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Review Article

Clinical interventions for severe and critical COVID-19: what are the options

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Abstract: The coronavirus disease 2019 (COVID-19) has been ongoing outbreak and declared as a global public health emergency by the World Health Organization. Severe and critical COVID-19 has high fatality rate due to complications like acute respiratory distress syndrome, acute respiratory failure or multiple organ failure. So far, there have been mounting research on the epidemiological and clinical characteristics of COVID-19. However, the information regarding treatment of severe and critical COVID-19 is limited. The current study reviewed published evidence of clinical interventions of severe and critical COVID-19, aiming to provide an up-to-date reference for further clinical treatment.

Keywords: COVID-19, SARS-CoV-2, severe pneumonia, intervention

Introduction

In late December 2019, cases of unidentified pneumonia were reported in Wuhan, China. Several days later, the causative agent of this pneumonia was identified as 2019 novel coronavirus (2019-nCoV) and its full-genome sequencing was revealed by several independent laboratories [1-3]. Later evidence revealed that there could be human-to-human transmission among close contacts [4, 5]. The 2019-nCoV infected pneumonia was then named by the World Health Organization (WHO) as coronavirus disease 2019 (COVID-19). As the COVID-19 outbreak has been rapidly increasing in the number of cases, deaths, and countries affected, WHO declared it as a global public health emergency. The International Committee on Taxonomy of Viruses has also proposed severe acute respiratory syndrome coronavirus (SARS-CoV-2) as the name of 2019-nCoV that causes COVID-19 [6].

Many countries have taken various medical and public health responses, including testing, screening, contact tracing, social distancing, travel restrictions, and orders to stay at home [7-9]. Despite these tough restrictions, since 12 December 2019 when the case was first reported, 2,074,529 cases have been confirmed of SARS-CoV-2 infection and 139,378 cases of death in a total of 207 countries, areas or territories, and it is still spreading fast according to the WHO data updated on 17 April 2020 [10]. For patients with SARS-CoV-2 infection, most present symptoms like fever, dry cough, fatigue, muscle pain and have good prognosis, however, there are also a considerable amount of COVID-19 patients under severe or even critical condition complicated with severe pneumonia, acute respiratory distress syndrome (ARDS), acute respiratory failure or multiple organ failure [11-13]. These severe and critical cases require immediate and intensive care, and effective management of severe and critical COVID-19 patients are critical to reducing case fatality rate (CFR). So far, there have been mounting studies on the epidemiological and clinical characteristics of COVID-19, however, the information regarding the treatment of severe COVID-19 is limited [13-16]. In the current study, we reviewed the clinical interventions on severe and critical COVID-19 based on the published evidence, aiming to provide an up-to-date reference for further clinical treat-

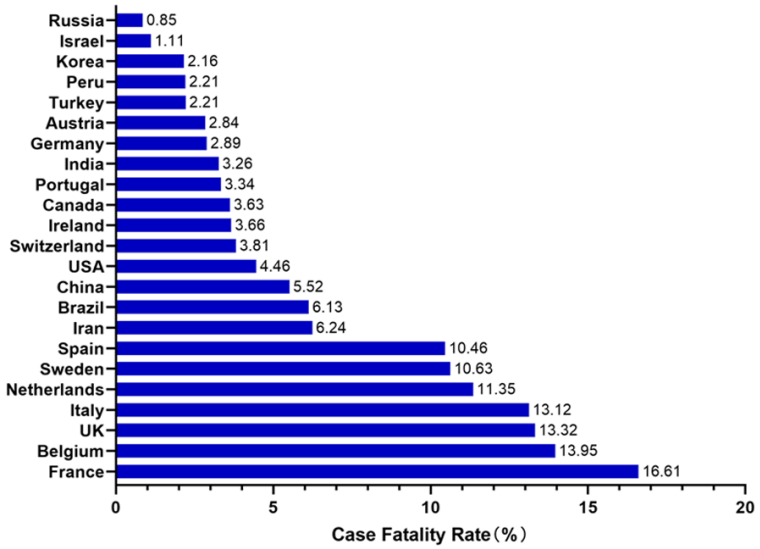

Figure 1. The case fatality rates among the countries with more than 10,000 cases confirmed according to WHO data updated at 17/04/2020.

ment of severe and critical COVID-19 to reduce CFR.

Clinical manifestations of severe COVID-19

According to the data of WHO, so far, the worldwide CFR in patients with COVID-19 is 6.72% (139,378/2,074,529) [10]. However, it varies notably from country to country. For instance, among the countries with more than 10,000 cases, France has the highest CFR of 16.61% (17,899/107,778), while Russia has the lowest CFR of 0.85% (273/32,008) (**Figure 1**). The differences in the statistical methods of death cases as well as the demographic data may lead to the diversity. In addition, shortage of medical resources, including medical personnel, hospital beds and intensive care facilities may also explain the high CFR in Italy [17]. Recently, Swiss Academy Of Medical Sciences approved a guideline for intensive-care treatment under resource scarcity, and defined the patients who could be treated in ICU as priority, in order to save the largest possible number of lives [18], but it also raises the ethnic question of whether certain group of patients like complicated with basic diseases that require more medical resources shall be abandoned. Proper recognition and treatment of these severe to critical cases could improve the overall medical efficiency, which could add chances of survival to these patients.

The most common clinical manifestations of 2019-nCoV infection include fever, cough and dyspnea, with radiological evidence of viral pneumonia [19, 20]. Several basic research studies have revealed that angiotensin-converting enzyme 2 (ACE2) has a protracted role in the pathogenesis of COVID-19 as it is a critical receptor for viral entry [21]. In addition, it has a broad expression in type II alveolar cells in the lungs, the gastrointestinal system, heart, and kidney [22], which could also cause damage to multiple organs, including heart, kidney, gastrointestinal system, etc. Severe to critical patients are prone to a variety of complications, including ARDS, acute heart injury, impaired renal function, abnormal liver function and secondary infection [19, 20, 23, 24].

According to the National Health Committee (NHC) of China [25, 26], the severity of COVID-19 is divided into four degrees. Severe COVID-19 is defined as dyspnea, respiratory frequency ≥ 30/min, blood oxygen saturation ≤ 93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or lung infiltrates > 50% within 24 to 48 hours. And critical COVID-19 is defined as presence of respiratory failure, and/or septic shock, and/or multiple organ dysfunction or failure (**Table 1**). As there is no global severe and critical COVID-19 rate data so far, we summarized the data published from China NHC [27] and found the daily severe and critical COVID-19 rate ranged from 13.23% to 34.16% (**Figure 2**).

Guan et al. [11] reported a total of 173 severe cases, among which there were 27 cases of ARDS (15.6%), 11 cases of septic shock (6.4%) and 5 cases of acute kidney injury (2.9%). A primary composite end-point event (transferring to ICU, receiving invasive mechanical ventilation, or death) was observed in 43 patients (24.9%). In a retrospective multicenter study, a total of 119 severe to critical cases were confirmed, with 54 cases of death (45.4%) at the end of study [28]. Wu et al. [25]

Table 1. Clinical severity type of COVID-19

Type	Criterion
Mild	Mild clinical symptoms, no imaging findings of pneumonia
Moderate	Fever, respiratory symptoms, imaging findings of pneumonia
Severe	Meet any of the followings: 1. Respiratory distress, RR ≥ 30/min 2. SPO_2 ≤ 93% at rest 3. PaO_2/FiO_2 ≤ 300 mmHg dyspnea, respiratory frequency ≥ 30/min, blood oxygen 4. Patients showing a rapid progression (> 50%) on CT imaging within 24-48 hours
Critical	Meet any of the followings: 1. Respiratory failure 2. Septic shock 3. Multiple organ dysfunction or failure

RR: respiratory rate, SpO_2: blood oxygen saturation, FiO_2: fraction of inspired oxygen, PaO_2: partial pressure of oxygen.

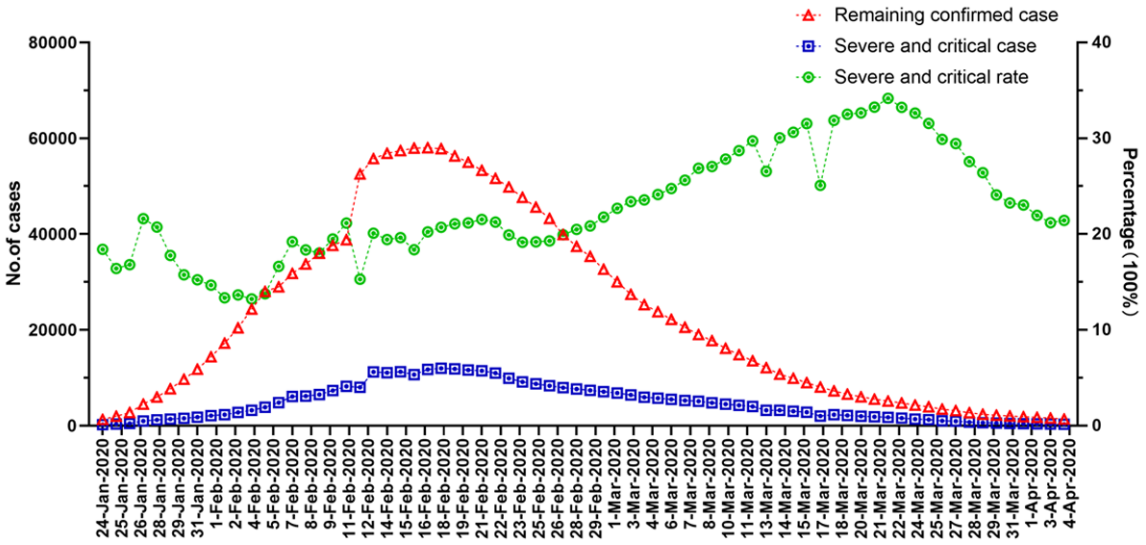

Figure 2. Dynamic data of confirmed case and severe and critical COVID-19 case according to China NHC.

reported 44,672 confirmed cases of COVID-19 in China, found most of the cases were diagnosed in Hubei Province, China (75%). Among the 44,672 cases, 81% of cases were classified as mild to moderate, 14% of the cases were severe, and 5% of the cases were critical. With respect to the CFR, the overall CFR was 2.3% (1,023/44,672), but the CFR was up to 49.0% among the critical cases. No death was observed in the group aged 9 years and younger, but for the cases aged 70 to 79 years, the CFR could be up to 8.0%, and for the cases aged 80 years and older, the CFR could reach 14.8%. Older patients with comorbid conditions including cardiovascular disease, diabetes, chronic respiratory disease, hypertension and cancer could easily develop into severe or even critical conditions, which could partially explain the higher mortality rates. Another study by Wu et al. revealed that 84 in 201 patients with COVID-19 (41.8%) developed ARDS, among which 44 (52.4%) died. The authors indicate that older age is associated with greater risk of ARDS and death, possibly owing to a less rigorous immune response [29].

Principles of treating severe and critical COVID-19

So far, besides supportive care, there has been no proven specific drug available. A recent treatment advice for severe and critical COVID-19 is to ameliorate the symptoms, target the underlying diseases, actively prevent potential complications and secondary infection and provide timely measures to support organ function

[30]. Fluid management, microcirculation improvement, prevention of deep vein thrombosis and stress-induced gastrointestinal bleeding, blood glucose control etc. should be provided to support the severe and critical COVID-19 patients.

Oxygen therapy

Oxygen therapy invloves nasal catheter, mask oxygen, high flow nasal oxygen therapy (HFNO), non-invasive ventilation (NIV) or invasive mechanical ventilation (IMV). Under the support of HFNO (the demand for FiO_2 > 70% and gas flow > 50 L/min) or NIV, if ARDS still exists or even acutely deteriorates, invasive mechanical ventilation should be implemented as soon as possible in COVID-19 patients [30]. In one study by Guan et al. [11], mechanical ventilation was initiated in more severe patients than in those with nonsevere diseases (NIV, 32.4% vs. 0%; IMV, 14.5% vs. 0%). Mo et al. [31] retrospectively studied 85 cases of refractory COVID-19 and found 72 cases (84.7%) receiving oxygen therapy. These findings suggest that oxygen therapy should be immediately applied to severe and critical COVID-19 patients.

Extracorporeal membrane oxygenation (ECMO) can also be used in some severe to critical COVID-19 patients with ARDS (lung injury score > 3 or pH < 7.2 due to uncompensated hypercapnia) [30]. The WHO interim guidelines make general recommendations for ARDS treatment in this setting, suggesting referring the patients with refractory hypoxemia to expert centers capable of providing extracorporeal membrane oxygenation (ECMO) [32]. However, MacLaren et al. [33] suggest that considering the mechanism of COVID-19 death includes septic shock or refractory multiorgan failure in a substantial number of patients, the most severe patients would be less likely to benefit from ECMO. And they suggest that ECMO should not be used in the patients with COVID-19. ECMO has been applied in severe COVID-19 patients in China according to several studies, however, these studies didn't report the outcomes of these patients [11, 20, 23, 28]. A substantial proportion of critical COVID-19 cases also have developed cardiac arrhythmias or shock [19], but it remains unknown of how many of them have developed or will develop refractory multiorgan failure, for which ECMO may be of less use.

Antiviral treatment

There have also been several case reports on old or new drugs given to COVID-19 patients with in vitro activity against SARS-CoV-2, such as remdesivir, ribavirin, oseltamivir, ganciclovir, lopinavir/ritonavir, favipiravir, umifenovir [29, 34]. Most of the drugs have been undergoing RCTs around the world to assess the safety and effectiveness for treating COVID-19 [35-37], but most of these results remain to be revealed. According to an RCT of lopinavir and ritonavir, 99 patients were treated with lopinavir and ritonavir (400 mg and 100 mg twice daily; orally; freely provided by the national health authority) along with standard care for 14 days, and 100 patients were treated with standard care alone for 14 days. The final results showed no merit with lopinavir-ritonavir treatment over standard care in terms of clinical improvement, mortality, or throat viral RNA detectability in the patients with serious COVID-19 [38]. In a compassionate-use remdesivir non RCT study, 53 patients hospitalized for severe COVID-19 received a 10-day course of remdesivir treatment, consisting of 200 mg administered intravenously on day 1, followed by 100 mg daily for the remaining 9 days. During the follow-up with a median of 18 days, 36 patients (68%) showed an improvement in oxygen-support class and 7 patients (13%) died; the mortality was 18% (6 of 34) in patients receiving invasive ventilation and 5% (1 of 19) in those not receiving invasive ventilation. Several other in vitro studies also identified chloroquine with antiviral acitivity, as it could block COVID-19 infection at a low-micromolar concentration [39]. And a report from China have demonstrated that chloroquine phosphate is superior to the control treatment for treating COVID-19 pneumonia improving lung imaging findings, promoting a virusnegative conversion, and shortening the disease course [40], but author didn't show the relevant data. Another recent study in France also showed that hydroxychloroquine treatment in COVID-19 patients could significantly reduce viral load and its effect could be further reinforced by combined application with azithromycin [41]. However, due to the small sample size and non-randomised nature, as well as its lack of better explanations for the inclusion criteria and the triage of patients to ensure patient safety, there have been great controversy and strong criti-

cisms of this study [42]. Hence, there is still a lack of solid data to support its clinical application. Interferons (IFN)-α and -β, which play key roles in viral innate immunity, could also inhibit the replication of SARS-CoV [43]. IFNs have been applied in several studies for treating severe COVID-19 patients, but the clinical outcomes remain unclear. In addition, despite that preclinical data suggest a potential mechanism of benefit, there is no direct clinical evidence suggest that targeting ACE2 could be effective for treating SARS-CoV-2-induced lung injury, and there is limited evidence to demonstrate that treatment with ACEIs could decrease the severity of pulmonary injury induced by SARS-CoV-2 [44].

Anti-inflammation therapy

COVID-19 patients have higher levels of inflammatory markers according to their laboratory tests [11, 23], and the treatment of cytokine storm is an important element for rescuing severe patients. A recent retrospective multicenter study of 150 cases of COVID-19 revealed several predictors of fatality, including elevated ferritin and Interleukin-6 (IL-6) [45], which has been revealed to play an important role in cytokine release syndrome. As Tocilizumab can effectively block IL-6 signal transduction pathway, it is a promising drug for patients with severe COVID-19. Fu et al. [46] reported preliminary data collected from 21 patients with severe and critical COVID-19 treated with tocilizumab, among these 21 patients, 20 patients have been recovered and discharged within 2 weeks after the tocilizumab therapy. One left patient is on recovery and has been out of ICU care. According to another study of 15 COVID-19 patients, the serum IL-6 level in 10 patients (66.7%) tended to spike shortly at first and then decreased, while the serum IL-6 level in the other 5 patients presented a marked increase, in which 3 patients died, 2 patient showed aggravation at the endpoint of study [47]. There are also several ongoing RCTs of Tocilizumab for treating patients with severe COVID-19, but the results have not been revealed yet [48]. As corticosteroid therapy has long been used for anti-inflammation, whether it could be effective for treating COVID-19 has been under investigation. In one study by Russell et al. [49], they summarized clinical evidence to date and found no clinical evidence indicating a net benefit from corticosteroids for treating respiratory infection due to RSV, influenza, SARS-CoV, or MERS-CoV. And they suggested that corticosteroid treatment should not be used for treating SARS-CoV-2 induced lung injury or shock outside of a clinical trial. However, in another study by Wu et al. [29], severe COVID-19 patients treated with methylprednisolone showed a decreased risk of death (HR, 0.38; 95% CI, 0.20-0.72). As the patients in septic shock often combine with bacterial infection, which could lead to vasoplegic shock and myocardial insufficiency [50], this may explain the net benefit of steroid treatment in severe COVID-19 patients.

Convalescent plasma therapy

From the perspective of immunology, most of the patients recovered from COVID-19 would produce specific antibodies against the SARS-CoV-2, and the antibodies from convalescent plasma might suppress viraemia. Several studies have showed that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events in SARS, Ebola virus disease, Middle East respiratory syndrome and H1N1 [51]. Hence, convalescent plasma therapy is also a worthwhile option for treating severe COVID-19 patients.

Antibiotic therapy

Enhancement of bacteriological surveillance should be performed and promptly appropriate antibacterial drugs should be applied when secondary bacterial infections were identified. Empirical antibacterial treatment in severe patients should cover all possible pathogens, with deescalating therapy until the pathogenic bacteria are clarified.

Other support therapy

Continuous renal replacement therapy (CRRT) [52] could be used for severe COVID-19 with kidney failure, hyperkalemia, acidosis, pulmonary edema or fluid management for multiple organ failure. In the study by guan et al. [11], 9 out of 173 (5.2%) severe COVID-19 patients received CRRT treatment. Huang et al. [23] reported 13 severe COVID-19 cases in ICU, among which 3 (23.1%) received CRRT treatment. Furthermore blood purification technology could be used to remove inflammatory factors, eliminate cytokine storm, correct electro-

lyte imbalance, maintain acid-base balance, and control patient's capacity load in an effective manner [16], which could be used in severe COVID-19 with cytokine storm.

Conclusions

In conclusion, severe and critical COVID-19 cases have a variety of complications, including ARDS, acute heart injury, impaired renal function, leading high case fatality rate. Effective management of severe and critical COVID-19 patients is critical to reducing the case fatality rate. So far, there is still lack of evidence supporting an effective drug for treating severe and critical COVID-19, and supportive treatment is crutial at this stage, including oxygen therapy, symptomatic treatment and complication management.

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Disclosure of conflict of interest

None.

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