Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

COVID-19 Pathogenesis and Clinical Manifestations

R. Alfonso Hernandez Acosta, MD[a], Zerelda Esquer Garrigos, MD[b], Jasmine R. Marcelin, MD[c], Prakhar Vijayvargiya, MBBS[b,*]

KEYWORDS

• COVID-19 • Severe acute respiratory syndrome coronavirus 2 • Pathogenesis
• Clinical manifestations • SARS-CoV-2

KEY POINTS

- SARS-CoV-2 can cause widespread damage in different organ systems mediated by the host's immune response. Severity of illness can range from asymptomatic infection to severe multiorgan failure.
- While SARS-CoV-2 is a respiratory virus, COVID-19 affects many organs and has a variety of clinical presentations. In this review, we cover various clinical manifestations of COVID-19 infection.
- Postacute sequelae of COVID-19 (also known as long COVID) is an area of developing knowledge that will require ongoing surveillance to fully characterize. It is generally defined as persistent symptoms for more than 3 months after initial infection.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a member of the *Betacoronavirus* genus (which also includes SARS 1 and Middle East respiratory syndrome–related coronavirus [MERS]), which are large positive-sense single-stranded RNA viruses (estimated size 70–200 nm) with zoonotic origins and transmissible from person to person. Coronaviruses are named after the projections from their membrane (*Corona*, Latin, "crown").[1] When it was first described, the virus had been named 2019-novel coronavirus, but was renamed SARS-CoV-2 owing to a greater similarity with SARS-CoV than initially thought. Since its emergence in late 2019 with the first cases described in Wuhan, China, its human-to-human transmission is clear, with uncounted active infections and millions of deaths worldwide. Furthermore, airborne spread[2] and transmission by asymptomatic individuals[3] further add to its potential for infection.

[a] Department of Internal Medicine, John H. Stroger Jr. Hospital of Cook County, Chicago, IL, USA; [b] Division of Infectious Diseases, University of Mississippi Medical Center, Jackson, MS, USA; [c] Division of Infectious Diseases, University of Nebraska Medical Center, Omaha, NE, USA
* Corresponding author. Division of Infectious Diseases, University of Mississippi Medical Center, 2500 N State Street, Jackson, MS 39216.
E-mail address: pvijayvargiya@umc.edu

Infect Dis Clin N Am 36 (2022) 231–249
https://doi.org/10.1016/j.idc.2022.01.003
id.theclinics.com

Global collaboration and sequencing technologies have helped to uncover the pathogenic mechanisms behind SARS-CoV-2 infection and its associated clinical manifestations, collectively called coronavirus disease 2019 (COVID-19). Nevertheless, COVID-19 remains a novel disease and its complete pathogenesis is yet to be elucidated. Several studies have been conducted to better understand the host–virus interactions and pathogenesis to develop strategies for prevention and treatment. Insight from previous infections caused by coronaviruses such as SARS and MERS has also been useful to understand the pathogenesis of this new virus. Even though several promising new (and repurposed) treatments are being studied, there is yet to be a clear and effective treatment modality. The development of effective vaccines as part of preventive strategies has also played a significant role in controlling this pandemic.[4] In this article, we review clinical and experimental evidence available for pathogenesis of COVID-19 and highlight various clinical presentations in human infection.

PATHOGENESIS

Structure of SARS-CoV-2

Coronaviruses have the largest RNA viral genomes, ranging from 26,000 to 32,000 bases,[5] and the genome is made up almost entirely of protein coding sequences.[6] SARS-CoV-2 is the seventh known coronavirus capable of causing human infection.[7] Whole genome sequencing revealed that SARS-CoV-2 has genomic similarities to be placed in the same *Betacoronavirus* clade like SARS-CoV, MERS-CoV, and SARS-like bat CoV; however, phylogenetic analysis and amino acid sequences have revealed enough differences in SARS-CoV-2 to confer structural and functional difference from other coronaviruses.[8] The genome of SARS-CoV-2 is about 29.9 kB[9] in length (in contrast, SARS-CoV is about 29.7 kB long[10]) of which about 79% to 82% includes a sequence[11] homology to SARS-CoV and 50% to MERS-CoV.[8] Unlike SARS-CoV, SARS-CoV-2 possesses a distinguishing polybasic cleavage site (RRAR) that is cleaved by furin and other proteases. The presence of this furin cleavage site has been suggested to confer SARS-CoV-2 with greater transmissibility than SARS-CoV and enhances its virulence.[12] Like SARS-CoV and other coronaviruses, SARS-CoV-2 codes for four structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). The viral envelope is created by S, E, and M proteins together, whereas the N protein binds to the viral RNA.[13]

Origin and Transmission

Coronaviruses are diverse and pathogenic to a variety of animals, including pigs, cows, dogs, cats, and chickens. Bats act as a reservoir for coronaviruses, including SARS-CoV-2.[6] When the first cases of pneumonia were described in the Hubei province in China in late 2019, genome sequencing and phylogenetic analysis identified the pathogen as a novel coronavirus with bat and pangolin genetic sequences, further adding evidence to a zoonotic origin of the virus.[14]

Viral Entry and Initial Infection

Infection occurs when the viral particles are inhaled, enter the airways, and bind to the receptors on host cell surface. Like other coronaviruses, the S protein of SARS-CoV-2 binds to the angiotensin-converting enzyme 2 (ACE2), a metalloproteinase found in large amounts in airway epithelial and endothelial cells that undergoes a conformational change to permit the fusion of viral and host cell membranes.[15] Although this mechanism is shared by SARS-CoV, a recent study using biophysical assays found

that the S protein of SARS-CoV-2 binds 10 to 20 times more strongly to ACE2.[16] The higher binding affinity to ACE2 has been proposed to be responsible for increased viral transmissibility and severity of disease compared with SARS-CoV.

The S protein is composed of 2 subunits: S1 and S2.[17] When the S1 subunit attaches to the ACE2 receptor on the host cell, a transmembrane protease, serine 2 (TMPRSS2) cleaves the S protein to reveal S2 subunit, and ACE2. The S protein undergoes dramatic conformational changes, leading to the fusion of the viral membrane with the host cell. The viral particle is then engulfed in an endosome. The virion escapes the endosome when it is cleaved by a host cell protease, cathepsin, or by a decrease in the pH (acidification).[18] Cathepsin has been proposed as a therapeutic target to prevent infection with SARS-CoV-2.[19]

High expression of ACE2 on the surface of lung alveolar epithelium and enterocytes of the small intestine was proposed to contribute to the viral entry of SARS-CoV, a mechanism that SARS-CoV-2 likely mirrors.[20] Besides these locations, ACE2 is widely expressed in various human tissues, including the heart, kidneys, and arterial and venous endothelial cells. The presence of ACE2 in these tissues likely contributes to extrapulmonary manifestations, such as diarrhea, acute renal injury, cardiac injury, and vascular endothelial damage with multisystem organ failure.[21] Children have lower ACE2 expression, which might explain lower early COVID-19 acquisition rates in children but higher rate of multisystem inflammatory syndrome in older children. The tissues expressing ACE2 do not participate equally in the pathogenesis of COVID-19, suggesting that other factors are involved in contributing to tissue damage.[22]

PHASES OF INFECTION

Early after the discovery of SARS-CoV-2, COVID-19 infection was described in 2 phases: a viral response phase and a host inflammatory response phase (also referred to as the cytokine storm phase) (**Fig. 1**). This general principle has remained relevant over time, but the relative contribution of each phase to the illness remains to be characterized. Viral loads of SARS-CoV-2 are high in the initial days of infection and decrease steadily over time in immunocompetent hosts (**Fig. 2**). In these first few days, SARS-CoV-2 infection can range from asymptomatic to mildly symptomatic in most patients, and generally includes upper respiratory symptoms and/or a systemic influenza-like illness. Severe COVID-19 usually develops at least after 1 week of illness onset, which could imply a greater role for a dysregulated immune response rather than a direct viral cytopathic effect. An evaluation of the timeline of events suggests that median time from onset of symptoms to hospital admission, dyspnea, acute respiratory distress syndrome (ARDS), mechanical ventilation, and intensive care unit (ICU) admission were 7.0, 8.0, 9.0, 10.5, and 10.5 days, respectively,[23] for the original virus, although the timelines differ slightly depending on the responsible variant, further supporting the hypothesis of dysregulated immune response driving severe COVID-19.

HOST IMMUNE RESPONSES

Innate Immune Response

The innate immune response is activated when pathogen-associated molecular patterns (PAMPs) are recognized by host receptors.[24] PAMPs are small molecules, such as lipopolysaccharides, peptidoglycan, lipoteichoic acid, and nucleic acids, that are present in different patterns and trigger immune cascades when recognized by the host. The protein receptors in the host responsible for detecting PAMPs are called pattern recognition receptors. These pattern recognition receptors include Toll-like receptors, C-type lectin receptors, NOD-like receptors, and RIG-I-like

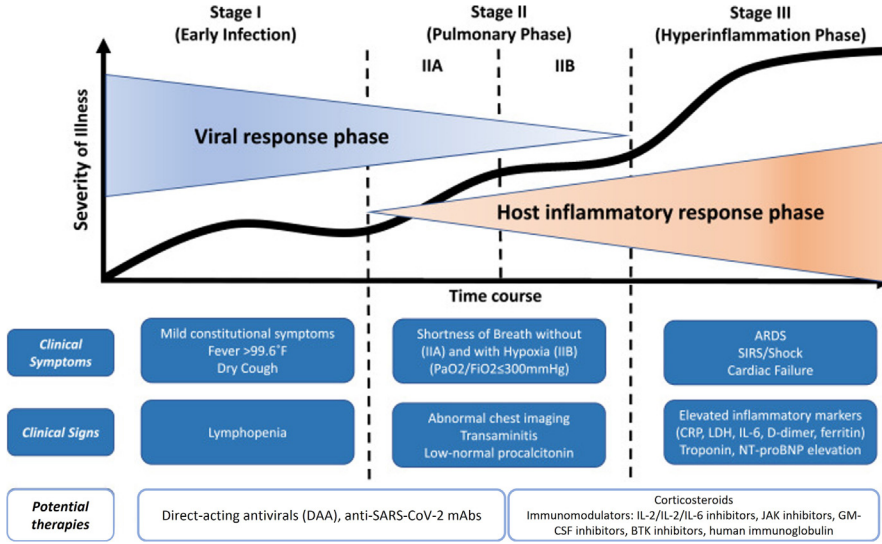

Fig. 1. Stages of SARS-CoV-2 infection, their correlation with clinical symptoms and potential therapies that have been identified. (*Adapted from*: Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. *J Heart Lung Transplant*. 2020 May;39(5):405–407. https://doi.org/10.1016/j.healun.2020.03.012 with permission from Elsevier)

receptors. Once activated, these receptors initiate downstream signaling pathways leading to secretion of type I and type III interferons, and the assembly and activation of the NOD-like receptor P3 inflammasome and other inflammasome complexes that promote secretion of proinflammatory cytokines including IL-1β and IL-18.[25] The activation of antigen-presenting cells by proinflammatory cytokines also recruits the adaptive immunity to enhance viral clearance by antibody-mediated neutralization and T-cell–mediated cytotoxicity.[24] The inflammasome pathway triggers the coagulation cascade, contributing to coagulopathy and the thrombotic events seen in severe COVID-19.[26]

Like PAMPs, host cells are also activated by damaged or stressed cells in the setting of inflammation,[24] necrosis, or hypoxia even if no microbial PAMPs are present. These are called damage-associated molecular patterns. Although the activated PAMP and damage-associated molecular pattern pathways contribute to viral clearance, an overactivated response leads to a dysregulated immune system and exacerbates inflammation and damage through a cytokine storm[26] (**Fig. 3**). These pathways have been described for viral infections in the past, but corresponding pathways specific to SARS-CoV-2 remain to be identified.

One proinflammatory cytokine, IL-6, garnered attention after reports of ARDS became common in patients with severe COVID-19. IL-6 is a mediator of both innate and adaptive immune responses and acts as both a proinflammatory cytokine and an anti-inflammatory myokine. IL-6 is secreted by macrophages when PAMPs bind to pattern recognition receptors. An elevated IL-6 was reported to be associated with a poor prognosis and, consequently, much emphasis was placed on the treatment of severe COVID-19 with IL-6 receptor antagonists.[4] Clinical trials have suggested there is some benefit to limiting hyperactive immune responses through blocking IL-6 in severe COVID-19.[27]

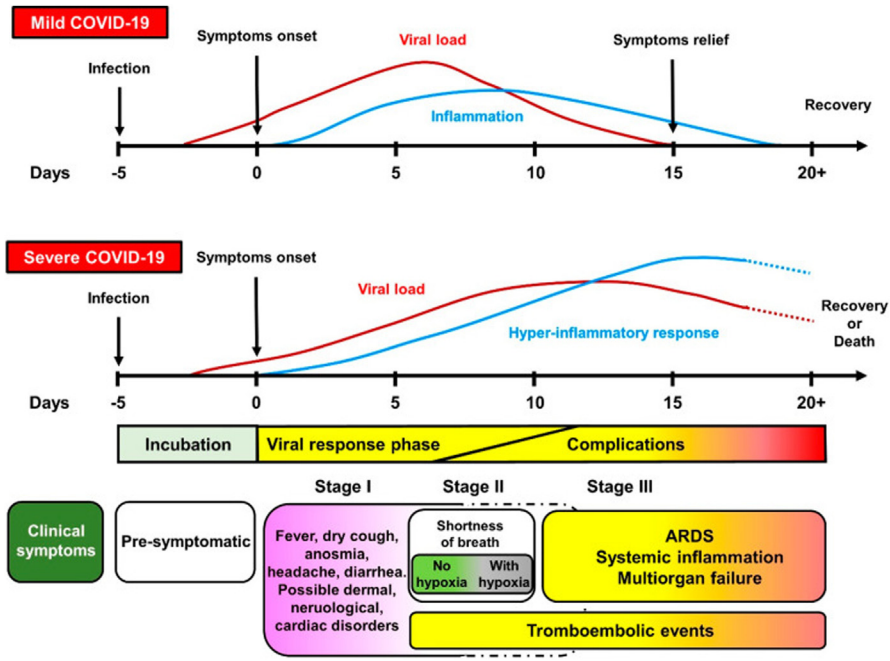

Fig. 2. Timeline of mild and severe COVID-19 and its correlation with viral activity and clinical manifestations. (*From* Lariccia and colleagues Challenges and Opportunities from Targeting Inflammatory Responses to SARS-CoV-2 Infection: A Narrative Review, *Journal of Clinical Medicine*. 2020; 9(12):4021. https://doi.org/10.3390/jcm9124021. © 2020 by the authors. Licensee MDPI, Basel, Switzerland. Under Creative Commons (CC BY 4.0) license)

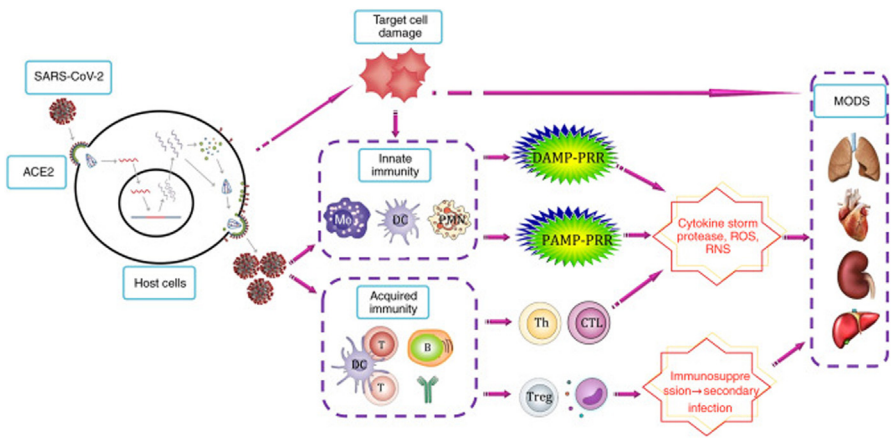

Fig. 3. Immune response to SARS-CoV-2 infection and its role in pathogenesis. (*From* Li C, He Q, Qian H, Liu J. Overview of the pathogenesis of COVID-19 (Review). *Exp Ther Med*. 2021;22(3):1011. https://doi.org/10.3892/etm.2021.10444. © Li and colleagues Under Creative Commons Attribution License)

An early innate immune response is critical in activating the T- and B-cell immune systems and terminating the infection at asymptomatic or mild to moderate stage.[28] A delayed or absent innate immune response, either by immune evasion by the virus or defective host immunity (or both), fails to prime the adaptive immune system and contributes to a high risk of severe or fatal COVID- 19.

Antigen Presentation

Antigen-presenting cells are the initial component of antiviral response by the host. The specific mechanism of antigen presentation of SARS-CoV-2 is not well-understood; however, some of it can be extrapolated based on data from other betacoronaviruses, which mainly depends on major histocompatibility complex 1 molecules. Several HLA types have been associated with increased susceptibility or protection against SARS-CoV.[29] It is highly likely there exist HLA alleles that predict increased susceptibility to SARS-CoV-2 and correlate with more severe outcomes, although research in diverse populations is ongoing.

Adaptive Immunity

Both humoral and cellular immune responses are activated by antigen-presenting cells as suggested by presence of virus-specific B and T cells in convalescent cases.[30] Coordinated humoral and cellular immune responses have been hypothesized to be protective, and an uncoordinated response has been blamed for uncontrolled disease[31] (**Fig. 4**.) Moreover, a delayed activation of adaptive immunity has been correlated with a higher viral burden and severe or fatal COVID-19. It has been hypothesized that the innate immune response attempts to fill the gap left by the absence of a functional adaptive immune system response, leading to an overactivated innate cytokine and chemokine responses and exacerbated neutrophil-driven lung damage, as evidenced by the presence of a substantial number of neutrophils in end-stage COVID-19.[28,32]

It has been demonstrated that neutralizing antibody titers and quantity of virus-specific T cells are positively correlated.[30] As with other acute viral infections, IgG and IgM subtype antibodies are produced, primarily against the S and N proteins.[33] IgM antibodies persist for 4 to 6 weeks after the onset of symptoms, whereas IgG persists for approximately 6 months after symptom onset in most cases. Persons who experienced asymptomatic infection have been shown to have lower seropositivity and delayed seroconversion when compared with persons who developed symptomatic COVID-19. Furthermore, antibodies in people who have recovered from COVID-19 may persist for well over 6 months.[30]

The T-cell response to SARS-CoV-2 includes both $CD4^+$ and $CD8^+$ T cells. It has been suggested that $CD4^+$ T cells are more abundant and effective against SARS-CoV-2 infection than $CD8^+$ T cells.[31] A predominantly $CD4^+$ T-cell response is seen against S, M, and N proteins, although $CD4^+$ cells respond against almost all SARS-CoV- 2 proteins. After symptom onset, a $CD4^+$ T-cell response can be detected within 2 to 4 days, whereas a $CD8^+$ T-cell response can be detected as early as 1 day after symptoms develop.[28]

A study found that although the overall number of CD4 and CD8 T cells in patients with COVID-19 is decreased, cells are excessively activated, with increased expression of proinflammatory HLAs and coreceptors. CD8 T cells were found to have an increased density of cytotoxic granules.[34] This factor likely contributes to the cytokine storm causing ARDS and systemic inflammation, through the release of proinflammatory cytokines (including interferon, IL-6, and tumor necrosis factor-α) and

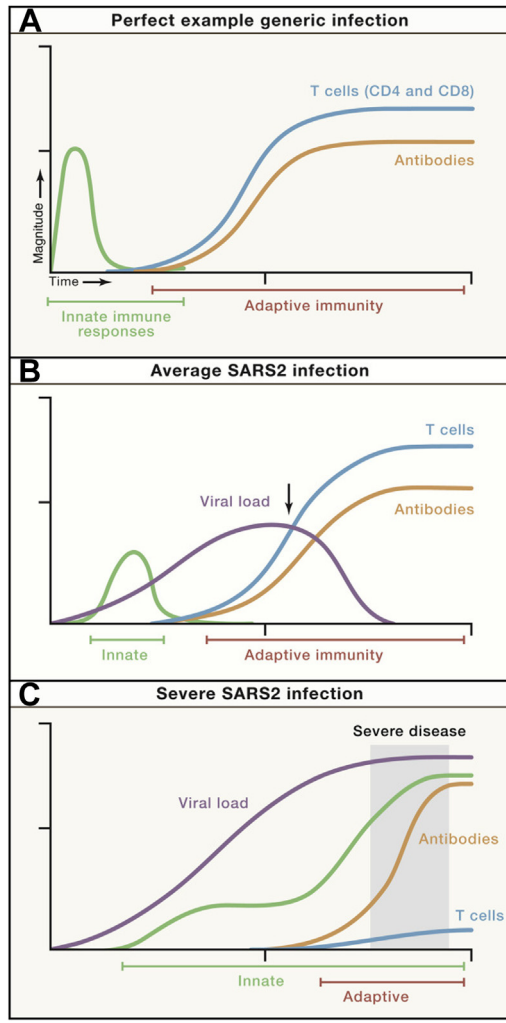

Fig. 4. Timeline of immune response and viral load in SARS-CoV-2 infection. (*A*) Perfect example generic infection. (*B*) Average SARS-CoV-2 infection. (*C*) Severe SARS-CoV-2 infection. (*From* Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell.* 184(4), 861–880. Copyright 2021 with permission from Elsevier; with permission)

chemokines (CCL5, CXCL8, etc). This exaggerated immune response is what leads to the multiorgan involvement and high mortality seen in COVID-19.

Although long-term memory immunity is not yet clarified for SARS-CoV-2, it is known that CD4 and CD8 memory T cells persist for years after recovery from SARS-CoV infection and can respond to SARS-CoV antigens even after 6 years. In contrast, it seems that memory B-cell response is almost absent after 6 years after recovery from SARS.[35] In follow-up of early SARS-CoV-2 infections and after vaccination, it also seems clear that T-cell responses are longer than antibody responses. Longer term follow-up will be required to fully elucidate the duration of postinfection responses.

Immune Evasion and Variants

It is believed that SARS-CoV-2 uses similar mechanisms to evade the host's immune response as other coronaviruses. Viral proteins interfere with the function and maturation of antigen-presenting cells and activate pathways that decrease the transcription and transport of antiviral proteins (such as interferons). Antigenic variation, particularly in the M protein, also decreases the production of interferons.[36]

Another mechanism of immune evasion of particular concern is S protein mutations, which alter the ultrastructure and function of the epitope domain, impairing the function of antibodies against the immunodominant protein.[37] These mutations in structural proteins have caused (and will continue to cause) the emergence of different variants of SARS-CoV-2. SARS-CoV-2 has undergone significant mutations, with some lineages emerging as variants of concern as defined by the World Health Organization. These variants are so named because of their potential for higher transmissibility, more severe disease, or high risk of immune escape. See William O. Hahn and Zanthia Wiley's article, "COVID-19 Vaccines," in this issue.

CLINICAL FEATURES

Several medical comorbidities have been identified as risk factors for severe COVID-19, including cardiovascular disease,[38] chronic kidney disease, immunocompromising conditions, and metabolic diseases.[39] It should be noted that the rates of infection, hospitalization, and death from COVID-19 in Black,[40] Hispanic,[41] and American Indian/Alaska Native communities[42] have been disproportionately higher than other racial or ethnic groups. The role of biology and the disproportionate prevalence of medical comorbidities has not been enough to explain these inequities, in addition to a wealth of data suggesting that these differences are driven by social and structural vulnerabilities resulting from the impacts of structural racism in these communities.[43,44] Additional details of inequities seen with COVID-19 will be presented elsewhere in this collection.

The severity of COVID-19 infection varies depending on both the virulence of the SARS-CoV-2 variant and the host immune response, with clinical manifestations ranging from asymptomatic infection to severe inflammatory syndrome and multiorgan dysfunction. As such, the National Institutes of Health established a classification system for COVID-19 disease, delineating the criteria for asymptomatic, mild, moderate, severe, and critical COVID-19. These categories are not mutually exclusive, and many patients progress from 1 category to another during the course of the disease.[45]

The incubation period following exposure to SARS-CoV-2 has been estimated anywhere between 2 and 14 days, and varies by variants of concern. In a pooled analysis of 181 confirmed COVID-19 cases from China the median incubation period was estimated to be 5.1 days (95% confidence interval, 4.5–5.8 days).[46] Noteworthy, compared with earlier variants of concern, shorter incubation periods have been documented in infections with Delta and Omicron variants, with a median incubation period of 4 days.[47]

Asymptomatic Infection

Asymptomatic infections involve individuals who test positive for SARS-CoV-2 but have no symptoms. It is estimated that 50% of persons who test positive for SARS-CoV-2 are asymptomatic at the time of diagnosis.[3] The overall proportion of asymptomatic infections was estimated at approximately 25% in one meta-analysis, but the proportion of asymptomatic infections is generally higher in persons with preexisting immunity.[48]

Asymptomatic infections are more common in young and middle-aged patients (<50 years of age), women, and individuals without underlying comorbid conditions.[49] In an early study including 55 cases of asymptomatic infection,[50] the median age at the time of diagnosis was 49 years. Despite absence of symptoms, more than half patients (37/55) in this study had evidence of pneumonia on computed tomography scans.

Importantly, a small proportion of patients initially classified as asymptomatic may eventually develop symptoms of infection, generally within 48 hours of SARS-CoV-2 RNA being detectable in the nasopharynx and are referred to as presymptomatic. However, many patients remain asymptomatic at follow-up.[49]

Mild Disease

Mild COVID-19 cases include individuals with symptoms of fever, sore throat, myalgia, and/or malaise, but without shortness of breath, dyspnea, or abnormal chest imaging indicating the presence of lower respiratory tract disease. The majority of symptomatic infections result in mild COVID-19 (81%).[51] Gastrointestinal symptoms such as diarrhea, nausea, and emesis have also been reported, but with lower frequencies (<20%) than in SARS or MERS infections.[52] The incidence of symptoms such as loss of smell or taste varies significantly among studies, with frequencies between 10% and 40%.[23] Loss of taste or smell (anosmia and ageusia, respectively), however, are often recognized by patients as a hallmark, or pathognomonic feature, of COVID-19, and frequently precede the onset of other flu-like symptoms. This peculiar manifestation has been studied, with one of the proposed theories being that the specialized cells in the olfactory bulb and olfactory epithelium have the ACE2 receptors for viral entry and subsequent infection, although there are detectable changes in brain imaging in some persons with anosmia.[53,54] Most patients recover over the course of a few weeks; however, persistent anosmia and ageusia are also frequently described and remain under study.

Moderate, Severe, and Critical Disease

Patients with moderate disease have evidence of lower respiratory disease on physical examination or chest imaging, but maintain an oxygen saturation of equal or greater than 94% on room air at sea level.[45] Individuals with severe disease have an oxygen saturation on room air of less than 94% at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of less than 300 mm Hg, or a respiratory rate of greater than 30 breaths/min, or lung infiltrates greater than 50%.[45] Critical disease is defined as respiratory failure, septic shock and/or multiorgan failure.[45]

During the initial phase of the pandemic, severe disease accounted for up to 14% of cases and critical illness was seen in about 5% of cases according to the Chinese Center for Disease Control and Prevention.[55] The rate of severe disease, however, varies depending on several factors, including history of prior infection, vaccination status, variant causing the infection and available health care resources. For example, the Omicron variant seems to be associated with milder disease compared with Delta variant.[56] The risk of progression to severe and critical disease is markedly decreased in persons with prior immunity, especially after vaccination.

The hallmark of COVID-19 is respiratory disease, which is the consequence of severe inflammation and damage of lung tissue. The pathogenesis of COVID-19 is still being extensively studied. The replication of the virus inside the respiratory epithelium causes a proinflammatory state through the production of chemokines and cytokines, including IL-1, IL-6, and tumor necrosis factor-α, among many others.[57] The main

mechanism of lung injury in COVID-19 is diffuse alveolar damage.[56] The damage to the endothelium mediated by fibrin and inflammation causes edema and thrombosis of lung vessels. This process can cause extensive injury and edema of the alveoli with formation of protein deposits and hyaline membranes. This inflammation in the lung parenchyma manifests as mucus production, cough, and dyspnea. On imaging, patchy opacities can be seen on radiograph or ground glass opacities on computed tomography scans. These opacities are usually of peripheral or subpleural distribution bilaterally. Pneumonia can be significant enough to cause hypoxemic respiratory failure and, in some cases, may progress to ARDS, and ultimately, death. Risk factors for progression to ARDS have been identified: age greater than 65 years, diabetes mellitus, hypertension, and obesity, and nonreceipt of SARS-CoV-2 vaccination, among other factors.[58]

Acute Respiratory Distress Syndrome

ARDS is a clinical entity that presents with bilateral pulmonary infiltrates and severe hypoxemia, which results from extensive damage and edema of the alveolar system owing to infiltration by inflammatory cells and mediators. Inflammatory cells, lytic enzymes, and cytokines produce thickening and fibrosis of the alveolar-blood barrier, destruction of alveoli, formation of proteinaceous hyaline membranes and severe edema of the interstitium. It is characterized by noncardiac pulmonary edema and severe hypoxemia with a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen of less than 300. The severity of disease is classified according to the ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.[59]

ARDS develops in approximately 30% to 50% of patients presenting with COVID-19 pneumonia and hypoxemia, although this number could change with the implementation of steroid therapy, vaccination, and outpatient therapeutics. In a study of 13 patients admitted to the ICU,[60] 30% developed ARDS at a median time of 9 days and 10% required mechanical ventilation. The mortality rate of ARDS in patients with COVID-19 seems to be higher than that of other causes of ARDS.[60] This could be due to multiple factors, including the added damage from the virus to the lung parenchyma and the thrombotic microangiopathy and thrombosis that develops in severe COVID-19.

COVID-19–Associated Pulmonary Aspergillosis

Like influenza, pulmonary epithelial damage resulting from COVID-19 increases risk of invasive pulmonary aspergillosis. A systematic review described 85 cases of invasive pulmonary aspergillosis in patients with critical COVID-19, with an estimated prevalence of 5% to 30%, although this high estimate has been questioned.[61] Risk factors for death from CAPA were age, male sex, and pre-existing lung disease. Importantly, not all patients had a predisposing immunosuppressive state for invasive disease, although many received corticosteroids.[61] It is important to note that not all cases of COVID-19–associated pulmonary aspergillosis clearly represent an infection versus colonization, and this clinical entity is an area of developing study, especially as cross-sectional imaging, bronchoalveolar lavage, and definitive diagnostics are often deferred in patients with COVID-19 to reduce transmission potential and procedures. Owing to the degree of lung damage and long duration of ventilation and extracorporeal life support required for some with critical COVID-19, it is important to keep vigilance for COVID-19–associated pulmonary aspergillosis and treat with appropriate antifungals if suspicion is high.

Extrapulmonary Manifestations of COVID-19

Cutaneous manifestations

Cutaneous manifestations are rare with reported rates of less than 2% and usually nonspecific.[62] However, certain features accompanying cutaneous manifestations have been reported in the literature. Urticarial rash is commonly associated with moderate to severe COVID-19.[62] A maculopapular rash can be observed after the onset of systemic symptoms whereas papulovesicular exanthems frequently occur before the onset of symptoms. Livedo racemosa-like pattern lesions are often associated with severe coagulopathy and acral ischemia with cyanosis of toes (so-called COVID toes), skin blisters, and dry gangrene have been reported in patients with severe COVID-19.[63]

Neurologic Manifestations

Dizziness and headache are among the most common neurologic symptoms reported in the literature, although the prevalence.[64] A minority of patients with severe COVID-19 can present with acute encephalopathy, cerebrovascular accidents, changes in vision, seizures and radiculopathy.[65] So-called brain fog has also been described, particularly as a sequela of COVID, referring to a nonspecific and subjective inability to concentrate or to perform certain tasks. One of the proposed mechanisms is direct viral interference in mitochondrial function in neurons, although studies are ongoing.[66]

The prevalence of ischemic stroke in patients with COVID-19 has been estimated to be approximately 5%, and it carries a high mortality rate of 30% to 40%.[67] It is most commonly seen in patients older than 70 years of age, but it has also been reported in younger, previously healthy patients.[68] Risk factors include prior cerebrovascular events, hypertension, diabetes, chronic kidney disease, and chronic liver disease, among others. Depending on the vascular territory affected, patients may present with facial droop, aphasia, dysarthria, or unilateral weakness. The management for stroke in the setting of COVID-19 is the same as for other patients: the use of the tissue plasminogen activator alteplase or mechanical thrombectomy if patients meet criteria for either.[67] It is not yet clear if patients have a higher risk of hemorrhagic complications with the use of alteplase.

Cardiac Injury

Cardiac injury by COVID-19 has been reported in the literature mainly in patients with underlying cardiovascular conditions and carries a poor prognosis.[69] The range of manifestations can go from asymptomatic troponin elevation to severe myocarditis and heart failure.

The proposed pathogenic mechanisms include direct viral infection, cytokine storm, pulmonary emboli, coronary thrombosis, hypercoagulability, and an imbalance between demand and supply.[69] A study of 40 patients who died with cardiac-related COVID-19 complications revealed that microthrombi were the most common pathologic cause of myocyte necrosis.[70] Of note, the composition of these microthrombi was different from that of patients without COVID-19. Myocarditis associated with COVID-19 has also been described. The risk of myocarditis in people with COVID-19 is approximately 16 times that of people without COVID-19, and the highest risk is found in children aged less than 16 years and elderly patients ages more than 75 years.[71] Although there has been concern about infrequent cases of myocarditis associated with SARS-CoV-2 vaccination, the risk of myocarditis owing to COVID-19 itself is 4- to 40-fold higher than from vaccination with one of the mRNA vaccines.[71,72]

Thrombotic Episodes

Significant thrombotic events have been described in persons with both symptomatic and asymptomatic SARS-CoV-2 infection, ranging from an increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE), to stroke, thrombotic microangiopathy and disseminated intravascular coagulation, all of which further increase the morbidity and mortality of the disease.[73]

SARS-CoV-2 infects host cells via ACE2, which is present in high concentrations in the endothelial cells. Proinflammatory pathways are triggered in endothelial cells, with indirect activation of the kallikrein-kinin system and increased levels of bradykinin, which increase vascular permeability. Activation of the complement and subsequent direct endothelial injury and death causes denudation of the endothelium.[74] Procoagulant pathways are activated in response to exposure of the basement membrane, which triggers microvascular thrombosis and hemorrhage.[75] This proposed cascade of events is consistent with what is seen macroscopically in autopsy studies, where platelet and fibrin rich thrombi have been found in the lungs of patients who have died of COVID-19.[76] Tissue factor expression induces coagulation pathways, and anticoagulants like protein C and tissue factor pathway inhibitor are inhibited by the overwhelming procoagulant activation. The damaged endothelium expresses adherence molecules and cytokines that not only stimulate the production of platelets, but also their adhesion to the endothelium and formation of clots.[74]

Venous Thromboembolism

Venous thromboembolism, consisting of DVT and PE, is a common complication of hospitalized patients with COVID-19, and less frequently in persons whose COVID-19 respiratory infection is not severe enough to merit hospitalization. The prevalence has been identified to be particularly high in patients admitted to the ICU (from 50% to 80% depending on the series[77,78]), even when the clinical suspicion may be low.[73] However, patients that are admitted to acute care units also have an increased risk of DVT (20%–30% of patients).[79] These thrombotic events can happen despite pharmacologic prophylactic doses of anticoagulant.[79] PE is another potentially life-threatening complication that is more prevalent in patients with COVID-19, particularly those admitted to the ICU (20%–30%). Persons admitted to acute care for COVID-19 have PE rates of 10% to 20%.[79,80] DVT can be seen both in lower and upper extremities, and presents identically to non-COVID–associated VTE, subclinical, and asymptomatic presentations. The diagnosis of PE in patients who are mechanically ventilated may be challenging, especially given the many reasons for physiologic shunt present owing to microthrombi, airspace disease from COVID-19 pneumonia, and superimposed bacterial or fungal infection, and ARDS. The preferred diagnostic modality is computed tomography angiography.

Arterial Thrombosis

Thrombotic complications in arterial vessels have also been described. Acute limb ischemia has been observed in patients with COVID-19, regardless of pre-existing peripheral arterial disease.[73] Arterial thrombosis manifests as severe pain and discoloration of an extremity, cold and clammy extremities, and decreased pulses. Thrombosis of the thoracic or abdominal aorta has also been reported, manifesting as unilateral limb ischemia, bilateral loss of pulses in the lower extremities, bilateral loss of sensation, or acute periumbilical/epigastric pain.[81] Mesenteric ischemia can present with diarrhea and severe abdominal pain.[82] Arterial thrombotic complications often cause a marked elevation of D-dimer as well as inflammatory markers such as

C-reactive protein, although these markers are often drastically elevated in persons with severe or critical COVID-19, and the difficulty in making these diagnoses can result in delays in detection, and further increase their morbidity and mortality.

COVID-19 IN CHILDREN

COVID-19 is a disease that has been proven to affect children of all ages, especially as the incidence of pediatric COVID-19 increased during infection waves attributable to the delta and omicron variants. The most common clinical presentation in children is fever with cough, similar to adult infections. Many infections are asymptomatic, and in the majority, disease is mild or moderate. Children younger than 1 year old may have a higher incidence of critical disease and gastrointestinal symptoms.[83]

In May 2020, the US Centers for Disease Control and Prevention reported a severe inflammatory syndrome that presented in otherwise healthy children that had features similar to Kawasaki disease, with persistent fever, rash, and other various neurologic, gastrointestinal, dermatologic, cardiac, and renal manifestations.[84] This syndrome had been linked to COVID-19 infection and was named multisystem inflammatory syndrome in children. Further description of manifestations of COVID-19 in pediatric populations is discussed in Andrasik and colleagues' article, "Awakening: The Unveiling of Historically Unaddressed Social Inequities During the COVID-19 Pandemic in the United States," in this issue.

POSTACUTE SEQUELAE OF COVID-19

Postacute sequelae of COVID-19, also colloquially termed long COVID or long-haul COVID-19, is a clinical entity that has gained recognition as the pandemic continued into its second year in 2021. Although there is no consensus for a single definition, in general, postacute sequelae of COVID-19 refers to the persistence of symptoms for more than 3 months after the onset of symptoms.[85] The most common reported symptoms are shortness of breath and fatigue; however, an extensive list of symptoms involving multiple systems has been described. These symptoms include cognitive dysfunction (brain fog), mental disorders (depression, anxiety), headache, musculoskeletal complaints (myalgia, joint pain, chest wall pain), taste and smell disorders, chronic cough, alopecia, and insomnia, among many others.[86] Further details on pathophysiology, manifestations, and proposed treatments for postacute sequelae of COVID-19 are discussed in Eric A. Meyerowitz and Aaron Richterman's article, "SARS-CoV-2 Transmission and Prevention in the Era of the Delta Variant," in this issue.

SUMMARY

COVID-19 is a disease that affects multiple organ systems, and the prevailing theory is that most symptoms outside of the upper respiratory tract are predominately triggered by an exaggerated inflammatory response in the host. This inflammatory process results in a wide variety of clinical presentations, ranging from asymptomatic to severe multiorgan dysfunction. COVID-19 affects people of all age groups, including children, who also suffer from severe disease. Groups of people with poor access to health care such as Black and Hispanic/Latino communities have been disproportionately impacted by COVID-19, fueling increased awareness of health care disparities. Furthermore, the persistence of symptoms in people who recover from COVID-19 adds to its morbidity and impact on the workforce, mental health, and economic impacts in the long term. The complete pathogenesis of SARS-CoV-2 is slowly being

unraveled through knowledge from similar respiratory viruses, as well as a rapid proliferation of research on this novel pathogen. Fully understanding the pathogenesis, especially of extrapulmonary manifestations of COVID-19 disease, will likely remain an area of developing knowledge for years to come.

CLINICS CARE POINTS

- COVID-19 can range from asymptomatic infection to severe multiorgan failure. The hallmark of the disease is exaggerated inflammation in the lung tissue that can progress to ARDS, although it also causes significant endothelial damage and thrombosis in other systems.
- COVID-19 affects different organs and systems, and the presentation depends on the organ systems affected. Not all patients present with respiratory symptoms.
- Although venous thrombosis is widely reported in COVID-19, arterial thrombosis can also be encountered as mesenteric or aortic thrombosis, as well as acute limb ischemia. These often cause significant elevations of D-dimer and C-reactive protein.
- Although COVID-19 is generally less severe in children than in adults, it can present with persistent fever, rash and multiorgan dysfunction (multisystem inflammatory syndrome in children) that often requires an ICU level of care.
- Postacute sequelae of COVID-19 (also known as long COVID) is generally defined as persistent symptoms for more than 3 months after the initial onset of symptoms of COVID-19.

DISCLOSURES

J.R. Marcelin Co-chairs the NIH/NIAID/CoVPN vaccine study CoVPN 3006/Prevent COVID U and receives salary support for this activity, not related to this article. All other authors have no potential conflicts of interest to disclose.

REFERENCES

1. Sawicki SG, Sawicki DL. Coronavirus transcription: a perspective. Coronavirus Replication Reverse Genet 2005;287:31–55.
2. Tabatabaeizadeh SA. Airborne transmission of COVID-19 and the role of face mask to prevent it: a systematic review and meta-analysis. Eur J Med Res 2021;26(1):1.
3. Prevalence of asymptomatic SARS-CoV-2 infection: a narrative review. Annals of Internal Medicine: vol 173, No 5. Available at: https://www.acpjournals.org/doi/10.7326/M20-3012. Accessed November 8, 2021.
4. Vijayvargiya P, Esquer Garrigos Z, Castillo Almeida NE, et al. Treatment considerations for COVID-19: a critical review of the evidence (or Lack Thereof). Mayo Clin Proc 2020;95(7):1454–66.
5. Frampton D, Rampling T, Cross A, et al. Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study. Lancet Infect Dis 2021;21(9):1246–56.
6. Singh D, Yi SV. On the origin and evolution of SARS-CoV-2. Exp Mol Med 2021;53(4):537–47.
7. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382(8):727–33.

8. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395(10224):565–74.
9. Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1, complete genome. 2020. Accessed. http://www.ncbi.nlm.nih.gov/nuccore/NC_045512.2. [Accessed 7 November 2021]. Available at:.
10. The Genome Sequence of the SARS-Associated Coronavirus. Accessed. https://www.science.org/doi/10.1126/science.1085953. [Accessed 7 November 2021]. Available at:.
11. Chan JFW, Kok KH, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect 2020;9(1):221–36.
12. Hu B, Guo H, Zhou P, et al. Characteristics of SARS-CoV-2 and COVID-19. Nat Rev Microbiol 2020;1–14. https://doi.org/10.1038/s41579-020-00459-7.
13. Walls AC, Park YJ, Tortorici MA, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020;181(2):281–92.e6.
14. Lau SKP, Luk HKH, Wong ACP, et al. Possible Bat origin of severe acute respiratory syndrome coronavirus 2. Emerg Infect Dis 2020;26(7):1542–7.
15. Li W, Moore MJ, Vasilieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature 2003;426(6965):450–4.
16. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020;367(6483):1260–3.
17. Huang Y, Yang C, Xin-Feng X, et al. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. Acta Pharmacol Sin 2020;41(9):1141–9.
18. Coronaviruses - a general introduction - CEBM. Available at: https://web.archive.org/web/20200522053938/https:/www.cebm.net/covid-19/coronaviruses-a-general-introduction/. Accessed November 8, 2021.
19. Zhao MM, Yang WL, Yang FY, et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. Signal Transduct Target Ther 2021;6(1):1–12.
20. Hamming I, Timens W, Bulthuis M, et al. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J Pathol 2004;203(2):631–7.
21. Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol 2020;16(12):747–64.
22. Eun LY. Is multisystem inflammatory syndrome related with coronavirus disease 2019, Kawasaki disease, and angiotensin-converting enzyme 2 in children? Clin Exp Pediatr 2021;64(5):225–6.
23. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020;395(10223):497–506.
24. Carty M, Guy C, Bowie AG. Detection of viral infections by innate immunity. Biochem Pharmacol 2021;183:114316.
25. Rodrigues TS, de Sá KSG, Ishimoto AY, et al. Inflammasomes are activated in response to SARS-CoV-2 infection and are associated with COVID-19 severity in patients. J Exp Med 2020;218(3):e20201707.
26. Inflammasome activation triggers blood clotting and host death through pyroptosis. Accessed. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6791531/. [Accessed 8 November 2021]. Available at:.

27. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med 2021;384(16):1491–502.
28. Sette A, Crotty S. Adaptive immunity to SARS-CoV-2 and COVID-19. Cell 2021; 184(4):861–80.
29. Chen YMA, Liang SY, Shih YP, et al. Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. J Clin Microbiol 2006; 44(2):359–65.
30. Ni L, Ye F, Cheng ML, et al. Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. Immunity 2020;52(6): 971–7.e3.
31. Rydyznski Moderbacher C, Ramirez SI, Dan JM, et al. Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. Cell 2020;183(4):996–1012.e19.
32. Kuri-Cervantes L, Pampena MB, Meng W, et al. Comprehensive mapping of immune perturbations associated with severe COVID-19. Sci Immunol 2020;5(49): eabd7114.
33. Zhang X, Lu S, Li H, et al. Viral and antibody kinetics of COVID-19 patients with different disease severities in acute and convalescent phases: a 6-month follow-up study. Virol Sin 2020;35(6):820–9.
34. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8(4):420–2.
35. Tang F, Quan Y, Xin ZT, et al. Lack of peripheral memory B cell responses in recovered patients with severe acute respiratory syndrome: a six-year follow-up study. J Immunol 2011;186(12):7264–8.
36. Bouayad A. Innate immune evasion by SARS-CoV-2: comparison with SARS-CoV. Rev Med Virol 2020;30(6):e2135.
37. Harvey WT, Carabelli AM, Jackson B, et al. SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol 2021;19(7):409–24.
38. Ssentongo P, Ssentongo AE, Heilbrunn ES, et al. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: a systematic review and meta-analysis. PLoS One 2020;15(8):e0238215.
39. Zhou Y, Yang Q, Chi J, et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: a systematic review and meta-analysis. Int J Infect Dis 2020;99:47–56.
40. Kullar R, Marcelin JR, Swartz TH, et al. Racial disparity of Coronavirus disease 2019 in African American communities. J Infect Dis 2020;222(6):890–3.
41. Macias Gil R, Marcelin JR, Zuniga-Blanco B, et al. COVID-19 pandemic: disparate health impact on the Hispanic/Latinx population in the United States. J Infect Dis 2020;222(10):1592–5.
42. Arrazola J, Masiello MM, Joshi S, et al. COVID-19 mortality among American Indian and Alaska Native persons — 14 States, January–June 2020. Morb Mortal Wkly Rep 2020;69(49):1853–6.
43. Khazanchi R, Evans CT, Marcelin JR. Racism, not race, drives inequity across the COVID-19 continuum. JAMA Netw Open 2020;3(9):e2019933.
44. Marcelin JR, Swartz TH, Bernice F, et al. Addressing and inspiring vaccine confidence in black, indigenous, and people of color during the Coronavirus disease 2019 pandemic. Open Forum Infect Dis 2021;8(9):ofab417.
45. Clinical Spectrum. COVID-19 treatment guidelines. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/. Accessed October 24, 2021.

46. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of Coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 2020;172(9):577–82.
47. Wang Y, Chen R, Hu F, et al. Transmission, viral kinetics and clinical characteristics of the emergent SARS-CoV-2 delta VOC in Guangzhou, China. EClinicalMedicine 2021;40:101129.
48. Syangtan G, Bista S, Dawadi P, et al. Asymptomatic SARS-CoV-2 carriers: a systematic review and meta-analysis. Front Public Health 2021;8:587374.
49. Meng H, Xiong R, He R, et al. CT imaging and clinical course of asymptomatic cases with COVID-19 pneumonia at admission in Wuhan, China. J Infect 2020; 81(1):e33–9.
50. Wang Y, Liu Y, Liu L, et al. Clinical outcomes in 55 patients with severe acute respiratory syndrome Coronavirus 2 who were asymptomatic at hospital admission in Shenzhen, China. J Infect Dis 2020;221(11):1770–4.
51. Stokes EK, Zambrano LD, Anderson KN, et al. Coronavirus disease 2019 case surveillance - United States, January 22-May 30, 2020. MMWR Morb Mortal Wkly Rep 2020;69(24):759–65.
52. Bleibtreu A, Bertine M, Bertin C, et al. Focus on middle east respiratory syndrome coronavirus (MERS-CoV). Med Mal Infect 2020;50(3):243–51.
53. Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. Sci Adv 2020;6(31):eabc5801.
54. Kandemirli SG, Altundag A, Yildirim D, et al. Olfactory bulb MRI and paranasal sinus CT findings in persistent COVID-19 anosmia. Acad Radiol 2021;28(1): 28–35.
55. Wu Z, McGoogan JM. Characteristics of and important lessons from the Coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323(13):1239–42.
56. Wang L, Berger NA, Kaelber DC, et al. Comparison of outcomes from COVID infection in pediatric and adult patients before and after the emergence of Omicron. medRxiv 2022. https://doi.org/10.1101/2021.12.30.21268495.
57. Azkur AK, Akdis M, Azkur D, et al. Immune response to SARS-CoV-2 and mechanisms of immunopathological changes in COVID-19. Allergy 2020. https://doi.org/10.1111/all.14364.
58. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with Coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med 2020;180(7):934–43.
59. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. In: Drazen JM, editor. N Engl J Med 2017;377(6):562–72.
60. Gibson PG, Qin L, Puah SH. COVID-19 acute respiratory distress syndrome (ARDS): clinical features and differences from typical pre-COVID-19 ARDS. Med J Aust 2020. https://doi.org/10.5694/mja2.50674.
61. Apostolopoulou A, Esquer Garrigos Z, Vijayvargiya P, et al. Invasive pulmonary aspergillosis in patients with SARS-CoV-2 infection: a systematic review of the literature. Diagnostics (Basel) 2020;10(10):E807.
62. Genovese G, Moltrasio C, Berti E, et al. Skin manifestations associated with COVID-19: current knowledge and future perspectives. Dermatology 2021; 237(1):1–12.

63. Zhang Y, Cao W, Xiao M, et al. [Clinical and coagulation characteristics of 7 patients with critical COVID-2019 pneumonia and acro-ischemia]. Zhonghua Xue Ye Xue Za Zhi 2020;41(0):E006.
64. Hassett CE, Gedansky A, Migdady I, et al. Neurologic complications of COVID-19. Cleve Clin J Med 2020;87(12):729–34.
65. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. Brain Behav Immun 2020;88:945–6.
66. Stefano GB, Ptacek R, Ptackova H, et al. Selective neuronal mitochondrial targeting in SARS-CoV-2 infection affects cognitive processes to induce "brain fog" and results in behavioral changes that favor viral survival. Med Sci Monit 2021;27:e930886.
67. Qureshi AI, Abd-Allah F, Al-Senani F, et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. Int J Stroke 2020;15(5):540–54.
68. Oxley TJ, Mocco J, Majidi S, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. N Engl J Med 2020;382(20):e60.
69. Tajbakhsh A, Gheibi Hayat SM, Taghizadeh H, et al. COVID-19 and cardiac injury: clinical manifestations, biomarkers, mechanisms, diagnosis, treatment, and follow up. Expert Rev Anti Infect Ther 2021;19(3):345–57.
70. Pellegrini D, Kawakami R, Guagliumi G, et al. Microthrombi as a major cause of cardiac injury in COVID-19: a pathologic study. Circulation 2021;143(10):1031–42.
71. Boehmer TK. Association between COVID-19 and myocarditis using hospital-based administrative data — United States, March 2020–January 2021. MMWR Morb Mortal Wkly Rep 2021;70(35):1228–32.
72. Patone M, Mei XW, Handunnetthi L, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nat Med 2021;14:1–13.
73. Avila J, Long B, Holladay D, et al. Thrombotic complications of COVID-19. Am J Emerg Med 2021;39:213–8.
74. Branchford BR, Carpenter SL. The role of inflammation in venous thromboembolism. Front Pediatr 2018;6:142.
75. Perico L, Benigni A, Casiraghi F, et al. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol 2020;1–19.
76. Fox SE, Akmatbekov A, Harbert JL, et al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med 2020;8(7):681–6.
77. Bo H, Li Y, Liu G, et al. Assessing the risk for development of deep vein thrombosis among Chinese patients using the 2010 Caprini risk assessment model: a prospective multicenter study. J Atheroscler Thromb 2020;27(8):801–8.
78. Nahum J, Morichau-Beauchant T, Daviaud F, et al. Venous thrombosis among critically ill patients with Coronavirus disease 2019 (COVID-19). JAMA Netw Open 2020;3(5):e2010478.
79. Artifoni M, Danic G, Gautier G, et al. Systematic assessment of venous thromboembolism in COVID-19 patients receiving thromboprophylaxis: incidence and role of D-dimer as predictive factors. J Thromb Thrombolysis 2020;50(1):211–6.
80. Grillet F, Behr J, Calame P, et al. Acute pulmonary embolism associated with COVID-19 pneumonia detected with pulmonary CT angiography. Radiology 2020;296(3):E186–8.
81. Kashi M, Jacquin A, Dakhil B, et al. Severe arterial thrombosis associated with Covid-19 infection. Thromb Res 2020;192:75–7.

82. Lia A B, Pacioni C, Ponton S, et al. Arterial mesenteric thrombosis as a complication of SARS-CoV-2 infection. Eur J Case Rep Intern Med 2020;7(5):001690.
83. Cui X, Zhao Z, Zhang T, et al. A systematic review and meta-analysis of children with Coronavirus disease 2019 (COVID-19). J Med Virol 2020. https://doi.org/10.1002/jmv.26398.
84. CDC. Multisystem inflammatory syndrome (MIS). Centers Dis Control Prev. 2020. Available at: https://www.cdc.gov/mis/mis-c.html. Accessed November 8, 2021.
85. Yomogida K. Post-acute sequelae of SARS-CoV-2 infection among adults aged ≥18 years — Long Beach, California, April 1–December 10, 2020. MMWR Morb Mortal Wkly Rep 2021;70(37):1274–7.
86. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond) Engl.:1-18. doi:10.1080/23744235.2021.1924397