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## Review

## Coronavirus 2019-nCoV: A brief perspective from the front line

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## SUMMARY

A novel coronavirus, designated as 2019-nCoV, hit the central Chinese city of Wuhan in late December 2019, and subsequently spread rapidly to all provinces of China and multiple countries. As of 0:00 am February 9, 2020, a total of 37,287 cases have been confirmed infection of 2019-nCoV in China mainland, and 302 cases have also been cumulatively reported from 24 countries. According to the latest data, a total of 813 deaths occurred in China mainland, with the mortality reaching approximately 2.2%. At present, there is no vaccine or specific drugs for the human coronavirus. Therefore, it is critical to understand the nature of the virus and its clinical characteristics, in order to respond to the 2019-nCoV outbreak. Thus, the present study briefly but comprehensively summarizes the not much but timely reports on the 2019-nCoV.

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## Introduction

Coronaviruses (CoVs) are enveloped, single positive stranded RNA viruses, which belong to the subfamily Coronavirinae. The CoVs genome, ranging from 26 to 32 kilobases in length, is probably the largest viral RNA known.<sup>1,2</sup> Previously, there are six CoVs known to cause human diseases, and these can be divided into low pathogenic and highly pathogenic CoVs.<sup>2,3</sup> The low pathogenic CoVs, including 229E, HKU1, OC43 and NL63, account for 10% to 30% of upper respiratory tract infections and typically cause mild respiratory diseases.<sup>3,4</sup> In contrast, the highly pathogenic CoVs, including Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) CoV, predominantly infect lower airways and cause fatal pneumonia.<sup>2,5</sup>

SARS-CoV emerged as a new human infection in South China in November 2002 and ended in July 2003. It infected 8096 people and caused 774 deaths with an overall mortality rate of about 9.6%.<sup>6,7</sup> MERS-CoV, another highly pathogenic CoV, first emerged in Saudi Arabiawas, has caused a total of 2494 laboratory-confirmed cases and 858 deaths from 27 countries (mortality rate,

34.4%) since September 2012. (<http://www.who.int/emergencies/mers-cov/en/>).<sup>8</sup> These two highly pathogenic  $\beta$ -CoVs have posed a substantial threat to public health.

In late December 2019, a novel CoV was identified as a pathogen that caused the outbreak of a SARS-like illness in the Chinese city of Wuhan, and this was officially named as 2019-nCoV by the World Health Organization (WHO). Subsequently, the full genomic sequence from the Shanghai Public Health Clinical Center argued for a bat origin for the 2019-nCoV.<sup>9</sup> From the beginning, clusters of cases of novel CoV infection were reported to be epidemiologically linked to the Huanan Seafood Wholesale Market.<sup>10</sup> Subsequently, the evidence for the human-to-human transmission of 2019-nCoV was further confirmed by the infection of 15 health-care practitioners after close contact with once infected patient in a Wuhan hospital.<sup>11</sup> As of February 9, 2020, 2019-nCoV has infected a total of 37,590 cases from all over the world.

Despite several decades of research, there is a lack of a specific vaccine or treatment for human CoVs. In this review, we summarize the advance of the nature of the 2019-nCoV and its clinical characteristics and therapeutics, which may be critical for the response to the 2019-nCoV outbreak.

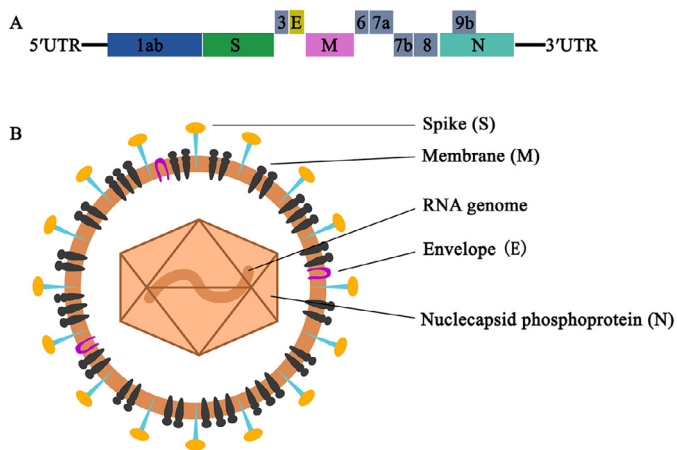
## Genomic and structure

The 2019-nCoV belongs to lineage B  $\beta$ -COVs, subgenus Sarbecovirus, which possesses a single-stranded positive-sense RNA surrounded by an envelope.<sup>9,12</sup> The RNA genome includes 29,891 nu-

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**Fig. 1. Genomic organization and virus structure of 2019-nCoV.** (A) 2019-nCoV genome comprises of 5' untranslated region (5' UTR) including 5' leader sequence, open reading frame (ORF) 1a/b, envelope, membrane and nucleoprotein, accessory proteins such as orf 3, 6, 7a, 7b, 8 and 9b and 3' untranslated region (3' UTR) in sequence. (B) 2019-nCoV structure consists of single-strand, positive-sense RNA as the genetic material surrounded by nucleocapsid protein in the core and an envelope containing four proteins: Spike protein, Envelope protein, Membrane protein.

cleotides (GenBank no. MN908947), encoding 9860 amino acids and this is arranged in the order of 5'UTR-replicase(orf1a/b)-Spike(S)-Envelope(E)-Membrane (M)-Nucleocapsid (N)-3'UTR, in which S, E, M, N encodes the structural proteins<sup>9</sup> (Fig. 1). Recently, phylogenetic analysis has revealed that the 2019-nCoV is most closely related to BatCoV RaTG13 from Yunnan, China in 2013 with a 96.3% sequence identity, and that this is more correlated two bat-derived SARS-like coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21 (approximately 88% identity) which came from Zhoushan, China in 2018. However, this is discordant with SARS-CoV (approximately 79% identity) and MERS-CoV (approximately 50% identity).<sup>9,12–14</sup>

The genome of the 2019-nCoV consists of six major functional open reading frames (ORFs), including ORF1a/b, S, E, M, N and several other accessory genes, such as ORF3b and ORF8. Replicase polyproteins pp1a and pp1ab, which are ORF1a/b would be proteolytic cleaved into 16 non-structural proteins (nsps) which are involved in the transcription and replication of the virus.<sup>9</sup> In addition, the ORF3b encoded a completely novel short protein without an exact function. The new ORF8 likely encodes a secreted protein formed by an alpha-helix, followed by betasheets that contain six strands that have no known functional domain or motif similarly.<sup>9</sup> The S gene of the 2019-nCoV has less than 75% sequence identity to those of the two CoVs, bat SARS-like CoVs (SL-CoVZXC21 and ZC45) and human SARS-CoV.<sup>14</sup> Similarly, the spike glycoprotein encoded by the S genes of the 2019-nCoV was longer than that of the SARS-CoV.<sup>12,14</sup> The spike protein, composed of S1 and S2 domain, was crucial to the determine host tropism and transmission capacity through the mediation of receptor binding and membrane fusion.<sup>12</sup> Among these, the S2 subunit of the 2019-nCoV is highly conserved and has a 99% identity with that of SARS-CoV.<sup>12</sup> The receptor-binding domain, is commonly located in the C-terminal domain of S1 to directly contact the human receptor. Although, the S1 domain of the 2019-nCoV only has approximately 70% identity with SARS-CoV, homology modelling revealed that the 2019-nCoV has a similar receptor-binding domain structure to that of SARS-CoV.<sup>9,12</sup> Notably, Zhou et al. found that the 2019-nCoV just like SARS-CoV may also use ACE2 as an entry receptor in the ACE2-expressing cells, and the majority of which are type II alveolar cells (AT2) in human lung.<sup>14,15</sup> Therefore, further investigations are

needed to determine whether ACE2 targeting drugs would be effective for the treatment of 2019-nCoV.

Since the genomic sequences of the 2019-nCoV obtained from different patients were extremely similar to each other, which exhibited more than 99.9% sequence identity,<sup>12,14</sup> it could be reasonably considered that the 2019-nCoV originated from one source rather than a mosaic and could be detected relatively rapidly. However, mutations need to be constantly monitored when the virus is transmitting to an increasing number of individuals.

## Epidemiology

On the basis of the initial investigation, the shared history of exposure to the Wuhan Seafood Wholesale Market highly suggested that wild animals sold in the market such as bamboo rats, raccoons, and snakes would be the original source of the novel virus.<sup>16</sup> Soon afterwards, the traceability analysis supported that the 2019-nCoV would be from Rhinolophus. This is with the phylogenetic analysis results that the 2019-nCoV was most related to BatCoV RaTG13 from the bat.<sup>13,17</sup> However, intermediate host is likely to exist between bats and humans which is similar to masked palm civet for SARS-CoV35 and dromedary camels for MERS-CoV. The newest research suspected pangolins are potential intermediate hosts for novel coronavirus but may not the only.

Epidemiologically, 2019-nCoV is highly infectious with about 2 h survive time in the air. The incubation period after infection is generally 4–8 days.<sup>10,18,19</sup> All age groups are susceptible to the virus, of which elderly patients with comorbidities are more likely to experience severe illness.<sup>10,18,19</sup> Importantly, the people who are primary, asymptomatic and in incubation period are the main sources of infection, which is of critical significance to the epidemic prevention and control.<sup>16</sup> Up to now, respiratory droplets is the major route of transmission. Besides, the fecal-oral route of transmission is considered but unconfirmed because 2019-nCoV nucleic acids could be detected in the stool samples of pneumonia patients with abdominal symptoms.<sup>20</sup> Vertical transmission between mothers and infants is another possible route based on the finding that a 30 h-old newborn was confirmed with 2019-nCoV in Wuhan Children's Hospital. Some researchers also warn that the transmission through the ocular surface must not be ignored considering human conjunctival epithelium can be contaminated easily by infectious droplets and body fluids.<sup>21</sup>

To our knowledge, basic reproduction rate (R0), as the rate reflecting the speed of disease transmission, differs in time periods estimated by researchers and is also substantially affected by reporting rate. The latest R0 is 2.68 estimated by Wu et al., roughly identical to the rate published by WHO and Chinese Center for Disease Control, all of which indicate that the number of infected patients will increase as long as R0 is greater than 1.<sup>16,22,23</sup> As a result, the WHO has declared the outbreak of 2019-nCoV pneumonia to be a public health emergency of international concern on January 30 and adopted control measures to reduce R0 rate to below 1 globally.

## Clinical characteristics

The present clinical data obtained from 31 provinces of China revealed that the 2019-nCoV shared many clinical features with SARS-CoV.<sup>24,25</sup> The median age of these patients was 47 years old, with a predominance of male patients (58.2%). The mean incubation time was 3.0 days (range: 0–24.0 days).<sup>24</sup> The most common symptoms are fever (87.9%), fatigue (69.6%), dry cough (67.7%) and myalgia (34.8%), and these are accompanied with rhinobyon, rhinorrhoea, pharyngalgia and diarrhea in few patients<sup>24</sup> (Table 1). Notably, fever may not necessarily be the first manifestation, which occurred in only 43.8% of patients on initial presentation. A part

**Table 1**  
Clinical Characteristics of patients with 2019-nCoV and SARS-CoV.

	2019-nCoV*	SARS-CoV
<b>Epidemiology</b>		
Outbreak date	December, 2019	November, 2002
Location of first case	Wuhan, China	Guangdong, China
Confirmed cases	37,590 (Feb9, 2020)	8096
Mortality	813 (2.2%) (Feb9, 2020)	744 (10%)
Healthcare practitioners	2.09%	23.1%
<b>Characteristics</b>		
Age, years (range)	47.0 (all spectrum of age)	39.9 (1-91)
Male: female ratio	1.39: 1	1: 1.25
Fever	87.9% (initial, 43.8%)	99-100%
Nonproductive cough	67.7%	25%–75%
Fatigue	38.1%	31.2%
Dyspnea	18.6%	40-42%
Myalgia or rthalgia	14.8%	49.3%–60.9%
Sore throat	13.9%	12.5%
Headache	13.6%	35.4%– 55.8%
Expectoration	13.3%	4.9%
Chills	11.4%	27.8%–73.2%
Nausea or vomiting	5.0%	19.4%–19.6%
Nasal congestion	4.8%	2.1%
Diarrhea	3.7%	20-25%
Tonsil swelling	2.1%	NR
Hemoptysis	0.9%	NR
Conjunctival congestion	0.8%	NR
Enlargement of lymph nodes	0.2%	NR
Rash	0.2%	NR

Data are n, age (range), or n (%) unless otherwise stated. 2019-nCoV=2019 novel coronavirus. SARS-CoV=severe acute respiratory syndrome coronavirus.

\* Clinical Characteristics of Coronavirus Disease 2019 in China reported by Wei-jie Guan and colleagues (reference 24). The date of SARS-CoV is from the review by Michael DC (reference 25). Case numbers and mortalities are updated up to 0:00 am Feb 9, 2020) as disclosed by the Chinese Health Commission.

of these patients were characterized by dyspnea and hypoxemia, which can rapidly progress to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, and even multiple organ dysfunction syndrome (MODS) in one week.<sup>18,24</sup>

Some laboratory tests could provide some hints of the early forms of the disease, such as lymphopenia (82.1%), thrombocytopenia (36.2%) and leukopenia (33.7%). Most patients demonstrated elevated levels of C-reactive protein (CRP). In addition, severe cases could have increasing levels of alanine aminotransferase, aspartate aminotransferase, creatine kinase and creatine.<sup>18,24</sup> All suspected patients are recommended to be examined by chest computerized tomography (CT). Most of the confirmed patients suffered from pneumonia (76.4%), and were characterized with ground-glass opacity (50.0%) and bilateral patchy shadowing (46.0%) in the chest CT, and even subsegmental consolidation in severe patients.<sup>24,26</sup> To date, most of these patients had a good prognosis. However, the mortality rate was higher in elder patients with chronic diseases (diabetes, hypertension and angiocardopathy, etc.) and intensive care unit (ICU) patients, reaching 17-38% in recent reports.<sup>18,19</sup>

The diagnosis is based on the epidemiological risks, clinical features and laboratory tests. Patients who have a history of travel from Chinese city of Wuhan or close contact with confirmed or suspected case of 2019-nCoV, and then present with fever or respiratory symptoms within incubation period should be suspected. In addition, due to the discovery of asymptomatic CoVcarriers and negative of viral nucleic acid test in many times before confirmed, the typical pulmonary imaging performance can not be ignored, and even can be used as a preliminary screening method. Positive of viral nucleic acid by real-time RT-PCR detection with specimens from the respiratory tract or serum are confirmed 2019-nCoV infection.<sup>14</sup>

## Treatments for 2019-nCoV

Despite several therapeutic options have been experimented in 2019-nCoV infected patients, there are still no specific therapies. As one kind of RNA virus, 2019-nCoV may possess some similar functional proteins for processing virus replication and assembly to human immunodeficiency virus (HIV). Thus, the HIV protease inhibitors may also effective to 2019-nCoV. At present, lopinavir/ritonavir (LPV/r) combination, which was previously confirmed effective in SARS-Cov and MERS-Cov, has been recommended for the treatment of 2019-nCoV in the latest guideline.<sup>27,28</sup> Besides, by homology modelling and molecular docking, another anti-HIV drug nelfinavir was predicted to be active against 2019-nCoV and could be a potential drugs.<sup>29</sup> Remdesivir (RDV, GS-5734), a novel nucleotide analogue prodrug in development, has been proved to be a potential effective pan-CoV antiviral.<sup>30,31</sup> Wang et al. showed that RDV could inhibit 2019-nCoV infection in vitro.<sup>32</sup> And the successful use of RDV in the first case of 2019-nCoV in the United States posted the bright perspective.<sup>33</sup> More promisingly, a randomized, double-blind, parallel-controlled phase 3 clinical trial of safety and efficacy of RDV is ongoing in Wuhan (NCT04252664). Meanwhile, Wang and his colleagues also provided evidence of the potential that chloroquine was also effective in the control of 2019-nCoV infection.<sup>32</sup> Arbidol has a broad-spectrum antiviral activity against respiratory viruses. Recent news reported that arbidol can inhibit 2019-nCoV in vitro. A phase 4 clinical trial of arbidol for new coronavirus pneumonia had been registered (NCT04246242).

As for monoclonal antibody (mAb), several researches showed that the combination of RDV and mAb would likely to be the ideal treatment for 2019-nCoV. Tian et al. reported for the first time that a SARS-CoV-specific human mAb, CR3022, could bind potently with 2019-nCoV receptor binding domain.<sup>34</sup> Therefore, CR3022 may be

developed to prevent and treat new coronavirus infection. Additionally, The janus kinase inhibitor baricitinib, which can disrupt receptor mediated endocytosis and interrupt the passage of the virus into cells, was identified to reduce the ability of the virus to infect lung cells and be a potential treatment for 2019-nCoV.<sup>35</sup>

In addition to the therapeutics discussed above, Chinese health-care practitioners also have started clinical trails of stem cell infusion and traditional Chinese medicine for severe patients. We expect that these therapies will improve clinical outcomes in 2019-nCoV patients.

## Discussion

The world has experienced three outbreaks of highly pathogenic CoVs, including the emergence of SARS-CoV in 2002, MERS-CoV in 2012 and now, the outbreak of 2019-nCoV.<sup>6–8</sup> It is clear that 2019-nCoV is another lineage B  $\beta$ -CoV and has been postulated that bat is the primary host.<sup>9</sup> Despite only 75% similarity in genetic sequence to SARS-CoV,<sup>9,14</sup> 2019-nCoV shares many features with SARS-CoV, such as epidemiology, clinical characteristics, and the entry receptor ACE2 and so on.<sup>14,15,24,25</sup>

The 2019-nCoV jumps unpredictably, spreads rapidly and has posed severe threat to public health. Although the overall mortality rate is lower than SARS-CoV and MARS-CoV, the mortality in elder patients with chronic diseases and intensive care unit (ICU) patients, reaching 17–38% in recent reports.<sup>18,19</sup> As yet, no specific therapy of proven efficacy has been recommended for human CoVs infection. Retrospective analysis showed that most deaths of the CoVs infection patients were due to severe pneumonia.<sup>2,5</sup> Previous studies indicated that viral evasion of host maladjusted immune responses are believed to play critical roles in acute lung injury (ALI), in addition to CoVs-induced direct cytopathic effects.<sup>5</sup> Indeed, changes of some immune index have been detected in the CoVs infection patients, such as lymphopenia, monocytosis and elevated cytokine levels.<sup>2,5,25</sup> The treatment of corticosteroids may reduce the risk of lung inflammation but also delay CoVs clearance in addition to other side effects.<sup>36–38</sup> Thus, the topic of corticosteroid use in patients with CoVs has been a matter of debate for years. The available clinical data tends to argue for no net benefit derived from corticosteroids in the treatment of SARS-CoV and MERS-CoV.<sup>38–40</sup> Recently, the study of the largest case series of 2019-nCoV from Wuhan showed that there was no effective outcomes were observed with usage of varied dose of methylprednisolone.<sup>25</sup>

The outbreak of 2019-nCoV poses a serious challenge to China. Currently, the most effective measures to 2019-nCoV are still early detection and quarantine of new sources of infection, and early diagnosis and supportive treatments for confirmed patients. Considerable advances have been made in preventing and controlling emerging infectious diseases since the SARS-CoV epidemic 17 years ago. In addition, based on the successful therapy of SARS-CoV, a series of effective treatments have been adopted for the patients with 2019-nCoV. Therefore, we are confident that these would effectively curb the outbreak of 2019-nCoV. The epidemic peak may soon be reached and the final victory is not far away.

## Declaration of Competing Interest

The authors declare that they have no competing interests.

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