Received: 31 March 2020 | Accepted: 1 June 2020

DOI: 10.1002/jmv.26123

REVIEW

JOURNAL OF MEDICAL VIROLOGY WILEY

SARS-CoV-2: A comprehensive review from pathogenicity of the virus to clinical consequences

Melika Lotfi[1,2] | Nima Rezaei[3,4,5]

[1]Department of Immunology, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran

[2]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Zanjan, Iran

[3]Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran

[4]Department of Immunology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[5]Network of Immunity in Infection, Malignancy and Autoimmunity (NIIMA), Universal Scientific Education and Research Network (USERN), Tehran, Iran

Correspondence
Nima Rezaei, Research Center for Immunodeficiencies, Children's Medical Center Hospital, Dr. Qarib St, Keshavarz Blvd, Tehran 14194, Iran.
Email: rezaei_nima@tums.ac.ir

Abstract

Nowadays, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which caused novel coronavirus disease (COVID-19) pandemic, is the worldwide challenge. The virus is highly contagious, and clinical consequences were very divers. It is estimated that if no effective action is taken, COVID-19 could plague 90% of the world's population and kill over 40 million people. So, it is essential to understand the virus pathogenicity and follow the preventive methods to control the high morbidity and mortality rates. Meanwhile our current knowledge of COVID-19 is still limited, despite hard efforts of scientists and clinicians during last few months. In this review article, we have collected the latest data about characteristics, pathogenesis, clinical manifestations, and diagnostic methods of SARS-CoV-2.

KEYWORDS

2019-nCoV, clinical manifestations, COVID-19, SARS-CoV-2, virulence

1 | INTRODUCTION

A novel coronavirus disease (COVID-19) along with a cluster of pneumonia cases appeared in Wuhan, a city in the Hubei province of China, late 2019, which was declared a pandemic by the World Health Organization (WHO) on 11th March 2020. There are seven coronaviruses which afford disease in humans.[1-3] Two pedigrees including Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV), possessing zoonotic origination, have been connected to outbreaks of severe respiratory diseases in humans in the past,[2] and now a novel coronavirus is the cause of severe respiratory diseases pandemic in humans. Although the novel coronavirus caused the outbreak of COVID-19 (named by WHO), initially named 2019-nCoV by WHO, Coronavirus Study Group of the International Committee suggested SARS-CoV-2.[4]

There is a rapid progression in morbidity and mortality rate of COVID-19 due to human-to-human transmission of the virus. Due to a lack of effective antiviral therapy against COVID-19, current therapies mainly focused on palliative and supportive therapies based on the study published via the National Health Commission of the People's Republic of China.[4] So, the emerging virus rapidly becomes a challenge for global public health.

This comprehensive review paper presents the latest information about characteristics, diagnostic methods, immunopathogenesis, and clinical manifestations of SARS-CoV-2.

2 | CHARACTERISTICS OF SARS-CoV-2

Initially, in 1966 Tyrell and Bynoe described coronaviruses.[5] There are four subfamilies, namely, alpha-, beta-, gamma-, and delta-coronaviruses. Although alpha- and beta-coronaviruses originate from mammals, particularly from bats, gamma- and delta-coronaviruses originate from pigs and birds.[4] The beta-coronaviruses might cause severe disease and fatalities in humans, while alpha-coronaviruses cause asymptomatic or mildly symptomatic infections.[6] SARS-CoV-2 from B lineage of the beta-coronavirus is an enveloped, positive-sense, and single-stranded 29.9 kb RNA virus.[7,8] Resembling the SARS and MERS, the 2019-nCoV genome is made of

a linear, single-stranded, monopartite RNA with a cap structure at its 5′ end and a poly-A tail at the 3′ end.[9] In addition, all coronaviruses possess specific genes (viral replicase gene) in a variable number[6-11] open reading frame (ORF) downstream regions that codify essential proteins for viral replication, nucleocapsid, and spikes formation including spike (S) glycoprotein (it is indispensable for the virus-cell receptor interactions during viral entry), small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein.[2,10,11] In the 5′-terminal two-thirds of viral RNA, chiefly located in the first ORF (ORF1a/b) translates two polyproteins, pp1a and pp1ab, and encodes 16 nonstructural proteins (NSP) such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase,[12] while the remaining ORFs encode accessory proteins that interfere with the host innate immune response.[2] Interestingly, the N-terminal exoribonuclease (ExoN) domain of NSP14 plays a proofreading role in the prevention of lethal mutagenesis.[13] At the protein level, there are no amino acid substitutions that occurred in NSP7, NSP13, envelope, matrix, or accessory proteins p6 and 8b, except in NSP2, NSP3, spike protein, underpinning subdomain, and receptor-binding domain (RBD).[14] Also, recent research suggested that the mutation in NSP2 and NSP3 has a critical role in the infectious potential and differentiation mechanism of SARS-CoV-2.[15] So, the proteins mentioned above are as noteworthy targets to develop antiviral agents against SARS-CoV and MERS-CoV, and since the most genomic encoded proteins of SARS-CoV-2 are 79.5%[4,16,17] similar to SARS-CoVs[18] former drugs used in SARS-CoV epidemic might be effective against SARS-CoV-2.

Resembling SARS-CoV, SARS-CoV-2 uses angiotensin-converting enzyme2 (ACE2) receptor to infect humans.[19] It must be mentioned that the high affinity of the virus to the ACE2 receptor is likely due to natural selection instead of deliberate manipulation.[20]

Although according to virus genome sequencing results and evolutionary analysis, SARS-CoV-2 is 96.2% identical to a bat CoV RaTG13,[19] a recent study suggested smuggled pangolins from Malaysia to China, as the probable virus origin,[21] which might infect human through probable alternative intermediate hosts like turtles and snacks.[22]

3 | ENTRANCE AND REPLICATION OF SARS-CoV-2

Coronavirus S protein has been shown as a remarkable determinative of virus entry into host cells.[23] The entrance of SARS-CoV into cells is primarily performed via direct membrane fusion between the virus and plasma membrane[24] like MERS-CoV,[25] which has evolved an abnormal two-step furin activation for membrane fusion as well. Belouzard et al[26] reported that a significant proteolytic cleavage event happened at SARS-CoV S protein at position (S2′) mediated the membrane fusion and viral infectivity. Alongside the membrane fusion, the clathrin-dependent and -independent endocytosis mediates the SARS-CoV entry as well.[27,28] After the virus entrance to the cells, the viral RNA genome is unleashed into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome initiates replication.[29] It must be mentioned that like human immunodeficiency virus (HIV), SARS-CoV-2 contains a potential cleavage site for furin proteases for activating the polyproteins.[30] The newly formed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi, and the nucleocapsid is created through the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment. Eventually, the vesicles containing the virus particles fuse with the plasma membrane to release the virus.[23]

4 | THE DIAGNOSIS OF SARS-CoV-2

Quantitative real-time polymerase chain reaction (qRT-PCR) test has prevalently been applied for the identification of causative viruses from respiratory secretions and final pathogenic diagnostics of COVID-19. At present, the mentioned technique is considered as a practical approach for confirming the diagnosis in clinical cases of COVID-19,[31] and more than seven types of SARS-CoV-2 nucleic acid test kit have been developed and approved rapidly.[31,32] Like the supreme Pure Viral RNA Kit (Roche), HiScript II, and one Step qRT-PCR SYBR Green Kit (Vazyme Biotech Co, Ltd).[33]

The diagnosis of COVID-19 based on the stage of infection can be made through detecting nucleic acids of SARS-CoV-2 in specimens like nasopharyngeal and oropharyngeal swabs,[34] sputum, lower respiratory tract secretions, stool, and blood.[35] It was found that the anal swabs gave more positive results than oral swabs in the later stages of the infection.[33] Hereupon, the clinicians have to be cautious while discharging any COVID-19 infected patient based on negative oral swab test results due to the possibility of fecal-oral transmission. Recently, the live virus was detected in the self-collected saliva of patients infected with COVID-19. These findings were confirmative of using saliva as a noninvasive specimen for the diagnosis of COVID-19.

However, due to the restriction of sampling materials, specifically in the early stage of the disease, the positive rate is relatively low. Also, these techniques are associated with unnecessary risks to health care workers due to close contact with patients.[36]

The patients infected with COVID-19 had elevated plasma angiotensin2 levels. The level of angiotensin2 was found to be linearly associated with the viral load and lung injury, indicating its potential as a diagnostic biomarker.[37]

In-house anti-SARS-CoV IgG and IgM enzyme-linked immunosorbent assay (ELISA) kits were extended applying SARS-CoV Rp3 NP as an antigen, that portioned above 90% amino acid identity to all SARS-CoVs.[7] For the IgG test, MaxiSorp Nunc-Immuno 96 well ELISA plates were coated (100 ng/well) overnight with recombinant NP, and the IgM test, MaxiSorp Nunc-Immuno 96 well ELISA plates were coated (500 ng/well) overnight with antihuman IgM (μ chain).[33] Also, there is a clinical trial for serological detecting of SARS-CoV-2 named, Clinical Performance of the VivaDiag COVID-19 IgM/IgG rapid test in early detecting the infection of COVID-19 (NCT04316728).

Chest computed tomography (CT) is a perfect diagnostic implement for recognizing viral pneumonia as the sensitivity of chest CT images was 97% with reference RT-PCR,[38] and the sensitivity of chest CT is far more superior to the X-ray.

Moreover, in asymptomatic patients of COVID-19, lung CT scans have shown pneumonia.[39] Thus, for early diagnosis of the virus, chest CT is preferable.[40]

Chest CT findings[41] are as follow: ground-glass opacity (86%), consolidation (29%), crazy-paving (19%), linear (14%), cavitation (0%), discrete nodules (0%), pleural effusion (0%), lymphadenopathy (0%), bilateral distribution (76%), and peripheral distribution (33%). Moreover, the primary focal unilateral ground-glass opacities may progress to diffuse bilateral ground-glass opacities and will further progress to or coexist with lung consolidations changes within 1 to 3 weeks.[42]

5 | THE SARS-CoV-2 PATHOGENESIS

CoVs induce inflammation in lung tissue. The histological examination of lung biopsy specimens received from COVID-19 infected patients revealed diffuse alveolar damage, desquamation of pneumocytes, hyaline membrane formation, and cellular fibromyxoid exudates connotative of acute respiratory distress syndrome (ARDS).[43] The latest autopsies have confirmed that lungs are filled with clear liquid jelly, much like the lungs of wet drowning.[43] Although the nature of the crystal clear jelly has not yet been recognized, there is a connection between it and ARDS,[44] which is the potential of death.

In the healthy human lung, the ACE2 receptor is expressed on type I and II alveolar epithelial cells. Not only 83% of the type II alveolar cells have ACE2 receptor expression, but men also had a higher ACE2 receptor level in their alveolar cells than women. Moreover, the level of ACE2 receptor expression in Asians' alveolar cells is higher than that of White and African American populations. So, it is why Asian men are at high risk of the infection.

The binding of SARS-CoV-2 to the ACE2 receptors causes an elevated expression of ACE2, which can lead to alveolar cell damages and, in turn, trigger a series of systemic reactions and even death. For preventing the alveolar cell damage and death, pulmonary mechanisms would be compromised via bronchoconstriction, airway congestion, secretions, and decreased mucociliary clearance.[45]

6 | CYTOKINE STORM

Lymphopenia, along with or without leukocyte abnormalities[40] and "cytokine storm," may have a crucial role in the pathogenesis of COVID-19.[46-49] The investigation of 41 hospitalized patients with high-levels of proinflammatory cytokines consists of interleukin-2 (IL-2), IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and tumor necrosis factor (TNF)-α were reported cytokine release syndrome or cytokine storm in the COVID-19 severe cases.[50] Cytokine storm could inchoate viral sepsis and inflammatory-induced lung injury, which results in other complications, including pneumonitis, ARDS,[51] respiratory failure, shock, organ failure, and potentially death. ARDS is the prevalent immunopathological event for SARS-CoV-2, SARS-CoV, and MERS-CoV infections.

One of the principal mechanisms for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of proinflammatory cytokines (interferon [IFN]-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, and TGFβ) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, and CXCL10) through immune effector cells in SARS-CoVs infection.[50,52-54] So, blocking IL-6, IL-1, and TNF may be useful for COVID-19 patients.

Moreover, lymphopenia is often reported in the severe stage of patients infected with COVID-19. The cytokine made through SARS-CoV-2 must be mediated via leukocytes other than T cells, as in patients getting CAR-T cell therapy, a high WBC-count is prevalent along with lymphopenia, which is as a differential diagnostic criterion for COVID-19.

7 | SARS-CoV-2 PATHOGENESIS VS INNATE IMMUNE RESPONSE

The host innate immune system identifies viral infections by applying pattern recognition receptors (PRRs) to detect pathogen-associated molecular patterns (PAMPs).[55]

Up until now, PRRs are divided into three types based on their forms of existence.[55,56] The membrane type consists toll-like receptor2 (TLR2), TLR4, mannose receptor, scavenger receptor; the secretory type contains mannose-binding lectin and C-reactive protein (CRP); and the cytoplasmic type comprising TLR3, TLR7/8, cGAS, IFI16, STING, DAI, and NOD-like receptor (NLR). It must be noticed that the JAK-STAT signaling pathways induce downstream IFNs production, and the interferon production-related PRRs are TLRs, RLRs, and NLRs.[57] Upon infecting plasma-like dendritic cells, the viral nucleic acids are detected through TLR7/TLR9 to stimulate the construction of inflammatory cytokines and type I IFNs.[58,59]

IFNs are the effective innate immune responses of human cells against viral infection.[60] An essential aspect of virulence and host adaptation of coronaviruses is the interactions of SARS-CoV and MERS-CoV with the antiviral interferons.[61] The broad antiviral activity of IFNs happens on various levels, including virus entry, viral polymerase function, host cell translation, RNA availability, RNA stability, particle budding, apoptosis, and general augmenting of innate and adaptive immune responses. Humans are capable of expressing one IFN-beta, 13 subtypes of IFN-alphas, and one each of IFN-kappa and IFN-omega. The type I interferon responses which is composed of alpha/beta-IFNs[62] and its downstream cascade which culminate in immunomodulation, controlling viral replication, and induction of effective adaptive immune response (NK cells, macrophage, and T/B lymphocytes) is not functional against COVID-19 as the SARS-CoV-2 has inhibited the induction, production,[63,64] and the JAK-STAT signaling pathway of the interferon.[61]

The complement system has a crucial role in the host immune response, which prepares a way for the innate immune system to detect and respond to foreign antigens, especially CoVs.[65] It is firmly controlled through inhibiting proteins in the serum, as it has the potential to damage host tissues. However, SARA-CoVs encoded proteins that inhibit the detection of the complement system through inhibiting proteins in the serum,[66] indicating that complements are essential to the antiviral response as C3a and C5a have strong proinflammatory properties and could induce inflammatory cell recruitment and neutrophil activation. So, their blockade acts as a therapy for acute lung injury as anti-C5a antibody reveals to protect mice from infection with MERS-CoV.[67]

8 | SARS-CoV-2 PATHOGENESIS VS ADAPTIVE IMMUNE RESPONSES AGAINST

Antigen presentation stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells.

In SARS-CoVs, both T and B cell epitopes were extensively mapped for the structural proteins, including S, N, M, and E protein.[68] Although only minimal percentages of monocytes/macrophages in the lung expressed ACE2 receptors,[1] SARS-CoV-2 directly infects macrophages and T cells.[69] Other receptors may exist, if the ACE2 receptor is minimally expressed in the potential target immune cells, or another cellular entry mode is applied, like antibody-dependent enhancement.

Cytokine microenvironment produced via antigen-presenting cells commands the direction of T cell responses, which is very important. Although helper T cells attune the overall adaptive response, $CD8^+$ or cytotoxic T cells are essential in the killing of virally infected cells response, so they need to be well controlled in order not to cause lung pathology. Generally, the T helper1 (Th1) immune response has a critical role in adaptive immunity against viral infections. Current pieces of evidence strongly indicated that Th1 response is a vital key for successful control of SARS-CoV and MERS-CoV and probably for SARS-CoV-2 as well. However, SARS-CoV-2 reduces the number of Th1 cells. The latest report demonstrated that not only the number of CD4+, and CD8+ T cells in the peripheral blood of SARS-CoV-2-infected patients is dramatically reduced especially among elderly patients (over the age of 60) and in patients needing intensive care unit (ICU),[70] but also the surviving T cells are functionally exhausted.[70] In addition, non-ICU patients, with total T cells, CD4+ T cells, and CD8+ T cells counts lower than 400/μL and 800/μL, 300/μL subsequently, might still require aggressive intervention even in the immediate absence of more extreme symptoms due to a high risk for more deterioration in condition.[71]

Although various clinical studies in China have declared the application of mesenchymal stromal/stem cells (MSCs) in severe stages of COVID-19 in infected patients, T cells are not well stimulated by SARS-CoV-2 infection. So, one significant alarm is that MSCs require activation through IFN-γ to make their anti-inflammatory effects that might be absent in severe stages of the disease. To increase the effectiveness of MSCs, one could consider employing the "licensing-approach": pretreat MSCs with IFN-γ with or without TNF or IL-1.[72]

Humoral immune response, especially the production of neutralizing antibody, plays a defensive role by controlling the persistent phase of CoVs infection, restricting infection at a later phase, and preventing reinfection in the future. Equivalent to common acute viral infections, the antibody profile vs the SARS-CoVs has a usual pattern of IgM and IgG production. At the end of week 12, the SARS-specific IgM antibodies vanish, while the IgG antibody (the SARS-specific IgG antibodies primarily are S-specific and N-specific antibodies[23]) can last for a long time, which shows that IgG antibody might chiefly play a protective role against COVID-19.[73] The antibodies isolated from patients who have survived MERS-CoV infection were MCA1, CDC-C2, CSC-C5, CDC-A2, CDC-A10, MERS-GD27, and MERS-GD33.[74,75]

Besides, monoclonal antibodies (mAbs) work together to target various antigenic domains on the envelope glycoprotein of the virus and scientists from all over the world have reported more than 20 kinds of monoclonal antibodies against MERS-CoV and SARS-CoV most of which are human or humanized antibodies.

Tocilizumab (TCZ) is a mAb against IL-6, which appears to be an effective therapeutic option against COVID-19 with a risk of the cytokine storm. Moreover, the repeated dose of the TCZ is recommended for critically ill patients with elevated IL-6.[76]

It must be mentioned that there is a phase II clinical trial, posted by the University of Washington Seattle, the United States, on 18th May 2020, for appraising the effects of IC14 (anti-CD14) which is a recombinant chimeric mAb in patients with COVID-19 (NCT04391309). Moreover, there is another IC14 clinical trial in Italy, lunched by Vita-Salute San Raffaele University Milano on 16th April 2020. As IC14 can attenuate the inflammatory cascade by binding to CD14 and blocking the CD14-mediated cellular activation through recognition of PAMPs and damage-associated molecular patterns, it can be effective against COVID-19.

Besides on 30th April 2020, a phase III study to evaluate the efficacy and safety of lenzilumab (a humanized class IgG1 kappa mAb that targets colony-stimulating factor 2 [CSF2]/granulocyte macrophage-CSF) in hospitalized patients with COVID-19 pneumonia has been launched in the United States (NCT04351152).

Also, there are more than 20 clinical trials recorded on clinicaltrials.gov for evaluating the efficacy of other mAbs like a phase II and phase III study of emapalumab and anakinra (NCT04324021), a phase II study of gimsilumab (NCT04351243) and leronlimab (NCT04343651), and sarilumab (NCT04386239).

In a recent study, the S309 antibody, an antibody against SARS infection, is proposed to be effective against COVID-19.[77]

Moreover, it has been shown that anakinra, a recombinant IL-1 receptor antagonist, can increase the survival of patients with COVID-19 and alleviate the respiratory symptoms.[78]

In addition to mAbs clinical trials, there are several other antiviral immunomodulatory therapy clinical trials like Wharton's jelly derived mesenchymal stem cells (NCT04390152), hydroxychloroquine (NCT04345653), and polyvalent immunoglobulin (NCT04350580).

Chloroquine and hydroxychloroquine inhibit major histocompatibility complex class II expression and reduce CD154 expression by T cells via Toll-like receptor signaling and cGAS stimulation of interferon genes, which leads to inhibition of antigen presentation and immune activation. Moreover, both can decrease the production of various proinflammatory cytokines, like IL-1, IL-6, IFN-α, and TNF.[79] However, several times, it has been reported that using hydroxychloroquine or chloroquine with or without macrolide increases both cardiac death and cardiac arrhythmia in patients with COVID-19, and they are not effective against the disease.[80,81] The recent multinational registry analysis of the use of hydroxychloroquine or chloroquine on 14 888 patients in 671 hospitals in six continents was also in agreement with these findings, and showed an increased risk of ventricular arrhythmias.[82] Therefore WHO recommended temporary pause of the use of this drug in trials for COVID-19.

It should be mentioned that numerous antiviral drugs, like lopinavir/ritonavir, have demonstrated no benefits.[83] However, the combination of an immunomodulatory agent to decrease the cytokine storm with an antiviral agent might give doctors more time to make supportive therapy for patients with COVID-19.

It must be taken into account that enhanced levels of inflammatory cytokines, including IL-6, IL-1, and TNF-α in the lungs of COVID-19 cases, can lead to hyaluronan or hyaluronic acid (HA) production by inducing the HA-synthase-2 and following ARDS and death.[84,85] So, suppressing HA production through hyaluronidase, 4-methylumbelliferone, and blocking the inflammatory cytokines can be useful for reducing the mortality rates and shortness of breath in COVID-19 patients.[86]

Among the immunomodulatory treatments, corticosteroids are commonly used in the clinic. Although the application of corticosteroids in patients with COVID-19 can lead to host immune suppression and delay viral clearance, a recent study at Xi'an Jiaotong-Liverpool University revealed that the application of corticosteroids did not affect viral clearance time and length of hospital stay in mild COVID-19 cases.[87] Thus, based on this study, the use of corticosteroids is effective in severe cases of COVID-19, especially in cases with ARDS.[88]

Colchicine is an immunomodulatory drug used in the treatment of gout, in which there are more than 10 clinical trials for evaluating its effectiveness against COVID-19, like NCT04392141, NCT04375202, and NCT04355143.[89]

Furthermore, other immunomodulatory therapies like intravenous immunoglobulin and Janus kinase inhibitors have been proposed for treating severe COVID-19.[90] However, it should be mentioned that the National Institutes of Health does not recommend the use of Janus kinase inhibitors like baricitinib[91] against COVID-19 due to their broad immunosuppressive effect.[92]

Moreover, in early March 2020, Chinese clinicians studied the use of ulinastatin, which is a serine protease inhibitor with anti-inflammatory properties (including inhibition of IL-6), against COVID-19 to reduce cytokine storm.[93]

It should be mentioned that the result of using triple combination therapy with interferon beta-1b, lopinavir-ritonavir, and ribavirin in a phase II clinical trial demonstrated its effectiveness against COVID-19.[94]

9 | CLINICAL MANIFESTATIONS

In one study, researchers concluded that the coronaviruses could often present itself as a common cold. Consequently, it has been suggested that the current definition of COVID-19, which emphasizes lower respiratory tract infection, might need to be changed.[95] The incubation period for COVID-19 is supposed to be within 14 days following exposure and after active or quarantined monitors,[96] with most cases occurring almost 4 to 5 days after exposure.[97,98] Besides, the mid-incubation period was 1/2 day, the average incubation period was 1.5 days, and mid-term incubation until the fever was 2.5 days. Besides, less than 1.2% of patients are symptomatic within 2.5 days, and in 1.2% of affected people, symptoms appear for up to 2.5 days.

A meta-analysis study of the new coronavirus with eight studies and 5732 patients found that the incidence of fever was 90.9%, cough 70.8%, fatigue 41%, ARDS 14.8%, abnormal lung CT scan 95.6%, and the mortality rate was 6.4%.[99] In another study, of 1099 patients with COVID-19[98] findings were as follow:

The most common clinical symptoms included fever (present in 4.9% of cases at admission and 5.9% of cases at admission), dry cough (in 1/2 of cases), nausea and vomiting (in 2% of cases), and diarrhea (in 1.5% of cases). Moreover, the most common radiology findings on CT at admission included ground-glass view (at 1/8) and patchy bilateral shadowing (view at 1/8). Also, laboratory findings consisted of lymphopenia (in 1.2% of cases), thrombocytopenia (in 1.5% of cases), leukopenia (in 1.5% of cases), and most patients had high CRP. Besides, 5% of patients are admitted to the ICU, 1.2% needed ventilation, and 1.2% died. In addition to laboratory findings mentioned above, increase in lactate dehydrogenase (LDH), aspartate aminotransferase, alanine transaminase, CRP, creatine kinase, erythrocyte sedimentation rate (ESR), white blood cell count, D-dimer level, procalcitonin, urea, and creatinine and decrease in hemoglobin, lymphocyte count or lymphocytopenia, eosinophil, and serum albumin have been reported in COVID-19 patients as well.[100]

It must be taken into account that other symptoms like sore throat, nasal congestion, malaise, headache, muscle pain, severe dyspnea, respiratory distress, tachypnea more than 30 breaths per minute, hypoxia less than 90% of SpO_2 on room air, and cyanosis have been reported in patients with COVID-19.[100,101]

Interestingly, viral conjunctivitis and rash on the skin or discoloration of fingers or toes should be regarded as a possible early manifestation of COVID-19.[102,103] Moreover, it has been reported that chilblain-like lesions in the toe are a sign of COVID-19, especially in young patients with a mild infection that goes away on its own.[104]

It should be mentioned that the American Academy of Otolaryngology has indicated the loss of sense of smell and taste disorder (anosmia and dyspepsia) in some patients who were

positive for COVID-19. Even in some, the loss of a sense of smell has been the only sign.[105]

Interestingly, recently a novel multisystem inflammatory syndrome has been related to COVID-19. The WHO recently introduced this COVID-19 related syndrome in children and adolescents. Some of the features of this syndrome are said to be similar to those of Kawasaki and toxic shock syndrome.

The WHO criteria for diagnosing this syndrome are as follow: all people between the ages of 0 to 19; and the existence of fever for at least 3 days; and increased inflammatory markers such as ESR, CRP, or procalcitonin; and lack of other microbial evidence; and evidence for the presence of a COVID-19 infection or close contact with an infected person; and two of the following: rash or nonpurulent bilateral conjunctivitis, or inflammatory symptoms of Moko Kotanus (mouth, hands, and feet), hypotension or shock, features of myocardial dysfunction, pericarditis, valvular inflammation, coronary vascular abnormalities, evidence of coagulopathy (according to prothrombin time, partial thromboplastin time, and D-dimer levels), and acute gastrointestinal problems (abdominal pain, diarrhea, and vomiting).[106]

As mentioned above, the COVID-19 symptoms have reportedly ranged from mild to severe that can eventually lead to death. Although diffuse alveolar damage and acute respiratory failure were the main characteristics of COVID-19,[107] the severe cases demonstrated respiratory, hepatic, gastrointestinal, and neurological complications that can lead to death. So, we have investigated the effects of SARS-CoV-2 on various vital organs in the following:

9.1 | The relationship between cardiovascular manifestations and COVID-19

Cardiovascular manifestations could be the initial presentation or appear throughout the whole course of COVID-19. Two studies have reported that patients with COVID-19 and hypertension or coronary artery disease had worse in-hospital outcomes.[108,109] The initial report of 41 cases with COVID-19 admitted from early December 2019 to early January 2020, revealed that acute cardiac injury occurs in 12% of patients.[110] Another case series study involving 138 patients with COVID-19 announced that cardiovascular complications of COVID-19 are not scares. Besides, arrhythmia and acute cardiac injury accounted for 16.7% and 7.2% of patients subsequently. The level of hypersensitive troponin I on admission was significantly higher in patients admitted to the intensive care unit[70] than patients who had not.[111] Besides, Kui et al investigated 137 cases with COVID-19 and figured out that 7.3% of patients complain of palpitation as an early symptom.[112]

9.2 | Gastrointestinal features and COVID-19

A vast number of studies have shown that the gastrointestinal tract tropism of SARS-CoV was verified through viral detection in biopsy and stool specimens even in discharged patients, which may partially explain gastrointestinal symptoms, potential recurrence, and transmission of the virus.[113] In particular, in the first corroborated case of the COVID-19 in the United States, a 2-day history of nausea and vomiting on admission and then passing a loose bowel movement on hospital day 2 was reported. Moreover, the viral nucleic acids in loose stool were detected, and both respiratory samples later tested positive.[114] Besides, the 2019-nCoV sequence can also be identified in the collected saliva of the most patients with COVID-19.[36]

9.3 | COVID-19 effects on the liver

The viral infection of liver cells might directly cause liver injury in patients with COVID-19 infection. Almost 2% to 10% of patients with COVID-19 present with diarrhea, as mentioned before, and SARS-CoV-2 RNA has been detected in stool and blood samples.[115] These documents revealed the feasibility of viral exposure in the liver and intestine. It has been reported in one study that more than one-third of 148 patients with COVID-19 admitted to the hospital had an abnormal liver function and were hospitalized for a more extended period.[116] Although pathological analysis of liver tissue from a patient died from COVID-19 demonstrated that viral inclusions were not observed in the liver,[43] pathological studies in patients infected with SARS-CoV confirmed the presence of the virus in liver tissue. Also, the viral titer was relatively low because viral inclusions were not observed.[117] So, it is feasible that the liver impairment is due to drug hepatotoxicity and cytokine storm and pneumonia-associated hypoxia in patients with the severe stage of COVID-19. Besides, liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment.

9.4 | The connection between kidney impairment and COVID-19

Although human tissue RNA sequencing data revealed that the ACE2 receptor expression in urinary organs[118] was much higher (nearly 100-fold) than that in respiratory organs (lung),[119] after lung infection the infiltrated virus might enter the blood circulation (as RT-PCR of the urine and plasma sample in some patients with COVID-19 were positive[107]), accumulate in the kidney, and cause damage to renal cells. Thus, the kidney impairment probably happened through coronavirus entering cells by the ACE2 receptors. Indeed, It has been reported that 6.7% of patients with the SARS developed acute renal impairment, and the mortality of patients infected with SARS-CoV with acute kidney injury (AKI) was 91.7%.[120] Therefore, the kidney impairment and outcome in patients infected by SARS-CoV-2, which is similar to SARS-CoV in 2003, were ensured. AKI is a syndrome of abrupt loss of kidney function that is strongly associated with higher mortality and morbidity,[121] which defined as an enhancement in serum creatinine[122] by 0.3 mg/dL within 48 hours or a 50% increase from the baseline within 7 days.[118]

Moreover, Kaplan-Meier analysis revealed a significantly high in-hospital death rate for patients with kidney impairments, including increased baseline serum creatinine, increased baseline blood urea nitrogen, proteinuria, hematuria, and AKI. In one cohort study,[123] the detection rate of AKI in patients with COVID-19 was 3.2%, which was similar to that reported in previous studies with small patients numbers[107,111,124] and higher than 0.5% in a large observational study.[125] Although the data of kidney specimens from patients with SARS demonstrated normal glomerular histology (the possibility of active immune-mediated glomerulonephritis was low) along with the absence of electron-dense deposits and, deposition of immune complexes of viral antigen or virus-induced specific immunological effector mechanisms (specific T lymphocyte or antibody) might damage the kidney. Moreover, virus-induced cytokines or mediators, which have indirect influences on renal tissue, such as hypoxia, shock, and rhabdomyolysis, might damage the kidney. Therefore, the etiology of kidney impairment in patients with COVID-19 is probably diverse and multifactorial, and not only early prevention of kidney impairment, including adequate hemodynamic support and avoiding nephrotoxic drugs, is particularly remarkable, but also early renal replacement treatment in patients with damaged kidney may improve the patients' prognosis.

9.5 | COVID-19 effects on the nervous system

CoVs infection can affect the nervous system through various ways like direct infection injury by blood circulation pathway and neural pathway, hypoxic injury, ACE2 receptor, and immune injury. It is believed that CoV, in coordination with the host's immune system, may turn these infections into persistent infections that can lead to neurological diseases. Therefore, patients with coronaviruses infections should be appraised early for neurological symptoms, such as headache, consciousness disorder, paresthesia, and other pathological signs.[126,127]

It should be mentioned that COVID-19 can lead to necrotizing hemorrhagic encephalopathy as well.[128] Besides, as some coronaviruses can spread via a synapse-connected route to the medullary cardiorespiratory center from the mechanoreceptors and chemoreceptors in the lung and lower respiratory airways, regarding the high similarity between SARS-CoV and SARS-CoV-2, it is not clear whether the potential invasion of SARS-CoV-2 is partially responsible for the acute respiratory failure of patients with COVID-19.[129] Moreover, as mentioned above, SARS-CoV-2 can cause anosmia and dyspepsia.

So, Health care workers should be aware that patients with COVID-19 can present with encephalopathy in the acute phase of the disease and during hospitalization.

The timely evaluation of cerebrospinal fluid, awareness, and management of neurological complications associated with infection is essential to improve the prognosis of patients with a critical illness.[126] Moreover, during the COVID-19 pandemic, when seeing individuals with neurologic manifestations, clinicians should suspect SARS-CoV-2 infection as a differential diagnosis to avoid delayed diagnosis or misdiagnosis and lose the chance to treat and prevent more contagion.[130]

10 | THE MORTALITY RATE AND RISK FACTORS

Age, the most common comorbidities,[131] diabetes, hypertension, cardiovascular disease, endocrine, and respiratory diseases, have been recognized as the common mortality risk factors.[132] Although the lymphopenia and coronary artery disease were not the risk factors of death, D-dimer more than one and higher sequential organ failure assessment score were the risk factors of death.[131] Moreover, patients with shortness of breath, confusion, chest pain at admission, and older men with underlying disease are also more likely to die[132,133] and the inadequate response of immune cells (especially the elderly patients), as well as inhibition of the essential stat1 protein (which enhance this response), is one of the crucial causes of suboptimal responses and mortality in patients with COVID-19. So, the use of interferons in the early stage of the disease has been emphasized as a control.[134] In the meanwhile, it must be mentioned that, based on the recent reports, obesity was reported to increase the vulnerability to infection.[135]

The mortality rates of COVID-19 are as follows: 2.3% (1023 of 44 672 confirmed cases), 14.8% in patients over the age 80 years (208 of 1408), 8.0% in patients aged 70 to 79 years (312 of 3918), and 49.0% in critical cases (1023 of 2087).[136] Moreover, in one study of 21 patients aged 43 to 92 who had the underlying disease in 85% of cases reported a mortality rate of 67% in patients with COVID-19 admitted in ICU with severe condition and admissions.[137]

For calculating the mortality rate, the number of deaths is divided by the total number of cases. Nevertheless, it should be noted that patients who died on a particular day were affected much earlier. On the one hand, in calculating the death rate, the number of deaths should be divided by the total number of cases at the same time that approximately one person died; on the other hand, asymptomatic or with mild symptoms, patients may not be included in the denominator. Accordingly, researchers have calculated the mortality rate of COVID-19 as 5.6% for Wuhan and 15.2% for out-of-China from the ratio of the number of deaths to the number of cases in the last 14 days[104] as of early March. They took into account the period of illness incubation as well as the interval between onset of symptoms and ICU admission.[138]

11 | PROGNOSTIC FACTORS OF COVID-19

Four factors could predict the progression of the disease to severe infection, including the existence of comorbid diseases, the age of more than 50 years, lymphopenia less than 1500/μL, and serum ferritin more than 400 ng/mL.[139]

In one study, which investigated 201 patients with a mean age of 51, 84 patients eventually developed ARDS, of which 44 died. In this

study, risk factors for death-related ARDS were: older age, neutrophilia, organ failure, and coagulopathy (higher LDH and D-dimer level).[88] The vital point in this study is that higher fever (≥39) increases the risk of ARDS but lower the risk of death.

Besides, the degree of lymphopenia and high concentration of cytokines or cytokine storm give an idea about the disease prognosis as it is found positively correlated with the disease severity.[40,50] Also, platelet to lymphocyte ratio and neutrophil to lymphocyte ratio (patients over the age of 50 years with a ratio of more than 3/13 must be treated promptly) are valuable prognostic factors.[140,141]

It must be mentioned that high levels of procalcitonin are associated with almost five times the severity of COVID-19.[142] So, it has been recommended that serial measurement of procalcitonin may play a critical role in determining the severity of the disease.

12 | CONCLUSION

In conclusion, SARS-CoV-2 is a mysterious virus, and the contemporary pieces of knowledge are vague and inadequate. Although scientists are making an effort to develop proper preventive and therapeutic intervention strategies containing monoclonal antibodies, interferon-based therapies, peptides, vaccines, and small-molecule drugs to overcome the SARS-CoV-2 and more than 200 clinical trials of COVID-19 have been recorded in https://clinicaltrials.gov/, it might take a long time to examine their efficacy in vitro/in vivo. So, that is why the WHO is conducting the solidarity clinical trial to accelerate the process of clinical trials.[143]

The latest information on the SARS-CoV-2 vaccine is fortunately positive. It has been reported that the Ad5 vectored COVID-19 vaccine had no severe side effects and was immunogenic. Moreover, both humoral immunity and neutralizing antibodies peaked on day 28 after vaccination, and the rapid response of type T cells was observed on day 14.[144] However, vaccine preparation for healthy individuals is time-consuming, and there is no effective therapy for infected individuals. Thus, current therapies of COVID-19 are supportive and symptomatic, and the best way to control the COVID-19 pandemic is to follow the preventive strategies.

ORCID

Nima Rezaei http://orcid.org/0000-0002-3836-1827

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How to cite this article: Lotfi M, Rezaei N. SARS-CoV-2: A comprehensive review from pathogenicity of the virus to clinical consequences. *J Med Virol*. 2020;92:1864–1874. https://doi.org/10.1002/jmv.26123