Clinical Perspective - A Review

# HYPERCOAGULABILITY AND ITS CARDIOVASCULAR IMPLICATIONS IN COVID-19 PATIENTS

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ABSTRACT

COVID-19, a viral respiratory illness caused by the severe acute respiratory syndromecoronavirus-2 (SARS-CoV-2), is a new comer to the infectious disease list. First documented in Wuhan china and since then it has rapidly spread around the globe. Perhaps the most devastating pandemic of the modern era, it was first considered to be primarilya respiratory illness. But it is now an established fact that it can affect other body systems as well and may predispose patients to thrombotic complications, both in the venous and arterial circulations. This virus is still new and continuous research is being done in order to fully understand its pathophysiology and different factors that are related to increased mortality. Many patients already receiving antithrombotic therapy may develop COVID-19, which can have implications for choice, dosing, and laboratory monitoring of antithrombotic therapy.The objective of this article is to address the current understanding of the pathogenesis and management of patients with COVID-19 who need prevention from thrombotic disease, patients who develop thrombotic cardiovascular complications, patients with pre-existing thromboticdisease who develop COVID-19 and patients with COVID-19 who developed DIC.

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## INTRODUCTION:

COVID-19, a much-heard terminology these days, stands for Corona virus disease 2019. It is the official name given to this deadly disease by WHO in a press release on February 11, 2020. While International Committee on Virus Taxonomy named this virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is a single-stranded RNA beta coronavirus, enveloped in a shell with spike like projection on surface. Its transmission capacity is much greater than previous SARS virus. Primary mode of transmission is through droplet inhalation generated by infected person. This virus belongs to a family of Corona viruses, six of which have been known to infect human beings. While most of the family members of this virus tend to cause common flu like illness, SARS-CoV causes severe acute respiratory distress syndrome while MERS-CoV causes Middle east respiratory syndrome (MERS). By July 2020, 12 017 118 cases have been reported worldwide including 549 276 deaths[1]. Although the infection rate is similar in males and females, the mortality rate is higher in men.[2]

## PATHOGENESIS AND CLINICAL PRESENTATION:

SARS-CoV-2gains entry into human cells via ACE2 receptors. After binding to these receptors there is a conformational change that results into fusion of virus envelope to host cell membrane and the viral RNA is released into the cell.The pathogenic mechanism that produces pneumonia and respiratory failure is quite complex.This assimilation of viral RNA into host cell is capable of ensuing a strong immune reaction. Various cytokines implicated in this inflammatory process include TNF-$\alpha$, IL-1$\beta$, IL-6, IL-8, IL-12, interferon-gamma inducible protein (IP10), monocyte chemoattractant protein 1 (MCP1) macrophage inflammatory protein 1A (MIP1A). IL-6 is the most important factor in this storm. It is produced by activated leukocytes. The most extreme form termed as ''cytokine storm'' is thought to result in respiratory injury resulting in ARDS. Along with this inflammatory damage, it is now believed that hypercoagulation with resulting thrombotic complications like myocardial infarction and ischemic stroke increases mortality in these patients[3].

The clinical presentation of COVID-19 is quite variable. It can range from asymptomatic to mild flu like symptoms to severe respiratory failure necessitating mechanical ventilation. Some patients develop features of sepsis and multiorgan failure while thrombotic complications like pulmonary embolism, acute myocardial infarction, deep venous thrombosis and cerebrovascular events can also occur.

## CARDIOVASCULAR IMPLICATIONS OF COVID 19

COVID-19 not only causes pneumonia but also has serious cardiovascular implications. Along with thrombotic complications like cerebrovascular accidents,ACS, and venous thromboembolism, myocarditis, heart failure and arrythmias have been reported to complicate the course of disease. Patients

with known CVD are more likely to develop cardiac injury than patients without underlying CVD.[4] Also such patients have higher mortality rates when affected by this virus.

Different mechanism postulated to cause cardiac injury are

1. Direct myocardial damage by viral invasion
2. Cytokine storm causing inflammatory damage to myocytes
3. Hypoxic injury from supply demand mismatch due to ARDS
4. Hypercoagulation and thrombosis due to platelet hyperactivation resulting in thrombotic complica tions like ACS
5. Arrythmias from electrolyte imbalances due to multiorgan failure and some pro arrhythmic drugs used for treatment of severe covid-19.

Thrombotic complications are seen more frequently in patients with known cardiovascular risk factors like DM, HTN and obesity.5Coagulation cascade is significantly deranged in COVID-19 patients with increased levels of d-dimers, fibrinogen and VWF.[6,7,8] Platelets also seem to play important role in this. It has been found out that platelets are in a hyperactive state in such patients. They not only promote thrombosis but also release certain inflammatory mediators, further contributing to inflammatory process. Also, a reduced platelet count in such patients is associated with higher overall mortality. Different possible mechanism of reduced platelets in such patients are thought to be, reduced platelet life span, reduced production andconsumptive coagulopathy resulting in reduced platelet count. While an associated finding may be lymphopenia with increased neutrophil to lymphocyte ratio(NLR).[9] The overall hemostatic abnormality seems to resemble the picture of DIC, but instead of increased bleeding complications, it is associated with thrombotic complications.A recent study showed that COVID-19 induced changes in platelets gene expression resulting in hyperactive platelets. These platelets showed faster aggregation and more rapid spread on fibrinogen and collagen thereby contributing to thrombosis and inflammation.[10]

Another interesting finding was that even though receptor for COVID-19 binding, ACE2, was not detected in plateletsstill viral mRNA was detected inside platelets suggesting some other mechanism of entry into these cells.Although mostly patients develop cardiovascular symptoms after the diagnosis of COVID-19, Isolated acute myocardial infarction as a result of covid-19 in the absence of any history of fever sore throat or gastrointestinalsymptoms has also been documented.[11]

## MANAGEMENT

All admitted patients with COVID-19 should undergo coagulation testing including platelet count, PT, APTT, fibrinogen level and D-dimers. These values are useful to understand the status of the coagulation system and safety of using anticoagulation. High d-dimers are associated with worse outcomes. Antithrombotics in such patients can be used either as prophylactic measure to prevent VTE or as treatment after a thrombotic event.

1. Covid-19 in patients on chronic antithrombotics

• Patients with COVID-19 who are taking anticoagulant or antiplatelet therapy for underlying medi cal conditions should continue their treatment unless significant bleeding develops or other contraindications are present.[12]

• NSAIDs have been identified as a potential risk factor forserious clinical presentation of SARS-CoV-2 infection. However, at the low dose administered in CCS, aspirin has very limited ant inflammatory effect so it should be continued.[13]

• Outpatients receiving warfarin who are unable to get international normalized ratio monitoring during isolation may be candidates for direct oral anticoagulant therapy. Patients with mechanical heart valves, ventricular assist devices, valvular atrial fibrillation, or antiphospholipid antibody syndrome or patients who are lactating should continue treatment with warfarin therapy[12]. If previous INR was stable an extended INR testing might be reasonable. Other options can be home based or drive through INR testing.

2. Antithrombotics for Prophylaxis of VTE

For prophylaxis of VTE following strategy may be adopted. (adapted from NIHCOVID-19 Treatment Guidelines)[12]

• For non-hospitalized patients with COVID-19, antithrombotics should not be initiated for prevention of venous thromboembolism (VTE) or arterial thrombosis

• Hospitalized adults with COVID-19 should receive VTE prophylaxis per the standard of care for other hospitalized patients
• In hospitalized patients Anticoagulants or antiplatelet therapy should not be used to prevent arterial thrombosis.
• Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis. Extended VTE prophylaxis can be considered in patients who are at low riskfor bleeding and high risk for VTE. FDA has approved two regimensrivaroxaban 10mg daily for 31 to 39 days, and betrixaban 160 mg on Day 1, followed by betrixaban 80 mg once daily for 35 to 42 days.
3. Antithrombotics for Thrombotic vascular complication

Following management strategies might be adopted for thrombotic events in such patients. (adapted from NIH COVID-19 Treatment Guidelines)[12]

• Any time anticoagulant or antiplatelet therapy is being used; consideration must be given topotential drug-drug interactions with other concomitant drugs used for covid-19 infection.
• Low molecular weight heparin or unfractionated heparin may be preferred in hospitalized, critically ill patients because of their shorter half-lives, ability to be administered intravenously or subcutaneously, and fewer drug-drug interactions compared with oral anticoagulants.
• Patients with COVID-19 who experience an incident thromboembolic event at a time when imaging is not possible, should be managed with therapeutic doses of anticoagulant therapy as per the standard of care for patients without COVID-19.
• Patients with COVID-19 who require extracorporeal membrane oxygenation or continuous renal replacement therapy or who have thrombosis of catheters or extracorporeal filters should betreated as

| | LOW-RISK COVID-19 | HIGH-RISK COVID-19† |
|---|---|---|
| HIGH-RISK ACS OR VTE* | **For ACS:**<br>• GDMT per ACS algorithm<br>• Urgent/emergent angiography and intervention<br>• Consider need and safety of hemodynamic support and monitoring<br>**For VTE:**<br>• Anticoagulant therapy<br>• If recurrent symptoms or deterioration, consider systemic thrombolysis or potentially catheter-directed therapy as an alternative<br>• Consider need and safety of hemodynamic support and monitoring‡ | **For ACS:**<br>• GDMT per ACS algorithm<br>• Consider emergent TTE<br>• Urgent/emergent angiography and intervention vs. systemic fibrinolysis<br>• Consider need and safety of hemodynamic support and monitoring in select patients<br>**For VTE:**<br>• Anticoagulant therapy<br>• Consider systemic fibrinolysis<br>• Catheter-directed or surgical therapies in case not suitable for systemic fibrinolysis<br>• Consider need and safety of hemodynamic support and monitoring |
| LOW/INTERMEDIATE RISK ACS OR VTE | **For ACS:**<br>• GDMT per ACS algorithm<br>• Angiography and intervention only if recurrent/persistent symptoms or decompensation<br>**For VTE:**<br>• Anticoagulant therapy<br>• Catheter-directed or surgical therapies only if recurrent/persistent symptoms or decompensation | **For ACS:**<br>• GDMT per ACS algorithm<br>• Other therapies reserved for select cases such as those with significant recurrent/persistent symptoms or decompensation<br>**For VTE:**<br>• Anticoagulant therapy<br>• Other therapies reserved for select cases such as those with significant recurrent/persistent symptoms or decompensation |

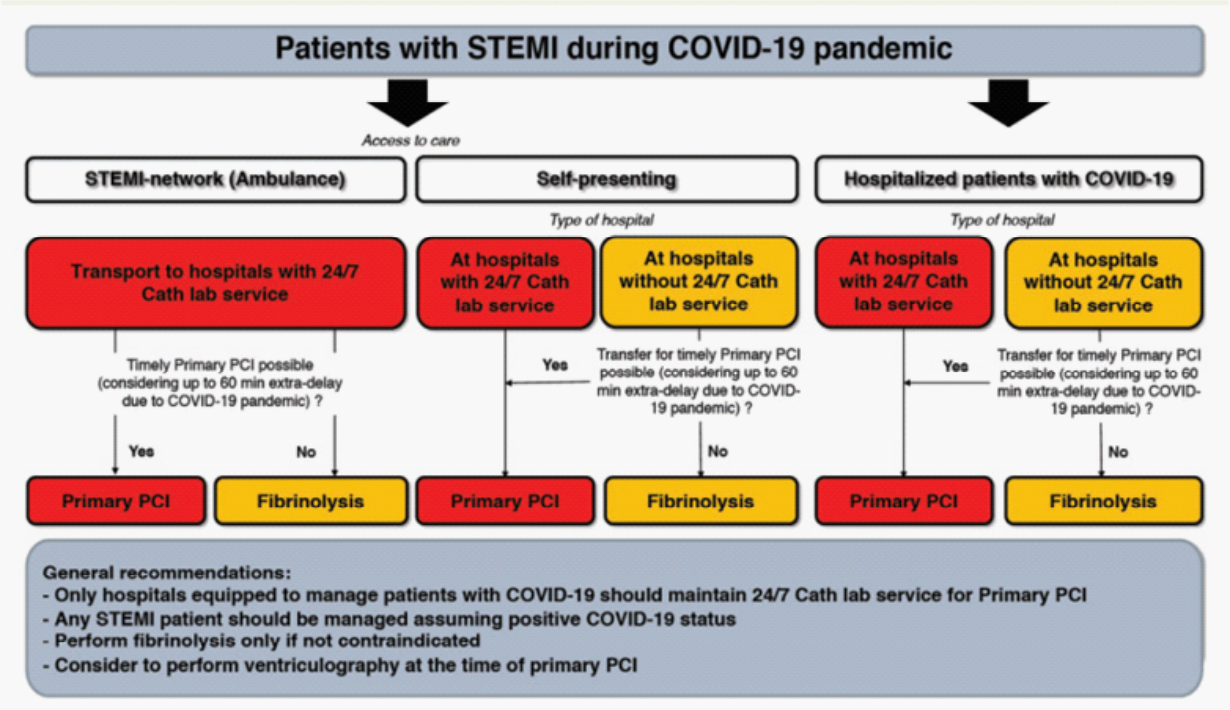
per the standard institutional protocols for those without COVID-19.

• For patients presenting with ACS, they can be categorized based upon presentation as: a)high risk ACS b)low/Intermediate risk ACS[14]. While diagnosing a patient as ACS, Increased level of Troponin in patients with COVID-19 should be interpreted considering the full clinical picture as it can be raised due to non-specific myocardial injury, renal dysfunction, myocarditis, pulmonary embolism and non-type-1 myocardial infarction. It is of prime importance to differentiate type-1 M.I from other causes of elevated troponin without coronary etiology as invasive coronary intervention would of no use in the latter setting.

## PROPOSED ALGORITHM TO RISK STRATIFY PATIENTS BASED ON SEVERITY OF ACS, VTE, WITH COVID-1914

*High-risk ACS refers to patients with hemodynamic instability, left ventricular dysfunction or focal wall motion abnormality, or worsening or refractory symptoms. High-risk VTE refers to patients with pulmonary embolism who are hemodynamically unstable, evidence of right ventricular dysfunction or dilatation, or worsening of refractory symptoms. †High-risk COVID-19 refers to patients with high viral load, and at risk for requiring intubation and aerosolizing viral particles. Hemodynamic support includes intra-aortic balloon pump, percutaneous ventricular assist device, and extracorporeal membrane oxygenation. Hemodynamic monitoring refers to Swan-Ganz catheter for invasive hemodynamic assessment

In patients with COVID-19 presenting with ACS, thrombolytics and antiplatelets should be given considering the baseline coagulation profile. Following recommendations are adapted from EAPCI Position Statement on Invasive management of Acute Coronary Syndromesduring the COVID-19 pandemic.[15]




• All STEMI patients should be managed as COVID-19 positive because there is no time to wait for nasopharyngeal swab result.

• Primary PCI is first-line therapy if it can be performed in a timely fashion-120 min from symptom onset.

• Fibrinolysis if not contraindicated can be considered when the delay is longer.

• Complete revascularization to be considered if indicated and appropriate.

• Very high-risk non-ST-segment elevation (NSTE)-ACS should follow the STEMI pathway. Others should undergo a nasopharyngeal swab immediately after admission.

• Left ventricular angiogram instead of echo to evaluate left ventricular function.
• Veno-arterial (VA) ECMO support is considered the device of choice in COVID-19 patients with hemodynamic and respiratory failure.
• Impella (or IABP) may be used to manage left ventricular over distension in patients receiving VA ECMO

4. COVID-19 Patients with DIC

•Patients with COVID-19 and in DIC but without overt bleeding, prophylactic anticoagulation should be administered.[14]
• COVID-19 patients who are on anticoagulants, and develop DIC without overt bleeding, anticoagulants may be continued in reduced dose along with assessment of thrombotic vs bleeding risk.[14]
• COVID-19 and an indication for dual antiplatelet therapy (e.g. PCI within the past 3 months or recent ACS) and with suspected or confirmed DIC without overt bleeding, it is reasonable to continue DAPT if platelet count is >50,000, reduce to single antiplatelet therapy if platelet count is >25,000 and <50,000, and discontinue if platelet count is <25,000. However, management should be individualized.14

## CONCLUSION:

The current understanding of COVID-19 and its cardiovascular effects, along with diagnostic and therapeutic challenges it poses need to be studied further. We are faced with a new pathogen whose behavior is yet to be defined properly and lack of immunity against this virus resulted in high number of infected people. In this challenging time and crisis of COVID-19 pandemic, we have no single solution except sharing our observations, experiences gained by patient management and research to provide best possible care of our patients. Understanding of disease is rapidly evolving and so does our approach to management.

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