Immunopathology and immunotherapeutic strategies in severe acute respiratory syndrome coronavirus 2 infection

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Summary
The outbreak of coronavirus disease 2019 (COVID-19) and pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a major concern globally. As of 14 April 2020, more than 1.9 million COVID-19 cases have been reported in 185 countries. Some patients with COVID-19 develop severe clinical manifestations, while others show mild symptoms, suggesting that dysregulation of the host immune response contributes to disease progression and severity. In this review, we have summarized and discussed recent immunological studies focusing on the response of the host immune system and the immunopathology of SARS-CoV-2 infection as well as immunotherapeutic strategies for COVID-19. Immune evasion by SARS-CoV-2, functional exhaustion of lymphocytes, and cytokine storm have been discussed as part of immunopathology mechanisms in SARS-CoV-2 infection. Some potential immunotherapeutic strategies to control the progression of COVID-19, such as passive antibody therapy and use of interferon αβ and IL-6 receptor (IL-6R) inhibitor, have also been discussed. This may help us to understand the immune status of patients with COVID-19, particularly those with severe clinical presentation, and form a basis for further immunotherapeutic investigations.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ADCC, antibody dependent cellular cytotoxicity; ARDS, acute respiratory distress syndrome; ASC, antibody-secreting cells; CCL-2, chemokine ligand-2; CoV, coronavirus; COVID-19, coronavirus disease 2019; CR5, cytokine storm syndrome; CTLA-4, cytotoxic T lymphocyte associated antigen-4; CXCL-10, CXC chemokine ligand-10; DC, dendritic cell; eIF2α, eukaryotic initiation factor 2 subunit-α; FDA, US Food and Drug Administration; GCSF, granulocyte colony stimulating factor; ICU, intensive care unit; IFN, interferon; Ig, immunoglobulin; IL, interleukin; IL-6R, IL-6 receptor; IP10, interferon gamma-induced protein 10; ISG, interferon stimulated genes; MCP1, monocyte chemoattractant protein 1; MERS-CoV, Middle East Respiratory Syndrome Coronavirus; MHC-I, major histocompatibility complex I; MIP1A, macrophage inflammatory protein 1-alpha; NR, natural killer; NKG2A, natural killer group 2 member A; NLR, nucleotide-binding and oligomerization domain (NOD)-like receptor; NP, internal nucleoprotein; PD-1, programmed death receptor-1; PD-L1, programmed death ligand-1; PHEIC, Public Health Emergency of International Concern; PKP, protein kinase R; PRR, pattern recognition receptor; RS, Reproductive number; RBD, receptor binding domain; RLR, retinoic acid-inducible gene I (RIG-I)-like receptors; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; ssRNA, single-stranded RNA; TCR, T cell receptor; TIGIT, T-cell immunoglobulin and ITIM domain; TLR, Toll-like receptor; TNF-α, tumor necrotic factor-α; WHO, World Health Organization.
INTRODUCTION

The outbreak of coronavirus disease 2019 (COVID-19) that started from the Hubei Province in China in December 2019\(^1\) was declared as a Public Health Emergency of International Concern (PHEIC) by the World Health Organization (WHO) on 30 January 2020,\(^2\) has now attained pandemic status affecting more than 200 countries.\(^3-5\) The infection is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that shares 79.6% sequence identity to severe acute respiratory syndrome coronavirus (SARS-CoV).\(^6\) As of 14 April 2020, based on COVID-19 Global Cases,\(^7\) 1,920,985 confirmed COVID-19 cases and 119,686 deaths have been reported in 185 countries. Several studies have demonstrated that the virus is more transmissible than SARS-CoV, with a mean reproductive number (\(R_0\)) ranging from 1.4 to 3.5,\(^8-10\) which means that one infected person can transmit the virus to up to three susceptible people. This situation prompted the WHO to declare the current COVID-19 outbreak as a global pandemic.\(^11\)

SARS-CoV-2 is a member of the coronavirus (CoV) family, a group of enveloped and positive-sense single-stranded RNA (ssRNA) viruses, with a genome ranging from 26 to 32 kb in size.\(^12\) SARS-CoV-2 belongs to the family Coronaviridae and subfamily Coronavirinae; this subfamily has been subdivided into four genera, Alphacoronavirus, Betacoronavirus, Gammacoronavirus, and Deltacoronavirus, based on serology and phylogenetic analysis.\(^13,14\) SARS-CoV-2 belongs to the genus Betacoronavirus together with SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). The virus consists of a membrane and a nucleocapsid. The membrane comprises three proteins: (a) spike (S) type I glycoprotein, forming peplomers on the virion surface; (b) membrane (M) protein, spanning the membrane three times and containing a short N-terminal ectodomain and cytoplasmic tail; and (c) small membrane protein (E), a highly hydrophobic protein.\(^15\) S protein is trimeric and processed by host cellular proteases to form two functional subunits S1 and S2, which remain non-covalently bound in the prefusion conformation.\(^16\) The S protein plays a major role in membrane fusion and viral entry into host cells through the cellular angiotensin-converting enzyme 2 (ACE2) receptor. Moreover, the receptor-binding domain (RBD) is located in the S1 subunit at the apex of the S protein of SARS-CoV.\(^17,18\)

Although some risk factors, such as age and the presence of comorbidity, have been associated with disease severity and mortality of patients with COVID-19,\(^19\) there is still a lack of understanding of the role of the immune system on disease severity and mortality rate. An initial study suggested clear changes in immune responses during disease progression in a patient with COVID-19.\(^20\) Therefore, dysregulated host-immune responses might be one of the important factors for the pathogenesis and disease severity of COVID-19. This review aims to collate the recent immunological studies from patients with COVID-19, which may give us an insight on (a) the interaction between the host immune system and the virus and (b) disease pathogenesis thereby, helping in developing effective immune-based therapies for SARS-CoV-2 infection.

INNATE IMMUNE RESPONSES AGAINST SARS-COV-2

As SARS-CoV-2 and SARS-CoV are similar,\(^6\) it is suggested that the biochemical interactions are likely to be similar. Like SARS-CoV, SARS-CoV-2 enters the host cells through ACE-2 receptors on type II pneumocytes in the lungs.\(^6,21,22\) After breaching the first line of immune defence, such as mucus and ciliated cells, the pathogen-associated molecular patterns (PAMPs) on the virus alert frontline innate immune cells such as monocytcs, alveolar macrophages, natural killer (NK) cells, and neutrophils to the presence of the invading virus.\(^23\) To mount the appropriate response, these innate immune cells express pattern recognition receptors (PRRs) such as toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) that recognize PAMPs. The interaction between PRR and PAMP induces phagocytosis and activates intracellular signaling pathways to stimulate the synthesis of proinflammatory cytokines, such as type I interferons (IFN-I, i.e., IFNα/β) and type II interferons (IFN-II, i.e., IFN-γ), and chemokines, such as CXCL-10 and CCL-2.\(^12,23,24\) IFN-I inhibit viral replication via multiple mechanisms.\(^25\) Infected cells with reduced major histocompatibility complex I (MHC-I) expression also activate NK cells to produce significant amounts of IFN-γ and induce apoptosis through cytotoxic granules and antibody-dependent cellular cytotoxicity (ADCC).\(^26,27\) In SARS-CoV infection, dendritic cells (DCs) and macrophages are the key players in innate immune responses as they possess the capacity to kill through phagocytosis and IFN release (i.e., plasmacytoid DCs utilize TLR-7 to sense viral nucleic acid leading to IFN-I secretion to lyse the viruses).\(^24\) More importantly, they are capable of presenting viral peptides to bridge to adaptive immune responses.\(^28\)

IFN-I, secreted by infected cells and innate immune cells, such as macrophages and DCs, is a potent cytokine in controlling viral infection and priming adaptive immune responses.\(^29\) IFN-I blocks viral replication by inducing hundreds of interferon stimulated genes (ISGs), including key components of the protein synthesis machinery, protein kinase R (PKR), and 2′-5′-oligoadenylate synthase (OAS)/RNase L.\(^29\) PKR halts general protein synthesis through phosphorylation of eukaryotic initiation factor 2 subunit-α (eIF2α) and OAS/RNase L degrades viral ssRNA, thereby effectively impairing viral replication.\(^25\) The key role played by PKR and OAS/RNase L in the innate immune responses to CoV is emphasized by MERS-CoV expressing protein NS4a to inhibit PKR activation\(^30\) and NS4b to inhibit RNase L activation.\(^31\) Moreover, IFN-I stimulates CD8+ T proliferation, promotes B
cell activation, antibody production, and class switching (ie, IgM to IgG), and activates NK cells and macrophages to clear the viruses.32 The role of IFN in SARS-CoV-2 infection, including other innate immune components and responses, is shown in Figure 1A. Pretreatment of nonlymphatic cells with IFN-α before infection with SARS-CoV induces substantial gene expression for IFN induction, IFN-signaling pathways, and antiviral effector proteins.34 An in vitro study shows that IFN-α can inhibit SARS-CoV as seen by the cytopathic effect, plaque assay, and immunoblot analysis.35 SARS-CoV-2 is sensitive to IFN-I pretreatment.36 In this study, Vero cells pretreated with recombinant IFN-I prior to infection with SARS-CoV-2 showed a significant reduction of SARS-CoV-2 replication—a 3 to 4 log drop in viral titer.36 This suggests that IFN-I has antiviral potential for SARS-CoV-2; therefore, further clinical trials are required to evaluate this potential.

3 | ANTIBODY RESPONSES AGAINST SARS-COV-2 INFECTION

The B cell response of humoral immunity is essential for controlling viral infection and replication of extracellular viruses through antibody

**FIGURE 1** Immune responses and immunotherapy strategy in SARS-CoV-2 infection. Immune response to SARS-CoV-2 involving innate and adaptive immunity. A1, SARS-CoV-2 enters the host cells by binding the receptor for angiotensin converting enzyme 2 (ACE2). The infected cells then release interferon type I (IFN-α/β); innate immune cells respond to the IFNs by establishing an antiviral state. In case of severe infection, the viruses are sensed by monocytes, tissue macrophages, and resident dendritic cells resulting in uncontrolled proinflammatory cytokine (IFN, TNF-α, IL-1β, and IL-6) production, leading to a phenomenon called the cytokine storm, which damages the host’s respiratory epithelial cells. Exhausted natural killer cells with increased expression of the inhibitory receptor, NKG2A, are also seen in SARS-CoV-2. A2, In SARS-CoV-2 infection, increased antibody production and poor T cell responses are observed (A2). CD4+ T cell and CD8+ T cell numbers decrease, and the exhausted phenotype, which is characterized by a higher expression of inhibitory receptors, such programmed death receptor-1 (PD-1) and cytotoxic T lymphocyte associated antigen-4 (CTLA-4), is seen. Immunotherapy strategies for SARS-CoV-2 have been proposed. B1, Transferring convalescent sera with neutralizing antibodies from the recovered patients. The antibodies can directly bind to SARS-CoV-2 and prevent the virus from infecting new cells (neutralization), enhance phagocytosis (opsonization), recruit complement to lyse infected cells or neutralize the viruses, and promote NK cell-mediated killing of infected cells through antibody-dependent cellular cytotoxicity (ADCC). B2, IFN α/β bind to IFN receptors and induce an antiviral response by expressing several interferon-stimulated genes (ISGs), such as PKR, OAS, and Mx. The protein product of ISGs controls viral infection. B3 The IL-6R inhibitor (such as tocilizumab) binds to the membrane-bound IL-6 receptor (mIL-6R) and soluble IL-6 receptor (soluble IL-6R). Binding of tocilizumab to IL-6R inhibits the IL-6 signaling pathway.
production, B cell activation is achieved through the crosslinking of two or more membrane immunoglobulins (Ig) to multiple antigenic molecules (epitopes or antigenic determinants). Moreover, T-cell-mediated immune responses lead to the generation of antibody secreting plasma cells and memory B cells. Antibodies control viral infection through several mechanisms, including neutralization, opsonization, phagocytosis, activation of the classical complement pathway, and ADCC (an NK cell mediated apoptosis), and therefore prevent extracellular viruses from replicating and further infecting healthy cells.

A study has found an increase in the number of antibody-secreting cells (ASCs) during SARS-CoV-2 infection. The median duration of detectable IgA and IgM is approximately 5 days (range from 2 to 6 days) and 14 days for IgG (range from 10 to 18 days) after the onset of symptoms. Although no crossreactivity was observed between SARS-CoV-2 nucleocapsid protein and positive human plasma for coronaviruses NL63, 229E, OC43, and HKU1, there was a strong crossreactivity with SARS-CoV positive plasma. The increased production of viruses NL63, 229E, OC43, and HKU1, there was a strong crossreactivity with SARS-CoV-2 nucleocapsid protein and positive human plasma for coronaviruses NL63, 229E, OC43, and HKU1, there was a strong crossreactivity with SARS-CoV positive plasma. The increased production of IgM and IgG in SARS-CoV-2 infection was detected in blood before the recovery of symptoms and persisted for at least 7 days after the full resolution of symptoms. Analysis of serum samples collected 14 days or longer after the onset of COVID-19 symptoms revealed 94% and 88% seropositivity rate for IgG and IgM, respectively, against the SARS-CoV-2 internal nucleoprotein (NP) antigen. For IgG and IgM against surface spike protein receptor binding domain (RBD), the seropositivity rates were higher, 100% and 94%, respectively. The level of antibodies against NP and RBD correlated with their neutralizing activities. Taken together, humoral responses were clearly activated with diverse isotypes of antibodies during SARS-CoV-2 infection (Figure 1A). An increased IgG response with a higher titer of total immunoglobulins in the patients with severe COVID-19 resulted in worse outcome, which suggests the possible role of antibody-dependent enhancement (ADE) during SARS-CoV-2 infection. However, how effective these antibodies are to neutralize extracellular viruses and to activate phagocytosis, classical complement pathway, and ADCC needs to be evaluated and further studies are warranted. In addition, impaired adaptive immune responses along with uncontrolled inflammatory innate responses were reported to be harmful, leading to local and systemic tissue damage. However, one study found that the level of antibodies detected in patients with COVID-19 is associated with virus neutralization titer, so highlighting the potential use of convalescent plasma of COVID-19 survivors or therapeutic monoclonal antibodies for patients with COVID-19.

4 IMMUNOPATHOLOGY IN SARS-COV-2 INFECTION

4.1 Immune evasion of SARS-CoV-2: Lessons from SARS-CoV

Groups of patients with COVID-19, mostly elderly and those having comorbidities, develop severe clinical manifestations and succumb to death. However, some young healthy adults, 20-40 years of age, have also developed severe clinical manifestations that require their admittance to the intensive care unit (ICU) and a small proportion (0.1% to 0.2%) has been reported to have died. This might suggest that the host immune responses in those groups were unable to control viral replication, leading to severe disease progression. The exact immunological reasons why some patients cannot deal with SARS-CoV-2 remain largely unknown.

During SARS-CoV infection, the virus employs strategies to block IFN production. In this context, the production of IFN-I induced by polyinosinic-polycytidylic acid (poly I:C) or Sendai virus was suppressed by the nucleocapsid (N) protein of the SARS-CoV. The SARS-CoV membrane protein also inhibits the formation of the TRAF3-TANK-TBK1/IKK complex, leading to decreased interferon regulatory factor (IRF)3/IRF7 transcription factor and hence reduces IFN production. The TRAF3-TANK-TBK1/IKK complex is required for the activation of IFN-gene promoters. SARS-CoV infection also downregulates gene expression of cathepsins and proteasomes, proteins required for antigen processing for MHC-I and II pathways, and reduces MHC-I expression in monocytes. SARS-CoV can infect and replicate in DCs, thereby inhibiting the maturation and antigen presentation capacity of DC, leading to impaired T cell activation for effective anti-viral cell-mediated immunity. SARS-CoV infection can induce production of cytokines, such as IL-6 and IL-8, from macrophages and DCs and upregulate CD40 and CD86 expression on DCs; IL-6 and IL-8 induction impaired the ability of DCs and macrophages to activate naïve T cells. Taken together, SARS-CoV blocks critical antiviral pathways and these evading mechanisms may also be utilized by SARS-CoV-2. However, extensive studies are required to elucidate the immune evasion of SARS-CoV-2.

4.2 Functional exhaustion in SARS-CoV-2 infection

Lymphocytes such as T cells (CD4+ and CD8+ T cells) and NK cells are important for viral clearance. T cells, particularly cytotoxic T cells (CD8+ T cells) target infected cells through the interaction of the T cell receptor (TCR) with MHC-I bound viral peptides. MHC-I and TCR ligation enables CD8+ T cells to degranulate cytotoxic factors, such as perforins and granzymes, to induce apoptosis of infected cells, thereby eliminating viral reservoirs. NK cells recognize distilled cells or cells with reduced surface MHC-I expression and control viral replication through the release of IFN-γ and activation of ADCC. Impaired responses of functional CD8+ T cells and NK cells are associated with disease progression.

The COVID-19 patients revealed leucopenia, lymphopenia, and thrombocytopenia on blood examination. Both cellular and humoral immune responses are believed to be responsible for COVID-19 pathogenesis. In addition, T-cell- and B-cell-mediated immunological mechanisms such as B cell activation along with detection and presentation of the antigen are initiated against SARS-CoV-2 to direct lymphocyte and macrophage stimulated responses. The probable...
involvement of helper T cells and cytotoxic T cells needs thorough evaluation. In this context, helper T cells may present virus antigens to B cells for production of antibodies and subsequent neutralization, whereas cytotoxic T cells may directly kill the virus.\textsuperscript{63,68} The SARS-CoV-2 is reported to attack respiratory epithelial cells followed by spread to other cells. Moreover, the virus infects peripheral leukocytes and lymphocytes particularly T cells.\textsuperscript{69} The damage caused by SARS-CoV-2 to lymphocytes including T cells leads to lymphopenia and predisposes the individuals to secondary bacterial infections and increased severity of the disease.\textsuperscript{69} The increase in proinflammatory and decrease in anti-inflammatory cytokines may indicate the T-cell-mediated response against SARS-CoV-2, resulting in cytokine storm associated hyperinflammation and subsequent severe pneumonia in COVID-19.\textsuperscript{57-69} The increased levels of proinflammatory cytokines may result in shock and severe tissue damage in heart, kidney, and liver along with respiratory and multiple organ failure.\textsuperscript{45} The severe and fatal cases of COVID-19 are characterized by lymphopenia and sustained inflammation.\textsuperscript{66}

A recent study has found a significant decrease of total T lymphocytes, CD8\textsuperscript{+} T cells, and NK cells in patients with COVID-19 and this reduction was more prominent among those with severe disease compared with those with a mild one.\textsuperscript{70} Moreover, NK cells become exhausted during SARS-CoV-2 infection, characterized by increased expression of inhibitory receptor, NKG2A (NK group 2 member A),\textsuperscript{70} which induces NK cell exhaustion in chronic viral infection (Figure 1A). In patients with COVID-19, significant decrease of CD107a\textsuperscript{+}NK, IFN-\gamma\textsuperscript{+} NK, IL-2\textsuperscript{+} NK, TNF-\alpha\textsuperscript{+}NK, and granzyme B\textsuperscript{+} NK cells has also been observed, most likely due to the overexpression of NKG2A.\textsuperscript{70} A study confirmed that the number of NK and CD8\textsuperscript{+} T cells was restored when the expression of NKG2A was reduced among COVID-19 survivors after treatment.\textsuperscript{70}

IFN-\gamma from CD4\textsuperscript{+} T cells is required to activate macrophages as potent killers of intracellular pathogens through the Th1 pathway; IFN-\gamma is also required for robust CD8\textsuperscript{+} T cell responses.\textsuperscript{71} TNF-\alpha, secreted by CD4\textsuperscript{+} T cells also has direct antiviral effects, resulting in reduced viral replication.\textsuperscript{72} In patients with SARS-CoV-2, there was a significant reduction of IFN-\gamma\textsuperscript{+}CD4\textsuperscript{+} T cells and TNF-\alpha\textsuperscript{+}CD4\textsuperscript{+} T cells in those with severe disease compared with those with a mild clinical manifestation.\textsuperscript{73} Moreover, the level of coinhibitory receptors, such as programmed death receptor-1 (PD-1), cytotoxic T lymphocyte associated antigen-4 (CTLA-4), and T-cell immunoglobulin and ITIM domain (TIGIT) increased in patients with COVID-19 compared with healthy controls.\textsuperscript{73} Increased expression of PD-1 and CTLA-4 reduces the function of CD4\textsuperscript{+} T cells and CD8\textsuperscript{+} T cells through the ligation of these molecules to inhibitory ligands, such as PD-L1 and CD80, on DCs.\textsuperscript{74} This mechanism might be important to reduce the activation and proliferation of T cells against SARS-CoV-2. T-cell subset analysis from 44 patients with COVID-19 revealed that the levels of helper T cells (CD3\textsuperscript{+}CD4\textsuperscript{+} T cells) and cytotoxic T cells (CD3\textsuperscript{+}CD8\textsuperscript{+} T cells) were below the normal range.\textsuperscript{75} In addition, an analysis of the blood sample from a patient with COVID-19 found increased follicular helper T cells (TFH cells) and activated CD4\textsuperscript{+} T cells and CD8\textsuperscript{+} T cells.\textsuperscript{76} Taken together, the evidence suggests that the number of lymphocytes, such as NK cells and T cells, in patients with COVID-19 decreased and were exhausted with increased expression of inhibitory receptors such as NKG2A, PD-1, and CTLA-4 (Figure 1A). Apart from the increase in the expression of inhibitory receptors, reduction of activation and proliferation capacities of lymphocytes may also be associated with low costimulatory receptor expression (CD28) and reduced growth cytokines, such as IL-2.\textsuperscript{75} The characteristics of impaired lymphocyte responses in SARS-CoV-2 infection, which may contribute to disease progression, are presented in Table 1.

### 4.3 | Cytokine storm

The COVID-19 associated deaths in severe forms were mostly attributed to respiratory failure\textsuperscript{64,68,69} probably caused by lethal pneumonia following hyperinflammation.\textsuperscript{64,68,69} The cytokine storm, dysregulated and uncontrolled release of proinflammatory cytokines, inducing systemic immune responses and inflammation, can lead to severe clinical manifestations, such as sepsis and multiple organ failure.\textsuperscript{76} A cytokine storm has been documented in several viral infections including

### TABLE 1 Summary of lymphocyte response in patients with COVID-19

| Immune component | COVID-19 compared with normal | Severe compared with mild | Ref. |
|------------------|------------------------------|---------------------------|------|
| NKG2A expression on NK cells | Increase | [70] |
| NKG2A\textsuperscript{+} NK cells | Increase | [70] |
| NKG2A\textsuperscript{+} CD8\textsuperscript{+} T cells | Increase | [70] |
| PD-1 | Increase | [73] |
| CTLA-4 | Increase | [73] |
| TIGIT | Increase | [73] |
| Total T lymphocytes | Decrease | Decrease | [70] |
| CD8\textsuperscript{+} T cells | Decrease | Decrease | [70] |
| Total NK cells | Decrease | Decrease | [70] |
| CD107α\textsuperscript{+} NK cells | Decrease | [70] |
| IFN-γ\textsuperscript{+} NK cells | Decrease | [70] |
| IL-2\textsuperscript{+} NK cells | Decrease | [70] |
| TNF-α\textsuperscript{+} NK cells | Decrease | [70] |
| Granzyme B\textsuperscript{+} NK cells | Decrease | [70] |
| IFN-γ\textsuperscript{+}CD4\textsuperscript{+} T cells | Decrease | [73] |
| TNF-α\textsuperscript{+}CD4\textsuperscript{+} T cells | Decrease | [73] |
| Helper T cells (CD3\textsuperscript{+}CD4\textsuperscript{+} T cells) | Decrease | [75] |
| Cytotoxic T cells (CD28\textsuperscript{+}CD8\textsuperscript{+} T cells) | Decrease | [75] |
SARS-CoV. Increased neutrophilic and monocytic inflammatory responses and cytokines, such as IL-1β, are the main characteristics of the cytokine storm. Acute lung injury is a common repercussion of the cytokine storm and is mostly associated with infection in the lungs and other organs.

The clinical signs associated with SARS-CoV-2 infection are fever, dry cough, sneezing, chest pain, and pneumonia along with ground glass opacities and bilaterally consolidated lungs on computed tomography (CT) scan. Moreover, clinical manifestations of COVID-19 include mild-flu-like symptoms in the beginning; a proportion of patients develop dyspnea, acute respiratory distress syndrome (ARDS), and death. These clinical characteristics bear some resemblance to those for SARS-CoV and MERS-CoV. A growing body of evidence suggests that a proportion of patients with severe COVID-19 may have the cytokine storm. Data from a retrospective multicenter study of 68 deaths and 82 discharged cases in Wuhan revealed that the level of IL-6 was significantly increased among patients in the death group compared with the survivor group. Compared with healthy controls, the level of plasma cytokines, such as IL-1β, IL-1α, IL-17, IL-8, IL-9, IL-10, IFN-γ, and TNFα; chemokines, such as macrophage inflammatory protein 1-alpha (MIP1α), MIP1β, and interferon gamma-induced protein 10 (IP10); chemokine ligands, such as monocyte chemotactic protein 1 (MCP1), growth factors and other proteins, such as granulocyte colony stimulating factor (GCSF) were higher in patients with both severe and nonsevere disease than healthy controls. The levels of cytokines, such as TNF-α, IL-2, and IL-7 and chemokines, such as GCSF, IP10, MCP1, and MIP1A were also higher in severe compared with nonsevere COVID-19. Release of higher amounts of proinflammatory cytokines, such as IL-1β and TNF-α, have a detrimental effect on the host cells as these molecules can induce a high influx of new immune cells to the site of infection and mount an excessive response, leading to severe tissue damage through the release of toxic granules. The advancement in lung damage due to hyperinflammation results into hypoxemia and, to compensate, shortness of breath along with cardiac arrest may take place leading to death. Therefore, immediate clinical care after the onset of clinical signs is crucial to prevent further COVID-19 associated pathology. In addition, histological examination performed on biopsy tissues from lung revealed desquamation of pneumocytes, diffuse alveolar damage, and presence of cellular fibromyxoid exudate along with formation of the hyaline membrane. Altogether, evidence indicates that the intensity of the cytokine storm in patients with COVID-19 increases with disease severity. Therefore, a strategy to inhibit the cytokine storm (i.e., to control the immune response in patients with COVID-19) is a promising immunotherapeutic approach for SARS-CoV-2 infection.

5 | IMMUNOTHERAPEUTIC STRATEGIES FOR SARS-COV-2 INFECTION

Disease outcome of viral infection is determined by the balance between the virulence of the virus and the host immune response against the infection. Although the host proinflammatory response is required for viral clearance in the early stages of infection, an excessive proinflammatory response at late stages of infection can exacerbate clinical manifestations. Immunotherapy strategies that involve promoting viral clearance or reducing hyperinflammatory responses could potentially be used to treat patients with COVID-19. Most of the efforts for developing therapeutics against coronavirus were targeted against the S protein which is the major inducer of neutralizing antibodies. Use of immunotherapies, such as passive antibody, IFN-1, and IL-6 receptor (IL-6R) inhibitor, that have been applied to treat SARS-CoV and MERS-CoV, either alone or in combination with other drugs are potentially being considered to treat patients with COVID-19 (Figure 1B). The immunotherapies attempted against SARS-CoV-2 include plasma therapy (polyclonal antibody), hormones for T cells maturation, neutralizing antibodies, ACE2 immunoadhesins, and monoclonal antibodies against IL-6. Moreover, other interventions like viral-vectors, inactivated whole virus, nanoparticles and DNA as vaccines along with monoclonal antibody were reported to be used for SARS-CoV and may prove promising against the SARS-CoV-2.

5.1 | Passive antibody therapy

Passive antibody therapy involves the administration of antibodies from recovered patients to new patients who suffer from the same infection. Historically, the use of passive antibody therapy to treat patients during the 1918 flu pandemic, Ebola hemorrhagic fever, influenza A (H5N1) infection, and SARS has been demonstrated to be a successful intervention strategy. The first report of successful passive antibody therapy (in combination with ribavirin and methylprednisolone) for coronavirus was published in March 2003 during the outbreak of SARS in Hong Kong. Later, a larger study involving 80 patients was done to test the efficacy of convalescent plasma of patients with SARS. The study highlighted that earlier administration of convalescent plasma (before day 14) was more effective and more likely to give a good outcome than administration after day 14, consistent with the concept of viremia peaks in the first week of infection. During the current COVID-19 outbreak in China, administration of convalescent plasma has reported a reduction in viral load and morbidity of patients. The mechanism of how passive antibody therapy works is given in brief in Figure 1.

According to the latest data, approximately 20% of patients have recovered from COVID-19 worldwide (COVID-19 Global Cases). Neutralizing antibodies can be prepared from pooled convalescent plasma or monoclonal antibodies can be developed by immortalizing B-cell repertoires of convalescent plasma. To increase efficacy, several factors, including the timing of plasma administration, antibody titer of the administered plasma, and screening of convalescent plasma for blood borne pathogens, need to be considered. To provide a timely response to the COVID-19 pandemic, the US Food and Drug Administration (FDA) has approved convalescent sera to be delivered to patients seriously ill with COVID-19.
patients with SARS who received IFN alfacon-1 with ribavirin restricts SARS-CoV and MERS-CoV replication in cell culture. High-dose IFN-α directly, by inhibiting viral replication, and indirectly, by stimulating the adaptive immune system. IFN- α and IFN-β form one of the first lines of host defence against invading viruses. Strong antiviral activities of IFN-α and IFN-β support the use of IFNs as antiviral therapy. High-dose IFN-α or IFN-β monotherapy or in combination with ribavirin restricts SARS-CoV and MERS-CoV replication in cell cultures. Patients with SARS who received IFN alfacon-1 with corticosteroids were reported to exhibit better disease outcome than those who received corticosteroids alone. Similarly, early combination therapy of pegylated IFN-α2a and ribavirin was reported to improve survival in patients with MERS-CoV. Although the treatment group exhibited anemia, no other adverse effect was present. Given the inhibitory effects of IFN on MERS-CoV and SARS-CoV, IFN therapy in SARS-CoV-2 has the potential to be used for treatment of patients with COVID-19. Currently, several clinical trials involving IFNs either as monotherapy or in combination are currently under way to evaluate the efficacy and safety of IFN in treating patients with COVID-19. Interestingly, standard care of patients with chronic viral infections has minimized the use of IFNs due to emerging evidence of IFN-associated immunopathology. Although IFN may be useful as adjunctive treatment, it can also exacerbate the clinical condition of critically ill patients, and therefore more results from controlled clinical trials are required before IFN can be used to treat COVID-19.

### 5.3 IL-6R inhibitor

Emerging evidence shows that patients with COVID-19 exhibit the cytokine storm syndrome, characterized by the release of a high level of proinflammatory cytokines, including a marked elevation of IL-6. The increased level of IL-6 was reported to be a reliable indicator of poor outcome in COVID-19 patients with severe forms of the disease. A high level of inflammatory cytokines is associated with pulmonary inflammation and severe lung damage. Treatment of hyperinflammation using existing, approved therapies that are readily available would benefit patients with severe COVID-19. Blocking the IL-6 receptor, using the relatively safe tocilizumab, has shown therapeutic benefit against inflammatory disease and rheumatoid arthritis. Tocilizumab, a humanized monoclonal antibody, competitively binds both membrane-bound and soluble IL-6 receptors, thus preventing IL-6 from binding to its receptor (Figure 1). Inhibition of the IL-6 signaling cascade leads to a decrease in circulating immune cells. Moreover, a clinical trial (ChiCTR2000029765) using tocilizumab was reported to be effective in quick control of fever along with improvement in respiratory function in patients with severe form of COVID-19. A number of clinical trials are currently being conducted to evaluate the safety and efficacy of tocilizumab for patients with COVID-19. A retrospective study reported that the use of tocilizumab effectively improved clinical symptoms and inhibited disease progression in patients with severe COVID-19, in China. The targeting of IL-6 and its receptor by tocilizumab and siltuximab could mitigate the cytokine storm-related clinical symptoms in severe form of COVID-19. However, IL-6 antagonism may weaken the immune system of the patient; severely ill patients have been found to be coinfected with bacteria and fungi and the risk of patients becoming more susceptible to secondary bacterial infection may outweigh the benefits of the treatment. Furthermore, the optimal timing of tocilizumab administration has not yet been determined. Although IL-6R inhibitors have been used to treat COVID-19 during the current pandemic, the results from ongoing controlled clinical trials are critical for further evaluation of this treatment.

### 6 CONCLUSION

The current COVID-19 pandemic continues to be a significant threat to global health. During SARS-CoV infection, lymphocytes become exhausted, which is characterized by the increased expression of inhibitory receptors such as PD-1, CTLA-4, and TIGIT on T cells and NKG2A on NK cells, resulting in the inhibition of their antiviral activities. Although the production of antibodies in patients with COVID-19 is evident, the effectiveness of these antibodies in controlling viral replication remains to be elucidated. Uncontrolled release of proinflammatory cytokines may explain the severe clinical manifestation in some patients as it induces unnecessary influx of immune cells to the infection site, enabling these cells to release toxic granules, which are harmful to the lung cells. Therefore, strategies involving use of agents, such as the IL-6R blocker, to control the hyperinflammatory response could be used as a potential approach to treat patients with COVID-19. In addition, strategies to enhance viral clearance, such as the use of passive antibodies and IFN-1 therapy, could have been promising in treating patients with severe COVID-19.

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CONFLICT OF INTEREST
The authors declare no competing interests.

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