ABSTRACT

Thrombotic complications in patients with coronavirus disease 2019 (COVID-19) infection have been increasingly recognized, particularly those affecting the cardiovascular system. Patients with COVID-19 infection can suffer from increased coagulopathy as well as myocardial injury. In this review, we discuss these complications with special focus on management challenges in patients with acute coronary disease based on the available evidence from published literature.

Key words: Acute coronary syndrome, coagulopathy, COVID-19, myocardial injury, percutaneous coronary intervention, SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2, thromboembolic disease

INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) was declared a pandemic on March 11, 2020, by the World Health Organization.[1-3] The confirmed cases as of August 14, 2020, are over 20.4 million with over 744,000 confirmed deaths in more than 200 countries and areas (https://www.who.int). Typical hosts of this zoonotic disease are bats and birds.[1] COVID-19 has significantly increased the number of hospitalizations due to pneumonia with multiple organ disease. The infection may evolve from asymptomatic to a life-threatening sepsis[4] or acute respiratory distress syndrome (ARDS). A growing body of evidence has shown that severe COVID-19 may be linked to an increased risk of thrombotic complications due to the prothrombotic state in such patients.[2] Moreover, cardiovascular complications have emerged as a critical threat in addition to the respiratory disease.[3] The current article discusses thrombotic manifestations of COVID-19 with a focus on pathogenesis and select challenges in the management of cardiac ischemic events in such patients. For the purpose of this review, “thrombotic disease” term will be used collectively to describe both arterial and venous thromboembolic diseases.

PATHOGENESIS OF COVID-19

SARS-CoV-2 is a single-strand, ribonucleic acid (RNA) coronavirus[1-3] in the Coronaviridae family.[1] The virus gains entry into the respiratory system via the inhalation of its particle. It may survive on different surfaces for 24–72 h.[3] To enter into target cells, SARS-CoV-2 binds angiotensin-converting enzyme 2 (ACE2) receptor which is expressed in the heart, lung, intestine, kidney,[1,3,5] and blood vessels.[5] ACE2 has...
antioxidant, anti-inflammatory, and vasodilatory effects unlike ACE which has pro-oxidative, pro-inflammatory, and vasoconstrictive effects by the cleavage of angiotensin I into angiotensin II. ACE2 is considered to have a protective effect in the lungs, thus when the receptor is downregulated by viral binding, an acute lung injury and ARDS may occur. Another factor that plays an important role in the pathogenesis of the disease is the immune-mediated inflammation.

When the virus invades the lungs, an antiviral immune response, both innate and adaptive, develops. However, the intense and persistent immune response against the virus may generate an excessive hyperinflammatory response that is similar to the cytokine storm which damages the host cells.\(^{[9]}\)

Initial symptoms of the disease such as fever, cough, shortness of breath, fatigue, headache, and myalgia are similar to those of other respiratory viral infections, with the potential to progress into severe illness such as systemic inflammatory response syndrome, ARDS, multiorgan impairment, and shock\(^{[3,5,6,8]}\).[Figure 1]

Clinical-therapeutic staging has been proposed based on the clinical and laboratory criteria considering the increased disease severity throughout the illness course. The nonvalidated classifications have suggested a possible treatment approach for each stage.\(^{[7,8]}\) Cardiovascular aspects have to be addressed in COVID-19. Previous history of cardiovascular diseases put the patients at an increased risk of adverse events, while incidence of cardiovascular complications can be experienced in individuals without previous cardiac diseases.\(^{[3]}\) The risk of arrhythmias\(^{[5,9]}\) and heart failure increases due to the pro-inflammatory status and enhanced sympathetic stimulation.\(^{[5]}\)

**COVID-19-ASSOCIATED COAGULOPATHY**

Coagulopathy in COVID-19 demonstrated by hemostatic changes leads to thrombotic events.\(^{[3]}\) The SARS-CoV-2 does not seem to have procoagulant properties,\(^{[1]}\) and the exact mechanism of the coagulopathy is not fully known.\(^{[1,3,10]}\) Several contributing factors may be implicated. Excessive hypoxemia that results in vasoconstriction in the pulmonary capillary beds may lead to the reduction in blood flow and occlusion of the vessels.\(^{[10]}\) Immense inflammation activates the defense system of the host, triggering the coagulation cascade and the resultant thrombin generation. The inflammatory response may be excessive in some patients, leading to a cytokine storm.\(^{[1]}\)

Severe SARS-CoV-2 infection in patients with severe pneumonia can also lead to sepsis which induces disseminated intravascular coagulation (DIC) in addition to the release of inflammatory cytokines.\(^{[11]}\) DIC in sepsis is characterized by low platelet count,

![Figure 1: Severity of illness categories](image-url)
prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), and hemorrhagic tendency due to coagulation system exhaustion.\textsuperscript{[12]}

A prospective study recruited patients with ARDS due to SARS-CoV-2 (n = 150), found that 30%–40% of patients with septic shock were diagnosed with DIC. However, no COVID-19 patient had overt DIC, which raised a question about the mechanism of DIC in COVID-19. Such mechanism can be different from that usually described in intensive care unit (ICU) patients,\textsuperscript{[10]} and that severe COVID-19-related DIC may be considered a discrete entity of coagulopathy. DIC may be associated with a more severe disease\textsuperscript{[2]} and with a significantly higher risk of mortality\textsuperscript{[13,14]} (88%)\textsuperscript{[15]} without the increased risk of bleeding events.\textsuperscript{[15]} unlike the clinical manifestations with other RNA-type viral infections such as Ebola, i.e., DIC with hemorrhagic pattern.\textsuperscript{[1,10]}

The thromboembolic events in COVID-19 are not only associated with a systemic hypercoagulability but there is also a microcirculatory clot formation, i.e., thrombotic microangiopathy due to microvascular endothelial injury that was found in the postmortem examination of the lungs which may have contributed to death.\textsuperscript{[1,15-19]} Moreover, endothelial injury may also explain the occurrence of myocardial ischemia, cerebrovascular complications, and other circulatory thrombotic complications.\textsuperscript{[1]}

**HEMOSTASIS PARAMETER ABNORMALITIES**

In patients with COVID-19, deranged laboratory parameters are common\textsuperscript{[8,3,20,21]} and are associated with adverse outcomes.\textsuperscript{[20]} Common abnormal parameters include coagulation markers such as D-dimer, PT, aPTT, fibrinogen, platelet count, and antiphospholipid antibodies.\textsuperscript{[1,3,10,20]}

Other parameters include lymphopenia and rise in lactate dehydrogenase levels and inflammatory markers such as erythrocyte sedimentation rate, C-reactive protein, ferritin, and interleukin-6 (IL-6).\textsuperscript{[1,3]} High IL-6 levels have been linked to elevated fibrinogen concentrations, indicating a correlation between inflammation and the procoagulant state.\textsuperscript{[1]} D-dimer has been associated with morbidity and mortality in the setting of COVID-19 infection.\textsuperscript{[1-3]}

Several studies have correlated higher D-dimer levels, i.e., by 2–5 folds\textsuperscript{[14,22-24]} with a more severe disease.\textsuperscript{[12,14,22-28]} and/or a higher mortality risk.\textsuperscript{[12,14,22-23,29,30]} The extent of PT prolongation,\textsuperscript{[2]} and its association with disease severity,\textsuperscript{[23,29,31]} had varied between studies, with a trend toward a shortening in aPTT.\textsuperscript{[22,23,30]} With regard to the association with mortality, results from studies were inconsistent as well.\textsuperscript{[14,28,28]} Fibrinogen levels exhibit initial rise with an advanced disease, but significantly decreased levels with lower antithrombin levels were observed in the nonsurvivors of COVID-19.\textsuperscript{[2]}

Mild thrombocytopenia is common and seems to be correlated with an increased risk of mortality.\textsuperscript{[3,29,32,33]} severe disease,\textsuperscript{[33]} mechanical ventilation need, and ICU admission.\textsuperscript{[3]} However, one study reported normal platelet count in the majority of the patients,\textsuperscript{[20]} whereas various studies did not find difference in the platelet count when compared ICU with non-ICU patients.\textsuperscript{[22,23,25]} Antiphospholipid antibodies including antiphospholipin immunoglobulin (lg) A and anti-beta₂-glycoprotein IgA and IgG were detected in a case series of severe COVID-19 patients with stroke (n = 3),\textsuperscript{[34]} and in 10% of the patients in another case series (n = 50).\textsuperscript{[35]} Lupus anticoagulant positivity may trigger thrombosis as well.\textsuperscript{[10,35]}

**THROMBOTIC MANIFESTATIONS IN COVID-19**

The inflammatory responses, hypoxia, and diffuse DIC in COVID-19 as described above, predispose patients to arterial and venous thrombotic diseases\textsuperscript{[36,37]} (Table 1). The incidence of thrombotic diseases has been reported in several studies. Early during the pandemic, Klok et al. described 31% cumulative incidence of both venous and arterial thrombotic diseases that affected 16.8% of the patients (n = 184) despite receiving standard thromboprophylaxis therapy.\textsuperscript{[37]} The 14-day study extension has confirmed the results with a cumulative incidence of 45%.

Thrombotic complications were associated with a higher risk of mortality (hazard ratio [HR]: 5.4, 95% confidence interval [CI]: 2.4–12).\textsuperscript{[38]} Other studies have reported thrombotic event rates in 20%–43% of ICU patients.\textsuperscript{[10,11,15,39-41]} In early data, venous thromboembolism (VTE) was diagnosed in 17%–20% of critically ill patients.\textsuperscript{[2]} Whereas, stroke occurred in 2.7%–3.8% of patients,\textsuperscript{[10,15,24,37,39]} up to 5%,\textsuperscript{[42]} leading to hospitalization.\textsuperscript{[15]} In one report (n = 19), myocardial infarction (MI) diagnosis in 1.1% of the patients led to the hospitalization of 75% of them.\textsuperscript{[15]}

**MYOCARDIAL INJURY IN COVID-19**

The marker of acute myocardial injury is the rise in the levels of cardiac biomarkers, i.e., high-sensitivity troponin (hs-troponin) and/or creatinine kinase-MB, above the 99th percentile of upper reference limit (URL).\textsuperscript{[5,43]}

Myocardial injury is also manifested by electrocardiographic and echocardiographic abnormalities.\textsuperscript{[43,44]} Myocardial injury in COVID-19 is
usually recognized in an advanced and severe stage of the disease,[5,43] especially with severe respiratory infection and ARDS.[43] Moreover, severe disease can subject susceptible patients to atherosclerotic plaque rupture when associated with immense inflammatory response and hemodynamic changes.[29] The injury of the myocardium can result in a wide range of manifestations, from asymptomatic cardiac troponin (cTn) rise to cardiogenic shock.

In a review of 26 studies (n = 11,685), the prevalence of acute myocardial injury was between 5% and 38%, with a pooled prevalence estimate of 20% (95% CI: 17%–23%).[8] The differences were significant between the survivors and nonsurvivors of the disease.[43,45] Furthermore, myocardial injury in COVID-19 was associated with a more severe disease and poorer outcomes.[43-47]

In a prospective design, the prevalence of cardiac involvement has been evaluated by cardiovascular magnetic resonance imaging (MRI) for the first time in COVID-19 patients (n = 100) at their early convalescent phase. Cardiac involvement and ongoing myocardial inflammation were detected in 78% and 60% of the patients, respectively, regardless of the presence of other comorbidities, or the characteristics of the course of the acute illness.[48] Elevation in troponin concentrations is common in COVID-19,[5,43] and may occur due to ischemic and nonischemic, for example, myocarditis, myocardial processes.[43,44,48] However, troponin levels in COVID-19 patients do not usually exhibit dynamic changes in values.[50]

A meta-analysis of four studies (n = 341) has shown that cardiac troponin I (cTnI) concentrations increased significantly with increased disease severity, but the heterogeneity between studies was substantially high.[44] Other reports have found slight increase in cTnI levels in all COVID-19 patients, with only 8%–12% of them exhibiting values above the 99th percentile in the URL.[20] Differential diagnosis for cTn elevation should be considered, including pulmonary embolism (PE), myocarditis, renal dysfunction and the resultant accumulation of cTn, nonspecific myocardial injury, and Type 2 MI (i.e., supply–demand mismatch).[5]

The proposed potential mechanisms for the cardiac myocytes damage include hypoxemia and respiratory failure; excessive inflammation and cytokine storm; ACE2 expression downregulation; cardiac endothelial injury; coronary thrombosis due to hypercoagulability; Type 1 (i.e., plaque rupture) or Type 2 MI due to stress and/or inflammation; and possible direct myocardial infiltration by the virus through ACE2 receptors on the heart myocytes.[6]  

**ACUTE CORONARY SYNDROME IN COVID-19**

Although the respiratory symptoms are cardinal in COVID-19, other symptoms may potentially overlap with those of acute coronary syndromes (ACS).[43,51,52] It is imperative to distinguish Type 1 MI from myocarditis and Type 2 MI.[53]

Published reports on COVID-19 showed that about 7% of the patients experienced acute cardiac injury, and may have presented with either myocarditis or Type 2 MI.[22,44] Although ST-segment elevation MI (STEMI) was the initial clinical presentation in all patients in one of the reports,[53] coronary angiography excluded Type 1 MI in 39.3% of the patients, i.e., unidentifiable culprit lesion.

The prevalence of ACS in COVID-19 may be underestimated due to the restricted availability of the coronary catheterization laboratories and the limited testing during the pandemic.[53] In a single-center study, among patients with STEMI (n = 83) who underwent primary percutaneous coronary intervention (PCI) during the outbreak, 13% of them had COVID-19.

The proportion of COVID-19 patients with an MI with nonobstructive coronary arteries (MINOCAs) was high, i.e., 54.5% of patients. COVID-19 patients had statistically significantly higher inflammatory markers and in-hospital mortality (27.3% vs. 5.6%, P = 0.016).[55] In a case series (n = 18) on COVID-19 patients with Type 1 MI, 50% of the patients underwent angiography, with two-third of them having obstructive lesions.[56]
Table 2: Case reports on COVID-19-positive patients with evidence of high thrombogenicity

| First author | Characteristics                                      | HPI                                      | Diagnostics                                                                 | CAG                                           | Medications                                 | Outcomes                                         |
|--------------|-------------------------------------------------------|------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------------------|----------------------------------------------|--------------------------------------------------|
| Soltani[64]  | A 63-year-old female, active smoker                   | SOB, cough, chills ×2 weeks; Chest pain ×24 h; resolved a day before admission; medical treatment only | ECG: anterolateral STEMI; CXR: mild interstitial edema; cardiomegaly; Cardiac CT: EF of 17%; LAD territory akinesis; apical aneurysm; measuring; LV thrombus; moderate RV hypokinesis with a small RV thrombus; multiple B/L pulmonary emboli | pLAD: 99% stenosis of the proximal LAD, with organized thrombi and TIMI-1 blood flow; Severe LV dysfunction with anterolateral akinesis, apical aneurysm, and thrombus | IV UFH and warfarin                           | Deteriorated Vasopressors and inotropic support Died of cardiogenic and pulmonary septic shock |
| Seif[65]     | A 58-year-old female                                 | Acute chest pain ×1 h; AKI; CRP; mild leukocytosis | ECG: infero-posterior STEMI (DAPT loading: aspirin, ticagrelor; fondaparinux) | EF: 40%                                       | Ticagrelor replaced by prasugrel Amiodarone for atrial tachycardia | Died 48 h after deterioration                      |
| Harari[71]   | A 40-year-old female                                 | Chest pain ×1 day; Cough and SOB ×1 week | ECG-1: sinus tachycardia and LV hypertrophy; ECG-2: Sinus tachycardia; new RBBB; STEMI in anterior, lateral, and inferior leads; Bedside ECHO: LV apex akinesia; no thrombus; EF 20% during CAG | PPCI                                           | Aspirin, clopidogrel Hospital Day 2: worsening chest pain | Emergent CAG                                      |
| Guagliumi[73] | A 43-year-old female                                 | Exertional sudden chest pain; transient episode of angina the day before Pain persisted on admission | ECG: infero-lateral STEMI; Focused ECHO: EF 25%; global hypokinesia and inferior and lateral akinesia; moderate pericardial effusion; no tamponade repeated ECG: diffuse ST-E; Repeated ECHO: severe LV dysfunction; progressive RV impairment; stable pericardial effusion | Normal epicardial coronary vessels; TIMI-2 flow (LAD); intense, persistent myocardial blush (dRCA) | Arunavir/cobicistat started in the ICU       | Cardiogenic shock; IABP upgraded to Impella Elevated inflammatory markers Died 48 h post-PCI |
| Siddamreddy[68] | A 61-year-old morbidly obese AA female, smoker | Left-sided chest pain ×1 h, SOB, cough body aches for few days; Elevated WBC, CK, CK-MB, TnI, BNP, LFTs (ALT, AST) | ECG: inferior wall STEMI; CXR: diffuse B/L pulmonary infiltrates consistent with cardiogenic edema; ECHO post CAG: EF 30-35%; ECHO 2018: 65% | RCA: subtotal occlusion; AT; DES | HCQ and azithromycin                        | Troponins trended down Elevated LDH and D-dimer In ICU on MV |

Contd...
Table 2: Contd...

| First author                  | Characteristics | HPI                  | Diagnostics                                                                 | CAG                          | Medications                           | Outcomes                          |
|-------------------------------|-----------------|----------------------|-----------------------------------------------------------------------------|------------------------------|---------------------------------------|------------------------------------|
| Shams[46]                     | A 28-year-old   | AA male              | Fever, dry cough, SOB, myalgias×3 days                                      | Day 9: acute severe          | Ostial-proximal LAD: thrombus with    | CV risk factor screening was       |
|                               | AA male         | No PMH               | Elevated CRP, ferritin, lactic acid Ceftriaxon, azithromycin, HCQ: responded well; stable by day 8 | left-sided chest pain,      | 100% stenosis; TIMI-0 flow;           | negative Follow-up in the clinic    |
|                               |                 |                      |                                                                             | radiating to his back       | AT; DES; TIMI-3 flow achieved         | managed                            |
|                               |                 |                      |                                                                             | ECG: anterior STEMI          | Postprocedure, epifibatide×18 h;      |                                    |
|                               |                 |                      |                                                                             | Elevated TsT                 | UFH×24 h                              |                                    |
|                               |                 |                      |                                                                             | ECHO: EF 28%; dilated LV;    |                                       |                                    |
|                               |                 |                      |                                                                             | SWMA; akinetic septal and apical segments |                                       |                                    |
| Dominguez-                     | A 64-year-old   | male                 | Acute STEMi Treated for COVID-19 a week before this admission but without VTE prophylaxis; discharged after 7 days, just hours before he returned to the hospital | -                            | pRCA: Critical                       | Discharged                         |
| Erquicia [36]                 | male            | No known CV          |                                                                             |                                                                             | thrombotic stenosis; no atheroma (by OCT) |                                    |
|                               | risk factors    |                      |                                                                             |                                                                             | RCA: AT; DES                         |                                    |
|                               |                 |                      |                                                                             |                                                                             | mLAD: nonocclusive                   |                                    |
|                               |                 |                      |                                                                             |                                                                             | thrombus without plaue            |                                    |
|                               |                 |                      |                                                                             |                                                                             | confirmed by OCT; medical treatment |                                    |
|                               |                 |                      |                                                                             |                                                                             | with LMWH x 7 days and DAPT       |                                    |
| Otero[33]                     | A 69-year-old   | male, smoker         | Exertional chest pain×6 days Avoided seeking medical care due to the COVID-19 pandemic | ECG: posterior STEMI; tenecteplase, clopidogrel, aspirin ECHO day 7: resolution of hemorrhagic pericardial effusion after tenecteplase | LCx: Culp 100%                       | Day 10: staged PCI for LAD          |
|                               | male            | HTN, DM, dyslipidemia, abdominal aortic aneurysm |                                                                             |                                                                             | thrombotic occlusion                | Day 19: discharge                  |
|                               | smoker          |                      |                                                                             |                                                                             | pLD: 90% occlusion                 |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | Unsuccessful balloon angioplasty   |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | (high thrombus burden); IABP        |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | inserted ECHO: EF 25%; small        |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | pericardial effusion; visible      |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | thrombus                        |                                    |
|                               | smoker          |                      |                                                                             |                                                                             |                                   |                                    |
| Ueki cl [60]                  | A 82-year-old   | male                 | ARDS complicated by STEMi and PE Elevated D-dimer, CRP, procalconitin      | ECG: Infero-posterior STEMI  | Intubated; PCI (DES) pLAd: thrombotic | ICU admission for further care     |
|                               | male            |                      |                                                                             | CT: Acute PE in right PA     | occlusion pLAd: 90% occlusion        |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | Unsuccessful balloon angioplasty   |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | (high thrombus burden); IABP        |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | inserted ECHO: EF 25%; small        |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | pericardial effusion; visible      |                                    |
|                               | smoker          |                      |                                                                             |                                                                             | thrombus                        |                                    |
|                               | smoker          |                      |                                                                             |                                                                             |                                   |                                    |
| Xiao [67]                     | A 78-year-old   | male                 | Sudden chest pain×5 h                                                        | ECG: Anterior wall AMI        | oLAd: thrombus plAd: 2 DEs Flow:    | Transferred to the general ward    |
| (Case 3)                      | male            | HTN                  |                                                                             |                                                                             | TIMI-3 after Ic tirofiban injection |                                    |
|                               |                 |                      |                                                                             |                                                                             | D-to-B time: 139 min              |                                    |

AA: African-American, AMI: Acute myocardial infarction, AKI: Acute kidney injury, ALT: Alanine aminotransferase, ARDS: Acute respiratory distress syndrome, AST: Aspartate aminotransferase, AT: Ascarii thrombectomy, aVL: Augmented vector left, B/L: Bilateral, BNP: Brain natriuretic peptide, CAD: Coronary artery disease, CAG: Coronary angiography, CK: Creatinine kinase, COPD: Chronic obstructive pulmonary disease, CPAP: Continuous positive airway pressure, CPR: Cardiopulmonary resuscitation, CRP: C-reactive protein, CT: Computed tomography, CV: Cardiovascular, COVID-19: Coronavirus disease 2019, CVA: Cerebrovascular accident, CXR: Chest radiograph, d: Distal, DAPT: Dual antiplatelets, DES: Drug-eluting stent, DM: Diabetes mellitus, D-to-B: door-to-balloon, ECG: Electrocardiogram, ECHO: Echocardiogram, EF: Ejection fraction, eGFR: Estimated glomerular filtration rate, GERD: Gastro-esophageal reflux disease, HCQ: Hydroxychloroquine, HTP: History of present illness, HTN: Hypertension, IA: Intra-arterial, IABP: Intra-aortic balloon pump, IC: Intra-coronary, ICU: Intensive care unit, IV: Intravenous, LAD: Left anterior descending artery, LCx: Left circumflex artery, LDH: Lactic acid dehydrogenase, LFTs: Liver function tests, LMWH: Low-molecular-weight heparin, LV: Left ventricle/ventricular, m: Mid, MV: Mechanical ventilation/ventilator, o: Ostial, OCT: Optical coherence tomography, OSA: Obstructive sleep apnea, p: Proximal, PA: Pulmonary artery, PE: Pulmonary embolism, (P): PCI (primary) percutaneous coronary intervention, PMI: Past medical history, RBBB: Right bundle branch block, RCA: Right coronary artery, RV: Right ventricular, SOB: Shortness of breath, ST-E: ST-segment elevation, STEMI: ST-segment elevation myocardial infarction, SR: Sinus rhythm, SWMA: Segmental wall motion abnormality, TIMI: Thrombolysis in myocardial infarction, Tnl: Troponin I, TsT: Troponin T, UFH: Unfractionated heparin, VT: Ventricular tachycardia, VTE: Venous thromboembolism, WBC: White blood cell

GENERAL ACUTE CORONARY SYNDROME MANAGEMENT

Diagnosis of myocardial injury should be confirmed through clinical examination, hs-troponin along with other markers, and imaging modalities, for example, echocardiography, cardiac MRI, cardiac computed tomography (CT), and diagnostic right and left heart catheterization. Persistent hs-troponin rise should be considered in the context of other inflammatory markers such as coagulation panel, ferritin, IL-6, and liver enzymes to confirm the etiology. Whereas, imaging modalities should be performed in selected cases if such modalities are anticipated to provide clinical benefit.[5]

The management of COVID-19 patients with Type 1 MI should be based on the published guideline recommendations such as the Society for Cardiovascular Angiography and Interventions (SCAI) and the American College of Cardiology (ACC). In their joined consensus statement, primary PCI is the gold standard of care for patients presenting with STEMI at PCI-capable facilities with fibrinolysis consideration in specific situations and in non-PCI-capable hospitals. [57,58] The SCAI and another expert groups have also recommended fibrinolysis in...
Table 3: Case reports on COVID-19-positive patients with stent thrombosis

| Author                  | Patient characteristics | HPI                                      | Diagnostics               | Coronary angiography                      | Medications                       | Outcomes                                                                 |
|-------------------------|-------------------------|------------------------------------------|---------------------------|-------------------------------------------|-----------------------------------|---------------------------------------------------------------------------|
| Lacour et al.[93]       | A 68-year-old male     | Acute chest pain × 4 h; Anterior STEMI; DAPT loading (aspirin, ticagrelor); Non-PCI facility; tenecteplase given | EF 15%                    | Rescue PCI; Recurrent chest pain after 2 h; NSVT and cardiogenic shock; Emergency CAG: LAD stent thrombosis; AT; balloon angioplasty; Inotrope support; IABP; IV UFH | Ticagrelor replaced by prasugrel | 36 h later: new episode of chest pain with ST-E; CAG; extensive LAD stent thrombosis; AT; refractory no reflow Died 24 h after hemodynamic deterioration Died a few hours after severe ARDS Elevated Scr, TrtT, CK; increased inotropes AF; cardiovascular Shock (septic and cardiac); extremes cyanosis; SCr rise; bacterial superinfection; multi organ failure; ARDS CVVHD-Ci-Ca; antibiotics; ventilation; ECMO was not suitable Hospital day 11: supportive therapy only; died Inotrope stopped; ECMO removed 2 days post-PCI Patient transferred to ward |
| Galeazzi et al.[99]    | A 79-year-old male     | Intense chest pain; AMI; Fever and cough × 1 week | ECG: inferior STEMI       | pRCA: in-stent thrombosis; treated        | -                                 |                                                                            |
| Hinterser et al.[89]   | A 65-year-old male     | Fever, dry cough, body aches; RRI O₂ of 92% at RA Day 3: ARDS; O₂ of 78% Elevated TnT, CK, BNP ICU; intubated; VF; electrical shock | Initial ECG: SR Initial ECHO: EF of 67%; no SWMA ECG: complete RBBB right bundle branch block with ST-E in aVR ECHO: severely reduced EF ECHO (post-CAG): EF 35% | LAD: occlusion of stented segment; new DES; TIMI-3 flow | Prasugrel, aspirin, ticagrelor |                                                                            |
| Xiao et al.[87]        | Case series (Case 2)   | Fever, dry cough, SOB × 1 month Hospital day 3: sudden chest pain; shortly, had signs of cardiac shock (hypotension, clamminess in extremities) | ECG: anterior STEMI       | Before CAG: inotrope; ECMO; IABP CAG: Thrombus occluding stent in LAD; dissection distal to stent in LAD; 2 DES in mLAD CTos in circumflex branch and RCA | -                                 |                                                                            |
| Prieto-Lobato et al.[93] | Case series (Case 1)   | A 49-year-old male                          | Lateral STEMI            | EF: 45%                                   | PCI for LCx with 2 DES (overlapping); chest pain after 30 min; ST-depression; LCx stent thrombosis; IC ticagrelor; stent overexpanded AT; ticagrelor; 2 DES; flow restored | Aspirin, ticagrelor, 24-h ticagrelor infusion Discharged on day 4 |
| Prieto-Lobato et al.[93] | Case series (Case 2)   | A 71-year-old male                          | EF: 55%                   |                             | AT; ticagrelor; 2 DES; flow restored | Aspirin, ticagrelor - |
| Prieto-Lobato et al.[93] | Case series (Case 3)   | A 86-year-old male                          | EF: 45%                   | Very late LAD stent thrombosis; new DES implanted | -                                 |                                                                            |
| Prieto-Lobato et al.[93] | Case series (Case 4)   | A 86-year-old male                          | Chest pain × 6 h; anterior STEMI | -                                      | -                                 |                                                                            |

ABG: Arterial blood gas; AF: Atrial fibrillation; AMI: Acute myocardial infarction; ARDS: Acute respiratory distress syndrome; aVR: Augmented vector right; BNP: Brain natriuretic peptide; CAD: Coronary artery disease; CK: Creatinine kinase; CKD: Chronic kidney disease; CRP: C-reactive protein; CT: Computed tomography; CTO: Chronic total occlusion; CVVHD-Ci-Ca: veno-venous hemodiafiltration with citrate, CXR: Chest radiography, DAPT: Dual antiplatelet therapy; ECG: Electrocardiogram, ECHO: Echocardiography, ECMO: Extracorporeal membrane oxygenation, EF: Ejection fraction, IABP: Intracoronary balloon pump, IC: Intracoronary, IVUS: Intravascular ultrasound, LAD: Left anterior descending artery, LCX: Left circumflex, LDLH: Lactic acid dehydrogenase, MI: Myocardial infarction, min: Minute(s), NIV: Noninvasive ventilation, NSTEMI: Non-ST-segment elevation myocardial infarction, NSVT: Nonsustained ventricular tachycardia, p: Proximal, PAD: Peripheral artery disease, PMH: Past medical history, (P) PCI: (primary) Percutaneous coronary intervention, RA: Room air, RBBB: Right bundle branch block, RTI: Respiratory tract infection, SCr: Serum creatinine, SR: Simus rhythm, ST-E: ST-segment elevation, STEMI: ST-segment elevation myocardial infarction, TIMI: Thrombolysis in myocardial infarction, TrtT: Tropinon T, SWMA: Segmental wall motion abnormalities, VF: Ventricular fibrillation.
select patients.\textsuperscript{49,59-62} In another document, SCAI and ACC discussed the issues and challenges encountered by the catheterization laboratory personnel during the pandemic while carefully balancing between patient benefit and personnel safety.\textsuperscript{54} There is only a limited number of case reports which had discussed the management of COVID-19 patients presenting with Type 1 MI.\textsuperscript{63-76}

**ANTITHROMBOTIC THERAPY IN COVID-19**

In Type 1 MI, the use of either anticoagulation and dual antiplatelet therapy (DAPT) is as per the respective published guidelines, unless contraindicated\textsuperscript{77-80} DAPT regimen with a less potent antiplatelet such as clopidogrel may be considered in patients at high risk of bleeding. Hospitalized COVID-19 patients should be risk stratified for VTE like other patients.\textsuperscript{2} Given the pro-inflammatory status in COVID-19, all confirmed or suspected cases should be prescribed thromboprophylaxis therapy, unless contraindicated.\textsuperscript{1,2} Intermittent pneumatic compression, therefore, may be considered.\textsuperscript{3} The ideal regimen for thromboprophylaxis is not established\textsuperscript{43} and evidence behind the relevant guideline recommendations are not specific for patients with COVID-19.\textsuperscript{81-86}

Parenteral anticoagulants, i.e., unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), are preferred in most of the cases given their safety in terms of drug–drug interactions with COVID-19 therapy.\textsuperscript{3,43} There is no universal consensus on the most appropriate dosing.\textsuperscript{2} However, due to increased rate of thrombotic events, anticoagulation therapy intensification has been debated.\textsuperscript{11} COVID-19 patients with indications for anticoagulation should be continued on their therapy. Therapeutic doses may be considered for patients with suspected PE. This has been justified by the difficulty in escorting ventilated patients to be scanned by CT; limiting staff exposure to COVID-19 patients; and the fact that D-dimer is not a useful measure given its high baseline levels in COVID-19 patients.

The use of therapeutic dose of anticoagulants has also been considered to prevent microvascular thrombosis in severe disease despite the absence of data to support it.\textsuperscript{13} The presence of microthrombi and coagulopathy has also proposed the use of tissue plasminogen activator as a possible treatment option.\textsuperscript{2} In addition to VTE prevention, the prophylactic-dose anticoagulation, mainly LMWH, was associated with a lower 28-day mortality in anticoagulation users who had sepsis-induced coagulopathy (40.0% vs. 64.2%, \( P = 0.029 \)) or a substantially elevated D-dimer (32.8% vs. 52.4%, \( P = 0.017 \)) compared to nonusers.\textsuperscript{87}

Thromboprophylaxis with LMWH may reduce the generation of thrombin and alter the course of DIC.\textsuperscript{3} Similarly, treatment-dose anticoagulation was associated with better hospital outcomes. Moreover, mechanically ventilated anticoagulation users had lower in-hospital mortality rate (29.1% vs. 62.7%) compared to nonusers. Longer anticoagulation therapy was associated with lower mortality risk (adjusted HR of 0.86 per day, 95% CI: 0.82–0.89; \( P < 0.001 \)).\textsuperscript{88}

### Table 4: Potential drug-drug interactions between P2Y12 inhibitors and selected off-label COVID-19 medications

| Medication* | Clopidogrel (CYP2C19 substrate) | Prasugrel (CYP3A4 and CYP2B6 substrate) | Ticagrelor (CYP3A4 substrate) |
|-------------|--------------------------------|---------------------------------------|-------------------------------|
| Darunavir/ | - | Minor DDI: no action needed | Major DDI: avoid combination |
| cubicistat (Protease inhibitor) | | Prasugrel’s active metabolite (s) serum levels may decrease | Ticagrelor’s active metabolite (s) serum levels increase but not active metabolite (s) levels |
| Inhibitors of | | MOI: inhibition of prasugrel metabolism to its active metabolite (s) | MOI: inhibition of ticagrelor metabolism to its active metabolite (s) |
| CYP3A4 (strong) | | | |
| Lopinavir/ | Moderate DDI: monitor therapy; consider alternative | Minor DDI: no action needed | Major DDI: avoid combination |
| ritonavir (Protease inhibitors) | Clopidogrel’s active metabolite (s) serum levels may decrease | Prasugrel’s active metabolite (s) serum levels may decrease | Ticagrelor’s active metabolite (s) serum levels decrease |
| Inhibitors of | MOI: roninav inhibition of clopidogrel metabolism to its active metabolite (s)\textsuperscript{a} | MOI: inhibition of prasugrel metabolism to its active metabolite (s) | MOI: inhibition of ticagrelor metabolism to its active metabolite (s) |
| CYP3A4 | and P-gp | | |
| Enhancer of CYP3A4 expression | - | - | Moderate DDI: monitor therapy |
| Tocilizumab (IL-6 inhibitor): | | | Ticagrelor serum levels decrease |
| Enhancer of CYP3A4 expression | | | Effect may persist several weeks after tocilizumab discontinuation due to its long half-life |

\textsuperscript{a}No documented DDI of azithromycin, corticosteroids, favipiravir, HCQ, interferon, remdesivir, and ribavirin with P2Y12 inhibitors. \textsuperscript{b}CYP3A4 inhibition can lead to reduction in clopidogrel efficacy despite being mostly metabolized by CYP2C19.\textsuperscript{15} Some other drug labeling states that this combination is contraindicated/should be avoided. Reference: Lexicomp\textsuperscript{a} available from [http://online.lexi.com/lco/action/interact - accessed on 14/08/2020. CYP: Cytochrome P450, DDI: Drug-drug interaction, IL-6L: Interleukin-6, MOI: Mechanism of interaction, RNA: Ribonucleic acid](http://online.lexi.com/lco/action/interact - accessed on 14/08/2020. CYP: Cytochrome P450, DDI: Drug-drug interaction, IL-6L: Interleukin-6, MOI: Mechanism of interaction, RNA: Ribonucleic acid).
Table 5: Potential drug-drug interactions between oral anticoagulation and selected off-label COVID-19 therapy

| Medication *a, b | Factor Xa inhibitors | Thrombin inhibitor | VKA |
|------------------|-----------------------|--------------------|-----|
|                  | Apixaban (CYP3A4 and P-gp substrate) | Edoxaban (CYP3A4 and P-gp substrate) | Rivaroxaban (CYP3A4 and P-gp substrate) | Dabigatran (P-gp substrate) |
| Azithromycin     | Minor DDI: No action needed | Moderate DDI: modify therapy (indication-dependent) | Minor DDI: no action needed | Moderate DDI: monitor therapy |
| Inhibitor of P-gp | Apixaban serum levels may increase | Edoxaban serum levels may increase | Rivaroxaban serum levels may increase | Dabigatran's active metabolite (s) serum levels may increase |
|                  | MOI: inhibition of P-gp transporter | MOI: inhibition of P-gp transporter | MOI: inhibition of P-gp transporter | MOI: inhibition of P-gp transporter |
| Corticosteroids  | -                      | -                  | -                           | -                            |
|                  |                        |                    |                              |                              |
| Darunavir/       | Moderate DDI: monitor therapy | Moderate DDI: avoid combination | Moderate DDI: monitor therapy with cobicistat | Moderate DDI: monitor therapy |
| cobicistat       | (protease inhibitor)    | with cobicistat     |                              |                              |
| Inhibitors of CYP3A4 (strong), inhibitor of P-gp (cobicistat) | Apixaban serum levels may increase | Rivaroxaban serum levels may increase | Dabigatran's active metabolite (s) serum levels may increase | VKA serum levels may increase |
| Interferon*      | -                      | -                  | -                           | -                            |
|                  |                        |                    |                              |                              |
| Lopinavir/       | Major DDI: modify therapy with ritonavir | Moderate DDI: avoid combination with ritonavir | Moderate DDI: no action needed | Moderate DDI: monitor therapy |
| ritonavir        | (protease inhibitor)    | Edoxaban serum levels may increase | Rivaroxaban serum levels may increase | VKA serum levels may decrease |
|                  | Apixaban serum levels may increase | MOI: Inhibition of P-gp transporter | MOI: Inhibition of P-gp transporter | MOI: Uncertain. |
|                  | MOI: Inhibition of CYP3A4 and P-gp transporter |                              |                              | For warfarin: may be by induction of CYP2C9 |
| Tocilizumab      | Moderate DDI: monitor therapy | Moderate DDI: no action needed | Minor DDI: no action needed | Moderate DDI: monitor therapy |
| (IL-6 inhibitor) | Apixaban serum levels may increase | Rivaroxaban serum levels may increase | Rivaroxaban serum levels may increase | VKA serum levels may decrease |
| Enhancer of CYP3A4 | -                      | -                  | -                           | -                            |

*aNo documented DDI of favipiravir, hydroxychloroquine, remdesivir, and ribavirin with OACs.
*bSignificance of the DDI should also consider the presence of another interacting drugs and renal function as appropriate.
*cDDI applies to interferon alfa-2a (2a, 2b, n3), Peginterferon alfa-2a (2a, 2b). Some other drug labeling states that this combination is contraindicated, should be avoided. Reference: Lexicomp® available from http://online.lexi.com/loc/action/interact - accessed on 14/08/2020. AF: Atrial fibrillation, DDI: Drug-drug interaction, IL-6: Interleukin-6, MOI: Mechanism of this interaction, OAC: Oral anticoagulant, P-gp: P-glycoprotein, VKA: Vitamin K antagonists

CHALLENGES IN THROMBOSIS MANAGEMENT

Coronary angiography setting

Delay in door-to-balloon time

During the pandemic, the rate of admission for ACS has been reduced as reported in some studies. The admission rate fell by 40% in 147 English hospitals early in the pandemic as compared to that in 2019. In addition, in the early phase of the pandemic, there have been reductions in PCI procedures for STEMI by 21%–40% and for non-STEMI by 37%. Some hospital systems have transitioned to fibrinolysis as an initial approach for acute MI management. Factors that may have contributed to a lower ACS admission rate include delay in seeking medical attention due to patients’ fear of contracting SARS-CoV-2 infection and delays in patient triage in emergency department or in activation of...
coronary catheterization laboratory due to additional steps needed for personnel safety. However, several reports have indicated that the drop in the ACS admission rate was temporary but then rebounded.

The rebound was probably linked to patients’ encouragement to seek medical attention if experiencing signs and symptoms of acute myocardial infarction, even during the pandemic. In one study, the rate of admission fell by only 16% late in the pandemic as compared with that of the previous year. It is well known that delays in acute MI presentation and management have been associated with MI-related complications and vice versa given the time-sensitive feature of STEMI. Reports on COVID-19 have described STEMI complications in patients who avoided seeking medical assistance and discussed potential increase in the risk of mortality.

**High thrombogenicity**

Findings from a single-center study in STEMI patients with concurrent COVID-19 demonstrated higher thrombus burden and worse outcomes compared to those without COVID-19. All patients underwent primary PCI. COVID-19 patients had higher thrombogenicity evidenced by significantly higher incidence of multi-vessel thrombosis, stent thrombosis, and high modified thrombus grade after first device, with significantly more glycoprotein IIb/IIIa inhibitors and aspiration thrombectomy use.

The myocardial blush grade and the left ventricular ejection fraction were significantly lower and the hs-troponin and D-dimer levels were significantly higher in COVID-19 patients, who experienced significantly higher rate of cardiac arrest. With regard to in-hospital outcomes, COVID-19 patients had significantly longer hospital length of stay and more ICU admissions.

At another center, the incidence of stent thrombosis increased from 0.13% to 4%, a rare, i.e., <1% incidence at 30 days, but a catastrophic complication of stent implantation. Some reports have raised the concern about the use of fibrinolysis over primary PCT. There are several published cases demonstrating higher thrombotic features of coronary angiography findings, as presented in Tables 2 and 3.

**Drug therapy in COVID-19**

**Efficacy of anticoagulation therapy**

When anticoagulated COVID-19 patients are admitted to hospital, especially to an ICU, specific drug-related problems arise with regard to their anticoagulation therapy. Patients on Vitamin K antagonists experience PT/international normalized ratio instability due to various causes. Furthermore, there have been concerns about UFH therapy and the frequent blood sampling for monitoring and clinical staff exposure to infection. Achieving UFH therapeutic aPTT targets is another issue, given the elevated fibrinogen levels, which is considered one of the many other factors for both hypercoagulability and heparin resistance. Thus, anti-Xa heparin levels have been suggested for monitoring.

**Drug–drug interaction**

Given that there is no definite treatment for COVID-19, different drugs such as anti-inflammatory and antiviral agents have been used without labeled indications in COVID-19. Their efficacy and safety in this setting are awaited to be proven. Several agents are well known to interact with various antithrombotic agents, which warrants particular attention when used. Drug–drug interactions between the off-label COVID-19 therapies and the commonly used P2Y12 inhibitors and oral anticoagulants are summarized in Tables 4 and 5.

**Drug–disease interaction**

DIC is common in critical illness including severe COVID-19 especially when it is associated with sepsis. In majority of DIC patients, it is recommended to discontinue long-acting antiplatelet agents unless unavoidable. Antiplatelet therapy should be individualized and considered for essential indications such as post-PCI in moderate or severe COVID-19 with DIC without excessive bleeding. Overt bleeding is rare in the setting of COVID-19 alone. However, when it occurs in association with DIC, management principles follow those in septic coagulopathy as per the International Society of Thrombosis and Haemostasis guidelines with regard to blood product transfusion.

**Angiotensin-converting enzyme 2 and therapeutic implications**

Because the entry of SARS-CoV-2 to human host occurs through ACE2 receptor, studies have suggested that the susceptibility to SARS-CoV-2 may be enhanced by ACE inhibitors (ACEi) and angiotensin receptor blockers (ARBs), which may upregulate ACE2. On the other hand, other reports found that ACEi/ARBs may have a protective effect on the lungs by lowering the levels of angiotensin II through its conversion to angiotensin.

**CONCLUSION**

Coagulation abnormalities are common in COVID-19 and predispose the patients to both venous and arterial thrombotic events. Antithrombotic agents play a key role in the prevention and treatment of the thrombotic events but should be balanced with their risk of bleeding and their interactions with other drugs and disease states. Currently, there is no consensus on the optimal management approach for ACS with many challenges to be taken up.
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