COVID-19–associated complications

November 2021
Coronavirus disease 2019 (COVID-19) is an infectious acute respiratory disease caused by a novel coronavirus. WHO was informed of cases of pneumonia of unknown microbial etiology associated with Wuhan City, Hubei Province, China on 31 December 2019. The WHO later announced that a novel coronavirus had been detected in samples taken from these patients.

Since then, the epidemic has escalated and rapidly spread around the world, with the WHO first declaring a public health emergency of international concern on 30 January 2020, and then formally declaring it a pandemic on 11 March 2020. Clinical trials and investigations to learn more about the virus, its origin, how it affects humans, and its management are ongoing.
The pathophysiology resembles that of other coronavirus infections. However, emerging evidence indicates that COVID-19 has distinctive pathophysiological features that set it apart from respiratory failure of other origins.

SARS-CoV-2 attaches to the angiotensin-converting enzyme-2 (ACE2) receptor on target host cells, followed by internalization and replication of the virus.

ACE2 receptors are highly expressed in the upper and lower respiratory tract cells, but are also expressed in myocardial cells, renal epithelial cells, enterocytes, and endothelial cells in multiple organs, which may explain the extra-pulmonary manifestations associated with the disease.
Potential Complications of COVID-19

Neurologic
- Cerebrovascular Disorders
- Corticospinal Damage
- Meningitis/Encephalitis
- Encephalopathy
- Cognitive + Motor Deficits

Cardiac
- MI (Types I & II)
- Heart Failure
- Viral Myocarditis
- Stress Cardiomyopathy
- Arrhythmia

Systemic
- Acute Liver Failure
- Acute Kidney Injury
- Cytokine Storm
- Secondary Infection
- Septic Shock
- MIS-C

Respiratory
- ARDS
- Pneumonia
- Dyspnoea

Hematologic
- Coagulopathy
  - PE
  - DVT
  - DIC
  - Organ Thromboemboli
  - Arterial emboli
  - Thrombocytopenia

Vascular
- Vasculitis
- Endothelitis

Cutaneous
- Erythema
- Chilblain-like lesions
- Urticaria-like lesions
- Vesicular lesions
Complications of COVID-19

- Venous thromboembolism
- Cytokine release syndrome
- Cardiovascular complications
- Acute kidney injury
- Acute liver injury
- Acute respiratory failure
- Neurologic complications
- Sepsis and septic shock
- Co-infections (especially fungal infections)
Venous thromboembolism

- The pooled incidence of venous thromboembolism, deep vein thrombosis, and pulmonary embolism among hospitalized patients was 14.7, 11.2%, and 7.8%, respectively.

- The prevalence was significantly higher in patients admitted to the intensive care unit, despite thromboprophylaxis.
While venous thromboembolism appears to be frequent in hospitalized COVID-19 patients, one systematic review and meta-analysis found that the overall risk of venous thromboembolism did not significantly differ between COVID-19 and non-COVID-19 cohorts with similar disease severity, except for patients admitted to the intensive care unit.

This suggests that severe disease that requires intensive care unit admission may be a risk factor for developing venous thromboembolism.
- Pulmonary embolism is rare in patients presenting to the emergency department, but the incidence is approximately 9-fold higher than in the general non-COVID-19 population.

- COVID-19 patients with thromboembolic events have 1.93 times the odds of dying compared with patients without venous thromboembolism.
- **Coagulopathy** in COVID-19 has a prothrombotic character, which may explain reports of thromboembolic complications.
- Patients may be predisposed to venous thromboembolism due to the direct effects of COVID-19, or the indirect effects of infection (e.g., severe inflammatory response, critical illness, traditional risk factors).
- **Thrombotic events** may be due to cytokine storm, hypoxic injury, endothelial dysfunction, hypercoagulability, and/or increased platelet activity.
SARS-CoV-2 and Virchow's Triad

Endothelial Injury
- Direct invasion of endothelial cells by SARS-CoV-2 via ACE2 receptor and increased angiogenesis
- Release of inflammatory cytokines like IL-6
- Intravascular catheters

Stasis
- Alternate and Lectin complement pathway activation C5b-9 (MAC), C4d, MASP2
- Immobilization in hospitalized patients

Hypercoagulable State
- Coagulation abnormalities
  - TEG findings:
    - Shortened R = Increased thrombin burst
    - Shortened K = Increased fibrin generation
    - Increased MA = Greater clot strength
    - Reduced LY30 = Reduced fibrinolysis
- Elevated vWF and Factor VIII
- Increased D-dimer
- Elevated fibrinogen
- Neutrophil extracellular traps
- Prothrombotic microparticles and anionic phospholipids

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Immunothrombosis or Thromboinflammation in COVID-19
Risk factors with the most evidence for being predictive of venous thromboembolism

✓ Older age
✓ Elevated D-dimer levels
✓ Male sex
✓ Obesity
✓ Mechanical ventilation
✓ ICU admission
**Recommendations**

(a) We **recommend** pharmacologic **VTE prophylaxis** for **all hospitalized** non-pregnant patients with confirmed or highly suspected COVID-19, **regardless of VTE risk assessment** score (e.g. IMPROVE [13], Padua [14], Caprini [15]) **unless a contraindication exists** (e.g. active bleeding, profound thrombocytopenia).

**Table 2. Management strategy**

<table>
<thead>
<tr>
<th>COVID-19+</th>
<th>Coagulation tests</th>
<th>Standard-dose VTE PPX</th>
<th>Escalated-dose* VTE PPX</th>
<th>Therap. dose anti-coagulation</th>
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<td>ARDS</td>
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* Journal of Thrombosis and Thrombolysis (2020) 50:72–81

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PATIENTS HOSPITALIZED WITH COVID-19

- Pharmacological VTE prophylaxis, unless contraindicated
- Careful assessment for incident thrombotic events
- Follow PT/INR, APTT, D-dimer, fibrinogen
- Continuation of precedent antithrombotic therapy based on clinical condition and assessment for drug-drug interaction [see Tables 3 and 4]


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Prophylaxis Regimen

Enoxaparin 40 mg daily or similar LMWH regimen (i.e., dalteparin 5000 u daily) can be administered with consideration of SC heparin (5000 u twice to three times per day) in patients with renal dysfunction (i.e., creatinine clearance < 30 mL/min). Once daily

Only a minority of the panel considered intermediate intensity (31.6%; i.e., enoxaparin 1 mg/kg/day, enoxaparin 40 mg BID, UFH with target PTT 50–70) to therapeutic anticoagulation (5.2%) reasonable.
Therapeutic anticoagulation

- Initial parenteral anticoagulation with a low molecular weight heparin or unfractionated heparin is preferred in acutely ill hospitalized patients; however, direct oral anticoagulants may be used provided there is no potential for drug-drug interactions.

- **Parenteral anticoagulation with a low molecular weight heparin is preferred over unfractionated heparin in critically ill patients.**

- Direct oral anticoagulants are the preferred option in outpatients provided there is no potential for drug-drug interactions, with warfarin considered a suitable alternative.
Initial treatment (first 5-21 days)

- **Apixaban**: 10 mg bid for 7 days
- **Dabigatran**: 150 mg bid preceded by LMWH for 5-10 days
- **Edoxaban**: 60 mg od (30 mg od if ClCr < 50-30 ml/min or concomitant potent P-P inhibitors) preceded by LMWH for 5-10 days
- **Rivaroxaban**: 15 mg od for 21 days
- **VKA** to achieve INR 2-3 preceded by LMWH for 5-10 days

Long term treatment (first 3-6 months)

- **Apixaban**: 5 mg bid; Apixaban 2.5 mg bid beyond 6 months

Extended treatment (following initial 3-6 months)

**Minimum of 3 months**
(d) We suggest that patients taking chronic oral anticoagulant in the outpatient setting be switched to shorter acting agents (e.g., LMWH or UFH) when initially hospitalized for COVID-19 in case of clinical deterioration, changes in renal function, or need for invasive procedures.
A high incidence (14.7%) of asymptomatic deep vein thrombosis was reported in a cohort of patients with COVID-19 pneumonia. An autopsy study of 12 patients revealed deep vein thrombosis in 58% of patients in whom venous thromboembolism was not suspected before death.

These studies highlight the importance of having a high suspicion for venous thromboembolism in patients who have signs of coagulopathy, including elevated D-dimer level.

While these patients are at higher risk of thrombotic events, they may also be at an elevated risk for bleeding. In a small retrospective study, 11% of patients at high risk of venous thromboembolism also had a high risk of bleeding.
Antiphospholipid antibodies (mainly lupus anticoagulant) were detected in nearly half of patients in one meta-analysis and systematic review, with an increased prevalence in patients with severe and critical disease.

However, there does not currently appear to be any association between this finding and disease outcomes (e.g., thrombosis, mortality).
Cytokine release syndrome

- Cytokine release syndrome may cause ARDS or multiple-organ dysfunction, which may lead to death.
- Elevated serum proinflammatory cytokines (e.g., tumor necrosis factor alpha, interleukin-2, interleukin-6, interleukin-8, interleukin-10, granulocyte-colony stimulating factor, monocyte chemoattractant protein 1) and inflammatory markers (e.g., C-reactive protein, serum ferritin) have been commonly reported in patients with severe COVID-19.
- This likely represents a type of virus-induced secondary hemophagocytic lymphohistiocytosis, which may be fatal.
- **Interleukin-6**, in particular, has been associated with severe COVID-19 and increased mortality.
Acute lung injury (ARDS)
Endothelial dysfunction (capillary leak syndrome, anemia, DIC etc.)
MOF (Multiorgan Failure) Death
Antiviral response

**Viral removal & tissue damage**

**Self-amplifying inflammatory cascade**

- Stem cell therapy: MSCs transfusion
- Corticosteroids "Immune regulation"
- IL-6/IL-6R blocker: Tocilizumab/Sarilumab/Clazakizumab/Siltuximab
- JAK inhibitor: Baricitinib/Ruxolitinib/Tofacitinib
- IL-1 blocker: Anakinra/Canakinumab
- Colchicine
- Blood purification therapy

**Key Pathways**
- CD8+ T cell
- Virus infected cell
- DAMPs
- PAMPs
- IFN-γ/ TNF-α
- Neutrophil
- ROS
- MMPs
- PPARγ
- Perioxidase
- Monocyte
- GM-CSF
- Antibodies
- Plasma cell
- Tfh cell
- CD4+ T cell
- CD8+ T cell
- NK cell
- Dendritic cell
- Macrophage

**Mechanisms**
- IFN-γ inhibitor: Emapalumab
- TNF-α inhibitor: Adalimumab
Cardiovascular complications

- COVID-19 is associated with a high inflammatory burden that can result in cardiovascular complications with a variety of clinical presentations. Inflammation in the myocardium can result in myocarditis, heart failure, arrhythmias, acute coronary syndrome, rapid deterioration, and sudden death.

- These complications can occur on presentation or develop as the severity of illness worsens.

- It is uncertain to what extent acute systolic heart failure is mediated by myocarditis, cytokine storm, small vessel thrombotic complications, microvascular dysfunction, or a variant of stress-induced cardiomyopathy.
Cardiovascular complications have been reported in 14.1% of patients during hospitalization, with an overall case fatality rate of 9.6%.

Patients with preexisting cardiovascular comorbidities or risk factors are at higher risk for cardiovascular complications and mortality.
Complications include:

- Arrhythmias or palpitations (18.4%)
- Myocardial injury (10.3%)
- Angina (10.2%)
- Acute myocardial infarction (3.5%)
- Acute heart failure (2%)

Cases of fulminant myocarditis, cardiac tamponade, cor pulmonale, takotsubo syndrome, and pericarditis have also been reported.
Risks

- Older Age
- Comorbidities - CVD, lung, renal, diabetes
- Systemic Inflammation
- Coagulation Abnormalities
- Severe Illness and Multiorgan Dysfunction
- Immobility

COVID-19

Complications

- Myocardial Injury and Myocarditis
- Acute Myocardial Infarction
- Heart Failure and Cardiomyopathy
- Arrhythmias
- Shock and Cardiac Arrest
- Venous Thromboembolic Event
A Cochrane review found that the most common cardiovascular complications were cardiac arrhythmias, heart failure, and arterial and venous occlusive events.

The most common arrhythmias reported during hospitalization were supraventricular and ventricular arrhythmias.

**QT interval changes** and St-segment deviation have been reported. QT interval prolongation has been reported independent of whether the patient is taking drugs that prolong the QT interval.
Laboratory biomarkers may help identify those at greater risk of developing cardiovascular complications and of death.

Elevated cardiac biomarkers and emerging arrhythmia are associated with the development of severe disease and the need for intensive care admission.
Prevalence of cardiac disease is high among patients who are severely or critically ill, and these patients usually require intensive care and have a poor prognosis and higher rate of in-hospital mortality.

These patients are more likely to require noninvasive or invasive ventilation, and have a higher risk of thromboembolic events and septic shock compared with patients without a history of cardiac disease.
A study of 100 patients who had recently recovered from COVID-19 found that cardiovascular magnetic resonance imaging revealed ongoing myocardial inflammation in 60% of patients, independent of preexisting conditions, severity and overall course of the acute illness, and time from the original diagnosis.
The pooled incidence of acute kidney injury is 10.6%, which is higher than the incidence in hospitalized patients without COVID-19.

Incidence varies widely across studies, with estimates of approximately 20% reported in some meta-analyses.

Patients with acute kidney injury have a significantly increased risk of in-hospital mortality.

Presence of diabetes, hypertension, chronic kidney disease, and tumor history was associated with increased incidence of acute kidney injury at population level across different settings.

Use of renin-angiotensin-aldosterone system blockade drugs is also significantly associated with an increased risk of acute kidney injury in hospitalized patients.
Acute liver injury

- Acute liver injury may be associated with preexisting liver disease, viral infection, drug toxicity, systemic inflammation, hypoxia, or hemodynamic issues.
- The overall prevalence has been reported as 25%.
- The prevalence of elevated alanine aminotransferase and aspartate aminotransferase was 19% and 22%, respectively. The prevalence of hypertransaminasemia was higher in patients with severe disease compared with patients with non-severe disease.
- Risk factors associated with severe liver injury include older age, preexisting liver disease, and severe COVID-19.
- Medications used in the treatment of COVID-19 (e.g., remdesivir, tocilizumab) may have a detrimental effect on liver injury.
Neurologic complications

- Patients commonly have central or peripheral neurologic complications, possibly due to viral invasion of the central nervous system, inflammatory response, or immune dysregulation.

- Neurologic complications occur across the lifespan in the context of infection, with and without known comorbidities, and with all disease severities (including asymptomatic patients). Neurologic manifestations have been reported in 22% to 35%.

- One third of patients received a neurologic or psychiatric diagnosis in the 6 months after diagnosis, and 13% received such a diagnosis for the first time.
Neurologic complications include:

- Acute cerebrovascular disease
- Impairment of consciousness
- Ataxia
- Seizures
- Corticospinal tract signs
- Meningoencephalitis
- Encephalopathy
- Encephalomyelitis (including acute disseminated encephalomyelitis)

Others: Guillain-Barre syndrome, peripheral demyelinating lesions, peripheral neuropathies, cerebral venous sinus thrombosis, myopathy, acute transverse myelitis, myasthenia gravis.
Patients may present with these manifestations, or they may develop them during the course of the disease.

Neurologic complications tend to develop 1 to 2 weeks after the onset of respiratory disease.

Acute cerebrovascular disease (including ischemic stroke, hemorrhagic stroke, cerebral venous thrombosis, and transient ischemic attack) has been reported in 0.5% to 5.9% of patients. The most common type was ischemic stroke (0.4% to 4.9%).

Stroke is relatively frequent among hospitalized COVID-19 patients relative to other viral respiratory infections, and has a high risk of in-hospital mortality. Risk factors include older age and male sex. Median time from onset of COVID-19 symptoms to stroke was 8 days.
Epidemiology: frequency ranges from 4.7% to 80% across observational studies, and occurs between 3 to 24 weeks after the acute phase or hospital discharge.

Potential risk factors include older age, age 40 to 49 years, female sex, obesity, severe clinical status, higher number of comorbidities, higher symptom load, hospital admission, and oxygen supplementation in the acute phase, although data is lacking.
In-hospital cardiac arrest is common in critically ill patients with COVID-19, and is associated with poor survival, particularly among older patients.

Risk factors included older age, male sex, presence of comorbidities, and admission to a hospital with a smaller number of intensive care unit beds.
Sepsis/septic shock

- Sepsis (diagnosed according to Sepsis-3 or according to the presence of infection-related organ dysfunction necessitating organ support/replacement) has been reported in 78% of intensive care unit patients and 33% of hospitalized patients.

- Guidelines for the management of shock in critically ill patients with COVID-19 recommend a conservative fluid strategy (crystalloids preferred over colloids, buffered/balanced crystalloids preferred over unbalanced crystalloids) and a vasoactive agent.

- Low-dose corticosteroid therapy is recommended for refractory shock.
Acute respiratory failure

- Patients with COVID-19 may have a higher risk of developing ventilator-associated pneumonia compared with patients without COVID-19.
- Overall, ventilator-associated pneumonia was reported in 48.2% of mechanically ventilated patients and the mortality rate was 51.4%. 
Co-infections (especially fungal infections)

- Besides, the diffuse alveolar damage with severe inflammatory exudation, COVID-19 patients always have immunosuppression with a decrease in CD4+ T and CD8+ T cells.

- Critically ill patients, especially the patients who were admitted to the intensive care unit (ICU) and required mechanical ventilation, or had a longer duration of hospital stays, even as long as 50 days, were more likely to develop fungal co-infections.

- Hence, it is important to notice that COVID-19 patients can develop further fungal infections during the middle and latter stages of this disease, especially severely ill ones.
Post-COVID-19 syndrome (long COVID)

- Also known as post-acute COVID-19, post-acute COVID-19 syndrome, chronic COVID, long-haul COVID, post-acute sequelae of SARS-CoV-2 infection (PASC), and post-COVID conditions.

- **Definition:** The World Health Organization defines it as a condition that occurs in people with a history of probable or confirmed SARS-CoV-2 infection, usually occurring 3 months from the onset of symptoms and lasting for at least 2 months, that cannot be explained by an alternative diagnosis.

- The UK National Institute for Health and Care Excellence defines it as signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks, and are not explained by an alternative diagnosis.

- The syndrome is not thought to be linked to disease severity or specific signs and symptoms during the acute phase of illness.
Signs and symptoms:

- Common long-term symptoms include persistent cough, low-grade fever, breathlessness, weakness, malaise, impairment of concentration, fatigue, pain, chest pain/tightness, palpitations, myalgia, arthralgia, headaches, vision changes, hearing loss, earache, tinnitus, sore throat, loss of taste/smell, impaired mobility, numbness in extremities, dizziness, tremors, memory loss, mood changes, skin rashes, gastrointestinal symptoms, neurocognitive difficulties, sleep disturbances, delirium (older people), and mental health conditions (e.g., anxiety, depression).

- Gastrointestinal sequels including loss of appetite, nausea, acid reflux, and diarrhea are common in patients 3 months after discharge.

- The inability to return to normal activities, emotional and mental health outcomes, and financial loss are common.
Management: give advice and information on self-management including ways to self-manage symptoms (e.g., set realistic goals, antipyretic for fever, breathing techniques for chronic cough, home pulse oximetry for monitoring breathlessness, pulmonary rehabilitation, staged return to exercise).
Thank You
For Your Attention