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The Coronavirus Disease 2019 (COVID-19): A Review

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

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Review Article

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ABSTRACT

Many details of the emergence of 2019 novel coronavirus infection such as its origin, spread, epidemiology, full spectrum of clinical illness, treatment and mortality rate has not been clearly defined. This review focuses the epidemiological evidences, clinical manifestations, investigations and treatment provided to the admitted cases of the 2019 novel coronavirus pneumonia in various hospitals of Wuhan city and other regions in China. Information have been gathered mainly from relevant researches and papers that were published recently. Clinical manifestations included fever, non-productive cough, dyspnoea, myalgia, fatigue, radiographic manifestations of pneumonia and detection of the novel virus by RT-PCR method. Some patients rapidly developed acute respiratory distress syndrome, acute respiratory failure, and other serious complications with fatal outcomes. There are neither vaccines nor effective treatments for the disease caused by the virus, but efforts are typically confined to symptomatic and supportive management. Antivirals and corticosteroids were used in severe illness but had no effective outcome.

Keywords: 2019-nCoV; pneumonia; novel coronavirus; SARS-CoV-2.

1. INTRODUCTION

During the month of Dec 2019, a considerable number of patient developed pneumonia of unknown cause in the capital city Wuhan of Hubei province in China, with clinical presentations greatly resembling viral pneumonia but some rapidly progressed to severe illness

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and fatal outcome [1]. These cases had a history of exposure to Huanan Seafood Wholesale Market where live animals were also on sale [2]. The disease then rapidly spread from Wuhan to other areas. By the first week of Jan 2020, a novel coronavirus was identified by the Chinese centre for disease control and prevention (CDC) from the throat swab sample of these patients, and the virus was named 2019 novel coronavirus (2019-nCoV). Although the initial spread had some link to exposure at the seafood and animal market, a growing number of patients reportedly had not exposed to animal markets, indicating human-to-human spread. An outbreak of the 2019-nCoV occurred, spreading rapidly to the other regions of China as well as in a number of other countries. Cases reported in countries other than China have predominantly been in people who have recently travelled to China, however some cases of local transmission have also occurred. Due to rapid global spread the World Health Organization (WHO) on January 30 declared the outbreak as a public health emergency of international concern [3]. On 11 February 2020, WHO announced that "COVID-19" (meaning coronavirus disease-2019) will be the official name of the disease. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses, which is responsible for naming new viruses, recognized this virus as a sister species to severe acute respiratory syndrome coronaviruses and on 11 Feb 2020, posted online a preprint paper designating it as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4].

So far till 11 Mar 2020, it has spread outside China with confirmed infection of 37,364 in 113 countries with a total fatality of 1130 outside China [5]. More and more countries are involved day by day with the increase in number of cases and fatality. In China, as on 11 Mar 2020, total confirmed cases were 80,995 and total deaths were 3162. WHO has been deeply concerned by the alarming levels of spread and therefore, on 11 Mar 2020 made the assessment that COVID-19 can be characterized as pandemic [5].

This paper, focuses on the epidemiology, clinical manifestations, investigations, and management of the 2019 novel coronavirus infection. Control and prevention of the coronavirus disease has not been discussed in this paper.

2. CORONAVIRUS

Coronaviruses are widely distributed in many different species of animals, including bats, cattle, cats, birds, and camels [6]. Coronavirus is also one of the pathogens that causes respiratory tract infection in human. The four other human coronaviruses (HCoV-OC43, HCoV-229E, HCoV-NL63, HCoV-HKU1) induce mild upper respiratory disease similar to common cold [7,8]. The two highly pathogenic viruses that emerged previously, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) cause more severe, pneumonia-like symptoms, severe acute respiratory syndrome (SARS) and sometimes fatality in humans [9-11]. The mortality rates were described to be 10% for SARS-CoV and 34.4% for MERS-CoV [12,13]. The major SARS-CoV outbreak emerged in Guangdong Province, China during 2002–2003 and spread to 29 countries globally [10,11,14]. MERS-CoV emerged in Middle East in 2012 but was also imported into China [15-17]. SARS-CoV was transmitted to humans from exotic animals in wet markets, whereas MERS-CoV is transmitted from camels to humans [18]. The 2019-nCoV is the 7th pathogen identified to cause human respiratory tract infection. 2019-nCoV is a beta-coronavirus, like MERS and SARS, both of which were believed to have their origins in bats. Zhu et al. [19] have identified and characterized 2019-nCoV which seemed to be a distinct from SARS-CoV and MERS-CoV. Electron micrographs of 2019-nCoV particles were generally spherical, enveloped with some pleomorphism. Diameter varied from about 60 to 140 nm. Coronavirus are RNA virus and the virus particles have quite distinctive spikes, about 9 to 12 nm, which give them the appearance of a solar corona. Due to, genetic similarities between the new coronavirus and the coronavirus that caused the SARS outbreak in 2002-2003, recently the new virus has been renamed as SARS-CoV-2 [4].

3. DEMOGRAPHIC FINDINGS

The virus is thought to have a zoonotic origin and bats have been held responsible [20]. It is unclear which animal is the intermediate species between bats and humans in the transmission of 2019-nCoV. For SARS it was civet cats, for MERS it is camel [21]. Although cases were originally reported to be associated with exposure to the seafood market in Wuhan, current epidemiologic data indicate that person-to-person transmission of 2019-nCoV is occurring [22-24]. Person-to-person spread is thought to occur mainly via respiratory droplets produced when an infected person coughs or

sneezes, similar to influenza and other respiratory pathogens spread. These droplets possibly land in the mouths or noses of people who are nearby or be inhaled into the lungs. Typically, people are thought to be most contagious when they are most symptomatic. It has an incubation period of between 2 and 14 days [25]. Li Q et al. [26] in their data analysis of 425 confirmed cases in Wuhan, found the mean incubation period of this virus as 5.2 days. The disease mostly affected older males with comorbidities, the median age was 59 years (range, 15 to 89) and 56% were male. In its early stages, the epidemic doubled in size every 7.4 days. The most recent study conducting data analysis by Wei-Jie et al. [27] with 1099 laboratory-confirmed COVID-19 patients from 552 hospitals in 30 provinces of China reported the median incubation period as 4 days, the median age of patients as 47 years, and a total of 41.9% as female. 23.7% had at least one coexisting illness (e.g., hypertension and chronic obstructive pulmonary disease) among the overall populations. Another retrospective, single-centre study conducted by Chen et al. [8], that included 99 confirmed cases of 2019-nCoV in one of the Wuhan Hospital from 01 Jan to 20 Jan 2020, revealed 50 (51%) patients having chronic diseases including cardiovascular and cerebrovascular diseases, endocrine system disease, digestive system disease, respiratory system disease, malignant tumour, and nervous system disease. The median duration of hospitalization was found 12.0 days [27].

Till now, it appears that compared with SARS and MERS, 2019-nCoV seems to have greater infectivity and a lower case fatality rate [28]. As on Mar 11, 2020, WHO reports that a total confirmed cases of 118,319 had SARS-CoV-2 worldwide, and of the confirmed cases 4292 (3.6%) patients died [5]. In comparison, the 2002-2003 outbreak of SARS had a case fatality rate of around 10%, while MERS killed 34.4% of people with the illness between 2012 and 2019 [13,29]. However, despite the lower case fatality rate, COVID-19 has so far resulted in much more deaths (4292) than SARS and MERS combined (1632).

4. PATHOPHYSIOLOGY

The pathophysiology of unusually high pathogenicity for 2019-nCoV has not been completely understood. The main target of COVID-19 infection is the lower respiratory tract causing severe pneumonia, combined with radiologic evidences of ground-glass opacities [22,30]. Significantly high blood levels of pro-inflammatory cytokines and chemokines were noted in patients with COVID-19 infection [8,22, 30]. Chen et al. [8] have postulated that virus particles spread through the respiratory mucosa and infect other cells, induce a cytokine storm in the body, generate a series of immune responses, and cause changes in peripheral white blood cells such as lymphocytes that have role in body immune response. They found that some patients progressed rapidly with acute respiratory distress syndrome (ARDS) and septic shock, which was eventually followed by multiple organ failure. The most common laboratory abnormality observed was decreased count of total lymphocytes. A substantial decrease in the total number of lymphocytes indicates that coronavirus consumes many immune cells and inhibits the body's cellular immune function. The study also observed prolonged prothrombin time, and elevated lactate dehydrogenase. Based on these abnormalities they suggested that 2019-nCoV infection may be associated with cellular immune deficiency, coagulation activation, myocardial injury, hepatic injury, and kidney injury. Other studies have also observed similar decrease in total lymphocyte count in most patients with COVID-19 [22,31].

5. CLINICAL MANIFESTATIONS

The complete clinical picture with regard to 2019-nCoV is not fully available. Reported studies have described the illnesses that have ranged from mild to severe disease, including death [8, 22,31]. Common symptoms at onset of illness were fever, dry cough, dyspnoea, fatigue, myalgia, and anorexia. Less common symptoms were headache, sore throat, rhinorrhoea, dizziness, abdominal pain, diarrhea, nausea, vomiting and confusion. Chen et al. [8] described clinical manifestations of fever in 83% of patients, cough in 82%, shortness of breath in 31%, muscle ache in 11%, confusion in 9% patients, headache in 8%, sore throat in 5%, rhinorrhoea 4%, chest pain in 2%, diarrhea in 2%, and nausea with vomiting in 1% of patients. Wang et al. [31] in their retrospective case series involving hospitalized 138 patients with confirmed NCIP at one Hospital in Wuhan, China also noticed a total of 14 patients (10.1%) initially presented with diarrhea and nausea 1 to 2 days prior to development of fever and dyspnoea. Huang et al [22] in their clinical study of 41 admitted hospital patients at Wuhan, identified as having laboratory-confirmed 2019-nCoV infection by Jan

2, 2020, found clinical manifestation of sputum production (28%), headache (8%), haemoptysis (5%), and diarrhea (3%). Few patients with 2019-nCoV infection were found to have prominent upper respiratory tract symptoms (e.g., rhinorrhoea, sneezing, or sore throat), indicating that the target cells might be located in the lower airway [22]. Most cases admitted to the hospital had pneumonia with infiltrates on chest x-ray and ground glass opacities on chest computed tomography [22,32]. Some patients rapidly developed to ARDS, acute respiratory failure, and other serious complications with fatal outcomes [22]. Wei-Jie et al. [27] in their study, found fever in 88.7% during hospitalization; cough in 67.8%; nausea or vomiting in 5.0% and diarrhea in 3.8%.

WHO [33] has recently classified 6 clinical syndromes associated with SARS-CoV-19 infection: uncomplicated illness, mild pneumonia, severe pneumonia, ARDS, sepsis and septic shock. In uncomplicated illness, the affected persons may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache, muscle pain or malaise. Patient with mild pneumonia have no signs of severe pneumonia. In severe pneumonia patients have fever or suspected respiratory infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or oxygen saturation <90% on room air. ARDS patients have worsening respiratory symptoms with chest imaging evidence of bilateral opacities. In sepsis, adults have life-threatening organ dysfunction. Adult patients with septic shock have persistent hypotension despite volume resuscitation, requires vasopressors to maintain mean arterial pressure ≥65 mmHg and serum lactate level >2 mmol/L.

6. COMPLICATIONS AND FATALITY

Complications such as severe pneumonia, hypoxemia, respiratory failure, ARDS, pulmonary oedema, secondary infection, sepsis, septic shock, cardiac injury, and multiple organ failure including fatal outcomes, have been reported in various studies at China [8,19,22]. Common complications among 138 patients in the study conducted by Wang et al. [31] included shock (8.7%), ARDS (19.6%), arrhythmia (16.7%), and acute cardiac injury (7.2%). The median time from first symptom to dyspnoea was 5.0 days, to hospital admission was 7.0 days, and to ARDS was 8.0 days. Cardiac injury was diagnosed if serum levels of cardiac biomarkers (e.g., troponin I) were above the 99th percentile upper reference limit, or new abnormalities were shown in electrocardiography and echocardiography. Huang et al. [22] described a fatality of 6 patients (15%) out of total 41confirmed hospitalized cases of SARS-CoV-2 pneumonia. Chen et al. [8] in their retrospective study described a fatality of 11%. 17% of the admitted patients developed ARDS and, among them, 11% patients worsened in a short period of time and died of multiple organ failure. In a study conducted by Liu et al. [34], data analysis of 137 patients admitted to hospitals in Hubei province revealed death of 16 (12%) SARS-CoV-2 infected individuals. Of those who died, many had pre-existing conditions, including hypertension, diabetes, or cardiovascular disease.

7. INVESTIGATIONS

Initially the diagnosis of pneumonia of unknown cause in Wuhan was based on clinical characteristics, chest imaging, and the ruling out of common bacterial, fungal and viral pathogens that cause pneumonia [22]. Respiratory specimens, including nasal and pharyngeal swabs, bronchoalveolar lavage, sputum, or bronchial aspirates were tested for common viruses, including influenza, parainfluenza virus, rhinovirus, respiratory syncytial virus, adenovirus, SARS-CoV and MERS-CoV using real-time reverse transcription polymerase chain reaction (RT-PCR) assays approved by the China Food and Drug Administration. Routine bacterial and fungal examinations were also performed. Then, during the 1st week of Jan 2020, a novel coronavirus, which was named 2019-nCoV, was isolated from lower respiratory tract specimen and a diagnostic test for this virus was developed soon after that. Chinese labs have successfully isolated and grown 2019-nCoV in cell culture. Chinese researchers also published the genetic sequence so that laboratories across the world could independently develop PCR tests to detect infection by the virus [35-38].

In the various studies carried out shortly during the outbreak, the presence of 2019-nCoV RNA in respiratory specimens (nasal swab, throat swab, bronchial aspirates) was confirmed by real-time RT-PCR assay [8,22,31]. Imaging (chest x-ray/ CT scan) showed bilateral patchy shadows or ground glass opacity in the lungs of all the admitted patients having pneumonia. Chen et al. [8] in their study found 75% of patients with bilateral pneumonia, 25% of patients with unilateral pneumonia, 14% of patients with multiple mottling and ground-glass opacity, and one (1%) patient had pneumothorax according to

imaging (chest x-ray and CT) examination. Of the 41 patients, 40 (98%) had bilateral involvement in the study of Huang et al. [22]. Wei-Jie et al. [27] in their data analysis, revealed abnormal results in 86.2% of chest CT scans. The most common patterns on chest CT were ground-glass opacity (56.4%) and bilateral patchy shadowing (51.8%).

Complete blood counts revealed lymphocytopenia in most of the hospitalized cases. Lymphocytopenia occurred in 70.3%, of hospitalized 138 patients in a study carried out by Wang et al. [29] and non-survivors developed more severe lymphocytopenia over time. On admission, Wei-Jie et al. [27] found, lymphocytopenia in 83.2% of the patients, thrombocytopenia in 36.2%, and leukopenia in 33.7%. Lymphocytopenia was defined as a lymphocyte count of less than 1500 cells per cubic millimetre. Most of the patients had elevated levels of C-reactive protein; less common were elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, and d-dimer. Patients with severe disease had more prominent laboratory abnormalities (including lymphocytopenia and leukopenia) than those with non-severe disease. In the study of Cheng et al. [8], out of 99 patients, 43 had various degrees of liver function abnormality, with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the normal range. Prothrombin time was seen to be prolonged, and lactate dehydrogenase elevated. Similarly, as the disease progressed and clinical status deteriorated, the levels of blood urea and creatinine progressively increased before death [31]. Viral RNA has been detected in blood in severely ill patients in China by real-time RT-PCR [22].

In the first US patient identified as described by Holshue et al. [32], 2019-nCoV RNA was also detected in a stool specimen collected on day 7 of the patient's illness. In the study of Huang et al. [22] hypersensitive troponin I (hs-cTnI) was increased substantially in five out of 41 patients, in whom the diagnosis of virus-related cardiac injury was made. WHO [33] in their interim guidance have advocated blood cultures for bacteria that cause pneumonia and sepsis, ideally before antimicrobial therapy. Specimens from both the upper respiratory tract (throat and nasal swabs) and lower respiratory tract (expectorated sputum) and in mechanically ventilated patients (endotracheal aspirate, or bronchoalveolar lavage) should be tested for 2019-nCoV testing by RT-PCR. In a patient with suspected novel coronavirus, especially with pneumonia or severe illness, a single upper respiratory tract sample does not exclude the diagnosis, and additional samples are recommended. In hospitalized patients with confirmed 2019-nCoV infection, repeat upper and lower respiratory tract samples should be collected to demonstrate viral clearance.

8. TREATMENT

Until now, no specific treatment has been recommended for this emerging coronavirus infection except for meticulous supportive care [39]. Antiviral treatment for 2019-nCoV infection has not been proven to be effective. All patients need to be treated in isolation. Currently, as described, the approach to this disease is to control the source of infection; use of personal protection precaution to reduce the risk of transmission; and early diagnosis, isolation, and supportive treatments for affected patients [31].

In the various studies, empirical antibiotics (including azithromycin, cephalosporins, quinolones, vancomycin, carbapenems, tigecycline) and investigational antivirals (including oseltamivir, remdesivir, lopinavir, ritonavir) were used in most cases for treatment of patients with 2019-nCoV infection, however, no effective outcomes were observed [8,21,22, 27,31,32]. Due to development of pneumonia, antibiotics were used to cover common pathogens and often methicillin resistant staphylococcus; when secondary bacterial infection occurred, medication was administered according to the results of bacterial culture and drug sensitivity. For symptom management, the patient received, antipyretic therapy as needed. Fluid therapy was need in most of the cases. Vasopressor therapy was also used for persistent hypotension as mentioned in studies. In the study of Wang et al. [31], 13 patients out of a total 138 admitted patients, received vasopressors. Oxygen support (e.g., nasal cannula, non-invasive mechanical ventilation and invasive mechanical ventilation) was administered to patients according to the severity of hypoxaemia [8,27,31]. In view of the high amount of cytokines induced by 2019-nCoV infections, corticosteroids (e.g. methylprednisolone, dexamethasone) were used frequently for treatment of patients with severe illness for possible benefit by reducing inflammation-induced lung injury [8,22,31]. However, current evidence in patients with

SARS and MERS suggests that receiving corticosteroids did not have an effect on mortality, but rather delayed viral clearance [40-42]. Therefore, corticosteroids should not be routinely given systemically, according to WHO interim guidance [33]. Some authors have advocated prompt administration of antibiotics to prevent infection and strengthening of immune support that may reduce complications and mortality in populations with low immune function, such as older people, diabetics, people with HIV infection, people with long-term use of immunosuppressive agents, and pregnant women, when they are infected with 2019-nCoV [8].

WHO [33] recommends when intravenous fluids are used, it should be used cautiously because aggressive fluid resuscitation may lead to volume overload including respiratory failure. Empiric antimicrobials should be given to treat all likely pathogens causing severe infection based on the clinical diagnosis (community-acquired pneumonia or sepsis), local epidemiology and susceptibility data, and treatment guidelines; therapy should be de-escalated on the basis of microbiology results and clinical judgment. WHO does not advocate routine use of systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason. In the management of septic shock, WHO advocates vasopressor (i.e. norepinephrine, epinephrine, vasopressin, and dopamine) administration when shock persists during or after fluid resuscitation.

At present, there is no vaccine or effective antiviral treatment for coronavirus. Trials with a considerable number of investigational agents like lopinavir, ritonavir, remdesivir, nelfinavir, interferon beta, chloroquine, Chinese traditional medicine are being carried out since Jan 2020; some of them were suggested that they may be effective for treating the 2019-nCoV; even that, the efficacy and long term safety of those drugs still need to be further confirmed by clinical experiments [33,43-45].

According to WHO the best prevention measure is cleaning of hands with soap and water or using alcohol based hand wash very frequently [46]. As a precautionary measure frequent touching the face, mouth, eyes and nose should be avoided.

9. CONCLUSION

With the emergence of the 2019 novel coronavirus (SARS-CoV-2), the knowledge of its epidemiology, infectivity rate, clinical manifestations, treatment and mortality rates is also in the development process and the full spectrum of the disease will be understood soon. The disease is more likely to occur in older people with comorbidities, and can result in severe and even fatal respiratory diseases. Till now there is no effective specific therapy, but supportive managements are given. Researches and trials are going on with investigational agents for the effective management of the disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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