

REVIEW

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A comprehensive review on clinical and mechanistic pathophysiological aspects of COVID-19 Malady: How far have we come?

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Abstract

Since its outbreak in 2019, the coronavirus disease (COVID-19) has become a pandemic, affecting more than 52 million people and causing more than 1 million mortalities globally till date. Current research reveals a wide array of disease manifestations and behaviors encompassing multiple organ systems in body and immense systemic inflammation, which have been summarized in this review. Data from a number of scientific reviews, research articles, case series, observational studies, and case reports were retrieved by utilizing online search engines such as Cochrane, PubMed, and Scopus from December 2019 to November 2020. The data for prevalence of signs and symptoms, underlying disease mechanisms and comorbidities were analyzed using SPSS version 25. This review will discuss a wide range of COVID-19 clinical presentations recorded till date, and the current understanding of both the underlying general as well as system specific pathophysiologic, and pathogenetic pathways. These include direct viral penetration into host cells through ACE2 receptors, induction of inflammosomes and immune response through viral proteins, and the initiation of system-wide inflammation and cytokine production. Moreover, peripheral organ damage and underlying comorbid diseases which can lead to short term and long term, reversible and irreversible damage to the body have also been studied. We concluded that underlying comorbidities and their pathological effects on the body contributed immensely and determine the resultant disease severity and mortality of the patients. Presently there is no drug approved for treatment of COVID-19, however multiple vaccines are now in use and research for more is underway.

Keywords: Pathology, COVID-19, Manifestations, Vaccine, Entry mechanism

Background

In late December 2019, a type of pneumonia with influenza-like symptoms (fever, dry cough, and fatigue) was reported in Wuhan, China [1]. The disease, caused by the betacoronavirus SARS-CoV-2, was later termed as the Coronavirus disease 2019 COVID-19. Declared a pandemic in March 2020 by the World Health Organization (WHO) [2], the disease has affected 52 million

individuals worldwide with more than 1 million mortalities at the time of this review. Presently, there is no definitive drug regimen to treat SARS-CoV-2 infection and vaccines are either in trial phases or approved for limited use only [3, 4]. Thus, infection prevention and control methods such as avoiding mass gatherings, obeying social distancing protocols and observing strict personal hygiene regimens such as wearing facemasks, washing of hands and using hand sanitizers remain important components of disease prevention and management [5].

Another major component of disease management is timely detection [6] and resultant supportive care.

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Unfortunately, a large percentage of COVID-19 patients get themselves days after the onset of symptoms while many never do due to a number of reasons; either because they are asymptomatic or due to inaccessibility and low awareness regarding the disease [7]. This therefore, calls for a deeper understanding and constant revision of knowledge of the disease presentation and course through continued scientific research.

Initially, the disease was believed to behave similarly to acute respiratory distress syndrome (ARDS) or other viral illnesses with symptoms such as cough, shortness of breath, sore throat, rhinorrhea, hemoptysis, chest pain, diarrhea, nausea and vomiting, myalgia and fatigue, headache and confusion. However, the immense research carried out by the scientific community across the globe shows that the disease is reported to have a much wider range of clinical manifestation; starting from complete absence of symptoms to mild ones mimicking typical flu-like symptoms to the more aggressive symptoms such as multiple organ involvement. The latter includes but not limited to the cardiovascular, renal, cerebrovascular, gastrointestinal, dermatological and ocular systems. The pandemic continues to affect millions globally since its first outbreak approximately a year ago and multiple studies regarding different aspects of the disease have been researched upon during the entire course of the on-going global outbreak. We present a comprehensive review of studies regarding clinical presentation of the disease described in the literature till writing.

Methodology

Search strategy and data selection

A comprehensive literature search and analyses were conducted to include data published from December 2019–November 2020 utilizing online search engines Cochrane, PubMed, Scopus and Google scholar. Thirteen original researches were included for pooled analyses of disease characteristics by considering sample size, impact factor and disease variables. Studies covering a wide range of age groups (18–90 years of age) were included. Data from Studies focused on a particular age group were not included for the pooled analyses, but mentioned separately in addition to the pooled analyses. Studies published in English or having a translated version in English were included. Studies published in Chinese or any other language and not having a translated version were excluded. Studies focused and presenting symptoms from only one organ system were excluded from the pooled analyses, but mentioned otherwise in the article (see “ocular manifestations” section below). Systematic reviews, cohort studies, cross-sectional studies, case series and case-reports were also included. Studies from different parts of the world—China, USA, Europe

and Southern America—were included. Studies for both adults and children were included and discussed under in separate sections of the paper. A string for the literature search has been provided as a supplementary material.

Data analysis

EndNote X8.0 software was used to manage, record and omit duplicates. Raw data from thirteen original studies which reported signs and symptoms were compiled and analyzed using SPSS software version 25. Data were analyzed and displayed using median % (interquartile range) as a measure of central tendency. For a particular sign, if the study had not recorded it, the total count of the study was deducted from the original pool for that particular variable. Signs and symptoms for all organ systems were recorded separately. Variables from case reports were discussed separately.

The underlying pathophysiological mechanisms for certain disease symptoms were illustrated using an online software BioRender.

Disease signs, symptoms and organ involvement

The disease is generally classified as asymptomatic, mild, moderate, severe, and critical which includes both involve intensive care unit (ICU) and mortality (Table 1). Presence of underlying comorbidities, such as diabetes, cardiovascular, and cerebrovascular diseases can worsen disease prognosis [8, 9].

Patients develop symptoms of COVID-19 infection following a mean incubation period of 5.2 days (95% CI, range: 4.1–7.0) [10]. The time period between development of COVID-19 symptoms and death varies from 6 to 41 days (median:14 days) [11], depending on the patient's age and immune status. It is shorter for patients older than 70 years of age than for patients under 70 years of age [11] as the disease affects the elderly more severely [12]. COVID-19 most frequently presents with fever, cough, and fatigue. Other symptoms include headache, sputum production, hemoptysis, dyspnea, diarrhea, and lymphopenia [13–15]. An estimated 67% (40.1–91.7) of patients in the review had fever (rest of the symptoms will be discussed later in association with relevant organ systems). Research shows that males, especially older, are more affected than females [16]. In the present analyses, mean percentage of male patients was 59.0% (SD 10.0). A recent study, focusing on patients suffering from mild to moderate symptoms, who had not received immunomodulatory treatment, revealed that males had higher levels of innate immune cytokines and chemokines including IL-8, IL-18, and CCL5 in their plasma, along with stronger induction of non-classical monocytes. Conversely, females manifested significantly more robust activation of T-cells than males during SARS-CoV-2

Table 1 Summarizes frequency of signs and symptoms by means of median and interquartile range (IQR) recorded for COVID-19 patients for studies included in the review

Organ system	Symptom	Frequency (%)		Studies reported
		Median	IQR	
Cerebrovascular	Headache	8.2%	7.1–16.0	7
	Confusion	9.1%	—	1
	Dizziness	9.4%	—	1
Eye*	—	—	—	0
Ear, Nose, Throat	Nasal Congestion/ Rhinorhea	16.7%	6.9–61.5	4
	Sore throat	11.1%	5.9–16.5	4
	Sputum Production	30.2%	10.0–39.7	4
	Tonsil swelling	2.0%	—	—
Chest/Pulmonary	Cough	71.4%	46.7–73.1	12
	Shortness of breath	36.7%	19.0–56.5	11
	Hemoptysis	4.9%	1.0–5.1	4
	Chest pain	2.0%	—	1
	Chest distress	23.8%	—	1
Gastrointestinal	Loss of appetite	39.9%	12.2–49.5	3
	Nausea/ Vomiting	12.7%	4.0–19.5	6
	Diarrhea	8.0%	3.2–11.8	10
Musculoskeletal	Abdominal pain	4.4%	4.3–5.8	3
	Fatigue	66.9%	49.9–73.6	4
Dermatological	Myalgia/Arthralgia	23.1%	14.6–33.5	9
*Eye	Rash	0.2%	—	1
	None of the original searches contained data on ocular signs and symptoms. A cohort [57], however, focused on ocular signs and symptoms revealed: eye pain (19.4%), photophobia (13.9%), flashes or floaters (11.8%), blurring of vision (11.1%), and eye redness (10.4%)			

Disease severity classification	Features (as per CDC guidelines)
Asymptomatic/presymptomatic	Patients who test positive for SARS-CoV-2 but have no symptoms suggestive for SARS-CoV-2 infection
Mild Illness	Patients having any of the various signs or symptoms of SARS-CoV-2 infection but do not have shortness of breath, dyspnea or abnormal chest imaging
Moderate Illness	Individuals who show signs of lower respiratory disease on clinical assessment or imaging and have an oxygen saturation (SpO_2) of $\geq 94\%$ on room air at sea level
Severe Illness	Individuals with $\text{SpO}_2 < 94\%$ on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) $< 300 \text{ mm Hg}$, respiratory frequency $> 30 \text{ breaths/min}$, or lung infiltrates $> 50\%$
Critical Illness	Individuals having respiratory failure, septic shock, and/or multiple organ dysfunction

The most common manifestation was cough, followed by fatigue. Shortness of breath, chest distress and chest pain were most prevalent among cases exhibiting severe symptoms. There were no ocular symptoms recorded for any of the studies included in this review

infection, which was sustained in old age. It also showed that a poor T-cell response was negatively correlated with patient's age and predisposed primarily males to worse disease outcomes. In contrast, higher innate immune cytokines in only females predicted worse disease progression[16]. Disease severity and mortality are known to vary across different populations due to variations in a wide array of biological and environment factors as listed below such as:

- Genetic variations in Human Leucocyte Antigens (HLA) and the resultant resulting immune response[17, 18]
- ACE2 allelic variability[19]
- ABO blood groups, A has a higher susceptibility (no established correlation with disease severity) to COVID-19 (OR, 1.45; 95% CI, 1.20–1.75; $p = 1.48 \times 10^{-4}$) while O has a protective effect (OR, 0.65; 95% CI, 0.53–0.79; $p = 1.06 \times 10^{-5}$))[20]

- iv. Genetic susceptibility (3p21.31 gene cluster in COVID-19 patients with respiratory failure) [21]
- v. The protective effect of BCG vaccine and fewer COVID-19 cases in a country with universal policies of BCG vaccination [22]
- vi. Ethnicity (black population has a higher predisposition to COVID-19) [7]
- vii. Environmental factors such as temperature and humidity with the unit increase resulting in decreased COVID-19 mortality [23],
- viii. Socioeconomic status[7].

Initially considered to present mainly with pulmonary symptoms, COVID-19 has shown to involve multiple organ systems along with nonconventional symptoms showing extra-pulmonary involvement. [24].

Head and neck

Cerebrovascular disease and neurological symptoms

About 36% of COVID-19 cases manifest neurological symptoms during acute phase of illness. An estimated 25% of these cases have shown direct central nervous system (CNS) involvement. The most frequently reported neurological symptoms include dizziness, headache, impaired consciousness and seizures [25], with or without a history of pre-existing neurological disorders. At the time of hospital discharge, one-third of the patients have manifested motor defects and cognitive impairment [26]. Patients have shown confusion, agitation and corticospinal tract abnormalities (such as enhanced tendon reflexes and clonus) while being admitted in ICUs. In patients with mild to moderate disease, olfactory (85.6%) and gustatory (88.0%) dysfunctions have also been reported. Importantly, in about 11% of patients, anosmia was reported as the presenting symptom of the illness [27].

Table 1 summarizes the cerebrovascular symptoms recorded in this review. Headache was the most commonly reported cerebrovascular symptom and experienced by a median of 8.2% (7.1–16.0) of the patients. Additionally, studies have reported sub-acute occurrence of the Miller-Fisher [28] and the Guillain-Barré syndromes [29] approximately 3 to 10 days after the onset of COVID-19 symptoms.

Cerebrovascular disease has been reported as an underlying condition in people with COVID-19 [30, 31]. Studies have reported large vessel stroke in young [32] and acute stroke in four cases of COVID-19 as presenting features of the disease [33]. A study suggests that T-cell hyper activation leads to paralysis which can result in pulmonary damage, cytokine release syndrome (CRS) and organ failure in individuals with severe COVID-19 disease [34]. Additionally, elevated D-dimer levels and

markedly reduced platelets in critically ill patients can lead to acute cerebrovascular complications [35].

The different mechanisms of cerebrovascular involvement

According to Heneka et al. [36], neurological signs and symptoms of COVID-19 may result from systemic inflammation, direct viral encephalitis, peripheral organ (liver, kidney, lung) dysfunction and cerebrovascular changes. Figure 1 describes these mechanisms in detail. This may be supported by the fact that firstly, SARS-CoV2 could induce cerebrovascular disorders including encephalitis, polyneuropathy and aortic ischemic stroke [37]; and secondly, the structure of SARS-CoV-2 is comparable to that of SARS-CoV (79.5%), and bat coronavirus (96%) [38]. Any one, or a combination of these pathological pathways, can predispose COVID-19 survivors to long-term neurological complications, either by exacerbating a preexisting neurological disorder or by triggering a new one [36].

Evidence suggests that activation of NLRP3 inflammasome contributes to lung injury, pathogenesis and adverse outcomes of ARDS [41]. In COVID-19 patients' levels of interleukins, especially interleukin-1 β and interleukin-18, are high which may be attributable to activation of NLRP3 inflammasome by coronavirus protein ORF3a [42], and ventilation-induced hypercapnia [43]. These processes and subsequent increased activation of pro-inflammatory pathways may disrupt cerebral homeostasis and function. Moreover, NLRP3 inflammasome-mediated inflammation has been linked to accumulation of neurodegeneration-associated peptides—such as fibrillar amyloid- β [44], which may aggravate neurodegeneration and progression of Alzheimer's disease [40, 45, 46].

The systemic inflammation [47, 48], ARDS [49], and chronic ventilation [50, 51] in COVID-19 patients may cause short-term and long-term cognitive decline and neurodegenerative changes. Moreover, the presence of SARS-CoV-2 in the cerebrospinal fluid [26] has been confirmed and viral encephalitis and direct viral infiltration of the brain (retrograde neuronal dissemination or hematogenous spread) have been reported [52].

Furthermore, due to mass hysteria, social dysfunction resulting from self-isolation and quarantine, xenophobia, disease-associated stigma, economic effects and disrupted work-related and academic activities, an increased sense of anxiety and restlessness is evident in large groups of people [53, 54]. Ahmed et al. [55] also noted that young people (aged 21–40 years) were more likely to succumb to mental health conditions and alcohol use. Provision of direct patient care, vicarious trauma, quarantine, or self-isolation during the COVID-19 pandemic may cause health care providers to experience psychological distress [56].

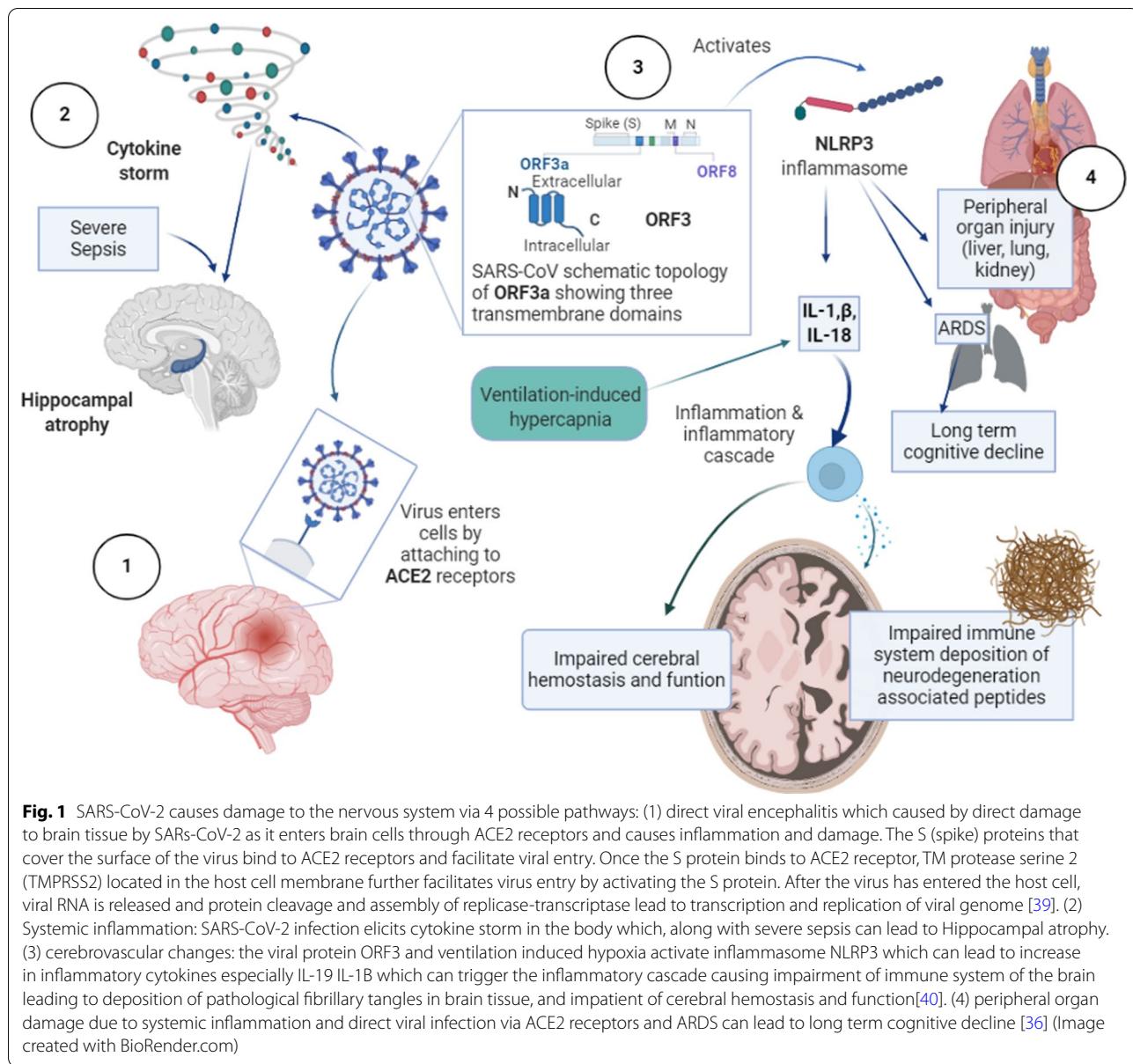


Fig. 1 SARS-CoV-2 causes damage to the nervous system via 4 possible pathways: (1) direct viral encephalitis which caused by direct damage to brain tissue by SARS-CoV-2 as it enters brain cells through ACE2 receptors and causes inflammation and damage. The S (spike) proteins that cover the surface of the virus bind to ACE2 receptors and facilitate viral entry. Once the S protein binds to ACE2 receptor, TM protease serine 2 (TMPRSS2) located in the host cell membrane further facilitates virus entry by activating the S protein. After the virus has entered the host cell, viral RNA is released and protein cleavage and assembly of replicase-transcriptase lead to transcription and replication of viral genome [39]. (2) Systemic inflammation: SARS-CoV-2 infection elicits cytokine storm in the body which, along with severe sepsis can lead to Hippocampal atrophy. (3) cerebrovascular changes: the viral protein ORF3 and ventilation induced hypoxia activate inflammasome NLRP3 which can lead to increase in inflammatory cytokines especially IL-19 IL-1B which can trigger the inflammatory cascade causing impairment of immune system of the brain leading to deposition of pathological fibrillary tangles in brain tissue, and impairment of cerebral hemostasis and function[40]. (4) peripheral organ damage due to systemic inflammation and direct viral infection via ACE2 receptors and ARDS can lead to long term cognitive decline [36] (Image created with BioRender.com)

Ocular signs and symptoms

None of the original researches included in this review had reported ocular symptoms. However, according to a recent cohort, eye pain (19.4%), photophobia (13.9%), flashes or floaters (11.8%), blurring of vision (11.1%), and eye redness (10.4%) have been the most frequently experienced ocular symptoms. The study found that ocular symptoms preceded the onset of systemic symptoms in only 20.6% (14/68) of cases. Twenty-six and a half percent (18/68) of respondents experienced persistent ocular symptoms despite recovery from systemic illness. Fifty-four percent (164/306) of COVID-19-negative patients reported experiencing at least one ocular

symptom, thereby establishing no significant association of the presence of ocular symptoms with COVID-19. Symptoms experienced were not significantly different for COVID-19 positive and negative patients. Amongst COVID-19-negative, survey respondents, red eye (21.9%) and excessive tearing (17.6%) were found at a significantly higher rate [57].

A study from China [58] revealed that patients with COVID-19 who tested positive through a nasopharyngeal swab experienced ocular symptoms indicative of conjunctivitis (including conjunctival hyperemia, chemosis and epiphora), and increased secretions. It was also established that patients with ocular symptoms were

more likely to have higher leukocyte count and neutrophil counts, and higher levels of procalcitonin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) than patients who did not report any ocular symptoms. Additionally, ocular symptoms were reportedly more common amongst patients with severe disease than those with mild or moderate disease. Two out of eleven, patients who tested positive with nasopharyngeal swab also had positive RT-PCR results with conjunctival swabs, thereby suggesting the eyes as a possible source of disease transmission. A case of acute kerato-conjunctivitis as the presenting feature of COVID-19 has also been reported [59]. Besides the aforementioned information,, a child was reported to present with conjunctivitis and eyelid dermatitis as the only presenting signs of COVID-19 [60]. Other reports have also noted conjunctivitis as the first [61, 62], or the sole presenting symptom of COVID-19 [63].

Since a lot of ophthalmic procedures require close contact and can cause aerosol transmission, the ophthalmic community has been posed with great dilemmas and challenges with regards to clinical and surgical practices [64].

Ear, nose, and throat

Amongst the earliest symptoms of COVID-19, pharyngodynia has been common (12.4%), nasal congestion not as frequent (3.7%), and rhinorrhea quite rare [65]. Cases with Tonsil swelling [30] and sputum production [13, 66] have also been presented. Table 1 summarizes the symptoms studied in this review. Sputum production was the most common symptom recorded affecting 30.2% (10.0–39) of the patients. Anosmia, also as sudden new-onset symptom [67, 68], and hyposmia have been reported in COVID-19 patients [69].

Nasal discharge from a patient with post-viral olfactory dysfunction has already shown presence of human coronavirus 229E [70]. Like SARS-CoV, SARS-CoV-2 enters through ACE2 receptor [71].

Chest and pulmonary

Most common chest and pulmonary signs and symptoms associated with COVID-19 are cough [30, 72], chest pain [73], chest distress/tightness [74], shortness of breath [13, 30], expectoration [75] and hemoptysis[13, 30].

Chest and pulmonary signs and symptoms studied in this review are also highlighted in Table 1. The most frequently experienced pulmonary symptom was cough [71.4% (46.7–73.1)] followed by shortness of breath [36.7% (19.0–56.5)], which has concurrently also been associated with disease severity [73].

The pulmonary features of COVID-19 consist of diffuse alveolar damage and focal reactive hyperplasia of

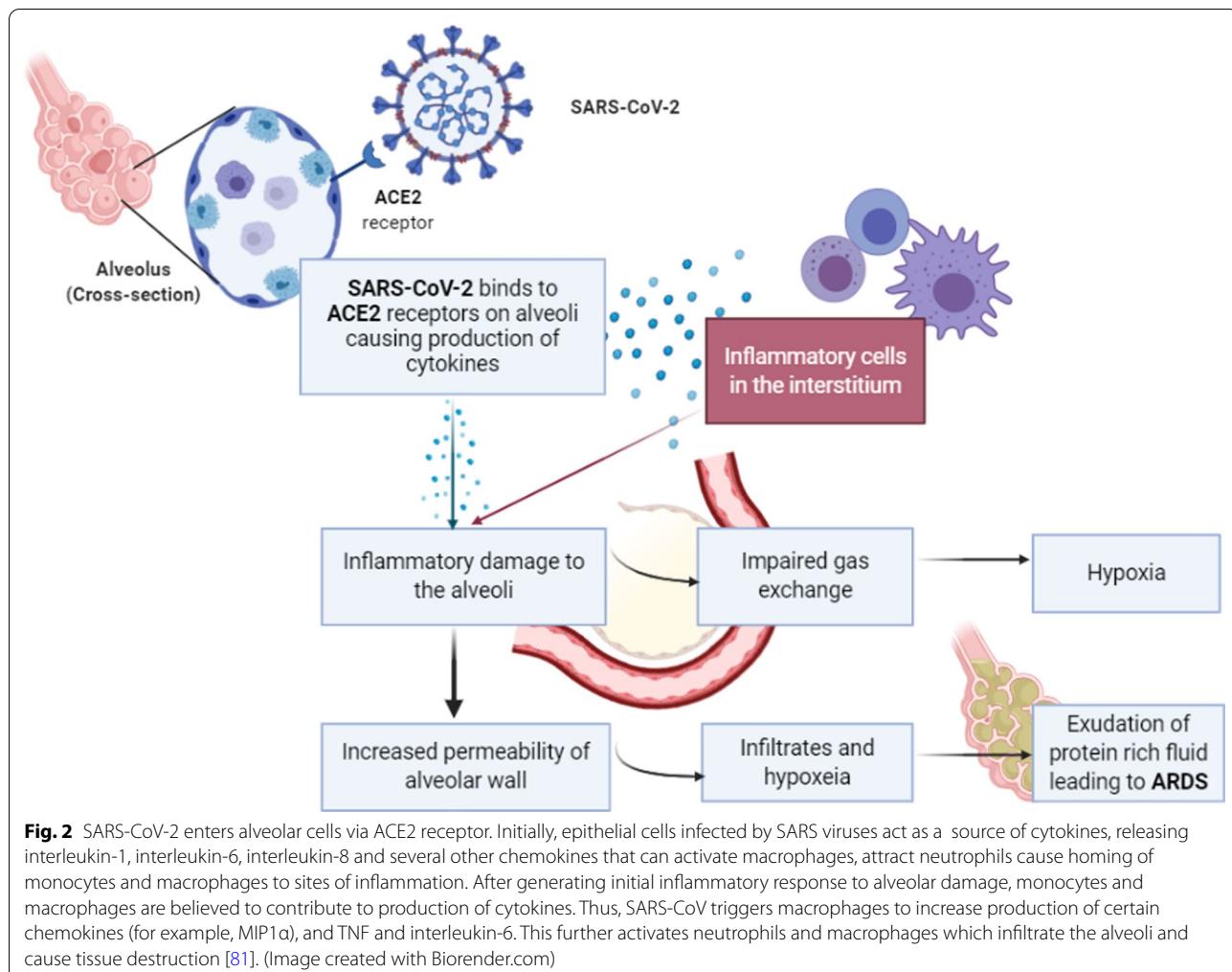
pneumocytes with patchy inflammatory cell infiltration (mostly monocytes and macrophages), vasculitis, hypercoagulability, and intravascular thrombosis [76, 77]. As a result, alveolar gas exchange is reportedly compromised (Fig. 2). The lungs of COVID-19 patients have high levels of inflammatory cytokines (IL-1, TNF) which are strong inducers of HA-synthase-2 (HAS2) in CD31⁺ endothelium, EpCAM⁺ lung alveolar epithelial cells, and fibroblasts [78]. Recent autopsies of COVID-19 patients have shown lungs filled with clear liquid jelly as can be seen in the case of wet drowning [79]. Although the composition of the jelly is yet to be determined, SARS infections have shown defective production of hyaluronan (HA), which is also associated with ARDS [80]. Patients with COVID-19 who require hospitalization and intensive care (ICU) have severe pneumonia with sub-acute hypoxic respiratory failure leading to ARDS, which can further precipitate shock— manifested as fever, lymphopenia, highly elevated proinflammatory cytokines, C-reactive protein (CRP), serum ferritin, and D-Dimers.

Cardiovascular system

Cardiac injury is common among hospitalized COVID-19 patients [82, 83]. One-fifth of the hospitalized patients have been known to develop significant cardiovascular disease (manifested as troponin elevation, reduced ejection fraction, tachyarrhythmias and thromboembolic events), which is significantly linked with increased risk of mortality [84, 85]. In comparison to those without any apparent cardiac injury, patients with cardiac injury have been found to present with more severe acute illness, indicated by abnormal laboratory findings (such as higher levels of CRP, NT-proBNP, and creatinine levels) and radiographic findings (higher levels of multiple mottling and ground-glass opacities), and a greater need for either non-invasive or invasive ventilation.

COVID-19 patients have been reported to present with new-onset signs and symptoms of cardiac injury. A 64-year lady, with hypertension and dyslipidemia presented with chest pain and ST elevation on ECG and no fever or pulmonary symptoms [86]. Cases of COVID-19 patients presenting with cardiogenic shock and decompensated heart failure have also been reported [86]. A classic case of Kawasaki disease was reported in a 6-month-old child with COVID-19 infection [87].

Additionally, low platelet count has been shown to increase risk of severe disease and mortality in patients with COVID-19 and thus should indicate worsening illness during hospitalization [88]. One study also reported hypercoagulability along with clinical findings of pulmonary embolism and/or deep vein thromboses of the lower limbs in some COVID-19 patients [89].



Gastrointestinal tract manifestations

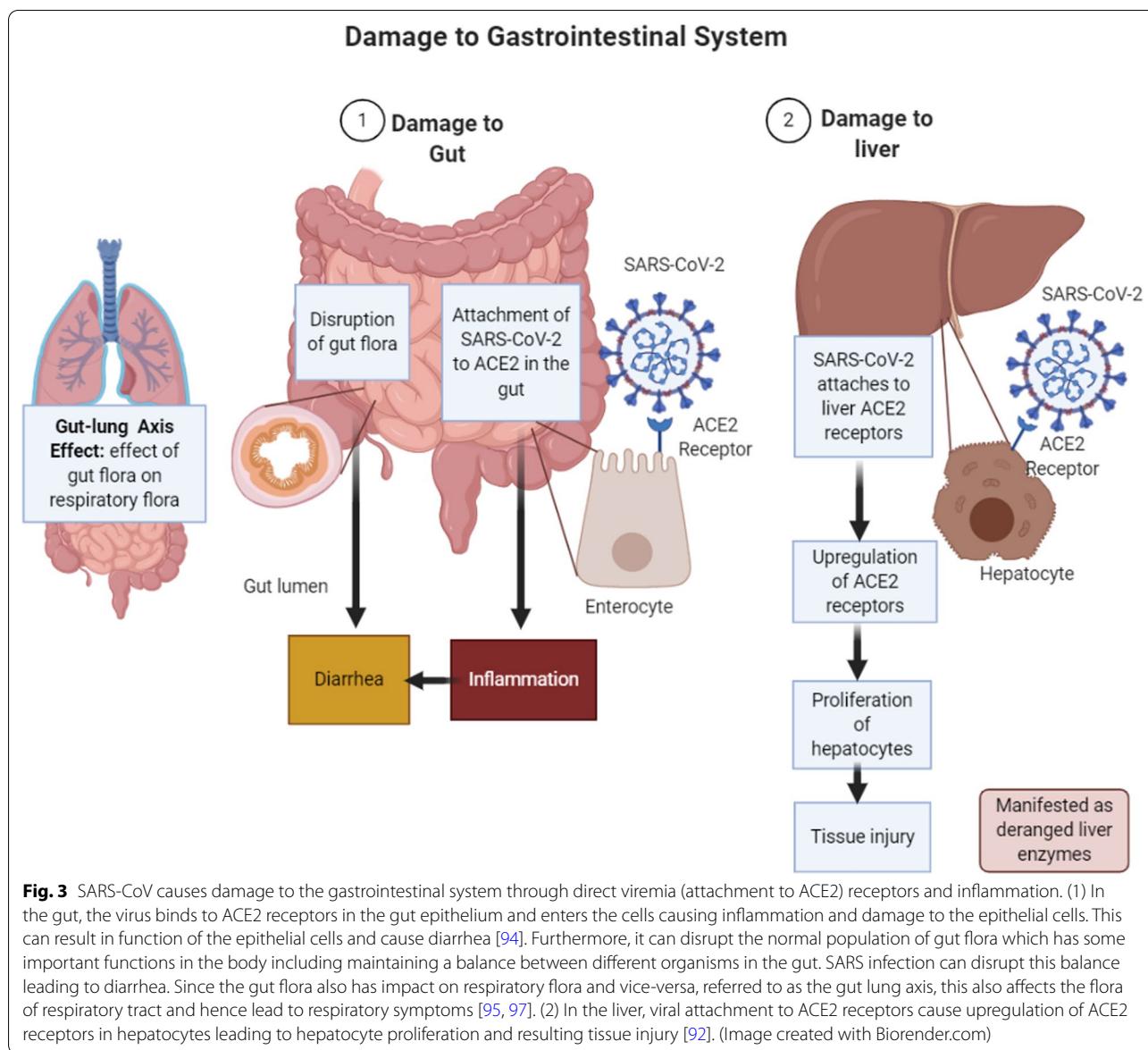
Since the outbreak of the disease, diarrhea has been considered an indicator of gastrointestinal (GI) tract involvement in COVID-19 patients (11.3%) [1]. The GI symptoms have been summed up in Table 1 [31, 74, 90]. Loss of appetite or decreased appetite, was the commonest symptom recorded for 39.9% (12.2–49.5) of the participants [74].

Han et al. found that COVID-19 patients experiencing digestive symptoms were likely to have a longer disease course between onset of symptoms and viral clearance than those who experienced only respiratory symptoms [73]. Additionally, patients with digestive symptoms took longer to seek medical care as noted by Pan et al. [91] which suggests delay in diagnosis resulting from delayed recognition of the disease.

Moreover, patients with digestive symptoms have been shown to have higher levels of liver enzymes, lower monocyte count, longer prothrombin time,

longer time from onset of symptoms to admission, and receive more antimicrobial treatment than those without these symptoms [91].

SARS-CoV-2 also adversely affects the digestive system through inflammation and viremia. Once the virus is bound to ACE2 receptor, ACE2 expression in hepatic tissue is upregulated, leading to compensatory proliferation of hepatocytes and resulting tissue injury [92] (Fig. 3). Studies have revealed presence of viral nucleic acid in stool samples of up to 53.4% of patients [93, 94]. The virus may also cause digestive symptoms by disrupting the intestinal microbiota which play a variety of significant physiological roles in the body, including maturation of the body's immune system, and antibacterial effects [95]. Alterations in the composition and function of the digestive tract microbiota can affect the respiratory tract due to common mucosal immune system, and vice versa. This "gut-lung axis" effect [96, 97] may be the reason why



patients with COVID-19 pneumonia often also experience digestive symptoms.

Musculoskeletal manifestations

Starting from the onset of symptoms to advanced stages of the COVID-19 disease, musculoskeletal symptoms, including myalgia, arthralgia, and fatigue are almost always present [98], although they do not seem to be associated with disease severity [30]. Musculoskeletal symptoms studied in this review are summarized in Table 1. Fatigue, recorded in 66.9% (49.9–73.6) of the patients was the most frequently experienced symptom.

Bridge to Rheumatology

A study from Korea observed an association between a rise in the incidence of Rheumatoid Arthritis (RA) and endemic human coronavirus, parainfluenza virus, and metapneumovirus infections [99], raising the concern that COVID-19 pandemic could potentially follow suit. However, currently no research suggests development of autoimmune inflammatory arthritis, such as RA because of infection with SARS-CoV-2 or any of the other known human coronaviruses.

The mode of action followed by pro-inflammatory effector cytokines in the alveolar membranes during severe COVID-19 is to some extent similar to that of primary cytokines targeted during treatment of RA

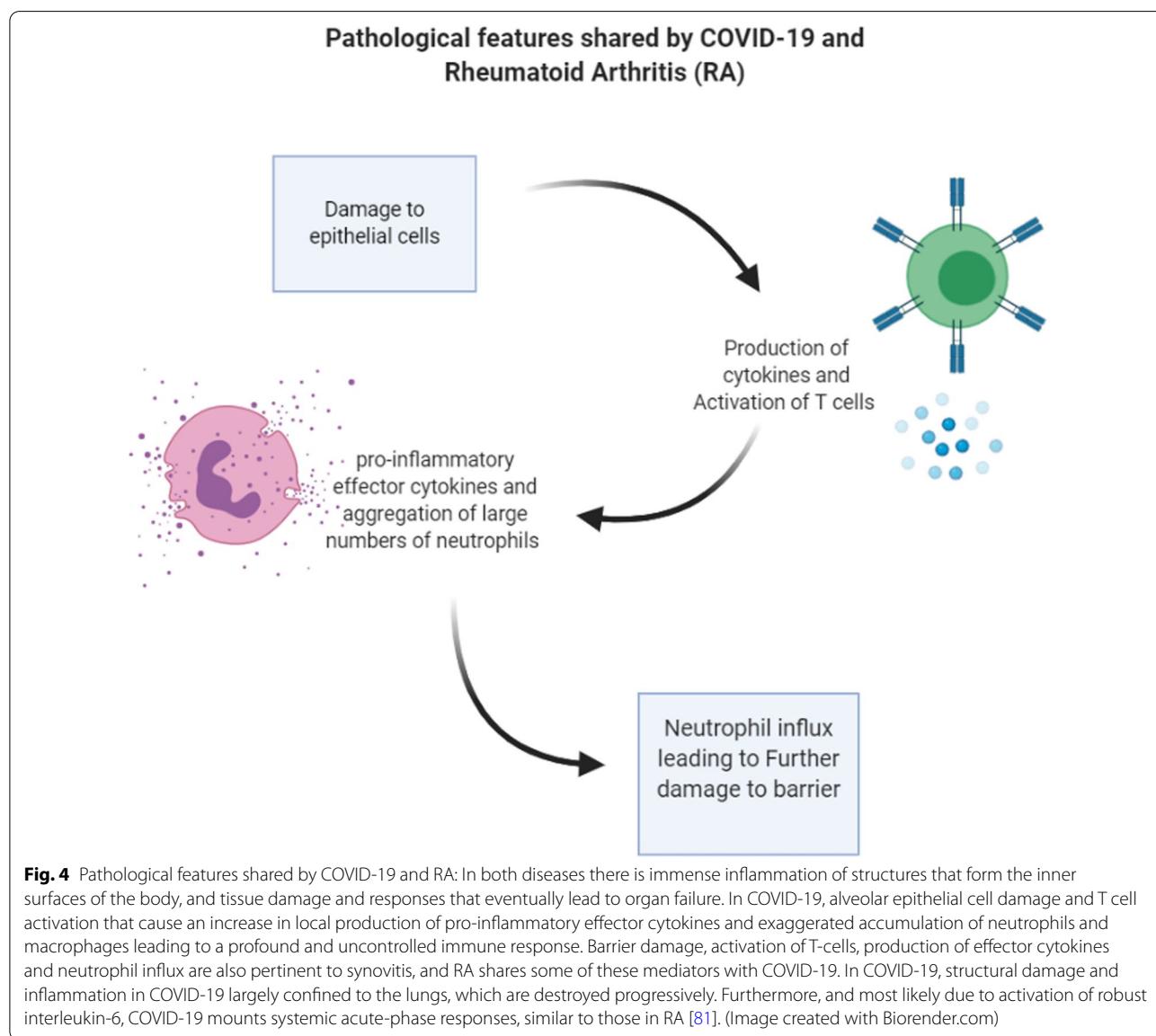
[81] (Fig. 4). Both diseases cause significant inflammation of structures present on inner surfaces of the body and can trigger tissue damage and responses that result in organ failure. COVID-19 comprises extensive or uncontrolled host immune response, manifested as alveolar epithelial cells damage and T-cell activation in the lungs. The result is an increase in local production of pro-inflammatory effector cytokines and exaggerated accumulation of neutrophils and macrophages. [81]. Barrier damage, activation of T-cells, production of effector cytokines and influx of neutrophils are also main features of synovitis, and some mediators are common to both COVID-19 and RA. Furthermore, most likely due to robust activation of interleukin-6 the acute-phase systemic responses of COVID-19 and RA

are similar. Cytokine inhibition, thus, may be a possible consideration for treatment of COVID-19, given the hyper-inflammatory state behind the pathology [81]. This may also affect treatment recommendations for RA. The risk of contracting COVID-19 is not higher for people with arthritis, and anti-rheumatic treatment should not be stopped pre-emptively, during the pandemic [81].

Dermatological manifestations

Of the studies reviewed, only one study reported non-specific "rash" in 0.18% of patients presenting with COVID-19 [30].

A study on dermatologic manifestations associated with COVID-19 revealed that out of a total of 88 patients,



18 manifested skin involvement, but only 8 developed skin lesions at the onset of the disease [100]. A high percentage of the 8 individuals had erythematous rashes, while 3 developed widespread urticaria and chicken-pox like vesicles [100]. A case of COVID-19 with fever and morbilliform rash as the primary presenting sign [101] and another patient with a petechial skin rash as the only presenting sign were also reported [102]. Additionally, two further cases of COVID-19 presenting with chilblain-like lesions were also recorded [103].

Minimally invasive autopsies of COVID-19 patients have revealed destruction and necrosis of the parenchyma with formation of hyaline thrombi in small vessels in lung and other organs [104]. These findings could explain the underlying pathology of dermal manifestations and the causes of acral ischemia reported in patients with COVID-19 in Italy [104]. Furthermore, cases have been shown to present initially with red–purple papules on hands and feet, which either evolved into hemorrhagic bullae or developed a blackish crust [105].

Comorbidities

Cardiovascular diseases including but not limited to hypertension, diabetes, renal disease, and chronic obstructive pulmonary diseases (COPD) as a result of smoking are among the most frequently reported underlying comorbidities in hospitalized patients with COVID-19 [106]. Table 2 summarizes the comorbidities recorded in this study. According to this review, hypertension [28.6% (10.8–45.4)] was the most common co-morbidity, followed by cardiovascular diseases (coronary artery disease, congestive heart failure, vasculitis) [14.6% (10.1–21.4)], and diabetes [13.2% (10.2–30.1)]. Chen et al. and Zhang et al. reported presence of cardiovascular and cerebrovascular diseases collectively in 40.4% and 14.3% of their participants respectively [72, 87].

Chen et al. and Zhang et al. also reported presence of underlying chronic gastrointestinal diseases in 11.1% and 9.3% of the population, and underlying endocrine diseases other than diabetes, such as thyroid disorders in 1.1% and 3.6% of the population respectively [72, 105].

Richardson et al. [107] and Goyal et al. [108] reported obesity in 60.6% and 35.8% of their participants. Chen et al. recorded presence of autoimmune disease in 1.1% of their participants [72]. Obstructive Sleep Apnea (OSA) was noted by Richardson et al. [107], Arentz et al. [109], and Bhatraju et al. [66] as a comorbidity amongst 2.7%, 28.8% and 20.8% of their participants respectively. The studies revealed no significant association of obesity with disease severity. Of the studies that recorded the smoking status of COVID-19 patients, 8.1% (5.4–18.1) smoked or had a history of smoking.

Table 2 Summarizes the frequencies of comorbidities in terms of median and interquartile range (IQR) recorded for COVID-19 patients by studies included in this review

Comorbidity	Frequency (%)		Studies reported
	Median (%)	IQR	
Hypertension	28.60	10.8–45.4	8
Cardiovascular diseases	14.60	10.1–21.4	9
Diabetes	13.20	10.2–30.1	12
Cerebrovascular diseases	8.30	2.1–14.3	6
Chronic lung disease	3.20	1.4–15.9	4
Chronic kidney disease	7.20	2.9–20.8	7
Immunocompromised state	4.80	1.1–11.4	6
Chronic liver disease	2.70	1.8–5.0	6

Diabetes was the most frequently recorded comorbidity but hypertension had the highest prevalence amongst patients of the studies that recorded hypertension as a comorbidity. Obesity, underlying endocrine disorders, autoimmune disease, gastrointestinal diseases and obstructive sleep apnea were also noted

Chen et al. [73] and Zhang et al. [83] reported presence of cardiovascular and cerebrovascular diseases collectively in 40.4% and 14.3% of their participants respectively

Chen et al. [73] and Zhang et al. [83] also reported presence of underlying chronic gastrointestinal diseases in 11.1% and 9.3%, and underlying endocrine diseases other than diabetes—such as thyroid disorders—in 1.1% and 3.6% of the patients respectively

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Obstructive Sleep Apnea (OSA) was noted by Richardson [106], Arentz [109], and Bhatraju [66] as comorbidity amongst 2.7%, 28.8% and 20.8% of their participants respectively

The link between comorbid conditions and COVID-19

Since several features of chronic diseases are similar to those of infectious disorders for example the pro-inflammatory state and weakened innate immune response, their pathogeneses may be linked to COVID-19. Diabetes results partly from release of inflammatory mediators, especially interleukin-1 β and TNF α , caused by aggregation of activated innate immune cells in metabolic tissues, thereby causing β -cell damage and systemic insulin resistance [110]. Metabolic disorders can also impair immune function by disrupting function of macrophage and lymphocyte [111] and through increasing the susceptibility to disease complications [112]. The levels of different inflammatory markers in the mortality group have understandably been considered to be higher than those in the survival group because the absolute count levels of CD3 $^{+}$ T cells, CD3 $^{+}$ CD8 $^{+}$ T cells, and CD3 $^{+}$ CD4 $^{+}$ T cells in the mortality group have been found to be significantly lower than those in the survival group [113]. Spinetti et al. found immune response dysfunction, manifested as reduced mHLA-DR expression on circulating CD14 $^{+}$ monocytes, was more common among ICU

patients with severe COVID-19 illness when compared to non-critically ill hospitalized COVID-19 patients [17]. Patients with diabetes or hypertension have higher plasma plasminogen levels [114]. It is hypothesized that plasminogen may increase the ability of SARS-CoV-2 to bind to ACE2 receptors and aid its entry into host cells [115]. Data also suggest increased ACE2 activity in patients with cardiovascular diseases and diabetes [116, 117]. Increased ACE2 in diabetic or hypertensive patients with ACE inhibitors (ACEIs) or angiotensin II type 1 receptor antagonists may promote SARS-CoV-2 infection [118]. While studying seasonal influenza in a prospective case-control study, Hong et al.[119] established that diabetes and chronic cardiovascular disease had a significant association with development of disease-associated complications, and that diabetes independently increased the risk for severe seasonal influenza (OR 3.63, 95% CI 1.15–11.51, $p=0.02$). Another study revealed that risk of mortality for patients with severe influenza was higher in those who had COPD (OR 1.49, 95% CI 1.10–2.01), and cardiovascular disease (OR 2.92, 95% CI 1.76–4.86) or hypertension (OR 1.49, 95% CI 1.10–2.10) [120].

A meta-analysis concluded that a history of Chronic Kidney Disease (CKD) in COVID-19 patients may increase the risk of disease severity [121]. Another study found that amongst patients with COVID-19 and underlying CKD, 83.93% of cases had severe disease with 53.33% mortality, while amongst those with liver diseases, 57.33% were severe with a mortality of 17. 65% [122].

Studies have shown obese COVID-19 patients to have a 37% higher rate of in-hospital death [123] and higher risk of contracting severe pneumonia [123] compared to non-obese patients. Smoking and older age group patients have a higher number of ACE2 receptors [15], which may explain why, overall, that severe cases belong to the older age group [31] with significantly more comorbidities than non-severe patients. Thus, as suggested by these results, age and comorbidities are risk factors for critical stage of the disease [9].

COVID-19 and children

On January 20th 2020, the first case of SARS-CoV-2 infection in pediatric age group was confirmed in Shenzhen, China [124]. Earlier in the course of the outbreak, SARS-CoV-2 infection was more relevant amongst adults and individual equal to or older than 15 years of age [125]. Early data from Chinese Centers for Diseases Control and Prevention reported that 0.9% of the total confirmed cases comprised children aged 0–10 years and 1.2% were individuals aged 10–19 years [126]. However, with the increase in the number infected adult contacts and more

disease screening, the number infected children and young adults also increased, mainly with mild infections [127]. This increase in prevalence of SAR-CoV-2 infection in younger age group following the initial course of the pandemic is somewhat similar to the increased prevalence of disease cases observed in younger age groups following the initial phases of the pandemic during in the 1918 Spanish Flu [128] and 2009 H1N1 influenza outbreak [129]. Currently, the virus is believed to infect both children and adults at a similar rate[130], however the disease in children is milder in an overwhelming majority of cases [131].

Clinical characteristics of children with COVID-19 can be asymptomatic infection, mild, common, severe, and critically severe [132]. Most children diagnosed with the disease experience mild symptoms, faster recovery, shorter detoxification time, and good prognosis [133]. Most children with COVID-19 have been found to present with fever and with some cases also having fatigue, myalgia, nasal congestion, runny nose, sneezing, sore throat, headache, dizziness, vomiting, and abdominal pain[125]. Children with COVID-19 are believed to experience characteristics of “family-aggregated” infections with a longer incubation period than adults[125] i.e., the mean incubation period for children is ~6.5 days, which is longer than 5.2 days for adults. Nasal and pharyngeal detoxification in children occurs in about 6–21 days (mean=12 days)[134]. A study from China found that 68% of children with COVID-19 had contact with an adult with SARS-CoV-2 infection. 90% of the participants were living closely with families [135].

While most children with COVID-19 experience a mild or asymptomatic infection, a rare complication—**Multisystem Inflammatory Syndrome in Children** (MIS-C)—has been associated with COVID-19 in children [136]. It manifests 4–6 weeks after infection as high-grade fever, organ dysfunction, and markedly raised inflammatory markers. Though unclear, the underlying pathology appears to have features of Kawasaki Disease (KD) and autoimmunity Although it has features similar to that of KD such as symptoms and organ dysfunction resulting from a hyperinflammatory response to an infections, T cell subgroups, interleukin (IL)-17A and presence of IL-6 in MIS-C in place of IL-1 in KD, and arterial damage biomarkers set the two apart. Involvement of multiple antibodies in the pathogenesis of MIS-C has been suggested. A study from New York found that all of fifteen individuals in the study (age<21 years) with MIS-C had fever at presentation [137]. Eighty-seven percent of the participants had gastrointestinal symptoms (vomiting, abdominal pain, and diarrhea). Three patients had cough or dyspnea, and two experienced chest pain. Almost half of the individuals had features suggestive of

KD: rash in 47%, conjunctivitis in 27%, and swollen hands and feet in 27% of the cases.

Current management options

Management of COVID-19

Presently, no drugs have been approved by the FDA for pre and post-exposure prophylaxis. Disease prevention and infection control therefore remain the major components of COVID-19 management and vary considerably across different parts of the world depending on local disease prevalence, resources, socioeconomic conditions and economy. Detailed recommendations for infection control and personal protection for both general public and healthcare workers can be viewed in detail at the Centers for Disease Control and Prevention (CDC) website: <https://www.cdc.gov/coronavirus/2019-ncov/index.html>

Treatment

Although as mentioned above, no drugs for COVID-19 treatment have been approved, a variety of drugs and investigational agents (summarized below and details of which can be viewed here: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>), are being assessed for the treatment of COVID-19 in multiple clinical trials around the world.

Remdesivir

Remdesivir is an intravenous (IV) investigational adenosine analog nucleotide pro-drug which has shown action against SARS-CoV-2 in vitro [138]. CDC recommends its use for the management of SARS-CoV-2 infection in hospitalized patients who at high risk of disease progression of receiving supplemental oxygen.

Other antiviral drugs

Chloroquine/Hydroxychloroquine are recommended for use in clinical trials but not for treatment of COVID-19. The combination of **hydroxychloroquine and azithromycin** is not recommended due to possible toxicities. HIV protease inhibitors, including **Lopinavir/ritonavir (AI)**, apart from disadvantageous pharmacodynamics, have not shown any therapeutic benefits against COVID-19 during clinical trials.

Immune-based therapy

Data favoring the use of convalescent plasma for management of COVID-19 is not sufficient as of writing [139, 140]. Plasma obtained from individuals who have recovered from COVID-19 contains SARS-CoV-2 antibodies, [139], and can serve to form a plasma-derived concentrated antibody preparation known as the SARS-CoV-2 immune globulins. Both products may repress viral

activity and inflammatory response. Additionally, neutralizing monoclonal bodies against SARS-CoV infection are under investigation in clinical trials.

Currently, the CDC does not have sufficient data to recommend either for or against the use of the recombinant human interleukin-1 receptor antagonist, Anakinra, or interferon-beta (for early disease in mild to moderate disease cases) for the treatment of COVID-19. The CDC panel, however, has recommended against the use of Anti-Intreleukin-6 receptor monoclonal antibodies (sarilumab, tocilizumab); or anti-Interleukin-6 monoclonal antibody (siltuximab), interferons alfa or beta (for severely or critically ill patients); and Janus kinase inhibitors (baricitinib, ruxolitinib, tofacitinib), and Bruton's tyrosine kinase inhibitors (acalabrutinib, ibrutinib, zanubrutinib) in COVID-19 patients.

Corticosteroids

Due to their strong anti-inflammatory properties, corticosteroids may prevent or alleviate systemic inflammatory responses in COVID-19 which may otherwise cause lung injury and multisystem organ dysfunction. Studies have reported both beneficial [141, 142] and harmful [143, 144] effects upon evaluating short courses of corticosteroids in patients with COVID-19.

Dexamethasone

The data from a large, randomized, multicenter, open-label ongoing trial for hospitalized COVID-19 patients in the United Kingdom, known as the RECOVERY trial, have suggested that patients who received dexamethasone as a part of management had a reduced mortality rate when compared to those who received standard of care without dexamethasone [145]. CDC recommends use of dexamethasone for treatment of COVID-19 cases with severe disease where patients are hospitalized and require supplemental oxygen, oxygen through high-flow device or extracorporeal membrane oxygenation (ECMO).

Pharmacologic therapy of COVID-19 based on disease severity can be viewed here: <https://www.covid19treatmentguidelines.nih.gov/therapeutic-management/>

Vaccine

As of writing, 89 vaccine candidates are enrolled in clinical trials involving humans, and at least 86 pre-clinical vaccines are under investigation on animals. A total of 26 vaccine candidates have reached phase 3 of clinical trials, 5 have been approved for limited use 8 approved for full (and emergency) use in some parts of the world, including the cavitines by Comirnaty (Pfizer-biontech), mRNA-1273 (Moderna), Vaxzevria (Astra-Zeneca), Convidecia (CanSinoBio), EpiVacCorona

(BEKTOP), BBIBP-CorV (Sinopharm) CoronaVac (Sinovac), and Sinopharm-Wuhan. Updated information regarding COVID-19 vaccines can be found here: <https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html>

Conclusions

This review comprehensively discusses and illustrates the underlying pathological mechanisms that orchestrate COVID-19 disease behavior and the huge spectrum of its clinical manifestations. It compiles and brings valuable pieces of information published till date to one table and links them with one another. Treatment and management options available till date have also been briefly discussed. While a number of vaccine candidates have shown promising results, factors such as cost and logistics will in part determine the magnitude of importance of vaccines in putting an end to the pandemic. Thus, disease prevention and infection control remain the cornerstones of management of the disease.

Our study shows that while certain signs and symptoms are often associated present in multiple ways which are not otherwise typical of the disease. This may suggest that COVID-19 can also present as a multisystem disease. The high prevalence of comorbidities should indicate increased severity of the disease, high risk of deterioration, prolonged hospital stay and associated mortality in a giving population. In a clinical and surgical setting, absence for pathognomonic symptoms in a patient should not be considered synonymous to absence COVID-19. Based on our understanding, SARS-CoV-2 infection in the nervous system may extend to and affect the neural retina. A prospective study including autopsy biopsies may be conducted.

Abbreviations

WHO: World Health Organization; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; CNS: Central nervous system; CRS: Cytokine release syndrome; CRP: C-reactive protein; LDH: Lactate dehydrogenase; HAS2: HA-synthase-2; COPD: Chronic obstructive pulmonary diseases; ECMO: Extracorporeal membrane oxygenation.

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