Coronavirus Disease of the 2019 (Covid-19): Virology, Epidemiology, Pathogenesis, Clinical Presentation, Diagnosis and Treatment

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ABSTRACT
On December 31, 2019, China alerted WHO to several cases of unusual pneumonia in Wuhan. This is a city with about 11 million people located in the central Hubei province. The virus was unknown when it was reported. Few weeks after the outbreak, the coronavirus pneumonia became an epidemic at the epicenter of the disease. It was discovered those infected during the period were those working at the Wuhan's Huanan Seafood Wholesale Market. The market was shut down on January 1, 2020. Since the epidemic, the COVID-19 outbreak has reached every continent on Earth becoming a global pandemic. Wuhan City experienced the worst of the initial outbreak but the trend has now shifted to several other countries and major cities are experiencing the massive health, economic, social and political effects of the coronavirus. Americas (United States) and Europe (Russia, Italy, Spain, UK and Germany) are the most hit regions. As of June 2, 2020, the global confirmed cases were reported by the European Centre for Disease Control and Prevention (ECDC) as 6,245,352 cases with global death recorded as 376,427 deaths.

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Introduction
Coronaviruses are the largest group of positive sense RNA viruses that causes infections in humans, mammals and birds [1]. It belongs to the family coronaiviidae and the viral envelope was surrounded by a spike-like structures from which the viral name was derived [2]. The coronaviruses that causes disease in humans are currently seven with four of them causing mild to moderate diseases and these are HCoV-229E, HCoV-OC43, HCoV-NL63 and HCoV-HKU1; the remaining three cause severe diseases particularly related to severe acute respiratory syndrome which include severe acute respiratory syndrome coronavirus (SARS-CoV), middle east respiratory syndrome (MERS-CoV) and the coronavirus disease of 2019 (COVID-19) [3].

Coronaviruses belong to the order Nidovirales, which is a large order of viruses that are subdivided into three main groups which include: Coronaviridae, Arteriviridae, and Roniviridae families. The Coronaviridae is made up of two major subfamilies which are the coronavirinae and torovirinae. The subfamily coronavirinae is further subdivided into the alpha, beta, gamma and delta coronaviruses [4].

Several cases of unusual pneumonia in Wuhan were reported by Wuhan Municipal Health Commission (WMHC) on December 12, 2019, with nine out of the total twenty-seven reported cases as critically ill. It was discovered that those infected during the period were those working at the Wuhan’s Huanan Seafood Wholesale Market where many sorts of animals including bats, poultry, snakes and other farm animals were been sold [3]. On December 31, 2019, China alerted WHO to these new cases of unusual pneumonia in Wuhan city comprising of about 11 million people located in the central Hubei province [5].

Within few weeks, the outbreak escalated to become an epidemic at the epicentre of the disease which led to the closure of the Huanan Seafood Market on January 1, 2020. The World Health Organization on January 7, 2020 identified the virus as a novel coronavirus and officially but tentatively named it as 2019-nCoV, the new coronavirus in 2019 [3, 6]. The purpose of this study was to give general overview of the COVID-19 with regards to the virology, epidemiology, pathogenesis, clinical presentation, diagnosis and treatment of this novel coronavirus based on the current available evidence.

Virology
COVID-19 is a β CoV virus belonging to the group 2B demonstrating more than 70% genomic similarity with SARS-CoV and therefore constituting the seventh member of the human coronaviruses that infect man [7]. It is a positive-sense, non-segmented, enveloped, single stranded RNA virus with the size of the genome ranging from 26-32 kilobases making it the largest viral RNA genome that can affect gastrointestinal (GI) tract, respiratory, renal or central nervous system [8]. The genome is nearly spherical with surface projections called spikes proteins and has a diameter of about 60-100nm with a length of about 29.9 kb [9].

There are four structural proteins in the genome namely: the Spike (S), Envelope (E), Membrane (M) and Nucleocapsid (N) proteins [10]. The spike protein aids the virus in attaching to the human tissues and is divided into two subunits: S1 subunit which has two domains, an N-terminal domain (NTD) and a receptor-binding domain (RBD); and the S2 subunit which consists of conserved fusion peptide (FP), heptad repeat (HR) 1 and 2, trans-membrane domain (TM), and cytoplasmic domain (CP) [11]. The receptor-
binding domain (RBD) of S1 subunit is further subdivided into two sub-domains: external and internal sub-domains. The direct viral interaction with the host receptor, human angiotensin-converting enzyme 2 (ACE2) is facilitated by the external sub-domain of the S1 subunit [12, 14].

The source of the COVID-19 has been attributed to bats due to over 96% genomic identity with the bat coronavirus genome and phylogenetic analysis on the complete viral genome have shown that the virus is closely related to a group of SARS-like coronavirus identified previously from bats in China [14]. In a study by Zhang and colleagues, Pangolin-CoV at the whole-genome level was found to be 91.02% identical to SARS-CoV-2 indicating the probable Pangolin origin of SARS-CoV-2, and this was supported by the consistency of the five main amino acids in the RBD between Pangolin-CoV and SARS-CoV-2 [15].

However, a unique RRAR motif in the spike protein of human SARS-CoV-2 that is not present in coronaviruses isolated from pangolins indicates that SARS-CoV-2 may not come directly from pangolins [16]. Additionally, some strains of SARS-CoV-2 were isolated a few months earlier before COVID-19 was officially reported, thus disputing bats as potential origin [17]. Furthermore, evidence from phyloepidemiological approaches suggests the possibility of importation of SARS-CoV-2 from other places to the Huanan Seafood Market [18]. Similarly, the virus was shown to be a recombinant virus between the bat coronavirus and another coronavirus with unknown origin with snake as the most likely animal reservoir [3].

Epidemiology

The main sources of infection are the COVID19 infected patients and the more severe the disease, the more contagious it is [19]. Additionally, individuals without clinical signs and symptoms of COVID19 (asymptomatic) were reported to be potential sources of infection as they were proven to shed the infectious virus [20]. The average incubation period is between 4-6 days, however, an incubation period of 1-19 days was reported in a familial cluster of five patients indicating that COVID-19 incubation period is almost similar to MERS and SARS but slightly longer than influenza [21].

The 19 days incubation period is a rare occurrence, therefore specialists and professionals suggest the maximum incubation period as 14 days especially for quarantine [22]. The disease can occur in three different patterns.

1. Non-severe comprising of asymptomatic without any clinical sign or symptom, mild with mild upper respiratory tract symptoms and moderate with symptoms of pneumonia.
2. Severe with severe symptoms of pneumonia requiring oxygen administration.
3. Critical with acute respiratory distress syndrome (ARDS) or respiratory failure, shock or multiple organ dysfunction [21].

Since the early report of COVID-19 identification from mainland China, the disease rapidly spread across the continent and the number of cases increased exponentially worldwide with the first imported case reported from Thailand on early January [24]. As of May 31, 2020, the COVID-19 pandemic has affected six geographical regions: Africa, Americas, Eastern Mediterranean region, Europe, South-East Asia and Western Pacific [6]. By June 2, 2020, the European Centre for Disease Prevention and Control (ECDC) reported the highest incidence of COVID-19 in Americas region (n= 2,956,532) with United States having the highest incidence worldwide (n=1,811,277), followed by Europe (n=1,975,341), Asia (n=1,151,637) and then Africa (n=152,485). Similarly, the number of new cases was highest in Americas region, followed by Europe, Asia and then Africa. However, the overall death rate was highest in Europe (n=175,572), followed by Americas (n=165,262), Asia (n=31,110) and then Africa (4,344) with the least death recorded in Oceania (ECDC COVID-19 Situation Update Worldwide, June 2, 2020).

Pathogenesis

The viral entry into the host tissues is facilitated by the spike proteins on the viral envelop which bind with the host receptor, human angiotensin-converting enzyme 2 (ACE2). The viral replication primarily occurs in the in mucosal epithelium of upper respiratory tract, and subsequently spread to the lower respiratory tract and gastrointestinal mucosa where further multiplication is presumed to occur producing mild viremia [8]. Viral multiplication can also occur in many organs like lung, heart, kidney, stomach, bladder and ileus due to expression of ACE2 receptors in these organs which consequently may result in multiple organ damage [25].
The mechanism of the viral invasion into the host cells consists of 5 steps: attachment, penetration, biosynthesis, maturation, and release. The viral binding with the ACE2 receptor (attachment) results in the mediation of the viral entry into the host tissues through the plasma membrane or by endocytosis (penetration) through the release of proteases. Following the entry, viral contents are released inside the host cells and the viral RNA enters the host's nucleus for replication in which the viral mRNA will produce viral proteins (biosynthesis). The viral proteins will then make new virinal particles (maturation) which is then released into the host tissues from the nucleus [26].

Figure 3: Viral attachment to the host’s tissue (adopted from Mousavizadeh and Ghasemi, 2020: Genotype and phenotype of COVID-19: Their roles in pathogenesis)

The viral entry into the host cells, triggers the host’s immune responses, initially innate immune responses but adaptive immune responses may be stimulated when the infection persist [26]. ACE2 receptors are predominantly expressed on the apical side of lung epithelial cells in the alveolar space, and therefore the first immune responses are stimulated by the three main components for innate immunity in the airway: Epithelial cells, dendritic cells (DCs) and alveolar macrophages [27]. DCs are found primarily underneath the epithelium while macrophages are located at the apical side of the epithelium. Thus, DCs and macrophages serve as innate immune cells to fight against viruses till adaptive immunity is involved. DCs and macrophages can phagocytize SARS-CoV-2 infected cells and then present the viral particles to the antigen presenting cells (APCs) [28]. The APCs then migrate to the draining lymph nodes to present viral antigens to T cells initiating T cell responses with CD4+ and CD8+ T cells playing the most important role: CD4+ T cells activate B cells to promote the production of virus-specific antibody, while CD8+ T cells can kill viral infected cells [26].

In severe cases of COVID-19, there is increased level of activated pro-inflammatory immune cells such as cytokines, including interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1α, and tumor necrosis factor (TNF)-α and this condition is called CYTOKINE STORM which may result in immune responses out of control (exaggerated) factor (TNF)-α and this condition is called CYTOKINE STORM that may lead to pulmonary tissue damage, functional impairment, and reduced lung capacity [14,8]. Cytokine Storm is an uncontrolled systemic inflammatory response that occur due to the release of pro-inflammatory cytokines and chemokines by immune effector cells resulting into an exaggerated inflammatory immune response that contributes to acute respiratory distress syndrome (ARDS), multiple organ failure, and finally death in severe cases of SARS-CoV-2 infection [29].

Also, increased levels of these pro-inflammatory cytokines can cause shock and tissue damage in the heart, liver and kidney, as well as respiratory failure or multiple organ failure. Additionally, extensive pulmonary pathology, leading to massive infiltration of neutrophils and macrophages, diffuse alveolar damage with the formation of hyaline membranes and a diffuse thickening of the alveolar wall was associated with high level of these proinflammatory cytokines. Similarly, autopsy of deceased patients showed necrosis of lymph nodes and spleen atrophy suggesting an immune-mediated damage [30].

Figure 4: Summary of COVID-19 Pathogenesis (Adopted from Jin et al, 2020: Virology, Epidemiology, Pathogenesis, and Control of COVID-19)

Clinical Presentation

The clinical spectrum of COVID-19 ranges from non-severe (comprising of asymptomatic, mild to moderate), severe to critical condition and the infection usually start with non-specific symptoms such as malaise, myalgia or fatigue which is then followed by high fever, dry cough and dyspnoea after a few days to a week [31]. According to the report by Chinese National Reporting System as of February, 2020, 80% of the confirmed cases were non-severe having either no symptoms of pneumonia or mild to moderate pneumonia; 15% were severe cases with severe symptoms of pneumonia; approximately 6% were critical cases under intensive care due to respiratory failure, shock, or multiple organ failure [31]. Additionally, in the early studies of clinical characteristics of patients with COVID-19 in Wuhan China, the most common symptoms were fever, cough and fatigue which are found in about 98%, 76% and 44% of the patients respectively. The less common symptoms were sputum production, headache, hemoptysis and diarrhea in about 28%, 8%, 5% and 3% of patients respectively [32]. In a cohort study of patients outside Wuhan, gastrointestinal (GI) symptoms like nausea, diarrhea and vomiting were found to be common in COVID-19 patients and patients with GI symptoms tend to have more severe and even critical conditions with family clustering, likely due to fluid depletion [33]. D’Amico and colleagues found out that diarrhea is one of the most frequent features in patients with COVID-19 with an incidence rate of 2%-50% which may precede or follow the respiratory symptoms [34]. The symptoms may be very similar to influenza consisting generally of fever, fatigue, dry cough, sore throat, headache, and occasionally nasal congestion, runny nose, and diarrhea which may progress to serious and life threatening symptoms of acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, and coagulation dysfunction [35]. For children with COVID-19, symptoms usually followed a close contact with infected family members and the most frequent clinical features are cough (65%) and fever (60%) [36]. In a systematic review of 58 patients, the most prevalent clinical manifestations were fever (88.7%, 95%CI 84.5-92.9%), cough (57.6%, 95%CI 40.8-74.4%)
and dyspnea (45.6%, 95%CI 10.9-80.4%); and the prevalence of fever is much higher in adults compared to children (92.8%, 95%CI 89.4-96.2%; versus 43.9%, 95%CI 28.2-59.6%) [37].

Many different types of cutaneous manifestations including urticarial, maculopapular, papulovesicular, purpuric, livedoid, and thrombotic ischemic lesions were reported in patients with COVID-19 [38]. In a multicenter European study of 417 COVID-19 patients, face pain and nasal obstruction were the most common disease-related otolaryngological symptoms with about 85.6% and 88.0% of patients reported olfactory and gustatory dysfunctions, respectively [39]. In a case series of 23 confirmed cases of COVID-19, about 70% of the patients present only with anosmia which is not related with any other cause and about 83% reported anosmia as their first symptom which is then followed by other symptoms [40].

Cardiac symptoms are also pertinent findings in patients with confirmed COVID-19 which occurs as a result of inflammatory storm in response to the infection leading to the direct viral invasion of cardiomyocytes, as well as a myocardial injury due to oxidative stress causing acute myocardial injury (AMI) [41].

**Figure 5:** Clinical features of COVID19 (adopted from Rothan and Byrareddy, 2020: The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak).

**Diagnosis**

The most effective method of controlling the spread of COVID-19 is through early and accurate detection of the virus and the current diagnostic tests include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP) [22]. The standard diagnostic assessment of COVID-19 set by the China National Health Commission was the laboratory examinations of the nasopharyngeal and oropharyngeal swab tests. Two one-step quantitative RT-PCR (qRT-PCR) assays were developed to identify patients earlier by detecting two different regions (ORF1b and N) of the SARS-CoV-2 genome.

Additionally, three novel RT-PCR assays targeting the RNA-dependent RNA polymerase (RdRp)/helicase (Hel), spike (S), and nucleocapsid (N) genes of SARS-CoV-2 were developed with the COVID-19-RdRp/Hel assay having high sensitivity and specificity out of the three that may help to improve the laboratory diagnosis of COVID-19 [42]. The main issue with these tests is the low detection limit and false negative results and this led to the invention of some improved rapid viral nucleic acid diagnostic tests like a nucleic acid test paper, which can be used for the rapid detection of SARS-CoV-2 with the naked eye observation within three minutes [22].

**Imaging technique** like chest radiograph or chest computed tomography (CT) should be used for diagnosis of patients suffering from fever, sore throat, fatigue, cough or dyspnea that is coupled with recent exposure despite negative RT-PCR results. The common CT findings include bilateral pulmonary parenchymal ground-glass and consolidative pulmonary opacities, sometimes with a rounded morphology and peripheral lung distribution [43]. However, lung cavitation, discrete pulmonary nodules, pleural effusions, and lymphadenopathy were typically absent [43]. Notably, asymptomatic COVID-19 patients may present with chest CT imaging abnormalities which evolve rapidly from focal unilateral to diffuse bilateral ground-glass opacities that may progress to consolidation within 1-3 weeks [30]. Other supportive diagnostic tests are full blood count, blood culture and C-reactive protein. The total white cell counts might be normal with decrease or normal lymphocytes count. Currently, the priority for COVID-19 diagnosis is the Point of Care Testing (POCT) of IgM/IgG in which patients are diagnosed without sending samples to centralized facilities thereby enabling communities without laboratory infrastructure to detect infected patients [44].

**Treatment**

Presently, no specific therapeutic agents or vaccines that have been confirmed as definitive treatment for COVID-19. Different therapeutic approaches have been considered and found effective in managing infected patients. Those available therapies are antiviral therapy, chloroquine and hydroxychloroquine, corticosteroids, protective monoclonal antibodies and convalescent plasma transfusion [22]. There are many antiviral drugs currently available but no evidence from randomized controlled trials (RCTs) to recommend any of them as a specific anti-SARS-CoV-2 treatment for patients with a suspected or confirmed COVID-19 infection.

However, the use of lopinavir/ritonavir in SARS patients was associated with reduced death rate (2.3% vs. 11.0%) in a retrospective cohort study [45]. Another potential antiviral agent is the Remdesivir which was used to treat the first case of COVID-19 infection in the United States and the patient’s clinical condition improved after only one day of remdesivir treatment [46]. Many trials of antiviral agents in patients with COVID-19 are ongoing and their efficacy and safety will be determined by these trials.

Chloroquine and hydroxychloroquine are commonly used anti-malarials and autoimmune disease drugs that have some biochemical properties with antiviral effects [47]. The drugs work by inhibiting the attachment of the virus to the host’s tissue by interfering with the glycosylation of cellular receptors, the ACE2 [48]. Although hydroxychloroquine is an analog of chloroquine but has less drug-drug interaction than chloroquine and was shown to be more potent than chloroquine in SARS-CoV-2-infected Vero cells [49].

The cytokine storm in severe COVID-19 patients which was caused by exaggerated immune responses can be modulated and suppressed by both chloroquine and hydroxychloroquine thereby preventing the development of multi-organ damage and subsequent death [50]. Many clinical studies have been launched to evaluate the efficacy, feasibility and safety of these agents in the treatment of COVID-19 infection and also to determine the dosage and duration of treatment, the patient’s age and the stage of the disease in which the drugs can be administered.
Corticosteroids have been associated with suppression of lung inflammation in many COVID-19 patients [50]. However, there is no evidence currently to suggest that patients with COVID-19 infection will benefit from corticosteroids, and such treatment may be harmful [51]. Protective Monoclonal Antibody (mAb) has been reported to significantly neutralize SARS-CoV and inhibit syncytia formation between cells expressing the S protein and those expressing the SARS-CoV receptor ACE2 [52].

Unlike other SARS-CoV RBD-directed antibodies 230, m396 and 80R, the SARS-CoV-specific human monoclonal antibody CR3022 binds potently with the COVID-19 RBD which only recognize a single epitope, and the anti-infective effect may be limited [53]. Another therapeutic agent is the use of convalescent plasma which has been widely recommended to be used for COVID-19, however, its efficacy and safety cannot, presently, be determined [22]. Other agents like vitamin D and C as well as zinc have been in use for supportive treatment of COVID-19 patients and were shown to reduce the risk of progression to severe pneumonia and ARDS [54-57].

Conclusion
COVID-19 is a new human coronavirus identified in mid-December from Wuhan city, China which was probably transmitted by bats. Genomic sequence analysis showed that it resembles SARS-CoV and MERS making it the seventh member of human coronaviruses. It is a single stranded, positive sense-RNA virus that is nearly spherical in shape with surface projections, called spikes. The source of the disease is COVID-19 infected individuals and is transmitted from person to person by direct contact. The most susceptible individuals are elderly or patients with associated comorbidities. The disease spread rapidly across the globe with over 6 million individuals infected and over 300 thousand deaths.

The virus enters human body by binding with the host receptor, human angiotensin-converting enzyme 2 (ACE2) and thus triggers host immune responses against the virus. The clinical features can be mild or severe and commonly present with fever, fatigue, dry cough, sore throat, headache, and occasionally nasal congestion, runny nose and diarrhea. The virus is commonly diagnosed with nucleic acid testing like real-time RT-PCR (rRT-PCR) or imaging technique such as chest radiograph or chest computerized tomography (CT).

Currently, no available definitive treatment or vaccines against COVID-19, but the following therapeutic modalities including antiviral therapy, chloroquine and hydroxychloroquine, corticosteroids, antibodies and convalescent plasma transfusion are widely considered and many are currently undergoing clinical studies. Therefore, clinical trials are still needed to devise correct and definitive treatment of this disease and to develop vaccines against it.

References


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