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Review Article

The Clinical Characteristics and Treatment Approaches of COVID-19: A Concise Review

Sajjad Eslamkhah[1#], Nazila Alizadeh[1#], Khalil Hajiasgharzadeh[1], Masoud Eslamkhah[2], Ahad Mokhtarzadeh[1], Behzad Baradaran[1,3,4*]

[1]*Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[2]*Islamic Azad University Central Tehran Branch, Tehran, Iran.*
[3]*Pharmaceutical Analysis Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*
[4]*Neurosciences Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.*

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Abstract

A series of cases of pneumonia occurred in China in late 2019. For this type of coronavirus, the World Health Organization (WHO) formally identified the condition as a coronavirus disease 2019 (COVID-19). They announced that this disease is the recent main concern of health problems in the world. Transfer of this novel coronavirus (nCoV) from human to human exists predominantly among family members, who have close contact with each other. This review article is provided based on the recent findings of COVID-19, which were retrieved by searching PubMed, Google Scholar, Scopus, and Web of Science until December 2020. Here, we highlighted the coronaviruses types, COVID-19 symptoms, epidemiology of the disease, transmission ways, and nCoV related pneumonia pathogenesis and continue with characteristic features and treatment methods. While no approved treatments are available for this type of infection therapy but several drugs may have potential benefits. It seems that identifying the detailed characteristics of the novel coronavirus disease offers the foundation for further research into the production of effective anti-COVID-19 drugs and vaccines.

Introduction

A series of pneumonia cases, a recently described coronavirus disease 2019 (COVID-19), occurred in China in late 2019.[1] The fast spread of this disease led the World Health Organization (WHO) to announce a global emergency in late January 2020. Following the public concerns, the researchers separated the SARS-CoV-2 from the infected samples, which led to the genome sequence of novel coronavirus (nCoV).[2] This virus is a β-coronavirus (subfamily Orthocoronavirinae) that belongs to nonsegmented and positive-sense RNA (subgenus sarbecovirus).[3] Coronaviruses are classified into four genera (alpha (α), beta (β), gamma (γ), and delta (γ) coronaviruses).[4,5] Mammals may infect with α- and β-CoV.[4,5] It was found that nCoV's genome sequence is 96% similar to a RaTG13 bat Coronaviruses, although it shares SARS-CoV's identity at 79.5 percent. Based on the findings of virus genome sequencing and evolutionary research, the bat founded to be a typical host with virus sources, yet nCOV may spread from bats to humans contaminated by unknown intermediate hosts. It is now clear that angiotensin-converting enzyme 2 (ACE2) is the same receptor for SARS and nCoV (SARS-CoV-2), which was used for attacking the human body.[6] At the first of spread outs times, the reservoirs and dissemination of the outbreak of acute respiratory tract infection likely were related to a seafood market in Wuhan, China, in late 2019. Bat CoV RaTG13 was analyzed in the COVID-19 virus genome sequence. Also, the genome sequence identity was found to be around 96%.7, suggesting that new coronavirus in bats and humans have the same source, even though bats are not eligible for selling in this market as seafood.[7] Besides, the similarity of protein sequences and phylogenetic research has shown that similar receptor residues have been found in many species, rendering alternative intermediate hosts, such as snacks, tortoises, and pangolins.[8]

Transferring of nCov from human to human exists predominantly among family members, who have closely interacted with patients. It confirmed that ~ 30% of recent patients traveled to Wuhan and around 72% of non-resident Wuhan patients contacted Wuhan patients.[8] Transmission between health care staff occurred in ~ 4% of nCoV positive patients, released on 14 February 2020 by China's National Health Commission. Conversely, SARS

*Corresponding Author: Behzad Baradaran, E-mail: baradaranb@tbzmed.ac.ir, #equally contributed to this article

and MERS-Coronavirus transmission are known to occur mainly via nosocomial transmission routes. Healthcare workers' infections between 33 to 42% of SARS cases and patient dissemination (between 62 to 79%), the most common infection pathway in MERS-Coronavirus cases. The primary transmission pathway of SARS-CoV-2 was accused of having a close connection with intermediate host animals or ingestion of them. But the source(s) of nCoV and the transmission routine(s) remain elusive.[8] Altogether, the outbreak of COVID-19 is considered a serious threat to public health. Despite the diversity of therapeutic strategies, there is no desired treatment to prevent potential death. Here, we are just beginning to uncover the clinical characteristics, receptors involved in virus entry and invasion, and the possible treatment approaches. Understanding the precise mechanisms that participate in this disease will lead to efficient therapies to eliminate the virus.

Epidemiology

Geographic spread of COVID-19

Upwards of 229,329,042 of verified COVID-19 cases have been identified worldwide (WHO, September 2021). Nearly 100,000 COVID-19 cases have been recorded in China after the first reports of Wuhan incidents, a city in Hubei Province of China, in late 2019, most of them come from Hubei and neighboring provinces. A joint WHO and China fact-finding team predicted that the outbreak of China would peak at the end of January and the beginning of 2020.[9] Nevertheless, cases were recorded in all continents, except Antarctica, and in several countries that have been slowly growing, such as the USA, several Western European countries (including the United Kingdom), and Iran.[10]

Distribution route

There is a lack of understanding of the risk of transmission. Around the onset of the epidemic, an epidemiological study in Wuhan established an initial link with a market for seafood that purchased animals, but most people operated or worked, and it was ultimately closed for disinfection.[9] Nevertheless, as the disease progressed, the primary mode of dissemination was distributed from person to person. Man-to-man transmission of nCoV is primarily believed to exist by respiratory droplets that mimic the transmission of influenza. The virus is entered into the respiratory system through the cough, sneeze, and speak by a person whether he/she is in close contact with mucous membranes. If a person comes in touch with a polluted surface and then reveals his/her eyes, nose, or mouth, contamination can also occur. Besides, we should mention the importance of aerosol transmission. Usually, the aerosol could not move more than 4 meters and could not stay in the air. It is estimated that the maximum transmission distance of this virus might be 4 meters from the COVID-19 patient.[11] The result of one study shows that nCoV remained viable for about 3 hours in experimentally produced aerosols, the importance of this event for the COVID-19 epidemiology and its clinical effects have not been identified yet.[12] In some cases, despite the existing confusion surrounding transmission mechanisms, airborne precautions are recommended. The blood and bowel specimens observed nCoV RNA.[13,14] In some cases, the live virus was cultured from the stool.[14] Nevertheless, according to the WHO report, transmission between fecal and oral subjects did not seem to be a pivotal factor in the spread of infection.[14] In general, speaking long-time and spreading viral aerosols in the air can significantly increase the chances of transmitting the disease.

Period of infection

The amount of time that a person with COVID-19 is infectious is unknown. Most of the evidence that raises this issue comes from respiratory and other specimen analysis studies that have been applied in the identification of viral RNA. However, the viral RNA identification does not indicate the existence of the viruses. Viral RNA rates tend to be higher in early on the onset of symptoms in comparison to the later stage of the disease;[15] It may render transfer more likely at an early step of infection, but more tests are required to test this assumption. The duration of the viral shedding is often variable, and a large number of variation appears to arise, which depends on the disease extent. In one sample of twenty-one patients with moderate illness, 90% had repeated negative RNA tests on nasopharyngeal swaps ten days following the onset of symptoms. Instead, RT-PCR was positive in all patients with severe symptoms, on or after the tenth day. The results in patients with more severe illness remained positive for long periods. Conversely, all critically ill patients still became positive beyond the tenth-day post-onset.[16] Generally, these results are similar to data from SARS-Cov disease in the years 2002-3, which can be a valuable indicator for assessing the disease severity.[16] The mean length of viral RNA discharge from oropharyngeal samples was twenty days in other 137 patients who endured COVID-19.[17] The reported transmission rates for patients with symptomatic infection vary in location and experience with infection control measures. According to a new WHO-China study, secondary COVID-SARS-CoV-2 prevalence was ranged from 1 to 5% of patients with near contacts to registered patients.[18] On a cruise ship, 2% of crew members acquired a reported infection.[19] In the United States, among 445 near contacts of 10 reported patients, the symptomatic secondary attack incidence was 0.45%.[20] The SARS-CoV-2 transmission from person to person during the incubation period is unclear. Large-scale serological screening can provide a clearer understanding of the prevalence of asymptomatic infections and provide advice on epidemiological analysis; multiple serological experiments are underway for SARS-CoV-2.

Coronavirus Classification

The name of coronavirus derives from its characteristic crown-like appearance in electron micrographs.[21] These

types of viruses classified into four genera, the largest recognized RNA viruses: α (alpha)-CoVs, β (Beta)-CoVs, γ (gamma)-CoVs, and δ (delta)-CoVs, of which α- and β-CoVs may contaminate mammals, while the other two types may affect birds and mammals.[4,5] The genome size of CoVs ranges from 26 to 32 kilobases. The genome includes a 5′ cap structure with a 3′ poly-A tail that enables it to serve as an mRNA for polyprotein replicase translation. Compared to the structural and accessory proteins that make up just about ten kilobases, the replication gene encoding the non-structural proteins comprises almost 2/3 of the genome and are 20 kilobases. Another end of the genome (5′ end) is a leader sequence and untranslated area comprising several stem-loop structures used to duplicate and transcribe the RNA. The 3′UTR also contains the RNA structures and are needed for viral replication of the RNA and then for synthesis. The coronavirus genome composition is 5′-leader-UTR-replicase, spike, envelope, membrane, nucleocapsid, and 3′UTR poly-A tail with an accessory gene interspersed at the 3′ end of the genome among the structural genes[22,23] (Figure 1). In the next subsections, we describe in detail the different characteristics of three types of coronaviruses. Table 1 provides a summary of comparisons between two SARS-CoVs and MERS-CoV.

SARS-CoV

In November 2002, after an epidemic in Guangdong Province, China, atypical pneumonia allegedly caused by SARS-CoV was reported for the first time. In March 2003, the virus spread exponentially to other countries in Southeast Asia and Canada. As the primary route of transmission, this disease has proven highly contagious with respiratory droplets. In some cases of cluster outbreaks, infected feces have played a significant part.[24] Many experiments have shown that SARS-Coronavirus RNA can be observed in SARS patient's plasma, as it is a respiratory illness. The first study was released on 10 April 2003.[25]

It is reported that unusually low amounts of viral RNA were in the plasma of the SARS cases in the acute phase of the disease. Nine days following the announcement of symptoms, the viral plasma content was low. The scientists were only able to identify SARS-CoV RNA using an internally produced nested PCR assay, with a viral load of 190 copies/mL after 2.0 mL of plasma ultracentrifugation.

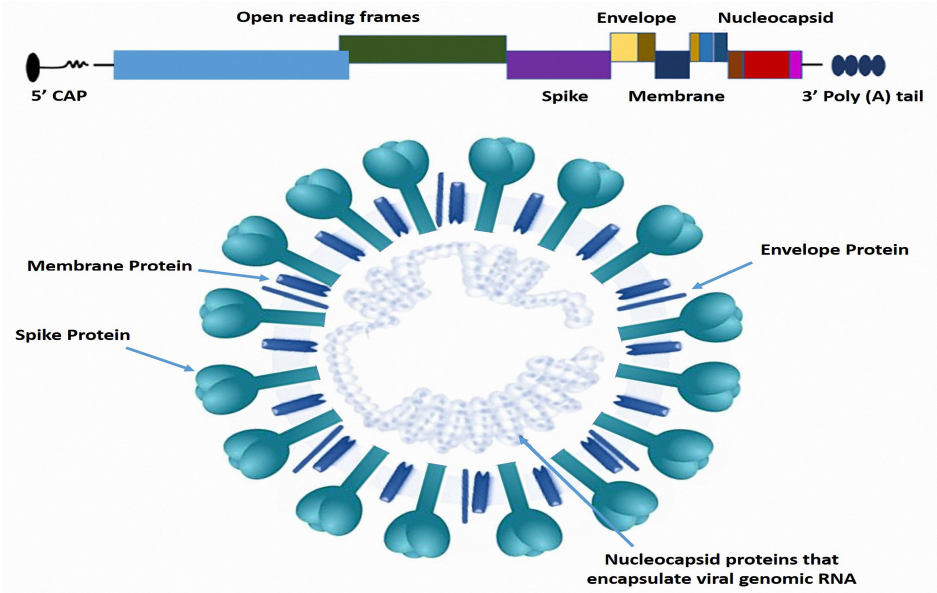

Figure 1. The organization of the genome and schematic structure of severe acute respiratory syndrome coronavirus 2.

Table 1. Summary of some comparisons between SARS-CoV, MERS-CoV, and SARS-CoV-2.

	SARS-CoV-2	SARS-CoV	MERS-CoV
Genus	Clade I, lineage B	Clade I, lineage B	Clade II, lineage C
Length of nucleotides	29.9 kilobases	29.75 kilobases	30.11 kilobases
First emergence	7 December 2019, Wuhan, China	16 November 2002, Foshan, China	4 April 2012, Zarqa, Jordan
Virus identification	January 2020	March 2003	June 2012
Recent status	Pandemic ongoing	Completely control	Sporadic continuous
Number of infected cases	Above 220 million	8096	2553

They were unable to detect viral RNA in plasma from two similar cases, although the sputum of one was positive for 3 of 4 various PCR assays, the viral load in sputum was as large as 6,33104 copies/mL.[26] WHO and food and drug administration (FDA) rely on this report. The other detailed guidelines on the safety of blood outlined for SARS virus transmission by blood transfusion. They also proposed several precautionary guidelines for individuals deferring blood donations from areas of recent local transmission. Two recent articles have centered on new approaches for the identification of SARS-CoV RNA by PCR. The sensitivity of plasma to diagnosis was equal to that of nasopharyngeal specimens within the first three days after the fever initiation. Some other studies revealed that the lymphocytes had a slightly higher level of SARS-CoV RNA amount than plasma, whether measured in acute or convalescent periods.[27] While plasma viral RNA was extracted from only five acute and five convalescent patients.[28] These results have shown that lymphocytes may be one of the targets for SARS-CoV and indicate the risk of transmission through high levels of donor lymphocytes in blood products. Whereas these results provided some evidence that SARS-CoV did indeed occur in plasma or lymphocyte patients with SARS. American Association of Blood Banks (AABB) suggested screening donors for SARS-CoV RNA or associated antibodies based on these factors:

1) SARS cases are not contagious during the incubation process, and the incubation period is fairly small. Virtually all SARS-CoV-infected patients have been identified.
2) The load of the virus from SARS plasma patients[29,30]
3) No cases of transfusion have been announced so far,[26] and the blood donation tests for SARS-CoV RNA did not detect any beneficial effects in 2003.[31]

In 2004, however, an opposing opinion had been articulated by Hong Kongian researchers.[32] Plasma tests from 3 out of 400 normal blood donors and 1 out of 131 non-pneumonic pediatric patients screened through the SARS epidemic proved positive for SARS-CoV IgG antibody. These findings verify in two western blotting analyses. Antibody presence does not imply infectious behavior. However, as Hong Kong was among the worst affected regions of the world through the previous SARS epidemic, it assumed that subclinical or non-pneumonic SARS-CoV infections occurred in Hong Kong, indicating a possible risk of transmission of SARS within blood products. Two Western blot analyses confirmed the results. The operation of the antibody does not indicate an infectious material. Shortly afterward, four various groups posed questions and challenges to the Hong Kong study centered on the precision of the experiments and the community representativeness.[33] The theoretical possibility of SARS-CoV transmission via blood transfusion is calculated to provide further details. The 2003 report estimated an average risk of 14.11 per million and a median risk of 23.57 per million as of 2 April 2003.[33]

MERS-CoV

The MERS virus was first detected in 2012 in an elderly man (nearly 60 y.o.) who had renal failure and acute pneumonia in Saudi Arabia with a fatal outcome.[34] The sixth known human coronavirus was MERS-CoV at the time. MERS is an exceptionally lethal infectious condition with a fatality rate worse than SARS.[26] Major nosocomial outbreaks occurred in Saudi Arabia in 2014 and Korea in 2015.[35] In a viral load study of various specimens of 37 MERS cases, researchers noticed that about half of the serum samples examined had a viral RNA signal through the first week of diagnosis and that the viral load ranged from about 2,1102 to 2,51105 copies/mL, respectively. Nevertheless, they could not isolate the virus from the sera. It is therefore not clear whether or not the live MERS virus was present in the serum.[36] While virtually all MERS subjects show extreme clinical symptoms, atypical cases were identified through the 2015 South Korean epidemic. Although the presentation of the blood virus was limited, the FDA suggested other SARS-like requirements.

SARS-CoV2

A variety of health care providers have reported clusters of unknown causes of pneumonia in patients epidemiologically linked to the Wuhan seafood industry, Hubei Province, in late Dec 2019. China.[37] CoVs cause disease in humans and in various animals, where β-CoVs mainly infect bats and humans[38] (Table 2). The pathogen, coronavirus, or SARS-CoV2, local hospitals have been detected using the pneumonia of unknown etiology surveillance system developed in the aftermath of the 2003 SARS outbreak to facilitate the timely detection of novel pathogens.[39] The WHO announced on Jan 2020 that SARS-CoV2 is a world emergency of public health.[40] The scientists sequenced and described a new β-coronavirus, the genome of which has 86.9 percent similarity to the coronavirus genome of the previously reported bee SARS, which is different from human SARS-coronavirus.[3] Patients with COVID-19 typically have respiratory symptoms, and the median incubation period is less than two weeks. Relevant tests revealed that patients with COVID-19 were able to identify viral RNA in plasma or serum. Viremia was seen in 15 percent of patients in the first 41 patients in Wuhan Area. The mean threshold value of the PCR cycle was 95%, suggesting a fairly low concentration of RNA.[41,42]

Now, AABB and FDA do not require any involvement in the processing and care of blood because no data is suggesting the risk of SARS-CoV-2 transfusion.[41] While the virus appears to need immediate treatment in China and is being tracked quite closely worldwide, the following issues may be important in the patient's management: 1) Serum or Plasma viral RNA could be identified in COVID-19 patients the first two to three days following the start of symptoms; 2) Most patients, particularly younger adults, had milder symptoms than older adults; 3) The asymptomatic carriers may donate blood; 4) The exact risk of infection of patients is unknown, and there is no

Table 2. International Committee of Taxonomy of Viruses (ICTV) classification of β-coronaviruses species and their reservoir hosts.

Coronavirus species	Abbreviations	Reservoir hosts		
China Rattus coronavirus HKU24	RtCoV-HKU24			Rat
Human coronavirus HKU1	HCoV-HKU1	Human		
Murine coronavirus (Murine hepatitis coronavirus)	MHV			Mouse
Bat Hp-betacoronavirus Zhejiang2013	BtHpCoV-ZJ13		Bat	
Hedgehog coronavirus 1	EriCoV-1			Hedgehog
Middle East respiratory syndrome-related coronavirus	MERSr-CoV	Human	Bat	
Pipistrellus bat coronavirus HKU5	BtPiCoV-HKU5		Bat	
Tylonycteris bat coronavirus HKU4	BtTyCoV-HKU4		Bat	
Rousettus bat coronavirus GCCDC1	BtEoCoV-GCCDC1		Bat	
Rousettus bat coronavirus HKU9	BtRoCoV-HKU9		Bat	
Severe acute respiratory syndrome-related coronavirus	SARSr-CoV	Human	Bat	
Betacoronavirus 1 (Human coronavirus OC43)	HCoV-OC43	Human		

plasma, serum, or lymphocyte viral load evidence between individuals during the incubation era.

Therefore, further investigation should be pursued as soon as possible if the risk of SARS-transfusion transmission is higher than other viruses. Some precautions about donor deferral, SARS-CoV-2 RNA monitoring, virus-related antibodies, or the usage of pathogen-inactivation blood products should be closely investigated.

Pathogenesis of COVID-19

COVID-19's extreme symptoms are correlated with growing numbers and death rates, especially in China's epidemic area.[43] The National Health Commission of China announced the reports of the first 17 deaths on 22 Jan 2020, and the deaths on 25 Jan 2020 increased up to 56 deaths. The number of mortality among 2684 confirmed cases of COVID-19 as of January 25, 2020, was roughly 2.84%, and the estimated age of death was 75 years.[44]

Patients diagnosed with COVID-19 displayed elevated amounts of leukocytes, irregular breathing results, and decreased rates of pro-inflammatory cytokines in plasma. One of the COVID-19 case studies indicated a patient with a cough, severe breathing noise in both lungs, and body temperature at 39° C at five days of fever. The sputum of the patient displayed positive results in the real-time PCR of the confirmed COVID-19 infection. Laboratory experiments revealed 2.91×10^9 cells/liter with leucopenia with leukocyte concentrations, 70% of which were neutrophils. In comparison, a blood C-reactive protein value of 16.16 mg/L has been found that is outside the standard range (0–10 mg/Litre). Strong levels of sedimentation with erythrocytes and D-dimer have also been observed.[45] The major pathogenesis of COVID-19 infection as a respiratory system that attacks the virus was extreme pneumonia and severe cardiac injury. In patients with COVID-19 infection relatively elevated blood levels of cytokines and chemokines were reported. Any of the extreme cases admitted to the ICU displayed elevation of pro-inflammatory cytokines like GCSF, IL7, IL2, IL10, IP10, MCP1, MIP1α, and TNFα, which were reasoned to encourage seriousness of the disease.[46]

Among those who have been contaminated, antibodies against the virus are produced. Preliminary data imply that some of these antibodies are reactive, although this remains unmistakably understood. It is uncertain if all affected patients are developing a protective immune reaction and how long this protecting impact will continue. The results of COVID-19 on defense immunity were evolving but still in rather initial steps. Case series analyzing convalescent plasma for COVID-19 therapy detected neutralizing behavior in recovered plasma patients that tended to be passed on to recipients after a plasma infusion.[22] The immune response is important for the prevention and regulation of CoV diseases, but it may also contribute to immune pathogenesis, and is synonymous with an out-of-control immune response. Coronavirus S proteins bind ACE2 to the host cells and bind to the membrane, releasing viral RNA. Pattern recognition receptors (PRRs) identify viral RNAs as pathogen-associated molecular trends (PAMPs). Toll-like receptor (TLR)-3, -7, -8, and -9 usually detect endosomal viral RNA and DNA.[47] Relevant induction adapters such as TIR-domain-containing adaptor proteins such as IFN-β (TRIF), antiviral signaling mitochondrial proteins (MAVS),[48] and protein interferon gene stimulator (STING)[49] to trigger molecules of downstream cascades, Form I Interferons (IFN-α/β) and a sequence of inflammatory cytokines, including the adaptor molecule MyD88, culminating in the activation of some inflammatory transcription factors.[50]

Virus cell interactions thus establish various immune responses against the intrusive virus.[51] Innate immunity is necessary for the removal of the virus and prevents immunopathology. Many plasma cytokines and chemokines were found in COVID-19 patients.[45,52] Of importance is the COVID-19 pneumonia body anatomy test,[45] suggested that COVID-19 triggered inflammatory reactions in the lower airways ducts and suffered lung damage. Collectively, the virus particles first penetrate the

respiratory mucosa and invade other cells, triggering a cascade of immune reactions and the creation of a cytokine storm within the body that may be associated with the critical state of COVID-19 patients.

Clinical Features of COVID-19

As an evolving acute respiratory infection, COVID-19 moves mainly through the airways at a low infectious dosage.[39] Otherwise, in Feb 2020, it is reported the isolation of nCoV from fecal (stool) swabs of a patient who has severe pneumonia.[39] In fecal and semen swabs, nCoV has been identified. ACE2 protein is unusually founded in epithelial lung alveolar cells and small intestinal enterocytes in abundance,[53] That can help to explain the routes of causes of infection and illness. The incubation time is 1 o 14 days, usually 3 to 7 days, depending on existing epidemiologic investigations. And the COVID-19 is contagious at latency.[54] Since nCoV has been authorized, there have undoubtedly been related symptoms in COVID-19 patients, such as weakness, malaise, and cough.[55] Most people or children with moderate flu-like symptoms of nCoV infection and in some cases are in serious condition, rapid progression of ARDS, cardiac and organ failure, and death.[46]

Criteria for diagnosis

Scientists attempted to identify SARS-CoV-2 utilizing Koch's classical postulates and established its morphological characteristics. To date, COVID-19's Golden Therapeutic Diagnosis System is a real-time PCR identification of nucleic acid in nasal or other respiratory tract samples accompanied by next-generation sequencing.[56]

Clinical symptoms

New screening analysis of about a thousand laboratory-confirmed cases showed that typical clinical symptoms involved fever (~89%), exhaustion (~39%), cough (~68%), sputum development (~34%), shortness of breath (~19%), sore throat (~14%), and headache (~14%), Loss of smell (15-30%), muscle pain or aches(~25%).[8] In comparison, several patients had gastrointestinal symptoms, including diarrhea (~4%) and vomiting (5%). Clinical manifestations were consistent with previous studies of 41, 99, and 138 patients in Hubei Province.[5,46] The major symptoms of fever and cough were upper respiratory and gastrointestinal symptoms, indicating an improvement in viral tropism compared to SARS-CoV,[57] MERS-CoV,[58] and influenza.[59] Elderly persons and others with neurological conditions rapidly evolved into ARDS, septic shock, hard to fix metabolic acidosis, and coagulation deficiency, contributing even to death.[46] Many other patients have normal or decreased WBC counts and lymphocytopenia in laboratory results.[60] Nonetheless, in acute situations, neutrophil, D-dimer, blood urea, and creatinine concentrations were slightly higher, and lymphocyte production continued to decline. Besides, inflammatory factors (IL-6, IL-10, TNF-α) have increased signaling. The studies showed that patients with ICU had higher plasma levels of various cytokines.[8] In comparison, computed tomography imaging has revealed that CT scan in the chest is ground glass variation (~57%) and longitudinal patchy shadowing (~52%),[8] often with rounded anatomy and peripheral lung distribution, examined from patients at Sun Yat-Sen University's Fifth Affiliated Hospital.[61] Clinicians became aware that the usual CT picture presentations tended to include a portion of the patients reported. Due to the low sensitivity of radiological diagnostic methods, clinical tests are needed for infection diagnosis.

Diagnosis of COVID-19

Serologic test

Patients with nCov infection exhibit acute serological responses.[62] Thus, the detection reagents rapidly developed in combination with immunochromatography, colloidal gold, and other technologies.

Genetic test

The two commonly used techniques for nucleic acid determination by nCoV are qRT-PCR and high-throughput sequencing (HTS). The main screening method for nCoV is the blood collection and the high-performance sequencing of the entire genome.[62] However, due to their equipment and costs, the use of HTC technologies in clinical diagnosis is limited. Thus, qRT-PCR is the most general, efficient, and easy method to identify pathogenic viruses in respiratory and blood secretions.[63]

CRISPR/Cas13 System

For samples at concentrations as low as one copy/ml, the Cas13-based specific high-sensitivity enzyme reporter unlocking (SHERLOCK) approach was widely used for Zika virus and Dengue Virus diagnosis.[64] Zhang *et al.*[65] recently published a SHERLOCK technique, focused on CRISPR / Cas13, to diagnose nCoV. The usefulness of this CRISPR/Cas13 method needs to confirmed in COVID-19 patients.

Radiography technology

Radiograph Imaging Engineering Monitoring or CT scan is an important tool in clinical practice for the detection of COVID-19. Some COVID-19 instances have specific features of CT images, including the reciprocal distribution of patchy shadows and the illumination of ground glass.[66] The tremendous advantages of the deep learning method, was introduced to evaluate the characteristics of the radiological graphics for the diagnosis of COVID-19. Artificial intelligence can correctly detect CT images of the most current suspected cases in the 20s, and the precision of the study results reached 96%, significantly improving diagnostic performance, and this approach is currently being used.[67]

Therapies and Management of COVID-19

The growing incidence of SARS-CoV2 infection worldwide has resulted in an immediate need for vaccine or clinical

action to avoid or cure COVID-19 disease. Applicants for drugs or vaccinations. However, due to the minimal extent of the SARS and MERS epidemics, few vaccine-generating or therapeutic studies have been conducted for other closely related coronaviruses that could potentially have COVID-19 infections. Clinical trials testing COVID-19 treatments are underway, although the results of large randomized studies remain uncertain at this point. Thus, the above sections are not to be taken as evidence-based health recommendations but reflect the professional experience with medical treatment, the extrapolation with observations from similar conditions (Figure 2).

Hydroxychloroquine (HCQ)

The medical usage of chloroquine stretches back several decades. Phosphate and sulfate derivatives are classified as antimalarial, and hydroxychloroquine (HCQ) is widely used as an immune-modulatory mechanism in systemic lupus erythematosus. By contrast, chloroquine has an antiviral function against the infection Chikungunya, pneumonia, seasonal CoV infection, and SARS-CoV virus.[68,69] In the case of these viruses, the entry, and reproduction of nCoV cells rely on endocytosis-dependent pH internalization and lysosomal fusion. Being a poor foundation, HCQ meets the cellular pH gradient and accumulates endolysosomes and other acid cell organelles in the acidic environment, thus alkalizing the endosome. Altogether, HCQ interferes with terminal ACE2 glycosylation, which interferes with a virus attachment.[68,69] The antiviral behavior of chloroquine derivatives against nCoV has been observed early in vitro.[70] Based on this, the product was soon placed into clinical use, and early tests showed improved virus clearance and health effects in COVID-19 patients receiving 10-day HCQ therapy.[71] Other experiments disputed findings and found little gain either in the outcome of the disease or in viral clearance.[72] It is disappointing that the largest study to date, HCQ alone or HCQ/azithromycin, found no benefit and increased risk of mortality among patients receiving HCQ.[73] Another analysis of chloroquine diphosphate has been forced to end in early steps due to questions about decreased mortality in the high-doses.[74] The immunomodulatory properties of HCQ are well established and can increase its therapeutic effectiveness.[75] Endosome alkalization reduces receptors functions and interferes with the treatment of epitopes shown by APCs.[76] This combination contributes to a decline in the synthesis of cytokines. Also, HCQ often impairs cell autophagia, a crucial phase of intestinal and adaptive immune

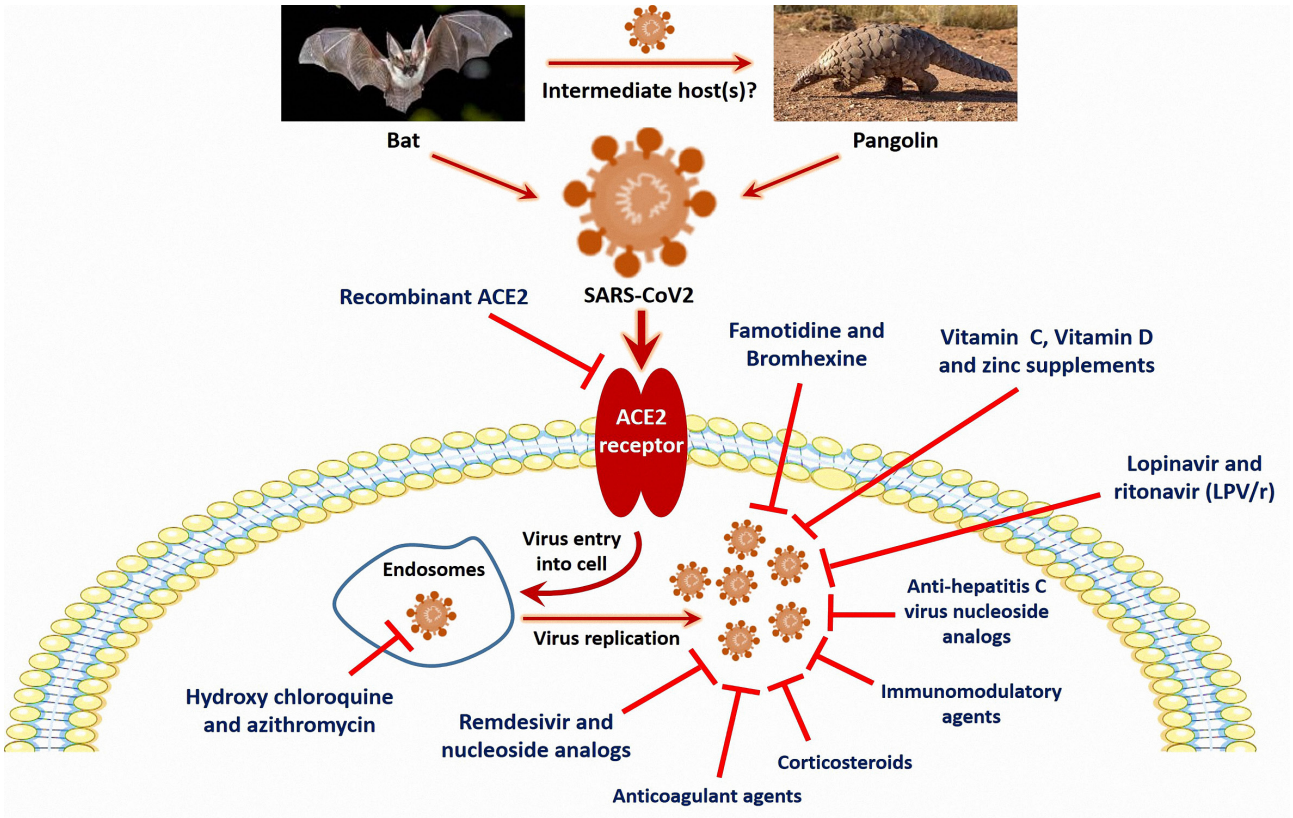

Figure 2. Potential therapeutic intervention in COVID-19 treatment. While no approved efficient therapies are available for this novel coronavirus therapy, but several drugs may have potential benefits. Hydroxy chloroquine in combination with azithromycin can change the pH of endosomes and reduce virus entry and replication. Antiviral treatment with protease inhibitors such as Lopinavir and ritonavir (LPV/r) can limit virus replication. Also, Remdesivir and nucleoside analogs have antiviral potential in this infection. Besides, recombinant ACE2 may bind SARS-CoV2 and/or mediate anti-inflammatory effects to prevent COVID-19 infection. Also, other agents including immunomodulatory and anticoagulant agents, Corticosteroids, Bromhexine and Famotidine, and Vitamin C, Vitamin D, and Zinc supplements may have therapeutic benefits.

activation.[77] Eventually, HCQ has anti-thrombotic effects, which may be useful in COVID-19, where inflammatory activation and endothelial proliferation induce coagulation and promote the formation of micro-thromboses.[78,79] Side effects include conduction dysfunction, heart failure, retinopathy, and hypoglycemia and the therapeutic scope of chloroquine is restricted.[80,81]

Azithromycin

The synergistic activities of azithromycin and HCQ against nCoV have been reported in vitro, which tend to be translated into clinical usage.[82-84] Ironically, azithromycin is often a low base with alkali reactions at least equal to HCQ. Azithromycin antagonizes macrophages cells to the anti-inflammatory M-2 phenotype and restricts the STAT1 and NFκB cascades.[85,86] In the form of anti-inflammatory activity, it is of particular importance for azithromycin to be used in ICU patients.[87-89] Due to the adverse cardiac side effects,[90] the evaluation of patient risk profile, ECG, fluid, and electrolyte status, and polypharmacy control is important in infected cases.[91]

Treatment with antivirals

Remdesivir and nucleoside analogs

Nucleoside analogs are known to be therapeutic alternatives for COVID-19. Applicants include galidesivir, favipiravir, remdesivir, and ribavirin, the latter having received the most coverage.[92,93] Remdesivir is an adenosine drug and has antiviral efficacy in the MERS and SARS in vitro.[94,95] Viral RNA-dependent RNA polymerase (RdRp) inhibited by remdesivir. In this case, substituting and vying with each other for adenosine in RNA synthesizing.[96] Human mitochondrial RdRp has a slightly lower remdesivir sensitivity compared to its viral equivalents and mitigates adverse effects for the host cell.[97] The existence of unique, re-reading exonucleases SARS-CoV2 capable of extracting phosphorylated remdesivir from the RNA chain may give rise to resistance growth. In the mouse model, remdesivir therapy for murine hepatitis virus showed that, while conferring immunity.[94] The timing of the administration of the EBOLA virus and MERS in animal models was critical to remodeling its efficacy, with the most benefit gained from early administration.[95] This is consistent with the above-mentioned cycles of disease with the maximum degree of viral replication at an early stage of the epidemic, and host-mediated immune response damage at later steps. However, the recent case report also highlights the continued benefits of delayed administration.[98] However, there are already trials in Europe and North America. With an effective reduction in pulmonary viral load in animal studies, an appropriate protection profile in Ebola subjects, and a limited community of COVID-19 subjects, remdesivir may provide an important and feasible alternative to treatment.

Remdesivir binds to RNA polymerase, which is dependent on viral RNA, inhibiting viral replication by premature termination of RNA transcription. Its activity against extreme acute coronavirus 2 respiratory syndrome has been demonstrated in in vitro studies.[99] Treatment with remdesivir was started shortly after inoculation in an animal model; remdesivir-treated animals had lower lung virus levels and less lung damage than control groups.[70] In hospitalized adult and pediatric patients (aged about 12 years and weighing about 40 kg), Remdesivir is approved by the FDA for COVID-19. It is also available via the FDA-EUA in hospitalized pediatric patients weighing 3.5 kg to <40 kg or <12 years of age and weighing >3.5 kg for the treatment of COVID-19 (2020-07-27).[100] As a nucleoside analog, remdesivir's active metabolite interferes with the action of viral RNA-dependent RNA polymerase and prevents viral exo-ribonuclease (ExoN) proofreading, causing the production of viral RNA to decrease.[101] For RNA-dependent RNA polymerases of MERS-CoV, SARS-CoV-1, and SARS-CoV-2, after three additional nucleotides have been integrated, RNA synthesis arrest occurs. Remdesivir is therefore known as a direct-acting antiviral agent that acts as a delayed terminator of the chain.[96]

Late administration Lopinavir and ritonavir combination (LPV/r) as protease inhibitors

A mixture of lopinavir and ritonavir (LPV/r), better known by trade names Kaletra ® and Aluvia ®, is a common anti-retroviral therapy for the human immune deficiency virus (HIV). The usage of these Two protease inhibitors inhibits the otherwise common activation of CYP3A4 and drug metabolism, resulting in a much-enhanced bioavailability of Lopinavir.[102] Proteases are important for the reproduction of the majority of viruses. These virus particles attach structural and functional proteins to viral polypeptide precursors. Requires the virus to evolve into a contagious virus. LPV/r is metabolized primarily in the liver and therefore a relative contraindication is considered to be pre-existing hepatic impairment.[102]

In the context of previous in vitro studies and limited clinical data available for Lopinavir and ritonavir in critically nCoV patients, a randomized open-label trial was conducted in China.[103] Almost two hundred COVID-19 patients were recruited, randomized to either standard therapy or two weeks of addition to Lopinavir and ritonavir. Although verifying the efficacy of LPV / r usage in COVID-19, there were no substantial variations in survival or recovery period between groups; thus, the investigators debated whether the combination of Lopinavir and ritonavir and the analog nucleoside, such as ribavirin, might lead to better therapeutic benefits.

Anti-hepatitis C virus nucleoside analogs

Anti-hepatitis C virus nucleoside analogs, including ribavirin, sofosbuvir, and daclatasvir, are being tested for COVID-19 treatment. Ribavirin is a purine nucleoside analog with broad-spectrum antiviral activity. It can be use for hepatitis C virus infection treatment.[104] This drug in combination with interferon was an suggested treatment

regimen for the management of the patients with Middle East coronavirus pneumonia.[105] In addition to ribavirin, sofosbuvir and daclatasvir are direct-acting antiviral drugs against the hepatitis C virus. Some findings suggest these agents may also be effective in COVID-19 therapy. Eslami *et al.*[106] evaluated the effectiveness of sofosbuvir in combination with daclatasvir and confirms these agents are effective in decreasing the mortality in COVID-19.[106] In another study, Abbaspour Kasgari and colleagues investigated the efficacy of sofosbuvir/daclatasvir/ribavirin for hospitalized COVID-19 patients and reveled that trends in favor of these approach for recovery and lower mortality.[107] But, other studies should be conducted to investigate the therapeutic benefits of these agents further.

Recombinant angiotensin-converting enzyme 2 (ACE2)

Since ACE2 was known as the key molecule for cell invasion, its treatment blockade for disease control and virus clearance assistance has been suggested.[108] However, the non-selective ACE blockade with currently active agents may be questionable because it may alter Ang-1 through-7, which has anti-inflammatory and anti-fibrotic effects. In some studies, ACE2 protects against acute respiratory distress syndrome.[109,110] Although ACE2 leads to pulmonary pathologies, such as fibrosis and oedema.[111] Consequently, in the absence of ACE2, angiotensin 2 build-ups can worsen disease and organ failure. As a result, the induction of ACE2 to COVID-19 therapy has recently been recommended.[112-115] Even then, the effects of ACE-2 will differ from tissue to the environment. Intestinal epithelial cells produce slightly higher levels of ACE2 than bronchial epithelial cells, which is notable since not many subjects have gastrointestinal issues and signs are mild when present, while some patients stay optimistic in stool samples long though the respiratory specimen has been negative.[44,53,116,117] Based on the above discussion, it may be suggested that high levels of ACE2 as seen in the intestine and as compared to the respiratory tract. Specific variables, such as immunological conditions or regionally variable microbiomes, greatly influence the absorption, replication, and evacuation of the virion. The specific purpose of angiotensin-converting enzyme 2 in nCoV remains to be revealed and may be complicated. The role of ACE2 in the sense of nCoV remains to be uncovered. The use of human rec-ACE2 to neutralize the virus before its connection to host cells is also being investigated.

Donation of plasma from improved patients

The use of convalescent plasma (CP) collected from previously infected patients for passive transfer of antibodies dates back almost a hundred years, with some evidence of benefit against influenza or Ebola disease, etc. Tends to result from the prospective study during MERS and SARS infections, recorded safety, and faster viral clearance after CP therapy, especially when taken early in the course of the disease.[118] Most patients recovering from infection with COVID-19 develop a circulating antibody response to distinct nCoV proteins two or three weeks after infection. These showed in at least two samples of nCoV-infected rhesus macaques that developed antibody reactions and could not be reinfected with the virus weeks or months later. Most of the existing and ongoing researches documented the benefits of CP usage. It can use to manage critically ill COVID-19 patients with no significant adverse effects. Many patients improve clinically and eliminate the virus, but the role of CP threat in these patients is unclear as all patients get other therapies, including antivirals, antibiotics, and corticosteroid antifungals.[119] There are no approved specific antiviral agents for novel coronavirus disease 2019 (COVID-19 Also, in a separate randomized clinical study reported to date, patients with severe but not intubated disease who received CP showed significant improvement. However, the trials ended early due to a lack of eligible patients at countrywide (Chinese) pandemic sites. The donors would have identified nCoV infection, would have been symptom-free for at least two weeks, and would have met the standard criteria for eligibility of blood donors. New plasma collection centers are established almost daily, and information is rapidly evolving.[120] CP therapy would be at risk of a) Allergic reactions, b) Lung disruption and breathing difficulty, c) Infection transmissions, such as HIV and HBV, and HCV.[120] Anyway, the risk of these infections is very low, as donated blood must meet certain requirements of the FDA. The blood donated must be tested for safety before it can be used. Then it undergoes a process of separating blood cells so that all that remains is antibody plasma.

Immunomodulatory agents

After the outbreak of COVID-19, numerous studies reported the clinical characteristics and cytokine profile of nCoV infected patients and suggested that increased expression of cytokines (Cytokine storm) could be associated with the severity of the disease.[46,121] Considering the pivotal role of the inflammatory responses in the pathogenesis of COVID-19, many anti-inflammatory agents such as TNF-α, IL-1, and IL-6 blocker agents decreased systemic inflammation, suggesting a potential target for controlling COVID-19 complications, and these agents have considered for therapy. Among them, IL-6 inhibitors such as tocilizumab have attracted great interest.[122] To date, many studies reviewed the role of inflammation in COVID-19 and the probable effect of immunomodulatory agents on SARS-COV 2.[123,124] Therefore, based on these findings of the anti-inflammatory agent's effect on the COVID-19, researchers hope these drugs will make efficient and promising treatments to improve systemic inflammation (especially lung tissue inflammation) in COVID-19 patients.

Corticosteroids

Steroid therapy as a global suppression strategy to combat inflammatory diseases.[125] During the SARS and MERS outbreaks, it was reported that these agents did not improve

the outcomes of the patients but increased the secondary infections rate.[126-128] Recently, Zha *et al.*[129] found evidence against the clinical benefits of corticosteroids for COVID-19 patients without acute respiratory distress syndrome.[129] Due to the controversial findings concerning the clinical benefits of steroid therapy, the WHO recommends against treating COVID-19 patients with corticosteroids, and more observational and randomized controlled trials are needed to confirm the effectiveness of corticosteroids appliances in the management of COVID-19.

Anticoagulant therapy

Accumulated evidence has strongly indicated the beneficial effects of anticoagulant agents in COVID-19 patients. It is well known that viral infections are linked to the increased risk of thrombosis. The incidence of pulmonary thrombosis in COVID-19 patients has been reported to be higher than in non-COVID-19 patients.[130,131] The anticoagulation therapy is currently less identified and is not commonly used to COVID-19 patients due to fears of hemorrhage as a side effect. Therefore, validation of the safety and effectiveness of anticoagulant-based treatments for SARS-CoV-2 infected patients is urgently needed.

Bamlanivimab

The neutralizing monoclonal antibody bamlanivimab (LY-CoV555) is intended for mild to moderate levels of Covid-19 treatment. Eli Lilly and Company developed this monoclonal antibody and received the FDA Emergency Use Authorisation (EUA) in Nov 2020 (2020-11-20). The medicine is available for Covid-19 test-positive adults and pediatric patients 12 years of age and older. They are at high risk of progression to serious Covid-19 and hospitalization. Bamlanivimab should be administered immediately to patients after a positive COVID-19 examination and ten days after the onset of symptoms.[132]

Bamlanivimab mechanism of action

Bamlanivimab is a type of recombinant human $IgG1_k$ monoclonal neutralizing antibody that binds to the SARS-CoV-2 spike protein receptor-binding domain and prevents ACE2 receptor attachment to the viral S protein. In the fragment crystallizable (Fc) area, the Covid-19 treatment is unmodified.[133]

Bromhexine and Famotidine

Bromhexine is a form of expectorant used specifically in the treatment of emphysema, bronchiectasis, chronic bronchitis, and chronic obstructive pulmonary disease. Some studies have claimed that Bromhexine is useful in COVID-19 therapy in adults and infants, but no results from a randomized clinical trial have been available. Other findings indicated that Bromhexine is a key protease inhibitor (TMPRSS2) for infection and transmission of novel coronavirus nCoV and has the benefit of low price and improved protection.[134] Bromhexine and its metabolites can also be competitively bound to ACE2.[135] This strongly inhibits the primary M proteases of nCov, promotes the release of endogenous active substances in the lungs, retains alveolar activity, and promotes the excretion of sputum.[136]

Famotidine is used as a suspension and a pill to be swallowed by mouth. Over-the-counter famotidine comes with a pill, a chewable tablet, and a capsule to be swallowed by mouth. In some studies, the beneficial effects of this medication have been identified in COVID-19 patients.[137] In comparison, the use of proton pump inhibitors has not been associated with a decreased risk for these outcomes. Previous anecdotal observations are thought to have suggested that famotidine could be partly protective of COVID-19.[138] In general, this improved survival trend is due to off-target, non-histamine-mediated famotidine-mediated properties that are not shared with cimetidine. Famotidine is presently being studied under the IND waiver for COVID–19 therapy in other studies at elevated intravenous doses in conjunction with either hydroxychloroquine or remdesivir.

Vitamin D, Vitamin C, and zinc supplements

Vitamin D's immuno-modulatory functions in COVID-19

Vitamin D is a fat-soluble steroid hormone precursor arising from exposure to UVB (ultraviolet B) radiation in the skin epidermis of 7-DHC (7-dehydrocholesterol) that has been converted into a circulating precursor of cholecalciferol. Cholecalciferol hydroxylates in the liver to form 25-hydroxyvitamin D and converts in the kidneys into the active hormone $1,25(OH)_2D$ (1,25-hydroxyvitamin D). In a large variety of body systems, vitamin D has functions, including in both innate and adaptive immune responses. Innate cellular immunity is enhanced by Vitamin D through stimulation of expression of antimicrobial peptides like defensins and cathelicidin. Defensins retain strong and gap junctions, promote and adhere to the expression of anti-oxidative genes. It is understood that viruses such as influenza greatly weaken the integrity of epithelial tight junctions, raising the risk of infection and pulmonary edema. The integrity of these junctions is maintained by vitamin D.[139] Low vitamin D receptor expression levels contribute to claudin-2 expression increasing and inflammation. Also, Vitamin D facilitates the division of monocytes into macrophages, thus the production of superoxide, phagocytosis, and destruction of bacteria increased. Besides, by suppressing the role of Th1 cells and decreasing the production of pro-inflammatory cytokines like INF-γ and IL-2, vitamin D can modulate the adaptive immune response. Th2-cell anti-inflammatory cytokines are also activated by vitamin D and indirectly suppress Th1 cells by diverting pro-inflammatory cells to anti-inflammatory phenotypes and activating suppressive regulatory T cells.[140] It has been proposed that vitamin D deficiency increases the rate of infection with COVID-19. COVID-19 patients have been shown to have lower vitamin D levels repeatedly, with mean plasma levels half that of the controls.[141]

Vitamin C's immuno-modulatory functions in COVID-19

Vitamin C has a significant role in improving innate immunity function and improving cellular and humoral immune response. Evidence has shown that insufficient micronutrient intake, including vitamin C, reduces infection resistance and increases disease complications.[142] Vitamin C strengthens the stability of the epithelial barrier, the first line of defense against external pathogens.[143] High oral dose administration of vitamin C (60 mg/kg) increases the natural killer cell's function, which plays a pivotal role in innate immunity against viral infection.[144] Vitamin C accumulates in neutrophils, which indicates that vitamin C plays a role in preserving the normal function of leukocytes.[145] Also, both the amount of leukocyte vitamin C and neutrophil activity tend to decrease with age.[146] As vitamin C enhances the integrity of the epithelial barrier, natural killer cell activity, neutrophil chemotaxis, and phagocytosis, daily vitamin C supplementation could strengthen the innate immune response to infection with SARS-CoV-2. IV vitamin C therapy for the treatment of COVID-19 has shown promising results in China. High-dose IV vitamin C administration decreased the risk of cytokine storm production during the late stage of COVID-19 infection.[147] The combination of vitamin C with glycyrrhizic acid and curcumin stimulated innate immunological antiviral response and prevented excessive inflammatory response, decreasing the risk of tissue damage caused by inflammation.[148]

Role of Zinc in COVID-19

Numerous studies indicated the crucial function of the zinc trace element in the immune system function.[149] Zinc deficiency has changed the number and malfunction of all immune cells. The subjects with suboptimal zinc status have an increased risk of some diseases.[150,151] This deficiency contributes to 16% of all deep respiratory infections worldwide,[152] offers an initial clear indication that zinc deficiency is associated with the risk of infection and severe development of COVID-19. Other studies show that fusion with the host membrane is prevented by zinc and reduces the work of viruses with polymerase, impairs the translation and processing of proteins, prevents the release of viral particles, and destabilizes the viral envelope.[153,154] Low-dose zinc supplementation in conjunction with low concentrations of zinc ionophore pyrithione or hinokitol reduced SARS-CoV RNA synthesis by directly inhibiting RNA-dependent virus RNA polymerase.[155,156]

Conclusion

Since the outbreak of COVID-19 in Wuhan and its dissemination in many countries across the world, scientists in different fields of biological science, including virology, epidemiology, immunology, have looked at the signs and complications of this disease. In this report, we briefly investigated the sources and forms of coronavirus and its prevalence. Throughout the sections, we addressed the differences between SARS, MERS, and SARS-CoV2 viruses and described their pathogenesis. Emerging pneumonia, COVID-19, triggered by SARS-CoV-2 (nCoV), has high infectivity but lower morbidity and mortality virulence relative to SARS and MERS infections. Originating from bat reservoirs and various intermediate species, the coronavirus binds to ACE2 with a strong affinity as a virus receptor to infect humans. In this disease, the vulnerable community comprises older persons, and persons with certain serious medical conditions require more care and support. However, concerns remain unanswered, and further experiments are needed to investigate the mode of transmission and pathogenicity of coronavirus development. Besides, we discussed the potential strategies to treat the disease. Additionally, the complexity of the viral entry and replication was highlighted, which offers the foundation for further work into the production of effective antiviral drugs and vaccines. Many of the infected people and medical staff face severe stress and health problems, including lack of protection, as well as overwork, frustration, and exhaustion.

Author Contributions

SE and NA: Participated in the design of the study and contribution in writing the manuscript, ME: Assistance in writing, KH: Preparing the figures, BB and AM: Supervising and revising the manuscript critically for important intellectual content before submission; editing the manuscript. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare that there is no competing interest.

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