Severe COVID-19: A distinct entity

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Abstract

Severe coronavirus disease-2019 (COVID-19) is a distinct entity that rapidly evolves and may abruptly culminate in to a critical illness. As per Chinese experience, approximately, 15% of patients of COVID-19 progress to severe disease and 5% become critically ill. The incidence of severe and critical illness is higher among men, patients older than 65 years of age and in persons with other medical comorbidities. Cytokine storm cause pronounced lung damage and multiorgan failure. Coagulopathy is a key component of severe COVID-19. Critically ill patients are generally predisposed to a high risk of thromboembolism as well. Lymphopenia predisposes to severe disease. None of the antiviral or immunomodulators has proven efficacy in severe COVID-19. Supplemental oxygen need be administered in patients with hypoxemia. Excessive breathing effort, acute respiratory distress syndrome (ARDS), encephalopathy, and multiorgan failure are indications for mechanical ventilation. In a large number of patients, the overall outcome is poor. Health care workers in intensive care units are exposed to the enormous risk of acquiring hospital acquired SARS-COV-2 infection.

Keywords: Coagulopathy, cytokine storm, hypoxemia, lymphopenia, mechanical ventilation, SARS-COV-2

Introduction

Severe coronavirus disease-2019 (COVID-19) patients may need prolonged hospitalization in the intensive care unit (ICU). In a large number of critically ill patients, the overall outcome is poor. Mild or moderate COVID-19 may abruptly and unexpectedly progress to a severe/critical illness. Prognosis of critical illness is generally poor. Health care workers in ICU are exposed to the enormous risk of acquiring nosocomial SARS-COV-2 viral infection during management of COVID-19-affected patients.

Epidemiology

The first case of COVID-19, in Wuhan, China, was noted on December 8, 2019, because of atypical pneumonia. The World Health Organization (WHO) announced the COVID-19 a global health crisis on January 30, 2020. WHO declared COVID-19 a pandemic on March 11, 2020. Currently, there were 37601848 proven COVID-19 cases along with 1077799 deaths globally. COVID-19 has been recorded from 235 countries. India, so far, reported 7175880 confirmed COVID-19 with 109856 deaths.[¹]

An initial dataset from China observed that, of 44,672 confirmed cases, approximately 14% and 5% of patients respectively had severe or critical COVID-19. Generally, the period from first symptom to hospitalization varies from 7 to 10 days. Median time to onset of dyspnea after first clinical manifestation is approximately 4‑5 days. Between 6 to 10 days severely ill patients need ICU admission.[²]

Retrospective data, of the first 1000 patients from the USA, revealed that 236 patients were directly admitted to an ICU or were transferred to ICU. Patients admitted to ICU were old and were predominantly male. Approximately, 4.4% (6/136) of patients needed endotracheal intubation and ventilation. Endotracheal intubation was done approximately after 4-5 days. Between 6 to 10 days severely ill patients need ICU admission.[³]
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14 days from the first symptom. Prospective data of 20,133 hospitalized patients from the UK revealed that at the time of reporting 17% (3001/18183) required admission to ICU. The median age of patients admitted to the hospital was 73 years (range 0-104).

We reviewed existing literature on severe COVID-19. We searched PubMed, Google Scholar, Scopus, preprint databases (medRxiv and bioRxiv). We used search terms, “severe COVID-19” and “critically ill COVID-19”. Full-text articles were acquired from journals’ websites. In addition to clinical aspects of COVID-19, we also focused on its current treatment.

Pathogenesis

Virology
The SARS-CoV-2 virus has been implicated in causation of COVID-19. The SARS-CoV-2 is grouped in to the Coronaviridae family. The SARS-CoV-2 is an enveloped, single-stranded, positive-sense RNA virus.

Viral invasion
The SARS-CoV-2 particle contains a helical capsid consisting of nucleocapsid proteins bound to the viral RNA. The SARS-CoV-2 virus genome is a single strand of RNA. Genetic material is encapsulated in a lipid capsule. The membrane, envelope, and spike proteins are attached with a capsule. The SARS-CoV-2 virus requires the angiotensin-converting enzyme 2 (ACE2) receptor present on inside the lungs intestinal epithelial cells and pneumocytes to enter inside. The spike protein is important for virus binding with the host cell. Cleavage of spike protein by the host's membrane serine peptidase enzyme allows the fusion of viral and cellular membranes. Transmembrane protease, serine 2 (TMPRSS2) is an enzyme that is encoded by the TMPRSS2 gene.

Cytokine storm
In severe cases, there is an unusually severe immunological response is noted that is termed as “cytokine storm”. The onset of the cytokine storm is usually abrupt and possibly, genetically determined. Cytokine storm is characterized by a unique cytokine profile. Interleukin-6 plays a dominant role in the pathogenesis of cytokine storm and often associated with adverse outcomes. In addition to interleukin-6, abrupt releases of other proinflammatory cytokines, interleukin -1β, and TNF-α, are major components of the cytokine storm. Cytokine storm leads to severe lung damage and multiorgan failure.

Coagulopathy
Coagulopathy is a key component of severe COVID-19. Critically ill patients are generally predisposed to a high risk of thromboembolism as well. Coagulopathy in COVID-19 is characterized by elevated D-dimers, elevated fibrinogen, mild prolongation of prothrombin time, and mild thrombocytopenia. In severe cases, there may be disseminated intravascular coagulation (DIC). In DIC, the coagulation profile demonstrates prolonged prothrombin time and thrombocytopenia.

Progression to severe disease
Severe COVID-19 is more common among men and elderly patients with other medical comorbidities. A prospective observational study, that included 348 mild cases, noted that 20 (5.7%) patients turned in to severe COVID-19. Many factors like, platelet counts, low serum sodium, C-reactive protein, prealbumin, and PaCO₂ were significant predictors of COVID-19. A higher C-reactive protein predicted a rapid conversion to severe disease.

An elevated counts of white blood cell and neutrophil along with a decreased count of lymphocyte is a hallmark characteristic of severe COVID-19. Similarly, elevated levels of inflammatory markers, D-dimer, fibrinogen, interleukin-6, CRP, ESR, alanine aminotransferase, aspartate aminotransferase and α-hydroxybutyrate dehydrogenase, are also strong predictors of severe COVID-19.

Genetics
Some recent observations suggested that the progression of the mild disease to severe COVID-19 might be genetically determined. Ellingham and colleagues identified a cluster of six genes, on chromosome 3p21.31, that predicted severe COVID-19. These genes regulate various immune functions. Ellingham and colleagues further noted that the risk of progression to severe disease was higher in the patients having blood group A. Blood group O had a protective effect. The genetic abnormalities, leading to abnormalities of angiotensin-converting enzyme 2 receptor expression, were implicated in genesis of neurological complications of COVID-19.

Comorbidities
The majority of the patients with severe diseases or those who succumb to illness have varied pre-existing comorbidities, like, high blood pressure, cardiac disease, diabetes mellitus, vascular diseases of brain, renal failure, chronic obstructive pulmonary disease and/or systemic malignancy [Table 1].

Lung pathology
In patients with COVID-19, lungs are the site of primary pathology. Histopathology demonstrates diffuse alveolar injury.

Table 1: Comorbidities associated with severe Covid-19

| Comorbidities                        |
|-------------------------------------|
| Advanced age                        |
| Coronary heart disease              |
| Diabetes mellitus                   |
| Hypertension                        |
| Chronic obstructive lung disease    |
| Systemic malignancy                 |
| Renal diseases                      |
| Obesity                             |
| Smoking                             |


with perivascular infiltration of T cell. There is severe endothelial injury. On electron microscopy, the intracellular virus can be demonstrated within the endothelial cells along with disrupted cell membranes. There is histopathological evidence of widespread thrombosis with microangiopathy. Capillary microthrombi are much more frequently noted in COVID-19-affected lungs than in influenza.\cite{17} Fox and co-workers demonstrated marked microangiopathy and thrombus formation in the small pulmonary vessels. Diffuse alveolar damage (including hyaline membranes) was demonstrated. In the myocardium, individual muscle cell necrosis was noted. These unique pathological findings were considered responsible for the death.\cite{18}

### Clinical features

Clinical presentation of COVID-19 varies from pre-symptomatic phase to severely affected critically ill cases.\cite{19} The common presenting symptoms are cough, fever, dyspnea, myalgias, diarrhoea, and nausea and vomiting. After about a week, COVID-19 manifests with viral pneumonia. A vast majority of patients, subsequently, show clinical improvement due to evolving immunity against the virus. A minority of patients COVID-19 abruptly progress to severe disease and some become critically ill. Critical COVID-19-related illness is characterized by ARDS, multi-organ failure, and death. The median time to death, from symptom initiation, is approximately 2–8 weeks. Some patients, though have minimal breathlessness, pulse oximetry may record alarmingly low oxygen saturation levels. This condition is termed as silent hypoxia [Tables 2 and 3].\cite{20,21}

Dyspnea is characteristically present in severe COVID-19. Dyspnea is often accompanied by alarming hypoxemia. In minority, dyspnea heralds hypoxemia that rapidly culminates in ARDS. ARDS is characterized with acute bilateral symmetrical lung infiltrates, severe hypoxemia in a patient, who does not have any possibility of cardiogenic lung edema.\cite{22}

In addition to pulmonary manifestation, there are a variety of extrapulmonary manifestations that complicate management of severe COVID-19. The Common extrapulmonary manifestations are widespread thromboembolic events, cardiac disorders and arrhythmia, acute renal damage, gastrointestinal manifestations, liver injury, hyperglycemia, encephalopathy, eye, and skin abnormalities [Table 4].\cite{23}

### Diagnosis

Real-time reverse transcription-polymerase chain reaction (RT-PCR) test is the molecular test of choice for identifying the SARS-CoV-2 virus in a biological specimen. A nasopharyngeal swab and/or an oropharyngeal swab are often used for performing RT-PCR.\cite{24}

### Biochemical changes

The commonest laboratory abnormality associated with severe COVID-19 is lymphopenia. Other commonly reported biochemical abnormalities that are indicative of excessive systemic inflammatory response against the virus. Abnormal parameters include CRP, D-dimers, ferritin, fibrinogen, lactate dehydrogenase, and troponin.\cite{25}

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**Table 2: The CDC list of common symptoms of COVID-19**\cite{15}

| Severity | Definition | Incidence | Type of care |
|----------|------------|-----------|--------------|
| Mild/moderate | Cough, fever, malaise, myalgias, headache, ageusia and anosmia | 80% | Home care |
| Severe | Breathlessness with respiratory rate of ≥30/min An oxygen level 93% or less PaO₂/FiO, of <300 mm Hg Infiltrates in >50% of the lung field | 15% | In hospital |
| Critical | ARDS, septic shock, or multiorgan dysfunction | 5% | In ICU |

ARDS=acute respiratory distress syndrome

**Table 3: Spectrum of disease severity in COVID-19**\cite{18}

| Severity | Definition | Incidence | Type of care |
|----------|------------|-----------|--------------|
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ARDS=acute respiratory distress syndrome

**Table 4: Various systemic complications of severe COVID-19**\cite{23}

| System | Severe complications | Possible pathogenetic mechanism |
|--------|----------------------|-------------------------------|
| Respiratory | Pulmonary Embolism Pulmonary Arterial Thrombosis ARDS | Direct viral invasion Cytokine storm Coagulopathy |
| Nervous system | Encephalopathy/encephalitis Stroke Guillain Barre syndrome Rhabdomyolysis | Direct viral invasion Cytokine storm Coagulopathy |
| Cardiovascular | Heart failure Myocarditis ST-elevation on ECG Acute coronary syndrome Pericarditis and pericardial effusion Dysrhythmias Venous thromboembolism Septic shock | Myocardial invasion via ACE2 receptor Cytokine storm |
| Renal | Acute kidney injury | Viral invasion of kidney Excessive inflammatory response |
| Liver | Liver enzyme abnormality | Immune-mediated inflammation and viral invasion |

ARDS=acute respiratory distress syndrome
Many of these biochemical parameters predict severe COVID-19 disease. Liu and co-workers noted that absolute lymphocyte count, albumin level, albumin/globulin ratio, lactate dehydrogenase, interleukin-6, ESR, globulin level, blood glucose, and old age were significantly correlated with the severity of COVID-19. Advancing age, absolute lymphocyte count, and interleukin-6 were independent predictors of disease severity. Similarly, Han and colleagues noted interleukin-6 and interleukin-10 were significant predictors of COVID-19 disease severity [Table 5].[26,27] A higher neutrophil/lymphocyte ratio is another strong determinant of severe disease and death.[39]

Lung Imaging

X-ray
Predominant finding in chest X-ray is of ground-glass opacities with evidence of peripheral consolidation. Serial X-rays may demonstrate first ground-glass opacities converting into consolidation and subsequently complete resolution of imaging abnormalities. In an X-ray-based study, lung consolidation was the most common imaging abnormality (30/64, 47%). The next common finding was ground-glass opacities (21/64, 33%). Lower regions of the lung are dominantly affected. Lesions of COVID-19 are commonly affect the peripheral part of the lungs. COVID-19-related lung involvement is characteristically bilateral and symmetrical. Pleural effusion is rare [Figure 1].[28]

Computed tomography (CT)
Ground-glass opacities and consolidation are more readily demonstrated on CT chest. CT imaging has confirmed that COVID-19 mainly affects the lower lobes of the lungs. Ground-glass imaging abnormalities and consolidation in the lung periphery are the imaging hallmarks.[39]

Lung ultrasound
Lung ultrasound is now important in the ICU setting as it readily helps in diagnosis and prognostication of COVID-19. Lung ultrasound can accurately detect inflammatory changes in superficial lung tissues. Lung ultrasound can also easily diagnose many of mechanical ventilation-related complications, like pneumothorax.[31]

Table 5: Common laboratory abnormalities in COVID-19[26-28]

| Laboratory abnormalities | Significance                                                                 |
|-------------------------|-----------------------------------------------------------------------------|
| Lymphopenia             | SARS-CoV-2 infect lymphocytes and lye them.                                 |
| Elevated hepatic enzymes| Acute liver injury                                                           |
| Elevated lactate dehydrogenase | A very high level of inflammation                                         |
| Elevated inflammatory markers | A high level of inflammatory response                                       |
| C-reactive protein       | It is an indicative of coagulopathy.                                        |
| Elevated Ferritin        | It is also an indicative of coagulopathy.                                   |
| Elevated D-dimer         | It is indicative of myocardial injury.                                       |
| Elevated prothrombin time| It is indicative of skeletal muscle injury.                                 |
| Elevated troponin        |                                                                             |
| Elevated creatine phosphokinase |                                                                              |

Treatment
Patients with severe disease require immediate hospitalization and careful monitoring. Critically ill patients need to be kept in ICU. In ICU, it is of paramount importance to prevent viral spread for a very strict infection control is needed. Most of the procedures performed in ICUs are aerosol-generating with a high risk of infection to health care workers. In a systematic review, Tran and colleagues noted that all the procedures performed in ICUs are associated with an enhanced risk of hospital acquired infection of health care workers. All the procedures that are performed to maintain ventilation, like endotracheal intubation, tracheotomy, and all kinds of ventilations, are associated with enormous risk of virus spread. All ICU procedures, like aspiration, body fluids suction, bronchoscopy, nebulization, high flow oxygen administration, oxygen mask adjustments, BiPAP mask, resuscitative procedures, nasogastric tube insertion, and broncho-alveolar lavage all have a very high risk of aerosol generation and virus spread to health-care workers.[32] Prevention of virus spread is of paramount importance. The use of recommended personal protective equipment is a must for all ICU workers.

Medical treatment
Drugs used in the management of severe COVID-19 either have anti-inflammatory properties or have an immunomodulatory role.

Hydroxychloroquine or chloroquine
The role of hydroxychloroquine or chloroquine to treat COVID-19 has always been controversial. The latest data suggest, that among hospitalized patients, hydroxychloroquine with or without azithromycin do not have any mortality benefit. Instead, patients receiving hydroxychloroquine were less likely to be discharged alive within 28 days than those in the control group.[33,34] The American College of Physicians also does not recommend the use of chloroquine or hydroxychloroquine (with or without azithromycin), neither in treatment and nor in prophylaxis.[35]
Remdesivir
Remdesivir is a nucleoside antiviral drug that acts as an RNA polymerase inhibitor. Remdesivir is considered beneficial in the treatment of COVID-19 and considered to enhance the rate of recovery (11 days versus 15 days). A recent systematic review, analysing data of 4 randomized trials, revealed that in hospitalised patients remdesivir helps in early recovery. However, there is limited benefit on mortality. This analysis further suggested that among patients, who do not require mechanical ventilation, a 5-day course is sufficient enough for early recovery.[36,37]

Tocilizumab
Tocilizumab (monoclonal antibody) acts as an interleukin-6 receptor blocker and thus blocks its inflammatory action. Tocilizumab lowers the risk of invasive ventilation and death, in critically patients with COVID-19. Tocilizumab is administered either by intravenous route (8 mg/kg in two infusions, 12 hourly interval) or by subcutaneous route (162 mg, in 2 doses). Critically ill patients, who receive tocilizumab, has higher risk of serious systemic infections.[38,39]

Lopinavir–ritonavir
Lopinavir–ritonavir are antiviral drugs used in HIV infection. Lopinavir–ritonavir in patients with severe Covid-19 failed to demonstrate any worthwhile clinical benefit.[40,41]

Corticosteroids
WHO recommends use of systemic corticosteroid therapy (dexamethasone 6 mg of orally or intravenously, or hydrocortisone 50 mg intravenously every 8 hours) is given for 7 to 10 days.[42] Horby and co-workers in a randomized trial (n = 2104) noted that the patients who received 6 mg daily of dexamethasone (for 10 days) had significantly reduced 28-day mortality in comparison to the patient who received standard care.[43] A meta-analysis, that analysed data of 1703 patients with severe COVID-19, noted that usage of corticosteroids has mortality benefits (mortality risk 32% with corticosteroids versus 40% mortality risk for control group). Mortality benefit was less among patients on invasive mechanical ventilation.[44] An early administration of intravenous methylprednisolone (0.5 to 1 mg/kg/day for 3 days) in patients with severe COVID-19 helps in reducing hospital stay.[45]

Plasma therapy
Infusion of plasma, obtained from convalescent Covid-19 patients has promise in the treatment of life-threatening COVID-19. In a series of 25 patients, convalescent plasma demonstrated encouraging results. After 14 days, 19 patients had shown clinical improvement, and 11 were discharged.[46]

However, a recently published systematic review noted only low-quality evidence on the effectiveness and safety of convalescent plasma therapy; all studies had a very high risk of bias, additionally, reporting quality was considered of low quality.[47] Observations, of a more recent Cochrane Systematic Review, was no different. After analysis of data of 5211 patients, authors expressed uncertainty whether convalescent plasma therapy at seven days has any beneficial effect.[48] Rogers and colleagues in a more recent study failed to demonstrate significant effect on deaths. In this study, 64 severe COVID-19 patients received convalescent plasma and 177 patients were in control group. The proportion of in-hospital deaths was 12.5% and 15.8% in the convalescent plasma and no-convalescent plasma groups, respectively.[49]

Anticoagulants
Anticoagulants for prophylaxis of any thromboembolic is needed for all patients with COVID-19 admitted in ICU. Subcutaneous low molecular weight heparin is usually recommended for this.[50] A recently published meta-analysis noted that anticoagulation in hospitalised COVID-19 patients is associated with mortality benefits. The study demonstrated that prophylactic anti-coagulation results in less number of deaths in patients with severe COVID-19 with raised levels of D-dimer and in patients who are on mechanical ventilation.[51] Enoxaparin is preferred prophylactic anticoagulant because its usage is associated with associated with reduced in-hospital mortality. The usual recommended prophylactic dose of enoxaparin is 40 mg/day. Enoxaparin is administered subcutaneously and continued for 14 days. Higher doses are needed for the treatment in critically ill individuals.[52]

Treatment of Respiratory Failure

Supplemental oxygen therapy
Patients with COVID-19 pneumonia who have hypoxemia need to be immediately shifted to an ICU. Supplemental oxygen should be administered to maintain oxygen saturation level between 92% and 96%.[22]

Low-flow oxygen
For patients with COVID-19, supplemental oxygenation with a low-flow system via nasal cannula, Venturi mask or a mask with reservoir bag. A low-flow system can administer up to 6 L/min of oxygen.[53]

High-flow oxygen
High-flow oxygen, in patients with higher oxygen requirements, is administered via a high-flow nasal cannula. A high-flow oxygen delivery system can deliver supplemental oxygen up to 60 L/min. The additional benefit of this system is that there is a lesser risk for aerosol generation.[53,54]

A recent publication indicated that in a resource-constrained country, humidified high-flow nasal oxygen is satisfactory option for administering supplemental oxygen. Approximately 50% of patients who receive it can be successfully weaned without the need for mechanical ventilation.[53]
Non-invasive ventilation
Non-invasive ventilation devices are indicated if there is limited availability of invasive ventilation. Both, continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP), can be used in severe hypoxemic respiratory distress. Non-invasive ventilation can avoid invasive mechanical ventilation in some patients. Non-invasive ventilation carries risk of aerosol generation and enhanced risk for nosocomial viral infection and also with high failure rates.[22,54]

Mechanical ventilation
Excessive breathing effort, refractory hypoxemia, encephalopathy and multiorgan failure are indications for urgent intubation and mechanical ventilation. The patients with severe acute hypoxic respiratory distress need invasive ventilation. The endotracheal intubation should essentially be done by an expert and after taking full preventive precaution against nosocomial viral infection. Intubated patients should be closely monitored for hemodynamic parameters.[25]

Extracorporeal membrane oxygenation (ECMO)
When hypoxia is refractory to invasive ventilation, extracorporeal membrane oxygenation (ECMO) can be used as rescue therapy. ECMO provides crucial respiratory support as ECMO replaces the gas exchange function of the lungs. ECMO reduces ventilator-associated lung injury, barotrauma, and oxygen toxicity, as well.[56] Experience from 1035 patients, who received ECMO support, noted that approximately 311 (30%) were benefitted from ECMO. These improved patients were either discharged home or were sent to a rehabilitation centre.[57]

Prone positioning
Prone position is usually helpful as it improves ventilation in severe Covid-19. The limitation of this form of treatment is that the position of the patient needs to be changed every 2 hours. At least 3 to 5 health care personnel are needed for that. The process of position change may be risky as persons involved may get virus infection.[38]

Prognosis
Data from the United States revealed that more than 50% of patients with COVID-19 require hospitalization. Among those hospitalized 647 (23.6%) patients required mechanical ventilation. Among those who received mechanical ventilation, only 105 could be discharged from the hospital. Rest were either died, still on mechanical ventilation, or extubated but hospitalized. On multivariate analysis, advanced age, male sex, heart failure, chronic renal failure, and obesity were strong predictors of hospitalization and the occurrence of critical illness.[39] Auld and co-workers also observed an unusually high mortality rate in ventilated patients. Among 217 critically-ill patients, mortality, among mechanically ventilated patients, was 36% (59/165). Significant predictors of death were advanced age, lower body mass index, chronic renal failure, multiorgan dysfunction, lower PaO2/FIO2 ratio, a high CRP, invasive ventilation, need for vasopressors and renal replacement therapy.[60] D-dimer is an important prognostic marker. Patients with raised D-dimer levels have an significantly enhanced risk of severe disease and mortality.[61]

Pulmonary aspergillosis
Aspergillosis is a common fungal infection in patients with severe/critical COVID-19. Aspergillosis further enhances the damage to lungs already inflicted by SARS-CoV-2. Aspergillus fumigatus and Aspergillus flavus are two common Aspergillus species isolated from the lung of COVID-19 patients. Pulmonary invasive aspergillosis is generally associated with high mortality. Early diagnosis and early treatment with voriconazole (an antifungal drug) is usually warranted.[62]

Relevance to family physicians
In majority of patients with COVID-19, the disease is mild and restricted to the upper respiratory system. Patients with mild symptoms need just symptomatic therapy and may be monitored at home. A subset of mild and moderate COVID-19 patients may progress to a severe disease. Advancing age and the presence of comorbidities, like diabetes and hypertension, are crucial in the pathogenesis of severe COVID-19. Early identification of characteristic lung imaging abnormalities, at times, help in making surprise diagnosis of COVID-19. Corticosteroids and remdesivir have shown to have clinical benefits in severe COVID-19. Many of these patients need ICU care and mechanical ventilation. D-dimer is an important prognostic marker. Many patients need prolonged ventilatory support. Health care workers in ICUs are exposed to the enormous risk of acquiring hospital acquired SARS-COV-2 infection. Necessary protective equipment are key to protection from nosocomial SARS-COV-2 infection.

Conclusion
Severe COVID-19 is distinct entity. Family physician taking care of mild- moderate COVID-19 patients need to be careful. Many mild- moderate COVID-19 patients unexpectedly and abruptly progress to a severe disease. Severe COVID-19 patients need ICU care. Remdesivir, corticosteroids and anticoagulants have shown benefits in severe COVID-19. Overall prognosis for patients on mechanical ventilation remains grim.

Key points
• Severe COVID-19 is a distinct entity that rapidly evolves and may abruptly culminate in a critical illness.
• Male sex, old age, pre-existing co-morbidities and elevated inflammatory markers predict progression to severe disease.
• Timely supplemental oxygen therapy for patients developing respiratory insufficiency is crucial.
• Remdesivir, corticosteroids, anticoagulants and other drugs have limited role in management of severe COVID-19.
• Convalescent plasma therapy yet not have definitive role in severe COVID-19.
• Prognosis is poor for patients, who are on mechanical ventilation.

Journal of Family Medicine and Primary Care 89 Volume 10 : Issue 1 : January 2021
• Safety of health care workers is crucial. Adequate personal protective equipment help in protection from nosocomial SARS-COV-2 infection.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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