Review Article

COVID-19: A review on the inflammatory profile of SARS-CoV-2 and the asymptomatic state

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Abstract

The COVID-19 pandemic caused by the novel coronavirus, SARS-CoV-2, has resulted in significant death, disease burden, and panic worldwide. Several studies have determined that COVID-19 is associated with an exaggerated cytokine storm. SARS-CoV-2 induces the proliferation of pro-inflammatory cytokines that results in vascular damage, hypercoagulation, and ultimately respiratory distress. This review presents a detailed and comprehensive look into the inflammatory profile of SARS-CoV-2 on the pulmonary epithelium and discusses immune regulation in the asymptomatic and mildly symptomatic state. In addition, this review highlights possible risk factors that have been correlated with severe COVID-19 disease. Understanding the immunological profile of SARS-CoV-2 is vital to early detection and diagnosis of infected patients. A comprehensive understanding of the SARS-CoV-2 host response may also assist in the development and discovery of therapeutic and preventative agents in the near future.

Keywords: COVID-19, Cytokine storm, Immune cell dysfunction, Asymptomatic, Inflammatory pathways, SARS-CoV-2

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel RNA enveloped betacoronavirus (1). Outbreaks of COVID-19 began in December 2019 in Wuhan, China (2). SARS-CoV-2 is responsible for the current global Coronavirus Disease 2019 (COVID-19) pandemic. Since then, SARS-CoV-2 has spread aggressively with over 100 million confirmed COVID-19 cases and over 2.5 million deaths globally (3). COVID-19 clinical outcomes are heterogeneous, with some people presenting asymptomatically and others requiring intensive care and external ventilation. While the exact reason for this heterogeneity in disease outcome remains unknown, it is likely due to the interaction between SARS-CoV-2 and the individual host immune response.

Human coronaviruses can be categorized as low or high pathogenic subtypes. Low pathogenic coronaviruses infect the upper respiratory tract and cause cold-like symptoms, while highly pathogenic variants predominantly infect lower airways and can cause fatal pneumonia and acute respiratory distress syndrome (ARDS) (1). Most infected patients present with fever, cough, fatigue, and chest tightness. Severe disease is associated with dyspnea, hypoxia, more than 50% lung involvement (as demonstrated on imaging studies), pneumonia (with a bilateral ground-glass appearance on imaging), respiratory failure, and systemic shock (4). Disease progression is associated with an exaggerated host inflammatory response leading to a cytokine storm (1). To further complicate matters, upon infection, the median incubation period is two to seven days, making testing and immediate detection more difficult (5).

SARS-CoV-2 has similar characteristics to other highly pathogenic coronaviruses which can also cause ARDS and cytokine storm production. These include SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). SARS-CoV-2 shares over 79% genetic similarity with SARS-CoV and shares some similarity with MERS-CoV; therefore, we can look towards these coronaviruses to learn more about SARS-CoV-2 (6,7). Despite its similarity to SARS-CoV and MERS-CoV, the morbidity and mortality associated with SARS-CoV-2 far surpass those of SARS-CoV and MERS-CoV. With over 34 million global confirmed cases and over one million confirmed global deaths, further investigation into the inflammatory profile and pathophysiology of SARS-CoV-2 remains of utmost importance to understand potential pharmaceutical targets, disease progression, and populations at risk (8). This review comprehensively summarizes the pathophysiology of SARS-CoV-2 and how it interacts with the host immune system to elicit an inflammatory profile and cytokine storm associated with severe COVID-19. In addition, this review explores the possible immunophenotypes of asymptomatic, mildly symptomatic, and presymptomatic SARS-CoV-2 infection to highlight the role of a dysregulated immune system in COVID-19.

Pathophysiology and cytokine storm

Viral entry into cells

Similar to SARS-CoV, SARS-CoV-2 employs angiotensin-converting enzyme (ACE) 2 as a receptor for cellular entry (Figure 1) (9). ACE2 is a cell membrane enzyme that plays a role in lowering blood pressure. Hydrolysis of ACE by ACE2 results in reduced production of angiotensin II, a vasoconstrictor peptide, thereby lowering blood pressure. ACE2 is highly expressed in cells of the lungs, arteries, heart, kidney, and intestine(9). Viral entry is contingent on the binding of the surface unit (S1) of the viral spike (S) glycoprotein to ACE2 (10). Viral S glycoprotein binding to ACE2 results in S protein cleavage which facilitates viral entry (10). The binding affinity of the viral SARS-CoV-2 S protein to the ACE2 enzyme is higher than in SARS-CoV (9,10). This higher affinity of SARS-CoV-2 could explain the increased pathogenicity, disease severity, and viral replication rate as compared to SARS-CoV (9-11).

SARS-CoV-2 cellular entry is also dependent on transmembrane serine protease 2 (TMPRSS2). TMPRSS2 is a serine protease that activates the viral S glycoproteins on SARS-CoV-2 through proteolytic cleavage(10). Proteolysis permits refolding of the cell membrane and the energy release required to create stable virus-cell linkages and subsequent viral and host cell membrane fusion(11). TMPRSS2 also facilitates SARS-CoV-2 uptake through ACE2 cleavage (Figure 1) (11). A kinetic study of SARS-CoV-2 inoculation into human intestinal cells resulted in ACE2 downregulation 4-6 days after infection(12). ACE2 downregulation is likely due to TMPRSS2 cleavage and the production of interleukin (IL)-4 and interferon (IFN) γ (12). TMPRSS2 has also been implicated in the spread of other pathogenic viruses, such as influenza A and MERS-CoV (10).

Co-expression of both ACE2 and TMPRSS2 are required for successful SARS-CoV-2 viral entry. ACE2 is thought to be the limiting factor in viral entry as its expression is limited to a transient secretory cell type (13). Both ACE2 and TMPRSS2 are highly expressed on cells of the respiratory tree, particularly nasal and bronchiolar epithelial cells, alveolar epithelial cells type II, goblet, and club cells (9-11,13). This is why SARS-CoV-2 predominantly causes nasopulmonary damage, pneumonia, and eventually ARDS in severe cases and also why disease does not initially affect multiple organ systems. Other cells that also highly express both ACE2 and TMPRSS2 include cells from the cornea, esophagus, ileum, colon, gallbladder, and common bile duct (9). SARS-CoV-2 activity and function have not been extensively studied in these cell sites and structural damage to these cells is not as extensive as cells of the respiratory tree (9).

The recruitment of monocytes and APCs

Following infection of host nasal epithelial cells, viral replication rate increases as the epithelial-endothelial barrier integrity breaks down (14). Infected host cells release damage-associated molecular patterns (DAMPs). Examples of DAMPs include adenosine triphosphate (ATP),

nucleic acids, and oligomers (15). Resident monocytes, neutrophils, and antigen-presenting cells recognize these DAMPs and are recruited to the area of initial infection using chemokines such as CCL3, CXCL10, and monocyte chemoattractant protein 1 (MCP1) (16).

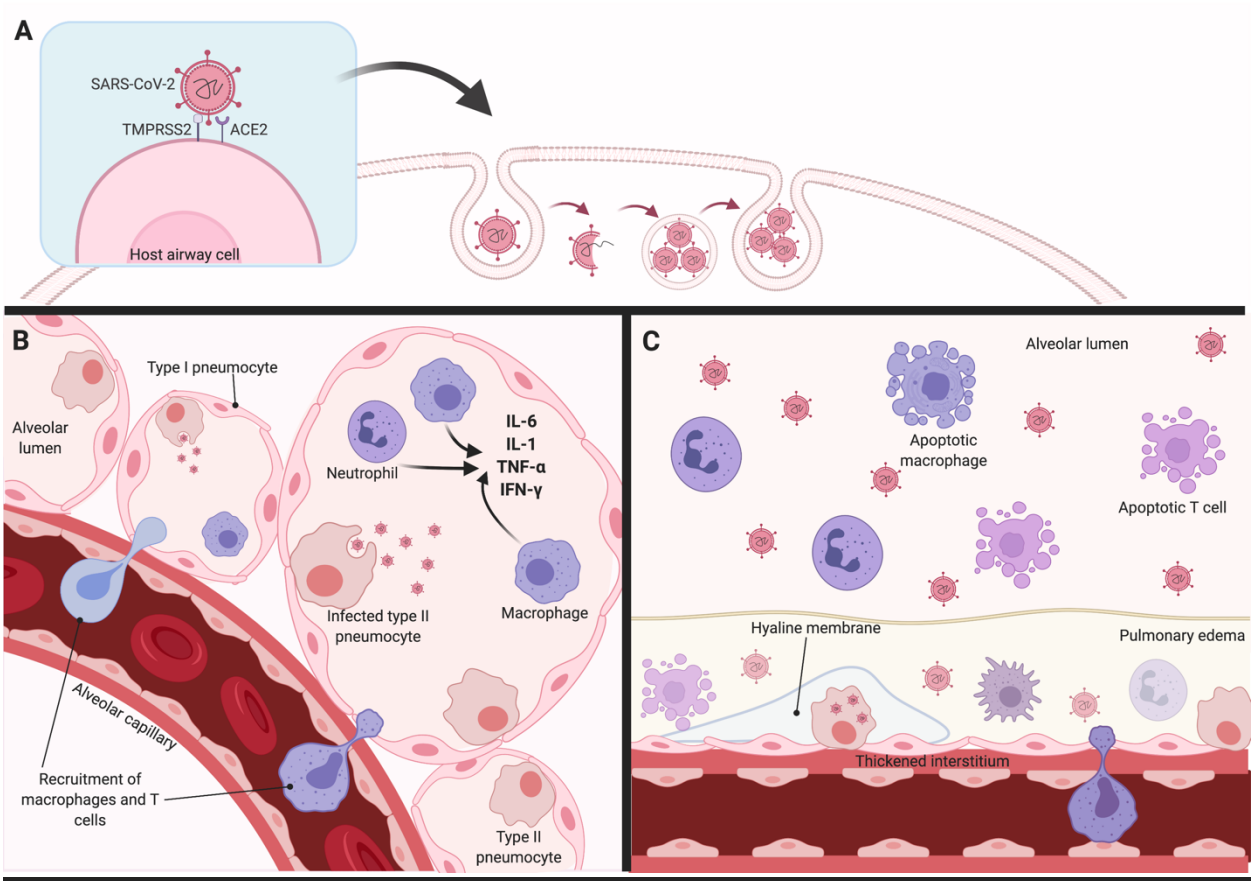

Figure 1. Possible mechanisms contributing to the exaggerated cytokine storm and cellular damage in COVID-19. (A) The SARS-CoV-2 virus enters alveolar epithelial cells through binding of the viral structural spike (S) glycoprotein to angiotensin-converting enzyme 2 (ACE2) receptor. Transmembrane serine protease 2 (TMPRSS2) facilitates viral entry by cleaving ACE2 and activating the SARS-CoV-2 S protein. (B) Infected type I and type II pneumocytes release viral progeny, causing viral titers to rapidly increase. Infected cells also release inflammatory signalling cytokines, such as interleukin (IL)-6, tumour necrosis factor (TNF)-α, IL-1, and interferon (IFN)-γ, which promote the activation of nearby monocytes and lymphocytes. Chemoattractants released by infected cells facilitate the recruitment of macrophages and T-cells to the site of infection. (C) In the late stage of COVID-19 infection, excessive inflammatory cytokine production leads to epithelial and pneumocyte apoptosis. The loss of barrier integrity can lead to alveolar airspace edema and hyaline membrane formation due to fibrotic damage, which may progress to acute respiratory distress syndrome (ARDS).

Monocyte activation and initial cytokine production

Activation of the monocytes triggers the release of pro-inflammatory cytokines (1,16). IL-6, macrophage inflammatory protein 1α (MIP-1α), tumour necrosis factor (TNF)-α, IFN- α and β, IL-1β, IL-6, and IL-12 have been associated with pulmonary inflammation in COVID-19 (Figure 1) (2,15,17,18).

In particular, IL-6 appears to be implicated in the disease progression and cellular damage present in SARS-CoV-2 infection. Plasma IL-6 levels are indicators of disease severity and morbidity in COVID-19 (19). In patients with severe disease, IL-6 is upregulated for 5 to 10 days following infection before tapering down (17). The sustained upregulation of IL-6 is thought to increase endothelial and interstitial nasopulmonary damage, contributing to more severe disease (16,20). IL-6 expression is also significantly correlated with increased expression of other inflammatory markers and acute-phase proteins such as C-reactive protein (CRP), serum amyloid A (SAA), antitrypsin, hepcidin, fibrinogen, and complement proteins (20). Upregulation of these acute phase proteins contributes to thickening of alveolar walls, infiltration of airspaces, and endothelialitis (14). IL-6 may also play a role in increased mucus production because it stimulates mucin gene (MUC5AC and MUC5B) expression in tracheobronchial epithelial cells (9).

The release of these inflammatory chemokines and cytokines results in significant airway infiltration and inflammation which manifest as symptoms of COVID-19 (Figure 1). IFN cytokines promote alveolar cell apoptosis through Fas/Fas ligand (FasL) signalling (1). This contributes to a compromised lung epithelial cell barrier causing microvascular leakage and alveolar edema. Interstitial monocyte infiltration and pulmonary edema result in hypoxia and eventually ARDS (14). The accumulation of inflammatory cells and cytokines causes the diffuse the thickening of alveolar walls and leads to impaired diffusion capacity. Eventually, the cytokine storm can circulate systematically to cause multi-organ dysfunction (21).

Adaptive T-cell response

In addition to the innate immune response, changes in adaptive immune cells have also been implicated in SARS-CoV-2 pathophysiology. Involvement of the adaptive immune response is unique when compared to other respiratory viruses, such as Influenza A and SARS-CoV, which elicit mainly innate immune responses (22). The cytokines expressed in response to SARS-CoV infection, such as IL-1β, IFN-γ, IP-10, and MCP1 promote a type 1 helper T-cell (Th1) response (18,21). High titers of IL-6 may be responsible for T helper 17 cell (Th17) differentiation in COVID-19 animal models (21). The involvement of the adaptive immune response is critical in defining outcomes of SARS-CoV-2 disease. T cells react to the spike protein to initiate an adaptive antiviral immune response which functions to upregulate cytotoxic T cells which recognize and eliminate virus-infected cells (3). This robust T-cell mediated immune response prevents viral titers from rising uncontrollably.

Despite T-cell activation in animal and *in vitro* models, patients with COVID-19 present with marked leukopenia (19). In patients with more severe COVID-19, significant leukopenia was evident as early as 3 days post-infection and persisted thereafter (17). Levels of helper T-cells (cluster of differentiation (CD)3^+ and $CD4^+$), cytotoxic T-cells ($CD3^+$ and $CD8^+$), and regulatory T-cells (Tregs) remain low in patients with severe disease (19). Altered APC function and impaired DC migration during infection may result in insufficient T-cell priming and decreased virus-specific T-cell recruitment in the lungs thereby minimizing detection of SARS-CoV-2 virions and promoting an unchecked cytokine storm synonymous with severe disease (23).

Another possible explanation for the marked leukopenia in COVID-19 includes T-cell exhaustion. In highly inflammatory viral infections like COVID-19, recent immunohistology studies have demonstrated that $CD8^+$ T-cells are unable to sustain long-term activation and enter an 'exhaustive stage' (24,25). Exhausted T-cells (Tex) are prone to apoptosis and express apoptotic-specific cell markers such as program cell death marker (PD-1) and T-cell immunoglobulin and mucin domain-3 (Tim-3)(24). Tex demonstrate a decrease in effector function and proliferative capacity which may contribute to the unchecked cytokine storm in COVID-19 (26). Lymphopenia and T-cell exhaustion could contribute to poor prognostic outcomes of COVID-19 as excessive cell death and upregulation of PD-1 contribute to fibrotic and inflammatory changes in the lung parenchyma (3).

Dysfunction of coagulation pathways

The inflammatory cytokines released during APC activation also activate coagulation pathways, which can lead to disseminated intravascular coagulation (DIC). DIC is a condition associated with microvascular and macrovascular thrombosis that leads to poor blood flow, thereby contributing to multiple organ dysfunction (MODs). Consumption of clotting factors and platelets can lead to hemorrhaging. Although the exact mechanism of this coagulation upregulation remains unknown, it is likely due to upregulation of tissue factor (TF) by activated mononuclear and vascular endothelial factors (2). TF promotes the coagulation cascade which in turn converts the soluble acute phase protein fibrinogen into fibrin, a key concluding step in the coagulation cascade. Furthermore, activated monocytes and dendritic cells also express oxidized phospholipids (OxPLs) which contribute oxidative stress, thereby promoting TF upregulation and thrombosis (14). Therefore, a positive feedback cycle is created in which host cell damage and recruited APCs contribute to peripheral thrombi formation. As such, patients with COVID-19 are at high risk for thromboembolic complications such as deep venous thrombosis, pulmonary embolism, and thrombotic arterial complications (27).

The battle between virus and the immune system

Both viral mechanisms and the host response are thought to play a role in the overamplification of the host immune response. SARS-CoV-2 encodes viral proteins, such as non-structural protein (NSP)1, NSP3, and open reading frame 3B (ORF3B). These viral proteins play a role in evading and antagonizing anti-viral IFN responses by inhibiting the activity of IFN regulatory factor 3 (IRF3) and IFN-I(28, 29). Inhibition of early IFN signalling from activated monocytes and host epithelial cells contribute to the evasion of early viral infection and allow viral titer to rise rapidly.

To further complicate matters, SARS-CoV-2 possesses a rapid virus replication rate which accelerates pulmonary epithelial damage (1). This push and pull between the virus and host immune response causes endothelial barrier disruption, dysfunctional capillary oxygen transmission, and impaired oxygen transmission which can lead to ARDS (21).

SARS-CoV-2 in the asymptomatic, presymptomatic, or mildly symptomatic state

Understanding and quantifying the asymptomatic state

Despite the ability of SARS-CoV-2 to elicit a cytokine storm and lead to respiratory distress, a percentage of individuals who are infected remain asymptomatic or mildly symptomatic (30). Studies have suggested asymptomatic infection rates between 2% to 41%, but the true value remains elusive because it inevitably includes a portion of presymptomatic individuals (31-33). The exact quantification of the asymptomatic population is further complicated because viral cultures are generally negative for SARS-CoV-2 eight days post-symptom onset, thus limiting the time frame for testing (34).

Asymptomatic carriers are classified based on the absence of overt symptoms, such as fever, cough, sneezing, and shortness of breath, at the time of testing or during the preceding 14 days despite the presence of detectable viral load (30). The viral load detected in both asymptomatic or minimally symptomatic patients is not significantly different from symptomatic patients (35,36). Consequently, asymptomatic patients likely have the ability to transmit the virus to uninfected individuals (37,38). Viral load in the upper respiratory tract appears to peak at symptom onset and viral shedding begins 2 or 3 days before symptom onset (38). Since the latent period is shorter than the incubation period (2 to 7 days) for SARS-CoV-2, there is a period of time in which the patient is presymptomatic but infectious (36,39). During the first week following infection, although symptoms may remain minimal or mild, pharyngeal shedding is high so individuals can be infectious before they realize they have COVID-19 (40). This viral transmission pattern is similar to seasonal influenza. Therefore, further investigation into the similarity between influenza and SARS-CoV-2 viral life cycles may shed more light on the infection pattern of SARS-CoV-2.

In addition to the lack of overt symptoms, upon testing, asymptomatic SARS-CoV-2 carriers also have normal or slightly low lymphocytic levels and normal acute-phase inflammatory protein markers, such as CRP levels, indicating no or minimal signs of immune upregulation (41,42). While a portion of these patients are pre-symptomatic and will, in the future, go on to develop overt symptoms and disease, some continue to remain asymptomatic. The asymptomatic and presymptomatic population is difficult to study and quantify. However, this population provides crucial information about the interplay between the host immune system and SARS-CoV-2 infection.

Possible mechanisms of asymptomaticity and implications for treatment development

The exact mechanism behind the immune regulation of the asymptomatic state remains elusive. It is possible that asymptomatic patients have a high titer of SARS-CoV-2-specific immunoglobulin (Ig)G neutralizing antibodies during the latent period of viral infection. These neutralizing antibodies are primed by asymptomatic primary infection and may protect against future infection. For example, asymptomatic Zika patients had expression of Zika-specific neutralizing IgG2a and IgG2b antibodies in maternal serum which prevented an overexaggerated type I IFN response and minimized viral load upon initial asymptomatic infection (43). Serologic testing in patients with asymptomatic or previously infected patients may shed further insight into this area (44). Current treatments being investigated for COVID-19 include polyclonal antibodies isolated from SARS-CoV-2-infected patients. SARS-CoV cross-reactive antibodies are being explored due to the genetic similarity between the S-proteins of the two coronaviruses (45). Recombinant human monoclonal neutralizing antibodies which bind cells expressing full-length S proteins of SARS-CoV and SARS-CoV-2 were recently isolated (46-48). This particular antibody targets the $S1_B$ receptor-binding domain (RBD) of SARS-CoV and SARS-CoV-2 and may shed more insight into the immunology of SARS-CoV-2 asymptomatic infections or may provide the basis for an effective pharmaceutical treatment (46,48). In SARS-CoV-2 mouse models, these S-protein monoclonal antibodies synergistically protected mice from weight loss, reduced viral load, and decreased pulmonary inflammation (48). Asymptomatic patients provide a unique insight into the interaction of SARS-CoV-2 with the ‘ideal’ immune response and should be investigated.

COVID-19 in children

Incidences of symptomatic COVID-19 in children have been minimal. Between 2% to 5% confirmed COVID-19 cases are in individuals under 18 years (49). More recent studies have highlighted that risk of infection in pediatric groups is similar to adults but infection is asymptomatic in nature (50,51). Mildly symptomatic profiles in children include nasal congestion, sore throat, sneezing and rhinorrhea, and cough (50). Most of these cases (over 75%)

resolved within 48 hours of hospitalization without intensive care or mechanical ventilation (50). Since ACE2 expression is similar in children and adults, the discrepancy between disease severity in the two age groups is likely due to the pediatric immune system (52). The immature immune system in children may delay or dampen kinetic upregulation of type I IFN responses in children leading to a more mildly symptomatic disease course (52,53). As children are more susceptible to infection by other respiratory viruses, including β-CoV, they possess a high-titer of multiple neutralizing antibodies which may offer cross-protection against SARS-CoV-2 infection. Further investigation into the immunological profile of SARS-CoV-2 in pediatric cases is necessary to understand the asymptomatic state and may also shed light on protective factors against SARS-CoV-2 infection.

An uncommon multi-inflammatory syndrome (MIS) has been described in children with SARS-CoV-2 infection (54). This illness has features of Kawasaki's disease, toxic shock syndrome, acute abdominal conditions and encephalopathy (55). Children diagnosed with this syndrome are often older (median age of 8 years), have cardiac involvement (up to 80% of patients) and evidence of a cytokine storm (in 92%) (54,56). MIC remains endemic to the pediatric age group although the reason for this remains elusive. MIC is a serious condition; children with MIS require intensive care and mechanical ventilation (56).

Factors associated with increased disease severity

Although a large number of patients infected with SARS-CoV-2 often recover or are asymptomatic, others experience severe respiratory distress and death. One of the questions that needs to be addressed is whether there are predisposing or presenting factors associated with increased disease severity. Initial studies of COVID-19 patients in Wuhan, China revealed that patients with severe disease often present with signs of respiratory distress upon 2-3 days of hospitalization (20,57). These patients often experience shortness of breath with a respiratory rate (RR) greater than 30 times per minute and oxygen saturation levels of less than 95% in resting state which are all initial signs of ARDS (20). Comparative cytokine kinetic studies in the severe disease group revealed higher levels of CRP, IL-6, IL-10, neutrophil-to-lymphocyte ratio (NLR), fibrinogen, and IFN-γ when compared to the milder group; these differences were sustained for over 10 days of hospitalization before tapering off (20,58). However, these patients were not longitudinally followed up and therefore, disease presentation before hospitalization was not observed and infection kinetics are difficult to pinpoint.

Metabolic comorbidities and COVID-19

A significant portion of the patients who experience severe disease (over 25%) often have co-morbid diseases, and this percentage is even higher in hospitalized patients (60% to 90%) (59). Examples of common comorbid diseases include hypertension (present in up to 57% of patients), type II diabetes mellitus (up to 34%), cardiovascular disease (up to 30%), chronic kidney disease

(up to 13%), chronic hepatitis B viral infection (up to 5%), and multiple myeloma (up to 3%) (59-62). Not only do these co-morbid chronic pathologies strain the immune system and impair its ability to timely respond to SARS-CoV-2 virus, but some of them also result in basal inflammatory states that may predispose these patients to higher titers of inflammatory cytokines. Chronic metabolic comorbidities may also dampen the immune system by decreasing macrophage and lymphocytic function (60). Older individuals (65 years and older) often have many comorbid conditions, making them disproportionately affected by COVID-19. Mortality from COVID-19 is highest in people 65 years and older (63). Hospitalized COVID-19 patients can also present with atypical symptoms, such as gastrointestinal symptoms, olfactory dysfunction, anosmia, or ageusia (64). Patients with COVID-19 and comorbidities have longer hospitalizations, a higher likelihood of progressing to severe disease (37.6% versus 20.5%), and a higher mortality rate (8.2% versus 5.2%) compared to patients without comorbidities (58,65).

Smoking and COVID-19

In addition to metabolic comorbidities, many studies have also highlighted a link between smoking and severe COVID disease (66,67). Studies have reported that between 19% to 25% of patients admitted with COVID are smokers (65,66). ICU admissions and mortality are also higher in COVID patients who are smokers (68). However, data on smoking history (in terms of packs per year and frequency) remains limited and the findings may not be generalizable to the public (67). This link in part may be due to the link between smoking, hypertension, dyslipidemia, and respiratory disorders; therefore, smokers often possess comorbid diseases that increase vulnerability to COVID-19. Smoking also increases ACE2 expression on alveolar epithelial cells, thereby increasing the point of entry receptor necessary for SARS-CoV-2 infection (68 69). In addition, tobacco smoke exposure predisposes individuals to higher levels of nitric oxide (NO) consumption (68), which have been associated with an increase in angiotensin I conversion to angiotensin II through ACE upregulation. Increased angiotensin II levels in turn contribute to higher ACE2 expression (68). Nicotine promotes an increase in inflammasome activity and higher levels of basal IL-2, TNF-α, IL-6, MCP-1, and IL-1 β levels (68,70). In addition to the inflammatory responses in the lungs, smoking also impairs the tight barrier junction of the lungs, increases oxidative stress, and impairs mucociliary clearance. These alterations in the pulmonary structure and function create an environment ideal for viral replication and infection (70). The lung damage and increase in the basal inflammatory state associated with smoking may likely promote a higher local tissue viral load and development of the cytokine storm seen in SARS-CoV-2 infection.

While there have been studies investigating the link between smoking and COVID-19 severity, the effects of vaping and electronic cigarettes on COVID-19 severity remain elusive and must be more extensively researched. This is especially important considering alarmingly increasing rates of vaping amongst youth and young adults.

Chronic respiratory pathologies in patients with COVID-19

In contrast to the recognizable link between metabolic disorders or smoking and increased COVID-19 severity, chronic respiratory problems, such as COPD and asthma, have been minimally reported as comorbidities in patients with SARS-CoV-2 infections (66,71). Only 10% of people with chronic respiratory problems have tested COVID positive (66). This paradox could be due to underdiagnosis or poor recognition of chronic respiratory disease in patients with COVID-19. Alternatively, a different type of immune response elicited by the chronic disease could promote early detection of the SARS-CoV-2 virus. For example, perhaps in patients with chronic asthma, an early and controlled type I IFN response promotes viral detection and prevents the cytokine storm. However, mortality of patients with comorbid COPD is increased compared to those without it, suggesting against early viral protection (71). A more likely explanation could be that the therapies used by patients with chronic respiratory diseases may prevent an exaggerated immune response and thereby limit disease severity or symptomatic initial infection (71). Inhaled corticosteroids are a mainstay treatment for asthma with up to 75% of asthmatics using inhaled corticosteroid therapeutics. In China, initial management of SARS-CoV-2 infection involves the administration of inhaled corticosteroids (71). *In vitro* murine studies have demonstrated that inhaled corticosteroids and bronchodilators can diminish SARS-CoV-2 replication and prevent disease progression (71-73). Early administration of inhaled corticosteroids may prevent viral proliferation and exaggerated cytokine production. Further investigation into the immunology of chronic respiratory disease and SARS-CoV-2 infection may provide more insight into the paradoxical lack of relationship between COVID-19 cases and chronic respiratory conditions. It may also highlight protective immunological therapies against SARS-CoV-2 infection.

Conclusion

Although there has been a surge of data investigating the inflammatory profile and immune interactions in patients with COVID-19, it is evident that an exaggerated inflammatory response contributes to disease severity. SARS-CoV-2 interactions with immune cells will need to be explored, which is necessary for the effective development of novel therapies and effective clinical therapies. While the majority of the research appears to focus on cytokines and the adaptive immune response, the role of other elements of the innate immune system, such as hemopoietic stem cells and innate lymphoid cells, remains largely unexplored. This review has attempted to categorize the SARS-CoV-2-induced immune response into either a “pro” and “anti” inflammatory nature, however, it is recognized that many cytokines and chemokines are contextual and may elicit varied responses in different environments. More research into longitudinal immune responses pre- and post- SARS-CoV-2 infection could further shed light on the role of these contextual immune modulators.

In addition to refining our understanding of the immunology of COVID-19, greater investigation into predisposing factors for increased disease severity is required to better understand populations at risk. Asymptomatic and mildly symptomatic patients remain an important reservoir for learning the intricacies between the host immune system and SARS-CoV-2.

The interactions of SARS-CoV-2 with the immune system have implications for future therapies and treatments. Multiple therapies targeting either the host or virus are currently being investigated and are in clinical trials. SARS-CoV-2 targeting therapies focus on interrupting the viral replication cycle of SARS-CoV-2 (74,75). RNA-dependent RNA polymerase inhibitors, remdesivir and favipiravir, are antiviral drugs currently being used in phase III clinical trials (NCT04252664 and NCT04257656)(76, 77). Anti-inflammatory agents, such as dexamethasone and methylprednisolone, are also being explored and have been shown to reduce rates of mechanical ventilation and mortality in patients with COVID-19 (78-80). The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial (NCT04381936) demonstrated that dexamethasone reduced 28-day mortality in COVID-19 patients (81). However, considering the toxicity of glucocorticoids, the dosage and precise guidelines on their use are not yet established (79). IL-6 is a critical cytokine in the SARS-CoV-2 immune response and has been correlated to disease severity. As such, over a dozen clinical trials are currently exploring monoclonal antibodies against IL-6, tocilizumab and sarilumab, as a treatment for COVID-19 patients (82). Initial results suggest that tocilizumab is effective in symptomatic relief for patients with severe COVID-19 when given in repetitive doses; however, many trials are still ongoing (83). These therapies highlight the importance of understanding the nuances of the host immune response in SARS-CoV-2 pathophysiology to elicit possible pharmacological defences.

The information and data collected on SARS-CoV-2 are fragmented and many areas of research need to be pursued to provide a comprehensive picture of this virus. Although it is difficult to conduct research in the midst of a pandemic, the data available from infected patients is invaluable not only for infected patients but also for the general public as a whole.

Declaration of competing Interests

The authors do not have any competing interests.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Figure created with BioRender.com.

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