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Clinical courses and risk factors of mortality among COVID-19 patients

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Abstract
Corona virus disease 2019 (COVID 19) is one of the most devastating zoonotic coronaviruses that is caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2). After the establishment of the infection in the host, the disease principally manifested by flu like symptoms of upper respiratory tracts within few days in the first week of infection. Later on, the disease gradually involves other organ systems deteriorating the prognosis of the disease. Older age and patients with obesities and comorbidities such as hypertension, diabetes, cardiovascular disease, pulmonary disease, coronary heart disease, chronic lung disease and the like are at high risk of death unless early identification of the pathogen implemented so that appropriate supportive therapy will be provided. The primary preventive measures of the disease mainly focus on eliminating exposure to droplets. However, for successful control and prevention, cross-disciplinary collaborations and interdisciplinary interventions involving veterinary, medical, Ecological and public health professionals are unquestionably significant.

Keywords: clinical course, COVID 19, mortality, risk factors, SARS CoV-2

Introduction

Coronaviruses are important human and animal pathogens. They are enveloped single-stranded RNA viruses that are zoonotic in nature and cause symptoms ranging from those similar to the common cold to more severe respiratory, enteric, hepatic, and neurological symptoms [1, 2]. Other than SARS-CoV-2, there are six known coronaviruses in humans: HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1, and MERS-CoV [3]. Coronavirus has caused two large-scale pandemics in the last two decades: SARS [4] and MERS [5]. The family Coronaviridae encompasses a broad spectrum of animal and human viruses, all characterized by a distinctive morphology. Prior to 2003 members of this family were believed to cause only mild respiratory illness in humans, other coronaviruses then known being largely of importance only to the livestock industry. But the emergence of severe acute respiratory virus (SARS-CoV) that year stimulated major research into these viruses, to the effect that many new coronaviruses have since been discovered, some with zoonotic potential of causing serious outbreaks of disease in humans. For instance SARS-CoV, MERS-CoV [6] and COVID-19 are the zoonotic coronaviruses causing serious pandemic health and economic impacts [2, 7]. On 31 December 2019, the Wuhan Municipal Health Commission in Wuhan City, Hubei province, China, reported a cluster of 27 pneumonia cases (including seven severe cases) of unknown etiology, with a common reported link to Wuhan's Huanan Seafood Wholesale Market, a wholesale fish and live animal market [8].The market was closed down on 1 January 2020. It is rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019 [9]. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-novel corona virus (2019-nCoV). By 20 January 2020, there were reports of confirmed cases from three countries outside China: Thailand, Japan and South Korea. These cases had all been exported from China [2, 10].
Few weeks later, the World Health Organization (WHO) declared this first outbreak of novel coronavirus a 'public health emergency of international concern', several countries implemented entry screening measures for arriving passengers from China. Soon, several major airlines suspended their flights from and to China. Over the following days, cases were reported from several other regions. WHO declared COVID-19 a global pandemic on 11 March 2020 [10, 11]. Between December 2019 to July 21, 2021, COVID-19 pandemic affected all continents causing 192,395,192 cases and 4,136,698 deaths (CFR=2.15%) globally. As of July 21, 2021, the USA reported the highest number of cases 35,081,719 and deaths 625,363 with CFR of 1.78% followed by India 31,216,337 cases and 418,511 deaths with a CFR of 1.34% [12]. WHO, [13] described three main transmission routes for the COVID-19: 1) droplets transmission, 2) contact transmission, and 3) aerosol transmission. Droplets transmission was reported to occur when respiratory droplets (as produced when an infected person coughs, sneezes or talks) are ingested or inhaled by individuals nearby in close proximity; these droplets can settle in the mouth or nasal mucosa and lungs of people with inhaled air. Contact transmission may occur when a subject touches a surface or object contaminated with the virus and subsequently touch their mouth, nose, or eyes; and aerosol transmission may occur when respiratory droplets mix into the air, forming aerosols and may cause infection when inhaled high dose of aerosols into the lungs in a relatively closed environment [14]. The extent to which transmission of SARS-CoV-2 from asymptomatic individuals (or individuals within the incubation period) occurs remains unknown [15]. Live virus has been cultured from stool in some cases [16], but according to a joint WHO-China report, fecal-oral transmission did not appear to be a significant factor in the spread of infection [1]. Based on the 2003

SARS-CoV epidemic experience, the Chinese government takes many effective measures including closing public transport, reducing migration and promoting personal protection with masks in Wuhan and other provinces [3]. The best way to prevent illness is to avoid being exposed to the virus. As the primary mode of transmission is droplet transmission, the preventive measures mainly focus on eliminating exposure to the droplets [2]. To avoid droplets transmission and spread of infection the main measures that should be adopted are the following: washing hands often with soap and water for at least 20 seconds especially after travelling to public place; avoid touching mouth, nose and eyes; stay at home when get sick; using hand sanitizers that contains at least 60% alcohol; avoiding close contact with people who are sick; keeping social distance for minimum of 1 meter; wearing face mask and cleaning and disinfecting frequently touched surfaces [17]. Major prevention and control measures including travel screenings should be implemented to control further spread of the virus [18]. The disease becomes the most devastating problem causing several millions of mortality and morbidity resulting in global economic crisis. Therefore, the objective of this review paper is to discuss the clinical courses and risk factors of mortality in COVID 19 patients.

Literature Review

Clinical signs and Clinical courses of COVID 19

The infection with COVID 19 causes manifestation of major respiratory clinical signs within the first week of occurrence of the onset of clinical signs and slow progression in to involvement of other organ systems. There will be significant relationship between the time of development of clinical signs and other organs (other than respiratory tract) affected directly by infection or by other comorbidities and the outcome of the disease (recovery or death). Before SARS-CoV cases, it was thought that human CoVs leads to cold-like upper respiratory infection and self-limiting lower respiratory infection. While most people with COVID-19 develop only mild (40%) or moderate (40%) disease, approximately 15% develop severe disease that requires hospitalization and oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi organ failure, including acute kidney and cardiac injury. As in other respiratory infected viruses and previous beta-CoVs, similarities present in the clinical aspects of COVID-19 infections, it is known that clinical picture varies from simple respiratory infection findings to septic shock. Similar to SARS CoV and MERS CoV that caused epidemics in the past years, the first symptoms are commonly defined as fever (83-99%), cough (59-82%), fatigue (44–70%), anorexia (40-84%), shortness of breath (31–40%) and myalgia (11–35%) [19, 20]. Other non-specific symptoms such as sore throat, chest pain, confusion, nausea, nasal congestion, headache, diarrhea, vomiting, loss of smell (anosmia) and/or loss of taste (ageusia) were noted [3, 13]. However, there are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. Therefore, the possibility of COVID-19 should be considered primarily in patients with new onset of fever and/or respiratory tract symptoms (e.g., cough and dyspnea). It should also be considered in patients with severe lower respiratory tract illness without any clear cause [21]. The first, or "mild," phase, commonly of benign evolution, occurs in the first 7 days with symptoms characteristic of upper respiratory tract infection. Nonspecific symptoms such as anosmia, ageusia, and gastrointestinal manifestations may also appear. Approximately 80% of the cases are resolved. The second phase, or moderate pneumonia, occurs approximately in 40% of the patients and from the tenth day the symptoms begin to worsen with dyspnea, cough, and oxygen saturation decrease, with signs and symptoms suggesting progression for lower respiratory tract infection without signs of severe pneumonia detected in moderate infection. Severe cases of COVID 19 infection is known by severe pneumonia characterized by fever, cough, dyspnea and fast breathing [22]. However, associated clinical manifestations like acute respiratory distress syndrome (ARDS), within one week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms; sepsis, which is acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection and septic shock, characterized by persistent hypotension despite volume resuscitation, requiring vasopressors to maintain mean arterial pressure (MAP) $\geq$ 65 mmHg and serum lactate level > 2 mmol/L were reported in critical disease condition of COVID 19. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia [20]. The study conducted by GAO Et Al., [23] on the Non-COVID 19 with pneumonia and COVID 19 patients showed that the two group presented similar onsets of symptoms after mean one week period. In many cases, neurological manifestations have been reported even without respiratory symptoms. Anxiety and depression appear to be common amongst people hospitalized for COVID-19, with one hospitalized cohort from Wuhan, China, revealing over 34% of people experiencing symptoms of anxiety and 28% experiencing symptoms of depression [24]. An observational case series from France found that 65% of people with COVID-19 in intensive care units (ICUs) showed signs of confusion (or delirium) and 69% experienced agitation [25]. Delirium, in particular, has been associated with increased mortality risk in the context of COVID-19 [3, 20, 25]. WHO has reported an incubation period for COVID-19 on average, 5–6 days, but can be up to 14 days. However, some literature suggests that the incubation period can last longer than two weeks and it is possible that a very long incubation period could reflect double exposure. Many studies support a 14-day medical observation period for people exposed to the pathogen [11].

While it is not surprising to see lower prevalence of fever in newborns because of the weaker fever response to infection, neonates had more severe clinical courses, as demonstrated by a number of measures. In addition to higher prevalence of death and lower proportion of discharge, neonates saw much shorter time from symptom onset to death (median of 2.5 days) and longer time from symptom onset to discharge (median 23.5 days). The time span from symptom onset to death was considered very short, even compared with elderly patients. For instance, a study on 85 fatal COVID-19 cases with a median age of 66 years revealed a median time of 6.4 days. Moreover, higher prevalence of dyspnea and sore throat was observed in neonates. More importantly, it

has been suggested that dyspnea was a risk factor for predicting mortality in patients with COVID-19 [26]. Coupled with the higher prevalence of sore throat, it appeared that neonates were susceptible to both upper and lower respiratory tract infection, as opposed to the case of children, mostly with upper airway infection [27]. On one hand, although trained immunity already takes place during the neonatal period, the innate immune system in newborns is still weak and immunization relies heavily on maternal antibodies that wane up to a year 20 upon metabolism [28]. Maternal antibodies are unlikely to provide protection to newborns given the novel coronavirus and the innate immunity in neonates is still not "well-trained," compared with infants. On the other hand, adults have dysfunctional overactive innate immune response in severe infection, which is not seen in children [27, 29]. Most COVID-19 patients had bilateral pneumonia with the feature of a multiple mottling and ground-glass opacity in CT images. In addition, somewhat like severe influenza (e.g. H7N9, H1N1), inflammation spread quickly in lungs of COVID-19 patients. CT scan may be a reliable test for screening Non-COVID-19 or COVID-19 patients, will compact quick classification of suspected cases or common patients [23]. On X-rays or thorax CT imaging of the examined patients, unilateral or bilateral was found, and bilateral multiple lobular and sub-segmental consolidation areas were observed in patients hospitalized in the intensive care unit [30]. The patients with underlying comorbidities such as diabetes mellitus, hypertension, and cardiovascular disease exhibited a more severe clinical course, as expected by the experience gained from the previous epidemics. The period from the onset of COVID-19 symptoms to death ranges from 6 to 41 days with a median of 14 days. This period is dependent on the age of the patient and status of the patient's immune system [16].

Risk factors of mortality in COVID 19 patients

Retrospective cohort study conducted in Wuhan identified several risk factors for death in adults in Wuhan who were hospitalised with COVID-19. In particular, older age, male patients, obesity, patients with underlying comorbidities such as hypertension, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, chronic kidney disease, HIV/AIDS, coronary heart disease, chronic lung disease, lymphopenia, leucopenia and Chronic liver disease were found among the major predisposing factors to COVID-19 severity and mortality [13]. Furthermore, d-dimer levels greater than 1μg/mL, and higher SOFA (sequential organ failure assessment) score on admission were associated with higher odds of in-hospital death [31]. Additionally, elevated levels of blood IL-6, high-sensitivity cardiac troponin I, and lactate dehydrogenase and lymphopenia were more commonly seen in severe COVID-19 illness [31, 32]. Age appears to be a significant risk factor for mortality of COVID-19. Eighty percent (80%) of deaths associated with COVID-19 were found to be among adults aged 65 and above years. Thus, advanced age was found to be a risk factor for mortality of COVID-19 [31]. A higher peak viral load was found among older age COVID-19 patients that were found to be associated with death in SARS-CoV 2 infected patients. Advanced age patients have a probably weaker immune response; therefore, they are more susceptible to the development of acute respiratory distress syndrome (ARDS) that leads to mortality. The age-dependent defects in T-cell (cell-mediated) and B-cell (humoral) immune function and the excess production of type 2 cytokines could lead to a deficiency in control of viral replication and more prolonged pro-inflammatory responses, potentially leading to poor outcome. The increased production of type 2 cytokines could weaken the control of viral replication and cause more prolonged proinflammatory responses and eventually, a poor outcome [33]. The strong effect of age might be because it not only links to comorbidities but also excess cytokine production may cause a worse result. Furthermore, advancing age is known to be predictor of decreased immune system, leading to increased viral persistence, or to an uncontrolled immune response that may cause severe clinical features in COVID 19 [34]. When patients are combined with comorbidities such as diabetes and hypertension, the body is in a state of stress for a long time and the immunity tends to be low. Moreover, the long term history of diabetes and hypertension will damage the vascular structure, and it is more likely to develop into critical disease in COVID 19 infection. Patients with chronic heart disease are more likely to be infected due to their weakened heart function and low immunity. When infected with SARS-CoV-2 they are more likely to have acute cardiovascular events and develop into severe diseases. When the patient has previous respiratory diseases such as chronic obstructive pulmonary disease, the patient's lung function is damaged. They have lower resistance to the virus and are prone to developing ARDS [35]. The previous data also seems to suggest that patients with cardiovascular disease are more likely to die in coronavirus infection [32]. On the other hand, studies have found that women are less susceptible to viral infection than men, possibly because of the protection of X and sex hormones, which play an important role in innate and adaptive immunity. At the same time, men tend to be associated with bad lifestyle habits such as smoking, drinking alcohol and underlying diseases. As a result, the majority of critical or mortal patients were recorded in male. Therefore, when the patient is male, over 65 years old and smoking, the patient has a higher risk of developing critical illness or death [35]. A retrospective cohort study conducted by Averedo *et al*., [22] indicated that among hypertensive patients, 21.3% had more severe SARS-CoV-2 infection and higher death rate when compared with the non-hypertension group, indicating that hypertension is a critical risk factor associated with poorer clinical outcomes. Additionally, hypertensive with COVID-19 patients presented higher concentrations of high-sensitivity CRP, procalcitonin, and IL-6 when compared to controls, indicating that hypertension enhances inflammation in SARS-CoV-2 infection. Hypertension seems to enhance the inflammatory profile in patients with SARS-CoV-2 infection, inferring that resistant hypertension possibly increases even more the risk for a more severe illness, as it was already demonstrated that these patients present higher levels of inflammatory biomarkers such as TNF-α and IL-6 [22]. Guo *et al*., [36] reported that the increase of serum troponin in patients with or without previous cardiovascular diseases (CVD) has been directly related with an increase of plasmatic NT-pro-BNP levels, increasing mortality, being characterized as a marker of poor prognosis. Nonetheless, the increase of troponin in individuals with previous cardiovascular disease characterized more severe clinical outcomes and higher mortality when compared to patients without previous heart

disease and increased troponin values. Hence, the presence of heart disease is an important risk factor regarding the prognosis of COVID-19 patients evolving with acute myocardial injury [22]. Heart failure is an important cause of death in patients with COVID-19 and occurs as a result of different myocardial aggression mechanisms such as direct myocardial injury by viral action, indirect and direct inflammatory damage, O2 supply–demand imbalance, and increase of atherothrombotic events due to inflammatory destabilization of atheromatous plaques resulting in acute myocardial dysfunction [36, 37]. Direct myocardial damage occurs as a result of SARSCoV-2 interaction with myocardial tissue by binding the viral glycoprotein Spike 1, after its activation by the serine 2 transmembrane protease expressed by the host to ACE2 receptors, expressed especially in cardiac pericytes, leading to direct tissue damage and, in a further moment, a downregulation of these receptors [22, 36]. Myocardial injury is a factor of worse prognosis and is directly associated with a higher mortality in COVID-19. Thus, it is imperative the implementation of a thorough screening through dosage of troponin, ECG, and bedside echocardiography, mainly in patients presenting signs of greater severity and critical infection, due to the association with exacerbated systemic inflammation [22, 26, 36, 37]. Acute respiratory distress syndrome (ARDS) is found at the early stages of COVID-19 infected patients and cytokine can lead to acute respiratory distress syndrome, which is one of the main reasons for fatality among COVID 19 patients [32]. According to the report of Pan *et al*., [38], in the course, patients in death event group showed a significantly higher ratio of ARDS than discharge group (100.0% vs. 5.7%). It indicated the survival rate was very low if the patients aggravated to this critical status and further exploration of the treatment to prevent ARDS is imperative. Although no significant difference in the period between initial symptom onset and admission was found between two groups, attention still should be paid to early diagnosis and treatment because the mean period of 11 days from symptom onset to admission is probably too late when the severe progression had occurred [38]. Tobacco smoking is a known risk factor for many respiratory infections and increases the severity of respiratory diseases. A review of studies by public health experts convened by WHO on 29 April 2020 found that smokers are more likely to develop severe disease with COVID-19, compared to non-smokers. Smoking impairs lung function making it harder for the body to fight off coronaviruses and other diseases. Tobacco is also a major risk factor for non-communicable diseases like cardiovascular disease, cancer, respiratory disease and diabetes which put people with these conditions at higher risk for developing severe illness when affected by COVID-19. Available research suggests that smokers are at higher risk of developing severe disease and death [39].

Conclusion

COVID-19 is the most important zoonotic coronaviruses causing serious pandemic impacts. After its isolation in China, it was rapidly spread resulting in a pandemic throughout the world. The disease is manifested primarily by respiratory signs within the first week and slow progression in to involvement of other organ systems. Hence, there is significant association between the time of the occurrence of clinical signs and involvement of different organ systems other than respiratory tract and the outcome of the disease (either recovery or death). The age, comorbidities and behavioral practices such as use of alcoholic beverages and smoking have direct impact on the outcome of the disease. The more the severity of comorbidities and addictive behaviors, there will be higher mortality cases due to the disease. Therefore, early diagnosis and supportive therapy will significantly reduce the unnecessary consequence of the disease, hence should be practiced. Furthermore, public health intervention should be made to aware the societies about the direct and indirect effects of addiction as well as on time treatment of comorbidities such as cardiovascular and respiratory problems in order to reduce mortality rate due to the disease.

Conflict of interest

The author declares that there is no conflict of interest.

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