



REVIEW

The deciphering of the immune cells and marker signature in COVID-19 pathogenesis: An update

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Abstract

The precise interaction between the immune system and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is critical in deciphering the pathogenesis of coronavirus disease 2019 (COVID-19) and is also vital for developing novel therapeutic tools, including monoclonal antibodies, antiviral drugs, and vaccines. Viral infections need innate and adaptive immune reactions since the various immune components, such as neutrophils, macrophages, CD4⁺ T, CD8⁺ T, and B lymphocytes, play different roles in various infections. Consequently, the characterization of innate and adaptive immune reactions toward SARS-CoV-2 is crucial for defining the pathogenicity of COVID-19. In this study, we explain what is currently understood concerning the conventional immune reactions to SARS-CoV-2 infection to shed light on the protective and pathogenic role of immune response in this case. Also, in particular, we investigate the in-depth roles of other immune mediators, including neutrophil elastase, serum amyloid A, and syndecan, in the immunopathogenesis of COVID-19.

KEYWORDS

adaptive immunity, COVID-19, innate immunity, neutrophil elastase, pathogenesis, syndecan

1 | INTRODUCTION

As the 2019 coronavirus disease (COVID-19) etiologic agent, the novel emerging coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), its gaps in deciphering the pathogenesis are just completing.¹⁻⁶ Early and moderate COVID-19 stays in the upper respiratory tract, eliciting a minimal innate immune response.⁷ Immune cells and molecules, including neutralizing antibodies (NAbs), are present in sufficient numbers in recovered individuals at this stage to assist in combat infection, and this is evidenced by their effective elimination of the virus.^{8,9}

The function of cellular immunity in a protective immune response to COVID-19 is becoming evident. Recent research has shown that SARS-CoV-2 elicits a strong and highly potent T-cell-mediated immunity (even in antibody-seronegative individuals), which provides long-term immunity.^{10,11} Many factors involved in immunity toward SARS-CoV-2 have been discovered, varying from innate to adaptive immunity.^{12,13} More T-cell activation is associated with less disease and mortality, according to research.¹⁴ Rehabilitation following COVID-19 requires a robust Th1 response, even though non-Th1 mediators have been associated with respiratory failure.^{15,16} Several studies have demonstrated the effectiveness of the antibody response, notably the immunoglobulin G (IgG) reaction in predicting patient survival.^{15,16} Furthermore, a synchronized T- and B-cell reaction, particularly anti-spike (S) IgG in combination with interleukin-2 (IL-2)/interferon- γ (IFN- γ) producing activated CD4⁺ and CD8⁺ T cells, is involved in viral elimination.^{17,18} Although an ordered adaptive immunity is required for mild illness, the significance of innate cytokines in establishing a significant T-cell reaction in COVID-19 remains unclear.¹⁹

Further information and insight into pathophysiological mechanisms underlying SARS-CoV-2 disease and COVID-19 development are starting to emerge, emphasizing the essential importance of immunological hyper-response, defined by widely spread endothelial dysfunction, systemic microangiopathy, and complement-induced blood coagulation in illness aggravation.²⁰ As previously discussed, the host's substantial proinflammatory reaction may promote endothelial dysfunction in COVID-19, notably through the activity of IL-6 as well as the concentration of tumor necrosis factor- α (TNF- α), which are significantly elevated in severe forms of the disease.^{20,21} Besides, COVID-19 appears to be more than simply a respiratory illness; it may be the result of a systemic malfunction brought on by a bradykinin storm that begins in the lungs.^{22,23} In this review, we summarize what is known about the innate and adaptive immunity to SARS-CoV-2, as well as the function of additional immunological mediators in COVID-19, such as neutrophil elastase (NE), serum amyloid A (SAA), and syndecan (SDC).

2 | COVID-19 IMMUNOPATHOGENESIS

The precise mechanism of the pathogenicity of COVID-19 is not entirely understood; however, many findings show that it is similar to another coronavirus, SARS-CoV-1.²⁴ The mode of transmission from

person to person has a significant impact on pathophysiology (Figure 1).^{25,26} A receptor for SARS-CoV-2 entrance is angiotensin-converting enzyme 2 (ACE2), whereas an activator for virus entry is proteases, and SARS-CoV-2 can also bind via CD147, making it easier for the virus to spread.²⁷⁻²⁹

The essential protease in activating SARS-CoV-2 is transmembrane serine protease 2/CD147.²⁴ In addition to ACE2, pattern recognition receptors (PRRs) play a role in the pathophysiology of virus-mediated immunopathology as well.²⁴ PRRs contribute to identifying pathogens, such as viruses.³⁰ Upon direct interaction with the viral receptors on the surface proteins, viruses trigger a variety of host immunity reactions, including the induction and enhancement of inflammatory mediators, the development and increased activity of dendritic cells (DCs), and the elevated expression of IFNs to block virus dissemination and replication.³⁰

An increasing body of research has improved our knowledge of how dysfunctional immune cells contribute to the inflammatory response in COVID-19 patients. Some groups have used RNA-sequencing (RNA-seq) as a method for investigating the functionality of various immune reactions. Yao et al.³¹ investigated the transcriptome of healthy and COVID-19 patient peripheral blood mononuclear cells (PBMCs) using RNA-seq. Although most immune cell compartments exhibited the predicted hyperinflammatory response in very unwell patients, they discovered that numerous essential pathways were malfunctioning, which may have contributed to their inability to manage the viral infection. In fact, PBMCs from the severe group exhibited a transcriptomic signal indicating deficits in virus-clearing processes, including cytotoxic killing in natural killer (NK) and CD8 T cells, B-cell activation, and reduced antigen presentation by monocytes.³¹

SARS-CoV-2 elicited various immune reactions in infected individuals.²⁴ Upon being activated by the virus, CD4⁺ T cells generate some mediators and cytokines that stimulate the production of B cells as well as cytotoxic T lymphocytes.²⁴ Activated B cells subsequently generate antibodies (IgG and immunoglobulin M (IgM)) specific to the virus.²⁴ The cytotoxicity is mediated by activated CD8⁺ T lymphocytes, engulfing and destroying the virus-infected cells. It is crucial to highlight that, even though the existence of complement factors (C3a and C5a) and antibodies are required to combat viral attacks, SARS-CoV-2 can evade host immunity by T-cell function via the induction of apoptosis in T cells.³² Serological examinations of rescued symptomatic individuals have shown elevated levels of virus-specific nAbs and enhanced synthesis of antibodies secreting B cells by the immune system.^{9,24} Moreover, several clinical investigations have demonstrated that recovered patients had a rise in T cells such as CD8⁺ and CD4⁺ cells and T follicular helper (TFH) cells.^{33,34} However, emerging reports have revealed that an excessive and disrupted immune reaction in severe COVID-19 patients with higher inflammatory mediators is assumed to be a starting point for pathophysiology and results in severe abnormalities and pulmonary worsening.³⁵

According to increasing data, COVID-19 pneumonia may be caused by the T helper type 17 (Th17) inflammatory response.

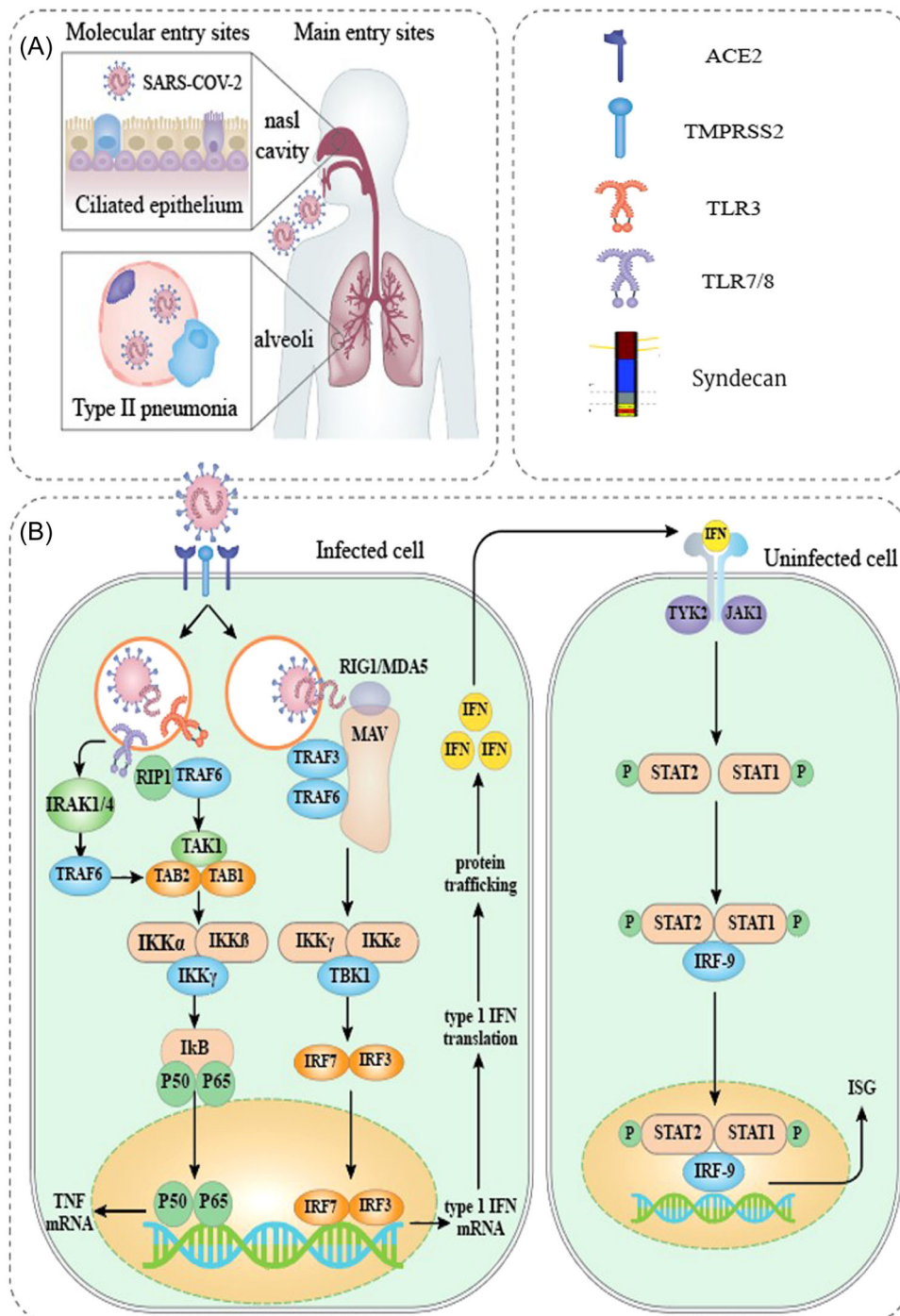


FIGURE 1 . The schematic representation of SARS-CoV-2 pathophysiology. (A) SARS-CoV-2 enters the body primarily through cells in the nasal cavity and the upper and lower respiratory tracts. (B) Several PRRs that identify foreign RNA, such as endosomal TLR3 and TLR7, and cytoplasmic RIG-I and MDA5, are thought to be involved in recognizing SARS-CoV-2. Results from genetic research, functional and clinical findings, interaction modeling, and CRISPR screens are used to estimate downstream signaling occurrences. Direct communication among viral or host proteins and interplay among SARS-CoV-2-derived proteins and cellular mechanisms as defined by interaction mapping derived information. ORF3b was found to be functionally active in the suppression of type I IFN, but no specific target was recognized.¹² CRISPR, clustered regularly interspaced short palindromic repeat; IFN, interferon; MDA5, melanoma differentiation-associated protein 5; ORF, open reading frame; PRR, pattern recognition receptor; TLR, Toll-like receptor; RIG-I, retinoic acid-inducible gene I; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

The release of cytokines such as IL-17 and granulocyte-macrophage colony-stimulating factor (GM-CSF), stimulation of neutrophil migration, and a decrease in the regulatory T-cell (Treg) response all contribute to the immune response's exaggeration. Treg cells, unlike

Th17 cells, produce anti-inflammatory mediators (IL-4, IL-10, and transforming growth factor- β [TGF- β]) and play a critical role in reducing hyperactive immune responses.³⁶ Patients with severe COVID-19 have a lower Treg/Th17 cell ratio, indicating that

proinflammatory responses are not adequately controlled.³⁷ COVID-19 patients may have a disproportionately high proportion of Tregs, rather than Th17 cells, in their immune system, which may contribute to the unregulated release of cytokines and chemokines, resulting in tissue damage.³⁶ Th17 cells in bronchoalveolar lavage fluid (BALF) from individuals with COVID-19 were shown to be more prevalent than in healthy subjects in several investigations.^{37,38}

Acute and chronic pulmonary repercussions in SARS-CoV-2 infected patients, including pneumonia, acute respiratory distress syndrome (ARDS), and lung fibrosis, continue to be key concerns despite rapid advancements in early detection, illness treatment, and vaccine development. In this regard, Wang et al.³⁹ studied the circulating soluble factors and single-cell RNA seq (scRNA-seq) of PBMCs in individuals with severe COVID-19. In pulmonary fibrosis-high patients, the expression of genes enriched in IFN signaling, innate immune response, and adaptive immune response were lower in T cells, NK cells, and monocytes than in pulmonary fibrosis-low patients. In conclusion, their findings suggested that reduced IFN-responsive genes and their associated signaling pathways may be crucial for the advancement of pulmonary fibrosis in COVID-19 patients. A multiomic single-cell immune profiling was carried out by Wilk et al.⁴⁰ in COVID-19 patients with varying degrees of disease severity, ranging from mild outpatient cases to fatal ones. They discovered the significant failure of innate immunity, including strong hyperactivation signals in neutrophils and NK cells, in severe and lethal COVID-19. They also discovered alterations in chromatin accessibility at nuclear factor- κ B (NF- κ B) binding sites within cytokine gene loci as a potential reason for the dramatic absence of proinflammatory cytokine production reported in monocytes with severe and fatal COVID-19. Wilk et al.⁴⁰ found further that emergency myelopoiesis is a key characteristic of COVID-19. These new findings show immunological phenotypes linked with disease severity in COVID-19 and suggest pathogenesis-related pathways that are possible treatment targets. Readers refer to other comprehensive reviews for more details on COVID-19 immunopathogenesis.^{37,41,42}

3 | IMMUNE REACTIONS AND COVID-19

Several molecular mechanisms have been described to better explain the complicated molecular mechanisms underlying the cytokine storm reaction in COVID-19 cases.⁴³ Since it promotes lymphopenia and lymphocyte malfunction, understanding the cytokine storm mechanism would be critical, and defects in cytotoxicity of NK cells from the innate immunity and cytolytic T cells from the adaptive immunity are cited as reasons for the cytokine storm's progression.^{44,45} Nevertheless, this dysfunctional state, whether hereditary or acquired, prevents cytolytic cells from inducing apoptosis in infected and activated antigen-presenting cells (APCs). Many proinflammatory mediators are produced as a result of the prolonged and excessive interplay among innate and adaptive immunity, and the analysis revealed that the amounts of immune cells, including NK, B,

CD4⁺ T, and CD8⁺ T cells are significantly altered in COVID-19 cases.⁴⁴ However, little is known about the immunological response in asymptomatic and re-detectable-positive individuals. PBMC samples from individuals with various COVID-19 presentations were examined by Vigón et al.⁴⁶ for some characteristics associated with the cellular immune response. They discovered that the severely cytotoxic CD8⁺ T-cell subset was present in low levels in individuals with serious COVID-19. In contrast, high Treg levels, low plasma IL-2 levels, and poor Th1 differentiation were associated with a significantly lower CD4 count. In this section, we look at how far we have come in decoding the immune reactions to COVID-19 (Figure 2).

3.1 | Innate immunity and COVID-19 pathogenesis

Effective immunity to pathogenic organisms prompts the initial stimulation of innate immune responses, as well as the maintenance of specific adaptive immune reactions, which significantly contribute to infection clearance and prevention of reinfection by the same infectious agent.⁴⁷⁻⁴⁹ When tissue-resident cells identify SARS-CoV-2, local immunological responses occur, resulting in the recruitment of several innate mediators from the bloodstream circulation.^{1,47}

SARS-CoV-2 can escape innate immunity identification, signaling, IFN production, and IFN-stimulated genes (ISGs) by expressing a plethora of viral proteins that disrupt these processes.⁵⁰ As a result, SARS-CoV-2-infected patients have lower rates of IFN-I or IFN-III in their lungs or peripheral blood compared to other respiratory pathogens.^{51,52} The generation of IFN-1 and IFN-III and ISGs in the upper airways is linked with lower disease severity, while the production of IFN-II and type I IFNs (but not ISGs) is associated with the severity of COVID-19.⁵³ COVID-19 would be life-threatening in those who have genetic abnormalities or auto-antibodies that impair IFN systems, as detailed below. Persistent IFN secretion is linked with poorer clinical outcomes in advanced stages, probably via the production of chemokines that attract inflammatory cellular infiltrates.⁵⁴⁻⁵⁶ Furthermore, COVID-19 is concomitant with a considerable decrease in the number of immunological sensor cells in the blood and lungs, both plasmacytoid DCs (pDCs) and conventional DCs (cDCs).⁵⁴ In this part, we describe the most recent research on innate immune cells and COVID-19 (Table 1).

3.1.1 | Macrophages

Among the principal determinants of innate immunity in reaction to COVID-19, macrophage activity is responsible for both inflammatory reactions and a benefit for the pathophysiology of COVID-19 in patients.⁷⁶ These macrophages can inhibit initial viral replication by triggering IFN-I activity and the inflammatory reaction that recruits further numbers of leukocytes.⁷⁷ Even though cytokine storms are necessary to activate the immune reactions toward SARS-CoV-2,

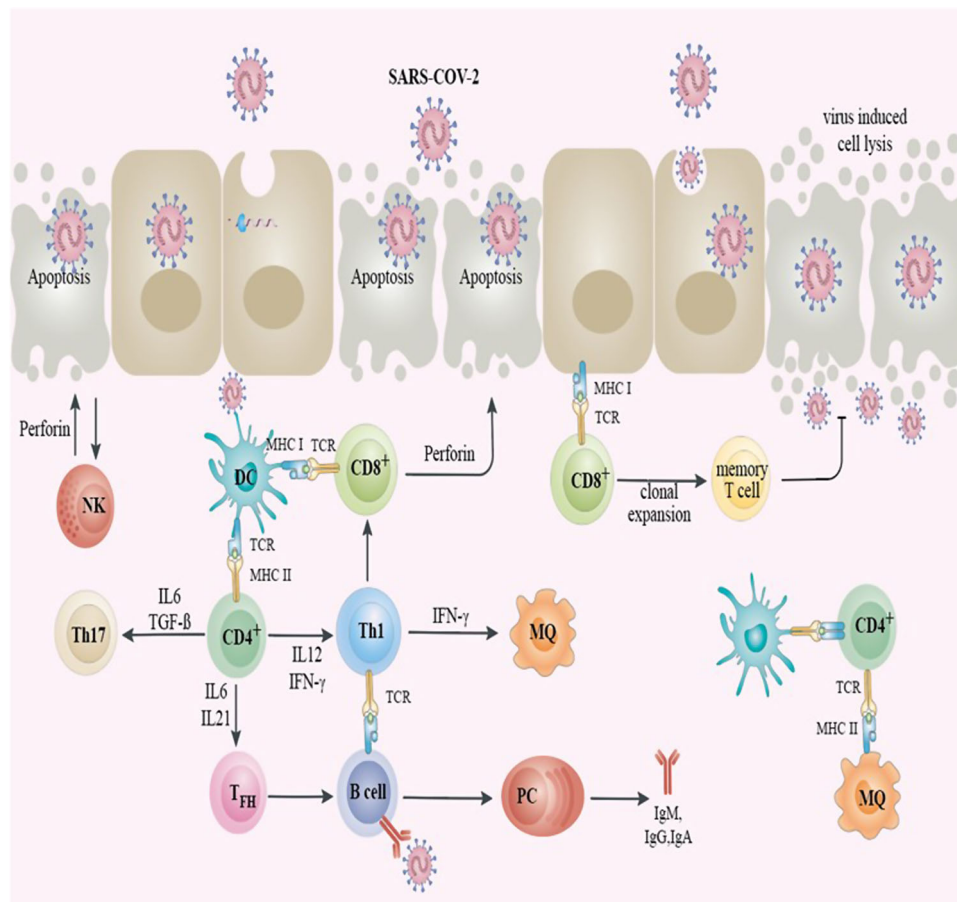


FIGURE 2 The schematic representation of the immune reaction against SARS-CoV-2. When SARS-CoV-2 infects the epithelium, cells may undergo lysis and significant injury to the epithelial cell during virus replication. The viral antigens were presented to $CD8^+$ T cells by the epithelial cell. $CD8^+$ T cells and NK cells could cytolyze the endothelial cells infected by SARS-CoV-2 with their perforin and granzymes, causing programmed cell death (apoptosis). DC in subepithelial recognize SARS-CoV-2 antigens and then the processed antigens presented to the T $CD4^+$, causing these T cells to differentiate toward memory Th1, Th17, and memory TFH. TFH supports the development of B cells into PC and the development of specific antibodies against SARS-CoV-2 (IgA, IgM, and IgG). Moreover, SARS-CoV-2 antigens were presented to the T $CD4^+$ cells by DCs and tissue MΦ.³³ DC, dendritic cell; Ig, immunoglobulin; MΦ, macrophage; NK, natural killer; PC, plasma cells; TFH, T follicular helper cells; Th, helper T cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

excessive inflammation leads to COVID-19-associated mortality.^{18,78} Macrophages in the lung include interstitial macrophages, which are found in the interstitial space, as well as alveolar macrophages (AMs), which are found in the alveolar space. They could be critical for limiting inflammatory responses in reactions to corona infection.⁷⁹ AMs have antiviral and proinflammatory functions, according to these observations while nerve- and airway-associated macrophages (NAMs) eliminate unnecessary and detrimental inflammatory reactions. Notably, NAMs decrease IL-6 secretion during influenza, suggesting that NAMs are a significant control in regulating IL-6 concentrations and, as a result, can govern the COVID-19 cytokine storm.⁸⁰ According to these findings, different macrophage communities were recognized in the lung of COVID-19 individuals. Even though these researchers did not examine NAMs, they did find a richness of anti-inflammatory macrophages in cases with moderate illness, while high numbers of inflammatory AM communities predominated in COVID-19 severe cases.⁸¹ These results suggest

that polarization of macrophages and the relative percentage of their subgroups are essential determinants in COVID-19 pathogenesis.

Because SARS-CoV-2 can infect macrophages, this suggests that the virus actively tries to manipulate macrophages to escape immune response.⁷⁶ However, it is not clear how SARS-CoV-2 infection affects macrophage activity; other coronaviruses have been shown to influence macrophage activity.⁸² The Middle East respiratory syndrome coronavirus may be interfering with major histocompatibility complex II (MHCII)'s presentation because MHC I, CD80, and CD86 are all strongly expressed in infected macrophages, but not MHC II.^{83,84} In monocytes and B cells of COVID-19 patients, MHC II was shown to be reduced.⁸⁵ Aside from that, human leukocyte antigen-DR isotype (HLA-DR) expressed on monocyte is significantly reduced in patients with severe COVID-19, whereas its expression could be partly reversed by an IL-6 antagonist.⁸⁶ MHC II downregulation is not fully recognized, although it is thought to be caused by alterations in the epigenetic landscape of infected cells,

TABLE 1 Overview of innate immune reactions to SARS-CoV-2

Innate immune response	Reaction	Outcome	References
Macrophage	<p>After SARS-CoV-2 infection, the renal, splenic, and alveolar macrophages are stimulated and then heightened the formation of proinflammatory cytokines such as IL-6, IL-10, and TNF-α.</p> <p>In sum, the accumulating evidence indicated that in severe cases with COVID-19, alveolar macrophages are likely to generate chemokines that select further neutrophils and monocytes to the lung, which contribute to the excessive formation of proinflammatory agents.</p>	Induction of highly inflammatory response and potent chemokines, ARDS	47,57-58
Neutrophil	<p>Neutrophils serve as hyperinflammation operators using increased cell degranulation and cytokine production in patients with COVID-19.</p> <p>Notably, investigations explained that the exhibition of neutrophils from healthy subjects to cases infected with SARS-CoV-2 sera supports the NET activity, suggesting that NETs might act as a possible target in severe cases with COVID-19.</p>	Tissue injury due to potent inflammatory reactions	59-61
NK cell	<p>The rate of CD56dimCD16⁺KIR⁺ NK cells was significantly decreased in the blood sample of COVID-19 patients, implying either disrupted maturation or expanded recruitment of NK toward tissues infected with SARS-CoV-2.</p> <p>The recent finding demonstrated that COVID-19 could modulate the cytotoxic activity of NK cells by provoking the upregulation of the NKG2A.</p> <p>The impaired cytotoxic activity and decreased number of NK cells in circulation were noticed in severe cases with COVID-19, in mild patients, and in dead versus survivor cases, proposing that the functional impairment of NK cells activity points to enhanced cell activation innate immunity with an extensive production of proinflammatory cytokine.</p>	The induction of massive production of proinflammatory cytokine due to increased activation of innate immunity cells	47,62-64
MDSC	<p>Current reports have indicated a dysregulation in the myeloid cells in COVID-19 severe cases, with heightened levels and activity of MDSC relating to disease severity.</p> <p>The enhanced ratio of MDSC to T CD8⁺ effector cells (memory) was found in severe COVID-19 cases with ARDS compared to moderate pneumonia cases with COVID-19; this finding showed that MDSC related to COVID-19 augmentation is directly associated with lymphopenia and heightened arginase activity.</p> <p>The accumulating data proposed that G-MDSCs and other myeloid cells signify unlimited negative feedback, eventually establishing pan-immunosuppression and following dysregulation in adaptive immune responses.</p>	Modulating immunity against SARS-CoV-2 (immunosuppressive properties) increases cytokine levels and other proinflammatory markers	65-69
Eosinophil	<p>Comprehensive examination showed that COVID-19 severity is correlated with intensified eosinophil-mediated pulmonary inflammation.</p> <p>The recent finding showed that SARS-CoV-2 infection distinct innate immune responses, including inflammatory conditions related to eosinophil and following Th2 reactions, contributing to severe pneumonia associated with COVID-19.</p>	Pulmonary inflammation	57,70-72
DCs	The investigation revealed that isolated pDCs are stimulated through diversification into P1 and P2, as well as P3 subpopulations.	Impaired IFN- α production	73-75

(Continues)

TABLE 1 (Continued)

Innate immune response	Reaction	Outcome	References
	It has been shown that BALFs from severe and critical COVID-19 cases comprise fewer pDCs than moderate cases. The pDCs stimulated in COVID-19 generate high concentrations of IFNs by the TLR-7 pathway.		

Abbreviations: ARDS, acute respiratory distress syndrome; BALF, bronchoalveolar lavage fluid; COVID-19, coronavirus disease 2019; DC, dendritic cell; IFN, interferon; IL, interleukin; G-MDSC, granulocyte-myeloid-derived suppressor cell; NET, neutrophil extracellular trap; NK, natural killer; NKG2A, NK group 2 member A; pDCs, plasmacytoid dendritic cells; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLR, Toll-like receptor 8; TNF- α , tumor necrosis factor- α .

partially responsible for this phenomenon.⁸⁷ The epigenetic event can decrease the expression of MHC II, which is a process conserved by other coronaviruses, such as the human coronavirus-EMC, which reprograms MHC II epigenetically.⁸⁸ Nevertheless, epigenetic reprogramming of antigen presentation is not typical; for instance, since SARS-CoV limits antigen presentation on MHC II, it is not a characteristic of this virus.⁸⁸

The recently discovered interaction of SARS-CoV-2 with the host provides some insights into how this virus interacts with the function of macrophages.⁸⁹ Specifically, nonstructural protein 5 (Nsp 5), a protein belonging to SARS-CoV-2, can interface with the histone deacetylase 2 (HDAC2) and can control MHC II generation and cytokine secretion.^{89–91} Since it is not determined whether SARS-CoV-2 suppresses or promotes HDAC2 function, this interplay suggests that the virus may directly influence the cytokine storm as well as antigen presentation. SARS-CoV-2 genes, namely, Nsp13 and open-reading frame 8 (ORF8), communicate with various parts of the Golgi trafficking network, which can be used to prevent MHC from exporting into the cell. According to current work, ORF8 bind to MHC I in the endoplasmic reticulum and direct it to autolysosomes, where it can degrade.⁹² To restrict the presentation of antigen via MHC I, viruses often redirect MHC transport to the Golgi, as the human immunodeficiency virus (HIV) Nef protein does.^{93,94} Nsp10 also interacts with Adaptor protein complex 2, which has a central role in regulating MHC II transportation to antigen-processing compartments.^{89,95,96}

3.1.2 | Neutrophils

Neutrophils are the main cells to be drawn to the inflamed tissue following the activation by chemotactic factors produced by infected cells, and they seem to play a substantial role in generating ARDS as well as acute lung injury, and as the disease progresses, the activation and recruitment of neutrophils is a common symptom.^{97–99} In this regard, the relationship between neutrophil infiltration and pathogenic events in COVID-19 has been noted.¹⁰⁰ Besides, the high number of peripheral neutrophils has been reported that can be considered a predictor of poor outcomes in COVID-19 patients with ARDS. As a result, the research found that individuals with more severe symptoms

had greater peripheral neutrophil count.^{101,102} Neutrophil chemoattractant chemokine (C-X-C motif) ligands 2 and 8 (CXCL 2 and 8) in COVID-19 patients' BALF and PBMCs can support the link between enhanced neutrophil recruitment and COVID-19 patients' disease severity.¹⁰³ Another important metric for predicting COVID pathogenesis is the neutrophil-to-lymphocyte ratio.¹⁰¹

Neutrophil pathology in COVID-19 patients may be caused by more than only infiltration.¹⁰⁴ As a result of neutrophil activation proteases, neutrophil extracellular traps (NETs), and reactive oxygen species (ROS) are potentially pathogenic substances.¹⁰⁴ Infection with SARS-CoV-2 generates redox imbalance and ROS, which leads to thrombosis, tissue damage, and red blood cell imbalance, all of which contribute to the severity of COVID-19.^{105,106} NETs generated by neutrophils are implicated in organ damage and death in COVID-19 cases.^{59,107} Finally, a cytokine storm can be caused by NETs.¹⁰⁷ Strategies that decrease NET synthesis or encourage fragmentation are proposed to treat COVID-19. Clinical studies have used inhibitors of NE, peptidyl arginine deiminase type 4, and gasdermin D to treat COVID-19.^{107,108} Taken together, targeting proinflammatory cytokines and neutrophil-produced compounds may be a viable way to treat COVID-19.

3.1.3 | NK cells

Both perforin-mediated and Ab cell-mediated cytotoxicity are necessary for the NK cell to detect and kill virus-infected cells to control viral infections.¹⁰⁹ NK cells, plus destroying, have immunoregulatory capabilities, as they may reduce the inflammatory response induced by a viral infection, limiting host injury and disease development.¹¹⁰ A considerable reduction in the proportion of CD56^{dim}CD16⁺KIR⁺ NK cells has been reported in whole blood samples from cases who were infected with SARS-CoV-2, indicating either delayed development or increased recruiting and selection of circulatory NK cells towards damaged tissue, respectively.^{62,63} Besides, NK group 2 member A (NKG2A), an inhibitory receptor, was shown to be upregulated by SARS-CoV-2, which has been linked to NK-mediated cytotoxicity.¹¹¹

Similarly, the NKG2A receptor is upregulated in NK cells of infected individuals with SARS-CoV-2 than in healthy controls,

although the production of stimulatory markers, namely, IFN- γ , IL-2, CD107a, and TNF- α , decreased.⁴⁷ The adverse impact of SARS-CoV-2 on the activation condition of NK cells and cytolytic capability is also associated with the upregulation of lymphocyte-activation gene 3 and T-cell immunoglobulin and mucin protein 3, which are found in NK cells.^{52,102} NKG2A and NK cell numbers were restored in COVID-19 individuals after they recovered from their diseases.^{55,111} A significant correlation exists between the rise in IL-6 levels in individuals who died from SARS-CoV-2 infection as well as decreased NK cell counts and decreased anti-inflammatory function in the most severe instances and in those who died versus those who survived. These findings suggest that the decreased NK cell activity results in an increased release of cytokines by innate immunity.^{47,55,64} In the initial stage of SARS-CoV-2 infection, the NK cells' function and immunoregulatory activity were exhausted, and this phenotype is correlated with disease development. A study performed on the alveolar compartment of COVID-19 subjects found that although resting NK cells were significantly reduced, no significant changes were detected in stimulated NK cells. However, another report indicates that individuals with severe COVID-19 had more numbers of NK cells in their alveolar compartment than those with moderately infected or healthy people.^{57,60} These findings on the presence of NK cells in the tissue of infected individuals are not fully completed and conflicting, most likely due to variations in specimen collection timing or sickness severity.

In a study by Leem et al.,¹¹² NK cells in the RNA-seq investigation had unique characteristics in comparison to healthy donors, including a notable enrichment of proinflammatory cytokine-mediated signaling pathways. Intriguingly, they discovered that NK-cell cytotoxicity reduced and the unusual CD56^{dim} CD16^{neg} NK-cell population of PBMCs from COVID-19 patients independent of the severity of the illness.¹¹² In patients with moderate COVID-19, the NK-cell population quickly returned to normal along with the elimination of unusual CD56^{dim} CD16^{neg} NK cells and the restoration of NK-cell cytotoxicity, but this process took much longer in patients with severe COVID-19. Finally, using scRNA-seq on PBMCs and isolated NK cells, Guo et al.¹¹³ identified a memory-like NK subpopulation (NK1) that increases with age and correlates with disease severity in COVID-19. Their findings suggested that memory-like NK2.1 cells may be used to create immunotherapies for COVID-19 to treat age-related immunological dysfunctions.

3.1.4 | Myeloid suppressor cells

Myeloid-derived suppressor cells (MDSCs) are innate immune cells that regulate adaptive immunological responses.⁶⁵ Various infectious diseases have been shown to increase the activity of MDSCs.^{65,114} Studies revealed that individuals with severe COVID-19 have dysregulated myeloid cell components with higher MDSCs and activity related to the severity of COVID-19.⁶⁵ Inflammatory monocytes (HLA-DR^{hi}CD11c^{hi}) with ISG signatures, indicating terminally differentiated monocytes, have been observed in mild

COVID-19 cases. A deficiency in type I IFNs, classical monocytes (HLA-DR^{low}), and neutrophils (CD10^{low}CD101⁻CXCR4^{+/-}) with immunosuppressive properties in the circulation and lungs of patients with severe COVID-19 are frequently reported in severe cases indicating the urgent myelopoiesis.¹¹⁵⁻¹¹⁷

According to the research, severe COVID-19 pneumonia patients had a greater MDSC to T-cell (CD8 effector memory) ratio compared to those with moderate COVID-19 pneumonia, and the formation of MDSC is directly linked to lymphopenia and enhanced arginase activity in patients.⁶⁶ Up to 90% of total blood mononuclear cells were found to be MDSCs in cases with severe conditions, while such a percentage would be 25% in patients with mild conditions, and this proportion is decreased when the disease condition is improved.¹¹⁸ In COVID-19, granulocytic markers are elevated and applied to distinguish between individuals with mild and severe forms of diseases, suggesting the contribution of polymorphonuclear leukocyte-MDSCs in the COVID-19 pathogenesis.¹¹⁹ Enhanced CD15⁺CD16⁺ neutrophil numbers, reduced integrin CD11b granulocytic expression, and decreased expression of chemoattractant receptor-homologous molecule expressed on Th2 cells associated with Th2 in eosinophils and basophils, effectively involved in the development of COVID-19 hallmarks. Also, regarding the basophils and eosinophils, the emergence of the expression of the programmed death-ligand 1 (PD-L1) checkpoint was linked to the severity of symptoms.¹¹⁹ Because myeloid cells are the predominant immune cell subgroups linked with COVID-19 severity, identifying their inflammatory and chemotactic profiles might have diagnostic and therapeutic implications.¹²⁰

3.1.5 | Eosinophil

Severe COVID-19 has been shown to have self-perpetuating pathological hyperinflammation situations like cytokine storm.¹²¹⁻¹²³ Cellular responses such as margination and apoptosis can be modulated by cytokines acting alone or in combination with one another under certain circumstances. Significantly, moderate-to-severe stress hinders cortisol responses, contributing to eosinopenia in other situations.^{124,125} Besides, systematic investigations of leukocyte subsets and plasma cytokines in COVID-19 patients have shown an array of intriguing results. Patients with COVID-19 who required hospitalization had a longitudinal profile of plasma cytokines and peripheral blood leukocytes, according to Lucas et al.⁵⁴ results. According to their results, increased aggravation was related to abnormal Th2 and eosinophil responses, comprising raised levels of IL-5, IL-13, immunoglobulin E, and eotaxin-2, as well as a rise in the eosinophil counts in the circulation. Rodriguez et al.¹²⁶ evaluated the circulatory immune cells of individuals who recovered from a severe form of COVID-19. They discovered a distinct subgroup of IFN-induced CD62L⁺ eosinophils that were promptly increased before worsening in COVID-19 patients. The above findings are rather surprising since proinflammatory stimulation generally leads to decreased expression of CD62L in eosinophils; consequently,

the therapeutic implications of this immunoregulatory response have yet to be determined.¹²⁷ Accordingly, Vitte et al.¹¹⁹ conducted an unbiased mapping investigation focusing on important surface indicators of circulatory leukocytes in COVID-19 patients. Eosinophil-mediated overexpression of PD-L1 is directly associated with clinical outcomes in these patients. Also, Onodi et al.⁷³ recently explored that IFN promotes PD-L1 upregulation in eosinophils. Numerous studies have indicated that IFN- γ acts as a critical element of cytokine storm in COVID-19.¹²¹ Eosinophils and their responses to COVID-19 can be better understood by studying the kinetics and dynamics of IFN production and signaling. Surprisingly, although the modulation of peripheral eosinophils occurred during the progression of this condition, few eosinophils have already been found in bronchoscopy samples and very rarely in lung tissue in postmortem specimens.^{128,129} Furthermore, Zein et al.¹³⁰ discovered that eosinophils have antiviral properties in addition to their involvement in inflammation. COVID-19 individuals who were given inhaled corticosteroids had a reduction in coronavirus proliferation, which was connected to better outcomes.¹³⁰ Nevertheless, the interaction of SARS-CoV-2 and eosinophil and its effect on COVID-19 require additional investigations. The relationship between eosinophilia and improved outcomes of COVID-19 is dependent on the inhaled corticosteroids. Prospective randomized controlled investigations are required to assess the function of inhaled corticosteroids in COVID-19 treatment and their interplay with eosinophilia.

3.1.6 | Other innate immune cells

APCs include DCs that effectively process and deliver antigens to T cells to prime T-cell activation to particular antigens.¹³¹ cDCs and pDCs are the two main types of DCs. There are two types of cDCs: type 1 cDCs (CD103 or CD8 expressing) and type 2 cDCs (CD11b⁺), which include cross-presentation and CD4⁺ T-cell responses.¹³² Many respiratory infections, especially COVID-19, might be caused by DC dysfunction because of their crucial role in protecting the body from respiratory infections.^{102,133} In severe forms of COVID-19, the rate of DCs is decreased in PBMCs from COVID-19 cases. In contrast to healthy donors, they did not increase the formation of costimulatory molecules like CD80 following maturation stimulation.¹³¹ Additionally, unlike cDCs obtained from healthy donors, cDCs obtained from severe cases are not capable of stimulating T-cell activation or the synthesis of antiviral compounds, implying that cDCs of severe patients are deficient for activation, and development of T cells.¹³³ This suggests that they are ineffective in eliciting an effective immune reaction following COVID-19. In addition to cDCs, pDCs, which are leading suppliers of type I IFNs, are reduced in the blood, and functionally impaired after COVID-19.¹¹⁷ Therefore, additional research is needed to determine if these abnormal DCs are linked to condition severity in COVID-19 patients.

Finally, basophils are decreased in COVID-19 patients, demonstrating higher recruitment of these types of cells to injured lungs.¹³⁴ Because basophil can play a significant activity in tissue healing and

create coagulants, its reduction sometimes causes long-term lung inflammation and thrombosis. Basophil depletion usually occurs before the onset of the disease.¹³⁵

3.1.7 | Innate lymphoid cells and COVID-19

To date, little is known about the role of innate lymphoid cells (ILCs) in COVID-19 pathophysiology. In reaction to an infectious agent or microenvironmental alterations, ILCs residing in pulmonary epithelial tissue play an important role in host defense and make a significant contribution to lung protection, pathophysiology, and diseases.¹³⁶ Because ILCs lack antigen-specific receptors, it is hypothesized that they trigger by proinflammatory cytokines and unknown receptors. ILC may be indirectly or directly stimulated by the combinations of pathogen-associated molecular patterns with PRRs.¹³⁷ Although helper ILC subtypes are mostly found in tissues, they could be present in the blood as well.^{138,139} As a result, our knowledge of COVID-19-derived ILC cells is primarily restricted to changes in the peripheral blood. The ILC2 subgroup in the lungs inhibits allergen and viral-induced type 2 reactions, eosinophil migration, inflammatory reaction cessation, and tissue healing.¹⁴⁰ Concerning the NK subset, overall amounts of the ILCs subgroups and ILC progenitors (ILCp) subsets are reduced in the peripheral blood of patients with mild and severe COVID-19; nevertheless, when estimated as a proportion of ILCs, only the ILC2 keeps increasing in the peripheral circulation of mild COVID-19 compared with normal individuals.^{141,142} The proportions of helper ILC in specimens from recovered cases are comparable to those found in healthy subjects.^{141,142} The SARS-CoV-2 is dependent on the papain-like proteases to produce functioning replicase complexes that control viral propagation and the innate immune system.¹⁴³ Throughout allergic inflammation and asthma, papain has been found to increase the respiratory capacity of ILC2 cells in the lungs.¹⁴⁴ It has been found that injection of SARS-CoV-2 papain-like proteases in the lungs of mice rises the levels of IL-5-producing ILC2 in pulmonary tissue.¹⁴⁵ Moderate COVID-19 cases had higher levels of IL-13, ILC2, and IL-5, as well as IL-33.¹⁴² Not only is there a general decline in the overall ILC number, but there are also changes in the expression of stimulation, migratory, and differentiating characteristics associated with disease severity in COVID-19 individuals.¹⁴⁶ ILC2 and ILCp show a greater degree of CD69 expression while exhibiting lower rates of CXCR3 and C-C motif chemokine receptor 4 expression.^{141,142} There seems to be an enhancement in the stimulating receptors NKG2D⁺ in the ILC2 subgroup and a substantial reduction in the inhibitory receptors CD25 and KLRG1 in severe COVID-19 cases.^{141,142} These findings imply that COVID-19 alters the rate of the whole ILC population in the peripheral circulation, and the ILC2 subgroup undergoes major modifications. These alterations in the ILC subtype in peripheral circulation are characterized by the formation of cytokines like IL-5 and IL-13, which are released by the ILC2.¹⁴² Furthermore, severe COVID-19 cases need hospitalization, and the length of hospital stay is associated with a decrease in the number of ILCs, showing the critical involvement of ILCs in COVID-19.¹⁴⁶

3.2 | Adaptive immunity and COVID-19 pathogenesis

Adaptive immunity is essential for the elimination and control of the majority of viral diseases.^{147,148} B lymphocytes (the producer of antibodies), CD4⁺, and CD8⁺ T cells constitute an essential part of adaptive immunity.^{5,149} There are still many unknowns about the role of CD4⁺, CD8⁺ T cells, and nAbs in controlling SARS-CoV-2 in COVID-19 cases.¹⁴⁷ SARS-CoV-2-induced CD4⁺ and CD8⁺ T cells are targeted against a variety of antigens comprising structural and Nsps and are strongly related to milder forms of COVID-19.¹⁷ Antibody-mediated reduction of CD8⁺ T cells in convalescent macaques reduces immunity toward SARS-CoV-2 rechallenge, implying a function for CD8⁺ T cells in the context of diminishing antibody reactions (Table 2).¹⁵³ The response of CD4⁺ T cells to protein S has been investigated for its importance in the production of nAbs using prediction models, peptide or protein priming, and T-cell isolation to protein S at significant depths in recovering and vaccinated individuals.^{150,165}

3.2.1 | B cells and COVID-19

The neutralization by specific antibodies is a crucial stage in viral eradication, although the specificity of the NAbs remained unclear.¹⁶⁶ The S protein of SARS-CoV-2 contains a 193 amino acid region called the receptor-binding domain (RBD). This area binds to the ACE2 receptor, and RBD is a primary target for NAbs.¹⁶⁶ In addition, earlier reported monoclonal antibodies toward other coronaviruses could also attach to SARS-CoV-2, although their epitope specificity might not even match with the ACE2-binding domain.¹⁶⁷

The activation of B cells and accelerated generation of antigen-specific antibodies by antibody-secreting cells (ASCs) are vital to managing viral diseases.¹⁶⁶ Several studies indicated decreased CD5⁺ B-cell counts, increased plasmablasts, and SARS-CoV-2-specific antibody production.^{14,166} Despite reports of lymphopenia, COVID-19 patients had a higher number of PBMCs and CD19⁺ B cells than control participants.¹⁶⁸ B cells contain five key communities: transitional, naïve, double-negative, memory, and ASCs, and these five basic populations were further classified into 14 subpopulations depending on their features.¹⁶⁹ Individuals with moderate diseases, individuals in the intensive care unit (ICU), and healthy individuals all had unique B-cell profiles, which were particularly notable.¹⁶⁸ The developments of ASCs and double-negative lymphocyte cells were found in B cells isolated from ICU cases.¹⁶⁸ In contrast, transitional cells were found in those patients with mild conditions.¹⁶⁶ Extrafollicular responses are known to involve these cell types, and interestingly, comparable B cells have been discovered in animal models of autoimmune and viral clearance.¹⁷⁰⁻¹⁷² As a result, individuals with a background of SARS-CoV-2 disease, especially those diagnosed with severe infection, should be closely examined for manifestations of autoimmunity.

Furthermore, as compared to patients with moderate illness, individuals in the ICU had greater levels of ASCs, suggesting that circulating ASCs have an immunopathologic function in severe COVID-19. The plasma cell maturation marker, or CD138, expressed on multiple ASCs, indicates that ASCs are exposed to a highly inflammatory environment in ICU cases.¹⁶⁸ Those in the ICU had higher levels of CD21^{lo} transitional B cells than those in the general population, as well, in which cells accounted for less than 25% of the B-cell population.¹⁶⁸ Next research must focus on elucidating the pathways through which CD21^{lo} transitional cells exert their protective effects.¹⁶⁸

Yao et al.³¹ investigated PBMCs of COVID-19 patients using RNA-seq, despite the reduced number of CD4⁺ T cells found in COVID-19 patients, their activity was normal. In contrast, pathways involved in B-cell activation were downregulated in the severe group, indicating a B-lymphocyte compartment malfunction that restricts their activity.

Interestingly, Kang et al.¹⁷³ assessed titers of various isotypes of Abs against SARS-CoV-2 antigens, phagocytic capacity, and memory B responses in PBMCs and plasma samples obtained from individuals who suffered asymptomatic, moderate, and severe disease 1 year after COVID-19. They demonstrated that the phagocytic capability of Abs and memory B-cell responses, which are key factors in guarding against reinfection with SARS-CoV-2, are linked with disease severity at 1 year post-COVID-19. To better our understanding of B cells and their Ab expression in COVID-19 and ultimately improve vaccination approaches, more research on these immune responses to SARS-CoV-2 is necessary.

3.2.2 | T cells and COVID-19

T cells are critical against viral infections and the fate of disease. CD4⁺ T cells assist B cells in synthesizing antibodies and stimulating the CD8⁺ T cells' response and other immune cells in the face of infection.¹⁷⁴ T-cell reactions emerge early and associate with survival, but they are significantly reduced in severe COVID-19 and are linked with high stimulation and lymphopenia. A fraction of seasonal coronavirus-sensitive T lymphocytes interact with SARS-CoV-2 and even contribute to clinical prevention, especially in the early stages of infection.¹⁷⁵ T-cell memory includes wide recognition of viral proteins, thought to be approximately 30 epitopes per individual, and appears to be successfully maintained thus far.¹⁷⁵ This diversity of identification has the potential to restrict the effect of particular viral alterations and is likely to support the defense against severe illnesses caused by viral variations such as Omicron.¹⁷⁶

CD4⁺ and CD8⁺ T-cell frequencies are significantly reduced in COVID-19 patients, while T-cell activity is increased.⁵⁴ Patients with severe COVID-19 had a deposit of mononuclear cells in the lungs and lower rates of hyperactive T cells in the circulation, according to postmortem data.¹⁷⁷ These results imply that T cells from the blood are transferred into infected lung tissues to inhibit viral infection.¹⁷⁴ Furthermore, the immune reaction demonstrates some components of therapeutic antiviral protection and subtle aspects of

TABLE 2 Overview of adaptive immune reactions to SARS-CoV-2

Adaptive immune response	Reaction	Outcome	Reference
T CD4 lymphocyte	<p>According to the research findings that examined CD4⁺ T cell reaction to proteins of SARS-CoV-2 in recovered COVID-19 patients, reactions were identified toward approximately all SARS-CoV-2 proteins, with CD4⁺ T-cell responses being unrecognizable only for one of the smallest proteins. Remarkably, CD4⁺ T cells special for SARS-CoV-2 were reported to significantly correlate with reduced COVID-19 disease severity.</p> <p>IFNγ is the prevailing cytokine generated by SARS-CoV-2-specific CD4⁺ T cells from cases with COVID-19, with a distinguishable IFNγ, TNF, and IL-2 protein signature of classical Th1 cells.</p> <p>A subset of T CD4⁺ expressed CCR6 specific to SARS-CoV-2 indicates underlying Th17 characteristics of those cells, but the reports have suggested the low or undetectable levels of IL-17α protein expression in COVID-19 patients.</p> <p>T CD4⁺ cells (SARS-CoV-2-specific) can express a high level of IL-22.</p>	<p>B-cell affinity maturation and antibody production, Initiation of CD8 T-cell proliferation and differentiation, direct cytotoxic activity, regulation of primary SARS-CoV-2 disease, reduction in COVID-19 pathogenicity, and increased viral removal</p>	17,34,147,150–152
T CD8 lymphocyte	<p>The existence of virus-specific CD8⁺ T cells has now been linked to improved COVID-19 consequences.</p> <p>T CD8⁺ cells recognize various SARS-CoV-2 antigens, including spike, nucleocapsid, M, and ORF3a.</p> <p>Specific CD8⁺ T for SARS-CoV-2 express many molecules related to potent cytotoxic activity, including IFNγ, perforin, CD107, and granzyme B.</p> <p>Furthermore, depending on the increased expression of inhibitory receptors, several researchers have described exhaustion phenotypes of CD8⁺ T cells in severe COVID-19 cases.</p>	<p>Protection against the expansion of severe COVID-19, the killing of virus-infected cells, the production of effector cytokines, and the impairment of host defense mechanisms</p>	17,150,153–159
B lymphocyte	<p>Upon infection with SARS-CoV-2, the naive B cells, or possibly pre-existing memory B cells from previous HCoV illnesses, are stimulated by antigen identification, and CD4⁺ T cells support.</p> <p>Definitions of circulatory B cells in the early weeks of an acute SARS-CoV-2 disease have revealed moderate relative B cell lymphopenia and changeable enhancement in plasmablasts frequencies, which in some cases exceeded 30% of total B cells.</p> <p>Plasma cells and memory B cells that secrete antibodies can access the blood and (presumably) the mucosa. They assisted in the battle against viral illness and defended against reinfection.</p> <p>Indeed, severe COVID-19 cases exhibited higher rates of the DN2 B cells as opposed to those with mild cases and additionally had higher plasmablast numbers.</p>	<p>Affinity maturation, resulting in long-lived plasma cells and memory B cells, particular antibody generation, rise in secondary reactions</p>	160–164

Abbreviations: COVID-19, coronavirus disease 2019; DN2 B cells, double-negative (DN) B cells; HCoV, human coronavirus; IL, interleukin; Th17, T helper 17 cells; TNF, tumor necrosis factor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

sepsis.^{135,178,179} Gamma delta T cells ($\gamma\delta$ T cells) have been proven to possess a protecting antiviral effect in influenza pneumonia and are hence expected to be beneficial in COVID-19.¹⁷⁹ Furthermore, COVID-19 severity is mediated by selective T-cell expansion, exhaustion, and depletion. Cytolytic memory CD8⁺ T effector cells

in patients versus healthy controls show that activated T cells can be used as a therapeutic tool for treating SARS-CoV-2 infection.¹³⁵ As a result, immunological linkages and other assays (including C-reactive protein (CRP) and D-dimer) may help identify individuals at high risk of severe illness.¹³⁵

After acquiring SARS-CoV disease and recovering, individuals who had a severe infection but subsequently survived produced specific memory T cells that remained active for 2 years after the illness.^{180,181} IL-2, IFN- γ , and TNF are produced by CD4⁺ T cells from SARS-CoV patients, indicating that cellular immunity is crucial for managing the disease and preventing its spread.^{182,183} The inflammatory mediators produced by these cells contribute to pathophysiology, but the viral elimination depends on this reaction since the loss of these cells causes significant lung inflammation in mice.^{174,184} Another benefit is that the growth of CD4⁺ and CD8⁺ T lymphocytes in the lung is increased by immunization with DCs expressing SARS CoV antigens.^{185,186} T cells have a critical role in infection management, as shown by transplanting these cells into immunodeficient animals improved resistance toward SARS-CoV disease.¹⁸⁶

Compared with healthy subjects, CD8⁺ T cells from individuals with COVID-19 had lower levels of inhibitory receptor expression.¹⁰² CD8⁺ T cells from patients with severe diseases have released fewer cytokines once stimulated.¹¹¹ On the other hand, other research found an overactive CD8⁺ T-cell reactivity, upregulation of NK-associated markers, and enhanced cytotoxicity.^{111,187,188} Moreover, increasing proportions of CD38⁺HLA-DR⁺ functional CD8⁺ T cells or propagating CD8⁺ T cells were detected in the majority of patients with COVID-19.^{160,189} It should be noted that this scenario is not true in all patients, indicating that CD8⁺ T-cell reactions in COVID-19 might manifest themselves in a variety of ways.¹⁶⁰ As a result, there appears to be variability in the immune reaction to SARS-CoV-2, and various immunotypes may be correlated with different clinical characteristics.^{86,160} Predictably, a study verified the relevance of respiratory CD8⁺ T cell reactions, which entail connections (especially the IFN axis) among CD8⁺ T cells and upper respiratory epithelial cells.^{57,190} However, mild COVID-19 may be linked with more powerful clonal proliferation of CD8⁺ T cells.¹⁹¹ Also, specific CD8⁺ T cells have been found in recovered cases, confirming the development of SARS-CoV-2-specific CD8⁺ T-cell reactions and the presence of CD8⁺ T-cell memory.^{150,192} The precise involvement of CD8⁺ T cells specific for SARS-CoV-2 in regulating the initial acute infection and providing protection against subsequent infections remains unknown.¹⁹³

In individuals with COVID-19, CD4⁺ T cells demonstrate impairments, as well as the upregulation, activation, and/or exhaustion markers.^{194,195} According to research, individuals with a moderate form of COVID-19 had a more significant percentage of IFN- γ -producing Th1-like cells than in severe cases.¹⁹⁶ There have been reports of SARS-CoV-2-specific CD4⁺ T cells throughout acute infection, and the inflammatory profile of these cells is consistent with that of a Th1.¹⁹⁷ A normal Th2 response is seen in moderate instances of COVID-19, but the relevance of these cells in severe cases is not yet clear.¹⁹⁸ The additional data reported the involvement of pathological Th17 cell reactions in severe COVID-19 patients, including a significant reaction by CD4⁺ T cells that coexpress CCR6.^{177,199} The presence of enhanced CD4⁺ T-cell reactions that produce TGF- β , as well as an elevated subset of CD4⁺ T-cell reactions that produce IL-6 and GM-CSF, has been found in COVID-19 cases.^{200,201} The presence of virus-specific memory

CD4⁺ T cells in individuals after recovery from COVID-19 is significant because it suggests the formation of the protective immune response.^{150,192,202} Likewise, individuals who survived mild COVID-19 established memory CD4⁺ T cells that indicated high numbers of the IL-7 receptors (IL-7R) throughout their recovery.²⁰²

Additionally, in a study, Sekine et al.¹⁵⁴ stimulated PBMCs with nucleocapsid, S, and membrane peptides to assess the functional capacities of memory CD8⁺ and CD4⁺ T cells in recovering COVID-19. They demonstrated that whereas CD8⁺ T cells are characterized by IFN production and mobilization CD107a expression, CD4⁺ T cells specific for SARS-CoV-2 produce IFN, IL-2, and TNF. Notably, membrane- and nucleocapsid-specific CD4⁺ T cells were developed into Th1 or Th1/Th17 cells, but S-specific CD4⁺ T cells were biased toward circulating TFH cells. In addition, Yao et al.³¹ discovered that CD8⁺ T lymphocytes cannot destroy cells, which may contribute to the pathobiology of ARDS in COVID-19 patients.

Furthermore, there are very few studies on COVID-19 subjects with double negative (CD3⁺CD4⁻ CD8⁻) T cells. In Zahran et al.²⁰³ study, they showed that double-negative T cells were higher in COVID-19 patients than in other lymphocyte subgroups. Besides, in some other studies, T-lymphocyte subset absolute counts (overall CD3⁺, CD3⁺CD4⁺, CD3⁺CD8⁺, CD3⁺CD4⁺CD8⁺ double positive, and CD3⁺CD4⁻CD8⁻ double negative) were lower in nonsurvivors and patients with severe illness compared with individuals who survived and nonsevere cases.²⁰⁴ Therefore, more investigation is required to determine the involvement of double-negative cells in the development and regulation of COVID-19.

4 | CYTOKINE STORM AND COVID-19

Cytokine release is excessive in severe COVID-19 patients named a cytokine storm and impacts the human body.²⁰⁵ The processes through which SARS-CoV-2 disease causes cytokine overproduction remain unknown. The ACE2 protein is present in the highest concentrations in lung respiratory epithelial cells and small intestine enterocytes.²⁰⁶ In addition, ACE2 is abundantly expressed in smooth muscle and endothelial cells of arteries and veins in all organs investigated.^{206,207} The evaluation of autopsy specimens obtained from SARS patients revealed that SARS-CoV predominantly infected pulmonary epithelium, which was consistent with ACE2 expression levels.²⁰⁷ Given the presence of ACE2 expression, SARS-CoV can infect and cause damage to immune cells, such as T lymphocytes, monocytes, and macrophages.^{206,207} Surprisingly, despite the presence of SARS-CoV virus particles in other cell types, such as gastrointestinal system epithelial cells, brain neurons, and renal cells, numerous organs with ACE2 activity maintained uninfected.^{206,207} These inconsistencies support the idea that SARS-CoV cell entrance is not completely dependent on ACE2.

After infection with SARS-CoV-2, CD4⁺ T cells are rapidly stimulated by pathogenic Th1 cells, which secrete GM-CSF, and produce CD14⁺CD16⁺ monocytes with high-speed IL-6, which intensifies the inflammatory response.²⁰⁵ According to single-cell

research, in COVID-19 patients, immune cell interplay is defined by a rise in a subgroup of CD14⁺IL-1⁺ monocytes, which may support enhanced IL-1 β release.¹⁹¹ Th17 cells produce some proinflammatory mediators, such as IL-17, which recruits monocytes/macrophages and neutrophils to the area of inflammation and stimulates other inflammatory cascades, including IL-1 and IL-6, among others.²⁰⁸ Among these mediators, IL-6 plays a vital role in developing cytokine storm in COVID-19 patients.²⁰⁵

The cytokine storm in COVID-19 is caused by many activated cells, including neutrophils, B, T, DC, NK, macrophage, and tissue-resident cells.⁴⁷ COVID-19 patients have a higher rate of proinflammatory cytokines and chemokines than healthy controls, including IL-1 β , IL-1 receptor antagonist, IL-2, IL-7, IL-6, TNF- α , IL-10, IFN- γ , GM-CSF, granulocyte-GCF (G-CSF), fibroblast growth factor, platelet-derived growth factor, vascular endothelial growth factor, chemokine (C-C motif) ligand (CCL) 2 (CCL2), CCL3, CCL4, CCL8, CXCL2, CXCL8, CXCL9, CXCL10, and CXCL16.⁴⁷ Furthermore, a statistically significant relationship has been found between the severity of COVID-19 and the blood levels of TNF, CXCL8, CXCL10, CCL2, CCL3, IL-1, IL-2, IL-6, IL-7, IL-10, and G-CSF, among others.^{47,51,199} Another supplementary result confirms that severe COVID-19 patients have considerably higher plasma concentrations of IL-6, IL-10, and TNF- α than those with moderate forms of COVID-19.^{209,210} In this regard, elevated concentrations of IL-6, TNF, and IL-10 found in severe COVID-19 cases are significantly correlated with lower levels of inflammatory T cells.¹⁹⁴ Longitudinal studies in individuals with mild to severe COVID-19 who had the same expression profiles of inflammatory markers for up to 10 days after the onset of infection showed that this is an important component in the COVID-19 pathogenesis. Meanwhile, in subsequent periods, levels of TNF- α , IL-6, and IL-10 decreased rapidly in patients with mild disease, but remained high in patients with severe COVID-19.⁵⁴ In this context, IL-6 is a useful biomarker since its plasma level correlates with both viral load and lung damage in critically ill patients.²¹¹

5 | OTHER MARKERS AND COVID-19 SEVERITY

Individuals with COVID-19 showed a variety of clinical characteristics, including mild, moderate, severe, and critical forms. Although the majority of COVID-19 individuals have mild to moderate signs and indications, a Chinese study found that around 14% of patients had severe symptoms and signs, and 5% had critical signs and indicators.²¹² Earlier research and clinical experience demonstrated that the degree of severity was related to clinical therapy and illness prognosis.^{25,212} The overall case-fatality rate of verified COVID-19 individuals was 2.3% on average, but this increased to 49% in critical patients.²¹² Misdiagnosis delays appropriate treatment and increases the likelihood of a poor outcome. The treatment for severe or critical COVID-19 patients, on the other hand, necessitates comprehensive medical resources, and multiple misdiagnoses will exhaust those resources and exacerbate the medical burden. As a result, early

diagnosis of individuals who are at risk of developing severe or critical COVID-19 is vital for clinical management and epidemic management. The severity of COVID-19 is classified into four stages, namely, mild, moderate, severe, and critical.²¹³ This categorization is mostly made based on signs, oxygen saturation (SaO₂), and computed tomography imaging data. However, there is no evidence of laboratory indicators to diagnose COVID-19. Previous research has linked lymphopenia, organ failure, coagulopathy, and high D-dimer concentrations to the severity of the disease.^{25,212,214}

Besides, the expression of numerous inflammation-related genes, such as arginase 1 and IL-1 receptor 2, was found to be highly increased in the PBMCs of COVID-19 patients, despite individual variances in Yang et al.²¹⁵ study. Patients with COVID-19 have abnormal levels of the coagulation-related genes Von Willebrand factor and protein S. Certain gene expression patterns, such as IL-1 receptor, were associated with their histone methylation marks. In the TGF- β , IL-1 β , IL-6, and IL-17 pathways, the majority of the dysregulated genes were found. Also, in Yang et al.²¹⁵ study the expression of bone marrow kinase X, which is part of the TEC family, was enhanced in the PBMCs of COVID-19 patients. We tried to summarize some of those factors linked with COVID-19 severity in this section.

6 | SERUM AMYLOID-A AND COVID-19

The acute-phase reaction, which includes various phenomena, indicates the existence of infection and inflammation, such as elevated temperature and hormonal and metabolic changes, and dramatically activates SAA.²¹⁶ Peripheral SAA levels, which are generally moderate under normal conditions (20–50 mg/l), may increase 1000-fold during the first 24 to 48 h of the acute-phase response. This is due to higher production in the liver, which is activated by a variety of factors like TNF- α , IFN- γ , IL-1 β , and IL-6.^{217,218} SAA, in turn, may stimulate the complement system activation and the nucleotide-binding domain leucine-rich repeat-containing family pyrin-domain containing 3 inflammasome, increasing IL-1 β , TNF- α , and IL-6 production and activating additional proinflammatory mediators, including IL-1 α and IL-23.^{219,220} Significantly, these agents have been demonstrated to display an essential activity in initiating the cytokine storm and its adverse clinical effects on COVID-19.²²¹ As a result, it is possible that the immediate rise in SAA levels in COVID-19 patients reflects the existence of acute phase response and anticipates the onset of the cytokine storm and, as an outcome, multiorgan collapse and an elevated chance of detrimental consequences.

Besides its possible function in the pathophysiology of the cytokine storm, it has recently been shown that SAA may also have procoagulant properties, facilitated by an elevation in fibrinogen and concurrent platelet aggregation and prothrombotic conditions.²²² In summary, pending further investigation, an acute increase in SAA levels may indicate an important component linking inflammatory processes and prothrombotic cascades. The interaction between

inflammatory response and thrombosis has also been found in COVID-19, a disorder frequently characterized by significant coagulation abnormalities and a prothrombotic situation, especially in individuals with severe forms of COVID-19.²²³

The blood levels of SAA in severe COVID-19 subjects are more than a thousand times greater than those reported in individuals with other malignancies or inflammatory disorders when SAA upregulation is correlated with systemic amyloidosis as a secondary disorder.^{224,225} SAA amyloidosis is defined by the production and accumulation of SAA amyloids in blood vasculature, resulting in thrombosis, inflammation, and, ultimately, organ failure.²²⁶ The prevalent consequence of SAA amyloidosis, such as renal dysfunction or elevated thrombosis rates, is observed in COVID-19 cases.^{226,227} The pattern of signs implies that SAA amyloidosis could increase COVID-19 symptoms.²²⁸

7 | NE AND COVID-19

Neutrophils perform a significant role in the development of ARDS by releasing toxic molecules, such as ROS and proteases, particularly elastase.^{229,230} Neutrophils may also release IL-6 in reaction to viral diseases, particularly single-stranded RNA viruses, including SARS-CoV-2, via a process involving the Toll-like receptor 8 (TLR8).²³¹ The lungs depend on these cells to produce soluble IL-6 receptors (IL-6Rs), which may play a role in developing chronic respiratory disorders characterized by pathogenic IL-6R *trans*-signaling.²³² The significance of this type of communication in cytokine release syndrome (CRS) establishment has been established in lymphoma patients who received chimeric antigen receptor T-cell therapy.²³³ According to this study, an elevated neutrophil count in individuals with ARDS may contribute to CRS and lung damage. The elastase enzyme produced by these cells has also been demonstrated to be one of the crucial proteolytic enzymes required to activate coronaviruses' S protein and alter the virus's entrance path to a low pH-independent pathway.²³⁴

Although it serves a physiological purpose as a potent host defense, NE is also recognized as one of the most detrimental enzymes in the human body.²³⁵ An excessive release of enzymatically active NE from the neutrophils might damage local tissue.²³⁵ In addition, it has been observed that NE may stimulate the COV protein S and cause the virus to enter the cell through a low pH-independent pathway.²³⁴ As a result, high NE levels were detected in patients with SARS-CoV-2 by Akgun et al.²³⁵ validates these results.

8 | SDC AND COVID-19

SDCs (SDC-1, SDC-2, SDC-3, and SDC-4) are type I transmembrane heparan sulfate proteoglycans that may interact with inflammatory mediators, adhesion molecules, proteolytic enzymes, and cytokines.²³⁶ SDCs and their ligands interact to initiate biological signaling events related to inflammation, angiogenesis, cell attachment, and tissue

repair.²³⁷ SDCs help maintains cellular homeostasis in normal conditions while also controlling inflammatory responses after trauma and diseases.²³⁸ SDC-1 has recently been shown to have a critical key role in developing inflammatory disorders, malignancies, and infectious diseases, according to research conducted on animal models of different conditions.²³⁷ In vitro and in vivo investigations have shown that these SDC-1 activities are crucial for understanding the pathogenesis of infectious diseases.²³⁹⁻²⁴¹ SDC-1 depletion or deletion confers considerable resistance to infection by various viral and bacterial pathogens.²³⁹⁻²⁴¹

A recent study has recently confirmed the role of SDC-1 in viral infection pathobiology. Bermejo-Jambrina et al.²⁴² found that the cell surface of heparan sulfate proteoglycan (HSPG), including SDC-1 and SDC-4, is required for SARS-CoV-2 infection in permissive cells, and SARS-CoV-2 infection in AMs was effectively impeded by low-molecular-weight heparins. Regarding the intriguing function of SDC-1 in the course of inflammatory conditions, such as respiratory viral disease, Karampoor et al.²³⁷ discovered dynamic changes in SDC-1 levels along with certain indicators, such as IL-6, IL-10, IL-18, CRP, and vitamin D in COVID-19 patients.

The primary receptor for SARS-CoV-2 cellular entrance has been identified to be ACE2. However, new research reveals that other membrane proteins, including HSPGs, have a role in SARS-CoV-2 internalization.²⁴³ Hudák et al.²⁴³ discovered that SDCs enable SARS-CoV-2 cellular entrance. Among SDCs, SDC-4 was the most effective in facilitating SARS-CoV-2 uptake in their investigation, although the upregulation of other isoforms, especially neuronal SDC-3, also boosted SARS-CoV-2 internalization. According to the literature, the S1 component of the SARS-CoV-2 S protein is crucial in the virus's interaction with SDCs.²⁴³ Other elements of the SDC ectodomain like the cell-attachment domain participate in the interface with SARS-CoV-2 in addition to the polyanionic heparan sulfates, which are binding sites for various viruses.²⁴³ SDCs colocalize with ACE2 during viral internalization, indicating that the two proteins are involved in the same internalization pathway.²⁴³ Both ACE2 and SDCs inhibitors were shown to be effective in inhibiting the cellular entrance of SARS-CoV-2, indicating that internalization is a multifaceted process.²⁴³

9 | TARGETING IMMUNE RESPONSES TOWARD COVID-19

Therapeutic approaches widely used for the treatment of SARS-CoV-2 are categorized as (1) treatments focused on IFNs, (2) therapies addressing pathological inflammatory reactions, and (3) therapies targeting noncanonical pathways.²⁴⁴ In addition, monoclonal antibodies that target the virus are effective in minimizing the pathophysiology and critical illnesses, but have not been further explored here.²⁴⁵ When delivered early, SARS-CoV-2 is particularly susceptible to IFN therapy in vitro and in vivo.^{246,247} Similarly, a retinoic acid-inducible gene I (RIG-I) PRR antagonists and stimulators of IFN genes, both prophylactically and timely after infection,

effectively limit the release of SARS-CoV-2 in vivo in an IFN-type I-dependent manner.^{248,249} Human IFN therapy is currently under investigation. A retrospective observational research examining the efficacy of intranasal aerosolized IFN α (IFN α 2B) therapy in COVID-19 participants revealed that prompt IFN α 2b delivery was linked with lower in-hospital death, but late treatments were correlated with greater death rates and delayed rehabilitation.²⁵⁰ Different investigations failed to discover the therapeutic benefits of subcutaneous pegylated IFN1 α and IFN on mild and moderate forms of COVID-19.^{251,252} In these circumstances, the pharmacological use of IFN- β based on its physiological effect and the absence of IFN- β -neutralizing autoantibodies in cases has been suggested in a large proportion of patients compared to the presence of such autoantibodies to IFN- α and IFN- ω .^{253,254} Significant worsening of symptoms reported after the late initiation of IFN α 2b is likely due to some proinflammatory action of IFNs, especially when associated with a preinflamed respiratory tract. For example, type I IFN substantially promotes ZBP1, which stimulates NF- κ B-driven proinflammatory cytokine production in response to SARS-CoV-2 infection.^{250,255} Surprisingly, the SARS-CoV-2 protein cleaves NSP3 ISG15 and alters the physiological role of ISG15 from supporting ISG production to increasing NF- κ B-driven proinflammatory mediators.²⁵⁶ In addition, IFN type I in invading proinflammatory monocytes destroys the pulmonary epithelium via TNF-associated apoptosis-inducing ligand.²⁵⁷ This, together with the effect of inhibiting IFN type I on alveolar epithelial cell growth, disrupts lung regeneration.²⁵⁸ The ectopic inflammatory process is the second treatment strategy for COVID-19. The clinical efficacy of dexamethasone provides conceptual evidence for this COVID-19 treatment.²⁵⁹ Furthermore, the findings of a pilot trial revealed that while anti-IL-17 antibody may lower the inflammatory reaction and improve oxygenation, it does not reduce the risk of death.²⁶⁰ Regarding TNF-directed medicines, descriptive clinical evidence and case series suggest the feasibility and promise of anti-TNF medications as a COVID-19 therapy, but broader clinical studies are required.²⁶¹ Finally, in severe COVID-19, the complement system remains a potential therapeutic target. In patients with COVID-19, for instance, currently, underway clinical trials are assessing the possibility of a humanized monoclonal C1 esterase antagonist as a multitarget suppressor of inflammatory feedback loops such as kinin-kallikrein, the contact activation system, and complement in attempting to reduce lung inflammation and pathogenesis.²⁶²

10 | CONCLUSION

SARS-CoV-2 infection overproduces proinflammatory cytokines, leading to cytokine syndrome. This condition leads to uncontrollable inflammation, which mostly leads to multiple organ failures. SARS-CoV-2 triggers both innate and adaptive immune reactions too much, resulting in tissue damage. Therefore, understanding the most important features and evolving intrinsic and adaptive immunity against this virus is crucial in predicting the consequences of

COVID-19 and in the administration of useful approaches for controlling the disease. The management of the inflammatory response is critical for targeting viral infection in this regard, thus it is critical to understand the processes driving hyperinflammation to develop a better treatment strategy to limit viral proliferation. COVID-19 prevention and treatment might benefit from ongoing clinical trials evaluating the immunogenicity of COVID-19-targeting medicines. We should look at all possible paths of study to find out how SARS-CoV-2 infection is affecting people's immune systems to properly implement a multifaceted strategy.

AUTHOR CONTRIBUTIONS

All authors equally contributed to this study. Saade Abdalkareem Jasim, Roaa Salih Mahdi, Dmitry Olegovich Bokov, Mazin A. A. Najm, Sajad Karampoor, and Rasoul Mirzaei participated in the study design, drafting of the manuscript, and collecting of the documentation materials. Guzal N. Sobirova, Zarnigor O. Bafoyeva, Ahmed Taifi, Ola Kamal A. Alkadir, and Yasser Fakri Mustafa participated in writing the manuscript and drawing figures. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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