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RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Clinical-Pathological Correlation of the Pathophysiology and Mechanism of Action of COVID-19 — a Primer for Clinicians

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Abstract

Purpose of Review Increasing knowledge of the pathogenesis of the SARS-CoV-2 infection and the complex interaction between host and viral factors have allowed clinicians to stratify the severity of COVID-19 infection. Epidemiological data has also helped to model viral carriage and infectivity. This review presents a comprehensive summary of the pathophysiology of COVID-19, the mechanisms of action of the SARS-CoV-2 virus, and the correlation with the clinical and biochemical characteristics of the disease.

Recent Findings ACE2 and TMPRSS2 receptors have emerged as a key player in the mechanism of infection of SARS-CoV-2. Their distribution throughout the body has been shown to impact the organ-specific manifestations of COVID-19. The immune-evasive and subsequently immunoregulative properties of SARS-CoV-2 are also shown to be implicated in disease proliferation and progression.

Summary Information gleaned from the virological properties of SARS-CoV-2 is consistent with and reflects the clinical behavior of the COVID-19 infection. Further study of specific clinical phenotypes and severity classes of COVID-19 may assist in the development of targeted therapeutics to halt progression of disease from mild to moderate-severe. As the understanding of the pathophysiology and mechanism of action of SARS-CoV-2 continues to grow, it is our hope that better and more effective treatment options continue to emerge.

Keywords COVID-19 · Pandemic · Epidemiology · Pathogenesis · Pathophysiology · Mechanism of action

Key messages
What is known:
• Significant headway has been made into understanding the molecular pathways affected in COVID-19, yet translation into clinical therapy is largely in the investigative stage.
What this paper adds:
• This review presents a comprehensive summary of the pathophysiology of COVID-19, mechanisms of action of the SARS-CoV-2 virus, and the correlation with the clinical and biochemical characteristics of the disease.

This article is part of the Topical Collection on *Rhinosinusitis*

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. As of 27 July 2020, 16.2 million people have confirmed infection with COVID-19, with over 648,000 deaths worldwide. As the pandemic rages on, doctors and researchers continue to seek understanding of the pathophysiology and mechanism of action of the disease.

The most common symptoms of COVID-19, as described by the WHO, are similar to those of the common cold, namely fever, dry cough, and lethargy [1]. Guan et al. reported the prevalence of fever at 88.7%, cough at 67.8%, and lethargy at 38%[2]. Olfactory and gustatory dysfunction has also been increasingly identified as a highly specific and prevalent symptom among COVID-19 patients [3–5]. Other symptoms include nasal congestion, headaches, sore throat, diarrhea, anorexia, and myalgia. These symptoms likely reflect the viral load distribution vis-à-vis sites of higher ACE2 expression.

Formal diagnosis of COVID-19 currently requires the detection of SARS-CoV-2 RNA in respiratory secretions via reverse transcriptase-polymerase chain reaction (RT-PCR). The gold standard for screening is a nasopharyngeal specimen obtained via nasopharyngeal swabs. Antigen tests are not available. In some countries, modified computed tomography protocols have been performed as a quick screening tool, and show bilateral consolidations or ground-glass opacities [6]. The sensitivity of chest CT in the identification of COVID-19-positive patients was found to be 97% in a study of 1014 patients [7].

Significant headway has been made into understanding the molecular pathways affected in COVID-19, yet translation into clinical therapies is largely in the investigative stage. In this review, we aim to present a comprehensive summary of the pathophysiology and mechanisms of action of the SARS-CoV-2 virus, particularly with regard to infection of the respiratory and olfactory epithelium, and the correlation with the clinical and biochemical characteristics of the disease.

Mechanism of Action SARS-COV-2 Infection and Clinical Implications

The Virus and How It Infects the Host

SARS-CoV-2 is an enveloped, non-segmented, positive-sense ribonucleic (RNA) virion [8] with a 79% sequence match [9••] with the severe acute respiratory syndrome virus (SARS-CoV) which caused the severe acute respiratory syndrome outbreak in 2002.

SARS-CoV-2, similar to SARS-CoV, binds to angiotensin-converting enzyme 2 (ACE2) [10]. The spike (S) glycoprotein is a transmembrane protein, one of the four main structural proteins on SARS-CoV-2. On contact with the host cell, the host transmembrane protease serine 2 activates the S glycoprotein, cleaving it into 2 subunits, S1 and S2. The S1 subunit is responsible for the binding to the ACE2 host target receptor, while the S2 subunit mediates fusion of the host and viral membranes to release the viral package into the host cytoplasm. The binding of the receptor-binding domain to the ACE2 receptor marks the beginning of the infective process.

SARS-CoV-2 and the Nose

Utilizing the rhesus macques model of coronavirus infection, it was found that the main pathogenic site of SARS-CoV-2 was the nose and throat, compared to the lung in SARS-CoV and MERS-CoV [11].

Sungnak et al. [12] reported that nasal epithelial cells, specifically goblet and ciliated cells, display the highest ACE2 expression across the upper and lower respiratory tract (Fig. 1). Correspondingly, a vast majority of patients present with upper respiratory tract symptoms, reflecting this viral preponderance.

Significant interest has also been paid to anosmia as a highly prevalent symptom in COVID-19 infection. Bilinska et al. further reported high expressions of ACE2 and TMPRSS2 within the sustentacular cells in the olfactory epithelium (Fig. 1) [13]. Because sustentacular cells play key roles in supporting olfactory neuron metabolism and odor sensing, it is proposed that that olfactory dysfunction in COVID-19 patients may be secondary to damage to these sustentacular cells [13].

ACE2 Receptors and Implications in Viral Entry and Organ Involvement

Studies have also shown that ACE2 receptors are highly expressed in airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, type II pneumocytes, corneal epithelial cells, upper esophageal and stratified epithelial cells, enterocytes, myocardial cells, renal epithelial cells, and bladder urothelial cells [14, 15].

In the lungs, the cascade that follows — decreasing angiotensin II degradation, increasing in angiotensin II levels, and increasing stimulation of angiotensin II receptor type I — results in acute inflammatory tissue injury [16, 17]. Furthermore, the binding of SARS-CoV-2 virus to ACE2 results in a decrease in the latter's function. This leads to dysregulation of the renin-angiotensin system, resulting in systemic inflammation and increase in vascular permeability [18]. This may explain why patients infected with SARS-CoV-2 may experience multisystemic organ dysfunction [2], including pulmonary [19], myocardial [20, 21], renal [22, 23], and gastroenteric [2] complications.

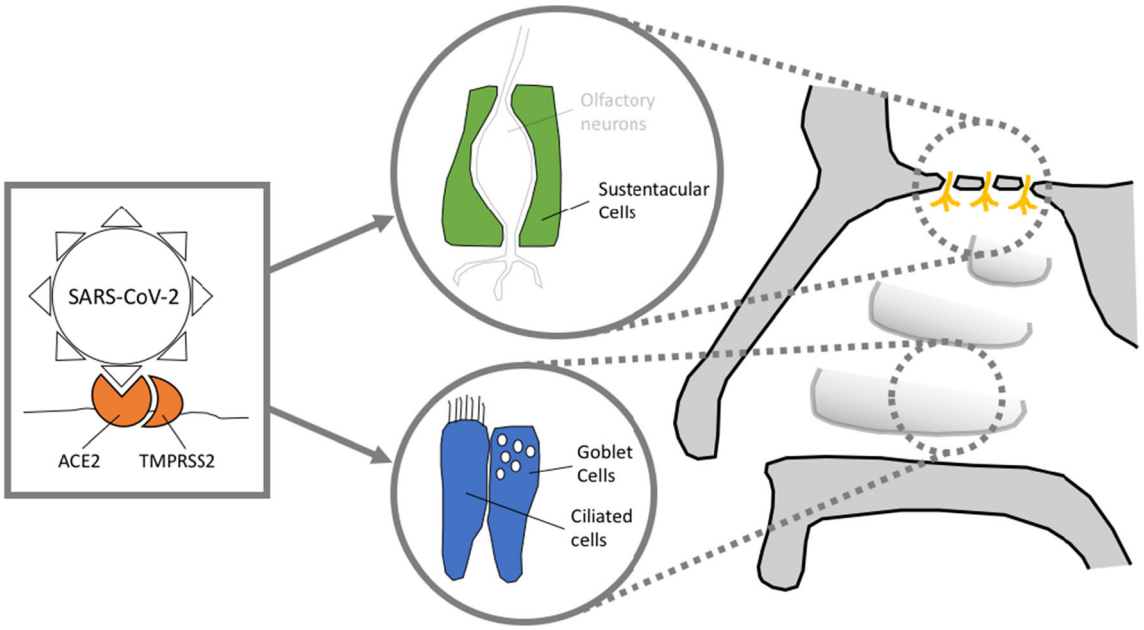

Fig. 1 SARS-CoV-2 and nasal viral entry. This figure simulates a sagittal view of the lateral wall of the nose. After inhalation, viral particles are captured within the mucus secretions. Cellular uptake is then mediated by the ACE2 and TMPRSS2 receptors. These receptors are found in the sustentacular cells of the olfactory epithelium and goblet and ciliated cells of the nasal respiratory epithelium

Expression of the ACE2 gene also differs among different demographic groups. Muus et al. [15] found that ACE2 and TMPRSS2 levels in specific cell types increase with increasing age, male gender, and smoking. ACE2 expression was notably lower in the young pediatric patients. An increase in ACE2 levels has been inferred to be correlated to more severe infection, presumably due to increased numbers of binding receptors. Studies have shown that older [24, 25] male [26] patients tended to have more severe disease, whereas the pediatric population [27, 28] was associated with lower viral loads and a lower incidence of severe disease. Similarly, it was found that cigarette smoke also causes a dose-dependent upregulation of ACE2 expression in human lungs [29]. Several meta-analyses reported that current smokers had a higher risk of requiring hospital admission, severe complications, and mortality compared to never smokers [30, 31].

Transmission Mechanics of SARS-CoV-2

Although SARS-CoV had a much higher case fatality rate compared to SARS-CoV-2, the infectivity of SARS-CoV-2 is higher. The hypothesized reason for increased infectivity include a more strongly binding ACE2 receptor-binding domain[32], as well as an extra furin-like cleavage site in the S protein[33]. The actual basic reproductive number (R_0) of COVID-19 (2.0 [34]–5.7 [35]) is controversial, but is higher than the R_0 of SARS (1.7–1.9) [34].

The primary source of transmission is the upper respiratory tract. Current evidence shows that COVID-19 is transmitted through respiratory droplets and fomite contact [36, 37]. Viral material within these droplets then enters the host through epithelial cells of the upper respiratory tract and conjunctiva. Droplets are generated and expelled primarily during high-pressure events such as coughing or sneezing. Asymptomatic shedding has been estimated to account for up to 60% of cases [38]. Nasal shedding is significantly longer and of higher viral load than other bodily secretions [39]. Nasal shedding precedes and may even outlast lower respiratory tract shedding [40], although evidence is mixed [41].

Evidence for aerosolization of COVID-19 is mixed. Van Doremalen et al. found viable virus in aerosols up to 3 h after high-pressure nebulization [37]. Liu et al. found airborne SARS-CoV-2 RNA in patients' toilet areas, as well as in areas prone to crowding within the hospital [42]. Guo et al. reported airborne SARS-CoV-2 RNA in 35% of specimens from the intensive care unit and in 12.5% of specimens obtained from a COVID-19 isolation ward [43]. Aerosol transmission was hypothesized to be one of the possible modes of spread in a shopping mall cluster in Wuhan, China [44]. However, direct long-range airborne transmission has not been reported [45]. More studies are required to elucidate the role of aerosol transmission in the spread of COVID-19.

Notably, SARS-CoV-2 has also been detected via RT-PCR in saliva [46, 47], sputum [46], broncho-alveolar lavage [46], blood, feces [48], and even semen [49]. Wang et al. tested the biodistribution of SARS-CoV-2 among 205 patients with COVID-19 [46] and found that bronchoalveolar lavage fluid specimens had the highest positive rates (93%), followed by sputum (72%), then oropharynx (32%), then feces (29%), and then blood (1%). However, the significance of viral RNA

detection in these sites in disease transmission remains uncertain.

Sun et al. isolated viable infectious SARS-CoV-2 from the urine of a COVID-19 patient [50]. Various researchers have also isolated viable infectious virus in patients with SARS-CoV-2 RNA-positive fecal specimens [51, 52]. This indicates the possibility of fecal-oral, fecal-fomite, or fecal-aerosol/droplet transmission of disease. As a consequence, areas with poor sanitation may be potential hot zones for transmission. Further research is needed to confirm the degree of transmission through the feco-oral route.

It is important to note that viral RNA detection by PCR does not equate to infectiousness or viable virus [53]. Wolfel et al. noted viral replication to be high within the first week, with declining active replication by 5–11 days [54•]. Epidemiological data from Hong Kong [55] and Taiwan [56] suggests that infectivity is diminished after 7–10 days [53]. This suggests clearance of viable virus within this same time-frame. In light of this, countries such as the USA and Singapore have moved towards a duration-based, rather than a swab-based, approach for deisolation of COVID-19 patients.

Pathophysiology of the COVID-19 Infection

How SARS-CoV-2 Evades the Host Immune Response

When viruses enter the respiratory system and contacts the surface of the respiratory epithelium, a host of cells from the innate immune system is activated, including dendritic cells and tissue macrophages. In a fully immunocompetent subject, these cells are activated by cytokines, and present the viral antigens to lymphocytes to facilitate destruction of the virus. While CD8+ cytotoxic T cells eliminate infected cells, the combination of CD4+ T cells and B cells results in the production of specific antibodies to eliminate further viral infection. Early clearance of the virus is achieved when sufficient antibodies are produced.

Immuno-evasive abilities of coronaviruses, including SARS-CoV, are well-reported [57]. This is achieved via a combination of avoidance of recognition, host cell mimicry [58], and inhibition of the INF signaling pathway [59], which eradicates and inhibits viral replication.

Multiple reports have shown lymphopenia to be a common hematological finding in COVID-19, especially in patients with severe disease [60, 61]. An autopsy of a COVID-19 fatality reported hyperaccumulation of lymphocytes in the lung, and low levels of T-cells in the peripheral blood [19]. Studies on SAR-CoV have attributed lymphopenia to three possible mechanisms—firstly, direct infection; secondly, redistribution of circulating lymphocytes; and finally, depletion of lymphocytes through pyroptosis [62].

Independent analyses of the SARS-CoV-2 virus have shown cytopathic effects in vitro [63, 64]. Cytopathic viruses are strongly associated with pyroptosis [65], which is a highly inflammatory form of programmed cell death that serves as a trigger for the exuberant post-infective inflammatory response. This results in a release of damage-associated molecular patterns, which are recognized by neighboring epithelial cells and macrophages, resulting in generation of proinflammatory cytokines and chemokines [66••]. The cytokine production, which ensues aggregate T cells at the site of injury, likely results in the observed lymphopenia with increased neutrophil-lymphocyte ration observed in up to 80% of patients with COVID-19 [2].

However, T cell responses may be diminished due to impaired dendritic cell migration. Dendritic cell death has been observed during early stages of HCoV-229E [67], while dendritic cell dysfunction has been observed in SARS-CoV infection [58]. In the acute phase of SARS-CoV infection, T cell responses were shown to be severely impaired [68]. Similarly, in SARS-CoV-2 infection, the decrease in quantity of circulating lymphocytes would impede clearance of viremia, while diminished T cell responses would result in attenuated local responses to viral invasion.

B cells are responsible for the development of neutralizing antibodies and hence lasting immunity. The clinical phenotype of this pathway would be that of mild-moderate disease. Data from the usage of convalescent plasma in the treatment of COVID-19 [69, 70] suggests that antibodies may be effective against SARS-CoV-2. It however remains to be seen if reinfection remains a possibility. On the other hand, non-neutralizing antibodies produced by B cells may worsen SARS-CoV-2 infection through antibody-dependent enhancement [66••].

The Implication of Viral Load

High levels of viral loads are hypothesized to be a key factor in the pathophysiology of SARS [71]. In 2004, Hung et al. reported that the viral load of SARS-CoV detected in nasopharyngeal aspirates was strongly associated with desaturation, need for mechanical ventilation, diarrhea, hepatic dysfunction, and death [72].

It is postulated that viremia occurs during the early infective phase of SARS-CoV-2 infection after infection of the respiratory tract, before pneumonia, and the subsequent severe or recovery phase [73]. Viral titers have been observed in some patients to peak even before the onset of pneumonia in some patients [74].

Among 76 patients with COVID-19 infection, Liu et al. reported that the mean viral load of mild cases was significantly lower than those of the severe cases both at time of admission and for the first 12 days after onset [75]. Mild cases were also found to have early viral clearance with 90% having

reproducible negative RT-PCR testing by day 10 post-onset. In contrast, all severe cases continued to test positive past day 10 post-onset. Zheng et al. also reported that patients with mild symptoms had peak viral loads in the second week, whereas patients in the severe group had persistently high viral loads at the third week post-onset [76]. Zhou et al. also reported detectable SARS-CoV-2 until death in all 54 non-survivors [25].

The above data suggests that the inability of the host to achieve viral clearance, whether reflected in the form of viral levels or duration of viremia, may be associated with more severe clinical outcomes. Swift viral clearance in the viremia or pneumonia phase would allow suppression of the infection, allowing the patient to move into the recovery phase [62]. The inability to do so before triggering the immune cascade is a likely contributor to the development of a more severe phenotype of COVID-19.

On the other hands, some patients do continue to progress to multisystemic organ failure even with undetectable viral loads. While it is likely that at some point during the course of illness, there was significant viral load in these patients, it is clear that viral load is not the only factor in determining severity of illness. The ability of the innate immune system, as well as the autoregulation of excessive cytokine production, is also of vital importance.

The Overzealous Immune Response

Acute respiratory distress syndrome (ARDS) can be caused by direct and indirect lung injury [77]. The hallmark of ARDS is increased vascular permeability and accumulation of protein-rich edema within alveoli. It represents the clinical manifestation of an exuberant, uncontrolled immune response. Huang et al. reported that acute respiratory distress syndrome (ARDS) was the main cause of death among patients with SARS-CoV-2[78]. In a systematic review conducted by Quah et al., mortality rates in critical SARS-CoV-2 infection requiring ICU care were not dissimilar to that of non-COVID-19 requiring ICU care [79].

Cytokines are a double-edged sword in the fight against infection. On one hand, they assist and facilitate with eradication of the viral infection by lymphocytes. On the other hand, dysregulated overproduction of cytokines may result in a downward spiral leading to increased vascular permeability, multiorgan failure, and possibly death.

The initial infection of susceptible host cells by SARS-CoV-2 kickstarts the innate immune system. As local infection and destruction of pulmonary tissue continues, increasing amounts of proinflammatory cytokines are drawn towards the site of infection. Cellular death also releases molecules such as purines and pyrimidines which further drive inflammation [71]. The persistence of viremia, whether from an inability of the innate immune system to achieve clearance or purely from an overwhelming viral load, is also likely to be key component in triggering this dysfunctional, exuberant immune response. A combination of the viral insult, host factors, and the host are likely to contribute to the development of the cytokine storm.

Studies in COVID-19-infected patients have shown increases in the serum neutrophil count, IL-6, C-reactive protein, IL-1β, and other proinflammatory cytokines and chemokines such as IP-10, MCP-1, MIP-1A, and tumor necrosis factor-alpha (TNFα) [80]. In a study of 41 patients, Huang et al. [78] identified higher plasma levels of IL2, IL7, IL10, GSCF, IP10, MCP1, MIP1A, and TNFα in ICU patients compared to those in non-ICU patients.

Interleukin-1α (IL-1α), IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) are the predominant cytokines implicated in the early inflammatory response, and they further upregulate the synthesis of other proinflammatory cytokines, signaling the beginning of the cytokine storm [81]. This is further aided by the immunosuppression resulting from dendritic cell, T cell, and B cell dysfunction and apoptosis [82].

Studies on SARS-CoV observed that severe SARS disease manifested at a time when respiratory tract viral loads were decreasing due to rising antibody titers, and that those who developed antibodies early on in the illness were more likely to develop severe disease compared to those who developed these antibodies later in the illness [83]. While the exact mechanism of a secondary immune complex–mediated response in COVID-19 has yet to be elucidated, it is postulated that a dysfunctional, hyper-stimulated complement activation and antibody-dependent cellular cytotoxicity [71].

The hyperinflammatory state arising from excessive circulating proinflammatory cytokines and immune complexes consequently culminates in the systemic manifestations of severe and critical COVID-19. Effects of cytokine upregulation and immune complex deposition results in not only direct cellular, but also indirect injury from endothelial dysfunction and vascular bed injury [57]. Endothelial cell infection and subsequent microvascular dysfunction has been observed in post-mortem kidney, small bowel, heart, and lung specimens [84], and may further explain the systemic nature of damage seen in COVID-19.

The Spectrum of COVID-19 Infection—Clinical Applications

WHO-China Joint Mission Classification of Severity

Like many other viral infections, COVID-19 has been observed to proceed sequentially through 4 stages: Incubation, early infection, pulmonary phase, followed by the hyperinflammatory phase. These clinical stages have been theorized to reflect the gradual tapering down of the viral

response, followed by the gradual upregulation of the host inflammatory response (Fig. 2).

The WHO-China Joint Mission on COVID-19 [85] classified patients into 4 main categories: mild, moderate, severe, and critical. The Chinese National Health Commission [86] defined mild cases as those with mild clinical symptoms with no sign of pneumonia on imaging. Moderate cases were those with fever and respiratory symptoms with radiological findings of pneumonia. Severe cases included any patient with significant tachypnea, blood oxygen saturation ≤93%, depressed arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ratio of less than 300 mmHg, or cases with chest imaging that shows progression >50% within 24–48 h. Critical cases were defined as any patient with respiratory failure requiring mechanical ventilation, shock, or with any organ failure requiring intensive care unit (ICU) care.

A large majority of patients have mild-moderate disease. Wu et al. [87] reported that 81% of patients treated in China had mild to moderate disease. Of these, a significant proportion may be asymptomatic, and up to 18% were estimated remained asymptomatic throughout the course of their disease [88, 89]. Up to 70% of asymptomatic patients develop computed tomographic (CT) evidence of airspace changes [90] in spite of their lack of symptoms.

Fourteen percent of patients were reported to have severe disease, and 5% developed critical disease [87]. Severe COVID-19 may lead to multiorgan failure with coagulopathy, cardiac, kidney, and liver injury. In Seattle, Bhatraju [91] reported that 75% of patients admitted to the ICU required mechanical ventilation. Half died, while 12.5% required prolonged mechanical ventilation. Among 2634 patients hospitalized for COVID-19 in New York City [92], 14% required ICU care, 12% required mechanical ventilation, and 88% of those who received mechanical ventilation died. Among 72,314 cases from Mainland China, there were no deaths from the mild and severe subgroup, while the fatality rate in the critical subgroup was 49%.

Predictors of Severity and Outcome

Many attempts have been made to risk-stratify patients to predict severity and treatment outcomes. Symptoms such as dyspnea [24]; comorbidities such as hypertension, cardiovascular disease, chronic liver disease, and chronic kidney disease [24]; diabetes [93]; obesity [94]; and cancer [95] have been reported to predict severity of disease. The United States Center for Disease Control and Prevention (CDC) also includes immunocompromising conditions and liver disease as potential risk factors for severe illness [96]. The concomitant immune dysfunction associated with the above comorbidities may explain a muted response to the virus, prolonged viral antigen exposure, and consequently a more florid systemic immune response.

A systematic review of 10 clinical prognostic prediction models revealed older age, sex, features derived from CT scoring, C-reactive protein, lactic dehydrogenase, and lymphocyte count as poor prognostic factors [26]. Additional factors reported to prognosticate mortality include platelet count [97], neutrophil count [97], D-dimer levels >1 μg/mL [25], and higher SOFA score on admission [25]. In keeping with the pathogenicity of SARS-CoV-2 described above, these factors reflect the immunological changes, coagulation abnormalities, and endothelial dysfunction associated with severe disease.

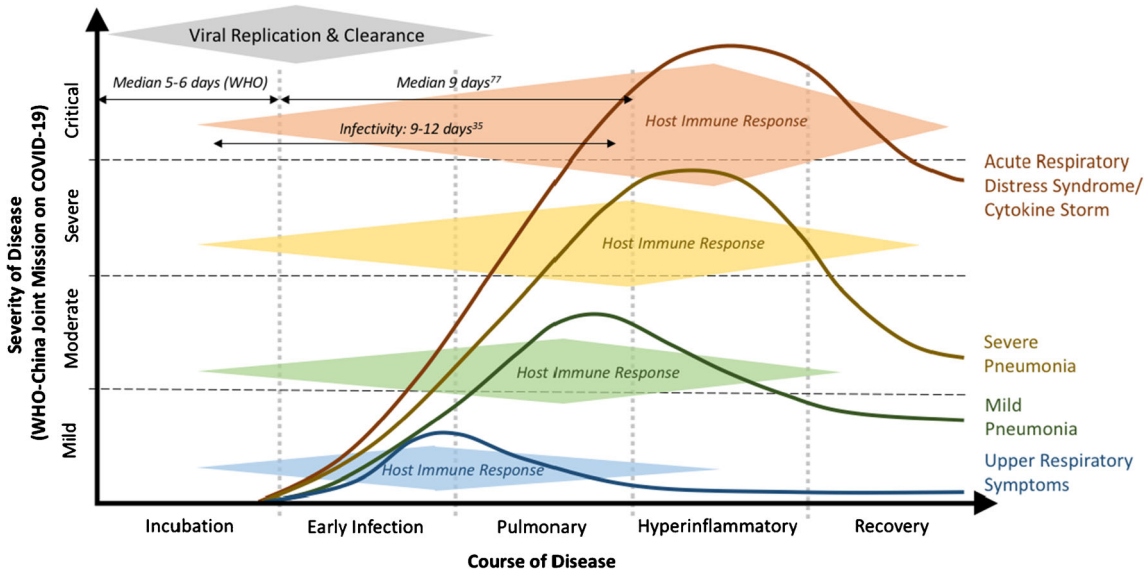

Fig. 2 Progress of severity of illness in relation to course of disease. WHO-China Joint Commission classes of severity of disease in COVID-19 infection as shown in proportion to the host immune response. This is mediated by a combination of viral load, viral clearance, and dysregulated hyperproliferation of the host immune system

The Way Forward

While viruses such as SARS and Ebola overwhelm the individual, as seen in the increased case fatality rate (15% and 50% respectively) [98], COVID-19 overwhelms the healthcare system with its high infectivity rates. Fortunately, increasing amounts of epidemiological data have emerged which has guided the appropriate usage of valuable and limited medical resources. Indeed, understanding the different spectra of COVID-19 infection is critical in dealing with the pandemic on a populational level — from screening criteria, to admission criteria, to criteria for deisolation.

On the individual patient level, however, it still remains unclear what factors contribute to differences in clinical phenotype and severity. Elucidating this may help to assist in targeted therapy to halt progression of disease from mild to moderate-severe. An independent review of adjunctive treatments ranging from corticosteroids to anti-malarials to anti-virals to convalescent plasma showed insufficient evidence to support any routine use over standard care outside clinical trials [99]. Furthermore, many studies continue to be mired in controversy [100]. Fortunately, high-quality evidence continues to emerge from reputable institutions. Recent preliminary evidence from the RECOVERY trial has indicated a significant mortality benefit among severe-critical patients who received dexamethasone compared to those who received standard care [101]. Dexamethasone is a potent anti-inflammatory drug which may halt the inflammatory cascade, and hence the progression of disease. As the understanding of the pathophysiology and mechanism of action of SARS-CoV-2 continues to grow, it is our hope that more targeted treatment options continue to emerge.

Conclusion

COVID-19 is a spectrum of disease ranging from mild to critical. Patients with mild disease have excellent outcomes, while a proportion of patients with severe to critical disease may experience significant morbidity and mortality. The pathogenesis of the SARS-CoV-2 infection involves a complex interaction between host factors and viral factors. A favorable combination of an immunocompetent host with acceptable viral loads portends better recovery, while an overwhelming viral load coupled with a dysfunctional and dysregulated immune system may result in multisystemic injury and poor outcomes.

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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