Review on Corona Virus Disease-19 [Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)]

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ABSTRACT

The cluster of pneumonia patient was found in Wuhan, China at the end of December 2019, later on WHO declare it as Coronavirus disease and its cause due to SARS-CoV-2. It can rapidly spread in China as well as globally. This is a zoonotic virus transmitted from bat to human via unknown intermediate animal. About 34673 confirmed cases were reported on 8 January 2020 in China. This article mainly focuses on basic introduction: includes history of a COVID-19, virology: includes family, types, and type of genome of coronaviruses, Epidemiology: includes transmissibility of infection, the number of patients to be infected, and a spectrum of clinical severity, Clinical features: include signs and symptoms of coronavirus, diagnosis: include an RT-PCR test for coronavirus, treatment: includes antimalarial, antiviral, other drugs which used on symptomatic treatment of coronavirus disease, and the last part of the article includes some guidelines which provided by WHO for prevention of coronavirus disease.

1. INTRODUCTION

In December 2019 some cluster of unknown etiology pneumonia patients was found in Wuhan, Hubei province, China[1]–[3]. This is new beta coronavirus[4]are rapidly spreading in China and nationwide[5]. On 7 January 2020 WHO and Chinese authorities are temporarily named it as *novel coronavirus 2019*(2019-nCoV)[6], [7]. On 10 January 2020, first whole-genome sequence of novel coronavirus 2019 was released, which is very helpful to researchers to find out the type of virus by using *Reverse-Transcription Polymerase Chain Reaction* (RT-PCR) method. On 21 January 2020 the first research article related to 2019-nCoV was published, which article mentions that 2019-nCoV coated with spike proteins which strongly interact and binds to the human ACE2 receptor[6]. On 31 January 2020 WHO announce the public health emergency of international Concern (PHEIC) for the 2019-nCoV outbreak. Later on, confirming that the transmission occurs from human to human[6]–[8]. On 11 February 2020 WHO was declared a new name to the disease which caused due to 19-nCoV is *Corona Virus Disease 2019* (COVID-19)[7], [9]. The International Committee on Taxonomy of Viruses (ICTV) is renamed 19 n-CoV to *Severe Acute Respiratory Syndrome Coronavirus 2* (SARS-CoV-2)[4]. On 11 March WHO announced that the COVID-19 is pandemic[1], [6], [10]. If we compare the SARS-CoV (2003) and SARS-CoV-2 (2019) in 2003 SARS-CoV infect 8098 peoples in 26 countries of world at the morality rate of 9%[11], [12], on other hand, in 2019 SARS-CoV-2 infect 120,00 peoples of 109 courtiers with a mortality rate of 2.9%, and still it has continued. By using above data, we conclude that the transmission rate of the SARS-CoV-2 is more than the SARS-CoV and the reason is genetic recombination event in RBD*(Receptor Binding Domain)*region in the S protein of SARS-CoV-2 is increasing its ability of transmission[12], [13].

Virology

Coronaviruses (CoVs) are belongs from Coronaviridae family and the order Nidovirales[11], [14] this is made up by enveloped of single stranded, positive sense RNA genome of 27-32KB, it has diameter 60-140 nm (observed via electron microscope)with its round or eclipse shape. It has mainly existed in its pleomorphic form its genome contain about 29891 nucleotides encoded via 9860 amino acids. All types of coronaviruses having same expression and organization of genome[13], [15]. The name corona due to its "crown-like (or corona in Latin) spikes" of protein on its surface[11], [13]. Previous studies show that the six different types of CoVs causes the human disease, and this is categorized into two different

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subgroups containing gently and extremely pathogenic CoVs. Gently pathogenic CoVs are 229E, HKU1, OC43 and NL63 which causes 10-30% Upper Respiratory Tract Infection. Instead, extremely pathogenic CoVs, contains *Middle East Respiratory Syndrome* (MERS), *Severe Acute Respiratory Syndrome* (SARS) and *Severe Acute Respiratory Syndrome Coronavirus* (SARS-Cov-2) mostly infect the lower respiratory tract and may lead to pneumonia[14], [16]. The protein synthesis rate of the extremely pathogens (MERS-CoV, SARS-CoV and SARS-CoV-2) is faster than gently pathogens (229E, HKU1, OC43 and NL63). This is due to the gently pathogen contain six human slow codons (GGT, GAT, CAT, TGT, TTT, and AGT) while extremely pathogens contain only two human slow codons (CTA, and ACC)[17]. Recent studies shows that SARS-CoV and SARS-coV-2 have 89.10% similarities in gene[6]. Orthocoronavirinae *(Subfamily of CoV)* having four different genera of CoVs: Alpha-coronavirus, Beta-coronavirus, Delta-coronavirus and Gamma-coronavirus. Bats and rodents are main genetic sources of alpha and beta-CoVs while the avian species are genetic source of delta and gamma-CoVs[15]. The alpha and beta genera are responsible to infect mammals while gamma and delta genera are responsible to infect both birds as well as mammals[8], [14]. The *Angiotensin-Converting Enzyme-2* (ACE-2) receptor is provide binding for SARS-CoV and SARS-CoV-2 to the human host cells by maintaining similar van der walls and electrostatic properties at the interface[13], [18]. Phylogenetic analysis shows that SARS-CoV-2 is 88-89% similar to the bat-SL-CoVZXC21 (GenBank accession no. MG772934.1) and bat-SL-CoVZc45 (GenBank accession no. MG772933.1) *(bat-derived SARS-like coronavirus)*[8] it also shows that SARS-CoV-2 is similar to horseshoes bats *(coronavirus circulating in Rhinolophus).* The partial *RNA-dependent RNA polymerase* (RdRp) gene of bat coronavirus strain BtCoV/4991 having 98.7% nucleotide similarity with SARS-CoV-2[9].

Epidemiology

The epidemic impact depends on a transmissibility of infection, the number of patients to be infected, and a spectrum of clinical severity[19]. From the last two decades, China is main witnessed for respiratory viruses that turns to epidemics: in 1997 avian influenza H5N1, in 2003 SARS-CoV, and the ongoing (2019-2020) SARS-CoV-2[20]. The cases of SARS-CoV-2 found in the Hunan seafood wholesale market (where the wild animals can sell) in Wuhan, China. In this market about 49-66% patients are in contact with each other[21], [22]. Human-to-human transmission is the major route of the virus to spread worldwide. Travelling and

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importing has played the most important role in for transmitting this virus into Korea, Japan, Middle East and Europe[20]. The human coronavirus is transmitted via the droplets, direct or indirect contact of human-to-human. Fecal-to-oral transmission also possible, but have very less evidence. Recent studies show that transmission of SARS-CoV-2 might be possible via contaminated surface. The SARS-CoV-2 are remain viable on surfaces like; glass, stainless steel, and plastic. The airborne transmission is still not reported[23], Gastrointestinal transmission is also possible because SARS-CoV-2 is found in stool sample of patients[24]. Transmission is identified by checking the relationship between infected and uninfected cases with confirmed cases[25]. The spreading rate of SARS-CoV-2 is more than previous SARS-CoV, and MERS. The SARS-CoV-2 require an incubation period about 2 to 14 days[10]. On 8 January 2020, first cases of pneumonia with unknown cause were identified by Shenzhen *Chinese Center for Disease Control and Prevention* (CDC)[26]and disclosed the genomic sequence on 11 January 2020[23]. On 8 February 2020 China reports 34673 confirmed and 27,656 suspected cases of *novel coronavirus pneumonia* (NCP) across 34 Chinese provinces[27]. Later on, as of 29 February 2020, have 83,652 confirmed cases of COVID-19 was found in China, out of that 2791 deaths (3.4% mortality rate) are recorded[28]. On 1 March 2020 about 87,137 confirmed cases were found in 59 countries of the world[29]. On mid-March 2020 drastic change occurs in China the number of patients was decreased with time; now the new hot spot is Italy and Iran from which it spread towards nearby countries up to 22 March 2020 the number of confirmed cases was reached to 1,41,858 with 7,319 deaths[30]. The clinical severity spectrum of COVID-19 is broad it ranges from mild to critically ill cases. About 16-26% patients suffering from severe acute respiratory distress that requires oxygen supplement and intensive care. The severity of disease depends on the age and comorbidities such as cardiovascular disease, diabetes, and hypertension[29], [31].

Clinical features

The COVID-19 have wide range of sign and symptoms, some patient is asymptomatic while some are shows septic shock and multiorgan dysfunction like signs. The sign and symptoms depend on the severity of disease. The disease is classified into mild, moderate, severe, and critical[32]. The mild patient didn't show positive sign while the sever patient shows the shortness of breath, difficulty to breath, moist rales in lungs, pneumonia, dullness in percussion, weakened breath sound and increased or decreased tactile speech tremor[33], [34], Conjunctivitis[35], Diarrhea[36]. The most common sign and symptoms are fever

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(88.2%) and cough(69.7%)[37]. Further studies show that fever is the one of the symptom of COVID-19 was identified only in 43.8% patients*(before hospitalization)*while about 88.7% patient develops fever after hospitalization[31]. The epidemiologic study shows the COVID-19 have signs of liver damage[38]. It also shows some neurological symptoms such as nausea and vomiting (1%), headache (8%)[39], Anosmia*(loss of sense of smell)*[40], [41] hypogeusia[41] or ageusia*(loss of sense of taste),* seizures*(sudden electrical disturbance in the brain)*, and ataxia*(loss of control on body movements)*[42].

Diagnosis

The diagnosis of SARS-CoV-2 is done via real time RT-PCR *(Reverse Transcription-Polymerase Chain Reaction)*[43]it is based on RNA detection[44]. But it gives negative results in some patient due to its sensitivity and reliability of RT-PCR. This test has a limitation of the viral load analysis for evaluating the disease progression and this is also unable to evaluate the efficiency of antiviral drug[37]. Chunhua Yang et al diagnoses the 610 hospitalized patient by using RT-PCR test they report that the RT-PCR test report are variable and unstable[45].RT-qPCR *(Quantitative real-time reverse transcriptase-polymerase chain reaction)* is mainly used to detect ORF1b and N regions of the genome of SARS-CoV-2[46]. Another test for diagnosis of SARS-CoV-2 is RT-LAMP *(reverse transcription loop-mediated isothermal amplification)* it has similarity in sensitivity with rRT-PCR *(A test used to detect MERS-CoV)*[47].

Treatment

The first step of treatment is avoiding transmission of disease from patient to the other contact, healthcare workers., isolate the patient of COVID-19., mild illness is managed at home with counseling serious signs and symptoms., Maintain the nutritional balance, hydration level, controlling cough and fever[48]. In present days no any vaccine or specific antiviral drug is available for COVID-19 so on this days we can provide or take supportive care of the patient by ventilation, oxygenation, fluid management, and by giving drugs like anti-viral, corticosteroids, anti-malarial, and herbal treatment is used[49]. The anti-malarial drugs like; Hydroxychloroquine and Chloroquine are labeled as "game changer" for COVID-19[50]. Chloroquine treats the patients of COVID-19 pneumonia due to its anti-inflammatory and anti-viral activity[51]. Hydroxychloroquine is an analogue of Chloroquine out of that Hydroxychloroquine are safer (during long term use) than Chloroquine. And it produces less

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drug-drug interaction than chloroquine[52]. The mechanism of action of Chloroquine and Hydroxychloroquine is identical[53]. Previous studies show that the SARS-CoV-2 enter into host cell via the binding with the ACE-2 receptor, the chloroquine act by interfering with this binding and inhibit the terminal glycosylation while Hydroxychloroquine act via the gangliosides which inhibit the contact of SARS-CoV-2 with ACE-2 receptor. Additionally, both the drugs can enters into endosome and lysosome and increases the pH of the intracellular components. Normally it required low pH range for homeostasis. Due to increase in pH results their dysfunction, leads to exocytosis and endocytosis, degradation of protein, which required for propagation, and replication of SARS-CoV-2[50]. These drugs have some adverse effect like vomiting, diarrhea, and gastrointestinal upset[50].

The anti-viral drug, Ramdesvir was invented for the Ebola virus, it shows broad-spectrum activity against several RNA viruses. It reduces the viral load of lungs and improve the pulmonary function[47]. Ramdesivir (GS-5734), is viral RNA-dependent, RNA-polymerase inhibitor are active against SARS-CoV and MERS. Earlier studies show that it also active against SARS-CoV-2[54]. Another antiviral drug Zanamivir is also active against SARS-CoV-2. The activity of Zanamivir is studied by In-silico protein docking study[44].

The use of NSAID *(Non-Steroidal Anti Inflammatory Drug)* is safe or harmful in patients of COVID-19 is unknown. But NSAID is responsible to prevent cytokine storm of COVID-19. Ibuprofen is commonly prescribed NSAID in COVID-19. Several previous studies shows that anti-IL-6 is a useful treatment for COVID-19, ibuprofen is reduces interluken-6 (IL-6) in humans[55]. Paracetamol plays an important role in sleep in immune defense while other NSAID needs to treat the other symptoms like musculoskeletal pain[56]. The in vitro-in vivo study of the Indomethacin shows antiviral activity against canine coronavirus by inhibiting viral replication and protect the host cell from viral damage. It's in vivo study also shows the activity against the human SARS-CoV with dose 1mg/kg[57]. WHO declares that still not have any evidence of death with use of NSAID inCOVID-19[55].But, regular use of NSAID should not recommended for symptomatic treatment of COVID-19[56].

Most of the studies are carried out with the use of corticosteroids *(e.g., dexamethasone)* for the treatment of COVID-19 rather than NSAID. Overall corticosteroids shows positive outcomes than an NSAID for COVID-19. Corticosteroids are widely used due to its ability to modulate the inflammatory responses and reduces the immunopathological damage[57]. The

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WHO has recommended the corticosteroids for routine symptomatic treatment of COVID-19[58].

The treatment of COVID-19 patient with Tocilizumab reduces the mortality and improve the clinical symptoms effectively. It is an effective treatment for the severe COVID-19 patient[59]. IL-6 is cytokine responsible for inflammatory reaction and immune response. The previous study shows that the most common cytokines involve in COVID-19 is IL-6[60]. Tocilizumab is recombinant humanized antihuman IL-6 receptor monoclonal antibody which having high affinity to IL-6 receptor it specifically bind mIL-6R and sIL-6R and inhibit signal transduction[59].

Tangfeng Lv and et al reported that convalescent plasma therapy is specific and effective for COVID-19[61]. A patient treated with convalescent plasma therapy are having lower mortality and short hospital stay compared to the patient not treated with convalescent plasma therapy[62].

Prevention

There are no guidelines are available for complete prevention of COVID-19 but WHO and ECDC provides some basic guidelines. Because many studies are gives proof of human-to-human transmission of these disease from Wuhan, China. Air born transmission also reported by some studies. According to WHO, some general guidelines are published to avoid transmission such, as separate the COVID-19 positive patient from another family member, air born precaution, and droplet precaution. ECDC *(European Center for Disease Prevention and Control)* also publish some basic guidelines for public health such as avoid visiting to the market, avoid the visiting to the market where live or dead animals are handle, avoid contact with peoples particularly those with cough, wash hands with sanitizer or soap with water before eating[63].

CONCLUSION

The COVID-19 is still challenging task with limited treatment and prevention measures. The available information related to SARS-CoV, MERS-CoV helps us to how to handle the current pandemic situation of SARS-CoV-2. Nowadays no any specific vaccine and antiviral drugs are available to treat coronavirus disease, but by using previous anti-malarial (Hydroxychloroquine), antiviral (Ramdesvir) drug the symptomatic treatment of coronavirus

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disease is possible. We can prevent the human-to-human transmission of disease by following guidelines provided by WHO like social distancing, washing hands, and wearing masks etc.

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