

Multiorgan Involvement in COVID-19 and Possible Therapies

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Abstract

In late 2019, China reported cases of respiratory illness in humans, which involved a novel Coronavirus SARS-CoV-2 (also known as 2019-nCoV). The World Health Organization (WHO) termed the disease COVID-19 (i.e., Coronavirus disease 2019). Most of the morbidity and mortality from COVID-19 is largely due to acute viral pneumonitis that leads to acute respiratory distress syndrome (ARDS). This article will discuss the clinical features of the multiorgan involvement in COVID-19 as well as the management of patients who become critically ill due to COVID-19.

Keywords

- ▶ COVID-19
- ▶ multiorgan involvement
- ▶ possible therapies

Introduction

In late 2019, China reported cases of respiratory illness in humans, which involved a novel Coronavirus SARS-CoV-2 (also known as 2019-nCoV). The World Health Organization (WHO) termed the disease COVID-19 (i.e., Coronavirus disease 2019). Most of the morbidity and mortality from COVID-19 is largely due to acute viral pneumonitis that leads to acute respiratory distress syndrome (ARDS). This article will discuss the clinical features of the multiorgan involvement in COVID-19 as well as the management of patients who become critically ill due to COVID-19.

Causative Agent and Epidemiology

COVID-19 is caused by a β coronavirus named SARS-CoV-2. Corona viruses are enveloped viruses with a single positive-stranded RNA genome (~26–32 kb in length). The structure of the receptor-binding gene region is very similar to that of the SARS coronavirus, and the virus has been shown to use the same receptor, the angiotensin-converting enzyme 2 (ACE2), for cell entry.² The disease has a mean incubation period of 5 days, median of 3 to 4 days, with wide range up to 24 days (common range 2–7 days). The number of people diagnosed with COVID-19 worldwide crossed the 3 million mark on April 27, 2020; and 3.4% was the mortality rate estimate by the WHO as of March 3.³ A review by the WHO-China Joint Mission of 55, 924 laboratory-confirmed

cases in China said 6.1% were classified as critical (respiratory failure, shock, and multiple organ dysfunction or failure) and 13.8% as severe (dyspnea, respiratory rate ≥ 30 breaths per min, oxygen saturation $\leq 93\%$, partial pressure of arterial oxygen to fraction of inspired oxygen [PaO₂/FiO₂] ratio 50% within 24–48 hours).⁴ In Italy, until March 29, 2020, up to 12 to 14% of all positive cases required ICU admission.^{5,6}

Clinical Features

The median time from symptom onset to ICU transfer is around 12 days. Timing of onset of sepsis from onset of illness is approximately 9 days (range 7–13 days), while ARDS typically presents at around 12 days (range 8–15 days) from the onset of illness.⁷ SARS-CoV-2 is known to cause multiorgan dysfunction, so it is important that the clinician is aware of the organs it affects and the way it presents.

ARDS

Autopsy studies of COVID-19 associated lung disease have demonstrated bilateral diffuse alveolar damage with cellular fibromyxoid exudates, desquamation of pneumocytes, pulmonary edema, and hyaline membrane formation. These studies show that there is also some evidence of direct viral injury to lung tissue, not just due to inflammatory sequelae.⁸ Some patients with COVID-related lung disease have significantly higher compliance than that is typical for their shunt

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fraction, which indicates this may be a very different phenotype than typical ARDS. The explanation remains unclear, with dysregulation of pulmonary perfusion considered a possible explanation, as postulated by Gattinoni et al.⁹

According to Gattinoni et al, there are two types of COVID-19 patients with ARDS. In type-1 patients, severe hypoxemia is always associated with a respiratory system compliance of $>50\text{ mL/cmH}_2\text{O}$. The lung's gas volume is high and the recruitability is minimal. In 20 to 30% of the type 2 patients admitted to the intensive care unit (ICU), severe hypoxemia is associated with compliance values $<40\text{ mL/cmH}_2\text{O}$, indicating severe ARDS.¹⁰

Cardiac Involvement

Various forms of cardiac involvement such as acute cardiac injury, arrhythmias, pericarditis, myocarditis and, possibly, acute coronary syndrome (ACS) are known to occur in COVID-19 patients. The definition of acute cardiac injury differs in studies and is nonspecific. More recent studies define as troponin >99 th percentile upper limit of normal; earlier studies include abnormal ECG or echocardiographic findings.^{7,11} The mechanism through which SARS-CoV-2 causes cardiac injury is unknown, although several have been proposed, based on very limited data outside of case series and reports.

- A) Viral invasion into cardiac myocytes causing possible direct toxicity (i.e., myocarditis).
- B) ACS and demand ischemia.
- C) Stress cardiomyopathy (i.e., Takotsubo's).
- D) Profound inflammatory response/cytokine storm, leading to viral invasion into cardiac myocytes¹²⁻¹⁴

The occurrence of unspecified arrhythmias in 17% of hospitalized patients with COVID-19 ($n = 23$ of 138) have been reported in case series. Higher rates were observed in ICU patients (44%, $n = 16$) compared with non-ICU patients (7%, $n = 7$).¹⁵ The rate of ventricular arrhythmia (VT)/ventricular fibrillation (VF) was 5.9% in a study of 189 hospitalized patients in Wuhan, China.¹⁶

There is nil current available data on the incidence of ACS in COVID. However, it is presumed that due to the presence of ACE2 receptors on the endothelium, and the known increased risk of ACS in influenza, there is a possible increased incidence of ACS among COVID-19 patients.

Neurological Involvement

There is much still to be learned about the central nervous system (CNS) involvement of COVID-19, but lessons from scientific and clinical experience from other human Coronaviruses suggest neuroinvasive potential of SARS-CoV-2. The incidence of neurologic manifestations varies between 36.4 to 69% of hospitalized COVID-19 patients. Delirium, confusion, or executive dysfunction are particularly common, and may occur in a majority of patients. Other common neurologic manifestations were dizziness (16.8%), headache (13.1%), impaired consciousness (7.5%), hypogeusia (5.6%), hyposmia (5.1%), or stroke (2.8–5%).^{17,18} New case

reports of rarer complications are emerging that have reported Guillain–Barre Syndrome (GBS),¹⁹ Miller–Fisher Syndrome (MFS),²⁰ encephalitis,²¹ and acute necrotizing encephalopathy.²²

Liver Disease

Present literature reveals that approximately 15 to 50% of patients with COVID-19 have abnormal liver function tests (LFTs).^{23,24} The variability in the incidence may be explained by the differences in disease severity, multiple etiologies of hepatic injury (such as direct viral injury, indirect inflammatory injury, and drug-induced injury), as well as nonhepatic causes of elevated transaminases. The pattern of injury is predominately hepatocellular. Elevations are of almost all liver enzymes are seen with AST, ALT and LDH elevations being the most common. Liver injury associated with COVID-19 is often mild, even in patients with severe disease, and is self-resolving.²⁵ To date, acute liver failure has not been reported, even in the severely ill and those with chronic liver disease.^{24,26}

Acute Kidney Injury (AKI)

The incidence of AKI in COVID-19 varies widely, but estimates range from 0.5% to 27%.^{25,27} The wide range of estimates of AKI incidence may reflect different populations included in studies (e.g., ward vs. ICU patients). The most likely etiology of AKI in COVID-19 is acute tubular necrosis (ATN). An autopsy series from China found severe ATN and interstitial infiltration with CD68+ macrophages on histopathologic examination of kidney tissue. Membrane attack complex protein (C5b-9) deposition was also seen in the tubules, suggesting that activation of the alternative complement pathway may play a role in tubular injury as well. ACE2 receptors in renal vasculature may also play a role for specific nephrotoxicity.

Hematological Involvement

In ICU patients, cumulative incidences range from 20% to 40% in patients on varying levels of prophylactic anticoagulation.²⁸ Higher D-dimer and fibrin and fibrinogen degradation product (FDP) levels track with multiorgan dysfunction syndrome and poorer prognosis.^{7,15} The mechanism for venous thromboembolism (VTE) is not known currently and likely due to multifactorial reasons such as systemic inflammatory response syndrome (SIRS), as seen in sepsis, and possible direct endothelial damage from viral injury/ACE2 binding. Disseminated intravascular coagulation (DIC) was found in 16 of 183 hospitalized patients in Wuhan. Median time to onset of DIC was 4 days into hospital admission.²⁹

Cytokine Activation Syndrome

Apart from septic shock and cardiogenic shock, cytokine activation syndrome per se can also present as circulatory shock in COVID-19 patients. A subgroup of patients with severe COVID-19 may have cytokine activation syndrome

and secondary hemophagocytic lymphohistiocytosis (HLH).³⁰ Patients who had cytokine activation developed rapid progression to ARDS, shock, and multiorgan failure. Neutrophil activation likely contributes to the pathogenesis of cytokine storm with elevated IL6 levels and ARDS. Wu et al found that COVID-19 confirmed patients with ARDS have higher neutrophil counts, average 7.04 (95% CI: 3.98 to 10.12) versus those without ARDS, whose average is 3.06 (2.03 to 5.56).³¹ Similar patterns of cytokine storm and ARDS have been seen with SARS and MERS. Other studies have suggested that increased proinflammatory cytokines in the serum are associated with pulmonary injury in SARS, MERS, and COVID-19.

Diagnosis

There is multifold rise in the number of areas with community transmission worldwide and also substantial risk of missing cases early in a local outbreak; therefore, ICU practitioners should have a very high-index of suspicion and a low-threshold for diagnostic testing for any patient presenting with severe acute respiratory infection. Diagnosis is based on RT-PCR assays for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Falsely negative upper respiratory tract samples are seen in patients with pneumonia.³² Sampling from the lower respiratory tract is recommended by WHO, such as with sputum and endotracheal aspirates. These procedures potentially generate aerosol and must be done with strict airborne precautions. Bronchoscopy should generally be avoided if possible to minimize exposure of healthcare workers to SARS-CoV-2, although the diagnostic yield of bronchoalveolar lavage for COVID-19 might be high.³³ The sensitivity of RT-PCR assays for the critically ill patients is currently unknown. Repeated sampling might be required when initial tests are negative despite suspicious clinical features.

Management

ARDS

Before Intubation

The management options available are supplemental oxygen, continuous positive airway pressure (CPAP), noninvasive ventilation (NIV), high-flow nasal cannula (HFNC), and

awake prone positioning. Target nonvigorous breathing to avoid self-inflicted lung injury in patient (► **Table 1**).

During Ventilation

The goals of mechanical ventilation are to minimize pulmonary stress, optimize oxygenation, and avoid ventilator-induced lung injury. Consider extracorporeal membrane oxygenation (ECMO) in refractory hypoxemia.

Avoid excessive positive fluid balance. Transition to spontaneous breathing to be done cautiously, and spontaneous trials to be done only at the very end of the weaning process.³⁴

Other Intensive Care Management

- A) Blood cultures to be sent; empiric antibiotics to be considered (secondary infections reported are high).
- B) Measurement of lactate levels; cautious fluids for hypovolemia; check preload responsiveness; echocardiography; vasopressors or inotropes to be added if needed.
- C) To avoid routine use of corticosteroids.
- D) Unnecessary patient transfers to be avoided; use point-of-care tests such as ultrasound wherever possible.
- E) Renal replacement therapy if indicated.
- F) Protocolized sedation practice.
- G) Early enteral nutrition and adequate glycemic control to be achieved.
- H) Early physical therapy.
- I) Prevention of nosocomial infections.
- J) Deep vein thrombosis prophylaxis.
- K) Stress ulcer prophylaxis.³⁵

Therapeutics in COVID-19

Remdesivir

Remdesivir is a nucleotide prodrug metabolized to an analog of adenosine triphosphate, which inhibits viral RNA-dependent RNA polymerase, causing premature termination of RNA transcription. This drug has shown in vitro activity against SARS-CoV-2.³⁶ A case series of compassionate use remdesivir which analyzed 53 patients, in whom 68% had improvement in their oxygen-support class, 47% were discharged, and 13% passed away. But without a control group to compare, it is unclear if the use of remdesivir altered the natural progression of COVID-19 disease in these patients.³⁷

An NIH press release has commented on the adaptive NIAID trial that had evaluated 1063 patients with COVID-19. This study was a randomized, placebo-controlled trial at 68 sites. Full details of the trial are not yet available, but remdesivir was reported to result in a median time to recovery of 11 days versus 15 days in the placebo group (31% reduction, $p < 0.001$) and a mortality rate of 8% in the remdesivir arm versus 11.6% in the placebo arm ($p = 0.059$). A full publication is expected shortly.

Hydroxychloroquine and Chloroquine

Hydroxychloroquine (HCQ) is an antimalarial 4-aminoquinoline shown to have in vitro (but not yet in vivo) activity against diverse RNA viruses. HCQ is thought to act against viruses through multiple mechanisms such as inhibition

Table 1 Ventilation strategies for different phenotypes in COVID-19

Type 1 (Minimal recruitability)	Type 2 (Low compliance)
Consider lower PEEP (< 10 cm H2O)	Use higher PEEP (< 15 cm H2O)
Can use more liberal tidal volume (7–9 mL/kg) as needed	Lower tidal volume (5–7 mL/kg) to be used
Consider prone positioning	Implement prone positioning

Abbreviation: PEEP, positive end-expiratory pressure.

of viral entry, inhibition of viral release into the host cell, reduction of viral infectivity, and immune modulation. Even though some unpublished small studies showed promise,³⁸ recent studies have shown no difference in outcomes and some recent studies show even harm.³⁹

Lopinavir and Ritonavir (LPV/r)

Lopinavir and ritonavir are both protease inhibitors. Lopinavir may theoretically work against coronaviruses like SARS-CoV-2 by inhibiting 3-chymotrypsin-like protease. A recent randomized, controlled, open-label trial which assessed lopinavir-ritonavir ($n = 99$) versus standard of care ($n = 100$) in SARS-CoV-2 patients found that treatment with LPV/r was not associated with a difference in time to clinical improvement or mortality. However, randomization did not occur until a median of 13 days after symptom onset, so the window for benefit may have already closed.⁴⁰

Convalescent Plasma (Immunotherapy)

Convalescent plasma is taken from patients who have previously recovered from a COVID-19 viral infection and are now able to donate their immunoglobulin-containing blood. The presumed mechanism of action is that antibodies present in convalescent plasma may suppress viremia. Shen et al⁴¹ reported on five critically ill COVID-19 patients who received convalescent plasma, four of five who saw temperature normalization within 3 days and three of five who have been discharged (days 51, 53, and 55), with the other two in stable condition at the time of the publication. The most recent case series reported out on 10 severe COVID-19 disease patients who received convalescent plasma and tolerated it well.⁴²

Tocilizumab

IL-6 activates T cells and macrophages, among other cell types. IL-6 inhibitors are approved for cytokine activation syndrome complications related to Chimeric Antigen Receptor T cell (CAR-T) therapy.⁴³ Even though unpublished studies report success, large randomized controlled trials are needed. In severe cases of COVID-19 with suspicion of cytokine activation syndrome, one can consider use in conjunction with rheumatology and infectious diseases consultation.

Glucocorticoids

The Centre for Disease Control and Prevention (CDC) and the WHO recommend that glucocorticoids should not be routinely administered to patients with COVID-19, unless there is a separate evidence-based indication in that patient (e.g., asthma or chronic obstructive lung disease exacerbation, refractory septic shock, and adrenal insufficiency). However, their administration in ICU patients with COVID-19-related ARDS is controversial.

Others

Intravenous immunoglobulin and favipiravir (RNA-dependent RNA polymerase inhibitor) to date do not have peer-reviewed, published safety data available for SARS-CoV-2. Hence, these modalities are not recommended unless part of a clinical trial.

Convective therapies for removal of inflammatory cytokines during cytokine storm is another novel therapy considered for COVID-19 patients with severe inflammation. Monitoring inflammation and antibodies are important, especially in patients infected by virus with persistent fever or abnormal coagulopathy. Expedient control of the cytokine storm in early phase might be beneficial to selective patients, and case reports and small series from China and European countries have been published.⁴⁴

A recent review by Ronco et al mentions that in the absence of established drugs or vaccines for COVID-19, pathophysiological rationale may support the application of the extracorporeal therapies which might help patients who are critically ill with COVID-19 with situations such as shock-like syndrome, the need for vasopressors and capillary leak syndrome, and laboratory criteria such as the levels of IL-6 and other cytokines, as a rescue therapy.⁴⁵

Conclusion

Although COVID-19 starts as a respiratory illness, it has the possibility of affecting various organs directly (direct organotropism) or indirectly (systemic inflammatory processes or sepsis like syndromes), presenting a multitude of problems. On the one hand, atypical presentations to specific specialties and nonrecognition/missing of primary disorders (COVID-19) may put many HCWs at risk of exposure, on the other hand, it may complicate the clinical course of the patient.

Indirect involvement of various organs represents a more severe subset of patients, and lack of specific therapies puts them at higher mortality prediction, making case for well-planned trials for novel therapies.

Conflicts of Interest

None declared.

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