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Advances in SARS-CoV-2: a systematic review

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Abstract. – OBJECTIVE: In December 2019, Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection broke out in Wuhan, China. However, we still lack a comprehensive understanding of this emerging virus. In this manuscript, we collected relevant articles and reviewed the characteristics about SARS-CoV-2.

MATERIALS AND METHODS: We performed an online search on PubMed and Web of Science with the keywords COVID-19, 2019-nCoV and SARS-CoV-2, and summarized the epidemiology, virology, clinical features and treatments of SARS-CoV-2 infection.

RESULTS: We retrieved 157 published papers about SARS-CoV-2 from January, 2020 to April, 2020. We found that SARS-CoV-2 was a kind of virus with low mortality rate and high infectivity. This virus can enter human cells through angiotensin-converting enzyme 2 (ACE2) in alveoli and activate immune response in human body. SARS-CoV-2 infection can be classified as asymptomatic, mild, common, severe, and critical. We summarized antiviral drugs against SARS-CoV-2, such as remdesivir, hydroxychloroquine and favipiravir. Because the vaccine of SARS-CoV-2 is developing, more clinical studies are needed to verify the safety and efficacy of these treatments.

CONCLUSIONS: SARS-CoV-2 is a novel coronavirus that has caused a global pandemic. We should pay more attention to prevent SARS-CoV-2 and try to control it sooner.

Key Words:
SARS-CoV-2, 2019-nCoV, COVID-19, Global health, Novel coronavirus, Treatments.

Introduction

In December 2019, a new type of pneumonia caused by a new coronavirus broke out in Wuhan, China. The World Health Organization (WHO) named this new virus as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)[1,2], by which Coronavirus Disease 2019 (COVID-19) had been caused. Until now, this disease has caused a global pandemic, infecting more than 2,354,000 people worldwide. Although the mortality of SARS-CoV-2 is lower than that of other Coronaviruses, such as SARS-CoV and MERS-CoV, while the high transmissibility of SARS-CoV-2 remains a significant challenge for global health security. There have been many reports about various aspects of SARS-CoV-2 published online, but we still lack a comprehensive understanding of SARS-CoV-2 and COVID-19. Therefore, we performed an online search on PubMed and Web of Science with the keywords COVID-19, 2019-nCoV and SARS-CoV-2, then, we summarized and reviewed the epidemiology, virology, clinical features and treatment strategies of SARS-CoV-2 infection[3].

Epidemiology

According to current studies[2,3], SARS-CoV-2 was first identified in China. It causes a disease called Coronavirus 2019 (COVID-19) which has resulted in severe illness and death in China and has spread to several other countries. The association of initially confirmed SARS-CoV-2 cases with Huanan Seafood market suggested that the marketplace has played a role in the early spreading[3,4], however, whether it is the origin of the outbreak and what is the native host(s) of SARS-CoV-2 remain uncertain. In fact, the firstly documented patient was not linked to Huanan Seafood market[4].

The main route of transmission is respiratory droplets and close contact with the infected patient[5,6]. Remarkably, asymptomatic infections can also be contagious[5]. Meanwhile, exposure of aerosol in a relatively closed environment for a long time has also been regarded as one transmission way. At present, it has been suggested that

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virus strains can be isolated from the urine, feces, and tears of patients with COVID-19, but no cases of urine, fecal, or tear infection have been reported[7]. The population is generally susceptible to SARS-CoV-2 infection[8]. It has been reported that the basic reproduction number, which is also called R0, could clearly describe the infectivity of this infectious disease[9]. A previous epidemiological study analyzed nearly 9,000 cases uploaded to medRxiv and calculated that R0 of SARS-CoV-2 was approximately 3.77. As China actively applied a series of effective preventive measures such as blockade of cities and the quarantine of populations, the R0 of SARS-CoV-2 had declined[2,10,11].

To date, a total of 2,354,474 cases have been confirmed worldwide. Currently, most patients are reported to be between 30 and 79 years old (87%, 38,680), with a median age of 47 years[12]. 58.1% of COVID-19 patients were male. Most of these patients were classified as mild cases (81%, 36,160 cases), while 14% of these patients were classified as severe cases. The mortality of SARS-CoV-2 was 2.3%. According to a study based on 1,099 confirmed cases, 1.9% of patients had a history of wildlife exposure. In China, 43.9% of the patients were diagnosed in Wuhan, and 72.3% of the other patients had gone to Wuhan or had contacted with Wuhan residents. A total of 23.7% had more than one underlying disease, including hypertension, diabetes, cerebrovascular disease, cancer, etc. The median incubation period was 4 days (interquartile range, 2 to 7). Until now, 3.5% of infectious patients were medical staff[12]. More than 3,400 medical staffs were infected with SARS-CoV-2. More than 90% of the infectious medical staffs came from Hubei Province. According to current reports[12], 15 medical staffs died from SARS-CoV-2 infection.

Virology and Pathogenesis

The coronavirus, which has been named due to the coronal coating, is a single-stranded positive-sense RNA virus. Coronaviruses are divided into four genus, *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*, according to their genomic characteristics. Usually, *Alphacoronavirus* and *Betacoronavirus* can infect mammals and humans[13,14]. In contrast, *Gammacoronavirus* and *Deltacoronavirus* infect birds and fish, but some can also infect mammals. Among them, HCoV-229E, HCoV-OC43, HCoV-NL63, and HKU1 generally cause mild upper respiratory disease[15]. SARS-CoV, MERS-CoV and SARS-CoV-2 may infect the lower respiratory tract and cause severe respiratory syndrome in humans[16,17]. Although SARS-CoV-2, SARS-CoV and MERS-CoV are all members of *Betacoronavirus*, the homology between SARS-CoV-2 and the other two viruses is approximately 80%, which suggests that the genetic distance of these three viruses is far[2]. Previous studies[3,8] suggested that SARS-CoV-2 found in Wuhan was a recently emerged recombinant virus, possibly from natural recombination.

SARS-CoV-2 has an envelope. Its particles are round, elliptic, or pleomorphic. Its diameter is 60-140 nm. The SARS-CoV-2 is sensitive to ultraviolet light and heat, and can be inactivated at 56°C for 30 minutes[18]. Lipid solvents, such as ethanoic acid, 75% ethanol, chlorine-containing disinfectant, peroxyacetic acid, and chloroform can effectively kill the virus. But chlorhexidine cannot effectively inactivate the virus[19,20].

The spike protein of coronavirus is a critical protein that determines the host tropism and transmission capacity. It is functionally divided into S1 domains, which are responsible for receptor binding and S2 domains, which are responsible for cell membrane fusion. A phylogenetic analysis of the receptor-binding domain in different lineaments of four Coronavirus species showed that although SARS-CoV-2 was closer to bat-SL-CoVZC45 and bat-SL-CoVZXC21 at the whole-genome level, the receptor-binding domain of SARS-CoV-2 was within lineage B and closer to that of SARS-CoV[2,21]. SARS-CoV-2 may also use angiotensin-converting enzyme 2 (ACE2) as a cell receptor, and several key residues are responsible for this receptor-ligand binding[2]. ACE2 is widely distributed in lung, kidney, heart, liver, and other organs of humans. A previous study reported that SARS-CoV-2 only invaded human lungs and no virus was found in the liver and heart from the evidence of an autopsy. The histopathological examination of the lung, liver and heart in this patient indicated that the lung showed typical ARDS-like changes, mainly lymphocyte infiltration. Moreover, the liver tissue of this patient presented moderate microvascular steatosis. No significant histological changes were observed in the heart[19].

Clinical Features

According to clinical manifestations and imaging characteristics, patients can be divided into five types: asymptomatic, mild, common, severe, and critical. Some retrospective studies[22,23] ana-

lyzed the clinical features of 99 COVID-19 patients and showed that more than 80% of patients had fever, more than 80% had cough, more than 30% had shortness of breath, and 10% had muscle aches, as well as headache, sore throat, diarrhea, and nausea. Notably, 56.2% of patients were reported to be admitted without fever[24]. Nearly 60% were asymptomatic or mild in the population of positive nucleic acid, which makes it more difficult to prevent and control this epidemic[25].

Examination

RT-PCR

Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) was used to detect the nucleic acids of viruses. The diagnosis can be made by the positive examination of viral nucleic acids from the samples of the patient's blood, throat swabs, alveolar lavage and sputum[26]. Diagnosed patients can be discharged by two consecutively negative RT-PCR test results separated by at least 24 hours. However, this examination also needs to be improved due to its false-positive or -negative.

Chest CT Scan

Although the use of RT-PCR for viral nucleic acid testing is still definitive, a chest CT scan is useful for early diagnosis of COVID-19 and monitoring for disease changes. The most common chest CT findings were ground-glass opacities (56.4%) and patchy bilateral shadowing (51.8%). According to a report, 157 (17.9%) of the 877 patients with nonserious diseases had no imaging abnormalities. Of the 173 cases of severe disease, 5 (2.9%) had no imaging abnormalities[27,28]. Other symptoms included consolidation, linear opacities, crazy-paving pattern, and bronchial wall thickening. Compared with mild patients, severe patients have more significant chest CT changes.

Laboratory Tests

In recent reports, 83.2% of COVID-19 patients had lymphocytopenia, 36.2% had thrombocytopenia, and 33.7% had leukopenia. C-reactive protein (CRP) levels were found to be elevated in most patients. Elevated levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase, creatine, and d-dimer have also been reported. Meanwhile, severe patients had significantly higher d-dimer (2-fold), CRP (1.7-fold), and calcitonin (2-fold) values than mild patients[29]. Sometimes, serum procalcitonin level might not change greatly in initial phase of this disease, but it could increase gradually as the disease progressed implicating a potential to serve as a predictor of poor prognosis[30]. Plasma levels of inflammatory cytokines interleukin (IL)-2, IL-6, IL-7, IL-10, granulocyte colony-stimulating factor, interferon-alpha, monocyte chemoattractant protein 1, macrophage inflammatory protein 1A and TNF in patients with severe COVID-19 were reported higher than those in mild cases. The levels of CD4+ T cells, CD8+ T cells, and natural killer cells in severe patients were lower than those in mild patients, suggesting that severe patients may have significant immunosuppression.

Treatment

General Treatment

General treatment includes nutritional support, the maintenance of internal stability, and timely administration of effective oxygen therapy. According to a systematic review, vitamins A, B, C, D, and E, omega-3, selenium, zinc, and iron are all likely to be helpful for COVID-19 patients. It is also essential that patients keep adequate caloric intake and maintain water and electrolyte balance. Oxygen therapy is very vital for patients with COVID-19, including a nasal catheter, mask, and transnasal high-flow oxygen therapy. Especially for severe patients, oxygen therapy should be administered promptly, as well as an assessment of respiratory distress and hypoxemia for remission. If the condition does not improve or even worsens within a short time (1-2 hours), tracheal intubation and invasive mechanical ventilation should be performed on time.

Antiviral Therapy

Interferons

Zhang and Liu[31] have shown that interferon (IFN)-α, a type I IFN, can inhibit the replication of coronavirus. According to China's seventh edition guidelines[31] for the diagnosis and treatment of novel coronavirus pneumonia, IFN-α atomization can be clinically used to treat COVID-19.

Remdesivir

Remdesivir is a kind of adenosine analog that can incorporate into nascent viral RNA chains, which results in premature termination. Remdesivir is currently being used for the clinical treatment of Ebola virus infection and has recently been recognized as an agent targeting various RNA viruses (including SARS/MERS-CoV) in the cultured cell,

mouse and nonhuman primate (NHP) models[32]. Previously, the United States reported that the first case of SARS-CoV-2 infection chieved excellent results with remdesivir[23]. At present, five clinical trials about the treatment of SARS-CoV-2 using remdesivir have been registered online. According to a recent study[33], after compassionate-use of remdesivir, 68% of patients experienced improvement in oxygen-support class (36/53), and 47% of them were discharged. Until now, many clinical trials are still underway, and further results are needed to verify its efficacy and safety.

Chloroquine and hydroxychloroquine

Chloroquine (CQ) is a widely used drug against malaria and autoimmune diseases and has recently been reported as a potential broad-spectrum antiviral drug. As reported, SARS-CoV-2 used ACE2 as a single receptor[31,34]. Inhibiting the interaction between spike protein and ACE2 is of great significance for anti-coronavirus therapy. CQ is thought to play an antiviral role by blocking the binding of the spike protein of coronavirus to ACE2[32]. In addition to its antiviral activity, CQ also has immunomodulatory activity, which can synergistically enhance the antiviral effect *in vivo*. CQ has been used in clinical practice for more than 70 years, with high safety and low cost. Hydroxychloroquine sulfate (HCQ) is a derivative of CQ. In animal experiments, HCQ is believed to have similar antiviral effects to CQ and has been shown less toxicity than CQ. Currently, seven clinical trials have been registered using HCQ to control SARS-CoV-2 infection in the Chinese clinical trial registry website (http://www.chictr.org.cn). Further results are warranted to explain the safety and efficacy of HCQ and CQ[35].

Lopinavir (LPV)/ritonavir (RTV)

The combination of LPV/RTV is widely used in the treatment of AIDS as a boosted protease inhibitor[31]. Previous reports[31,36] have shown that the combination of LPV/RTV with IFN can improve the prognosis of patients with SARS-CoV and MERS-CoV. However, a recent open-label clinical trial[37] showed that LPV/RTV did not benefit severe patients with SARS-CoV-2 infection. We need more clinical trials to confirm the therapeutic effect of LTV/RTV or triple therapy on SARS-CoV-2 infections.

Ribavirin

Ribavirin is a broad-spectrum antiviral drug commonly used to treat hepatitis. Some investigations[31,38] have shown that ribavirin has limited clinical anti-SARS-CoV activity, but ribavirin and IFNs have a high degree of synergy. The combination of ribavirin and IFN not only can be used as a preventive agent but also can effectively treat patients with SARS-CoV infection[31]. Therefore, the combination of ribavirin and IFN is also tried in the treatment of patients with SARS-CoV-2 infection[38]. According to China's seventh edition guidelines for the diagnosis and treatment of novel coronavirus pneumonia, ribavirin, LPV/RTV, and type I interferon should be used in combination. It is worth noting that antiviral drugs should not be used in more than three combinations and patients should be closely monitored for their side effects. It is necessary to adjust the antiviral treatment plan in time according to the patient's performance.

Arbidol

Arbidol (ARB) is a small indole-derivative molecule and is the only available antiviral drug that targets hemagglutinin envelope glycoprotein (HA)[39]. Arbidol has been approved in China for the prevention and treatment of influenza and respiratory virus infections. Arbidol is also effective against Ebola virus and Lassa virus. Moreover, it has also been reported to have anti-SARS activity in cell cultures. Therefore, Arbidol is regarded as a promising drug for the treatment of novel coronavirus pneumonia.

Favipiravir

Favipiravir is a novel drug used to treat influenza viruses. It is an RNA-dependent RNA polymerase (RdRp) inhibitor that blocks the replication of several viruses[40,41]. Favipiravir may have a potent antiviral effect on RNA virus SARS-CoV-2. At present, a clinical trial comparing favipiravir with lopinavir/ritonavir for efficacy against SARS-CoV-2 showed that more stronger antiviral effect and better safety were observed in the group receiving favipiravir treatment[40]. Another clinical trial of favipiravir *vs.* arbidol for COVID-19 treatment showed that symptoms like fever and cough in the favipiravir group recovered faster than those in the arbidol group. Therefore, Favipiravir may be considered as a promising drug against SARS-CoV-2, while it still needs more evidence to be verified.

Treatment for Severe and Critical Patients

Glucocorticoids

The use of systemic glucocorticoid therapy in viral pneumonia has been controversial. Some believe that the use of glucocorticoids in viral pneu-

monia may suppress the body's immune function, making it difficult to clear the virus and increasing the risk of secondary infections[42]. Some scholars believe that the use of systemic glucocorticoids can inhibit inflammatory responses, avoid the progression of lung lesions, improve respiratory symptoms and hypoxemia, and reduce lung injury. One study showed that 58% of COVID-19 patients were given systemic glucocorticoid therapy during hospitalization, and patients with more severe conditions received higher dosages of glucocorticoids[12].

Convalescent plasma

Convalescent plasma therapy is a passive immunotherapy strategy. It has been reported that patients infected with SARS-CoV, H1N1 and MERS-CoV were successfully treated with convalescent plasma[43,44]. Convalescent plasma therapy may be effective because neutralizing antibodies from convalescent plasma might inhibit viremia. Currently, since there is no specific vaccine or drug for SARS-CoV-2, WHO recommends using convalescent plasma to treat COVID-19 patients who are progressing rapidly, or severely or critically ill. At present, convalescent plasma has been used to treat COVID-19 patients in China and the safety and efficacy need to be further verified[45,46].

ECMO

Extracorporeal membrane oxygenation (ECMO) is a first-aid device that can temporarily replace the cardiopulmonary function of the patient, reduce the patient's cardiopulmonary burden, and earn more treatment time for medical staff. ECMO is often used for respiratory failure and cardiac arrest[47]. Previous studies[47,48] have shown that the transfer of critically ill H1N1 patients to centers with ECMO support conditions can reduce mortality by 50%. In this Novel Coronavirus pneumonia epidemic, ECMO can indeed play an essential role in saving the lives of patients when traditional ventilators are powerless[48].

Other Treatments

Immunotherapy

Tocilizumab, as an antagonist of IL-6, has been used in the treatment of active rheumatoid arthritis and has achieved beneficial outcomes. Tocilizumab can be used to treat SARS-CoV-2 infected patients with extensive bilateral lung lesions or severely ill patients with elevated plasma IL-6 levels. Xu et al[49] uploaded on ChinaXiv showed that after an average of 13.5 days of treatment with tocilizumab, 19 cases of COVID-19 patients were discharged from the hospital, demonstrating the therapeutic potential of tocilizumab. The efficacy and safety of tocilizumab for COVID-19 treatment need to be further confirmed by more clinical trials.

Blood Purification Treatment

Blood purification treatment includes plasma exchange, adsorption, perfusion, hemofiltration, plasma filtration, etc., which can remove inflammatory factors and block the "cytokine storm" to reduce the damage of inflammatory reactions to the body. Blood purification can be used for the treatment of severe and critical patients with cytokine storms in the early and middle stages.

Traditional Chinese Medicine Treatment

Traditional Chinese medicine has been used in the treatment of SARS-CoV-2 in Hubei Province, but further studies are needed to prove its efficacy and safety.

Conclusions

SARS-CoV-2 is a novel coronavirus that has caused a global pandemic. Recently, SARS-CoV-2 has been partially controlled in China but remains a serious threat to public health in other countries. By studying epidemiology, virology, pathogenesis, clinical features and treatments, we have a better understanding of SARS-CoV-2. Currently, there are only some means of broad-spectrum antiviral and symptomatic treatments against SARS-CoV-2 and no specific antiviral treatments are available. Although drugs, such as remdesivir have shown promising results in fighting SARS-CoV-2, more clinical trials are needed to verify the safety and efficacy of these drugs.

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Author Contributions

BYX, XYH, and WX collaborated in data collection, literature review, and writing the manuscript. MKW and SC analyzed the data. GY and QS contributed to the writing of the report. All authors were involved in writing the manuscript. All authors read and approved the final manuscript.

Conflict of Interests

The authors declare no conflict of interest.

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