European Review for Medical and Pharmacological Sciences 2020; 24: 4576-4584

The viral, epidemiologic, clinical characteristics and potential therapy options for COVID-19: a review

C. LI, B.-H. XU

Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Abstract. – Coronavirus Disease-2019 (COVID-19) caused by SARS-CoV-2 infection has rapidly spread all over the world, in just two months. As of 27 March, globally, 509,164 cases confirmed included 23,335 deaths in approximately 150 countries. Recently, WHO has defined COVID-19 as a global pandemic, and considerable researches have focused on the identification and prevention of SARS-CoV-2. As a result, accumulated publications successively reported their early findings, leading to the constant updating of information, which might make confusion for readers. Therefore, this review summarized the current researches about the genomic evolution, variation of SARS-CoV-2, and demonstrated its viral structure for pathogenesis. Meanwhile, we analyzed the epidemiologic and clinical characteristics of COVID-19, in order to provide recommendations for present clinical treatments and inspirations for potential therapy options.

Key Words:
SARS-CoV-2, COVID-19, Genomic structure, Pathogenesis, Epidemiology, Clinical characteristics, Therapy options.

Introduction

Coronaviruses (CoVs) are enveloped positive-sense, single-stranded RNA viruses. It belongs to the family Coronaviridae and the order Nidovirales, including four genera: α-CoVs, β-CoVs, γ-CoVs and δ-CoVs[1]. Six human CoVs have been previously identified, including two highly pathogenic coronaviruses. The severe acute respiratory syndrome coronavirus (SARS-CoV) and The Middle East respiratory syndrome coronavirus (MERS- CoV) caused severe disease in China from 2002 to 2003 and in the Middle East in 2012, respectively[2]. Both were dangerous zoonotic coronaviruses emerged in past two decades. Until now, there has no effectively specific drugs or vaccines for human coronavirus infection.

Recently, a seventh human CoVs were isolated and first reported from the emerging unknown severe viral pneumonia patients with unknown source in Wuhan, China. It was identified as β-CoVs, similar to SARS-CoV and MERS-CoV. Thus, it was officially known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[3]. However, it still has distinct features from the previous findings on SARS-CoV and MERS-CoV about viral structures, epidemiology and clinic pathophysiology[4]. All these novel features caused considerable challenges in the public prevention/control, clinical treatments, and novel effective drugs inventions in this emergent outbreak. Currently, researches have reported evidence in the genomic, epidemiologic and clinical characteristics of SARS-CoV-2; but their statistics were independent, limited and unilateral to some degree, since the urgent demand and isolated data from specific designed hospital. Therefore, this review aims to summarize all the current knowledge on viral features and clinical characteristics, in order to draw a comprehensive understanding of SARS-CoV-2 and provide some informative inspirations for clinical practice and further investigation.

Genomic Evolution and Variation Characteristics

Initially, the genomic structure of SARS-CoV-2 was sequenced shortly after the outbreak, which enabled the immediate development of Real Time-PCR test for rapid diagnosis. In order to further investigate the evolution source

Corresponding Author: Binghe Xu, MD; e-mail: xubinghe@medmail.com.cn

and variation, several researchers conducted in-depth genomic sequence analysis. Preliminary genomic analysis demonstrated that the SARS-CoV-2 belonged to the β-CoV and possessed 14 open reading frames (ORFs) encoding 27 proteins. Particularly, the orf1ab and orf1a genes in the 5'-terminus encode the pp1ab and pp1a proteins respectively, and the 3'-terminus of the genome encodes four structural proteins, including glycoproteins spike(S), envelope(E), membrane(M) and nucleocapsid(N). Importantly, the S protein plays an essential role in binding to receptor on targeted host cells[5]. Then, in order to explore the evolution sources, a depth genomic annotation and comparison among the related coronaviruses was conducted by Wu et al[6]. Their results indicated that SARS-CoV-2 was closer to the SARS-like bat CoVs than to SARS-CoV, and relatively distant to MERS-CoV, both in terms of the whole genome sequences and nucleocapsid genes. Furthermore, ten genome sequences of SARS-CoV-2 obtained from nine patients were detected in Lu et al[7]. They further determined that the SARS-CoV-2 genome sequence was much similar to two bat-derived coronavirus, bat-SL-CoVZC45, and bat-SL-CoVZXC21. Moreover, the subsequent reports illustrated that SARS-CoV-2 shared 96.2% identical genomic sequence to a bat coronavirus, while 80.26% identity to SARS-CoV and 51.8% identity to MERS-CoV[3]. Apparently, the present studies supported the hypothesis that SARS-CoV-2 transmitted from bats after mutation and conferring ability to infect humans[8]. However, whether variations accumulated during the transmission of SARS-CoV-2 is another urgent problem to determine. Actually, there have been several studies analyzed the genomic sequence identity of specimens from patients. Firstly, in Lu et al[7], ten isolated virus sequences from patients exhibited more than 99-98% sequence identity. Secondly, in Ceraolo et al[5], the 56 isolated SARS-CoV-2 genomes shared >99% sequence identity, with only two core positions showing high variability, in ORF1 and ORF8, respectively. Besides, another notable research analyzed the whole coding sequence of essential proteins in 26 viral genomes of SARS-CoV-2. Surprisingly, an isolate from phylogenetic trees exhibited evident variations in the whole genome and the coding sequences of P, N, S proteins. It indicated that there were at least two different SARS-CoV-2 strains involved in this outbreak[9]. Together, these results determined a low variability in SARS-CoV-2 genomic sequence and highlighted that at least two viral strains were involved in this outbreak.

Viral Structures and Pathogenesis

It is well accepted that the S protein of SARS-CoV-2 plays a key role in the entry into human host cells, in which it utilizes human angiotensin-converting enzyme 2 (ACE2) as a receptor. Recently, the structure of this S trimer has been determined, which consists of three receptor-binding domains (RBDs) and forms a receptor-accessible conformation by S1 and S2 subunit. Particularly, the S protein can exist in a relatively stable pre-fusion conformation and undergo a drastic structural rearrangement to facilitate the fusion process[10-12]. Firstly, the S1 subunit binds to the receptor, considered as "up" conformation, a state accessible to the receptor. Then, the S1 undergoes a chain-like conformation, which temporarily hides or exposes the determinants of receptor binding. Next, followed by the shedding of S1, the S2 subunit binds to receptor, with a much more stable "down" conformation[13]. Moreover, the S2 consists of the heptad repeat 1 (HR1) and heptad repeat 2 (HR2), which can interact to form a six-helical bundle (6-HB) to induce the viral and host cellular membranes fusion (Figure 1)[14]. Furthermore, the binding affinity between ACE2 and the ectodomain structure of the S protein determines the human transmission capability. An initial study declared a fast assessment of the binding capability of SARS-CoV-2, demonstrating about 73% affinity of SARS-CoV. However, the latest research demonstrated that the binding affinity between ACE2 and the ectodomain structure of SARS-CoV-2 S protein was 15 nM, which is 10-20 times to the binding affinity of SARS-CoV S protein to ACE2[13]. These convincingly explained why this novel virus showed more extensive human to human transmission than SARS-CoV. Besides, it is well accepted that the ACE2 located in the alveolar epithelial cells is the major pathogenic mechanism. However, ACE2 is widely expressed on a variety of tissues, most of which express much higher level ACE2 than lung. Thus, it is hard to explain why the other organs are rarely attacked. As expected, a subsequent study found that the angiotensin II receptor type 2 (AGTR2) was highly expressed in lung with a high tissue specificity and had a close interaction with ACE2. Moreover, it was illustrated that the AGTR2 even had a higher binding affinity to the S protein in SARS-CoV-2, compared to ACE2,

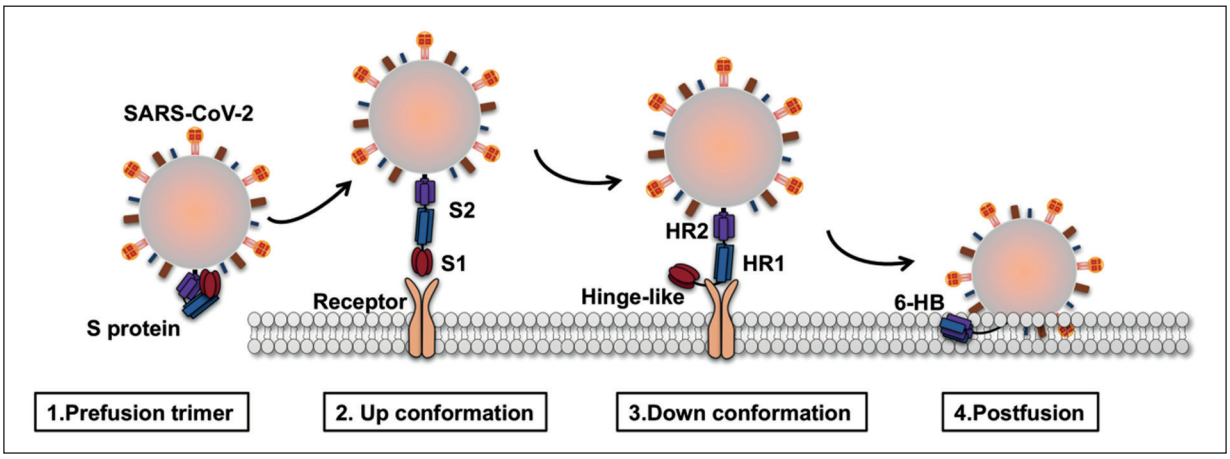

Figure 1. The schematic diagram of SARS-CoV-2 binding to receptor and fusion.

which revealed a novel structure for the entry into human host cells[15]. In conclusion, the S protein plays a key role in the entry into human host cells, indicating that ACE2 and AGTR2 might be potential blocking targets for novel drug invention in SARS-CoV-2.

Original Transmission and Epidemiologic Characteristics

Early on 31 December 2019, the Wuhan Municipal Health Commission announced a cluster of cases with unexplained viral pneumonia. Among the first 41 confirmed cases, approximately 70% were reported to have exposure to Huanan seafood market. They were most reported to be either shop owners, or people who visited the market before getting infected[16]. However, there was no specific animal association confirmed, though primary examinations about the environmental specimens in the wet market revealed SARS-CoV-2 positive[17]. Thus, it was initially assumed that the market was the source of zoonotic infections. Recently, there are controversies about the real possible animal reservoir. The initially speculated snake reservoir was dismissed by some researchers, and the most recent consensus refers to a wide range of animal reservoir, including birds. Actually, the subsequent reports indicated the possible episodes of human-to-human transmission and included two different family's clusters. The family members had no recent visit to Wuhan but confirmed with SARS-CoV-2 infection after contacting with the members back from Wuhan, which provided evidence for human to human transmission of SARS-CoV-2[18]. Moreover, according to recent data, all ages were susceptible, with a median age of 47 years. Meanwhile, in a latest report, including 1099 patients from 552 hospitals in 30 provinces in China, 58% of the patients were men[19]. It indicated that there was a sex predisposition to COVID-19. This sex predisposition might be associated with a higher smoking rate in men. In addition, a single-cell sequencing study found that expression of ACE2 was remarkably elevated in Asian men, which convincingly explained a higher prevalence of COVID-19 infection in this subgroup than in women and other ethnicities[20].

Since the initial cases confirmed, the development of this epidemic follows an exponential growth. The estimated mean incubation period was 5.2 days (95% confidence interval [CI], 4.1 to 7.0), the 95th percentile of the distribution was 12.5 days (95% CI, 9.2 to 18) and the doubling time was 7.4 days (95% CI, 4.2 to 14)[21]. These data provided an important evidence to support a 14-day medical observation period from exposure. In comparison, the incubation period of SARS-CoV-2 is longer than SARS (mean 4.0 days, 95% CI: 3,6-4.4) and MERS (range of incubation times 4.5-5.2 days, mean value 95% CI not reported)[22,23]. In addition, another key parameter, R_0 is reported to be 2.2 (95% CI, 1.4 -3.9), which means, on average, each infected patient has been spreading to 2.2 other people. In comparison, it is slightly higher than the R_0 of SARS (1.7-1.9) and munch higher than MERS (<1), which aggravates the pressure for novel infection diagnose and disease control[21,24]. Meanwhile, Wu et al[25] used a susceptible-exposed-infectious-recovered metapopulation model to estimate the epidemics across all major cities in China. In this research, R_0 was estimated to be 2.68 (95% CI: 2.47-2.86)

and the doubling time was estimated to be 6.4 days (95% CI 5.8-7.1). Besides, they indicated that the Wuhan epidemic would peak around April, 2020, and local epidemics across major cities in China would be followed by 1-2 weeks, if there was no reduction in transmissibility. However, if the transmission could be reduced by 25% through effective measures, the epidemic peak would be delayed by about 1 month and the whole magnitude would be reduced by about 50%[25].

Up until now, based on the WHO reports, the COVID-19 can be considered as a global pandemic. According to the latest statistics, there were 509,164 confirmed cases (23,335 deaths) in around 150 countries globally, including 82,078 cases (3298 deaths) in China (Figure 2, Table I). Apparently, all these epidemiological statistics indicated the elevated difficulty in identifying and isolating cases at an early stage of disease, particularly in the incubation period. Therefore, it is necessary to proactively find cases in outpatient clinics and emergency departments. These not only requires the sensitive laboratory test, but more crucially demands the early detections for suspicious clinical symptoms.

Clinical Characteristics

The most common symptoms since onset of infection were fever (86-97%), cough (59-76%), fatigue (34-68%), and dyspnea (20-40%)[26], while diarrhea, vomiting, hemoptysis, headache, shock, and other symptoms were only occurred in a small part of patients. In addition, the most frequent acute complication was acute respiratory distress syndrome (ARDS) (14.8%), followed by acute renal injury, acute cardiac injury and septic shock, with disease progression. Importantly, a large part of patients had underlying chronic medical conditions, particularly the severe patients in intensive care unit (ICU). The most prevalent comorbidities were hypertension (14-22%), diabetes (6-11%), cardiovascular diseases (4-7%) and respiratory system disease (1-3%)[26]. Generally, data from China have indicated that 18.1% of patients developed severe diseases and the mortality rate was reported to be 4.3%[27].

Notably, hypertension or diabetes patients have three to four-fold increased prevalence to be admitted into ICU and treated with mechanical ventilation. Importantly, these patients are frequently treated with inhibitors of the renin-angiotensin-aldosterone system (RAAS), including angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin II type 1 receptor blockers (ARBs)[28]. However, latest researches indicated that ACE-Is and ARBs could upregulate the expression of ACE2, which was a key receptor for viral cell entry in COVID-19 patients[29]. Thus, there was a hypothesis that the increased expression of ACE2 in hypertension and diabetes patients would lead an increased risk for COVIDs-19 infection[30].

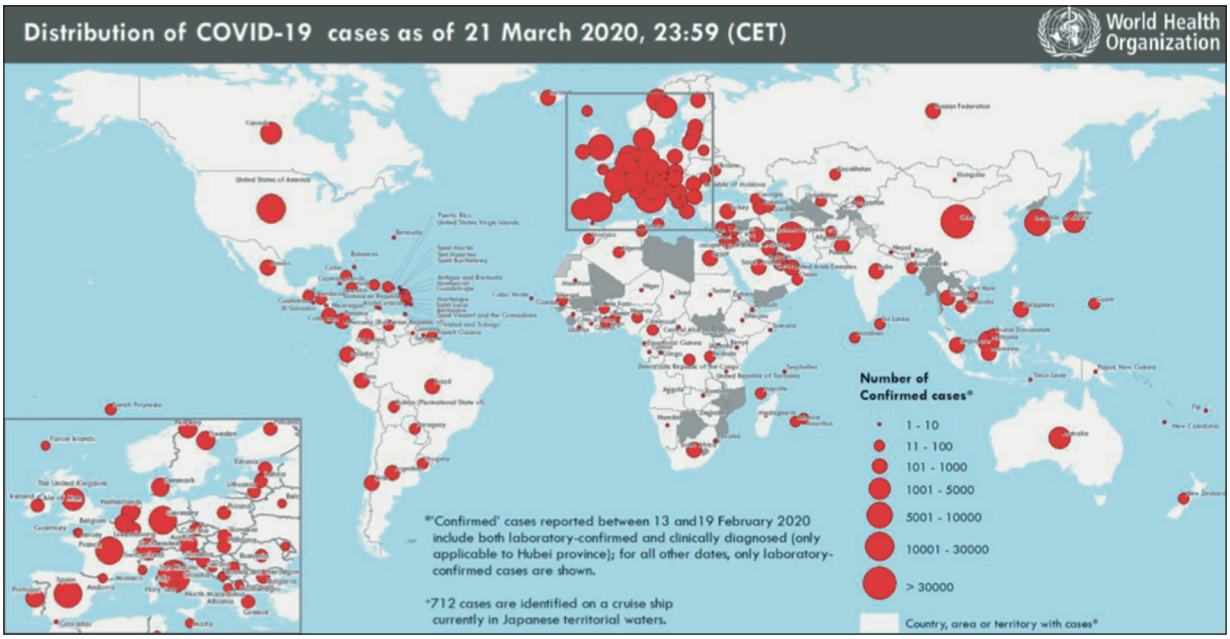

Figure 2. WHO Situation report dated 21 March 2020 (Adapted from WHO).

Table I. Global confirmed COVID-19 cases and deaths (WHO data as of 27 March 2020).

WHO region	Confirmed cases	Total death
China	82,078	3298
Western Pacific region	100,018	3567
European region	286,697	16105
South-East Asia region	2932	105
Eastern Mediterranean region	35,249	2336
Region of Americas	81,137	1176
African region	2419	39
International conveyance (Diamond princess)	712	7

As for the laboratory parameters, the significant findings primarily reflect on the differences between patients admitted to the ICU or not. In general, the ICU patients showed significantly decreased total lymphocytes, prolonged prothrombin time, and elevated lactate dehydrogenase, as well as higher level of D-dimer[31]. Moreover, these blood indexes developed a dynamic change during the illness progression. In most non-survivals, continually increasing neutrophil count, higher and higher D-dimer, blood urea, creatinine levels, and decreasing lymphocyte counts were developed until death[31]. Furthermore, higher concentrations of GCSF, IP10, MCP1, and TNFα existed in more severe patients, suggesting that the cytokine storm was highly associated with disease severity[32]. Therefore, the neutrophilia might be related to cytokine storm induced by virus invasion, and the coagulation activation could be induced by sustained inflammatory response. However, on the contrary, an increased secretion of Th2 cytokines, such as IL-4 and IL-10 that suppress inflammation, was also detected in some infected patients[16]. These indicated that the body immune response intensity might be closely correlated to the prognosis of disease. Together, all these abnormalities suggest that COVID-19 might be associated with immune disfunction and coagulation activation, which could further lead to the multiple organs disfunctions and shock.

Apart from this, the previously reported chest X-ray and CT findings revealed that almost all the patients showed bilateral involvement in chest CT scan. A recent meta-analysis concluded 293 patients from nine different datasets. They illustrated that the bilateral involvement of chest CT was observed in 82% of patients, the rare scan, including lymphadenopathy (4%), pericardial effusion (5%), and pleural effusion (7%)[33]. Apparently, bilateral pneumonia is a typical CT feature for COVID-19. In addition, the result from Song et al[34] research showed that there were more consolidated lesions in the patients with CT interval > 4 days and in the elder patients. It suggested that the consolidation increase could forebode disease progression, which could serve as an alert in the development of COVID-19.

In addition, the early reported patients were mainly elderly peoples, from 40 to 60 years old. However, with the development of this infection, the epidemiological survey has demonstrated that the general population is susceptible. Currently, a total of 63 children, aged from 6 months to 14 years old, have confirmed with COVID-19 in Wuhan and Shenzhen, China. According to the researches, we found that the children patients were mainly caused by family cluster outbreak and imported cases[35]. In addition, the clinical characteristics in children are much more non-specific and milder than those in adults. They mainly manifested as fever, cough, and even no specific symptoms, few in acute complications. Furthermore, the laboratory abnormities were relative rare and milder. Several children patients manifested increased white blood cell counts, elevated C-reactive protein, and lactic dehydrogenase D-Dimers levels[36]. Besides, the chest CT images mostly showed nodular ground glass, which was not typical in COVID-19[37]. All these results emphasized the importance of viral nucleic acid dynamic review in children infection.

Present Clinical Treatments and Potential Therapy Options

Until now, no specific and effective treatment has been recommended for COVID-19. Actually, several options can be investigated to control the infections of SARS-CoV-2, including vaccines, monoclonal antibodies, interferon, and small-molecule targeted drugs[38]. However, these new interventions require a long time for inves-

tigation and clinical trial. Therefore, the current clinical treatments are essentially supportive and symptomatic. According to the "Guidelines for the Diagnosis and Treatment of Novel Coronavirus (SARS-CoV-2) Infection by the National Health Commission (Trial Version 5)", as for antiviral therapy, chloroquine phosphate (500 mg for adults, twice daily) and Abidol (200 mg for adults, three times daily) were included, and ribavirin was recommended in combination with interferon or lopinavir/ritonavir[39]. In addition, another commonly used therapy was oxygen therapy, including general oxygen therapy, high-flow oxygen, invasive mechanical ventilation, and noninvasive ventilation. As for glucocorticoid therapy, an immunosuppressant, it was not recommended in the early treatment, since the important role of immune system in resisting the virus in the early infection. However, for severe and critically ill patients, the virus may trigger a storm of inflammatory factors. In order to suppress cytokine storm complications, such as ARDS, acute heart injuries, acute kidney injuries, a lower dose of glucocorticoid for short-term treatment may be considered as appropriate. In addition, the Continuous Renal Replacement Therapy (CRRT) and Extracorporeal Membrane Oxygenation (ECMO) were effective in severe patients with multiple organs disfunction, but resources constraints limited their applications in clinical practice.

Importantly, since hypertension was the most prevalent comorbidity in COVID-19 patients, it was essential to consider a suitable therapeutic regimen adjustment for them. Recently, as the reported upregulation of ACE2 induced by inhibitors of the renin-angiotensin system, whether ACE-Is and ARBs should be withdrawn in COVID-19 patients was a controversial notion. Actually, there is no data showing a causal relationship between the ACE2 activity and COVID-19 mortality[28]. However, many studies demonstrated the prognostically beneficial and mortality reduction from ACE-Is and ARBs in hypertension and diabetes patients heart failure therapy[40,41]. Moreover, according to the data from the China PEACE Million Persons Project, fewer than one third hypertension patients received standardized treatment, and less than 10% achieved blood pressure control[42]. These indicated that the underlying factors, such as older ages, more frequently hypertensive and diabetic, might be the real risks for infection and poor prognosis. Furthermore, Kuba et al[43] reported a protective role of ARBs in SARS-CoV associated lung injury. Therefore, based on the recent available data, it is not advisable to withdraw the ACE-Is and ARBs in the treatment of COVID-19 patients. On the contrary, it should be maintained in patients with hypertension or heart failure, in order to avoid the cardiovascular mortality in severe COVID-19 patients. In addition, non-steroidal anti-inflammatory drugs (NSAIDs) are used for temporary symptom relief in COVID-19, such as headache. However, NSAIDs was shown to increase blood pressure levels and increase the risk of serious complications such as cardiovascular disease and kidney injury[44,45]. However, whether it leads to COVID-19 disease deteriorations needs to be further investigated. According to the recent researches, we recommend that blood pressure should be monitored even with short-term NSAIDs therapy in COVID-19 patients with hypertension. Furthermore, as for patients with treatment-resistant hypertension or high cardiovascular risk, we recommend that NSAIDs should be avoided if possible[46].

Actually, given the rapidly increasing number of COVID-19 patients, it is urgent to investigate specific agents to target the viral structure and effectively inhibit the viral pathogenicity of SARS-CoV-2. Except the interferon and small molecular agents, the neutralizing antibody is another potential effective blocking drug against the specific functional structure. This kind of neutralizing antibody could specifically block the virus' attacking and entering targeted cells. Since the S protein plays a key role in binding to receptors on the host cells, such as ACE2, which is the same in SARS-CoV. We hypothesized that the previously approved SARS-CoV RBDs-specific monoclonal antibodies could have cross-reactivity in SARS-CoV-2. However, a recent study has tested the published SARS-CoV RBDs-specific antibodies, and demonstrated that there was limited antibody cross-reactivity between these two virus[13]. This emphasized the necessity to develop novel monoclonal antibodies specifically binding to SARS-CoV-2 RBD. Intriguingly, a SARS-CoV specific human monoclonal antibody, CR3022, which is independent to the ACE2 binding site, has been reported to bind potently with SARS-CoV-2 RBDs. It suggests that CR3022 may be a potential therapeutics, both alone or combined with other neutralizing antibodies[47]. In addition, the inhibitory designed peptides for SARS-CoV-2 HR1 and HR2 were also proved to be promising targets for inhibiting the virus fusion and entry[14].

However, these novel monoclonal antibodies and targeted drugs demand a long time to design and investigate, which emphasized the necessary and urgent need to repurpose the existed antivirus agents for SARS-CoV-2. Surprisingly, a recent study has collected and analyzed the potential existing antiviral agents for SARS-CoV-2 infection[48]. Firstly, the commercially approved nucleoside analogues, including favipiravir and ribavirin could target the RNA-dependent RNA polymerase and block viral RNA synthesis in SARS-CoV-2[49]. Next, the protease inhibitors, including disulfiram, lopinavir, and ritonavir, have been approved to inhibit the papain-like protease of in MERS and SARS. These might also be effective in inhibiting the papain-like proteases of SARS-CoV-2[50]. More importantly, the innate antiviral responses in patients are absolute vital to eliminate the virus. Thus, the host-targeted immune modulator agents, such as pegylated interferon, and chloroquine, have been reported to show inhibitory effects for SARS-CoV-2, and are being investigated in clinical trials[48,51]. In conclusion, the suddenly outbreak and rapid spread of this infection has emphasized the urgent need to repurpose approved antivirus agents and develop broad-spectrum antiviral agents.

Conclusions

Two or more different viral strains of SARS-CoV-2 were involved in this outbreak, the real evolution origin of this novel virus still remains to be disclosed. From the recent epidemiologic statistics, efforts should be focused on the identification and isolation of suspicious cases, which is the major challenge for epidemic control. Also, the limited medical resources are far from being sufficient for the rapidly increasing number of patients. Therefore, efficient and optional emergent measures to reduce transmission are urgent for the communities. Given that there is no specific treatment recommended for COVID-19 infection, except for meticulous supportive care, it is urgent to investigate novel potential targeted drugs. Based on the specific viral structure and pathogenic mechanism, ACE2 and AGTR2 might be the promising targeted blocking sites for further investigation. Especially, the S protein structures and the S1, S2 induced fusion mechanism were determined. In addition, based on the antivirus experiences from SARS and MERS, this review points out the potential repurpose therapy options, including virus targeted agents, protease inhibitors, and host immune modulate agents. However, the most appropriate and efficacious action currently is to control the source of infection, improve personal protection precaution, reduce the potential risk of transmission, and provide adequate supportive treatments for infected patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Cui J, Li F, Shi Z. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019; 34: 181-192.
2) Ashour HM, Elkhatib WF, Rahman MM, Elshabrawy HA. Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks. Pathogens 2020; 9: 186.
3) Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, Jiang YZ, Xiong Y, Li YJ, Li XW, Li H, Fan GH, Gu XY, Xiao Y, Gao H, Xu JY, Yang F, Wang XM, Wu C, Chen L, Liu YW, Liu B, Yang J, Wang XR, Dong J, Li L, Huang CL, Zhao JP, Hu Y, Cheng ZS, Liu LL, Qian ZH, Qin C, Jin Q, Cao B, Wang JW. Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl) 2020. Doi: 10.1097/CM9.0000000000000722. [Epub ahead of print].
4) Chen J. Pathogenicity and transmissibility of 2019-nCoV-A quick overview and comparison with other emerging viruses. Microbes Infect 2020; 22: 69-71.
5) Ceraolo C, Giorgi FM. Genomic variance of the 2019-nCoV coronavirus. J Med Virol 2020; 92: 522-528.
6) Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, Meng J, Zhu Z, Zhang Z, Wang J, Sheng J, Quan L, Xia Z, Tan W, Cheng G, Jiang T. Genome composition and divergence of the Novel Coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020; 27: 325-328.
7) Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 22-28.
8) Benvenuto D, Giovanetti M, Ciccozzi A, Spoto S, Angeletti S, Ciccozzi M. The 2019-new coronavirus epidemic: evidence for virus evolution. J Med Virol 2020; 92: 455-459.

9) Xiong C, Jiang L, Chen Y, Jiang Q. Evolution and variation of 2019-novel coronavirus. bioRxiv 2020. Doi: 10.1101/2020.01.30.926477.

10) Pallesen J, Wang N, Corbett KS, Wrapp D, Kirchdoerfer RN, Turner HL, Cottrell CA, Becker MM, Wang L, Shi W, Kong WP, Andres EL, Kettenbach AN, Denison M R, Chappell JD, Graham BS, Ward AB, McLellan JS. Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. Proc Natl Acad Sci U S A 2017; 114: E7348-E7357.

11) Walls AC, Tortorici MA, Snijder J, Xiong X, Bosch BJ, Rey FA, Veesler D. Tectonic conformational changes of a coronavirus spike glycoprotein promote membrane fusion. Proc Natl Acad Sci U S A 2017; 114: 11157-11162.

12) Gui M, Song W, Zhou H, Xu J, Chen S, Xiang Y, Wang X. Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding. Cell Res 2016; 27: 119-129.

13) Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, Graham BS, McLellan JS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020; 367: 1260-1263.

14) Xia S, Zhu Y, Liu M, Lan Q, Xu W, Wu Y, Ying T, Liu S, Shi Z, Jiang S, Lu L. Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. Cell Mol Immunol 2020. Doi: 10.1038/s41423-020-0374-2. [Epub ahead of print].

15) Cui Q, Cui C, Huang C, Zhou W, Ji X, Zhang F, Wang L, Zhou Y. AGTR2, one possible novel key gene for the entry of 2019-nCoV into human cells. Preprints 2020; Doi: 10.20944/preprints202002.0194.v1.

16) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.

17) Kannan S, Shaik Syed Ali P, Sheeza A, Hemalatha K. COVID-19 (Novel Coronavirus 2019) - recent trends. Eur Rev Med Pharmacol Sci 2020; 24: 2006-2011.

18) Chan JF, Yuan S, Kok KH, To KK, Chu H, Yang J, Xing F, Liu J, Yip CC, Poon RW, Tsoi HW, Lo SK, Chan KH, Poon VK, Chan WM, Ip JD, Cai JP, Cheng VC, Chen H, Hui CK, Yuen KY. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020; 395: 514-523.

19) Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, Liu L, Shan H, Lei CL, Hui DSC, Du B, Li LJ, Zeng G, Yuen KY, Chen RC, Tang CL, Wang T, Chen PY, Xiang J, Li SY, Wang JL, Liang ZJ, Peng YX, Wei L, Liu Y, Hu YH, Peng P, Wang JM, Liu JY, Chen Z, Li G, Zheng ZJ, Qiu SQ, Luo J, Ye CJ, Zhu SY, Zhong NS; China Medical Treatment Expert Group for C. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020. Doi: 10.1056/NEJMoa2002032. [Epub ahead of print].

20) Cai H. Sex difference and smoking predisposition in patients with COVID-19. Lancet Respir Med 2020. Doi: 10.1016/s2213-2600(20)30117-x. [Epub ahead of print].

21) Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, Ren R, Leung KSM, Lau EHY, Wong JY, Xing X, Xiang N, Wu Y, Li C, Chen Q, Li D, Liu T, Zhao J, Liu M, Tu W, Chen C, Jin L, Yang R, Wang Q, Zhou S, Wang R, Liu H, Luo Y, Liu Y, Shao G, Li H, Tao Z, Yang Y, Deng Z, Liu B, Ma Z, Zhang Y, Shi G, Lam TTY, Wu JT, Gao GF, Cowling BJ, Yang B, Leung GM, Feng Z. Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. N Engl J Med 2020; 382: 1199-1207.

22) Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DA. Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis 2009; 9: 291-300.

23) Park JE, Jung S, Kim A, Park JE. MERS transmission and risk factors: a systematic review. BMC Public Health 2018; 18: 574.

24) Petrosillo N, Viceconte G, Ergonul O, Ippolito G, Petersen E. COVID-19, SARS and MERS: are they closely related? Clin Microbiol Infect 2020. Doi: 10.1016/j.cmi.2020.03.026. [Epub ahead of print].

25) Wu JT, Leung K, Leung GM. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. Lancet 2020; 29: 689-697.

26) Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. Int J Infect Dis 2020. Doi: 10.1016/j.ijid.2020.03.017. [Epub ahead of print].

27) Sun P, Qie S, Liu Z, Ren J, Li K, Xi J. Clinical characteristics of 50 466 hospitalized patients with 2019-nCoV infection. J Med Virol 2020. Doi: 10.1002/jmv.25735. [Epub ahead of print].

28) Kuster GM, Pfister O, Burkard T, Zhou Q, Twerenbold R, Haaf P, Widmer AF, Osswald S. SARS-CoV2: should inhibitors of the renin-angiotensin system be withdrawn in patients with COVID-19? Eur Heart J 2020 Mar 20. Doi: 10.1093/eurheartj/ehaa235. [Epub ahead of print].

29) Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J Virol 2020; 94: 127.

30) Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med 2020. Doi: 10.1016/s2213-2600(20)30116-8. [Epub ahead of print].

31) Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospital-

ized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAMA 2020. Doi: 10.1001/jama.2020.1585. [Epub ahead of print].

32) Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395: 507-513.

33) Vaseghi G, Mansourian M, Karimi R, Heshmat GK, Baradaran MS, Pezeshki A, Ataei B, Zandifar A, Shafaat O, Haghjoo JS. Clinical characterization and chest CT findings in laboratory-confirmed COVID-19: a systematic review and meta-analysis. medRxiv 2020. Doi: 10.1101/2020.03.05.20031518.

34) Song F, Shi N, Shan F, Zhang Z, Shen J, Lu H, Ling Y, Jiang Y, Shi Y. Emerging 2019 novel Coronavirus (2019-nCoV) pneumonia. Radiology 2020; 295: 210-217.

35) Shen K, Yang Y, Wang T, Zhao D, Jiang Y, Jin R, Zheng Y, Xu B, Xie Z, Lin L, Shang Y, Lu X, Shu S, Bai Y, Deng J, Lu M, Ye L, Wang X, Wang Y, Gao L. Diagnosis, treatment, and prevention of 2019 novel coronavirus infection in children: experts' consensus statement. World J Pediatr 2020 Feb 7. Doi: 10.1007/s12519-020-00343-7. [Epub ahead of print].

36) Wang XF, Yuan J, Zheng YJ, Chen J, Bao YM, Wang YR, Wang LF, Li H, Zeng J X, Zhang YH, Liu YX, Liu L. [Retracted: Clinical and epidemiological characteristics of 34 children with 2019 novel coronavirus infection in Shenzhen]. Zhonghua Er Ke Za Zhi 2020; 58: E008.

37) Feng K, Yun YX, Wang XF, Yang GD, Zheng YJ, Lin CM, Wang LF. [Analysis of CT features of 15 children with 2019 novel coronavirus infection]. Zhonghua Er Ke Za Zhi 2020; 58: 275-278.

38) Chen ZM, Fu JF, Shu Q, Chen YH, Hua CZ, Li FB, Lin R, Tang LF, Wang TL, Wang W, Wang YS, Xu WZ, Yang ZH, Ye S, Yuan TM, Zhang CM, Zhang YY. Diagnosis and treatment recommendations for pediatric respiratory infection caused by the 2019 novel coronavirus. World J Pediatr 2020. Doi: 10.1007/s12519-020-00345-5. [Epub ahead of print].

39) Lin L, Li TS. [Interpretation of "Guidelines for the diagnosis and treatment of novel Coronavirus (2019-nCoV) infection by the National Health Commission (Trial Version 5)"]. Zhonghua Yi Xue Za Zhi 2020; 100: 805-807.

40) Emrich IE, Bohm M, Mahfoud F. The 2018 ESC/ESH Guidelines for the management of arterial hypertension: a German point of view. Eur Heart J 2019; 40: 1830-1831.

41) Pflugfelder PW, Baird G, Tonkon MJ, DiBianco R, Pitt B. Clinical consequences of angiotensin-converting enzyme inhibitor withdrawl in chronic heart failure: a double-blind, placebo-controlled study of quinapril. J Am Coll Cardiol 1993; 22: 1557-1563.

42) Lu J, Lu Y, Wang X, Li X, Linderman GC, Wu C, Cheng X, Mu L, Zhang H, Liu J, Su M, Zhao H, Spatz ES, Spertus JA, Masoudi FA, Krumholz HM, Jiang L. Prevalence, awareness, treatment, and control of hypertension in China: data from 1·7 million adults in a population-based screening study (China PEACE Million Persons Project). Lancet 2017; 390: 2549-2558.

43) Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med 2005; 11: 875-879.

44) Elliott M. Antman M. Evaluating the cardiovascular safety of nonsteroidal anti-inflammatory drugs. Circulation 2017; 135: 2062-2072.

45) Harirforoosh S, Jamali F. Renal adverse effects of nonsteroidal anti-inflammatory drugs. Expert Opin Drug Saf 2009; 8: 669-681.

46) Szeto CC, Sugano K, Wang JG, Fujimoto K, Whittle S, Modi GK, Chen CH, Park JB, Tam LS, Vareesangthip K, Tsoi KKF, Chan FKL. Non-steroidal anti-inflammatory drug (NSAID) therapy in patients with hypertension, cardiovascular, renal or gastrointestinal comorbidities: joint APAGE/APLAR/APSDE/APSH/APSN/PoA recommendations. Gut 2020; 69: 617-629.

47) Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, Lu L, Jiang S, Yang Z, Wu Y, Ying T. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus specific human monoclonal antibody. Emerg Microbes Infect 2020; 9: 382-385.

48) Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). Nat Rev Drug Discov 2020; 19: 149-150.

49) De Clercq E. New nucleoside analogues for the treatment of hemorrhagic fever virus infections. Chem Asian J 2019; 14: 3962-3968.

50) Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov 2016; 15: 327-347.

51) Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269-271.