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Review

New understanding of the damage of SARS-CoV-2 infection outside the respiratory system

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ABSTRACT

Since early December 2019, a number of pneumonia cases associated with unknown coronavirus infection were identified in Wuhan, China, and many additional cases were identified in other regions of China and in other countries within 3 months. Currently, more than 80,000 cases have been diagnosed in China, including more than 3000 deaths. The epidemic is spreading to the rest of the world, posing a grave challenge to prevention and control. On February 12, 2020, the International Committee on Taxonomy of Viruses and the World Health Organization officially named the novel coronavirus and associated pneumonia as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19), respectively. According to the recent research on SARS-CoV-2, the virus mainly infects the respiratory system but may cause damage to other systems. In this paper, we will systematically review the pathogenic features, transmission routes, and infection mechanisms of SARS-CoV-2, as well as any adverse effects on the digestive system, urogenital system, central nervous system, and circulatory system, in order to provide a theoretical and clinical basis for the diagnosis, classification, treatment, and prognosis assessment of SARS-CoV-2 infection.

1. Background

In early December 2019, pneumonia cases associated with unknown coronavirus infection were identified in some hospitals in Wuhan, China. Based on laboratory tests and epidemiological observation, 27 patients were initially diagnosed with viral pneumonia. On January 7, 2020, Chinese scientists announced their identification of a novel coronavirus and its whole-genome sequencing. Moreover, the reverse transcription–polymerase chain reaction (RT-PCR) assay for the detection of nucleic acid from the novel coronavirus identified 15 positive cases of novel coronavirus infection, and the virus was successfully isolated from the respiratory secretions of one patient. Electron microscopy revealed that the virus has a typical coronavirus morphology. On January 23, Shi et al. reported that the novel coronavirus is highly homologous (96 %) to the coronavirus that infects certain bats. Further alignment of seven conserved nonstructural viral proteins confirmed that the novel coronavirus belongs to SARSr-CoV, the same genus of severe acute respiratory syndrome coronavirus (SARS-CoV). Moreover, researchers have identified that the novel coronavirus enters cells via the same mechanism as SARS-CoV, by binding to angiotensin-converting enzyme 2 (ACE2), a receptor on the cell surface [1]. On January 24, the National Institute for Viral Disease Control and Prevention, Chinese Centers for Disease Control and Prevention, officially published the information on the first novel coronavirus strain, including strain type, electron micrographs, and sequences of primers and probes for detection of its nucleic acid by RT-PCR. On January 25, Chinese researchers published an article in the *New England Journal of Medicine* and formally identify the novel coronavirus as the seventh member of

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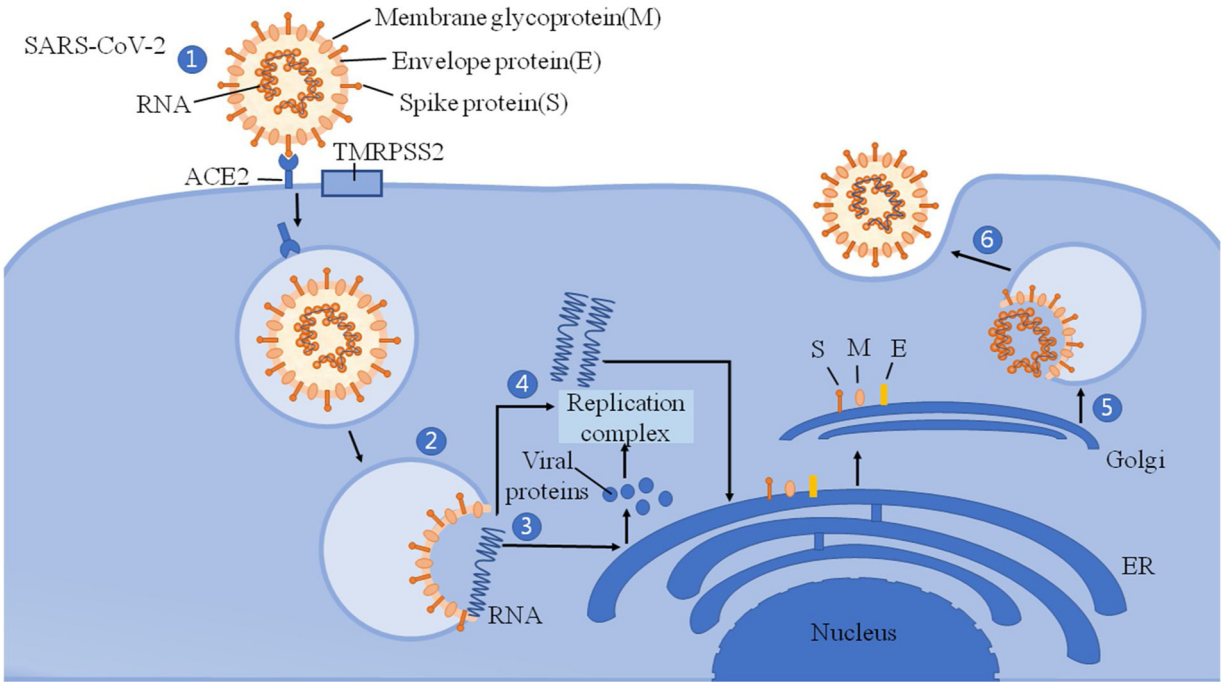

Fig. 1. SARS-CoV-2 invades cellular mechanisms. ①SARS-CoV-2 entry. ②Membrane fusion and viral RNA release. ③Translation. ④Some of these proteins from 3 and RNA from 2 form a replication complex to make more RNA. ⑤SARS-CoV-2 packaging in golgi. ⑥SARS-CoV-2 release.

the coronavirus family that can infect humans [2]. On January 30, the World Health Organization (WHO) held an official meeting and decided that the novel coronavirus outbreak is a public health emergency of international concern. On February 12, the International Committee on Taxonomy of Viruses and WHO officially named the novel coronavirus and associated pneumonia as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 2019 (COVID-19), respectively.

Since the outbreak, all levels of the Chinese government have taken strict prevention and control measures, but the situation is still grave. On February 8, Han et al. published an article on the risk of SARS-CoV-2 infection in different human organs based on single-cell RNA sequencing technology. The results showed that ACE2 is expressed in many tissues, including heart, esophagus, ileum, kidneys, and bladder, at a level that is even higher than that in the alveolar cells, suggesting that SARS-CoV-2 may affect many systems [3]. Therefore, besides the respiratory system, its potential targets may be the digestive system, circulatory system, urogenital system, and even the central nervous system. A study based on a clinical sample showed that a small percentage of blood samples had positive PCR test results(about 1%), suggesting that infection sometimes may be systemic [4]. Transmission of the SARS-CoV-2 by respiratory and extrarespiratory routes may help explain the rapid spread of COVID-19.In addition, the latest guidelines for diagnosis and treatment of COVID-19 from the National Health Commission (China) and other related study also showed that the detection of viral nucleic acids in blood is one of the important diagnostic criteria. It can be inferred that SARS-CoV-2 can spread to other organs except the lungs through the blood route, but the specific mechanism needs to be further studied [5,6].

In this paper, we will review the pathogenic features, transmission routes, and infection mechanisms of SARS-CoV-2, as well as any adverse effects on the digestive system, urogenital system, central nervous system, and circulatory system, in order to provide a theoretical and clinical basis for the diagnosis, classification, treatment, and prognosis of SARS-CoV-2 infection and new directions for COVID-19 prevention and control.

2. Pathogenic features of SARS-CoV-2

SARS-CoV-2 is a β coronavirus (enveloped, single-stranded, positive-sense RNA virus), with an average diameter of 60–140 nm. The viral particles are oval or round with spikes. Its genetic information is encoded by nearly 29,000 ribonucleotides. The entire genome sequence of SARS-CoV-2 has been published on virological.org, nextstrain.org, and bioRxiv. SARS-CoV-2 is highly homologous (> 85 %) to a bat SARS-like coronavirus (bat-SL-CoVZC45) [7]. Like HIV gp120 protein, SARS-CoV-2 spike protein recognizes cell surface receptors, allowing the virus to enter cells; the difference lies in specific receptors and target cells—SARS-CoV-2 binds to ACE2 and enters mucosal epithelial cells, while HIV binds to cluster of differentiation 4 (CD4) receptor and enters $CD4^+$ T cells [8]. Researchers have determined how long it takes SARS-CoV-2 to enter cells by in vitro virus isolation and culture—-approximately 96 h for SARS-CoV-2 to enter human respiratory epithelial cells and approximately 6 days for SARS-CoV-2 to enter cell lines such as Vero E6 and Huh-7. SARS-CoV-2 does not attack T cells, $CD4^+$ cells, or ACE2– cells. Moreover, up to seven nucleotide variations are identified in the known SARS-CoV-2 sequence, suggesting that SARS-CoV-2 did not attack humans until very recently.

3. Transmission routes of SARS-CoV-2

Like the pathogens of SARS and the Middle East respiratory syndrome (MERS), SARS-CoV-2 is a member of the coronavirus family, but it is genetically distinct from other coronaviruses. According to the latest guidelines for diagnosis and treatment of COVID-19 from the National Health Commission (China), infected individuals are the main source of SARS-CoV-2 infection, and some asymptomatic patients may be potential sources of infection. Respiratory droplets and close contact are the two most important routes of transmission. In closed spaces, prolonged exposure to a high concentration of SARS-CoV-2 aerosols may cause viral transmission [5]. Recently, the nucleic acid of SARS-CoV-2 has been detected in fecal samples, suggesting that the digestive tract is a potential route of transmission, although further research is needed to validate this hypothesis.

4. Mechanism of SARS-CoV-2 infection

Based on SARS and MERS research and the latest SARS-CoV-2 sequence, these three coronaviruses capable of infecting humans share the same receptor (ACE2). The infection mechanism is shown in Fig. 1. ACE2, also known as ACEH, is a member of the angiotensin-converting enzyme (ACE) family of dipeptidyl-carboxydipeptidase and is highly homologous to ACE1. ACE1 and ACE2 convert angiotensin 1 into angiotensin (Ang) 1–9 and angiotensin 2 into Ang 1 − 7. ACE2 has high affinity to Ang II type 1 and type 2 receptors and plays an important role in many physiological functions, such as cell proliferation and hypertrophy, inflammatory response, blood pressure, and fluid balance. ACE2 is specifically expressed in certain organs and tissues, suggesting that it plays an important role in regulating cardiovascular, renal, and reproductive functions [9,10]. The S-glycoprotein functional receptors for SARS-CoV and HCoV-NL63 are encoded by the ACE2 gene. RNA sequencing has been used to analyze 27 different types of tissues and 95 human tissue samples, showing that the expression of ACE2 is high in duodenum and small intestine and low in lung. Moreover, ACE2 expression is detected in placental choriocarcinoma cells (BEWO), immortalized human epidermal cells (HaCaT), liver cancer cells (HepG2), acute promyelocytic leukemia cells (NB-4), multiple myeloma cells (RPMI 8226), bladder cancer cells (RT4), and glioblastoma cells (SH-SY5Y). In another study, the ACE2 protein level was determined in human organs and tissues, including respiratory mucosa, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain. The results showed that ACE2 is abundantly expressed in the lungs and small intestine and is highly expressed in endothelial cells and smooth muscle cells of virtually all organs. Therefore, once in the circulatory system, SARS-CoV-2 is likely to spread via blood flow [11]. These data suggest that SARS-CoV-2 not only affects the respiratory system but is also a potential threat to the digestive system, urogenital system, central nervous system, and circulatory system.

5. SARS-CoV-2 and the digestive system

Based on current clinical and epidemiological data, the clinical symptoms of SARS-CoV-2 infection vary a great deal from patient to patient. The virus first affects the respiratory epithelial cells and alveolar cells, followed by the digestive system. Evidence from previous studies about SARS proved that coronavirus has a tropism to the gastrointestinal tract. The viral nucleic acid could be readily detected in stool specimens of patients who have been infected with SARS. In addition, the replication process of this virus in the intestinal tissue is very active according to the observation of vivisection and autopsy under the electron microscope. The kind of tropism above may explain the frequent occurrence of diarrhoea in coronavirus infection. Wong et al's research showed that SARS-CoV-2 has the ability of encoding and expressing the spike (S) glycoproteins that could bind to the entry receptor ACE2. It is worth noting that in cytoplasm of gastric, duodenal and rectal epithelium, the expression of viral nucleocapsid protein is visualized [12,13]. Some SARS-CoV-2 cases present with diarrhea as the initial symptom. SARS-CoV-2 enters cells via the cell-surface receptor ACE2, and ACE2 regulates intestinal inflammatory response, which can be used to track SARS-CoV-2-mediated routes of transmission. Single-cell RNA sequencing showed that ACE2 mRNA is abundantly expressed in intestinal cells of healthy adults; in contrast, the expression level is relatively low in the lungs. Moreover, ACE2 expression is high in epithelial cells of the proximal and distal intestines. The intestinal epithelium is in direct contact with exogenous pathogens, and we surmise that after consumption of SARS-CoV-2–infected wild animals, small intestinal epithelial cells are the first affected by the virus, and diarrhea may be an important sign of infection and clinical manifestation. This suggests that clinicians should pay attention to suspected patients who have diarrhea [14]. Lan and Cai performed RNA sequencing and found high, specific ACE2 expression in bile duct cells, suggesting that it is important to monitor liver function of SARS-CoV-2 patients, especially liver indicators involving bile duct function. In case of liver dysfunction, targeted treatment and care should be given in a timely manner [15].

ACE2 expression in the lungs reduces SARS-CoV-2 spike protein–induced lung injury via the renin-angiotensin system. In the intestines, ACE2 plays an important role in maintaining amino acid balance and regulating the expression of antimicrobial peptides and the equilibrium of the intestinal flora. A recent RNA sequencing analysis in patients with inflammatory bowel disease (IBD) or colitis showed that ACE2 expression in colon cells was positively correlated with the regulation of viral infection and congenital cellular immunity and was negatively correlated with viral transcription, protein translation, phagocytosis, and complement activation [16]. Therefore, ACE2-mediated SARS-CoV-2 infection may be a double-edged sword with respect to susceptibility and immunity.

In summary, during clinical diagnosis and treatment of patients with SARS-CoV-2 infection, clinicians should pay attention to patients who present digestive symptoms (especially diarrhea) as the initial symptoms. Moreover, should diarrhea or other related symptoms of intestinal infection arise during treatment, the patient should receive prompt integrative treatment as needed, including anti-diarrhea therapy, hydration, correction of electrolyte disturbance, and antiviral therapy. In addition, because the virus and antiviral therapy may cause liver damage, patients should be closely monitored for liver function and receive liver-protective therapy as needed.

6. SARS-CoV-2 and the urogenital system

SARS-CoV-2 shares the same receptor as SARS-CoV. A retrospective analysis found that among SARS patients, the proportion of patients with acute renal insufficiency (ARI) was low but the mortality rate was more than 90 %. As a control, the researchers conducted a clinical study to assess kidney function in 59 patients with SARS-CoV-2 infection, including 28 severe cases and three deaths. The results showed that 19 % of the patients had elevated serum creatinine, 27 % had elevated urea nitrogen, and 63 % had urine protein (+ to + +). Kidney CT was abnormal in all the patients [17]. In addition, three separate clinical studies in six, 41, and 99 patients with SARS-CoV-2 infection, respectively, showed that besides severe respiratory dysfunction, 3 %–10 % of the patients had renal insufficiency, and 7 % had acute kidney injury [18]. Zhong et al. showed that viral nucleic acid was isolated from the urine samples of SARS-CoV-2 patients. These data indicate that the incidence of kidney dysfunction is high after SARS-CoV-2 infection. The bladder may also be affected and may ultimately lead to multiple-organ failure and death.

Fan et al. further investigated the effect of SARS-CoV-2 infection on the urinary system and the male reproductive system. The researchers analyzed the online database and plotted ACE2 expression in various organs. The results showed that ACE2 is highly expressed in renal tubular cells, mesenchymal cells, and testicular and vas deferens cells. Surprisingly, ACE2 mRNA and protein levels are higher in testis than in any other organ. The researchers surmise that SARS-CoV-2 binds to ACE2 to affect the kidneys and testis and subsequently causes their dysfunction [18]. Wang et al. found that ACE2 was predominantly enriched in spermatogonia and Leydig and Sertoli cells. Gene Set Enrichment Analysis (GSEA) indicated that Gene Ontology (GO) categories associated with viral reproduction and transmission were highly expressed in ACE2-positive spermatogonia, but terms which related to male gamete generation showed significantly low expression [[19]]. Both viral infection and antiviral therapy have potential nephrotoxicity and may cause kidney injury. Therefore, SARS-CoV-2 patients should be closely monitored for fluid and electrolyte disturbance and kidney function and receive specific targeted treatment and care as needed. Patients with chronic renal insufficiency should undergo hemodialysis

or renal replacement therapy if necessary to facilitate metabolic waste removal. In addition, the virus may affect testicular tissue, and clinicians should assess the risk of testicular lesions in younger patients during the hospital treatment and follow-up and provide prompt prevention and treatment for potential SARS-CoV-2–related reproductive injury.

7. SARS-CoV-2 and the central nervous system [20]

SARS-CoV-2 may infect the central nervous system(CNS), as the viral nucleic acid has been detected in patient's cerebrospinal fluid and brain tissue from autopsy. As for the route of virus entering the CNS, the blood route still needs to be further verified due to the existence of blood-brain barrier. But on the other hand, neuronal pathway is important vehicles for neurotropic viruses to enter the CNS. Viruses can migrate after infecting sensory or motor nerve endings. Under the action of motor proteins, dynein and kinesins, the viruses can achieve neuronal transport in a way of retrograde or anterograde. Here's a classic example. Based on the unique anatomical structure of olfactory nerves and olfactory bulb, it becomes a channel between the nasal epithelium and the CNS. In the early stages of SARS-CoV-2 infection of the respiratory system, Olfactory tract becomes an important channel for virus transmission to brain. In addition to the above research, an Gu et al. study of gene sequences in neurons in the brain showed that coronavirus can invade the CNS from the periphery through neural pathways [21,22,24].

In addition, as the life center of human body, the brainstem controls vital functions such as heart beating, blood pressure maintenance and respiration. Studies have shown that some coronaviruses can invade brainstem via a synapse-connected route from the lungs and airways. The potential invasion to CNS of SARS-CoV-2 may be one reason for the acute respiratory failure. Therefore, it is of great significance for the treatment of severe patients to clarify the disease mechanism of patients with respiratory failure clinically whether it is caused by pulmonary lesions or viral infection of the brainstem [23].

Some confirmed cases present with specific headache, epilepsy, and confusion, which are similar to symptoms of intracranial infection. In some cases, intracranial infection–related symptoms have been the initial symptoms, coming before the symptoms of pulmonary infection, such as cough, fever, and dyspnea. Therefore, for suspected SARS-CoV-2 cases with intracranial symptoms, plain and enhanced brain magnetic resonance imaging and lumbar puncture (SARS-CoV-2 nucleic acid test on cerebral spinal fluid) are essential. For SARS-CoV-2 patients with intracranial symptoms, early treatment should be given to in addition to routine anti-infective therapy, including rehydration (reduce intracranial pressure), nerve nourishment, epilepsy prevention, and acid suppression.

Since SARS-CoV-2 binds to ACE2, some patients with underlying hypertension may have unusually high blood pressure and increased risk of intracranial hemorrhage after SARS-CoV-2 infection. Severely low platelets is also an important manifestation of critical SARS-CoV-2 infection, as well as an independent risk factor for acute cerebrovascular events. Angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may increase the expression of ACE2. Therefore, it is important to adjust antihypertensive drug dosages in SARS-CoV-2 patients with underlying hypertension. Diuretics and calcium channel blockers are alternatives for management of blood pressure.

Moreover, some patients may have primary or secondary muscle injury, such as limb pain, fatigue, and elevated muscle enzymes, which may result from the inflammatory response or direct muscle damage following viral infection. Patients with SARS-CoV-2 infection and muscle injury should receive appropriate nutritional support, and γ-globulin injection in case of severe muscle injury.

Such as viral encephalitis, infectious toxic encephalopathy and some kind of acute cerebrovascular diseases, they are all related to coronavirus infections. For mechanisms by which SARS-CoV-2 infection may cause neurological damage, in addition to direct damage associated with ACE2 receptors, when SARS-CoV-2 proliferates in lung tissue cells, diffuse alveolar, interstitial inflammatory exudation and edema are all very common pathological changes. It causes alveolar gas exchange disorders and hypoxia in the CNS. Due to anaerobic metabolism in the mitochondria in brain and excessive accumulation of acid metabolites, relevant clinical manifestations will appear such as swelling of brain cells, interstitial edema, obstruction of cerebral blood flow, headache due to ischemia and congestion and even a coma. Additionally, previous studies showed that when coronavirus attacked primary glial cells, a large amount of inflammatory factors such as IL-6, IL-12, IL-15, and TNF-α after being infected were released. This is also one of the pathophysiological processes of CNS damage caused by inflammatory factors [21,23].

8. SARS-CoV-2 and the circulatory system

Huang et al. showed that five of the 41 patients first diagnosed with SARS-CoV-2 infection in Wuhan, China, had viral myocarditis, mainly manifested as elevated hs-cTnl. Among them, four patients developed severe conditions, accounting for 31 % of all severe cases. The mean systolic blood pressure was significantly higher in severe cases than in nonsevere cases (145 mm Hg vs 122 mm Hg). Clinical data show that an increasing number of SARS-CoV-2 patients present circulatory symptoms (palpitations, chest tightness, short of breath) as the initial symptoms [25]. On January 23, the National Health Commission (China) released a report on 17 deaths, which shows that two patients had no underlying cardiovascular disease but developed apparent cardiac symptoms after the diagnosis of SARS-CoV-2 infection. One patient had changes in the ST segment on electrocardiogram and persistent abnormal myocardial enzymes, and one patient had sudden progressive decline in heart rate and undetectable heart sounds.

Hou *et al* published an analysis of 84 cases of SARS-CoV-2 infection, which showed that elevated creatine kinase and creatine kinase isoenzyme MB during treatment is a sign of severe condition and disease progression. After SARS-CoV-2 infection in humans, immune disorders exacerbate the inflammatory response, which directly or indirectly leads to high risk of cardiovascular symptoms and diseases.

At present, researchers believe that three mechanisms may be involved in how SARS-CoV-2 infection induces acute myocardial injury. First, the virus infects the heart and causes myocardial injury directly. Second, Xu et al. showed that SARS-CoV-2 binds to highly expressed ACE2 receptors in the cardiovascular system to cause myocardial injury via certain signaling pathways [26]. Third, Huang et al. showed that in SARS-CoV-2 patients, Th1/Th2 imbalance triggers cytokine cascade, and the release of a large amount of cytokines causes myocardial injury [25]. In addition, hypoxaemia and respiratory dysfunction instigated by SARS-CoV-2 may also cause damage to myocardial cells. Meanwhile, plasma high-sensitivity C-reactive protein (hsCRP) is one of the most classical inflammation markers, as well as levels of cytokines linked to cardiovascular risk, are also related to adverse outcomes and could be some potential biomarkers to assess the disease progression [27,28].

9. SARS-CoV-2 and the inflammatory cascade

In the wake of SARS epidemic in late 2002 in Guangdong, China, many researchers investigated the pathogenesis of SARS in humans. Inflammatory cytokines and chemical factors are significantly elevated in SARS patients, but it is unclear whether these factors are the culprit or a secondary virus-induced cytopathology. Moreover, researchers are still debating whether the type 1 interferon response is involved during SARS-CoV infection. In vitro studies showed minimal interferon induction and signaling, while other studies reached different conclusions after analyzing peripheral white blood cells from patients with SARS-CoV infection.

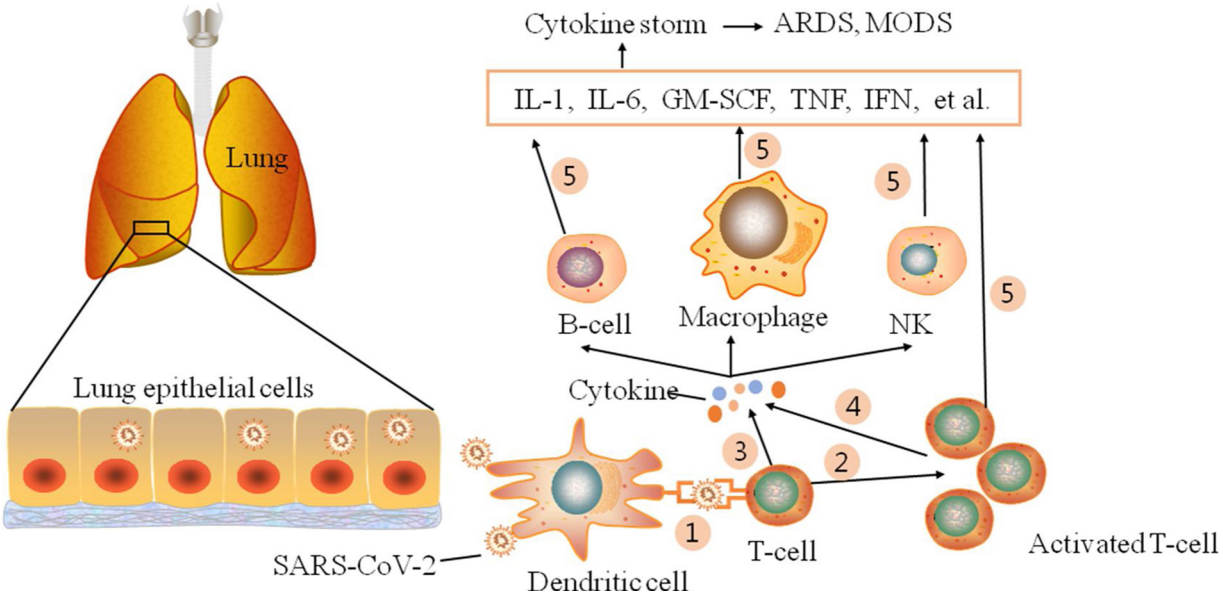

Fig. 2. Inflammatory storm mechanism. ①Antigen presenting. ②T cells activate and start reproducing. ③A large amount of cytokine are secreted during T cell activation. B cells, macrophage and NK cells will be activated by these cytokine. ④Activated T cells release cytokine and activate more B cells, macrophage and NK cells. ⑤Cytokine secreted.

Since the recent outbreak, cytokine cascades have been observed in many severe SARS-CoV-2 cases [25,29]. Fig. 2 shows the mechanism of cytokine cascade, also known as an inflammatory cascade. Pathogen infection triggers an intense immune response and inflammatory response and rapid release of a large amount of cytokines (such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, and interferon-γ (IFN-γ)). In this context, patients with viral infection are particularly susceptible to acute respiratory distress syndrome and multiple-organ failure. Cytokine cascades and low lymphocytes are also specific in other severe coronavirus diseases (such as SARS and MERS) and are positively related to disease progression and severity [30–32]. Recent studies have confirmed this conclusion, showing low lymphocytes and elevated inflammatory cytokines in most SARS-CoV-2 cases [33,34]. Once triggered, the cytokine cascade may cause rapid failure of one or more organs with extremely adverse prognosis if not treated promptly. It is considered an important risk factor for mortality in critical SARS-CoV-2 cases. Wei et al. and Xu et al. from the University of Science and Technology of China conducted immunological analyses of blood samples from 33 patients with SARS-CoV-2 infection to investigate how the cytokine cascade occurs in severe SARS-CoV-2 cases. The results showed that SARS-CoV-2 rapidly activates pathogenic T cells and induces the release of a large amount of inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1, IL-6, and IFN-γ. GM-CSF activates $CD14^+$ cells, $CD16^+$ cells, and monocytes, resulting in further release of inflammatory cytokines such as IL-6. This process continues to strengthen the inflammatory cascade. The intense immune response causes damage to the lungs and other vital organs. Li *et.al* also found that the direct attack on other organs by disseminated SARS-CoV-2, the immune pathogenesis caused by the systemic cytokine storm, and the microcirculation dysfunctions together lead to viral sepsis. Therefore, effective antiviral treatment and measures to modulate the innate immune response and restore the adaptive immune response are important for breaking the vicious cycle and improving the treatment effect [6].

10. Conclusion and outlook

While SARS-CoV-2 is highly infectious, with a basic reproduction number (R_0) of 3.77 (for SARS, R_0 = 3–5) [35,36], most cases are mild, and the overall mortality is low. Based on current data, the mortality rate is higher in patients aged 60 or above and in patients with underlying diseases such as hypertension, diabetes, and cardiovascular disease. At present, although epidemic prevention and control efforts have achieved remarkable results in China, SARS-CoV-2 is emerging as a pandemic world-wide. In addition, although Wuhan was the "place of discovery" of SARS-CoV-2, it was probably not the "place of origin". Many recent studies have shown that there are many possibilities for the origin of this virus [37–39]. Moreover, gene sequence analysis has proved that patients with SARS-CoV-2 infection in some countries had no history of exposure to Wuhan, and the relevant virus had no homology, with significant differences [40,41]. SARS-CoV-2 is a novel coronavirus, and we are still trying to understand how it spreads and causes disease, which makes it more challenging to prevent and control the epidemic [42,43].

Since the outbreak, in addition to strict controls based on epidemiological characteristics, the development of vaccines and targeted antiviral drugs is under way, and attention is being paid to supportive care and rescue of severe cases [44]. The new infectious disease manifests mainly as respiratory symptoms, but more and more studies have shown that the virus affects many other systems in humans as well. This complicates potential clinical manifestations and makes it harder to treat such cases [45,46]. However, with a deeper understanding of this virus from biomedical research and epidemiological observation, researchers will know more about how SARS-CoV-2 damages the respiratory system, circulatory system, digestive system, urogenital system, and central nervous system in the near future, which will provide important clues to etiologic research, diagnosis, differential diagnosis, treatment, and prognostic assessment. When developing the treatment plan for SARS-CoV-2 patients, it is important to perform a comprehensive assessment of vital organ function and provide symptomatic treatment. Specifically, patients should be monitored for liver and kidney function and receive supportive care as needed, in order to reduce the risk of inflammatory cascade and improve overall treatment outcomes. In addition, it is important to investigate the structural and functional variation and patterns of SARS-CoV-2 to investigate its molecular mechanisms in different organs and look for potential targets or receptors in order to aid in the development of vaccines and screens of antiviral drugs. Table 1 lists some traits of known coronaviruses as a reference for researchers. The homology of SARS-CoV-2 and the common poultry coronavirus genome is 40.3 % ~ 51.7 %, and that of

Table 1
Coronavirus Classification.

Name	Host	Site of infection				
		Respiratory System	Digestive System (Intestinal Tract)	Digestive System (Liver)	Central Nervous System	Other
HCoV 229 E	Human	√			?	
HCoV NL63	Human	√				
Porcine transmissible gastroenteritis virus	Pig	√	√			√
Porcine epidemic diarrhea virus	Pig					
Porcine respiratory coronavirus	Pig	√				
Canine coronavirus	dog		√			
Feline enteric coronavirus	Cat		√			
Feline infectious virus	Cat	√	√	√	√	√
Rabbit coronavirus	Rabbit		√			√
Bat coronavirus HKU2	Bat					
HCoV OC43	Human	√	?		?	
HCoV HKU1	Human	√				
SARS-CoV	Civet, Human	√	√		√	√
SARS-CoV-2	Bat, Human	√	√	?	√	√
Hemagglutinating encephalomyelitis virus	Pig	√	√		√	
Murine hepatitis virus	Mouse	√	√	√	√	
Rat sialodacryoadenitis virus	Rat					√
Bovine coronavirus	Cattle		√			
Bat coronavirus HKU1	Bat					
Infectious bronchitis coronavirus	Chicken	√		√		√
Turkey coronavirus	Turkey	√	√			

* Other coronavirus diseases include immune disorders (leukopenia, lymphopenia, autoimmune disorders), peritonitis, hypoplasia,nephritis, meningitis, parotitis, myocarditis, and sialodacryoadenitis.

the common poultry β-coronavirus genome is 49.5 % ~ 51.7 %, indicating that the homology of common poultry coronavirus and SARS-CoV-2 is less than 52 %, showing a distant relationship. The results of S protein analysis showed that the homology of S-protein gene sequence of SARS-CoV-2 and common poultry coronavirus was 37.1 % ~ 46.2 %, and the homology of S-protein amino acid sequence was very low, less than 31 % [47–49]. In addition, since the genomic homology between SARS-CoV-2 and poultry coronavirus is only about 50 %, it can be considered that cross-species infection is difficult to achieve. Overall, in terms of susceptibility, except for the seven coronaviruses that can infect humans, poultry or other host-related coronaviruses appear to be less susceptible to human disease in the present study [50,51].

We believe that with concerted efforts among the government, healthcare professionals, and biomedical researchers, the COVID-19 epidemic will be brought under control in the near future. The treatment outcomes of confirmed cases will improve, and the mortality of critical cases will decrease. We will win this battle against this epidemic that affects not only the population of 10 million in Wuhan but the rest of the world as well. We sincerely appreciate the sacrifice and efforts of front-line healthcare professionals.

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Availability of data and materials

The datasets used and analysed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

YHZ and XCG were the major contributors to the writing and revision of the manuscript. YLT, QL and CX collected the related references and participated in discussions. JLX, LCH and ZMZ revised this article critically for important intellectual content. XPL provided help in the production of manuscript figures. FLL and HW gave approval for the final version of the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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References

[1] P. Zhou, X.L. Yang, X.G. Wang, B. Hu, L. Zhang, W. Zhang, et al., A pneumonia outbreak associated with a new coronavirus of probable bat origin, Nature 579 (7798) (2020) 270–273.
[2] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, et al., A Novel Coronavirus from

Patients with Pneumonia in China, 2019, New England J. Med. Surg. Collat. Branches Sci. 382 (8) (2020) 727–733.
[3] X. Zou, K. Chen, J.W. Zou, P.Y. Han, J. Hao, Z.G. Han, The single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection, Fronts Med. (2020), https://doi.org/10.1007/s11684-020-0754-0.
[4] W. Wang, Y. Xu, R. Gao, R. Lu, K. Han, G. Wu, et al., Detection of SARS-CoV-2 in different types of clinical specimens, JAMA (2020) e203786, , https://doi.org/10.1001/jama.2020.3786.
[5] National health commission of China, Diagnosis and Treatment of Novel Coronavirus Pneumonia (trial Version 7), (2020).
[6] H. Li, L. Liu, D.Y. Zhang, J.Y. Xu, H.P. Dai, N. Tang, SARS-CoV-2 and viral sepsis: observations and hypotheses, Lancet S0140-6736 (20) (2020) 30920–X.
[7] R. Lu, X. Zhao, J. Li, P. Niu, B. Yang, H. Wu, et al., Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding, Lancet 395 (10224) (2020) 565–574.
[8] H.J. Li, L. Li, X. Wang, et al., HIV/AIDS[M]// Radiology of Infectious Diseases vol. 1, Springer, Netherlands, 2015.
[9] A.J. Turner, Chapter 25 - ACE2 cell biology, regulation, and physiological functions, in: T. Unger, U.M. Steckelings, R.A.S. dos Santos (Eds.), The Protective Arm of the Renin Angiotensin System (RAS), Academic Press, Boston, 2015, pp. 185–189.
[10] E.M. Richards, M.K. Raizada, ACE2 and pACE2: a pair of aces for pulmonary arterial hypertension treatment? Am. J. Respir. Crit. Care Med. 198 (4) (2018) 422–423.
[11] I. Hamming, W. Timens, M.L.C. Bulthuis, A.T. Lely, G.J. Navis, H. van Goor, Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis, J. Pathol. 203 (2) (2004) 631–637.
[12] R. Mao, J. Liang, J. Shen, S. Ghosh, L.R. Zhu, H. Yang, et al., Implications of COVID-19 for patients with pre-existing digestive diseases, Lancet Gastroenterol. Hepatol. 5 (5) (2020) 426–428.
[13] S.H. Wong, R.N. Lui, J.J. Sung, Covid-19 and the digestive system, J. Gastroenterol. Hepatol. (2020), https://doi.org/10.1111/jgh.15047.
[14] W. Liang, Z. Feng, S. Rao, C. Xiao, Z. Lin, Q. Zhang, et al., Diarrhea May Be Underestimated: a Missing Link in 2019 Novel Coronavirus, (2020) 2020.02.03.20020289.
[15] X. Chai, L. Hu, Y. Zhang, W. Han, Z. Lu, A. Ke, et al., Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection, (2020) 2020.02.03.931766.
[16] J. Wang, S. Zhao, M. Liu, Z. Zhao, Y. Xu, P. Wang, et al., ACE2 Expression by Colonic Epithelial Cells Is Associated With Viral Infection, Immunity and Energy Metabolism, (2020) 2020.02.05.20020545.
[17] Z. Li, M. Wu, J. Guo, J. Yao, X. Liao, S. Song, et al., Caution on Kidney Dysfunctions of 2019-nCoV Patients, (2020) 2020.02.08.20021212.
[18] C. Fan, K. Li, Y. Ding, W.L. Lu, J. Wang, ACE2 Expression in Kidney and Testis May Cause Kidney and Testis Damage After 2019-nCoV Infection, (2020) 2020.02.12.20022418.
[19] Z. Wang, X. Xu, scRNA-seq Profiling of Human Testes Reveals the Presence of the ACE2 Receptor, A Target for SARS-CoV-2 Infection in Spermatogonia, Leydig and Sertoli Cells, Cells 9 (4) (2020).
[20] Coronary Virus Disease (COVID-19) Clinical Prevention Strategies Experts Compilation Group, 2019 expert consensus on clinical prevention and treatment of coronavirus disease (COVID-19), Chin. J. Neuro. 53 (0) (2020) E001.
[21] Y. Wu, X. Xu, Z. Chen, J. Duan, K. Hashimoto, L. Yang, et al., Nervous system involvement after infection with COVID-19 and other coronaviruses, Brain Behav. Immun. 20 (2020) 30357-3.
[22] L. Zhou, M. Zhang, J. Wang, J. Gao, Sars-Cov-2: underestimated damage to nervous system, Travel Med. Infect. Dis. (2020) 101642, , https://doi.org/10.1016/j.tmaid.2020.101642.
[23] Y.C. Li, W.Z. Bai, T. Hashikawa, The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25728.
[24] T. Sun, J. Guan, Novel coronavirus and central nervous system, Eur. J. Neurol. (2020), https://doi.org/10.1111/ene.14227.
[25] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506.
[26] X.T. Xu, P. Chen, J.F. Wang, J.N. Feng, H. Zhou, X. Li, et al., Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission, Sci. China-Life Sci. 63 (3) (2020) 457–460.
[27] R. Adao, T.J. Guzik, Inside the heart of COVID-19, Cardiovasc. Res. 116 (6) (2020) e59–e61.
[28] M. Madjid, P. Safavi-Naeini, S.D. Solomon, O. Vardeny, Potential effects of coronaviruses on the cardiovascular system: a review, JAMA Cardiol. (2020), https://doi.org/10.1001/jamacardio.2020.1286.
[29] S. Wan, Q. Yi, S. Fan, J. Lv, X. Zhang, L. Guo, et al., Characteristics of Lymphocyte Subsets and Cytokines in Peripheral Blood of 123 Hospitalized Patients with 2019 Novel Coronavirus Pneumonia (NCP), (2020) 2020.02.10.20021832.
[30] J.R. Tisoncik, M.J. Korth, C.P. Simmons, J. Farrar, T.R. Martin, M.G. Katze, Into the eye of the cytokine storm, Microbiol. Mol. Biol. Rev. 76 (1) (2012) 16–32.
[31] C.G. Li, P.H. Yang, Y.L. Zhang, Y. Sun, W. Wang, Z. Zou, et al., Corticosteroid treatment ameliorates acute lung injury induced by 2009 swine origin influenza a (H1N1) virus in mice, PLoS One 7 (8) (2012).
[32] P. Younan, M. Iampietro, A. Nishida, P. Ramanathan, R.I. Santos, M. Dutta, et al., Ebola virus binding to Tim-1 on t lymphocytes induces a cytokine storm, Mbio. 8 (5) (2017).
[33] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, et al., Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China, JAMA (2020) e201585, , https://doi.org/10.1001/jama.2020.1585.
[34] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, et al., Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study, Lancet 395 (10223) (2020) 507–513.
[35] Y. Yang, Q. Lu, M. Liu, Y. Wang, A. Zhang, N. Jalali, et al., Epidemiological and Clinical Features of the 2019 Novel Coronavirus Outbreak in China, (2020) 2020.02.10.20021675.
[36] Q. Li, X. Guan, P. Wu, X. Wang, L. Zhou, Y. Tong, et al., Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia, New England J. Med. Surg. Collat. Branches Sci. 382 (13) (2020) 1199–1207.
[37] C.L. Huang, Y.M. Wang, X.W. Li, L.L. Ren, J.P. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet. 395 (10223) (2020) 497–506.
[38] John Cohen, Wuhan seafood market may not be source of novel virus spreading globally, Science (2020), https://doi.org/10.1126/science.abb0611.
[39] K.G. Andersen, A. Rambaut, W.I. Lipkin, E.C. Holmes, R.F. Garry, et al., The proximal origin of SARS-CoV-2, Nat. Med. 26 (4) (2020) 450–452.
[40] T. Phan, Genetic diversity and evolution of SARS-CoV-2, Infect. Genet. Evol. 81 (2020) 104260.
[41] X. Tang, C. Wu, X. Li, Y. Song, X. Yao, X. Wu, et al., On the origin and continuing evolution of SARS-CoV-2, Sci. Rev. (2020), https://doi.org/10.1093/nsr/nwaa036.
[42] C. Wang, P.W. Horby, F.G. Hayden, G.F. Gao, A novel coronavirus outbreak of global health concern, Lancet 395 (10223) (2020) 470–473.
[43] W.Y. Khot, M.Y. Nadkar, The 2019 novel coronavirus outbreak - A global threat, The J Associa Physic India 68 (3) (2020) 67–71.
[44] S. Lu, Timely development of vaccines against SARS-CoV-2, Emerg Microbes Infec. 9 (1) (2020) 542–544.
[45] S.B. Jiang, S. Xia, T.L. Ying, L. Lu, A novel coronavirus (2019-nCoV) causing pneumonia-associated respiratory syndrome, Cell. Mol. Immunol. (2020), https://doi.org/10.1038/s41423-020-0372-4.
[46] J. Li, W. Liu, Puzzle of highly pathogenic human coronaviruses (2019-nCoV), Protein Cell 11 (4) (2020) 235–238.
[47] A. Grifoni, J. Sidney, Y. Zhang, R.H. Scheuermann, B. Peters, A. Sette, A sequence homology and bioinformatic approach can predict candidate targets for immune responses to SARS-CoV-2, Cell Host Microbe 27 (4) (2020) 671–680 e2.
[48] D. Cyranoski, Mystery deepens over animal source of coronavirus, Nature 579 (7797) (2020) 18–19.
[49] D. Niemeyer, K. Mosbauer, E.M. Klein, A. Sieberg, R.C. Mettelman, A.M. Mielech, et al., The papain-like protease determines a virulence trait that varies among members of the SARS-coronavirus species, PLoS Pathog. 14 (9) (2018) e1007296.
[50] J. Cui, F. Li, Z.L. Shi, Origin and evolution of pathogenic coronaviruses, Nat. Rev. Microbiol. 17 (3) (2019) 181–192.
[51] S. Su, G. Wong, W. Shi, J. Liu, A.C.K. Lai, J. Zhou, et al., Epidemiology, genetic recombination, and pathogenesis of coronaviruses, Trends Microbiol. 24 (6) (2016) 490–502.