

Clinical features, treatments and outcomes of severe and critical severe patients infected with COVID-19: A system review and meta-analysis

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Abstract

Backgrounds: The outbreak of COVID-19 caused by a novel coronavirus, SARS-CoV-2, has been listed as a public health emergency of international concern by WHO. Most COVID-19 patients presented with a mild infection, but many challenges exist in therapy of severe and critical severe patients. This paper systematically reviewed clinical features, treatments and outcomes of severe and critical severe patients infected COVID-19.

Methods: The clinical, laboratory, imaging features, treatment and outcomes of COVID-19 were collected. The data were analyzed by using STATA 15 statistical software to estimate the prevalence and 95% CI in severe and critical severe patients with COVID-19. A random or fixed effect model was used to estimate the prevalence and 95% CI.

Results: After screening, 8 studies including a total of 275 patients were included in this meta-analysis. The percentage of severe and critical severe patients in confirmed COVID-19 cases was 25% (95% CI 16-36%). Fever, cough, dyspnea, lymphopenia and bilateral distribution of patchy shadows were the most prevalent findings in these patients. Utilization rate of antiviral drugs, corticosteroid, non-invasive ventilation, invasive mechanical ventilation was high in therapy strategies. The most prevalent complications were ARDS, shock, and acute cardiac injury.

Discussion: Severe and critical severe COVID-19 patients usually had complications even a fatal outcome. As vaccines and anti-coronaviral drugs are under development, the principles of treatment for these patients should be focused on improving oxygenation, lung protective and function support of multiple organs.

Background

In December 2019, a novel coronavirus (SARS-CoV-2)-infected pneumonia occur in Wuhan, China [1–4]. Studies reported the evidence of person-to-person transmission in both community and hospital [5–9]. SARS-CoV-2 appears to be highly contagious, and has rapidly spread worldwide. The World Health Organization (WHO) has declared that COVID-19 is a public health emergency of international concern [10]. As of March 2, 2020, a total of 80151 cases with laboratory-confirmed COVID-19 have been detected in China mainland reported by National Health Commission of China. Recently, the number of newly confirmed cases continues to decline in China. While, the epidemics in the Republic of Korea, Italy, Iran and Japan are greatest concern of WHO [11].

Even most of COVID-19 patients were mild infection, a part of cases will soon develop into severe, critical type, and even die due to multiple organ failure (MOF). Most of severe and critical severe patients were elderly, accompanied with hypertension, cardiovascular diseases, chronic pulmonary diseases, other basic diseases, and had complications of acute respiratory distress syndrome (ARDS), shock, and fatal outcomes. Vaccines and antiviral drugs are under development. The principles of treatment for severe and critical severe patients are focused on improving oxygenation, lung protection and multiple organ function support. Challenges, particularly in oxygen supporting of severe and critical severe cases are a critical issue. Oxygen supporting includes common nasal cannula, high-flow nasal cannula oxygen therapy (HFNC), non-invasive ventilation (NIV), invasive mechanical ventilation (IMV) and extracorporeal membrane oxygenation (ECMO). The time point of ending NIV and initiating IMV supporting is a big challenge in severe and critical severe patients. After analyzed treatment regimens and prognosis of 137 COVID-19 infected patients, in Wuhan, the authors put out the point that early

respiratory support facilitated disease recovery and improved prognosis [12]. Many studies reported the disease evolution and outcomes of COVID-19 [13–16], but most of them were signal center or case reports. In this article, we systematically reviewed available on clinical, laboratory, imaging features, utilization rate of different oxygen supporting, prevalence of comorbidities, and outcomes of severe and critical severe COVID-19 patients in published literatures.

Methods

Search strategy

Databases including PubMed, EMBASE, The Cochrane Central Register of Controlled Trials and China National Knowledge Infrastructure(CNKI) were searched. Initial keywords included “Novel coronavirus 2019”, “2019 nCoV”, “COVID-19”, “Wuhan pneumonia,” “SARS-CoV-2.” We searched publications in English and Chinese from December 31, 2019 to March 1, 2020. Reference lists of relevant studies were also included.

Study Selection

The results of the initial search strategy were firstly screened by title and abstract. The full texts of relevant articles were examined by inclusion and exclusion criteria. Inclusion criteria as follows: severe, critical severe or ICU admission patients with COVID-19; clinical, laboratory, imagine features, treatment, and outcomes of COVID-19; published peer-reviewed case-control and cohort studies articles. The definition of severe, critical severe patients with COVID-19 was according to the Diagnosis and Treatment of Novel Coronavirus Pneumonia (5th edition) in China [17]. Severe patient should meet no less than one requirement: respiratory distress, $RR \geq 30$ /minute; oxygen saturation $\leq 93\%$; $PaO_2/FiO_2 \leq 300$ mmHg. The same principle applied to critical severe patient: respiratory failure, requiring mechanical ventilation; shock; complicated with other organ failure and need admitted to ICU. Exclusion criteria: no laboratory (RT-PCR) confirmed COVID-19 infection, reports with incomplete information. Duplicate information from the same patient in different studies should be combined and counted as a single case.

Data extraction and quality assessment

Six main categories of data were extracted: characteristics of included studies (e.g., author, journal, publication date, country); baseline characteristics of samples (e.g., age, sex, smoking situation, comorbidities); clinical features (e.g., fever, cough, dyspnea); laboratory findings (e.g., lymphopenia, leukopenia, high LDH, high CRP); treatment(e.g., antiviral, glucocorticoid, oxygen supporting); outcomes and complications independently by three investigators. Another researcher checked data extractions to ensure there were no duplicate and missing information.

Quality assessment of included studies was performed by using Hoy’s risk of bias tool [18]. Item 1 to 4 assess selection and nonresponse bias, and item 5 to 10 assess represent measurement bias and analysis bias. Quality score that ranged from 1 to 10 and was divided into three risk of bias: low (8–10), moderate (5–7) and high (≤ 4). Publication bias was assessed by standard error of logit event rate.

Data analysis

The meta-analyses were performed by using STATA package version 15.0. Percentages and means \pm SDs were calculated to describe the counting data and measurement data, respectively. Heterogeneity was assessed by using I-squared statistic (I^2) and Q statistic tests. If $I^2 \geq 50\%$ or Q test $P \leq 0.05$ (significant heterogeneity among studies), we use random effect model to analyze, otherwise the fixed effect model was used. Forest plots were used to reflect the meta-analysis results.

Results

A total of 1358 articles were retrieved after initial systematic search. After screening titles and abstracts, 32 articles remained. After full text examination, 8 studies were included in this systematic review. The screening process of studies was depicted in Fig. 1. The 8 studies were from China, including 5 in English and 3 in Chinese, with a total of 275 patients. The quality score of included studies was showed in Table 1. The funnel-plot for the Standard Error by Logit Event rate showed no significantly publication bias of 8 studies.

Meta-analysis of baseline characteristics of severe and critical severe patients infected with COVID-19

Table 2 summarized the meta-analysis result. The percentage of severe and critical severe patients in confirmed COVID cases was 25% (95% CI 15–36%). The mean age of severe, critical patients was 60 ± 18.3 years old, being male 67% (95% CI 61–73%). The prevalence of comorbidities was 60% (95% CI 47–73%), the most prevalent base diseases were hypertension (38%, 95% CI 26–50%), diabetes (16%, 95% CI 7–24%), cardiovascular disease (12%, 95% CI 7–17%), CPD (9%, 95% CI 5–13%), and cerebrovascular disease (9%, 95% CI 5–13%).

Meta-analysis of clinical characteristics and laboratory findings of severe and critical severe patients with COVID-19

Table 3 summarized the meta-analysis result. The most prevalent manifestation were fever (79%, 95%CI 58–100%), cough (70%, 95% CI 62–78%), dyspnea (48%, 95% CI 26–72), and then fatigue(48%, 95% CI 24–73%), myalgia (27%, 95% CI 8–46%), sputum production(24%, 95% CI 17–31%), diarrhea(9%, 95% CI 4–14%). The most prevalent laboratory finding is lymphopenia (76%, 95% CI 67–84%). The prevalence of leukocytosis, leukopenia, high levels of PCT, high levels of creatinine were 25% (95% CI 6–44%), 11% (95% CI 1–17%), 12% (95% CI 3–20%), and 9% (95% CI 3–15%). Limited to the few numbers of included articles, we can't analyze other indicators of liver, kidney function and inflammation in detail. Nearly all of severe and critical severe patients had imaging features of bilateral distribution of patchy shadows or GGO.

Meta-analysis of treatment and outcomes of severe and critical severe patients with COVID-19

In therapy strategy, 71% (95% CI 45–97%) patients were given antiviral therapy, additionally, 60% (95% CI 53–67%) patients received corticosteroid therapy. In oxygen supporting, 10% (95% CI 2–18%) patients received oxygen inhalation, and 48% (95% CI 41–56%) NIV, 36% (95% CI 25–48%) IMV, 10% (95% CI 6–14%) ECMO. The most prevalent complications were ARDS (54%, 95% CI 34–74%); shock (21%, 95% CI 9–12%), acute cardiac injury (18%, 95% CI 5–31%) and AKI (12%, 95%,CI 4–20%). The fatality rate of severe and critical severe patients

was 28% (95%CI 9–47%), however, 51% (95%CI 2–82%) patients were still hospitalization until the included studies published (Table 4).

Discussion

The COVID-19 is an emerging situation firstly found in Wuhan, with a high contagious [19–21]. By early March, the infection has spread to more than 50 countries around the world. The mortality of COVID-19 is less than SARS-COV (~ 10%) and much less than MERS-COV (~ 40%) [21]. Clinical researches showed that most of the COVID-19 patients are mild, a part of cases will rapidly evolve into severe, critical infection and need ICU care [12, 13]. However, more information on biological and epidemiological features of the virus is needed in urgent to further assess the risk and trend of the virus. As vaccines and anti-coronaviral drugs are still under development and pre-clinical/ clinical trials [22], there are great challenges in treatment of COVID-19, particularly for severe and critical severe patients.

In this article, we systemically reviewed the baseline characteristic, clinical features, laboratory findings, treatment strategies and outcomes in severe and critical severe COVID-19 patients to provide references for front line clinicians (Table 5 and Fig. 2).

The system review showed that severe and critical severe patients were elderly, with the percentage of 25% in confirmed COVID-19 infection. More than half cases had comorbidities, and hypertension was mostly common, then diabetes, cardiovascular disease, cerebrovascular disease, chronic pulmonary disease and malignancy in turn. Only two included articles described the smoking situation of patients, we can't get the correlation between disease severity and current smoking situation. Compared with another meta-analysis [23], the prevalence of comorbidities was higher in severe and critical severe patients than all COVID-19 confirmed hospitalized patients (60% vs 36.8%). Therefore, elderly with underlying comorbidities of confirmed COVID-19 patients have highly risk of evolving into severe, critical severe cases and require additional care.

As firstly reported, the COVID-19 patients presented with fever and cough [7]. The most common clinical manifestation of severe and critical severe patients were cough, fever, dyspnea in this article. The present of continuous fever of patients have the trend of aggravation. Besides, patients getting a fever again after undergoing a defervescence period for 1 week are usually associated with second infection. This could explain the prevalence of leukocytosis (25%, 95% CI 6–44%) in severe and critical severe patients. Decline of oxygen saturation continuously ($\leq 93\%$) is an indicator of disease aggravation. Lymphopenia is one important laboratory finding in COVID-19 patients. Clinical researches showed decline of lymphocyte of ICU admission patients was more remarkably than non-ICU patients [13, 25]. High levels of CRP, were also found in COVID patients, and plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNF α were higher in ICU patients than non-ICU patients [26]. That indicted that cytokine storm was associated with disease severity. But these indicators were not analyzed limited to few numbers of included articles. Nearly all of severe and critical severe patients had imaging features of bilateral distribution of patchy shadows or GGO. However, more pathological analysis is needed for comprehensive understanding of COVID-19.

More than half included patients were given antiviral and glucocorticoid therapy. Generally, appropriate glucocorticoid admission could alleviate pulmonary exudates and inhibit a systemic cytokine storm in acute lung injury, in theory. However, no included article assessed the effect of glucocorticoid in this meta-analysis.

Research reported that after treated with methylprednisolone 40 mg/day (iv) for 6 days, the lung CT test of one COVID-19 case showed significant lesion progression, and the patient died ultimately[12]. Glucocorticoids usage in viral pneumonia is controversial. Glucocorticoids can inhibit the inflammation response in lung, at the same time suppress immune function of body to prolong the clearance of virus [27]. Experts suggested that given low doses (equal to methylprednisolone, 1–2 mg/kg/days) and short-term (3–5 days) glucocorticoids according to basic disease and disease severity of patients, should provide benefits [28].

Oxygen supporting plays a pivotal role in the treatment of severe and critical severe patients. We systemically reviewed the usage rate of different oxygen supporting methods, and fund NIV, IMV were highly given to severe and critical severe patients. Identifying failure of high-flow nasal cannula oxygen therapy (HFNC) and NIV in early phase, and then initiating IMV or ECMO in early phase is the key and difficult points of oxygen supporting. The Diagnosis and Treatment of Novel Coronavirus Pneumonia (5th edition) suggested patients can consider given HFNC or NIV when respiratory distress or hypoxemia cannot be relieved after standard oxygen therapy, it also pointed out that if the condition cannot be improved or even worsen within a short time (1–2 h), IMV should be timely performed[17]. According to the clinical experience, we think IMV should be performed early for patients who present respiratory failure in early onset. Neap tide volume (4–6 ml/kg) and low inspiratory pressure (platform pressure \leq 30 cm H₂O) is the normal mode to reduce ventilator related lung injury. Up to now, the benefits of application of ECMO are not clear in Hubei Province. The effects of ECMO need more clinical data to assess. The highest prevalence of complication in severe and critical severe patients is ARDS, then shock, acute cardiovascular disease in turn, in this system review. 28% patients had a fatal outcome, although 51% patients were still hospitalization until the included studies published. Therefore, prevention and control of complications, treatment basic diseases, prevention of secondary infections, improve of oxygenation, and providing organ function support as soon as possible are essential in severe and critical severe COVID-19 patients.

Limitations

There were some limitations to this review. Firstly, few studies were included and all of enrolled patients came from China; much more multicenter studies are needed to get better understanding of COVID-19; secondly, ICU admission patients were considered as severe and critical severe patients of included studies published in English; thirdly, many patients were still hospitalization when data were collected. Long-term studies with follow-up period are needed to assess the outcomes of severe and critical severe patients.

Conclusions

The COVID-19 is an emerging disease with a high contagious. Elderly male patients with underlying disease are susceptible to develop into severe and critical severe cases and have many complications even a fatal outcome. Fever, cough, dyspnea are common clinical manifestations; lymphopenia, high levels of PCT, leukocytosis and leukopenia in laboratory tests and bilateral distribution of patchy shadows or GGO in imaging features are fund in severe and critical sever patients. IMV should be performed early for patients who present respiratory failure in early onset. More multicenter studies with follow-up period are needed to assess the effect of glucocorticoid, to make the time point of initiating IMV or ECOM support in severe and critical severe COVID-19 patients.

Abbreviations

MOF: multiple organ failure; ARDS: acute respiratory distress syndrome; CNKI: China National Knowledge Infrastructure; GGO: ground glass opacity; HFNC: high-flow nasal cannula oxygen therapy; NIV: non-invasive ventilation; IMV: invasive mechanical ventilation ECMO: extracorporeal membrane oxygenation

Declarations

Acknowledgments

Not applicable.

Authors' contributions

ZJG conceived and designed the study. FZJ performed statistical analyses, HYZ, MS, YCL, XJW performed literature search, data extraction. HYZ drafted the manuscript. All authors reviewed and revised the manuscript, and approved it for submission.

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Availability of data and materials

All relevant data for this study are presented in tables, figures

Consent for publication

Not applicable.

Conflict of Interest

The authors of this manuscript do not have a commercial or other association that might pose a conflict of interest.

Ethical Approval: Approval was not required.

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Tables

Due to technical limitations, Tables 1-5 are provided in the Supplementary Files section.

Figures

Figure 1 Flowchart and study selection

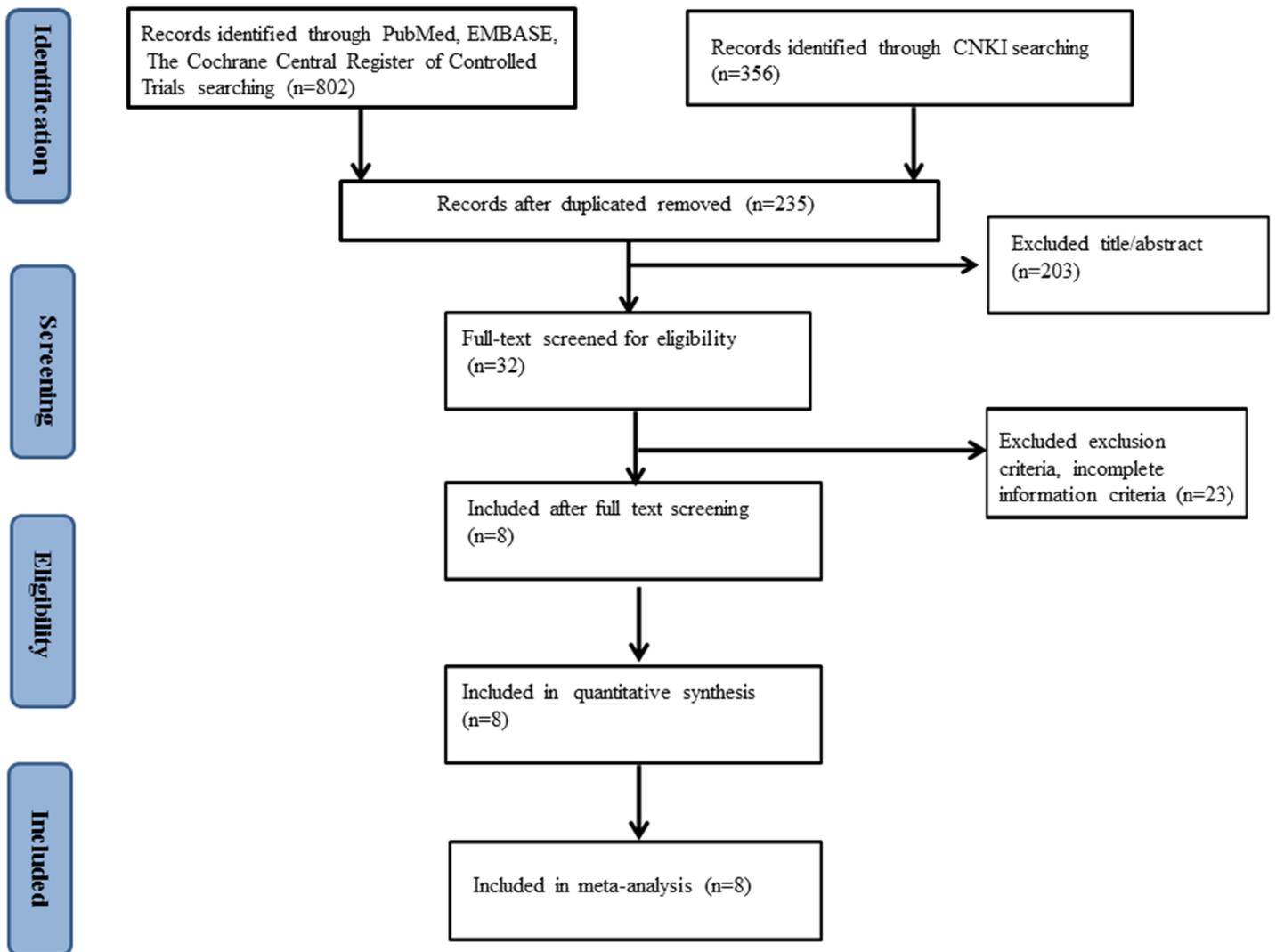


Figure 1

Flowchart and study selection

Figure 2 Pool prevalences forest plots of findings described in Table 5



Figure 2

Forest plots of research of findings described in Table 2-5

Supplementary Files

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