COVID-19 immunopathology: From acute diseases to chronic sequelae

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Abstract
The clinical manifestation of coronavirus disease 2019 (COVID-19) mainly targets the lung as a primary affected organ, which is also a critical site of immune cell activation by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, recent reports also suggest the involvement of extrapulmonary tissues in COVID-19 pathology. The interplay of both innate and adaptive immune responses is key to COVID-19 management. As a result, a robust innate immune response provides the first line of defense, concomitantly, adaptive immunity neutralizes the infection and builds memory for long-term protection. However, dysregulated immunity, both innate and adaptive, can skew towards immunopathology both in acute and chronic cases. Here we have summarized some of the recent findings that provide critical insight into the immunopathology caused by SARS-CoV-2, in acute and post-acute cases. Finally, we further discuss some of the immunomodulatory drugs in preclinical and clinical trials for dampening the immunopathology caused by COVID-19.

KEYWORDS
immunopathology, immune responses, respiratory tract, SARS coronavirus

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent for coronavirus disease 2019 (COVID-19), has resulted in the loss of lives, and financial and physical distress worldwide on a large scale. As of September 2022, there have been over 600 million infected people with more than 6 million deaths worldwide.1 The emergence of new variants of concern as a result of the mutation in the structural and nonstructural proteins (NSP) of SARS-CoV-2 is making the vaccine less efficient, creating inevitable hurdles in the vaccination programs.2

The pathophysiology of COVID-19 is mainly attributed due to the dysfunction of innate and adaptive immune response by SARS-CoV-2. This dysfunctional or uncontrolled innate and/or adaptive immune response leads to delayed viral clearance, inflammation, and tissue damage, which is not only restricted to the lungs but systemically, affecting other organs and leading to multiorgan failure.3,4 One of the hallmarks of COVID-19 is lymphopenia in the blood, a condition where there is a lower-than-normal number of lymphocytes such as T cells, B cells, and innate lymphoid cells.5,6 On the other hand, there is an increased aberrant activation and recruitment of myeloid cells in COVID-19 that may contribute to...
Furthermore, patients with severe COVID-19 are characterized by increased circulatory inflammatory cytokines, which are significantly associated with acute lung injury in COVID-19. Further, cytokines and chemokines are highly expressed in the bronchoalveolar lavage (BAL) fluid as compared to blood in patients with severe COVID-19, suggesting continuous exposure to viral stimulation in the lung microenvironment resulting in heightened inflammatory status locally. Collectively, all this exacerbated immune response eventually leads to pneumonia with vascular leakage, resulting in respiratory failure due to acute respiratory distress syndrome (ARDS) (Figure 1). In addition, extrapulmonary clinical features have also been reported in several COVID-19 patients such as cardiovascular disorders, thrombotic events, and kidney and liver injury, suggesting that COVID-19 is not just limited to lungs but also systemically. Furthermore, the rise in postacute COVID-19 conditions because of chronic tissue and systemic sequelae has been creating new obstacles in combating the ongoing COVID-19 pandemic.

In this review, we have summed up some of the recent findings on the innate and adaptive arms of immune response in acute and post-acute COVID-19. In addition, we discussed the pathophysiology that arises because of immune dysfunction in COVID-19 patients, both in acute and chronic sequelae. Finally, we discuss by providing some direct evidence from clinical trials on immunomodulatory drugs that are currently in use for the mitigation of the COVID-19 pandemic.

2 | CLINICAL FEATURES OF ACUTE COVID-19 IMMUNOPATHOLOGY

Acute COVID-19 encompasses a multispectrum diseased state with its epicenter majorly in the lungs. Most infected individuals exhibit nonsymptomatic to mild symptoms including fever, coughing, sneezing, running nose, headaches, and fatigue. However, a percentage of individuals may develop severe forms of the diseases,
characterized by pulmonary dysfunction and ARDS to systemic organ dysfunction. These patients may often require mechanical ventilation support and typically exhibit an increased risk of mortality. Reports also indicate co-expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) gene at multiple organs, which may suggest the potential for direct viral-induced pathology to extrapulmonary sites. In addition, excessive systemic inflammation may further contribute to extrapulmonary disease. Cumulatively, these events can be observed as pathological features diagnosed in severe patients, which may progress to multiorgan failure and death.

2.1 | Pulmonary clinical features

2.1.1 | Acute lung injury and ARDS

Around 6%–10% of SARS-CoV-2 infected severe patients experience acute lung injury conditions called ARDS with a high mortality rate. ARDS can be characterized by hypoxemia, ground-glass opacities, and the presence of bilateral infiltrates in the lungs. Histological analysis of lungs from COVID-19 patients identified lung injury as reflected by marked pulmonary inflammation, diffuse alveolar damage, and fibrosis resulting in fatal outcomes. Deceased COVID-19 patient lungs exhibit loss of type II alveolar epithelial cells and show the presence of increased perivascular lymphocyte cytotoxicity. Furthermore, the accumulation of inflammatory neutrophils and monocytes results in persistent inflammation leading to acute lung injury. The clinical outcome of COVID-19 is further worsened by endothelial dysfunction, either due to direct infection or systemic inflammation, leveraging the pathological features of COVID-19. These patients eventually advance to mechanical intubation and ventilator support due to ARDS and may require lung transplantation due to irreversible lung damage.

2.1.2 | Fibrosis

Pulmonary fibrosis is characterized by the accumulation of fibroblasts, and excessive deposition of collagen and extracellular matrix, resulting in loss of pulmonary function. The patients that may survive acute illness as a result of ARDS are at high risk of development of pulmonary fibrosis resulting in a high rate of mortality. Intensive fibrosis and collagen deposition have been observed across several COVID-19 patient autopsy studies. Lung from COVID-19 patients with prolonged diseases also showed enhanced pulmonary injury and fibrosis, without the presence of SARS-CoV-2 RNA, suggesting sustained tissue damage even after virus clearance. Molecular analyses of the lung tissue from autopsy samples revealed the aberrant activation of interleukin (IL)-1β-producing macrophages/monocytes favoring the expansion of pathological fibroblasts that further contribute to fibrosis. Furthermore, fibrosis-associated genes such as CCL18, LGMN, SPP1, and TGFB1 were enriched in newly recruited CD163+ pulmonary monocyte-derived macrophages, which also harbor viral transcripts. Moreover, aberrant accumulation of transforming growth factor-β1 (TGF-β1) in the lungs as well as type-III collagen deposition, can further potentiate the risk of terminal pulmonary fibrosis. Of note, patients with pre-existing idiopathic pulmonary fibrosis (IPF) are at high risk for COVID-19-related pathology and clinical outcomes. Additionally, as the gene signatures from COVID-19 lungs resemble patients who have IPF, antifibrotic therapy may improve outcomes for COVID-19 patients with an increased risk of development of fibrosis.

2.1.3 | Thrombosis

Severe SARS-CoV-2 infection is associated with an increased incidence of thrombosis-associated complications. Pulmonary embolism and deep vein thrombosis are the most prominent thrombosis events that are reported in hospitalized COVID-19 patients. Currently, there is no clear mechanism for the activation of thrombogenic pathways, although it is believed that a series of complement activation, platelet activation, and/or cytokine storm may trigger thrombotic events in severely infected patients. Microvascular injury and thrombosis have been observed in conjunction with aberrant activation of the alternative and lectin complement pathways. In addition, as platelets express both ACE2 and TMPRSS2, SARS-CoV-2 can directly stimulate platelets via the ACE2/mitogen-activated protein kinase pathway. Upon stimulation, the platelets secrete coagulation factors, resulting in the formation of leukocyte–platelet aggregates. Transcriptomic analysis of platelets from COVID-19 patients revealed enrichment of pathways including IL-6, tumor necrosis factor (TNF)-α, blood coagulation, and hemostasis, suggesting the role of platelet activation in the development of thrombosis. Postmortem examination of lungs also revealed microvascular thrombi in association with neutrophil extracellular traps (NETs) and platelets, suggesting NET-triggered thrombosis. As the development of thrombosis has been associated with poor prognosis in hospitalized COVID-19 patients, early prediction of thrombosis and thromboprophylaxis may improve the clinical outcome.

2.2 | Extrapulmonary clinical features

COVID-19 is primarily a respiratory disease, however, increasing evidence suggests that extrapulmonary organs may be subject to direct viral injury or indirect immunopathology caused by SARS-CoV-2. Organs, such as the brain, heart, kidney, liver, and so forth, are reported to be severely affected as several studies indicate increased risk of neurologic illness, myocardial dysfunction, thrombotic events, kidney injury, and hepatocellular injury following COVID-19 infection.
The SARS-CoV-2 infection has been associated with several cardiovascular disorders including myocardial injury, cardiomyopathy, arrhythmias, and cardiogenic shock. Moreover, individuals with pre-existing cardiovascular disease exhibit an elevated risk of severe disease and/or death. Some of the studies reported the incidence of acute cardiac injury in COVID-19 patients. Patients have also reported neurological and cognitive defects in COVID-19. Hence, in this section, we will discuss the entry of SARS-CoV-2, a protective as well as a pathogenic innate immune response to COVID-19.

3 | PROTECTIVE INNATE IMMUNE RESPONSES IN ACUTE COVID-19

As a majority of COVID-19 infections could be asymptomatic or milder symptomatic, it is suggested that a robust innate immune response may be elicited that is required for viral containment. However, patients with severe disease often had sustained and exacerbated innate responses, which may be induced by sustained viral replication. To completely understand the dynamics of COVID-19 infection, we need to properly address the recognition of SARS-CoV-2 by the innate immune system together with the protective and pathogenic innate response to COVID-19. Hence, in this section, we will discuss the entry of SARS-CoV-2, a protective as well as a pathogenic innate immune response to COVID-19.

3.1 | Recognition of SARS-CoV-2

SARS-CoV-2 entry to the host cell requires interaction with the ACE2 receptor via viral spike protein in addition, a host serine protease, TRMPSS2, further facilitates spike protein priming which is important for viral entry. However, to initiate an innate immune response viral genomic single-stranded RNA and replicative double-stranded RNA both can be recognized by Toll-like receptors (TLRs) and RIG-I-like receptors (RLRs). In the case of SARS-CoV-2, retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5) can sense viral RNA and drive inflammation in Calu-3 cells. Conditioned media from these epithelial cells can further lead to propagating inflammation in primary human monocyte-derived macrophages. However, in primary human epithelial cells, RIG-I can sense SARS-CoV-2 but failed to activate mitochondrial antiviral-signaling protein-dependent pathways resulting in reduced interferons (IFNs) and inflammatory cytokines production. Furthermore, TLR2 has been involved in eliciting the proinflammatory immune response in both human and murine macrophages. A reduction in IL-6 level was observed in TLR2−/− mice treated with SARS-CoV-2 E protein, and TLR2 inhibition in human ACE2 (hACE2) transgenic mice infected with SARS-CoV-2 reduces inflammation and mortality. In addition, gene variants in viral sensing such as TLR3 and TLR7 were also observed that are associated with weak IFN response and severity of COVID-19 in a small number of individuals. Overall, these observational studies suggest the critical role of the mediators of the innate immune system, which can act differentially following SARS-CoV-2 infection. As the current understanding of these mediators is still naïve, we expect more studies are required in this direction.

3.2 | The double-edged sword of IFN responses

Early protection against COVID-19 can be achieved by balanced and robust innate immune responses. Innate immune cells contribute to providing the first line of defense against viral and bacterial infection. During early infection, IFN response is necessary to limit viral replication. Early IFN levels were reported in COVID-19 patients, which was further correlated with the lower viral count in BAL fluid and improved outcomes. A study from the SARS-CoV-2 infection in macaques also presented that robust IFN response is generated from macrophages and T lymphocyte population during acute infection. This elevated early IFN response eventually serves to clear viremia. Furthermore, transcriptomic analysis of blood and BAL samples from severe COVID-19 patients revealed diminished IFN-responsive genes (interferon-stimulated gene [ISG]) response in BAL fluid as compared to paired blood samples. In addition, downregulation of ISG genes such as MX1, IFITM1, and IFIT2 were reported in critical COVID-19 patients, and undetected messenger RNA (mRNA) and protein levels of IFN-β, and impaired IFN-α production were observed in the blood of severe patients, suggesting impaired type I IFN responses may promote disease progression. Thus, a robust and early type I IFN response is required to activate a cellular antiviral state and achieve antiviral immunity by stimulating the activation of immune cells such as natural killer (NK) and dendritic cells (DCs). In addition, type I IFN response may promote T and B cell recruitment at the site of infection facilitating viral clearance. SARS-CoV-2 infection in cells can block IFN signaling via its proteins such as nsp6, nsp13, and ORF6, which are known to suppress IRF3 phosphorylation and nuclear translocation. Collectively these reports indicate that disease severity is associated with weak IFN response in severe patients. This was further supported by that about 10% of patients with severe COVID-19 have neutralizing antibodies against type I IFN rendering ineffective IFN response, which may also advocate the protective function of type I IFN. The plasma from these patients was further able to block the protective action of IFN-α2 in vitro as evident by enhanced SARS-CoV-2 replication in Huh7.5 cells. Type III IFN response shares a similar ISG expression pattern as with type I, only differing in causing lesser inflammation during severe viral infection. Study with influenza infection suggests the protective
function of type III IFN in respiratory viral infection, which is also reflected in SARS-CoV-2 severity as in mild COVID-19 patients the levels of type III IFN is higher as compared to severe patients.69 Nevertheless, more studies are required to delineate the role of type III IFN in the context of COVID-19.

Type II IFN, IFN-γ, is secreted by a type I innate lymphoid cells (ILC1s), NK cells, and T-cells.70,71 Although IFN-γ also has the antiviral ability but sustained IFN-γ levels in COVID-19 patients are associated with mortality.72 Intriguingly, elevated levels of all IFN such as IFN-α, IFN-γ, and IFN-λ have been reported in severe patients during acute infection; however, only elevated IFN-λ was correlated with lower viral load.52,73 This report suggests that type I and II IFNs fail to control infection in severe patients and could be associated with pathology if released in an uncontrolled manner. Furthermore, type I and type III IFN have been associated with activation of antiproliferative and cell death pathways in primary murine airway epithelial cells by a respiratory viral infection,74 suggesting that sustained and/or delayed IFNs could be detrimental in tissue repair. The transcriptome of classical monocyte from severe COVID-19 patients revealed enrichment of ISG expression.75 The ISG hence identified in COVID-19 cases were found to be proinflammatory due to the presence of inflammatory mediators or regulators,76 advocating detrimental instead of the protective function of IFNs. In this regard, blocking the IFN-stimulated response with IFN-alpha and beta receptor subunit 2 antibodies enhanced lung recovery and was observed in humanized mice model of chronic SARS-CoV-2 infection.77 Altogether, these contrasting reports suggest the duality in the IFN response, and hence balanced IFN is required for a protective immune response to COVID-19.78 Till this point, it is suggested that IFN protective response is time-dependent, where early increased levels are beneficial and late can be detrimental.79,80 Nevertheless, this paradoxical nature of IFN signaling is subjected to further clarification.

3.3 | Protective cellular innate responses

Alveolar macrophages (AMs) are the tissue-resident macrophages in the lung and are indispensable for maintaining lung immune homeostasis. AM population was depleted in the BAL fluid of critical COVID-19 patients,81 suggesting that AMs are necessary for protection. In a recent preprint study, a monocyte-derived proliferating Slamf9⁻ Spp1⁺ macrophages subset was shown to be resistive to SARS-CoV-2 induced cell death and helps us to clear the virus in Syrian hamsters.82 These macrophages were then differentiated into triggering receptors expressed on myeloid cells 2⁺ and fructose-bisphosphatase 1⁺ macrophages to resolve inflammation and reconstitute AM population, altogether aiding in lung repair.82 The role of NK cells has not been completely studied in the context of COVID-19. Although some studies show that the NK population not only decreased but also was in a dysfunctional state in COVID-19 cases,83-85 indicating its role in providing protection. In accordance with the latter observations, it was found that NK cells purified from healthy individuals can reduce SARS-CoV-2 load in Calu-3 and Vero E6 cell lines.86 Relatively abundant NK cells in some COVID-19 patients were also correlated with the rapid decline of viral load as compared to patients with lower NK levels.86 Convalescent patients with higher frequencies of ILC subset NK cell-activating receptor group 2D⁺ (NKG2D⁺) ILC2s demonstrated a significant reduction of the hospitalization time,87 also suggesting the beneficial role of ILCs. Plasmacytoid dendritic cells (pDCs) are capable of IFN-α production following the viral encounter; however, as pDCs are depleted in peripheral blood mononuclear cells (PBMCs) of COVID-19 patients,88,89 their protective functions are largely compromised. Altogether these reports point to the fact that even though these cellular innate responses have intrinsic antiviral defense capacity, in COVID-19 all these responses are either weakened or dysfunctional eventually leading to pathological outcomes.

4 | PATHOGENIC INNATE RESPONSES IN ACUTE COVID-19

A balanced and robust innate immune response is critical to encountering COVID-19. However, an uncontrolled or misfired innate immune response could be detrimental to the host, resulting in acute severe diseases. Here, in this section, we have discussed some of the pathological features of innate immune cells in response to SARS-CoV-2 infection.

4.1 | Pathogen-associated molecular patterns and damage-associated molecular patterns

The innate immune response is elicited by recognition of evolutionarily conserved structures on pathogens known as pathogen-associated molecular patterns (PAMPs). Damage-associated molecular patterns (DAMPs) are molecules released by stressed or dead cells.90 DAMPs and PAMPs are detected by pattern recognition receptors (PRR), such as TLR and RLR, and can initiate inflammation upon binding and may cause tissue damage leading to acute lung injury.91 Elevated levels of DAMPs and PAMPs have been reported in a recent study comprising a longitudinal evaluation of serum and endotracheal aspirate from severe COVID-19 patients.91 Alarmins $S100A8$ were found to be upregulated by SARS-CoV-2 infection in rhesus macaques and in hACE2 transgenic mice.92 Likewise, high levels of $S100A8/9$ were reported in the plasma of severe COVID-19 individuals, which positively correlated with the adversity of the disease.93,94 Another prognosis marker of COVID-19 severity has been reported is circulating mitochondrial DNA (MT-DNA), which is a member of a group of mitochondrial DAMPs.95 In severe or deceased COVID-19 patients, the levels of MT-DNA were reportedly high.95 DAMP molecule IL-33 levels are high in the serum of COVID-19 cases and are indicative of disease severity.87,96 IL-33 has been shown to be secreted by human epithelial cells following SARS-CoV-2 infection.97 However, after disease resolution, induction of IL-33 in
4.2 | Neutrophils

Neutrophils are among the first cell types to migrate to the infected sites and encounter pathogens. An increase in the neutrophil count (neutrophilia) in the blood and nasopharyngeal epithelium of severe patients is among the first findings that suggest the importance of neutrophils in the pathology of SARS-CoV-2. Freshly isolated neutrophils showed the presence of inflammasome activation which may play important role in supporting cytokine storm. In a further study, it was shown that neutrophils isolated from COVID-19 patients have an increased hypoxia-inducible factor 1 subunit alpha (HIF-1α) and glycolysis activity. These studies might explain the inflammatory nature of neutrophils in COVID-19 patients thereby suggesting a pathogenic response of neutrophils in the advent of COVID-19.

NETs are web-like structures of DNA containing neutrophil histones and granule-derived enzymes. The plasma of severe to critical condition patients was found to be enriched in NETs. Recently, it was shown that neutrophils from COVID-19 patients with ARDS are primed to form NETs as compared to COVID-19 with non-ARDS. Furthermore, neutrophils isolated from COVID-19 patients are more susceptible to release NETs as compared to healthy donors. In a different study, sera of COVID-19 patients were demonstrated to have an increased level of myeloperoxidase DNA and citrullinated histone H3, markers for NET. Additionally, serum from these COVID-19 patients was able to induce NET formation in healthy neutrophils, indicating that both serum and intrinsic factors in neutrophils can govern NET formation. Similarly, a recent preprint study showed that serum from pediatric acute COVID-19 can trigger the NET formation in healthy neutrophils. Furthermore, this study showed that the spike immune complex generated by the dilution of plasma with spike protein on beads was the major driver for NET formation, suggesting the role of viral spike protein complexes in NET formation. Those NETosing neutrophils have a positive correlation with a novel subset of inflammatory neutrophils in severe and critical COVID-19 patients.

A higher level of NETs was observed in serum, tracheal aspirants, and lung tissues of COVID-19 patients. Immunofluorescence and immunohistochemistry studies on lung biopsy tissue from deceased and severe COVID-19 patients also confirmed the presence of NET. The NET formation was further associated with inflammatory interstitial lesions, vascular compartments, and the Airways of COVID-19 injured lungs. Hence, increased neutrophile-induced inflammatory NETs are a major cause of pathology in COVID-19, which is further worsened by delayed tissue repair and thrombosis induced by NETs. These observations suggested that neutrophils not only play a critical role in inducing inflammation in critical COVID-19 patients but also result in lung damage and interfere with tissue repair through the NET formation.

4.3 | Monocytes

Long-term analysis of monocytes showed that the monocyte number, frequency, and activation markers are deeply influenced in acute and convalescent COVID-19 patients. The number as well as the absolute count of monocytes increases from 15 to 30 days of infection to 4–5 months postinfection. Similarly, the frequency of monocyte subsets such as classical, intermediate, and nonclassical monocytes, alter with time. Circulating monocyte activation markers, such as soluble CD14, CD163, and C-reactive protein levels were also found to increase after acute infection, suggesting long-term activation of monocyte postacute COVID-19. The SARS-CoV-2 infection leads to distinct transcriptomic features in monocytes, which is further regulated by infection kinetics and disease severity. High-dimensional profiling of human blood and BAL sample from patients with severe COVID-19 showed upregulation of viral sensing, IFN response genes together with IL-6, TNF-α, and IL-8, which were associated with increased risk of casualties with COVID-19. The enhanced inflammatory characteristic in human monocyte is further supported by aerobic glycolysis, which also supports SARS-CoV-2 replication in these monocytes. Infected human monocytes, as well as monocytes from severe COVID-19 patients, observed high expression of HIF-1α which is stabilized by mitochondria reactive oxygen species production in response to infection. The stabilized HIF-1α is required to upregulate glycolytic genes during SARS-CoV-2 infection and was suggested that targeting HIF-1α and/or glycolysis may be beneficial for COVID-19 management.

Active NLRP3 inflammasome and elevated levels of caspase-1 activity in patients in PBMC from COVID-19 patients have also been reported on the day of hospitalization. The increased caspase-1 levels dropped significantly thereafter suggesting the role of
inflammation in causing acute lung pathology.\textsuperscript{120} Recently, it was reported that about 10\% of monocyte gets infected by SARS-CoV-2 in COVID-19 patients via Fc-γ receptors (FcyR)-mediated uptake of antibody-coated virus.\textsuperscript{121} Additionally, infected monocytes have activated inflammasome, caspase-1, and gasein D (GSDMD) leading to pyroptosis, which further adds up to lung injury.\textsuperscript{121} Additionally, monocyte isolated from a healthy individual infected with SARS-CoV-2 in vitro also contribute to the fibrotic phenotype,\textsuperscript{29} suggesting a role of direct infection of monocytes in promoting fibrosis.

4.4  Macrophages

Myeloid cells population such as interstitial macrophages, monocyte-derived macrophages, and AMs are among the most enriched immune cells in the lungs of COVID-19 patients.\textsuperscript{122} Using humanized mice model, it was recently demonstrated that SARS-CoV-2 can infect and replicate in human macrophages. These infected macrophages have an inflammatory phenotype characterized by inflammasome activation, which also contributes to sustained IFN response.\textsuperscript{77} Indeed, these infected macrophages have an inflammatory signature which was evident by enrichment in the expression of several cytokines (IL1A, IL18, and IL27) and chemokines (CXCL10, CCL18, CCL3, CCL7, CCL8, CCL20, and CXCL8).\textsuperscript{77} In addition, morphological analysis of the infected macrophages revealed the sign of pyroptosis. Apoptosis-associated speck-like protein containing a CARD (ASC), which is a marker for inflammasome activation, was formed in the infected macrophages. Finally, both lactate dehydrogenase (LDH) and GSDMD levels in serum were increased in the infected mice which further suggested the involvement of the pyroptosis pathway.\textsuperscript{77} Similarly, clinical data from the COVID-19 patients also demonstrated enhanced IL-18, LDH, and GSDMD levels in severe patients. Lung biopsies further revealed activation of ASC more prominently in CD14+-infected lung macrophages.\textsuperscript{121} The activation of pyroptosis-dependent cell death in macrophages is meant to abort viral replication; however, it also leads to the release of inflammatory mediators that further add up to the immunopathology.\textsuperscript{121} These two recent studies have shown conclusive evidence that how infected macrophages can trigger inflammation. Nevertheless, more studies are required to further delineate the underlying mechanism of infected macrophages in the regulation of immunopathology.

AMs are the major sentinels of the lungs and are involved in engulfing inhaled particles and allergens, and aid in tissue repair, which is critical for maintaining lung homeostasis.\textsuperscript{123} Following lung insults, the self-renewal ability of AM is required to repopulate the alveolar space and aid in tissue repair.\textsuperscript{123} However, during COVID-19, AMs can result in an inflammatory response. RNA-sequencing data from the public dataset reflects that AMs derived from COVID-19 patients show an increase in inflammatory properties with a concomitant decrease in reparative ability.\textsuperscript{123} In COVID-19 patients, there is a decrease in the AM population in the BAL fluid.\textsuperscript{81} The lung is later repopulated by CD11b+ interstitial macrophages, probably to aid lung repair.\textsuperscript{124,125} As AMs can be readily infected with SARS-CoV-2 similar to other coronaviruses,\textsuperscript{126,127} it is speculated that AMs may be critical for virus propagation.\textsuperscript{128} AMs isolated from BAL fluid of severe COVID-19 patients within 48 h after intubation also showed the presence of SARS-CoV-2 viral transcript.\textsuperscript{128} These AMs then secret T-cell chemokines, recruiting more T-cells in the vicinity resulting in T-cell-dependent IFN-γ secretion, eventually leading to AM inflammatory response. This feedback loop may be functional for long period due to infection of monocyte-derived macrophages with SARS-CoV-2, contributing to lung injury.\textsuperscript{128} Furthermore, AMs can be programmed to inflammatory M1 phenotype causing lung damage by SARS-CoV-2 infection and facilitating viral replication.\textsuperscript{129–131} Furthermore, depletion of AMs by clodronate results in effective virus clearance and lung recovery in the hACE2 transgenic mouse model,\textsuperscript{130} suggesting a pathological response of AMs in COVID-19. However, as these AMs are primarily of inflammatory phenotype, the pathological outcome is excepted. Nevertheless, it is still largely unknown how AMs are skewed towards inflammatory phenotype upon direct SARS-CoV-2 infection.

4.5  Other innate cell populations

Several other innate cells are depleted in COVID-19 cases such as DCs, eosinophils, and NK cells.\textsuperscript{75,132,133} Also, among them, the most prominent depletion occurred in DCs, eosinophils, and NK cells and was associated with disease severity.\textsuperscript{132–134} COVID-19-associated NK cells were found to be in a dysfunctional state with lower antiviral activity.\textsuperscript{85} In addition to compromised function, NK cells from COVID-19 patients also display profibrotic gene expressions such as AREG, DUSP2, ZFP36L2, and TSC22D3, which is similar to that of NK phenotype in lung fibrosis.\textsuperscript{84} Likewise, circulatory DCs were diminished in COVID-19 samples, both in acute and postacute cases.\textsuperscript{135–137} pDCs, which are a major contributor to IFN-α production, were also reduced in COVID-19 patients,\textsuperscript{84} which may answer why there is delayed IFN-α response in some patients.\textsuperscript{64} The DCs isolated from COVID-19 patients also has a reduced ability to stimulate naïve T-cells leading to a weak adaptive immune response.\textsuperscript{137} Furthermore, an in vitro study showed that despite low expression of the ACE2 receptor, SARS-CoV-2 can infect human DCs. Following infection, the infected DCs are unable to mount IFN responses, which are supposedly considered to delay viral clearance and may also contribute to immunopathology.\textsuperscript{138} Intriguingly, lung resident DCs are responsible for IFN-λ production upon viral RNA stimulation via the TLR3 pathway suggesting a pathogenic role of DCs.\textsuperscript{139} Furthermore, sustained IFN-λ by DCs has been predisposed to lung epithelial damage and secondary bacterial infection.\textsuperscript{139}

ILCs are among the major innate immune cell population in the lungs and promotes tissue repair after respiratory viral infection.\textsuperscript{140} However, its role in the context of SARS-CoV-2 infection is poorly studied. ILCs have been reported to be depleted in severe
COVID-19 and were inversely related to inflammation. In addition to depletion, ILC2s, and ILC precursors showed a higher frequency of CD69+ cells, a reflection of an activated state, and dysregulated ILC tissue migration resulting in pathogenic outcomes. Additionally, chemokine receptor expression, CXCR3, and CCR6 were decreased on ILC2s in COVID-19 individuals. In contrast, convalescent patients that have higher numbers of ILC subset NKG2D+ ILC2s together with elevated serum IL-13 levels demonstrated a significant reduction in hospitalization length. Overall advocating the protective role of ILCs in SARS-CoV-2 infection. However, IL-13 has been associated with COVID-19 severity and IL-13 neutralization by dupilumab in asthmatic patients resulted in lower mortality and hospitalization rate by COVID-19. Hence, it is still unclear about the role of ILCs in the regulation of COVID-19 pathogenesis. The role of mast cells has also been studied in COVID-19-induced epithelial inflammation and lung injury. The SARS-CoV-2 infection triggers mast cell degranulation in lungs in both humanized mice and nonhuman primates, which is further suggested to induce lung injury.

5 | PROTECTIVE ADAPTIVE IMMUNE RESPONSES IN ACUTE COVID-19

The adaptive immune response system, including B and T lymphocytes, carries out body defense in humans. Despite they can take days to become established, activated B and T cells have critical roles in controlling and shaping the immune response by providing various immune functions and long-lasting protection. SARS-CoV-2 infection of the respiratory tract induces virus-specific B and T cells, mediating viral clearance at the infection sites and preventing viral dissemination through antibodies and T cell effector functions. Indeed, many studies have shown that COVID-19 patients generated neutralizing antibodies and virus-specific T cells in the peripheral blood and the respiratory tract (Figure 2). It was also indicated that patients developed SARS-CoV-2-specific CD8+ T and CD4+ T, and B cell memory in the lungs, lung-associated lymph nodes, and other organs for up to 6 months following natural infection of SARS-CoV-2. Together, these findings suggest the persistence of humoral and cellular immune responses to SARS-CoV-2 infection in humans.

**FIGURE 2** The protective versus pathogenic adaptive immune responses in COVID-19. Left: When SARS-CoV-2 invades the host respiratory tract, the viral antigen can be detected and presented by DCs to either CD4+ T or CD8+ T cells for their activation. Naïve CD4+ T cells mainly differentiate into T helper 1 (Th1) and T follicular helper cells (Tfh). Th1 cells possess antiviral effects by producing higher levels of IFN-γ, TNF, and IL-2. Tfh cells provide help to B cells for somatic hypermutations and affinity maturation of germinal center reactions to generate memory B cells and long-lived antibody-producing plasma cells. The viral-specific antibodies secreted by plasma cells play a protective role by neutralizing the virus. Activated CD8+ T cells produce effector cytokines and cytotoxic molecules, including IFN-γ, TNF, IL-2, and granzyme B, controlling viral infections. After viral clearance, memory CD4+ T, CD8+ T, and B cells are developed in the circulation and lungs to protect against secondary infections. Right: Excessive T cell responses are associated with severe COVID-19, including IL-6 and GM-CSF-producing Th1 or Th17 cells, CD16+ cytotoxic T cells, CXCR6+ CD8+ T cells, as well as dysregulated Treg cells. On the other hand, the production of autoantibodies, the formation of immune complexes, and complement activation also contribute to the disease progression of COVID-19. ACE2, angiotensin-converting enzyme 2; BRM, resident memory B; COVID-19, coronavirus disease 2019; DC, dendritic cell; FcγR, Fc-γ receptor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN-γ, interferon-γ; IL-2, interleukin 2; MAC, Membrane attack complex; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane serine protease 2; TNF, tumor necrosis factor; Treg, regulatory T cell; TRM, tissue-resident memory.
5.1 | T cell immunity

Generally, T cells can be divided into two subsets: CD4+ T helper cells and CD8+ cytotoxic T cells, both of which contribute to the protection against respiratory virus infections. Upon activation, naïve CD4+ T cells mainly differentiate into T helper 1 (Th1) and T follicular helper cells (Tfh) during viral infection. Th1 has antiviral properties by triggering cell-mediated immune responses through activating other immune cells, while Tfh specializes in help to B cells for somatic hypermutations and affinity maturation of germinal center reactions and thus are vital for the generation of high-affinity neutralizing antibodies, as well as for the development of memory B cells. Activated CD8+ T cells control viral infections by eliminating virus-infected cells and producing effector cytokines. After viral clearance, memory CD8+ and CD4+ T cells are developed in tissues to protect the host against secondary infections.

SARS-CoV-2-specific T cells are well detected in most donors during acute infection and at the convalescent stage. CD4+ T cells were predominantly exhibiting Th1 phenotype in mild patients, producing higher levels of IFN-γ, TNF, and IL-2, and rare Th2- and Th17-related cytokines were detected. SARS-CoV-2-specific CD8+ T cells possess high levels of effector molecules, including IFN-γ, granzyme B, TNF, IL-2, perforin, and CD107a, which have been associated with a better outcome. One study tracked T cell response and viral burden longitudinally after symptom onset and found patients with the presence of robust early T cell responses were associated with mild disease and rapid viral clearance. Conversely, individuals with very few virus-specific T cells early on were associated with the persistence of high viral loads and the development of severe COVID-19. Another study observed a positive association between the presence of SARS-CoV-2-specific CD4+ T and CD8+ T cells and reduced disease severity. Furthermore, a study revealed that SARS-CoV-2-specific CD8+ T cell response was significantly associated with mild disease and high antiviral efficacy. Overall, these studies linked SARS-CoV-2-specific T cell responses to rapid viral clearance and/or better clinical outcomes, suggesting an active role of T cells in the control and clearance of SARS-CoV-2. Interestingly, virus-specific T cells appear to be functionally superior in asymptomatic individuals with a similar frequency of SARS-CoV-2-specific T cells, but higher production of Th1 cytokines IFN-γ and IL-2 compared to symptomatic patients.

Pre-existing SARS-CoV-2-specific T cells were also detected in individuals with no history of SARS, COVID-19, or contact with individuals who had SARS and/or COVID-19, and these T cells frequently targeted NSP7 and NSP13 of SARS-CoV-2 as well as structure nucleocapsid protein, which are highly conserved among different coronavirus. Similarly, a recent study has shown pre-existing memory T cells that were more frequently directed against replication transcription complex proteins (RTC, including NSP7, NSP12, and NSP13) were enriched and expanded in vivo in seronegative healthcare workers (SN-HCWs), whereas T cells from mild COVID-19 individuals preferentially recognized structural proteins. SN-HCWs with strong RTC-specific T cells had high induction of IFN-inducible transcript IFI127 in the blood, a robust early innate signature of SARS-CoV-2 infection. These two studies suggest that boosting pre-existing memory T cells could be a potential target for epitope-based vaccine design. Additionally, many studies found that SARS-CoV-2-specific memory CD4+ and CD8+ T cell responses were durable over time after infection. Wragg et al. reported that SARS-CoV-2 infection and/or vaccination-induced memory CD4+ T cells and circulating T follicular helper are efficiently recalled after antigen re-exposure, suggesting a long-term protection capability.

γδ T cells are an innate-like T cell subset that expresses γδ T-cell receptor (TCR) and is mainly present in the epithelial layer of mucosa. Upon activation, γδ T cells produce a variety of cytokines, including IFN-γ, TNF, and IL-17, as well as the cytotoxic molecules perforin and granzymes, to combat invaders. To date, there is limited information on how γδ T cells are involved in COVID-19. One study reported that deceased COVID-19 patients had lower Vγ9Vδ2 T cells, the dominant γδ T-cell population in adults, compared to surviving patients. In the patients who survived, Vγ9Vδ2 T cell number was comparable to healthy controls, with 26% of cells shifted to an effector (memory) phenotype. Similarly, Carter et al. observed γδ T cell lymphopenia and activation in the acute phase of children with the multisystem inflammatory syndrome and returned to normal by convalescence. Collectively, these studies evidenced that γδ T cells participate in the host immune response against SARS-CoV-2 infection. Further investigations are needed to characterize the functional role of γδ T cells in COVID-19.

5.2 | Humoral immunity

Humoral responses are another part of adaptive immunity against viral infection. SARS-CoV-2 infection induces robust humoral immune responses and generates potent neutralizing antibodies (nAbs) against the spike (S) protein. The receptor-binding domain of S protein is dominantly targeted by about 90% of nAbs. nAbs prevent the entry of SARS-CoV-2 into host cells, primarily by blocking S protein engaging its cognate receptor ACE2. A body of evidence indicates that nAbs are strongly correlated with protection from SARS-CoV-2 infection. The presence of nAbs induced by a previous infection has also been shown to provide protection against subsequent reinfection. The development of humoral immunity is dependent on the activation of antigen-specific B cells, which result in the germinal center formation and differentiate into long-lived plasma cells or memory B cells. nAbs are detectable within 7–14 days postsymptom onsite, peak until 23 days, and maintained for at least 16 months after infection. In addition, S-specific long-lived bone marrow plasma cells are still detectable for at least 11 months. SARS-CoV-2-specific memory B cells also persisted for at least 15 months. Memory B cells can be reactivated to elicit an antibody response within a few days upon SARS-CoV-2 infection and are likely protective; however, no direct
evidence shows the protective role of memory B cells in humans. The mucosal immune system is involved in protection at the sites of infection. As SARS-CoV-2 infects the respiratory tract, it could induce robust mucosal immunity. Indeed, studies have demonstrated that COVID-19 convalescents had significantly higher levels of nAbs against D614G, Delta, and Omicron in the BAL compared to mRNA-vaccinated individuals.

6 PATHOGENIC ADAPTIVE IMMUNE RESPONSES IN ACUTE COVID-19

6.1 Dysregulated T-cell responses in COVID-19

Virus-specific T-cell responses are mainly thought to be protective. However, dysregulated T-cell responses can contribute to disease progression in COVID-19 patients (Figure 2). In many cohorts of critically ill patients, the numbers of SARS-CoV-2-specific CD4+ T and CD8+ T cells were comparable to or higher than those in mild patients, and such polyfunctional antigen-specific T cells were predisposed to a cytotoxic phenotype, which likely play an important role in causing higher disease severity and leading to tissue damage. Consistent with this notion, a recent study revealed that higher frequencies of IFN-γ- and TNF-α-producing SARS-CoV-2-specific T cells in the peripheral blood of COVID-19 patients with postacute syndrome are associated with increased systemic inflammation (plasma IL-6) and worsen lung function (forced expiratory volume in 1 s). SARS-CoV-2-specific regulatory T cells (Tregs) were also found elevated in fatal COVID-19 cases, likely associated with the poor SARS-CoV-2-specific T cell responses observed in these patients. Furthermore, activated CD4+ T and CD8+ T cells have been found to infiltrate the lungs of severe COVID-19 patients and are associated with inflammation, endothelial dysfunction, and fibrosis.

T cell hyperactivation and/or "exhaustion" have been described in COVID-19. High expression of effector molecules, including GZMH, KLRL1, and SLC9A3R1, by CD8+ T cells in COVID-19 patients, is linked to improved clinical outcomes. However, excessive T cell activation may be detrimental, as reported by Mathew et al. that hyperactivated CD4+ T and CD8+ T cells are associated with disease severity and poor outcomes. Conversely, upregulation of inhibitory receptor expression on CD8+ T cells including PD-1, TIM-3, LAG-3, TIGIT, CTLA-4, and NKG2A has been observed during acute infection, reflecting T cell overactivation and dysfunction in acute disease. Nevertheless, these elevated inhibitory receptors may not be exhausted, especially in the early phase, they can represent ongoing activation as evidenced by PD-1-expressing SARS-CoV-2-specific CD8+ T cells being functional. Both CD38 and HLA-DR are well-known activation markers that are expressed on activated T cells during the acute phase of viral infections in humans, including human immunodeficiency virus, dengue virus, Ebola virus, pandemic H1N1,193 and H7N9. The increasing number of CD38+HLA-DR+Ki-67+ CD4+ T and CD8+ T cells were also found in the acute phase of severe COVID-19 patients. These CD38+HLA-DR+CD8+ T cells express high levels of effector and proinflammatory cytokines, including IFN-γ and GZMB, contributing to viral control. These studies indicate that early prevalence of an activated CD38+HLA-DR+CD8+ T cell subset is associated with patient survival, whereas prolonged activated T cells with expression of inhibitory immune checkpoint receptors PD-1, CTLA-4, TIM-3, LAG-3, and TIGIT may lead to severe and fatal COVID-19. Yet, it remains unclear whether such T cells are antigen-specific. Interestingly, bystander-activated CD38+HLA-DR+CD8+ T cells were identified in acute hepatitis A patients and chronic hepatitis C patients and are significantly associated with liver injury, suggesting non-SARS-CoV-2-specific CD38+HLA-DR+CD8+ T and/or CD4+ T cells could play a pathogenic role in fatal COVID-19 patients. Further studies with larger patient cohorts might provide details on whether such prolonged with functionally exhausted CD38+HLA-DR+PD-1+ CD8+ T and CD4+ T cells could predict disease severity and outcome.

Severe COVID-19 patients have been shown to exhibit elevated BAL and/or serum levels of cytokines, including IL-6, IL-2, IL-1β, IL-8, IL-10, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor, IFN-γ, and TNF-α, and are associated with disease severity and mortality. An interesting question is whether acutely activated T cells secrete these cytokines and how they contribute to immunopathogenesis in COVID-19. Zhou et al. reported that a subset of CD4+ Th1 cells from COVID-19 patients in both intensive care units (ICU) and non-ICU express high levels of GM-CSF, IL-6, and IFN-γ compared to healthy controls, while ICU patients with more severe pneumonia had a higher percentage of GM-CSF+ and IL-6+ CD4+ T cells. They proposed that these pathogenic CD4+ Th1 cells were rapidly activated to produce GM-CSF and other cytokines to prime inflammatory monocytes (IL-6CD14+CD16+) entering pulmonary circulation, eventually leading to pulmonary inflammation and injury. The higher proportion of IL-6-expressing SARS-CoV-2-specific CD8+ T cells were also detected in the non-survivor than in the survivor of severe COVID-19. Similarly, another study found IL-6 and GM-CSF were associated with COVID-19 severity and accompanied by elevated markers of endothelial injury and thrombosis. Of interest, a subset of clonally expanded, GM-CSF expressing tissue-resident memory-like Th17 (TRM17) cells have been identified in the lungs of patients with severe COVID-19 that persist even after viral clearance. These GM-CSF expressing TRM17 cells together with IL-1β-expressing proinflammatory macrophage and cytotoxic CD8+ T cells forming a pathogenic milieu in the lung could promote inflammatory tissue injury. In general, these studies suggest that pathogenic T cells may contribute to the production of IL-6 and GM-CSF in patients with severe COVID-19.

Tregs are a subset of CD4+ T cells that have been critically involved in the regulation of immune responses to maintain immune homeostasis. In humans and mice, during respiratory virus infection or acute lung injury, Tregs could migrate into the inflamed lung to suppress inflammatory responses, ameliorate viral pneumonia and...
promote lung tissue repair. Hence, Tregs are likely protective in COVID-19 patients with cytokine storm. To date, the changes in Treg cell frequency and cell number in the blood of COVID-19 patients remain controversial, as many studies have shown decreased proportions of naïve Tregs and a shift towards effector Tregs, especially in those with severe disease, while others observed increased or unchanged Treg frequency. The limited study reported the increased proportion of Tregs in the BAL fluid of COVID-19 patients. The expansion of effector Tregs may be attributable to the establishment of a dysfunctional lung immune environment and the pathogenesis of COVID-19. Interestingly, a study reported that the frequency of Tregs and the expression level of FoxP3 were increased in severe COVID-19 patients and were correlated with poor outcomes. These Tregs have distinctive transcriptional signatures with high levels of effectors and proinflammatory molecules and share many similarities with tumor-infiltrating Tregs that are generally associated with poor prognosis, suggesting such Tregs may suppress antiviral T cell responses in the acute phase while promoting inflammatory responses. The authors also noted that IL-6 and IL-18 potentially contributed to the upregulation of FoxP3 and the unique transcriptional signatures of these Tregs, respectively. Nevertheless, activated Tregs with high suppressive activity in the early phase of the disease are presumably beneficial for the immune system to avoid tissue damage by activated immune cells. In contrast, the lower number of naïve Tregs in combination with higher active Tregs in severe cases or later stages of the disease may exacerbate the cytokine storm that leads to ARDS.

Chemokine receptors are important in the control of T cell migration to several tissues in disease states or after infections, most notably to the lungs. CCR6, CXCR3, and CXCR6 are found to be upregulated in CD4+ and CD8+ T cells in PBMCs and BAL fluid of patients with COVID-19. Early polyfunctional CXCR3+CD8+ T cells infiltration of the lungs have a potential role in disease control. However, a study reported that CXCR3 and CCR6 are highly expressed in activated CD16+ CD4+ and CD8+ T cells in severe COVID-19. The SARS-CoV-2 infection triggers complement activation, which creates an inflammatory environment that drives the differentiation of CD16+, highly cytotoxic CD4+ and CD8+ T cells. Expression of CXCR3 and CCR6 may facilitate the migration of these activated CD16+ T cells into the lungs, leading to endothelial cell damage and release of chemokines CXCL8 and CCL2. CXCR6 is important for the migration of CD8+ T RM cells to the airways in response to respiratory virus infection. Recent studies showed PDI+CXCR6+CD8+ T cells were accumulated in patients with nonalcoholic steatohepatitis (NASH) and in the liver of NASH mice and mediated the immune pathology in NASH through "autoaggressive" activation, suggesting that CXCR6 might play a pathogenic role in T cell homing to inflamed tissues in diseases. Genome-wide association studies (GWAS) indicated that CXCR6 is associated with COVID-19 severity. Bost et al. showed that CXCR6 was only detected in the BAL T RM (resident memory) and TEM (effector memory), suggesting a protective effect of CXCR6+ T cells. Another study demonstrated that circulating CXCR6+CD8+ T cells were significantly reduced in both mild and severe COVID-19 patients compared to controls, but significantly increased in individuals aged over 65. In aged individuals, those CXCR6+ T cells may drive lung damage, resulting in severe symptoms and poor outcomes. Together, the effector functions of chemokine receptor-expressing T cells may be beneficial in early antiviral immunity; however, the prolonged activated effect of these T cells may contribute to the persistent respiratory viral symptoms and fibrosis during or after the resolution of acute SARS-CoV-2 infection.

6.2 | Humoral responses associated with COVID-19 severity

Severe COVID-19 distinctly altered the B cell compartment of adaptive immunity. The absence of a germinal center was reported in the spleen and lymph nodes of COVID-19 patients, probably due to the failure of differentiation of BCL6+ Tfh as well as the aberrant local accumulation of TNF in lymphoid organs. This might partially explain the low levels of somatic hypermutation among B cells seen in some cases of COVID-19. It also might skew humoral response toward an extrafollicular B cell response. Indeed, one study reported critically ill COVID-19 patients displayed hallmarks of extrafollicular B cell responses and high nAb titers, similar to those in human systemic lupus erythematosus. Besides, highly prevalent immunoglobulin G (IgG) responses against nonstructural/accessory proteins were observed in COVID-19 patients and were positively associated with disease severity and worse clinical outcomes. Taken together, these findings suggest that excessive humoral responses contribute to disease exacerbation.

Antigen-specific antibodies can form an immune complex with viral particles or viral antigens and induce a hyperinflammatory response via activating FcγRs on myeloid cells. It has been known that human IgG antibodies can worsen pathology by triggering proinflammatory cytokine release. Several studies have revealed aberrant glycosylation, afucosylation, in the Fc tail of anti-spike (S) IgG in severely ill COVID-19 patients but not mild patients. It might skew humoral response toward an extrafollicular B cell response. Indeed, one study reported critically ill COVID-19 patients displayed hallmarks of extrafollicular B cell responses and high nAb titers, similar to those in human systemic lupus erythematosus. Besides, highly prevalent immunoglobulin G (IgG) responses against nonstructural/accessory proteins were observed in COVID-19 patients and were positively associated with disease severity and worse clinical outcomes. Taken together, these findings suggest that excessive humoral responses contribute to disease exacerbation.

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kidneys, and other organs of severe COVID-19 patients.\textsuperscript{232–236} It has been shown that virus-specific IgG and IgM antibodies could activate the classical pathway,\textsuperscript{234} providing evidence that antigen-antibody immune complex may play a role in complement-mediated pathogenesis in advanced COVID-19. However, the role of these antibodies in activating complement and progressing disease has not been fully defined.

### 6.3 | Autoantibody production in COVID-19

Several studies have described the prevalence of autoantibodies (auto-Abs) in COVID-19 patients, particularly those that neutralize type I IFNs, including IFN-α2 and IFN-ω, found in about 10% of patients and are associated with critical COVID-19 pneumonia.\textsuperscript{67,237-240} These auto-Abs were not found in asymptomatic or mild patients and only 0.33% of healthy individuals before the pandemic and in a few patients tested before SARS-CoV-2 infection contain detectable auto-Abs.\textsuperscript{67} Notably, one study measured auto-Abs neutralizing lower, more physiological, the concentration of IFN-α and/or IFN-ω (100 pg/ml) in COVID-19 patients across different disease severity and ages and found auto-Abs in 6.5% and 13.6% of patients with severe and critical COVID-19, respectively, and in 18% of deceased patients.\textsuperscript{237} Such auto-Abs were more prevalent in critical patients older than 65 and were greater in men than women.\textsuperscript{237} More interestingly, testing a larger cohort of individuals aged 20–100 years from the general population showed a sharp increase of auto-Abs against IFN-α and/or IFN-ω after the age of 70 years.\textsuperscript{237} These auto-Abs might contribute to the higher risk of critical COVID-19 in the elderly.

Of importance, IFN auto-Abs were also detected in the upper respiratory tract (nasopharyngeal swabs) and lower respiratory tract (BAL fluid) of COVID-19 patients and revealed that the IFN auto-Abs in the nasopharyngeal swabs were linked with poor IFN-stimulated responses among the nasal epithelial cells in severe COVID-19 individuals,\textsuperscript{241-243} allowing higher or persistent viral replication in the respiratory tract and potentiating excessive respiratory inflammation that could drive severe pneumonia. Indeed, the IFN auto-Abs were shown to block the antiviral activity of IFN-α against SARS-CoV-2 infection in vitro\textsuperscript{67} and in vivo,\textsuperscript{238} providing a potential explanation for weaker antiviral immunity in some severe patients in the acute phase. However, if such auto-Abs are still present in patients with long COVID, particularly in their airways, the potential pathogenic roles of these auto-Abs need to be investigated.

### 7 | IMMUNOMODULATORY DRUGS FOR ACUTE COVID-19

In the fight against COVID-19, currently, antiviral drugs and vaccines are viable options. However, the rise in several variants of concerns has lowered the efficacy of most vaccines and antiviral drugs are usually not effective in severe COVID-19 patients. A plethora of evidence, both from preclinical and clinical studies, have demonstrated the beneficial effect of immunomodulatory drugs such as corticosteroids, metformin, recombinant IFNs and GM-CSF, IL-6, and TNF-alpha targeting monoclonal antibody (mAb) in treating COVID-19 (Figure 3). Here, in this section, we have discussed some of the most used immunomodulatory drugs for COVID-19 and their mode of action.

#### 7.1 | Corticosteroids

Methylprednisolone is a frequently recommended corticosteroid to COVID-19 patients to dampen inflammatory response due to the presence of increased proinflammatory cytokines (IL-2, TNF-α, IL-1β, IFN-γ, and IL-6) and chemokines (CCL2 and MIP-1α).\textsuperscript{105} According to some meta-analysis studies, methylprednisolone treatment has shown reduced mortality in severe patients.\textsuperscript{244,245} However, some of the clinical findings indicate that the use of methylprednisolone therapy has resulted in delayed viral clearance and prolonged hospitalization,\textsuperscript{246-248} further discouraging its use outside the clinical trials.

Dexamethasone is another immunosuppressive corticosteroid that was previously shown to improve mortality in COVID-19 patients.\textsuperscript{249} In severe COVID-19 patients, dexamethasone administration has been beneficial in improving clinical parameters of lung epithelial and endothelial injury without affecting the viral load.\textsuperscript{250} Mechanistically, dexamethasone can suppress IFN-activated neutrophils and limit neutrophil-induced immunopathology.\textsuperscript{251} Nevertheless, cautious administration of dexamethasone has been recommended, particularly in the early phase of infection, due to its several side effects and possible suppression of antiviral immune responses.\textsuperscript{252} In a recently published large multicenter cohort study, severe COVID-19 patients under dexamethasone treatment are found to develop more risk of ICU-acquired respiratory tract infection.\textsuperscript{253} However, these clinical trials skip the use of antiviral, remdesivir, which further leads to the notion that dexamethasone administration along with antiviral therapy may prove clinically useful.\textsuperscript{254}

#### 7.2 | Metformin

SARS-CoV-2 infection is also known to alter the metabolic profile of infected monocytes,\textsuperscript{119} which is mediated by its spike protein,\textsuperscript{255} leading to HIF-1α-dependent enhanced inflammation.\textsuperscript{119,255} Metformin is an antidiabetic drug that has been suggested as a repurposed drug for COVID-19 due to its anti-inflammatory property.\textsuperscript{256} In addition to its anti-inflammatory property, metformin is known to phosphorylate the entry receptor for SARS-CoV-2, the ACE2, suggesting its possible role in blocking the entry of SARS-CoV-2.\textsuperscript{257} Metformin injection in SARS-CoV-2 infected hACE2 transgenic mice improved the morbidity and rescued the mice from ARDS.\textsuperscript{258} In an in vitro setting, it was also demonstrated that metformin results in the rescue of monocytes from inflammation.\textsuperscript{255}
However, in clinical trials, metformin showed uncertainty. In a retrospective cohort analysis, the use of metformin was not associated with a reduced risk of mortality in total samples of both men and women from COVID-19. Of note, in the case of women, there was a reduced risk of mortality, indicating the sex-dependent effect of metformin.259 In a recent randomized clinical trial, the effect of early treatment with metformin was assessed for high-risk patients with early COVID-19, and metformin treatment failed to improve the primary endpoints including hypoxemia, emergency department visit, hospitalization, or death.260 Likewise, metformin was not able to provide clinical benefits even given early.261 These clinical observations failed to indicate any beneficial role of metformin. Nevertheless, in clinical trials involving COVID-19 patients with type 2 diabetes, there appeared a reduced risk of mortality associated with the metformin treatment.262,263 Altogether, more randomized clinical trials are required to further confirm these claims.

7.3 | Baricitinib

Baricitinib is a selective inhibitor of Janus kinase 1 and 2 with known anti-inflammatory properties.264 Baricitinib treatment in rhesus monkeys rescued the inflammatory phenotype of macrophages isolated from BAL, in particular, IL-6 and TNF expression.265 However, baricitinib was able to suppress SARS-CoV-2-induced pathology of the lung but it did not limit SARS-CoV-2 infection in the rhesus monkey. In addition to dampening the inflammatory properties of macrophages, the baricitinib treatment abolished the degranulation of neutrophils and NET formation.265 In humans, baricitinib administration increased virus-specific IgG and lowered the serum levels of IL-6, IL-1β, and TNF-α. Furthermore, the treated patients further needed no oxygen support as a result of the improved oxygenation index.266 Along with antiviral drug remdesivir, baricitinib treatment may help to accelerate the recovery of COVID-19 patients.267
7.4 | Tocilizumab

Tocilizumab is a mAb that can bind to the membrane-bound or soluble IL-6 receptor. Excessive systemic inflammation because of inflammatory cytokines including IL-6 levels was associated with adverse clinical outcomes in patients hospitalized with COVID-19. Hence, for achieving therapeutic benefits, the use of several IL-6 antagonists was studied in several randomized clinical trials. In a randomized clinical trial, tocilizumab was not associated with improved clinical outcomes in severe COVID-19 patients. However, with oxygen support, the COVID-19 patients on tocilizumab therapy showed improved mortality. Intriguingly, in a different study tocilizumab treatment at the early inflammatory stage at moderate dosage resulted in improved mortality of severe COVID-19 patients. These contradictory reports may prompt clinicians to critically assess the timing and dose of tocilizumab for improved benefits.

7.5 | TNF inhibitor

The concept of blocking TNF as a potential therapy stems from observation clinical studies that show that severe patients have increased TNF in serum and BAL fluid. TNF inhibitors that are mostly used in clinical trials are anti-TNF antibodies (such as infliximab, adalimumab, and golimumab) etanercept (TNF-R2 Ig-Fc fusion protein), and certolizumab pegol (monovalent Fab fragment of a humanized mAb without Fc region). In a large cohort of more than 6000 COVID-19 patients, anti-TNF monotherapy proved to be associated with a lower risk of COVID-19-induced pathology. Similarly, a meta-analysis of 34 studies also advocates the beneficial role of anti-TNF therapy in lowering the hospitalization rate due to COVID-19 severity.

7.6 | IFN treatment

Following SARS-CoV-2 infection, there was a reduction in type I and type III IFN response. As robust IFN response is required for antiviral defenses, recombinant IFNs such as IFN-α, IFN-β, and IFN-λ are currently being investigated as a potential therapy in several clinical trials (clinical trial identifier number NCT04276688, NCT04343976, NCT04354259, NCT04388709, and NCT04344600). A recent report involved 446 patients tested for IFN-α treatment, both during early and late infection. Early treatment with recombinant IFN via aerosol resulted in decreased mortality, whereas late treatment increased mortality. Hence, these studies must proceed with caution due to heterogeneity in IFN response among COVID-19 samples and timing of the IFN treatment.

7.7 | GM-CSF mAb

Pathogenic T cells may contribute to the production of GM-CSF in patients with severe COVID-19, suggesting GM-CSF blockade as a therapeutic target in COVID-19. Human mAbs targeting GM-CSF, such as otilimab, gimsilumab, lenzilumab, and namilumab, or GM-CSF receptors, such as mavrilimumab, have been assessed in several clinical trials. A meta-analysis of GM-CSF mAbs therapy for COVID-19 patients was performed with six eligible studies involving 1501 patients. The analysis revealed that the GM-CSF mAbs therapy was associated with reduced mortality (3.8%–26.9%), a decreased incidence of invasive mechanical ventilation (5.3%–28.7%), and improved ventilation (23.3%–50.0%) in severe COVID-19 patients. They also found there was no increased incidence of secondary infection in COVID-19 patients between GM-CSF mAbs group and control, whereas similar immunomodulatory strategy IL-6 receptor mAbs therapy showed increased secondary infection. Given the crucial role of GM-CSF in AM homeostasis and lung viral clearance, recombinant GM-CSF administration may be more beneficial in earlier-stage COVID-19, whereas GM-CSF mAbs therapy could be beneficial for more severe COVID-19 patients. Overall, the safety and efficacy of GM-CSF blockade in the treatment of COVID-19 patients are still controversial, and more random clinical trials are required to evaluate these therapeutics in COVID-19.

8 | IMMUNOPATHOLOGY IN LONG COVID

Apart from the acute manifestations of disease during COVID-19 illness, increasing evidence points to the development of chronic pulmonary and extrapulmonary sequelae termed the postacute sequelae of SARS-CoV-2 infection (PASC) or long COVID following the resolution of primary SARS-CoV-2 infection. Specifically, PASC is defined by the persistence of disease greater than 28 days following the onset of symptoms, a phenomenon observed in 27%–80% of convalescent individuals. Symptoms range from brain fog, general fatigue, dyspnea, and joint pain to multiorgan impairments (Figure 4). Patients often exhibit diminished lung function and exercise capacity in addition to several radiological anomalies including ground-glass opacities, atelectasis, and reticulation, with evidence of persistent inflammation and fibrotic-like changes. Although the pathophysiology of pulmonary abnormalities has been most widely studied thus far, extrapulmonary manifestations including thrombotic complications, myocardial injury, and neuropsychiatric symptoms have also been frequently observed. Despite ongoing efforts, however, PASC the etiology of chronic sequelae following acute COVID-19 remains poorly understood. Long-term persistence of SARS-CoV-2 viral remnants has been observed in numerous sites including the lungs, brain, kidneys, and the gut suggesting possibly instigating aberrant immune responses and pathology. In support of this notion, longitudinal studies have revealed sustained dysregulation of immune responses in PASC - highly activated myeloid cells, T-cells, elevated proinflammatory cytokine levels, and a reduction in naïve T- and B-cells. Moreover, sustained reduction of circulating cortisol, an immunosuppressive factor, has been reported in independent
Postviral pulmonary sequelae are not unique to SARS-CoV-2 and have been reported following several other respiratory viral infections, potentially driven by the immune system as well. For the remainder of this review, we specifically focus on various immune mediators implicated in the development of PASC and highlight potential therapeutic avenues to mitigate chronic disease.

8.1 | Innate cells

The accumulation of a monocyte-derived CD163+ macrophage pool was observed during severe COVID-19. The cells exhibited an M2-like phenotype, which although crucial for the resolution of inflammation and wound repair, may also promote fibrotic changes within the microenvironment. Moreover, these cells were observed in close association with pockets of collagen deposition and exhibited a profibrotic transcriptional phenotype with remarkable similarity to macrophage populations in IPF patients. Notably, the degree of radiological abnormalities correlated with myeloid cell numbers within the BAL fluid. PASC patients also exhibit persistent elevation of chemokines known to recruit monocytes, such as CCL-2, further suggesting a detrimental role of these cells in long-term pathology. While rapid induction of IFNs following infection is typically associated with improved viral clearance and outcomes, long-term studies have identified sustained elevation of type I and type III IFNs up to 8 months postinfection in patients. This chronic activation of IFNs and downstream pathways has been shown to adversely affect epithelial repair following injury. However, the exact roles of types I–III IFNs during PASC remain unclear and warrant further investigation. The maintenance of a chronic proinflammatory state is also known to prevent the differentiation of alveolar type II cells to alveolar type I cells during repair, promoting their accumulation and impaired regeneration. In support of this, an accumulation of keratin 8+ transitional cells has been observed in lethal COVID, similar to IPF, potentially driven by monocyte/macrophage-derived IL-1β. Chronic elevation of circulating IL-1β, along with IL-6 and TNF in PASC patients indicates a self-sustaining
feed-forward loop, likely contributing to the establishment of a proinflammatory environment.299 Furthermore, PASC patients with persistent interstitial lung changes maintain an immune signature associated with sustained neutrophilic inflammation, indicating a potential role for neutrophils in driving chronic sequelae.300,301 In addition to pulmonary sequelae, myeloid cells have been found to contribute to cognitive impairments associated with PASC—typically referred to as “brain fog.” Microglia undergo significant perturbations during acute COVID-19, exhibiting enhanced reactivity which has previously been linked to loss of oligodendrocytes and myelinated axons.302

8.2 Adaptive cells

During acute infection, AMs were found to recruit CD8⁺ T-cells, which in turn secrete IFNγ establishing a positive feedback loop between macrophage activation and T-cell recruitment.128 Additional chemokines such as CXCL-9, CXCL-10, and CXCL-11 were also found to remain elevated in PASC patients in the absence of active infection, likely recruiting and maintaining several adaptive immune populations.297 Further indicating a lack of resolution of inflammation, PASC patients were found to harbor CD8⁺ TRM cells in the airways at least 90 days following acute disease.151,290 The persistence of CD8⁺ TRM cells in the BAL fluid was associated with increased epithelial damage, and the CD69⁺CD103⁻ subset, in particular, negatively correlated with lung function in convalescents.151,303 Notably, the cells were enriched for TCR signaling pathway genes suggesting antigen-mediated stimulation.291 However, the nature of the antigen—whether residual viral remnants or self-antigen is unknown and will likely be answered by comprehensive profiling of chronically activated T-cell subsets following infection. Alternatively, antigen-independent mechanisms may be at play, as an auto-aggressive CXCR6⁺ TRM subset previously described in the liver was also identified in the airways of COVID-19 convalescents.293 While the origins of pathological CD8⁺ TRM subsets are unknown, early COVID-19 studies identified a deleterious CD8⁺ T-cell subset (CXCR4⁺), which may potentially seed the CD69⁺CD103⁻ TRM population within the lung.156,218 CD4⁺ TRM cells were also persistently enriched within the airways of PASC patients, potentially orchestrating fibrotic responses and negatively influencing lung repair.297 In addition to the exuberant activity of the immune system, inhibition of regulatory activities may also contribute to chronic disease. Notch4 expression on T₅₇ cells was found to correlate with disease severity, limiting resolution of inflammation and amphiregulin-dependent tissue repair.304

Apart from T-cell mediated pathology, B-cells and antibodies induced during acute infection may contribute to the development of chronic sequelae. B-cell numbers correlated with the incidence of radiological abnormalities and impaired gas exchange.297 Although direct mechanisms are still under investigation, auto-Abs have been hypothesized to drive long-term symptoms, with IFNα-2 auto-Ab uniquely correlating with pulmonary sequelae.238,294 However, a recent report profiling auto-Abs against extracellular and secreted proteins in PASC patients failed to show an association with symptoms.295 Other immunoglobulin signatures during acute infection have also been found to predict the development of PASC, which may instead reflect the inflammatory milieu responsible for poor control of viral replication.305 However, further studies are required to elucidate the underlying mechanisms.

8.3 Potential therapy for long COVID-19

Several studies have identified severity and damage accrued during acute infection to be the strongest predictor of chronic pulmonary sequelae in the context of COVID-19.306-308 Furthermore, host factors such as advanced age and comorbidities including metabolic syndrome, cardiovascular disease, immunosuppression, and so forth, have been associated with long-term adverse outcomes.309 However, it is unclear if this association is due to the increased risk of severe disease or a direct predisposition toward the development of chronic sequelae. Nevertheless, dysregulated immune responses are a common theme in both scenarios which contribute significantly to postviral lung disease, as exemplified over the course of the COVID-19 pandemic.302,297 Thus, the aforementioned drugs targeting the immune system as well as vaccines are likely effective in attenuating postviral disease. In addition, cellular and molecular mediators relevant to PASC may also be targeted however further clinical studies are required to determine their efficacy. The exuberant activity of myeloid cells in the aftermath of the acute disease may be dampened by blocking chemokines such as CCL-2, CXCL-17, and so forth, and their receptors to prevent continuous recruitments of monocytes and neutrophils. Similar strategies may be utilized to inhibit CXCR3-mediated recruitment and maintenance of adaptive cells such as CD8⁺ T-cells, CD4⁺ T-cells, and B-cells in the lung. Moreover, specific pathologic subsets of CD8⁺ TRM responsible for impaired pulmonary function and adverse outcomes can be targeted for ablation. Alternatively, cytokines and immunological mediators such as IL-22 and amphiregulin, known to contribute to epithelial repair may be administered to augment the epithelial repair. Recent studies have also shown potential for the use of IPF drugs in the dampening of fibrotic disease following COVID-19, however, further investigations are required to characterize their efficacy in PASC.310

9 CONCLUDING REMARKS

In wake of the current COVID-19 pandemic, there is an unprecedented growth in the development of vaccines and therapeutics to halt the damage caused by SARS-CoV-2. However, to first delineate the course of a successful vaccine or therapeutic design, we must first investigate the pathophysiology caused by SARS-CoV-2. By taking advantage of current advanced tools and techniques we are now able to answer any questions that remained unanswered until recently regarding the immunopathology caused by
SARS-CoV-2. Having a detailed bird’s eye view of the pathogenic immune responses in acute and chronic pathophysiology following SARS-CoV-2 infection, it is anticipated that critical information may be unearthed, which will be beneficial for designing novel therapeutics.

Apart from vaccines, several immune-based therapies have shown some success in mitigating the current pandemic. However, due to complexity such as variable immune response to therapies, and heterogeneity in host and virus, there have been lots of challenges in adopting immunomodulatory drugs. Additionally, while acute COVID-19 is still a threat, complications rising due to PASC are recently making headlines in the scientific community. Nevertheless, these challenges could likely be answered through precision or evidence-based immune therapies in the future. Some of the highlights of precision therapy are that the therapy is largely influenced by the patient’s immune condition, disease course, and use of cointervention apart from drugs. Therefore, immune profiling and lung function examination before immunotherapy may provide critical insight into a patient’s condition. Incorporation of these approaches may help increase the efficacy of current immunomodulatory drugs and could help to curb the current pandemic.

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Jie Sun is a consultant for TeneoFour company.

**DATA AVAILABILITY STATEMENT**
All data reviewed in this manuscript are from published papers.

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