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Literature Review on COVID-19 and Its Association with Anticoagulation Pathway and Thrombosis

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Introduction

The SARS-CoV-2 virus causes Coronavirus Disease 2019 (COVID-19) disease which usually manifests with respiratory symptoms.[1] Fever, cough, myalgia, and fatigue are common in patients. There are more male cases (60%) than in female cases. Like the MERS-CoV and the SARS-CoV, the SARS-CoV-2 is also a beta virus belonging to Coronaviridae family. SARS-CoV-2 has spike proteins that are responsible for the tissue tropism that the virus displays. SARS CoV-2 seems to preferably chooses respiratory epithelium where it enters through angiotensin-converting enzyme.[2] Middle East Respiratory Syndrome is caused by the MERS-CoV virus, also known as Camel Flu, whereas Severe Acute Respiratory Syndrome is caused by SARS-CoV. MERS-CoV first reported in 2012, and the SARS-CoV outbreak happened in 2003. These viruses did not have the capability of spreading than the SARS-CoV-2 virus so their outbreak was much more easily controlled than SARS-CoV-2. There are 2494 cases seen in MERS-CoV worldwide. The virus spread to 27 countries and caused the death of 858 people, according to WHO. In the SARS-CoV outbreak in 2003, the virus spread to 29 countries with a death number 810 in a total of 8096 cases. Bats are the common descent of all three viruses. However, the exact source of SARS-CoV-2 is unknown. It was first detected in Wuhan, China, in December 2019 and spread to 213 countries and territories around the world. It is well established that virus gets into body from mouth, nose or eyes and infect patients. It is almost certain that people to people transmission is the only way of getting virus because virus cannot leave outside the body for a lot of time. People who got severely sick shows mostly single organ failure, which is the respiratory problem, but some develop multiple organ dysfunction.[3]

Patients with severe COVID-19 may show coagulation disorders, which is similar to disseminated intravascular coagulation or thrombotic microangiopathy, but COVID-19 shows some different symptoms.[4] Hospitalized patients with COVID-19 show coagulopathy with elevated fibrinogen and D-dimer levels. However, prolongation of prothrombin time is minimal, thrombocytopenia is modest, and microangiopathy risk is low, unlike the disseminated intravascular coagulation. Hospitalized patients with COVID-19 seldom progress to a condition that checks the criteria for overt disseminated intravascular coagulation of International Society on Thrombosis and Homeostasis. Usually, DIC reflected by severe thrombocytopenia, prolongation of prothrombin time, extremely high D-dimer levels, and decreased fibrinogen.

COVID-19 associated coagulopathy is usually seen with patients having severe disease than mild disease.

Furthermore, disseminated intravascular coagulation criterion of the International Society of Thrombosis and Homeostasis most probably achieved by the patients who die than the patients who survive. Coagulation activation from organ failure, sepsis or cytokine storm indicates elevated death rates, which correlates with increased D-dimer at acceptance to hospital and during hospital stay.[2] Monitoring platelet count, prothrombin time, D-dimer, and fibrinogen count are recommended in patients with COVID-19 associated coagulopathy.[2,3,4,5] Parameter changes indicate the degree of infection, specifically D-dimer levels.[6] COVID-19 pneumonia may cause several problems such as sepsis-induced coagulopathy and, if not controlled may cause disseminated intravascular coagulation.[1] Disseminated intravascular coagulation clinically manifest by the boost of intravascular thrombin production, microthrombi from bleeding through endothelial leakage and organ dysfunction.[1] Moreover, venous thromboembolism might progress from platelet released thrombin, which may cause pulmonary embolism or deep vein thromboembolism.[7] Venous thromboembolism risk also changes for different ethnicities. Venous thromboembolism risk is higher in African Americans than Caucasians and higher in Caucasians than Chinese.[7] More aggressive critical care or so-called experimental therapies such as plasma exchange might be needed.[3] As for all coagulation problems, understanding the underlying condition is the key. COVID-19 may lead to bleeding even though the patient has normal coagulation parameters. In this case, therapeutic anticoagulation might be applied depending on the individual. If the patient is not bleeding, giving medication to improve the patient's coagulation parameters does not significantly change the outcome.

In this review, first brief information will be given about the clinical manifestation of the disease. Second, current situation in the diagnosis techniques and the important parameters will be discussed. Third, up to date treatment methods will be compiled based on the available data.

Key Words: COVID-19,D-dimer, prothrombin time, platelet count, fibrinogen, disseminated intravascular coagulation, pulmonary intravascular coagulation, VTE prophylaxis, low-molecular-weight heparin, unfractionated heparin, POCUS, thrombosis, tissue plasminogen activator, enoxaparin,

Clinical Manifestation

Fever, myalgia, cough, dyspnoea, and less common headaches, diarrhea, nausea, and vomiting are seen in COVID-19 patients.[1] SARS-CoV2 binds to ACE2 receptors on vascular endothelial cells, and cells undergo lysis, which leads to the endothelium, causing procoagulant activity and activates accumulation of fibrin and fibrin degraded products in pulmonary microcapillary venous vessels.[1] Viral, bacterial, or fungal infections cause systemic inflammation as part of the immune system.[2] Immune system activation results in activation of coagulation pathway and thrombin generation as different humoral and cellular feedback pathways, which is called immunothrombosis.[2] Coagulation abnormalities like disseminated intravascular coagulation or thrombotic microangiopathy might be mimicked with severe COVID-19 patients, but COVID-19 has some different features.[4] Normally in disseminated intravascular coagulation, thrombocytopenia (platelet count < 150 x 10^9) is the important information that should be looked at.[5] However, according to a cohort study from China with 191 adult COVID-19 patients with analyzed laboratory results, 54 non-surviving patients had an average platelet count of 165.5 x 10^9/L (107.0–229.0), and prothrombin time of 11.4 s (10.4–12.6) which falls within the normal range (11– 13.5 s).[5] It can be said that COVID-19 is a combination of low-level disseminated intravascular coagulation and pulmonary thrombotic microangiopathy, which have a

significant effect on organ dysfunction in the most severe cases.[4] Furthermore, pulmonary intravascular coagulopathy is first named by McGonagle et al. which is a type of immunothrombosis distinct from DIC. Proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukins (IL), including IL-1 and IL-6.7 IL-6 are also associated with severe COVID-19 can start coagulation activation, and thrombin generation.[8] CD61 and von Willebrand Factor stained megakaryocytes further promotes the hypothesis that the local coagulation is the main factor of process.[8]

Diagnostic Approach

D-dimers, prothrombin time and platelet count measurement is suggested in all COVID-19 patients.[3,4] According to Dr Harenberg and Dr Favaloro, increase in neutrophils, SAA, PCT, CRP, cTnI, D-dimer, LDH and lactate levels, and the decrease in lymphocyte number, can indicate disease progression.[1]

Initial test set (expected outcome)	– C-reactive protein (CRP; elevated) – Lactate dehydrogenase (LDH; elevated) – Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (elevated) – D-dimer (elevated) – Fibrinogen (elevated) – PT (slight elevation) – APTT (shortened in acute phase, potentially elevated later) – Albumin (decreased) – Full/complete blood count (platelets and lymphocytes decreased)
Tests potentially useful for monitoring patient status	– CRP (monitoring of infection/inflammatory response) – LDH (identification of lung injury and/or multiple organ failure) – ALT/AST/Bilirubin (identification of liver injury) – Albumin (identification of liver failure) – Cardiac troponins (identification of cardiac injury) – Creatinine and blood urea nitrogen (identification of kidney injury and/or failure) – Procalcitonin (identification of bacterial co-infections) – Full/complete blood count (platelets, lymphocytes, neutrophils) – D-dimer, fibrinogen, PT(/APTT) (identification of ongoing [consumption or thrombotic] coagulopathy including DIC) – Electrolytes and glucose (identification of metabolic derangement) – Lactate dehydrogenase (identification of lung injury and/or multiple organ failure) – Creatine kinase (identification of muscle injury) – Lipase (identification of pancreatic injury) – Brain natriuretic peptide[b] (identification of cardiac failure) – Ferritin (monitoring of infection/inflammatory response) – Presepsin[c] (monitoring of severity of viral infection)

[a]'Gating rule': unless clinically justified, testing should not generally be reordered within 24 h of an existing test. [b]For selected patients with signs of multiple organ failure or systemic inflammatory response syndrome. Discuss with expert (laboratory) clinician/senior or clinical scientist. [c]For patients under intensive care. Modified from Favaloro and Lippi [30].

Figure 1: Laboratory tests that could be beneficial in COVID-19.[5]

Elevated D-dimer levels are essential for COVID-19. One big analysis which included data regarding 1099 patients with confirmed Covid-19 from over 550 hospitals in China, a D-dimer ≥0.5 mg/liter was obtained in 260 of 560 which equals to a ratio of 46.4%, patients measured with only 43% having raised D-dimer with non-severe illness, and approximately 6 of every 10 patients had progressive illness.[3] In another study which is conducted by Dr Tang in 183 patients with COVID-19 in China, an average D-dimer concentration of 2.12 mg/L (range 0.77–5.27) was measured in non-survivors vs concentration of 0.61 mg/L (0.35–1.29) in survivors where the normal range is below 0.50 μg/ml.[3,4] Significantly higher D-dimer concentrations with a mean of 2.4 mg/L were observed in a study conducted by Dr Huang about the patients in an intensive care unit (ICU) than patients who received no ICU care with a mean of 0.5 mg/L.[3,4] In one more study, patients who have bigger than 1 mg/L D-dimer on admission had 18.42-times increased chance of mortality.[6]

Second, the prothrombin time is one of the most critical parameters after D-dimer levels. Also according to Tang study, the prothrombin time in

severe COVID-19 patients was only slightly increased (15.6 s, range 14.4–16.3) in the non-survivors versus survivors (13.6 s, 13.0–14.3).2 Furthermore, The prothrombin time was also mildly prolonged at admission as 12.2 s (range 11.2–13.4) in those who needed ICU versus the non-ICU patients as 10·7 s (range 9.8–12.1) respectively.[3,4] It should be said, however, these slight changes might be obtained as not significant when the international normalized ratio (INR) is used.[3]

Third, the platelet count is also a vital coagulation parameter in patients with severe COVID-19. Thrombocytopenia is usually regarded as a sign of mortality from sepsis; however, this is not true for many COVID-19 patients.[3] A study in the Lancet which conducted by Dr Lippi says, in the analysis of 41 patients, platelet counts less than 10^{11}/L was seen in 2 of 40 patients with one each in ICU and non-ICU support while platelet count less than 1,5 x 10^{11}/L was seen in 38 of 40 (95%) with ICU and non-ICU patients.[3] According to this study, lower platelet count was associated with mortality.[3] Thrombocytopenia also correlates with having five times more odds of having severe disease.[3] In DIC, thrombocytopenia (platelet count <150 x 10^9/L) is a crucial finding. However, according to the cohort of 191 patients in China, patients who could not survive had an average platelet count of 165.5 x 10^9/L (107.0–229.0), which is in the normal levels.[5] Furthermore, thrombocytopenia is an indicator of the severity of disease according to the meta-analysis of 1779 patients with COVID-19.9 According to this study, thrombocytopenia at admission was an indicator of increased risk of severe disease and mortality, with a mean difference of 31 × 109/L between severe versus non-severe disease with thrombocytopenia range is between 4-57%.[6]

Usually, average fibrinogen levels in patients with COVID-19 are at the upper limits of the standard range, which is thought to be an acute phase response.[4] However, fibrinogen concentrations of less than 1.0 g/L in plasma was detected before death in some patients in China.[4] According to another study, fibrinogen levels are elevated in the admission, and they may decrease in the later phase, which signals death.[6] In a study of 83 patients which have a median age of 64.There was significantly elevated fibrinogen values with a median value of 4.7 on the initial phase, with levels stayed increased with no patient having less than 2g/L fibrinogen at any time during hospitalization.[7] This increase is thought to be an acute stage reaction, because of significantly elevated levels of C-reactive protein with a median value of 56 mg/L where the normal range is between 0-5 mg/L.[7]

There are other laboratory findings that might be associated with coagulopathy in COVID-19 such as lactate dehydrogenase (LDH) and high ferritin concentrations left from thrombotic microangiopathy.[4]

In another study with 183 COVID-19 patients, including a complete evaluation of coagulation parameters, such as D-dimer, prothrombin time, fibrinogen, and antithrombin, was analyzed.[2] Patients who could not survive had an indication of overt DIC with decreased fibrinogen, increased D-dimer, and increased prothrombin time, occurring ten days after admission, even though sepsis was not evident.[2]

Treatment

Heparins are found to be helpful to treat disseminated intravascular coagulation and venous thromboembolism and also to reduce mortality by many scientific groups.[1] Many centers in France and Netherlands even increased the dose of low molecular weight heparin to 0.5mg/kg enoxaparin which is considered as "intermediate density" doses.[1,2] A laboratory-based report to determine the optimum dose of low molecular weight heparin was published, and according to this report 31.6% of patients need intermediate density dose, 5.2% need a therapeutic dose, and the rest need in a standard dose.[1]

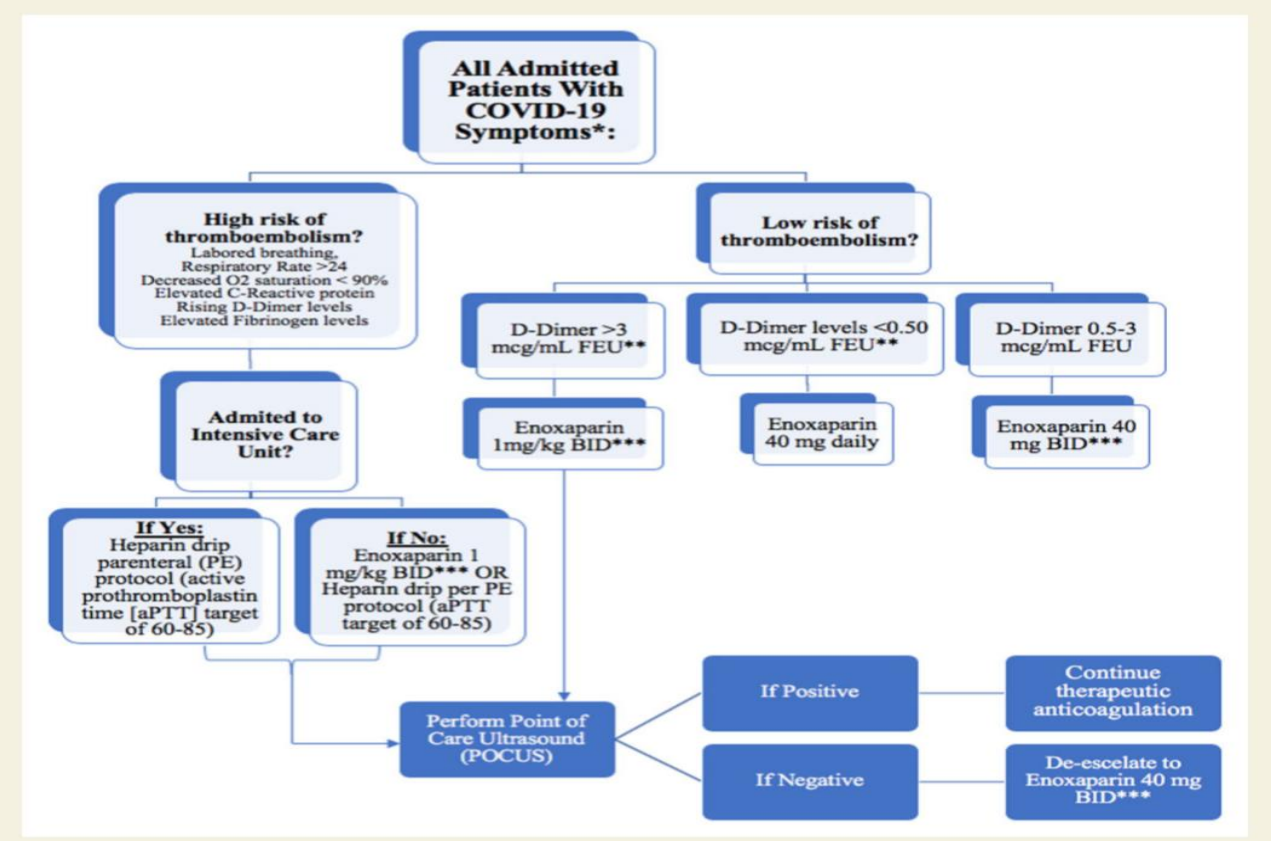

Figure 2: Tailoredalgorithm/protocol for COVID-19 associated coagulopathy. *Patients who have a high bleeding risk are excluded. Patients with a platelet count less than 50000 and INR value bigger than 2 are also excluded. **FEU stands for fibrinogen equivalent unit.***Enoxaparin dose should be adjusted in the case of renalfailure.[5]

Heparin treatment seems like a clear way to stop the hypercoagulation process with its anti-inflammatory, anti-complement, antithrombin, direct antiviral effects.[6] Heparin, especially unfractionated heparin or low molecular weight heparin, is thought to be useful in binding spike proteins and decreasing interleukin-6, which normally increases in COVID-19 patients.[5] The International Society of Thrombosis and Homeostasis suggests usage of low molecular weight heparin and unfractionated heparin in critically ill but non-bleeding patients even though there is no direct evidence. Because of this lack of evidence, treatment beyond VTE prophylaxis is not recommended by the International Society of Thrombosis and American Society of Hematology.[6]

Up to date approach to applying on high-risk patients is to use point-of-care ultrasound screening and continuing VTE prophylaxis.[6] Patients are divided into three categories such that; the first category is patients who have D-dimer greater than 3000ng/mL and no evidence of venous thromboembolism, the second category is D-dimer greater than 3000ng/mL but point-of-care ultrasound screen result is negative, the third category is patients having thrombosis.[6] In the article standard VTE prophylaxis for group 1, intensified VTE prophylaxis for group 2 and maximum anticoagulation for group 3 patients are recommended.[6]

For the patients in dialysis circuits having continuous renal replacement therapy should be given unfractionated heparin 500U/h. If clotting cannot be stopped, systemic heparin should be increased to get activated partial thromboplastin time to normal levels.[6]

Duration of anticoagulation treatment should be six weeks for catheter-associated thrombosis and a minimum of 3 months for venous

thromboembolism.[6] Patients having D-dimer levels more than two times of the upper limit may get the benefit of treatment.[6]

For patients with obesity, standard treatment with 40 mg of enoxaparin is not enough in many cases.[2]Based on the heavier weight of patients, UFH 7,5 x 100 units or 80 mg enoxaparin doses were easily tolerated.[2]

In a retrospective study including 449 patients admitted to hospital because of severe COVID-19 in China, 99 patients received VTE prophylaxis treatment for a minimum of 7 days which 94 of them received enoxaparin 40-60mg a day and 5 of them receiving unfractionated heparin 10000-15000 U per day.[2] 28 day mortality was not significantly changed between patients having VTE prophylaxis vs patients not having any heparin treatment in general.[2,3,5] However, in patients having levels of D-dimer more than six times of the upper limit and having a sepsis-induced coagulopathy score bigger than 4, lower mortality rates were observed when patients treated with heparin.[2,4,5,6]

If VTE prophylaxis treatment is not helpful to prevent progression and incubation of disseminated intravascular coagulation, secondary pulmonary hypertension, and cardiac insufficiency can be seen.[8] In this case, usage of tissue plasminogen activator or defibrotide is recommended.[8] Patients with severe hypoxia and with elevated D-dimer levels benefited from oxygenation after usage of tissue plasminogen activator.[6] However, further research in this treatment is needed.[6,8]

Increase in D-dimer, inflammatory cytokines and decrease in T- and B-cell lymphocytes weaken the immune system in COVID-19.[1] Intravenous immunoglobulin IgG might be a possible option in the case of immune thrombocytopenic purpura or heparin-induced thrombocytopenia.[5] Also, tissue plasminogen activator is found to be effective in 3 patients having Acute Respiratory Distress Syndrome.[1] Bleeding is rarely seen in COVID-19 but if it happens International Society of Thrombosis guidelines of blood transfusions might be applied.[3] Plasma exchange is still an experimental therapy, but it can be used to recover ADAMTS-13 and complement proteins and removing inflammatory mediators in the treatment of thrombotic microangiopathy by supplying plasma.[4] Other experimental therapies that need to be further evaluated are antithrombin supplementation, recombinant thrombomodulin and hydroxychloroquine.

Conclusion

COVID-19 usually causes symptoms like fever, cough, difficulty breathing or chest pain. However respiratory system is not the only system it affects. COVID-19 associated coagulopathy is one of the main concerns of scientists around the world. COVID-19 has a complicated pathology, and disease situation differs from patient to patient. We can see different characteristics of disease in different ethnicities such as Caucasian, Asian and African American. Attitudes of this pathogen seems to be very complicated and scientists are trying to figure this out. That is one of the main reasons that a vaccine could not be found yet. Disseminated intravascular coagulation is one of the main problems that arise. Increase in D-dimer is the leading laboratory findings of the disease. Other than D-dimers measurement of prothrombin time, platelet count and fibrinogen are recommended. The severity of the disease is correlated with D-dimer levels and patients having D-dimers greater than 3000ng/mL carry the greatest risk of venous thromboembolism and death. VTE prophylaxis which includes low molecular weight heparin and unfractionated heparin, should be given to all hospitalized patients. Heparin prevents progression of disseminated intravascular coagulation in many instances. Patients should be monitored by point-of-care ultrasound imaging, and the dose of heparin needs to be increased or decreased according to results. If there is no evidence of venous thromboembolism, patients should continue to get low molecular weight heparin. If venous thromboembolism is evident high-

intensity prophylaxis should be applied. In case of bleeding, guidelines of the International Society of Thrombosis should be followed. We will have more information with increasing numbers of autopsies every day. More experimental therapies like tissue fibrinogen activator or defibrotide might be considered in a case of pulmonary intravascular coagulation. It should be noted that current management of coagulopathy is based mainly on case reports, so randomized controlled studies should be done to have a better understanding. We will have a better fight against this new pathogen in the recent future when more research has been done.

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