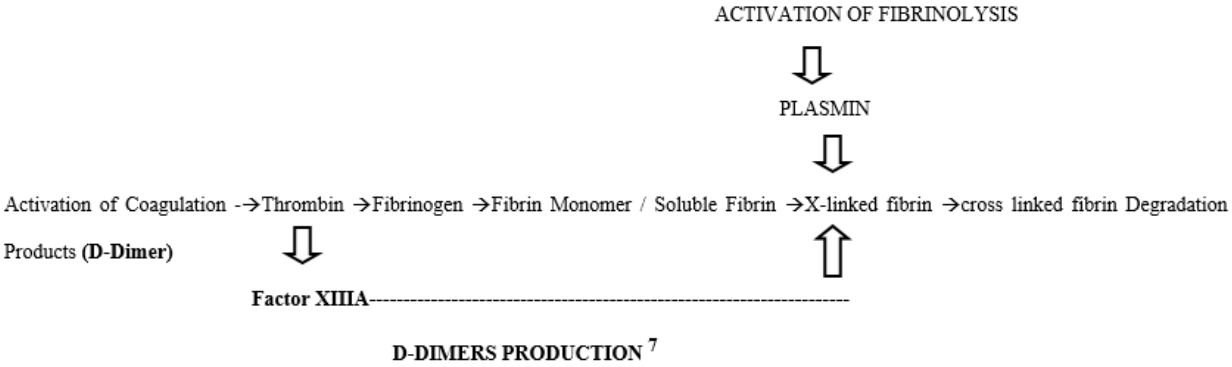

Figure 3

Special Investigations:

- CT Lung scan
- A ventilation
- Perfusion scan (V/Q) lung scan followed by pulmonary Angiography in conjunction with a low probability lung scan is generally considered to be the standard diagnostic strategy.
- DD when measured with a quantitative assay, is nearly always increased in acute PE (sensitivity 85%–99%), and a low value virtually rules it out.

Management

Coagulopathy profile should be monitored frequently as depending on the severity of the case. It should be managed as it would be for any critically ill patient, following the established practice of using thromboembolic prophylaxis for critically ill hospitalized patients, and standard supportive care measures for those with sepsis-induced coagulopathy or DIC. Presently the current data do not suggest the use of full intensity anticoagulation doses unless otherwise clinically indicated [14]. A metaanalysis reported decreased mortality with the use of early low-molecular weight heparin (LMWH) in a non-COVID-19 ARDS population. It suggests that heparin may possess anti-viral properties by acting on SARS-CoV-2 surface receptor binding proteins and inhibiting viral attachment. [15]

2. Conclusion

The COVID-19-associated coagulopathy (CAC) are distinct from those seen with bacterial Sepsis-Induced Coagulopathy (SIC) and disseminated intravascular coagulation (DIC). The CAC usually shows increased D-dimer and fibrinogen levels with minimal abnormalities in Prothrombin time and platelet count.Coagulopathy is a common characteristic of severe COVID-19disease as part of the systemic inflammatory response syndrome. Hematological changes that can occur are: elevated D-dimer, prolonged PT and aPTT, thrombocytopenia, and/or elevated fibrinogen levels. COVID-19 is more characterized by thrombotic events that are associated with coagulopathy, especially venous thromboembolism. Hemorrhagic events are not so frequent in the course of the disease. The severity of COVID-19 infection is represented by the worsening of laboratory parameters related to coagulation, while the improvement of these parameters, together with the relief of symptoms suggests a positive evolution of the disease.

References

[1] Kit-San Yuen *et al*. SARS-2 and COVID -19, Cell Biosci. 2020; 10:40. Published online 2020, Mar. 16, doi: 10.1186/s13578-020-00404-4.
[2] Richard C. Becker, J, COVID-19 update: COVID-19-associated coagulopathy, Thrombolysis. 2020 May 15: 1–14. doi: 10.1007/s11239-020-02134-3.
[3] Zhou P, Yang XL *et al*. A pneumonia outbreak associated with a new coronavirus of probable bat origin. 2020; 579(7798):270-273.- 03 February 2020
[4] Tanaka.KA*et al*. Blood Coagulation: Hemostasis and Thrombin Regulation, Anesthesia and Analgesia, 01 May. 2009; 108(5):1433-1446.
[5] Brenner B, Francis CW, Marder VJ. The role of soluble cross-linked fibrin in D-dimer immunoreactivity of plasmic digests". J Lab Clin Med. 1989; 113:682-8.
[6] Pfitzner SA, Dempfle CE, Heene DL. Fibrin detected in plasma of patients with disseminated intravascular coagulation by fibrin-specific antibodies consists primarily of high molecular weight factor XIIIa-crosslinked and plasmin-modified complexes partially containing fibrinopeptide. A. ThrombHaemost. 1997; 78:1069-78.
[7] Wakai A, Gleeson D. Winter, Role of fibrin D-dimer testing in emergency medicine, Emerg.Med J: first published as 10.1136/emj.20.4.319 on 1 July 2003
[8] Anoop J. Chauhan*et al*, COVID-19: a collision of complement, coagulation and inflammatory pathways, First published: 30 June, 2020.
[9] Van Beusekom Mary. News Writer, Autopsies of COVID-19 patients reveal clotting concerns, Filed Under, COVID-19, | CIDRAP News, May 07, 2020
[10] Marcel Levi *et al*, Coagulation abnormalities and thrombosis in patients with COVID-19, Published online- may, 11, 2020.
[11] Jean M, Connors Jerrold, H Levy *et al*. COVID-19 and its implications for thrombosis and anticoagulation, Perspective June 4, 2020.
[12] Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J ThrombHaemost.2020; 18(4).
[13] Mr. Saskiamiddeldorp *et al*. Incidence of venous thromboembolism in hospitalized patients with COVID-19; 2020; 18(8):1995-2002. doi: 10.1111/jth.14888. Epub 2020 Jul 27.

[14] Brandon M et al. Coagulopathy in COVID-19: Review and Recommendations"
[15] 15. Evangelos.Terpos et al. Hematological findings and complications of COVID 19 13 April; https://doi.org/10.1002/ajh.25829; American Journal of Haematology. 2020; 95(7).
[16] Seo, J.-W.; Kim, D.-Y.; Yun, N.; Kim, D.-M. Coronavirus Disease 2019-Associated Coagulopathy. Microorganisms **2022**, 10, 1556.
[17] Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E, et al. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up. J Am CollCardiol. 2020 Jun 16;75(23):2950-2973 doi:10.1016/j.jacc.2020.04.031.

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