Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review Article

Coronaviruses disease 2019 (COVID-19): Causative agent, mental health concerns, and potential management options

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ABSTRACT

Coronavirus disease-2019 (COVID-19) pandemic started from Wuhan, China has infected more than 6.7 million individuals and killed more than 390,000 individuals globally. Due to the higher transmissibility and infectiousness, asymptomatic infection, and lack of effective treatment options and vaccine, fatalities and morbidities are increasing day by day globally. Despite physical health consequences, COVID-19 pandemic has created stress and anxiety, as result there is an increased risk of mental illnesses both in the infected and normal individuals. To eradicate these risks, it is necessary to determine the COVID-19 zoonotic source of transmission to humans and clinical manifestations in infected individuals. Although, identification or development of the highly effective therapeutic agents is necessary, however, development of protective strategies against the COVID-19 by enhancing immune responses will be an asset in the current scenarios of the COVID-19 pandemic. In this paper, we discuss the transmission, health consequences, and potential management (therapeutic and preventive) options for COVID-19 disease.

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Introduction

The new decade of the 21st century (2020) started with a deadly coronavirus disease 2019 (COVID-19) pandemic caused by a novel coronavirus (SARS-CoV-2) in Wuhan, China [1]. In December 2019, various cases of pneumonia with unknown etiology were reported in Wuhan, China. Later, on 10th January 2020, the disease was confirmed as viral pneumonia and found epidemiologically linked with Huanan seafood market of Wuhan, where wild animals including bats were sold [2,3]. Soon after the Chinese authorities declared an emergency situation in Wuhan, other countries in the world started reporting COVID-19 cases [4]. Due to high spread, morbidity, mortality, and infectiousness, WHO declared COVID-19 outbreak as a pandemic [5]. As of June 6, 2020, more than 6.7 millions confirmed cases and more than 390,000 deaths are reported from COVID-19 pandemic (Walker, 2020). To curb the risk of spread and manage the adverse impacts of virus, it is necessary to know the medical consequences associated with COVID-19 infection. In this article, we briefly describe the consequences of highly infectous human corona viruses, and elaborate the transmission and health consequences (both physical and mental health) of COVID-19 disease. We further discuss the potential therapeutic and preventive strategies, and required research investigations that may help managing and controlling the spread of COVID-19 disease.

SARS CoV2 as one of coronaviruses

Before COVID-19, severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV during 2002 in Guangdong, China affected 8098 individuals and killed 774 individuals in 29 different countries [6]. Only a decade later (during 2012), the world witnessed the Middle East respiratory syndrome (MERS) outbreak caused by MERS-CoV in the Middle East [7]. Until 2020, MERS-CoV infected 2468 individuals and caused 851 fatalities worldwide [8]. While researchers were still investigating the mechanisms to develop therapeutic strategies against MERS, another member of coronaviruses called SARS-CoV-2, emerged in Wuhan [9]. Market civets were thought to be the possible source of SARS-CoV transmission to human, however, the virus strains in civets were found transmitted from horseshoe bats [10]. MERS-CoV strains obtained from camels were highly similar to those isolated from humans; with highly prevalent MERS-CoV-specific antibodies in camels from the Middle East, Africa, and Asia [7,11–13]. These observations suggest that MERS-CoV transmitted from camel to human. However, genome sequencing analysis revealed that MERS-CoV is phylogenetically related to bat coronaviruses [14]. The zoonotic source of SARS-CoV-2 is not confirmed, however, its genome sequence exhibited close relatedness with two bat-derived SARS-like coronaviruses [15,16]. Thus, it is thought that bats are the possible source of origination for SARS-CoV-2. Like MERS-CoV and SARS-CoV, SARS-CoV-2 belongs to betacoronavirus (subgenus; Sarbecovirus) [3,17]. Reportedly, the genome sequencing analysis has revealed over 80% similarity between SARS-CoV-2 and SARS-CoV, however, there are some differences at the structural protein levels. For instance, the 8a protein was reported missing while the aminoacids number in 8b and 3c protein were found fluctuating in SARS-CoV-2 [17]. These differences can help in studying the infectiousness, transmission, and health impacts of COVID-19 infection.

Transmission of SARS-CoV-2

Although bats are thought to be the source of origin for SARS-CoV-2, the intermediate animal that caused the transmission of virus to humans, is still unknown [3]. Once SARS-COV-2 transfers from zoonotic source to human, it can potentially transmit from human-to-human, mainly through respiratory droplets from an infected individual *via* coughing or sneezing [18]. The virus can also transmit from an asymptomatic infected individual to infect healthy individual [19]. The entry of virus to host cell occurs in several steps including binding to a target host cell *via* cellular receptors, fusing the envelope with a cellular membrane, and forking over its genetic material inside the cell [20,21]. This process is highly dependent upon binding specificity to receptors, proteolytic activation, and endocytosis efficiency. This entry process is facilitated by glycosylated spike (S) fusion protein, which is capable of significant structural rearrangement, thus plays an important role in fusing the viral membrane with the host cell membrane [15]. The spike glycoproteins are comprised of two subunits known as S1 and S2, where S2 subunit contains fusion peptide [22]. This fusion process is the key to virus entry into a cell, however, the fusion process is linked with the accessibility of the receptor determined by hinge-like conformational movements of the receptor-binding domain (RBD) of S1. The RBD can transiently hide or expose the determinants of receptor binding [23]. Soon after the entrance of the virus to the host cell, transcription of polyprotein 1a/1ab (pp1a/pp1ab) is initiated by the activity of the replication-transcription complex (RTC) [22]. Binding of S protein to the cellular receptor ACE2 initiates the life cycle of SARS-CoV-2 in host cells [22].

Studying the infectiousness mechanism further can help to understand the source of origination and transmission. Knowing the intermediate sources of transmission is important in disease control. A recently report indicated pangolin as the possible intermediate source that might have transferred the virus to humans after receiving it from bat [24]. The main reasons for the high rate of transmission are not well documented however, the higher affinity of RBD for binding to ACE2 receptors is considered to be one of the possibilities for the high rate of infectiousness [17,25]. The RBD amino acids (L455, F486, Q493, S494, N501, and Y505) in SARS-CoV-2 can play a role in the determination of the host range [25]. Further research is required to investigate these RBD amino-acids in a wide range of animal species. Despite the RBD aminoacids, proteases associated with infectiousness such as furin, can also help to determine host range. This determination can further be facilitated by studying the higher genetic variation in spike glycoproteins [3,25]. It has been reported that the mutation found in polybasic cleavage site in SARS-CoV-2 from humans was dissimilar to that in bat and pangolin viruses [25], suggesting its association transmission and infection in humans. These observations indicate the need for further research on understanding the impact of polybasic cleavage on transmissibility and pathogenesis. Without knowing the zoonotic source of transmission, range of animals hosts, and source of origination, it may be impossible to eradicate the virus.

Health consequences COVID-19

COVID-19 disease has caused millions of morbidities and hundred of thousands of mortalities worldwide (Walker, 2020). The clinical manifestations of COVID-19 are characterized by fever, cough, dyspnea, and bilateral infiltrates on chest imaging [26]. After infection, the majority of individuals show moderate symptoms whereas approximately, 20% of the infected patients show severe illness of respiratory failure, septic shock [26], gastrointestinal complications [26,27], myalgias, lymphopenia, and parenchymal lung abnormalities [2]. The severity of symptoms and death causing ability of the virus are highly dependent on underlying diseases such as cancer, hypertension, and cardiopulmonary diseases [3,26]. The infection has been reported to cause high mortalities in older people [28] and individuals with blood group A [29]. Moreover, pregnant women with confirmed COVID-19 pneumonia can face adverse pregnancy and neonatal impacts [30]. The individuals at higher risk of developing severe disease after contracting the infection should be give the priority for treatment and providing

the mangeemtn and health servicesConsidering the importance of COVID-19 in the aspects of the asymptomatic spread of the virus and adverse health impacts, it is deemed necessary to investigate the factors associated with the rate of infectiousness and severity of symptoms.

COVID-19 infection and mental illnesses

COVID-19 outbreak is affecting physical health as well as mental health, however, the primary attention is given to physical health [9]. Fear of being infected due to close contact with infected patients, prolonged working schedules without proper rest, and disturbed wake and sleep routines have increased the risk of stress and anxiety in the healthcare workers [9]. The consequences can be alarming as mental illnesses have been reported to alter immunity, thus increasing the vulnerability to diseases [31]. It might be one of the risk factors for higher COVID-19 mediated morbidity among medical staff and clinical workers. Although, the risk communication team of WHO has already launched an information platform (WHO Information Network for Epidemics) [32], a large population has no access to this information. Therefore, a large number of people rely on electronic and social media, in an attempt to win the race, share forged news also termed as infodemia, thereby, increasing the risk of stress, fear, and anxiety [32,33].

Normal daily routines are inevitable to maintain normal rhythms, however, due to the current restrictions to outdoor activities, millions of people rely on indoor activities. These individuals may experience disturbance in eating routines, exposure to irregular light-dark cycles and disturbed sleep-wake behaviors which may dysregulate circadian rhythms and mood [34]. While, mistimed exposure to light and disrupted sleep perturb the circadian rhythm that may lead to mental illnesses including stress and anxiety [35,36]. Notably, children have no or limited exposure to the open environment and playgrounds, indicating that they may have more access to electronic devices or smartphones. These situations can lead to severe mental illnesses in the future [37,38].. Nonetheless, the researchers should conduct psychological investigations and identify the mental health concerns if any, not only in children but also in women, elder individuals, and healthcare workers, so that timely treatment and psychological assistance are provided

Potential therapeutic and vaccines options available against the COVID-19 infection

Currently, no promising treatment options are available against the COVID-19. However, to contain the COVID-19, several therapeutic strategies have been evaluated. Among the trialed antiviral drugs, remdesivir alone or in combination with chloroquine or interferon beta showed effectiveness against the COVID-19 infection [39]. Chloroquine efficacy against the COVID-19 may be linked with its ability to prevent binding and cellular entry of the SARS-CoV-2 through interfering with ACE2. While remdesivir inhibits the action of viral RNA polymerase to prevent viral replication [40]. Currently, clinical clinical trials are underway in different regions of the world, while China based preliminary data has demonstrated benefits of chloroquine in patients with pneumonia, as the drug significantly eliminatied the virus and improved recovery from COVID-19 disease [41]. Thus, it was included in the Guidelines for the Prevention, Diagnosis, and Treatment of COVID-19 disease, Chinese National Health Commission [41,42]. However, chloroquine is also known to have toxicity and side effects to central nervious system [42]. On the other hand, a multi-center trial of remdesivir showed serious side effects in 12 out of the 53 COVID-19 patients, although 36 of them were reported clinically recovered [43]. Therfore, both remdesivir and chloroquine should further be evaluated for their suitability against COVID-19. Baricitinib an approved drug for the treatment of rheumatoid arthritis has been considered as the potential candidate to treat COVID-19. This drug inhibits the endocytosis regulating enzymes (AP2-associated protein kinase 1) [44], thus, can inhibit endocytosis of SARS-CoV-2 into the cell. Thus, it could be another potential candidate to treat COVID-19 [42], however, wide range of clinical trials are necessary to evaluate its effectiveness Furthermore, ritonavir and lopinavir are promising protease inhibitors, which have been included in the list of anti-COVID-19 drugs. Although, earlier treatment of COVID-19 patients with ritonavir and lopinavir in Wuhan, China, did not indicate sufficient benefits of these drugs [45], however, their combination may successfully inhibit both protease cytochrome P4503A4 which can reduce metabolism and inhibit viral replication [46]. Therefore, further clincal trials with combination of these drugs are required to evaluate their effectiveness. Recently another antiviral drug known as favipiravir designed for influenza that inhibits RNA-dependent RNA polymerase, was found effective against the COVID-19. However, further studies are required to find its broad term efficacy and associated side effects [47].

Moreover, some antiviral drugs in combination with traditional Chinese medicines are currently being evaluated in COVID-19 patients. It is thought that lower mortality and higher recovery rate from COVID-19 disease in China may be linked to the treatment with tradiations Chinese medicines in combined with Western medicines, as approximately 85% patients in China received these combinations [42,48]. However, we did not find convincing evidence to conclude that traditional Chinese medicines are siginifanclty effective, thereore, further investigations are required to determine their effects against COVID-19 disease. Despite the afore-mentioned therapeutic options, further studies are necessary to develop promising therapeutic strategies against COVID-19 infection. The serious concern with coronaviruses is the ability to suppress counteracting response from the host innate interferons [6], thus, utilizing interferon inducers or recombinant interferons may help to treat COVID-19 pneumonia. Surface structural spike protein (S) and ACE2 play a critical role in the process of pathogenicity through facilitating SARS-CoV-2 entry into the host cells [6,16]. Targeting these regions through monoclonal antibodies or fusion inhibitors [6] may be effective therapeutic options against coronaviruses. Therefore, antiviral peptides such as HP2P-M2 that target S protein [6] should be evaluated against the SARS-CoV-2.

Effective vaccines are important to prevent and control sporadic epidemics of emerging viruses. Although SARS-CoV was fully controlled during 2003, and MERS-CoV spreads poorly, yet the SARS-CoV-2 is spreading efficiently, thus the availability of vaccine is necessary to control further spread of the disease. Viral vectors, recombinant protein, viral-like particles, rhesusθ-defensin-1, and protein cage-nanoparticles are generally effective in prevention against coronaviruses [6], therefore such vaccination strategies can be developed for individuals at high risk of COVID-19 infection, to control the ongoing pandemics [49]. Interestingly, some vaccines are in pipelines such as mRNA based vaccine developed by the National Institute of Allergy and Infectious Diseases in the USA, which is currently in phase 1 clinical trial. INO-4800, a DNA based vaccine has already been developed by the Inovio pharmaceuticals and put under clinical trials in the United States (Inovio pharmaceuticals 2020) [42]. Recently, the Centre for Disease Control and Prevention (CDC) in China and Stermirna Therapeutics have announced the designing of an inactivated virus vaccine and mRNA based vaccines, respectively [42].

Conclusion and perspective

COVID-19 disesae has created an alarming situation worldwide and therefore, it requires serious attention from healthcare author-

ities and research communities in the aspects of transmission, treatment and prevention. After originating in bats, SARS-CoV-2 emerged in Wuhan, spread all over the world through human to human transmission, and infected millions of individuals. Currently, each pasing day, the virus is causing deaths in thousands of COVID-19 infected individuals across the globe. Although, the virus mainly affects lungs to cause severe to moderate pneumonia, it may adversely impact mental health to develop stress, anxiety and depression. To control the spread of COVID-19 infection, there is a need for developing therapeutic options, vaccines and proper management of daily activities and human to human interactions. Given the importance of the COVID-19 pandemic, further studies are necessary to understand replication, pathogenesis, and biological properties in order to control COVID-19 disease and prevent novel emerging diseases in future. The research work should focus on identifying or designing therapeutic agents and developing effective vaccines. Testing the drugs for coronaviruses requires suitable animal models prior to their use in humans. However, the currently established models for SARS and MERS are not promising except few small animals such as transgenic mice expressing human ACE2 and mouse-adapted SARS-CoV strains [6]. Therefore, more animal models from mouse to non-human primates are needed to be developed. Neverthelesss, healthcareworkers and medical professionals should focus on helping the public to cope with the mental health concerns. They should further educate the people to understand the spread mechanisms, infection consequences and required management to control the spread.

Declaration

The authors of this manuscript declare that there is no conflict of interest

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