Review Article

Severe COVID-19: A distinct entity

Ravindra Kumar Garg[1], Gyan Prakash Singh[2], Rajiv Garg[3], Neeraj Kumar[1], Anit Parihar[4]

Departments of [1]Neurology, [2]Anaesthesia, [3]Respiratory Medicine, [4]Radiodiagnosis, King George Medical University, Lucknow, Uttar Pradesh, India

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

Address for correspondence: Dr. Ravindra Kumar Garg, Department of Neurology, King George Medical University, Lucknow - 226 003, Uttar Pradesh, India.
E-mail: garg50@yahoo.com

Received: 06-08-2020 **Revised:** 05-10-2020
Accepted: 19-11-2020 **Published:** 30-01-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_1600_20

How to cite this article: Garg RK, Singh GP, Garg R, Kumar N, Parihar A. Severe COVID-19: A distinct entity. J Family Med Prim Care 2021;10:84-92.

14 days from the first symptom.[3] 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).[4]

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.[5]

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.[6,7]

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.[8,9]

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 $PaCO_2$ were significant predictors of COVID-19. A higher C-reactive protein predicted a rapid conversion to severe disease.[10]

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.[11,12]

Genetics

Some recent observations suggested that the progression of the mild disease to severe COVID-19 might be genetically determined. Ellinghaus and colleagues identified a cluster of six genes, on chromosome 3p21.31, that predicted severe COVID-19. These genes regulate various immune functions. Ellinghaus 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.[13] The genetic abnormalities, leading to abnormalities of angiotensin-converting enzyme 2 receptor expression, were implicated in genesis of neurological complications of COVID-19.[14]

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].[15,16]

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[3,15,16]

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.[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.[18]

Clinical features

Clinical presentation of COVID-19 varies from pre-symptomatic phase to severely affected critically ill cases.[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].[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.[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].[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.[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.[25]

Table 2: The CDC list of common symptoms of COVID-19[15]

Fever
Cough
Dysnoea
Fatigue
Myalgia
Headache
Anosmia or ageusia
Sore throat
A stuffy or congested nose
Nausea or vomiting
Loose motions

Symptoms appear approximately several days after viral exposure

Table 3: Spectrum of disease severity in COVID-19[18]

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 Pao_2:Fio_2 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 4: Various systemic complications of severe COVID-19[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.[28]

Lung Imaging

X-ray

Predominant finding in chest X-ray is of ground-glass opacities with evidence pf 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].[29]

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.[30]

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 lyse 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 that 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 enourmous 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 bronco-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]

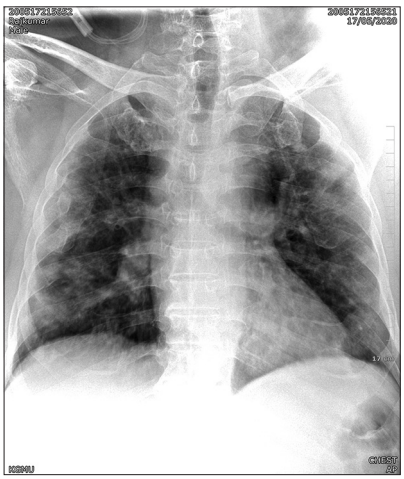

Figure 1: X-ray chest shows bilateral peripheral lung field ground glass opacities predominantly in mid and lower lung zones. Costophrenic angles of both side are clear

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.[55]

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 hypoxemic 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.[22]

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.[58]

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.[59] 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.

- 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.

References

1. World Health Organization. Coronavirus disease (COVID-19) outbreak situation. [Last Assessed on 2020 Oct 13]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019.
2. The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19)—China 2020. [Last accessed on 2020 Jul 12]. Available from: http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51.
3. Argenziano MG, Bruce SL, Slater CL, Tiao JR, Baldwin MR, Barr RG, *et al.* Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: Retrospective case series. BMJ 2020;369:m1996.
4. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, *et al.* Features of 20133 UK patients in hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: Prospective observational cohort study. BMJ 2020;369:m1985.
5. Pillay TS. Gene of the month: the 2019-nCoV/SARS-CoV-2 novel coronavirus spike protein. J Clin Pathol 2020;73:366-9.
6. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int 2020;44:1792-7.
7. Gao Y-M, Xu G, Wang B, Liu B-C. Cytokine storm syndrome in coronavirus disease 2019: A narrative review. J Intern Med 2020. doi: 10.1111/joim. 13144.
8. Pujhari S, Paul S, Ahluwalia J, Rasgon JL. Clotting disorder in severe acute respiratory syndrome coronavirus 2. Rev Med Virol 2020. doi: 10.1002/rmv. 2177.
9. The Lancet Haematology. COVID-19 coagulopathy: An evolving story. Lancet Haematol 2020;7:e425.
10. Duan J, Wang X, Chi J, Chen H, Bai L, Hu Q, *et al.* Correlation between the variables collected at admission and progression to severe cases during hospitalization among COVID-19 patients in Chongqing. J Med Virol 2020. doi: 10.1002/jmv. 26082.
11. Dong Y, Zhou H, Li M, Zhang Z, Guo W, Yu T, *et al.* A novel simple scoring model for predicting severity of patients with SARS-CoV-2 infection. Transbound Emerg Dis 2020. doi: 10.1111/tbed. 13651.
12. Wang C-Z, Hu S-L, Wang L, Li M, Li H-T. Early risk factors of the exacerbation of Coronavirus disease 2019 pneumonia. J Med Virol 2020. doi: 10.1002/jmv. 26071.
13. Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, *et al.* Genomewide association study of severe Covid-19 with respiratory failure. N Engl J Med 2020;383:1522-34.
14. Strafella C, Caputo V, Termine A, Barati S, Gambardella S, Borgiani P, *et al.* Analysis of *ACE2* genetic variability among populations highlights a possible link with COVID-19-related neurological complications. Genes (Basel) 2020;11:741.
15. Zhang B, Zhou X, Qiu Y, Song Y, Feng F, Feng J, *et al.* Clinical characteristics of 82 cases of death from COVID-19. PLoS One 2020;15:e0235458.
16. Nandy K, Salunke A, Pathak SK, Pandey A, Doctor C, Puj K, *et al.* Coronavirus disease (COVID-19): A systematic review and meta-analysis to evaluate the impact of various comorbidities on serious events. Diabetes Metab Syndr 2020;14:1017-25.
17. Ackermann M, Verleden SE, Kuehnel M, Haverich A, Welte T, Laenger F, *et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. N Engl J Med 2020;383:120-8.
18. Fox SE, Akmatbekov A, Harbert JL, Li G, Brown JQ, Vander Heide RS. Pulmonary and cardiac pathology in African American patients with COVID-19: An autopsy series from New Orleans. Lancet Respir Med 2020;8:681-6.
19. CDC. Symptoms of Coronavirus. [Last accessed on 2020 May 31]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
20. Wilkerson RG, Adler JD, Shah NG, Brown R. Silent hypoxia: A harbinger of clinical deterioration in patients with COVID-19. Am J Emerg Med 2020. doi: 10.1016/j.ajem.2020.05.044.
21. Goyal P, Choi JJ, Pinheiro LC, Schenck EJ, Chen R, Jabri A, *et al.* Clinical characteristics of Covid-19 in New York city. N Engl J Med 2020;382:2372-4.
22. Berlin DA, Gulick RM, Martinez FJ. Severe Covid-19. N Engl J Med 2020. doi: 10.1056/NEJMcp2009575.
23. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, *et al.* Extrapulmonary manifestations of COVID-19. Nat Med 2020;26:1017-32.
24. LeBlanc JJ, Gubbay JB, Li Y, Needle R, Arneson SR, Marcino D, *et al.* Real-time PCR-based SARS-CoV-2 detection in Canadian laboratories. J Clin Virol 2020;128:104433.
25. Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. Clin Chem Lab Med 2020;58:1021-8.
26. Han H, Ma Q, Li C, Liu R, Zhao L, Wang W, *et al.* Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect 2020;9:1123-30.
27. Liu X, Shi S, Xiao J, Wang H, Chen L, Li J, *et al.* Prediction of the severity of Corona Virus Disease 2019 and its adverse clinical outcomes. Jpn J Infect Dis 2020. doi: 10.7883/yoken.JJID.2020.194.
28. Cheng B, Hu J, Zuo X, Chen J, Li X, Chen Y, *et al.* Predictors of progression from moderate to severe COVID-19: A retrospective cohort. Clin Microbiol Infect 2020;26:1400-5.
29. Wong HYF, Lam HYS, Fong AH, Leung ST, Chen TWY, Lo CSY, *et al.* Frequency and distribution of chest radiographic findings in COVID-19 positive patients. Radiology 2020;296:E72-8.
30. Haseli S, Khalili N, Bakhshayeshkaram M, Taheri MS, Moharramzad Y. Lobar distribution of COVID-19 pneumonia based on chest computed tomography findings; A retrospective study. Arch Acad Emerg Med 2020;8:e55.

31. Yang Y, Huang Y, Gao F, Yuan L, Wang Z. Lung ultrasonography versus chest CT in COVID-19 pneumonia: A two-centered retrospective comparison study from China. Intensive Care Med 2020;46:1761-3.
32. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: A systematic review. PLoS One 2012;7:e35797.
33. Kashour Z, Riaz M, Garbati MA, AlDosary O, Tlayjeh H, Gerberi D, *et al.* Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: A systematic review and meta-analysis. J Antimicrob Chemother 2020. doi: 10.1093/jac/dkaa403.
34. RECOVERY Collaborative Group, Horby P, Mafham M, Linsell L, Bell JL, Staplin N, Emberson JR, *et al.* Effect of hydroxychloroquine in hospitalized patients with Covid-19. N Engl J Med 2020. doi: 10.1056/NEJMoa2022926.
35. Qaseem A, Yost J, Etxeandia-Ikobaltzeta I, Miller MC, Abraham GM, Obley AJ, *et al.* Update alert: Should clinicians use chloroquine or hydroxychloroquine alone or in combination with azithromycin for the prophylaxis or treatment of COVID-19? Living practice points from the American College of Physicians. Ann Intern Med 2020;173:W48-51.
36. Dolin R, Hirsch MS. Remdesivir-An important first step. N Engl J Med 2020. doi: 10.1056/NEJMe2018715.
37. Wilt TJ, Kaka AS, MacDonald R, Greer N, Obley A, Duan-Porter W. Remdesivir for adults with COVID-19: A living systematic review for an American College of Physicians Practice Points. Ann Intern Med 2020. doi: 10.7326/M20-5752.
38. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, *et al.* Tocilizumab in patients with severe COVID-19: A retrospective cohort study. Lancet Rheumatol 2020;2:e474-84.
39. Somers EC, Eschenauer GA, Troost JP, Golob JL, Gandhi TN, Wang L, *et al.* Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa954.
40. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, *et al.* A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020;382:1787-99.
41. RECOVERY Collaborative Group: Horby PW, Mafham M, Bell JL, *et al.* Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): A randomised, controlled, open-label, platform trial. Lancet 2020;396:1345-52.
42. World Health Organization. Corticosteroids for COVID-19: Living guidance; 2020 [cited 2020 Sep 2]. World Health Organization. Available from: https://apps.who.int/iris/handle/10665/334125.
43. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al.* Dexamethasone in hospitalized patients with Covid-19-Preliminary report. N Engl J Med 2020. doi: 10.1056/NEJMoa2021436.
44. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Viller J, Angus DC, *et al.* Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: A meta-analysis. JAMA 2020;324:1330-41.
45. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, *et al.* Early short course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa601.
46. Salazar E, Perez KK, Ashraf M, Chen J, Castillo B, Christensen PA, *et al.* Treatment of COVID-19 patients with convalescent plasma. Am J Pathol 2020;190:1680-90.
47. Devasenapathy N, Ye Z, Loeb M, Fang F, Najafabadi BT, Xiao Y, *et al.* Efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections: A systematic review and meta-analysis. CMAJ 2020;192:E745-55.
48. Chai KL, Valk SJ, Piechotta V, Kimber C, Monsef I, Doree C, *et al.* Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: A living systematic review. Cochrane Database Syst Rev 2020;10:CD013600.
49. Rogers R, Shehadeh F, Mylona EK, Rich J, Neill M, Touzard-Romo F, *et al.* Convalescent plasma for patients with severe COVID-19: A matched cohort study. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa1548.
50. Ambrosino P, Di Minno A, Maniscalco M, Di Minno MND. COVID-19 and venous thromboembolism: Current insights and prophylactic strategies. Ann Med 2020;52:239-42.
51. Kamel AM, Sobhy M, Magdy N, Sabry N, Farid S. Anticoagulation outcomes in hospitalized Covid-19 patients: A systematic review and meta-analysis of case-control and cohort studies. Rev Med Virol 2020. doi: 10.1002/rmv. 2180.
52. Albani F, Sepe L, Fusina F, Prezioso C, Baronio M, Caminiti F, *et al.* Thromboprophylaxis with enoxaparin is associated with a lower death rate in patients hospitalized with SARS-CoV-2 infection. A cohort study. EClinicalMedicine 2020;27:100562.
53. Whittle JS, Pavlov I, Sacchetti AD, Atwood C, Rosenberg MS. Respiratory support for adult patients with COVID-19. J Am Coll Emerg Physicians Open 2020;1:95-101.
54. Li J, Fink JB, Ehrmann S. High-flow nasal cannula for COVID-19 patients: Low risk of bio-aerosol dispersion. Eur Respir J 2020;55:2000892.
55. Calligaro GL, Lalla U, Audley G, Gina P, Miller MG, Mendelson M, *et al.* The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: A multi-centre prospective observational study. EClinicalMedicine 2020. doi: 10.1016/j.eclinm. 2020.100570.
56. Savarimuthu S, BinSaeid J, Harky A. The role of ECMO in COVID-19: Can it provide rescue therapy in those who are critically ill? J Card Surg 2020;35:1298-301.
57. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, *et al.* Extracorporeal membrane oxygenation support in COVID-19: An international cohort study of the Extracorporeal Life Support Organization registry. Lancet 2020;396:1071-8.
58. Ghelichkhani P, Esmaeili M. Prone position in management of COVID-19 patients; A commentary. Arch Acad Emerg Med 2020;8:e48.
59. Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, *et al.* Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: Prospective cohort study. BMJ 2020;369:m1966.
60. Auld SC, Caridi-Scheible M, Blum JM, Robichaux C, Kraft C, Jacob JT, *et al.* ICU and ventilator mortality among critically ill adults with coronavirus disease 2019. Crit Care Med 2020;48:e799-e804.

61. Shah S, Shah K, Patel SB, Patel FS, Osman M, Velagapudi P, *et al*. Elevated D-dimer levels are associated with increased risk of mortality in coronavirus disease 2019: A systematic review and meta-analysis. Cardiol Rev 2020;28:295-302.
62. Lai CC, Yu WL. COVID-19 associated with pulmonary aspergillosis: A literature review. J Microbiol Immunol Infect 2020. doi: 10.1016/j.jmii.2020.09.004.