

COVID-19 and cardiovascular complications - A review on thromboembolic phenomenon

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Abstract

To review the cardiac outcomes and effect of venous thromboembolism in patients with COVID-19.

All Confirmed cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) COVID 19 infection by positive result on polymerase chain reaction testing of a nasopharyngeal sample, who were admitted to Indraprastha Apollo Hospital, Delhi, were reviewed. The article reviewed the cardiovascular correlation and COVID 19 infection with emphasis on the effect of venous thromboembolism on mortality and morbidity in these patients.

Keywords: COVID 19; corona virus ; cardiovascular system; venous thromboembolism; anticoagulation

Introduction

Since 2019, COVID-19 or corona virus has rapidly spread across the globe resulting in a pandemic. The virus invades cells through the angiotensin-converting enzyme 2 receptor and leads to spread of infection. Previous literature states that pre-existing cardiovascular disease (CVD) and CV risk factors enhance vulnerability to COVID-19. This infection has been associated with cardiovascular conditions including acute myocardial injury, myocarditis, arrhythmias. As per literature patients with COVID-19 and associated cardiovascular comorbidities have higher mortality,¹ and the severity of COVID-19 disease correlates with cardiovascular manifestations.² The pivotal finding of the infection has been the pro coagulant effect of the virus leading to venous thromboembolism and latter pulmonary embolism. It is these complications associated with the infection which resulted in sudden cardiac deaths worldwide. It is important to understand the interaction of COVID-19 and this procoagulant

etiology leading to cardiovascular mortality and morbidity. This review is aimed at understanding the interrelationship of these cardiovascular factors and COVID 19 pandemic with the role of venous thromboembolism in the view of its diagnosis and prevention in COVID 19 infection.

The fundamentals of COVID 19 and Cardiovascular system

Though primary target for SARS-CoV-2 is the respiratory system but there are several mechanism of cardiovascular system involvement:

The common manifestations of cardiovascular system leading to CV complications are:^{3,4}

1. Direct myocardial injury –
The binding of SARS-CoV-2 to ACE2 can result in alteration of ACE2 signalling pathways, leading to acute myocardial and lung injury.

2. Systemic inflammation – COVID-19 lead to acute systemic inflammatory response and cytokine storm, resulting in multi organ failure.^{5,6}
3. Disproportionate myocardial demand-supply – Impaired myocardial oxygen demand-supply relationship secondary to systemic infection and hypoxia can lead to acute myocardial injury.
4. Plaque rupture, Hypercoagulability and coronary thrombosis – Systemic inflammation leading to prothrombotic milieu can precipitate plaque rupture resulting in acute myocardial infarction.
5. Electrolyte imbalances – Electrolyte imbalances can occur in systemic illness and precipitate arrhythmias, esp. in patients with cardiac comorbidities.

Cardiovascular comorbidities

The literature till date has shown that in patients, severity of COVID-19 disease is related to pre-existing cardiovascular diseases. The studies also showed these comorbidities to be directly proportional to the clinical outcomes.^{4,6-8}

A meta-analysis of six studies of 1527 patients with COVID-19 positivity showed 9.7%, 16.4% and 17.1% prevalence of diabetes, cerebrovascular disease and hypertension respectively.⁴ Although in the single centre Indian study of COVID 19 and cardiovascular correlation done by us, the risk factors were slightly higher with the prevalence being 38% for diabetics and 45% for hypertensive.

A report from the Chinese Centre for Disease Control and Prevention described that the case fatality rate (CFR) was 2.3% in 44672 confirmed cases of COVID-19.⁹ When associated with cardiac comorbidities the fatality rate increased to 6%, 7.3% and 10.5% in patients with hypertension, diabetes and CVD respectively. It has been postulated that the impact of various cardiovascular co morbidities on outcome of COVID vary among various ethnicity and geographic locations. The various studies done have not been able to show any significant correlation between comorbidities and morbidity or mortality when comparing on ethnicity and geography.

Venous thromboembolism

Patients with covid-19 are at increased risk of VTE which may be related to prolonged immobilisation, hypercoagulable state, active inflammation and propensity for DIC.¹⁰⁻¹² They have significant higher level of D-dimer, fibrin degradation products (FDP), and fibrinogen, compared with healthy controls.¹³ Also the levels of D-dimer and FDP titres were higher in patients with severe COVID-19 than those with mild disease.¹³

Our data showed similar findings in patients in COVID positive patients having raised d Dimer and Ferritin levels. Also in our study the levels of these inflammatory markers was higher in non survivors compared to survivors.

Lab parameters – “The values say it all”

Laboratory parameters play an important role in patients with COVID 19 and are helpful in prognostication of these patients. The abnormalities include lymphopenia,¹⁴ thrombocytopenia, elevation in lactate dehydrogenase and raised inflammatory markers such as C-reactive protein, D-dimer and ferritin.¹⁵ IL-6 levels have been found to directly correlate with the severity and procoagulant profile of the COVID patients.¹⁶

Among all the parameters – thrombocytopenia¹⁷ and increased D-dimer levels¹⁸ are the most consistently deranged laboratory values with COVID-19, also these have been associated with a higher risk of requiring mechanical ventilation, intensive care unit (ICU) admission and death . When considering other lab parameters , the data is less certain and often contradictory.^{19,20}

Recently, Tang et al.²¹ assessed 183 COVID positive patients, 21 (11.5%) of whom died. Among the notable and significant difference between the non survivors and survivors was the increased levels of D-dimer.

D-dimer has been an important marker for venous thromboembolism, and it has been attributed that many sudden deaths may be due to pulmonary embolism secondary to VTE. Thus the use of prophylactic parenteral anticoagulation may show the single most important benefit in prevention of this cardiovascular disease by reducing mortality and morbidity.

Treatment strategies “the game changer agents”

Anticoagulant therapy

Due to the high rate of associated arterial thromboembolism and VTE, prophylactic anticoagulation is essential in the management of hospitalised patients with covid-19,^{22,23} although the optimal thromboprophylaxis regimen is unclear. In a retrospective study of 449 patients with severe covid-19, 99 patients received unfractionated heparin or low molecular weight heparin for at least 7 days.²⁴

In previous literature various other viral outbreaks like SARS, MERS, Influenza also have been shown to have VTE as a thrombotic and thromboembolic event. These VTE may be the result of Inflammatory cytokine release. Recent studies have shown similar mechanism in COVID 19, where inflammatory response may lead to thrombotic events.

It is yet unknown whether the haemostatic changes are the direct and specific effect of the virus per se or a consequence of cytokine storm that precipitates the onset of Severe respiratory inflammatory syndrome.²⁵⁻²⁸ In our study we were able to confirm the raised levels of D-dimer, LDH, Ferritin with Thrombocytopenia between survivors and non survivors.

COVID-19 and VTE – “The correlation for prognosis”

A recent study from China indicated that 40% of COVID-19 positive hospitalized patients were at higher risk of Venous Thromboembolism.²⁹ Studies have concluded that hospitalized patients with COVID-19 who have respiratory failure, cardiac and procoagulant comorbidities,³⁰ patients who are bedridden and those admitted in intensive care units should receive pharmacological VTE prophylaxis unless any significant contraindications. Also, the choice of agents and dosing should be based on the available guideline for VTE.³¹⁻³³ The World Health Organization recommends prophylactic daily low-molecular-weight heparins (LMWHs), or twice daily subcutaneous unfractionated heparin (UFH).³⁴ If these pharmacological prophylaxis has absolute contraindication then mechanical VTE

prophylaxis (intermittent pneumatic compression) should be considered.³⁴⁻³⁵

In our patients the use of LMWH prophylaxis was initiated late considering the recent inflow of literature on their use worldwide. The number of patients on VTE prophylaxis were low but all showed good and rapid recovery. Thus emphasising that the use of VTE prophylaxis in COVID 19 may be a key aspect.

The risk of VTE is increased during pregnancy and the postpartum period, though the data regarding this is lacking.^{36,37}

All patients of primigravida, full term pregnancy and COVID positive received prophylactic anticoagulation in our study, this could have led to good outcomes in their case.

Post discharge anticoagulation

extended prophylaxis with LMWH³⁸⁻⁴² can reduce the risk of VTE but at the cost of increase in bleeding events.⁴³⁻⁴⁴ Although no data specific to COVID-19 exists, it is reasonable to consider extended prophylaxis for patients with elevated risk of VTE who have low risk of bleeding.⁴²⁻⁴⁶

Thought the final decision has to be based on an individualized risk stratification for thrombotic vs haemorrhagic risk.

Empirical anticoagulation without evidence of VTE

VTE remains under diagnosed in many patients with severe COVID-19. The diagnosis of VTE is vital in COVID 19 as many patients develop ARDS. Moreover, ARDS in patients with COVID-19 is itself a potential aetiology for hypoxic pulmonary vasoconstriction, pulmonary hypertension, and right ventricular failure. Thus presence of VTE in severe COVID 19 patients who are susceptible to ARDS makes them prone to poor prognosis, thus increasing mortality and morbidity.

In the background of this scenario,⁴⁷ some clinicians use intermediate- or full-dose (therapeutic) parenteral anticoagulation (rather than prophylactic dosing) for routine care of patients with COVID-19,⁴⁷ hypothesizing that it may confer benefit to prevent micro vascular thrombosis.

However, the existing data are very limited. A single-centre study from China suggested that D-dimer levels > 1,500 ng/ml has a sensitivity of 85.0% and specificity of 88.5% for detecting VTE events. Although practitioners use a variety of prophylactic or therapeutic doses of anticoagulants in patients, the optimal dosing in patients with severe COVID-19 remains unknown and warrants further prospective investigation.

Points to ponder

1. Which is the optimal investigation for assessment of the risk of VTE in patients with COVID-19?
2. What is the best investigation for the diagnosis of VTE in patients with COVID-19?
3. What is the optimal duration of prophylactic/therapeutic anticoagulation?
4. What is the best method for risk stratification and VTE prophylaxis after hospital discharge?
5. To determine if routine use of VTE prophylaxis is needed at discharge.
6. To determine the duration and efficacy of NOACs in COVID 19 patients after discharge.

Conclusions and future directions

More studies with multivariate analysis are needed to determine how COVID-19 and thrombotic events interact. The data could help to illustrate the various co morbidities associated with COVID-19 especially thromboembolic events. It would also help to identify management strategies to improve outcomes in these patients.

We assume thromboembolic disease and thrombotic events may be a precedent factor or incident complications noted in patients with COVID-19. The need for use of anticoagulation as preventive and therapeutic strategies should be kept in mind to mitigate the thrombotic and haemorrhagic events in these high-risk patients.

Though further studies from round the globe with enough numbers is needed to establish these correlations.

A large international registry of patients with venous thromboembolism-The RIETE registry⁴⁸ is in process and would help us answer these questions.

Another prospective registry- CORONA-VTE registry is being initiated to study COVID-19 and other cardiovascular outcomes.

Limitations

There were many limitations in our study

1. The cardiovascular investigation and management approach was on non-uniform and on discretion of the respective treating physician.
2. Evaluation of various COVID patient with echocardiography and venous doppler was dependent of the availability of the echocardiographer and discretion of COVID team specialists.

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