Review Article

Coronavirus disease 2019 (COVID-19): A Review of Literature

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Abstract

Since the beginning of 21st century, coronaviruses (CoVs) have been associated with significant disease outbreaks in East Asia and the Middle East that too with significant mortality. Firstly, severe acute respiratory syndrome (SARS) followed by Middle East respiratory syndrome (MERS) began to emerge in 2002 and 2012, respectively. Recently, a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), emerged in later part of 2019. It has posed a global health threat, causing an ongoing pandemic in many countries and territories including India. The symptoms are usually fever, cough, sore throat, breathlessness, fatigue, malaise among others. The disease is mild in most people; in some (usually the elderly and those with comorbidities), it may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction. Many people are asymptomatic. The case fatality rate is estimated to range from 2 to 3%. Diagnosis is by demonstration of the virus in respiratory secretions by special molecular tests. Treatment is essentially supportive; role of antiviral agents is yet to be established. Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. The virus spreads faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but has lower fatality. The global impact of this new epidemic is yet uncertain. In this literature review, the causative agent, pathogenesis and immune responses, epidemiology, diagnosis, treatment and management of the disease, control and preventions strategies are all reviewed.

Keywords: Corona Virus Disease 2019, COVID 19 Review, Pandemic, SARS-CoV-2.

Introduction

The world has witnessed a number of epidemics and pandemics that have affected millions of lives on this earth in various time frames. Despite our advances in healthcare sector, we faced new pathogens that pose a threat to human lives with global economic impact. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus that was first identified in Wuhan, Hubei province, central China, and is responsible for the 2019-20 pandemic. On December 31, 2019, the China Health Authority alerted the World Health Organization (WHO) about several pneumonia cases of some unknown etiology in Wuhan City.

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The cases had been reported in many patients worked at or lived around the local Huanan Seafood Wholesale Market since December 8, 2019[1].On January 7, a novel coronavirus, originally abbreviated as 2019-nCoV by WHO, was identified from the throat swab sample of a patient with unkown etiology[2]. Coronavirus Study Group later renamed this virus as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3].The disease was named as coronavirus disease 2019 (COVID-19) by the WHO after this. UptoJanuary 30th, 7736 confirmed and 12,167 suspected cases had been reported in China with 82 confirmed cases had been detected in 18 other countries worldwide[4]. On the same day, WHO declared the SARS-CoV-2 outbreak as a Public Health Emergency of International Concern (PHEIC)[4]. According to the National Health Commission of China,the mortality rate among confirmed cased in China was reported to be 2.1% as of February 4 and

compared to the mortality rate of 0.2% among cases outside China[5,6]. Among patients admitted to hospitals,the mortality rate ranged between 11% and 15%[7,8] which was higher significantly. COVID-19 is moderately infectious with a relatively high mortality rate, but the information available in public reports and published literature is rapidly increasing. The aim of this review article is to discuss the current trends of COVID-19 including causative agent, disease pathogenesis, its diagnosis and management the cases, as well as control and prevention policies.

Discussion

THE VIRUS

SARS-CoV-2 is a member of the order Nidovirales, family Coronaviridae, subfamily Orthocoronavirinae, which is subdivided into four genera, viz., Alpha coronavirus, Beta coronavirus, Gamma coronavirus , and Delta coronavirus [9]. Corona viruses possess an unsegmented, single-stranded, positive-sense RNA genome of around 30 kb, enclosed by a 5=-cap and 3=-poly(A) tail[10]. The genome of SARS-CoV-2 is 29,891 bp long, with a GC content of 38%[11]. These viruses are encircled with an envelope containing viral nucleocapsid. The nucleocapsids in CoVs are arranged in helical symmetry, which reflects an atypical attribute in positive-sense RNA viruses[10].The electron micrographs of SARS-CoV-2 revealed a diverging spherical outline with some degree of pleomorphism, virion diameters varying from 60 to 140 nm, and distinct spikes of 9 to 12 nm, giving the virus the appearance of a solar corona[9].The CoV genome is arranged linearly as 5=-leader-UTR-replicase-structural genes (S-E-M-N)-3= UTR-poly(A)[12]. Accessory genes, such as 3a/b, 4a/b, and the hemagglutinin-esterase gene (HE), are also seen intermingled with the structural genes[10]. SARS-CoV-2 has also been found to be arranged similarly and encodes several accessory proteins, although it lacks the HE, which is characteristic of some beta coronaviruses[11]. The positive-sense genome of CoVs serves as the mRNA and is translated to polyprotein 1a/1ab (pp1a/1ab)[13]. A replication-transcription complex (RTC) is formed in double-membrane vesicles (DMVs) by nonstructural proteins (nsps), encoded by the polyprotein gene[13]. Subsequently, the RTC synthesizes a nested set of subgenomic RNAs (sgRNAs) via discontinuous transcription[12].

Transmission

The role of the Huanan Seafood Wholesale Market in propagating disease is unclear. Many initial COVID-19 cases were linked to this market suggesting that SARS-CoV-2 was transmitted from animals to humans[13]. However, a genomic study has provided evidence that the virus was introduced from another, yet unknown location, into the market where it spread more rapidly, although human-to-human transmission may have occurred earlier[14].Clusters of infected family members and medical workers have confirmed the presence of person-to-person transmission[15].After January 1, less than 10% of patients had market exposure and more than 70% patients had no exposure to the market[13]. Person-to-person transmission is thought to occur among close contacts mainly via respiratory droplets produced when an infected person coughs or sneezes. Fomites may be a large source of transmission, as SARS-CoV has been found to persist on surfaces up to 96 h[16] and other coronaviruses for up to 9 day[17].Whether or not there is asymptomatic transmission of disease is controversial. One initial study published on January 30 reported asymptomatic transmission,[18] but later it was found that the researchers had not directly interviewed the patient, who did in fact have symptoms prior to transmitting disease[19]. A more recent study published on February 21 also purported asymptomatic transmission, [20]but any such study could be limited by errors in self-reported symptoms or contact with other cases and fomites. Findings about disease characteristics are rapidly changing and subject to selection bias. A study indicated the mean incubation period was 5.2 days (95% confidence interval [95%CI]: 4.1–7.0) [13]. The incubation period has been found to be as long as 19 or 24 days[21,22] although case definitions typically rely on a 14 day window[23]. The basic reproductive number (R0) has been estimated with varying results and interpretations. R0 measures the average number of infections that could result from one infected individual in a fully susceptible population[24].Studies from previous outbreaks found R0 to be 2.7 for SARS[25] and 2.4 for 2009 pandemic H1N1 influenza [26]. One study estimated that that basic reproductive number (R0) was 2.2 (95% CI: 1.4–3.9) [13]. However, later in a further analysis of 12 available studies found that R0 was 3.28[27]. Because R0 represents an average value it is also important to consider the role of super spreaders, who may be hugely responsible for outbreaks within large clusters but who would notlargely influence the value of R0[28]. During the acute phase of an outbreak or prepandemic, R0 may be unstable [24]. In pregnancy, a study of nine pregnancy women who developed COVID-19 in late pregnancy suggested COVID-19 did not lead to substantially worse symptoms than in nonpregnant persons and there is no evidence for intrauterine infection caused by

vertical transmission[29].In hospital setting, a study involving 138 COVID-19 suggested that hospital-associated transmission of SARS-CoV-2 occurred in 41% of patients[30]. Moreover, another study on 425 patients found that the proportion of cases in health care workers gradually increased by time[13]. These cases likely reflect exposure to a higher concentration of virus from sustained contact in close quarters. Outside China, as of February 12, 2020, there were 441 confirmed COVID-19 cases reported in 24 countries[31] of which the first imported case was reported in Thailand on January 13, 2020[31].

Clinical Features

The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The common clinical features include fever (not in all), cough, sore throat, headache, fatigue, headache, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα[32]. The median time from onset of symptoms to dyspnea was 5 d, hospitalization 7 d and acute respiratory distress syndrome (ARDS) 8 d. The need for intensive care admission was in 25–30% of affected patients in published series. Complications witnessed included acute lung injury, ARDS, shock and acute kidney injury. Recovery started in the 2nd or 3rd wk. The median duration of hospital stay in those who recovered was 10 d. Adverse outcomes and death are more common in the elderly and those with underlying co-morbidities (50–75% of fatal cases). Fatality rate in hospitalized adult patients ranged from 4 to 11%. The overall case fatality rate is estimated to range between 2 and 3%[33].Interestingly, disease in patients outside Hubei province has been reported to be milder than those from Wuhan[33].Similarly, the severity and case fatality rate in patients outside China has been reported to be milder[32]. This may either be due to selection bias wherein the cases reporting from Wuhan included only the severe cases or due to predisposition of the Asian population to the virus due to higher expression of ACE2 receptors on the respiratory mucosa. Disease in neonates, infants and children has been also reported to be significantly milder than their adult counterparts. In a series of 34 children admitted to a hospital in Shenzhen, China between January 19th and February 7th, there were 14 males and 20 females. The median age was 8 y 11 mo and in 28 children the infection was linked to a family member and 26 children had history of travel/residence to Hubei province in China. All the patients were either asymptomatic (9%) or had mild disease. No severe or critical cases were seen. The most common symptoms were fever (50%) and cough (38%). All patients recovered with symptomatic therapy and there were no deaths. One case of severe pneumonia and multiorgan dysfunction in a child has also been reporte[34]. Similarly the neonatal cases that have been reported have been mild[35].

Diagnosis

SARS-CoV-2 RNA is detected via reverse-transcription polymerase chain reaction (RT-PCR) most commonly collected from nasopharyngeal (NP) swabs. In the United States, the CDC recommends the collection of NP swabs for asymptomatic individuals. Instead, specimens from symptomatic patients should be collected from bilateral anterior nares and midturbinate. An oropharyngeal (OP) swab could be collected if an NP swab is not possible. The CDC also recommends collecting sputum in patients with a productive cough, however sputum induction is not recommended. Also, when clinically indicted (i.e., patients who are mechanically intubated), a lower respiratory tract sample via a bronchioalveolar lavage (BAL) should be collected[36,37]. The accuracy of SARS-CoV-2 testing is yet to be established. It has been noted that RT-PCR testing for SARS-CoV-2 could be falsely negative either due to insufficient viral load if the specimen is collected too early or too late in the disease course, or due to technical errors like being handled or shipped improperly[36,37]. There have been cases reported of patients presenting with classic computed tomography (CT) chest findings (bilateral peripheral distribution with multifocal lower lung involvement) combined with high clinical suspicion for SARS-CoV-2 infection who test negative on RT-PCR[39]. Lower respiratory tract samples (i.e., BAL) are more likely to yield a positive result compared to upper respiratory tract samples. In a study involving 205 patients, 93% of BAL specimens (14 out of 15) were positive compared to 72% of NP swab specimens (72 out of 104)[40]. Consequently, if initial testing is negative but clinical suspicion remains high, the WHO recommends repeat testing, preferably from a lower respiratory tract specimen, if possible. Given that SARS-CoV-2 is a newly discovered virus, the antibody response in COVID-19 patients remains largely unknown. As of now, RT-PCR-based viral RNA is the current reference standard diagnostic tool for COVID-19 infections, but several studies are suggesting the incorporation of serologic antibody testing to aid in

diagnosis of COVID-19 infections. These can be particularly useful in suspected patients with negative RT-PCR-based viral RNA and those with asymptomatic infections. In addition, these tests may improve the sensitivity of COVID-19 pathogenic diagnosis when combined with RT–PCRbased viral RNA testing. In a study conducted by Zhao et al., among 173 patients with SARS-CoV-2 infection, the median seroconversion time for total antibodies, immunoglobulin-M (IgM), and immunoglobulinG (IgG) against SARS-CoV-2 were day-11, day-12 and day14, respectively. The presence of antibodies was < 4 × 109 per L) in 25% of patients, normal leukocyte counts (4–10 × 109 per L) in 45% of patients, and leukocytosis (>10 × 109 per L) in 30% of patients. Lymphopenia (< 1 × 109 per L) was found in 63% of patients[35]. Another study by Guan et al. showed that leukopenia was present in 33.7% of patients on admission and 36.2% of the cases had thrombocytopenia[41]. In a systematic review and meta-analysis of 43 studies involving 3,600 patients, the most common laboratory abnormalities included elevated C-reactive protein (68.6%), lymphopenia (57.4%), and elevated lactate dehydrogenase (LDH) (51.6%) [44]. A study done by Zhou et al. showed that elevated levels of LDH, serum ferritin, IL-6, and high sensitivity cardiac troponin I were all associated with worsening illness and higher mortality[45]. One of the most common laboratory findings in hospitalized patients with COVID-19 is an increased d-dimer level. In a large retrospective analysis study of 1,099 patients with confirmed COVID-19 in China, patients with more severe illness were more likely to have an elevated d- dimer level compared to patients with non-severe illness[40]. In another retrospective analysis study of 183 patients with confirmed COVID-19 pneumonia in Wahun, non-survivors were found to have significantly higher ddimer and fibrin degradation product (FDP) levels, and longer prothrombin time (PT) on admission compared to survivors. Fibrinogen and antithrombin (AT) levels were also significantly lower in non-survivors. Also, 71.4% of non-survivors had overt disseminated intravascular coagulation (DIC) during their hospitalization compared to only 0.6% of survivors. The results imply that abnormal coagulation parameters during COVID19 pneumonia were significantly associated with poor prognosis[46]. Studies also showed that blood urea nitrogen and creatinine levels progressively increased in critically ill Patients[47].

Radiological Findings

Chest CT abnormalities during the early stages of COVID-19 are usually peripheral and focal or multifocal ground-glass opacities affecting both lungs in ∼50–75% of patients. As the disease progresses, crazy paving and consolidation become the dominant CT findings, peaking around 9–13 days followed by slow clearing at ∼1 month and beyond. Up to 50% of patients with COVID-19 infection may have normal chest CT scans 0– 2 days after the onset of symptoms [48]. On the other hand, it has been shown that abnormal chest CT findings may develop in asymptomatic patients[49]. In one study, chest CT images from patients with SARS-CoV-2 who were admitted to the hospital showed some level of abnormality in all patients and bilateral lung involvement in around 98% of patients (40 out of 41) 40. Another study showed 86.2% of chest CT images on COVID-19 positive patients were abnormal and only 17.9% of patients had normal chest CT images, all of whom had mild disease [41]. During pandemics, physicians rely more on portable chest xray (CXR) since it is widely available and creates less exposure risk for staff compared to CT.

Treatments

Similar to MERS-CoV and SARS-CoV, there is still no specific antiviral treatment for COVID-1950,[51]. Isolation and supportive care including oxygen therapy, fluid management, and antibiotics treatment for secondary bacterial infections is recommended[52]. Some COVID-19 patients progressed rapidly to ARDS and septic shock, which was eventually followed by multiple organ failure[7,8]. Therefore,the effort on initial management of COVID-19 must be addressed to the early recognition of the suspect and contain the disease spread by immediate isolation and infection control measures[53]. Currently, no vaccination is available, but even if one was available, uptake might be suboptimal. A study of intention to vaccinate during the H1N1 pandemic in the United States was around 50% at the start of the pandemic in May 2009 but had decreased to 16% by January 2010[54]. Neither is a treatment available. Therefore, the management of the disease has been mostly supportive referring to the disease severity which has been introduced by WHO. If sepsis is identified, empiric antibiotic should be administered based on clinical diagnosis and local epidemiology and susceptibility information. Routine glucocorticoids administration are not recommended to use unless there are another indication[55]. Clinical evidence also does not support corticosteroid treatment[56]. Use of intravenous immunoglobulin might help for severely ill patients[8]. Drugs are being evaluated in line with past investigations into therapeutic treatments for SARS and MERS[57]. Overall,there is not robust evidence thatthese antivirals

can significantly improve clinical outcomes A. Antiviral drugs such as oseltamivir combined with empirical antibiotic treatment have also been used to treat COVID19 patients[7]. Remdesivir which was developed for Ebola virus, has been used to treat imported COVID-19 cases in US[58]. A brief report of treatment combination of Lopinavir/Ritonavir, Arbidol, and Shufeng Jiedu Capsule (SFJDC), a traditional Chinese medicine, showed a clinical benefit to three of four COVID-19 patients[59]. There is an ongoing clinical trial evaluating the safety and efficacy of lopinavir-ritonavir and interferon- 2b in patients with COVID19. [52]Ramsedivir, a broad spectrum antivirus has demonstrated in vitro and in vivo efficacy against SARS-CoV-2 and has also initiated its clinical trial [60,61]. In addition, other potential drugs from existing antiviral agent have also been proposed [62,63].

Prevention

Since at this time there are no approved treatments for this infection, prevention is crucial. Several properties of this virus make prevention difficult namely, non-specific features of the disease, the infectivity even before onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness and transmission even after clinical recovery. Isolation of confirmed or suspected cases with mild illness at home is recommended. The ventilation at home should be good with sunlight to allow for destruction of virus. Patients should be asked to wear a simple surgical mask and practice cough hygiene. Caregivers should be asked to wear a surgical mask when in the same room as patient and use hand hygiene every 15–20 min. The greatest risk in COVID-19 is transmission to healthcare workers. In the SARS outbreak of 2002, 21% of those affected were healthcare workers[64]. Till date, almost 1500 healthcare workers in China have been infected with 6 deaths. The doctor who first warned about the virus has died too. It is important to protect healthcare workers to ensure continuity of care and to prevent transmission of infection to other patients. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission, infection control measures recommended are those for category A agents (cholera, plague). Patients should be placed in separate rooms or cohorted together. Negative pressure rooms are not generally needed. The rooms and surfaces and equipment should undergo regular decontamination preferably with sodium hypochlorite. Healthcare workers should be provided with fit tested N95 respirators and protective suits and goggles. Airborne transmission precautions should be taken during aerosol generating procedures such as intubation, suction and tracheostomies. All contacts including healthcare workers should be monitored for development of symptoms of COVID-19. Patients can be discharged from isolation once they are afebrile for atleast 3 d and have two consecutive negative molecular tests at 1 d sampling interval. This recommendation is different from pandemic flu where patients were asked to resume work/school once afebrile for 24 h or by day 7 of illness. Negative molecular tests were not a prerequisite for discharge. At the community level, people should be asked to avoid crowded areas and postpone non-essential travel to places with ongoing transmission. They should be asked to practice cough hygiene by coughing in sleeve/ tissue rather than hands and practice hand hygiene frequently every 15–20 min. Patients with respiratory symptoms should be asked to use surgical masks. The use of mask by healthy people in public places has not shown to protect against respiratory viral infections and is currently not recommended by WHO. However, in China, the public has been asked to wear masks in public and especially in crowded places and large scale gatherings are prohibited (entertainment parks etc). China is also considering introducing legislation to prohibit selling and trading of wild animals[64]. The international response has been dramatic. Initially, there were massive travel restrictions to China and people returning from China/ evacuated from China are being evaluated for clinical symptoms, isolated and tested for COVID-19 for 2 wks even if asymptomatic. However, now with rapid world wide spread of the virus these travel restrictions have extended to other countries. Whether these efforts will lead to slowing of viral spread is not known. A candidate vaccine is under development.

Conclusion

Corona virus was spreading human to human to transmission by close contact via airborne droplets generating by coughing, sneezing, kissing and smooching. So avoid these activities with infected partners and family members. Corona virus may transmit through pet animals such as dog, cat, pig, cow, turkeys. So avoid contact and separate them if observed any infection activities like diarrhea, cold, fever. As per WHO and ECDC guideline avoid the contact with sick person and also avoid the market or public place as per possible. There are no anti corona virus vaccine to prevent or treatment but some supporting therapy work. Future research needed to fight with corona virus. Till only ‘Distance is rescue’.

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